

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Country Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Poland		
N	134	63
Baseline	143.0	148.5
% change to endpoint	-38.90 (19.9)	-40.70 (19.8)
Germany		
N	51	27
Baseline	145.07	151.50
% change to endpoint	-43.2 (18.4)	-43.07 (11.4)
India		
N	32	18
Baseline	129.83	133.70
% change to endpoint	-41.04 (20.7)	-44.03 (13.1)
Netherlands		
N	46	20
Baseline	145.5	142.1
% change to endpoint	-43.1 (20.8)	-48.3 (12.5)
Denmark		
N	6	5
Baseline	165.5	152.13
% change to endpoint	-43.9 (13.8)	-44.9 (12.6)
UK		
N	5	2
Baseline	148.3	131.7
% change to endpoint	-40.1 (9.4)	-63.9 (0.94)

Subjects who were enrolled in India appeared to have lower mean LDL values at baseline compared with the other countries (129.8 mg/dL in the pitavastatin 4 mg group; 133.7mg/dL in the atorvastatin 20 mg group). Baseline mean LDL was at least 142 mg/dL in the other countries, excluding Denmark and the UK. In Denmark, baseline mean LDL was higher than in any of the other countries both in the pitavastatin 4 mg group (165.5mg/dL) and in the atorvastatin 20 mg group (152.1 mg/dL). In the UK, baseline mean LDL in the pitavastatin 4 mg group was lower than in Denmark but higher than in the other countries (148.3mg/dL) whereas in the atorvastatin 20 mg group it was lower than in the other countries (131.7mg/dL). However, the numbers of subjects enrolled in Denmark and the UK were too low for meaningful comparison.

Baseline mean LDL was higher in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group in Poland, Germany and India, while in the Netherlands, the baseline mean LDL was higher in the pitavastatin 4 mg group.

The mean percent change from baseline to endpoint in mean LDL was approximately -43% in both treatment groups in Germany, whereas in the other countries the mean percent change from baseline was consistently lower in the pitavastatin 4 mg group compared with the atorvastatin 20 mg group. However, the mean percent change from baseline in the atorvastatin 20 mg group in the Netherlands was higher than in the other countries. In India, where mean baseline LDL was lower than in the other countries, the mean percent change from baseline to endpoint was comparable to that achieved in the other countries.

LDL by Age:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by age in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Age Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
<65 years		
N	190	91
Baseline	141.2	145.2
% change to endpoint	-40.28 (19.4)	-41.71 (16.8)
≥65 years		
N	84	44
Baseline	146.6	147.9
% change to endpoint	-41.90 (20.1)	-46.43 (15.3)

Approximately 70% of the study population was in the age group <65 years. In this age group, baseline LDL was lower in the pitavastatin 4 mg group compared with the atorvastatin 20 mg group. In older subjects (≥65 years), the difference between baseline means in the two groups was less marked compared with younger subjects. The p-value for the interaction between treatment and age was P=0.477.

Older subjects showed greater reductions in LDL than the younger subjects in both treatment groups. This difference was larger in the atorvastatin 20 mg group resulting in a greater treatment group difference in older subjects.

LDL by Sex:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by sex in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Sex Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Male		
N	155	78
Baseline	139.2	143.6
% change to endpoint	-38.39 (20.210)	-44.85 (12.990)
Female		
N	119	57
Baseline	147.7	149.3
% change to endpoint	-43.9 (18.4)	-41.05 (20.0)

A higher mean baseline LDL level was found in females compared with males in both treatment groups. There was a greater mean percent decrease from baseline to endpoint in LDL among males in the atorvastatin 20 mg group compared with males in the pitavastatin 4 mg group; whereas among females there was a greater change from baseline in subjects treated with pitavastatin 4 mg compared with those in the atorvastatin 20 mg group. These differences resulted in a statistically significant treatment-by-sex interaction (P=0.017). However, in the PP population, the p-value for the interaction between treatment and sex was not significant (P=0.324).

LDL by Race:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by race in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Race Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Caucasian		
N	242	116
Baseline	144.6	148.0
% change to endpoint	-40.7 (19.5)	-42.9 (16.8)
Non-Caucasian		
N	32	19
Baseline	129.8	133.7
% change to endpoint	-41.0 (20.7)	-45.4 (14.0)

All of the non-Caucasian subjects were Indian. Caucasian subjects had lower mean baseline LDL compared with Caucasians in both treatment groups. In addition, mean baseline LDL was lower in the pitavastatin 4 mg group compared with the atorvastatin 20 mg in both race subgroup categories.

In both Caucasians and non-Caucasians, there was a greater mean percent decrease from baseline to endpoint in LDL in the atorvastatin 20 mg group compared with subjects in the pitavastatin 4 mg group, the difference being more remarkable among non-Caucasians. Within the same treatment group, a greater mean percent reduction from baseline was observed among non-Caucasians compared with Caucasians in the atorvastatin 20 mg group, while similar percent reductions were observed among the two races in the pitavastatin 4 mg group. The p-value for the interaction between treatment and race was not significant (P=0.894).

LDL by BMI Category:

The mean percent changes from baseline to endpoint in LDL for the FAS are presented by BMI category in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by BMI Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
<25 kg/m²		
N	27	15
Baseline	139.0	142.7
% change to endpoint	-41.5 (26.1)	-47.8 (9.1)
25-<30 kg/m²		
N	124	61
Baseline	143.3	149.6
% change to endpoint	-40.8 (18.7)	-43.4 (15.4)
≥30 kg/m²		
N	123	59
Baseline	143.2	143.2
% change to endpoint	-40.6 (19.0)	-41.9 (18.6)

Pitavastatin subjects had lower mean baseline LDL levels than atorvastatin subjects for the low and medium BMI categories but not for the high category. There was a greater mean percent decrease in LDL in subjects in the atorvastatin 20 mg group compared with subjects in the pitavastatin 4 mg group, with the greatest difference between the groups occurring in subjects with a BMI of $<25 \text{ kg/m}^2$, that however included overall only 42 subjects. In the pitavastatin 4 mg group, a mean decrease from baseline of approximately 41% was observed across the three BMI subgroups, while in the atorvastatin 20 mg group the mean percent reduction from baseline in LDL decreased from the $<25 \text{ kg/m}^2$ subgroup to the $\geq 30 \text{ kg/m}^2$ BMI subgroup. The p-value for the interaction between treatment and BMI category was $P=0.739$.

LDL by Screening HbA_{1c}:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by screening HbA_{1c} category in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Screening HbA_{1c} Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
≤6.5%		
N	141	73
Baseline	144.91	146.09
% change to endpoint	-39.8 (19.9)	-44.7 (14.9)
>6.5%		
N	132	62
Baseline	140.8	146.0
% change to endpoint	-41.8 (19.4)	-41.5 (17.9)

Mean baseline LDL was lower in the pitavastatin 4 mg group compared with the atorvastatin 20 mg group in both of the baseline HbA_{1c} subgroup categories.

The advantage of atorvastatin 20 mg in mean percent reduction of LDL was pronounced in the subjects with well-controlled diabetes (HbA_{1c} ≤6.5%) while in subjects with HbA_{1c} >6.5%, the reduction in LDL was virtually the same in the two treatment groups. The p-value for the interaction between treatment and HbA_{1c} category was not statistically significant ($P=0.146$) for the FAS but was significant ($P=0.042$) for the PP population.

Secondary Efficacy Lipid Variables:

Total cholesterol (TC):

Changes from baseline in TC are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: TC (mg/dL) (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	233.1 (32.5)	235.8 (31.4)
Endpoint mean (SD)	166.9 (37.4)	160.9 (32.9)
Mean % change (SD)	-28.21 (13.5)	-31.56 (11.8)
Adjusted Mean Difference (95% CI)	-3.1 (-5.8; -0.5)	
P-value	0.02	

The mean percent decrease from baseline to endpoint in TC was higher in the atorvastatin 20 mg group (-31.6%) compared with the pitavastatin 4 mg group (-28.2%). The adjusted mean difference for the treatment group comparison was -3.1%, and was statistically significant (P=0.020).

High-Density Lipoprotein cholesterol (HDL):

Changes from baseline in HDL are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: HDL (mg/dL) (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	41.7 (9.2)	40.8 (7.5)
Endpoint mean (SD)	44.4 (9.8)	43.9 (9.2)
Mean % change (SD)	7.34 (15.8)	8.20 (16.2)
Adjusted Mean Difference (95% CI)	0.22 (-2.94; 3.4)	
P-value	0.893	

There was an increase in HDL values of 7.3% in the pitavastatin 4 mg group and 8.2% in the atorvastatin 20 mg group. The adjusted mean difference for the treatment group comparison was 0.22%, and was not statistically significant (P=0.893).

HDL by Screening HbA_{1c}

The mean percent change from baseline to endpoint in HDL for the FAS is presented by screening HbA_{1c} category in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in HDL (mg/dL) by Screening HbA_{1c} Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
≤6.5%		
N	141	73
Baseline	43.3	41.3
% change to endpoint	5.9 (17.7)	8.33 (18.3)
>6.5%		
N	132	63
Baseline	40.04	40.3
% change to endpoint	8.7 (13.4)	8.05 (13.4)

The mean percent change from baseline in HDL was lower for subjects with screening HbA_{1c} ≤6.5% treated with pitavastatin 4 mg compared with subjects in this subgroup treated with atorvastatin 20 mg. However, there was little difference between the treatment groups in mean percent change from baseline for subjects with screening HbA_{1c} >6.5%. The p-value for the interaction between treatment and HbA_{1c} category was P=0.533.

HDL by Baseline HDL:

The mean percent change from baseline to endpoint in HDL for the FAS is presented by baseline HDL in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in HDL (mg/dL) by Baseline HDL Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
<40 mg/dL		
N	127	63
Baseline	34.2	34.5
% change to endpoint	11.0 (16.4)	12.6 (15.9)
40 - <60 mg/dL		
N	136	71
Baseline	46.8	45.9
% change to endpoint	4.99 (14.5)	4.79 (15.6)
≥60 mg/dL		
N	11	2
Baseline	65.8	60.5
% change to endpoint	-5.60 (13.3)	-8.24 (4.6)

For both treatment groups, the mean percent increase from baseline in HDL was higher in subjects with baseline HDL <40 mg/dL compared with subjects in the subgroup 40-<60 mg/dL. There were only 13 subjects in the HDL subgroup ≥60 mg/dL, which is too few for meaningful comparison with the other subgroups. The p-value for the interaction between treatment and HbA_{1c} category was P=0.812.

The shift of the number of subjects in specific HDL categories is shown in the following table:

Shift Table of HDL (mg/dL) (FAS)							
Number of subjects With Change in Laboratory Value Range From Week 0 to Last Visit							
Pitavastatin 4 mg QD N=274				Atorvastatin 20 mg QD N=136			
Week 12 or Last Visit				Week 12 or Last Visit			
Baseline	<40	40-<60	≥60	Baseline	<40	40-<60	≥60
<40	84	42	1	<40	38	24	1
40-<60	11	114	11	40-<60	10	53	8
≥60	0	4	7	≥60	0	2	0

Shift tables of HDL categories illustrate that the HDL of most subjects remained in the same category before and after treatment. One subject in each treatment group had a shift from the low category (<40 mg/dL) to the high category (≥60 mg/dL). Forty-two subjects in the pitavastatin 4 mg group and 24 subjects in the atorvastatin 20 mg group had a shift in HDL from the low category to the medium category (40-<60 mg/dL).

HDL by Baseline Triglyceride (TG):

The mean percent change from baseline to endpoint in HDL for the FAS is presented by baseline TG category in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in HDL (mg/dL) by Baseline TG Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
<150 mg/dL		
N	7	1
Baseline	49.7	24.3
% change to endpoint	14.5 (20.7)	6.9
150 - <200 mg/dL		
N	79	39
Baseline	45.0	43.7
% change to endpoint	4.60 (15.6)	8.92 (14.3)
≥200 mg/dL		
N	188	96
Baseline	40.0	39.9
% change to endpoint	8.2 (15.6)	7.92 (17.0)

The mean percent increase from baseline in HDL was similar between the two treatment groups in the TG subgroup category ≥200 mg/dL. In the TG subgroup category 150-<200 mg/dL, the mean percent increase from baseline was greater in subjects in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group. There were only eight subjects in the TG subgroup <150 mg/dL, which is too few for meaningful comparison with the other subgroups. The p-value for the interaction between treatment and TG category was P=0.251.

Triglycerides (TG):

Changes from baseline in TG are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: TG (mg/dL) (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	244.5 (77.9)	245.2 (89.0)
Endpoint mean (SD)	195.9 (118.6)	174.3 (82.8)
Mean % change (SD)	-20.11 (29.5)	-27.16 (29.1)
Adjusted Mean Difference (95% CI)	-6.75 (-12.79; -0.71)	
P-value	0.029	

Triglycerides decreased by 20.1% in the pitavastatin 4 mg group and by 27.2% in the atorvastatin 20 mg group. The adjusted mean difference for the treatment group comparison was -6.8%, and was statistically significant (P=0.029).

Triglycerides (TG) by Screening HbA_{1c}

The mean percent change from baseline to endpoint in TG for the FAS is presented by screening HbA_{1c} category in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in TG (mg/dL) by Screening HbA_{1c} Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
≤6.5%		
N	141	73
Baseline	241.03	247.85
% change to endpoint	-17.69 (28.947)	-30.65 (24.168)
>6.5%		
N	132	63
Baseline	248.10	242.16
% change to endpoint	-22.57 (30.034)	-23.10 (33.655)

The mean percent change from baseline to endpoint in TG was greater for subjects with screening HbA_{1c} ≤6.5% treated with atorvastatin 20 mg compared with subjects in this subgroup treated with pitavastatin 4 mg. However, there was little difference between the treatment groups in mean percent change from baseline for subjects with screening HbA_{1c} >6.5%. The p-value for the interaction between treatment and HbA_{1c} category was significant for the FAS (P=0.048) though not for the PP population (P=0.234).

Triglycerides (TG) by Baseline HDL:

The mean percent change from baseline to endpoint in TG for the FAS is presented by baseline HDL in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in TG (mg/dL) by Baseline HDL Subgroup (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
<40 mg/dL		
N	127	63
Baseline	257.0	273.7
% change to endpoint	-23.3 (25.4)	-32.3 (30.8)
40 - <60 mg/dL		
N	136	71
Baseline	237.1	221.5
% change to endpoint	-17.64 (32.9)	-23.61 (26.0)
≥60 mg/dL		
N	11	2
Baseline	192.0	188.8
% change to endpoint	-13.73 (27.2)	10.26 (50.5)

The mean percent decrease from baseline in TG was greater in subjects in the atorvastatin 20 mg group compared with subjects in the pitavastatin 4 mg group both for subjects in the screening HDL subgroup <40 mg/dL and for the subgroup 40-<60 mg/dL. For both treatment groups, the reductions in TG were greater for the subgroup <40 mg/dL. There were only 13 subjects in the HDL subgroup ≥60 mg/dL, which is too few for meaningful comparison with the other subgroups. The p-value for the interaction between treatment and baseline HDL category was P=0.399.

Non-HDL:

Changes from baseline in Non-HDL cholesterol are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Non-HDL cholesterol (mg/dL) (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	191.3 (30.6)	195.0 (30.5)
Endpoint mean (SD)	122.6 (36.9)	117.1 (33.06)
Mean % change (SD)	-35.73 (17.6)	-39.72 (15.3)
Adjusted Mean Difference (95% CI)	-3.7 (-7.12; -0.32)	
P-value	0.032	

Non-HDL cholesterol was higher in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group at baseline and, similarly, the mean percent change from baseline to endpoint was greater in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group. The adjusted mean difference for the treatment group comparison was -3.7%, which was statistically significant (P=0.032).

Apolipoprotein B (Apo-B):

Changes from baseline in Apo-B are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Apo-B (mg/dL)
(FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	149.2 (26.6)	150.0 (24.0)
Endpoint mean (SD)	101.0 (27.2)	100.0 (25.0)
Mean % change (SD)	-31.69 (18.5)	-33.56 (15.5)
Adjusted Mean Difference (95% CI)	-1.59 (-5.17; 1.99)	
P-value	0.384	

Mean Apo-B decreased by a similar amount in both treatment groups. The adjusted mean difference for the treatment group comparison was -1.59%, which was not statistically significant (P=0.384).

Apolipoprotein A1 (Apo-A1):

Changes from baseline in Apo-A1 are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Apo-A1 (mg/dL)
(FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	155.9 (26.4)	153.3 (23.8)
Endpoint mean (SD)	163.4 (27.2)	158.3 (24.2)
Mean % change (SD)	5.92 (13.6)	4.46 (13.6)
Adjusted Mean Difference (95% CI)	-1.92 (-4.52; 0.69)	
P-value	0.149	

Mean Apo-A1 increased from baseline in both treatment groups. The adjusted mean difference for the treatment group comparison was -1.92%, which was not statistically significant (P=0.149).

Apo-B:Apo-A1 Ratio:

Changes from baseline in Apo-B:Apo-A1 ratio are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Apo-B:Apo-A1 ratio
(FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	0.98 (0.225)	1.00 (0.223)
Endpoint mean (SD)	0.63 (0.194)	0.65 (0.194)
Mean change (SD)	-0.35 (0.2)	-0.37 (0.2)
Adjusted Mean Difference (95% CI)	-0.00 (-0.04; 0.03)	
P-value	0.957	

The ratio of Apo-B:Apo-A1 was similar in the two treatment groups at baseline. At endpoint, there was a similar decrease from baseline in the two treatment groups. The adjusted mean difference between treatment groups was zero and was not statistically significant (P=0.957).

Non-HDL:HDL ratio:

Changes from baseline in non-HDL:HDL ratio are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Non-HDL:HDL ratio (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	4.82 (1.21)	4.96 (1.21)
Endpoint mean (SD)	2.91 (1.09)	2.80 (1.02)
Mean change (SD)	-1.91 (1.11)	-2.16 (1.20)
Adjusted Mean Difference (95% CI)	-0.167 (-0.36; 0.02)	
P-value	0.085	

At endpoint, the decrease in non-HDL:HDL ratio was greater in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group. The adjusted mean difference for the treatment group comparison was -0.17, which was not statistically significant in the FAS (P=0.085) but the difference between the groups was significant in the PP population (P=0.031).

TC:HDL Ratio:

Changes from baseline in TC:HDL ratio are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: TC:HDL ratio (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	5.82 (1.21)	5.959 (1.21)
Endpoint mean (SD)	3.91 (1.09)	3.796 (1.02)
Mean change (SD)	-1.91 (1.11)	-2.163 (1.19)
Adjusted Mean Difference (95% CI)	-0.17 (-0.356; 0.023)	
P-value	0.085	

At endpoint, the decrease in TC:HDL ratio was greater in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group. The adjusted mean difference for the treatment group comparison was -0.17, which was not statistically significant in the FAS (P=0.085) but the difference between the groups was significant in the PP population (P=0.031). It should be noted that this comparison ends up being the same as the comparison of the non-HDL:HDL ratio.

High Sensitivity C-Reactive Protein (hsCRP):

Changes from baseline in hsCRP are summarized for the FAS in the following group:

Change from Baseline in Secondary Efficacy Lipid Variables: hsCRP (mg/L) (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	4.08 (6.595)	3.11 (4.057)
Endpoint mean (SD)	3.93 (9.033)	2.85 (3.992)
Mean change (SD)	-1.4 (10.483)	-2.6 (4.279)
Adjusted Mean Difference (95% CI)		-8.6 (-2.44; 0.73)
P-value		0.288

Mean hsCRP values were higher in the pitavastatin 4 mg group compared with the atorvastatin 20 mg group at baseline. At endpoint, hsCRP decreased by 1.4 mg/L in the pitavastatin 4 mg group and by 2.6 mg/L in the atorvastatin 20 mg group. The adjusted mean difference between treatment groups was -8.6 mg/L, which was not statistically significant (P=0.288).

Small-Dense-LDL:

Changes from baseline in small-dense-LDL are summarized for the FAS in the following table:

**Change from Baseline in Secondary Efficacy Lipid Variables: Small-Dense-LDL
(nmol/L) (FAS)**

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	1289.6 (504.9)	1342.4 (475.0)
Endpoint mean (SD)	865.8 (367.9)	803.0 (335.6)
Mean change (SD)	-425.6 (437.8)	-526.90 (440.6)
Adjusted Mean Difference (95% CI)		-76.5 (-141.1; -12.1)
P-value		0.020

Mean small-dense-LDL values were higher in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group at baseline. At endpoint, the decrease in small-dense-LDL was greater in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group. The adjusted mean difference between treatment groups was -76.5nmol/L and was statistically significant (P=0.020).

Remnant-like particle cholesterol (RLP-C):

Changes from baseline in RLP-C are summarized for the FAS in the following table:

**Change from Baseline in Secondary Efficacy Lipid Variables: RLP-C (mg/dL)
(FAS)**

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	17.6 (9.4)	17.6 (10.1)
Endpoint mean (SD)	11.6 (6.9)	10.6 (5.3)
Mean change (SD)	-6.1 (8.6)	-7.1 (10.2)
Adjusted Mean Difference (95% CI)		-0.98 (-2.20; 0.25)
P-value		0.117

At baseline, RLP-C was similar in the two treatment groups. At endpoint, the decrease in RLP-C was greater in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group. The adjusted mean difference between treatment groups was -0.98 mg/dL, which was not statistically significant (P=0.117).

Adiponectin:

Changes from baseline in adiponectin are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Adiponectin (µg/mL) (FAS)

	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Baseline mean (SD)	7.68 (5.62)	6.61 (3.56)
Endpoint mean (SD)	7.34 (3.89)	7.93 (5.20)
Mean change (SD)	-0.29 (4.80)	1.19 (4.36)
Adjusted Mean Difference (95% CI)	0.83 (0.05; 1.61)	
P-value	0.036	

At baseline, adiponectin was higher in the pitavastatin 4 mg group compared with the atorvastatin 20 mg group. At endpoint, mean adiponectin values decreased by 0.29 µg/mL in the pitavastatin 4 mg group and increased by 1.19 µg/mL in the atorvastatin 20 mg group. The adjusted mean difference between treatment groups was 0.83 µg/mL, which was statistically significant in the FAS (P=0.036) but the difference between the groups was not statistically significant in the PP population (P=0.120).

Efficacy Conclusions:

- Pitavastatin 4 mg was NOT, non-inferior to atorvastatin 20 mg for the percent change from baseline to Week 12 or Endpoint in LDL in the FAS. The findings of the COM and PP populations support these results.
- The mean change from baseline to endpoint in LDL in the FAS was -40.8% in the pitavastatin 4 mg group and -43.3% in the atorvastatin 20 mg group. The adjusted mean difference between the treatments was -2.33%. The lower bound on the 95% CI, at -6.2%, was lower than -6%. Therefore, pitavastatin 4 mg was not non-inferior to atorvastatin 20 mg.
- There was a statistically significant treatment-by-sex interaction in the FAS (P=0.017). The mean percent change from baseline to endpoint in LDL was higher in males in the atorvastatin 20 mg group (-44.85%) compared with males in the pitavastatin 4 mg group (-38.39%). Among females, the mean percent change from baseline was -43.89% in the pitavastatin 4 mg group compared with -41.05% in the atorvastatin 20 mg group.
- There were statistically significantly greater changes from baseline to endpoint in TC, TG, non-HDL, small-dense-LDL, and adiponectin in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group.

- There were no significant differences in the change from baseline to endpoint between pitavastatin 4 mg and atorvastatin 20 mg for HDL, Apo-B, Apo-A1, non-HDL:HDL ratio, TC:HDL ratio, Apo-B:Apo-A1 ratio, hsCRP, RLP-C.

3.5 Study of Pitavastatin 1 mg vs. Pravastatin 10 mg, Pitavastatin 2 mg vs. Pravastatin 20 mg and Pitavastatin 4 mg vs. Pravastatin 40 mg (Following Up-Titration) in Elderly Subjects with Primary Hypercholesterolemia or Combined Dyslipidemia [NK-104-306]

First subject in date: 19 September 2005

Last subject out date: 12 May 2006

3.5.1.1 General Discussion of Study Objectives, Endpoints and Methods

Primary Objective:

- To demonstrate the non-inferiority of pitavastatin 1 mg QD vs. pravastatin 10 mg QD, pitavastatin 2 mg QD vs. pravastatin 20 mg QD, and pitavastatin 4 mg QD vs. pravastatin 40 mg QD with respect to the reduction of LDL, when administered for 12 weeks using an up-titration regimen for the highest doses, (i.e., 4 mg pitavastatin and 40 mg pravastatin).

Secondary Objectives:

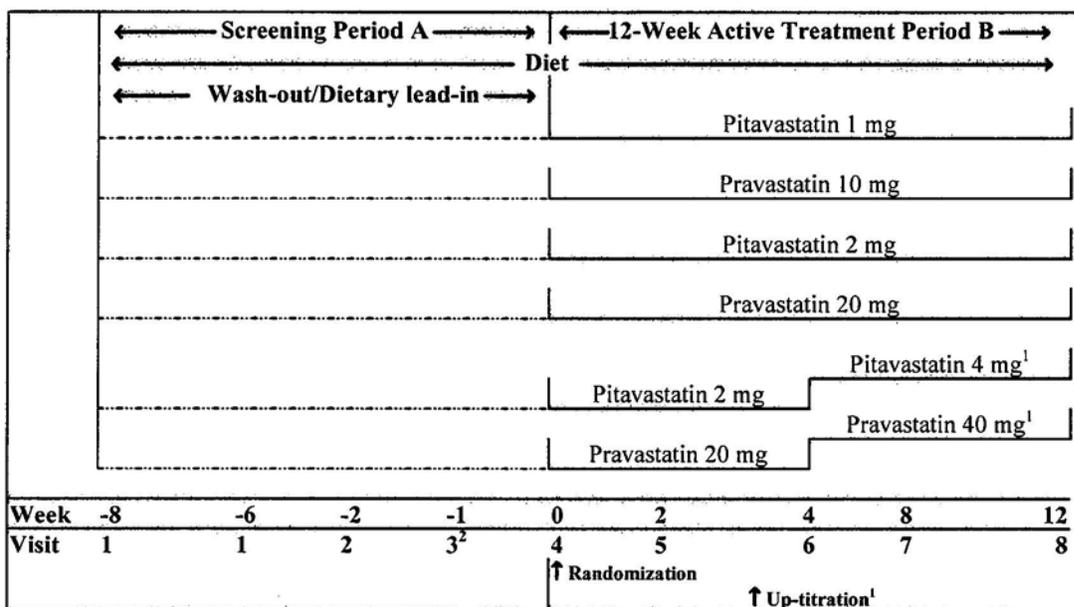
- To compare the efficacy of pitavastatin 1 mg QD vs. pravastatin 10 mg QD; pitavastatin 2 mg QD vs. pravastatin 20 mg, and pitavastatin 4 mg QD vs. pravastatin 40 mg QD with respect to LDL target attainment and to compare between-group changes in other lipid and lipoprotein fractions, as well as hsCRP, TC:HDL cholesterol ratio, Non-HDL cholesterol:HDL cholesterol ratio, TG, Apo-B, Apo-A1, and Apo-B:Apo-A1 ratio).
- To compare the safety and tolerability of pitavastatin 1 mg QD vs. pravastatin 10 mg QD, pitavastatin 2 mg QD vs. pravastatin 20 mg QD and pitavastatin 4 mg QD vs. pravastatin 40 mg QD when administered for 12 weeks using an up-titration regimen for the highest dose.

Study Design:

This was an 18 to 20-week, randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, study in elderly subjects (≥ 65 years) with primary hypercholesterolemia or combined dyslipidemia. Subjects who qualified entered a 6-8 week washout/dietary lead-in period followed by a 12-week treatment period. Subjects were randomly assigned to one of the 6 treatment groups: pitavastatin 1 mg QD, pitavastatin 2 mg QD, pitavastatin 4 mg QD, pravastatin 10 mg QD, pravastatin 20 mg QD or pravastatin 40 mg QD in a ratio of 2:2:2:1:1:1. Subjects assigned to pitavastatin 4 mg started with pitavastatin 2 mg at Visit 4 (Week 0) and had their dose titrated to 4 mg at Visit 6 (Week 4). Similarly, subjects assigned to pravastatin 40 mg started with pravastatin 20 mg at Visit 4 (Week 0) and had their dose titrated to 40 mg at Visit 6 (Week 4), as detailed in the study design schematic in the figure below.

Study drug was administered according to a double-dummy design and each dose consisted of one small tablet, one medium tablet, one large tablet, and one capsule.

Study Design:



Dose Selection:

Pravastatin was chosen as the comparator for its favorable efficacy and safety characteristics. Pravastatin is not significantly metabolized by cytochrome P450, and is therefore thought to be well suited to the treatment of elderly subjects who are often taking other medications. The selection of pravastatin doses for comparison was based on previous clinical studies and currently approved and recommended doses in clinical practice, in Europe.

The 6% non-inferiority margin was chosen because this has precedent in a number of published statin non-inferiority studies.

Selection of Study Population:

Subjects included in this study were elderly (≥65 years) of either sex, with a diagnosis of primary hypercholesterolemia or combined dyslipidemia, elevated plasma LDL (≥130 mg/dL and ≤220 mg/dL) and elevated TG (≤400 mg/dL). It was expected that an adequate number of subjects would be screened to ensure that 900 subjects were randomized.

Inclusion Criteria:

- Males and postmenopausal females (aged 65 years and older);
- Subjects who were eligible and able to participate in the study and who gave informed consent after the purpose and nature of the investigation was explained to them;
- To qualify for randomization, subjects had been following a fat and cholesterol restrictive diet in accordance with European guidelines during the dietary stabilization lead-in period, (i.e., for at least 8 weeks for subjects previously taking lipid-lowering medication and at least 6 weeks for subjects not previously taking lipid-lowering medication);

- To qualify for randomization at Visit 4 (Week 0), subjects presented with primary hypercholesterolemia or combined dyslipidemia, as defined by elevated plasma LDL (mean LDL ≥ 130 mg/dL and ≤ 220 mg/dL) despite dietary therapy, and elevated TG levels of ≤ 400 mg/dL at two consecutive visits during the dietary lead-in period (the mean of the two consecutive visits was used). If these criteria were not satisfied at Visits 2 (Week -2) and 3 (Week -1), or if the LDL concentration of the lower qualifying specimen differed by $\geq 15\%$ from the higher qualifying specimen, one additional lipid sample was permitted for both variables 1 week after Visit 3 (Visit 3A). In these circumstances the values from Visits 3 and 3A could be used to enable the patient to qualify for randomization;
- Serum creatine kinase (CK) was $\leq 1.5 \times$ ULRR at all permitted evaluations between Week -8/-6 (Visit 1) and -1 (Visit 3) for the patient to be eligible for further study participation. However, if at any visit during the screening period (Visits 1-3) serum CK was between 1.5 and $5 \times$ ULRR, a retest was allowed. In cases when the repeat CK was >1.5 and $<5 \times$ ULRR and had decreased compared to the previous measurement, the patient could be enrolled in the study after consultation and agreement between the investigator and the sponsor's medical representative; and
- Subjects who agreed to be available for every clinic visit, which occurred in the morning.

Exclusion Criteria:

- Homozygous familial hypercholesterolemia (heterozygous component of familial hypercholesterolemia was acceptable for inclusion);
- Any conditions that could have caused secondary dyslipidemia. This included, but was not restricted to, alcoholism, auto-immune disease, nephrotic syndrome, uremia, any viral, or non viral hepatitis clinically active within 12 months from study entry, obstructive hepatic or biliary disease, dys- or macroglobulinemia, multiple myeloma, glycogen storage disease, chronic pancreatitis, porphyria, and uncontrolled hypothyroidism or hyperthyroidism (controlled hypo- or hyperthyroidism [i.e., condition presenting with normal baseline serum TSH and treatment stable during at least the two months prior to study entry] were permitted);
- Uncontrolled diabetes mellitus as defined by glycosylated hemoglobin (HbA_{1c}) $>8\%$. Subjects with controlled Type 2 diabetes were allowed, provided the disease was stable during at least the three months prior to study entry;
- Any surgical or medical condition that might have significantly altered the absorption, distribution, metabolism, or excretion of any drug. The investigator was guided by the evidence of any of the following: history of major gastrointestinal tract surgery, (e.g., gastrectomy, gastroenterostomy, or small bowel resection), gastritis, current active ulcers, gastrointestinal or rectal bleeding;
- Current active or recurrent irritable bowel syndrome (IBS) or history of inflammatory bowel syndrome. Subjects with a history of IBS without symptoms for at least the 6 months prior to the study start were allowed to enter the study;
- Any history of pancreatic injury or pancreatitis, or impaired pancreatic function/injury as indicated by abnormal lipase or amylase;

- Liver injury as indicated by serum transaminase levels (alanine aminotransferase [ALAT]/serum glutamic pyruvic transaminase [SGPT]; ALAT/SGPT, aspartate aminotransferase [ASAT]/serum glutamic oxaloacetic transaminase [SGOT]; ASAT/SGOT) $>1.5 \times$ ULRR over the lead-in period. The ALAT and ASAT levels were $\leq 1.5 \times$ ULRR on at least two of the three evaluations between Visit 1 (Week -8/-6) and Visit 3 (Week -1) for the patient to have been eligible for further study participation. If ALAT and/or ASAT was $>2 \times$ ULRR at any time point between Visit 1 (Week -8/-6) and Visit 3 (Week -1), the patient was immediately excluded from further participation in the study;
- Impaired renal function as indicated by serum creatinine levels $>1.5 \times$ ULRR at Visit 1 (Week -8/-6). However, if creatinine was between 1.5 and $2 \times$ ULRR, one retest was permitted at Visit 2 (Week -2), provided all other criteria were fulfilled. Serum creatinine was $\leq 1.5 \times$ ULRR at the retest for the patient to be eligible for further study participation. If serum creatinine was $>2 \times$ ULRR at Visit 1 (Week -8/-6), the patient was immediately excluded from further study participation;
- Current (at the time of study screening) obstruction of the urinary tract or difficulty in voiding due to mechanical or inflammatory conditions that were likely to require intervention during the course of the study, or were regarded as clinically meaningful by the investigator;
- Serum CK $>5 \times$ ULRR. If at any visit during the screening period (Visits 1-3) serum CK was between 1.5 and $5 \times$ ULRR a retest was allowed. If the repeat CK was >1.5 and $<5 \times$ ULRR and had increased compared to the previous measurement, the patient was immediately excluded from further study participation. In cases when the repeat CK was >1.5 and $<5 \times$ ULRR and had decreased compared to the previous measurement, the patient could be enrolled in the study after consultation and agreement between the investigator and **the sponsor's medical representative.**
- Uncontrolled hypothyroidism defined as TSH $>$ ULRR. Subjects with TSH $>$ ULRR at Visit 1 were permitted to have a retest at Visit 2 and if TSH was also $>$ ULRR at Visit 2, the patient was excluded from the study;
- Any severe acute illness or severe trauma in the 3 months prior to Visit 1 (Week -8/-6);
- Major surgery, during the 3 months prior to Visit 1 (Week -8/-6);
- Significant CVD prior to randomization, such as myocardial infarction, coronary or peripheral artery angioplasty, bypass graft surgery or severe or unstable angina pectoris;
- Evidence of symptomatic heart failure (New York Heart Association class 3 or 4), gross cardiac enlargement (cardiothoracic ratio >0.5); significant heart block or cardiac arrhythmias. History of uncontrolled complex ventricular arrhythmia, uncontrolled atrial fibrillation, atrial flutter or uncontrolled supraventricular tachycardia with a ventricular response rate of >100 beats per minute at rest. Subjects whose electrophysiological instability was controlled with a pacemaker or implantable cardiac device were eligible;
- Left ventricular ejection fraction <0.25 ;
- History of symptomatic cerebrovascular disease including cerebrovascular hemorrhage, transient ischemic attack or carotid endarterectomy within 1 month prior to randomization;

- Any other medical or surgical conditions, at the discretion of the investigator, that placed the patient at higher risk from his or her participation in the study, which could have confounded the results of the study, or were likely to have prevented the patient from complying with the requirements of the study or completing the study period;
- Known human immunodeficiency virus infection;
- Poorly controlled or uncontrolled hypertension defined as a systolic blood pressure (SBP) >160 mmHg and diastolic blood pressure (DBP) >90 mmHg with or without antihypertensive therapy;
- Prior or current (at the time of screening) muscular or neuromuscular disease of any type;
- Current (at the time of screening) active neoplastic disease or subjects who were anticipated to require antineoplastic treatment during the course of the study. History of prior malignancy, except subjects who had been cancer free for >10 years prior to screening. Subjects with a history of basal cell carcinoma or squamous cell carcinoma of the skin were eligible if they had been cancer free for >5 years prior to screening;
- A history of drug abuse or continuous consumption of more than 65mL pure alcohol per day (e.g., more than 4 x 125 mL glasses of wine or three glasses of spirits per day) within the two years prior to randomization;
- Exposure to any investigational new drug within 30 days of study entry (Visit 1/Week -8/-6) or ingestion of any drug known to be toxic to a major organ system (such as those producing blood dyscrasias, nephrotoxicity, hepatotoxicity or neurotoxicity) within 12 weeks prior to study entry (Visit 1/Week -8/-6);
- Current (at the time of study screening) or recent (within 4 weeks of Visit 1/Week -8/-6) use of supplements known to alter lipid metabolism, (e.g., soluble fibers [including >2 teaspoons Metamucil or psyllium containing supplement per day]), or other dietary fiber supplements, fish oils, or other products at the discretion of the investigator;
- History of hypersensitivity reactions to other HMG-CoA reductase inhibitors;
- Any concomitant medication, listed below;

The following medications were identified as having the potential to interfere with the evaluation and interpretation of the results of the study and were, therefore, excluded. Subjects receiving such medications were excluded or, if ethically justified, the medication was gradually withdrawn (where appropriate):

1. All agents used for or under investigation for lowering or modifying plasma lipid levels, including statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors (including ezetimibe), and nicotinic acid >500 mg per day. Subjects on these medications could participate in the study, provided treatment was interrupted at least eight weeks prior to randomization;
2. Oral contraceptives or any systemic steroid hormones (including estrogens, progestins, androgens or glucocorticoids) for any condition, except for noncyclic (continuous) administration of estrogen/progesterone replacement therapy or sustained contraceptive preparations (e.g., implants or intramuscular injections) that must have been constant for at least the three months prior to study entry

(Visit 1/Week -8/-6) and were anticipated to remain unchanged for the duration of the study. Subjects on systemic steroidal treatment were permitted to enter the study if the treatment was discontinued at least 4 weeks prior to Visit 1 (Week -8/-6). Steroid hormones administered topically or as inhalers were permitted. Non-steroidal anti-inflammatory agents were allowed provided dosing was stable for at least four weeks prior to entry into the study but were disallowed if used for immunosuppressive therapy;

3. Anticoagulants and antiplatelet drugs, other than aspirin or ticlopidine in stable doses. Use of aspirin for pain relief, when required, was allowed;
 4. HIV protease inhibitors;
 5. Cyclosporine;
 6. Systemic azole antifungal agents (e.g., itraconazole or ketoconazole);
 7. Nefazodone (antidepressant);
 8. Continuous systemic erythromycin, clarithromycin, and telithromycin;
 9. Digoxin;
 10. Amiodarone and verapamil (calcium antagonists);
 11. Danazol (gonadotropin inhibitor);
 12. Grapefruit and grapefruit juice; and
 13. Glitazones/thiazolidinediones (pioglitazone, rosiglitazone).
- History of resistance to lipid-lowering medications. Known hypersensitivity or intolerance to any lipid-lowering agent, (i.e., elevated transaminases, myositis);
 - Excessive obesity defined as Body Mass Index (BMI) above 35 kg/m² (BMI = body weight in kg divided by squared height [m²]). Body Mass Index values were rounded to the nearest whole number: down at <0.5 and up at ≥0.5;
 - Any factor that made regular clinic attendance in the morning impractical (e.g., shift or night work); or
 - Any signs of mental dysfunction or other factors (including language problems) likely to limit the ability of the patient to cooperate with the performance of the study.

Withdrawal, Removal, and Replacement of Subjects:

The investigator documented whether or not each patient completed the clinical study. Subjects who discontinued prematurely from the study after randomization were not replaced. All subjects who discontinued prematurely were encouraged to complete all efficacy and safety evaluations corresponding to Visit 8 (Week 12) as soon as possible after discontinuation from study drug.

If for any subject, either study treatment or observations were discontinued the reason was recorded. Reasons that a patient discontinued participation in a clinical study were categorized into one of the following:

1. Adverse events (AEs) including laboratory AEs. Abnormal laboratory values or test results were only classified as AEs if they induced clinical signs or symptoms, were considered clinically significant or required therapy;
2. Abnormal laboratory value(s);
3. Abnormal test procedure result(s);
4. Unsatisfactory therapeutic effect;
5. Protocol violation;
6. Patient withdrew consent;
7. Lost to follow-up;
8. Administrative problems; or
9. Death.

Subjects who, following randomization, discontinued prematurely from the study due to AEs or abnormalities in laboratory values continued to be evaluated by the investigator or his or her designee until resolution of the condition/abnormality for up to 30 days after discontinuation. Information on follow-ups after discontinuation was documented in the patient's medical records.

Treatment:

Treatment was administered according to a double-dummy design. Each patient dose consisted of one small tablet, one medium tablet, one large tablet, and one capsule taken orally, QD, before bedtime with approximately 200mL of water. Either one of the tablets or the capsule was the active dose; the others were placebo.

Pitavastatin (manufactured by SkyePharma Production SAS, Saint Quentin-Fallavier, France) was supplied as tablets of 1 mg, 2 mg, and 4 mg contained within blister packages. Matching pitavastatin placebo tablets (manufactured by SkyePharma Production SAS, Saint Quentin-Fallavier, France) were contained within blister packages.

Pravastatin (manufactured by Bristol Myers Squibb) was supplied as tablets of 10 mg, 20 mg, and 40 mg strength. Pravastatin tablets were over encapsulated^{(b) (4)} [REDACTED]. Matching pravastatin placebo capsules^{(b) (4)} [REDACTED] were contained within blister packages.

Pitavastatin and pravastatin were repackaged^{(b) (4)} [REDACTED] in blister packs contained in a wallet having one small tablet, one medium tablet, one large tablet, and one capsule for each daily dose.

Study Population:

The following analysis populations were defined:

- **The Safety Population** was defined as all randomized subjects who receive at least one dose of the study drug.

- **The FAS Population** was defined as all randomized subjects who receive at least one dose of study drug and who had at least one on-treatment lipid assessment.
- **The PP Population** was defined as all subjects in the FAS, who had no major protocol violations, and who had an on-treatment lipid assessment at Week 12 (Visit 8).
- **The (COM) Population** was defined as all subjects, irrespective of protocol violations, who had a Week 12 (last week of measurement) measurements, whether or not on drug.

Sample Size Justification:

A sample size of 900 randomized subjects was planned, with 200 subjects in each of the pitavastatin 1 mg, 2 mg, and 4 mg groups and 100 subjects in each of the pravastatin 10 mg, 20 mg, and 40 mg groups. Assuming an SD of 12 (for percent reduction from baseline LDL), a non-inferiority limit of 6% for the treatment difference and a 1-tailed test at 2.5% significance level, this sample size provided 99% power to reject the null hypothesis that the mean percent decrease from baseline LDL was at least 6% greater in the pravastatin groups than in the corresponding pitavastatin group vs. the alternative that any advantage in the pravastatin groups was less than the non-inferiority limit.

Statistical Analysis of the Primary Efficacy Variable:

The percent change in LDL from baseline to endpoint for the FAS and the percent change in LDL from baseline to Week 12 (Visit 8) for the PP population were analyzed using analysis of covariance (ANCOVA), including treatment and country as factors and the baseline LDL as a covariate. The ANCOVA model included all six treatment groups. The p-values for each of the three comparisons came from the list of all possible pairwise comparisons using least squares means.

A 2-sided 95% CI was constructed for the adjusted mean difference between treatment groups, (i.e., pravastatin 10 mg minus pitavastatin 1 mg, pravastatin 20 mg minus pitavastatin 2 mg and pravastatin 40 mg minus pitavastatin 4 mg). Pitavastatin was considered non inferior to pravastatin at the doses tested if the lowest bound on the 95% CI was greater than -6% for all comparisons tested.

To test the assumptions of the ANCOVA, covariate slopes were compared using the treatment by covariate term in the model. In addition, normality was tested.

The primary efficacy variable was also analyzed to compare treatment groups within the following subgroups:

- Age;
- Sex;
- Race (Caucasian, Non-Caucasian);
- BMI (<25 kg/m², 25-<30 kg/m², ≥30 kg/m²);
- Risk Category (Low, Moderate, High [as defined by NCEP Guidelines]);
- Baseline LDL (<160 mg/dL, 160-<190 mg/dL, ≥190 mg/dL);
- Hypertension (Yes, No);

- Diabetes (Yes, No);
- Primary diagnosis (primary hypercholesterolemia, combined dyslipidemia, heterozygous familial hypercholesterolemia).

Treatment by subgroup interactions were tested (ANCOVA) for those subgroups where each level of the subgroup included $\geq 5\%$ of subjects.

Summary statistics of the percent change in LDL from baseline to endpoint were presented by treatment for each level of each subgroup.

Statistical Analysis of the Secondary Efficacy Variables:

Secondary efficacy lipid variables were evaluated using ANCOVA and 95% CIs on the mean differences between the pitavastatin groups and the corresponding pravastatin groups in terms of change from baseline values. Non-inferiority margins for secondary variables were not explicitly defined.

The LDL targets were calculated using data collected prior to randomization, based on the NCEP Adult Treatment Panel III Guidelines. Target attainment, using the NCEP criteria was determined using the LDL value from the last visit (endpoint for FAS or Week 12 for the PP population). The proportion of subjects who reached their LDL target was analyzed using a linear probability model, which assumes the identity link and binomial distribution including treatment, country, risk categories (high, medium or low risk as defined in the NCEP guidelines) and baseline LDL (categorized as defined in the NCEP guidelines), as factors, point estimates (and 95% CIs) of the differences between the pitavastatin groups and the corresponding pravastatin groups presented. The analysis was also performed using logistic regression, including treatment, country and risk categories as factors and baseline LDL as a covariate. If iterative calculations met the convergence criteria with the linear probability model, the results from this analysis would be presented.

Protocol Amendments:

There were two amendments to Protocol NK-104-306 dated 28 April 2005.

Amendment 1, - 04 August 2005

Amendment 1 was generated in response to two letters from the German Central Ethics Committee (dated 30 June 2005 and 21 July 2005). The resultant changes were:

- In cases where a CK level over $1.5 \times \text{ULRR}$ was observed, an additional control was performed after 2 days. If the value continued to increase, the patient was discontinued from the study.
- A serum potassium measurement was required at all scheduled visits.
- The study flowchart was amended.

Amendment 2, - 11 January 2006

Amendment 2 was generated to address a change in the protocol identification code, a delay in approval of the open-label extension study, and to specify TG criteria for randomization. The resultant changes were:

- To clarify that to be eligible for randomization into study NK-104-306, subjects also had to have TG values ≤ 400 mg/dL at both consecutive qualifying measurements.

Changes in the Planned Analysis:

The SAP was amended three times: the first time on 14 December 2006 before the data were unblinded, the second and third times on 04 May 2007 and 01 June 2007, after the data were unblinded and after the data were analyzed.

SAP Amendment 1, - 14 December 2006 Baseline Lipid Values:

The protocol specified that baseline lipid values would be calculated as the mean of the values obtained at Week -2 (Visit 2) and Week -1 (Visit 3). However, for LDL, TC, HDL cholesterol, TG, TC:HDL cholesterol ratio and Non-HDL cholesterol:HDL cholesterol ratio, the baseline was calculated as the mean of the lipid measurements from Week -2 (Visit 2), Week -1 (Visit 3) and Week 0 (Visit 4). If Visit 3A was required, the baseline value was the mean from Week -1 (Visit 3), Week -1 repeat (Visit 3A) and Week 0 (Visit 4). For subjects who had their Week 0 (Visit 4) blood sample taken after the first dose of study drug, baseline values were calculated as the mean of Week -2 (Visit 2) and Week -1 (Visit 3) or Week -1 (Visit 3) and Week -1 repeat (Visit 3A), as applicable. The result at Week 0 (Visit 4) was included in the calculation of baseline as it was the last measurement before study treatment commenced.

The baseline value for Apo-B, Apo-A1, Apo-B:Apo-A1 ratio, and hsCRP was the result at Week 0 (Visit 4), as this was the only time at which these parameters were measured prior to receiving study treatment.

Protocol Violations and Deviations:

Overall, 202 (21.0%) randomized subjects were excluded from the PP population. The proportion of excluded subjects was similar across treatment groups and there were no clear differences between the groups in reasons for exclusion. The main reason for exclusion was lack of lipid assessment at Week 12, which occurred in 88 (9.1%) subjects overall: 56 (8.6%) subjects in the pitavastatin groups and 32 (10.3%) subjects in the pravastatin groups. The next most common reasons for exclusion were data points for the Week 2 visit outside the 14 ± 3 -day window, 53 (5.5%) subjects overall: 33 (5.1%) subjects in the pitavastatin groups and 20 (6.4%) subjects in the pravastatin groups; and taking disallowed lipid-lowering medication during the lead-in period or during the study treatment period, 41 (4.3%) subjects overall: 30 (4.6%) subjects in the pitavastatin groups and 11 (3.5%) subjects in the pravastatin groups.

Disposition of Subjects:

Investigators at 56 centers randomized a total of 962 subjects: 651 subjects were randomized to treatment with pitavastatin, and 311 to pravastatin. Of the 962 subjects randomized, 942 received at least one dose of study drug (Safety population), 641 took pitavastatin and 301 took pravastatin. Overall, 315 (32.7%) of the subjects were randomized at 18 centers in the UK, 242 (25.2%) were randomized at five centers in Denmark, 207 (21.5%) were randomized at 14 centers in Germany, 144 (15.0%) were randomized at 10 centers in the Netherlands, and 54 (5.6%) were randomized at nine centers in Israel. The greatest number of subjects randomized at a single center was 86 (8.9% of all subjects), at Center 6103 in Denmark. A summary of patient disposition by treatment group and analysis population is presented in the following table:

Patient Disposition						
	Pitavastatin 1 mg QD	Pravastatin 10 mg QD	Pitavastatin 2 mg QD	Pravastatin 20 mg QD	Pitavastatin 4 mg QD	Pravastatin 40 mg QD
Number of Subjects Randomized	209	108	226	99	216	104
Safety Population	207 (99.0%)	103 (95.4%)	224 (99.1%)	96 (97.0%)	210 (97.2%)	102 (98.1%)
Full Analysis Set (FAS)	207 (99.0%)	103 (95.4%)	224 (99.1%)	96 (97.0%)	210 (97.2%)	102 (98.1%)
Completers (COM)	188 (90.0%)	89 (82.4%)	208 (92.0%)	88 (88.9%)	194 (89.8%)	95 (91.3%)
Per Protocol Population (PP)	171 (81.8%)	82 (75.9%)	179 (79.2%)	76 (76.8%)	170 (78.7%)	82 (78.8%)
Discontinued Study Drug	21 (10.0%)	18 (16.7%)	19 (8.4%)	9 (9.1%)	19 (8.8%)	11 (10.6%)
Reason for Discontinuation from Study						
Adverse Event	10 (4.8%)	8 (7.4%)	12 (5.3%)	2 (2.0%)	8 (3.7%)	5 (4.8%)
Abnormal laboratory value(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Protocol violation	5 (2.4%)	2 (1.9%)	4 (1.8%)	1 (1.0%)	3 (1.4%)	3 (2.9%)
Withdrew consent	6 (2.9%)	7 (6.5%)	2 (0.9%)	5 (5.1%)	4 (1.9%)	3 (2.9%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	0 (0.0%)
Administrative problems	0 (0.0%)	1 (0.9%)	1 (0.4%)	0 (0.0%)	1 (0.5%)	0 (0.0%)

Demographic and Other Baseline Characteristics:

The demographic data for the safety population are summarized in the following table:

Demographic and Other Baseline Characteristics (Safety Population)						
Demographic Characteristic	Pitavastatin 1 mg QD (N=207)	Pravastatin 10 mg QD (N=103)	Pitavastatin 2 mg QD (N=224)	Pravastatin 20 mg QD (N=96)	Pitavastatin 4 mg QD (N=210)	Pravastatin 40 mg QD (N=102)
Sex n (%)						
Male	89 (43.0)	49 (47.6)	100 (44.6)	48 (50.0)	89 (42.4)	42 (41.2)
Female	118 (57.0)	54 (52.4)	124 (55.4)	48 (50.0)	121 (57.6)	60 (58.8)
Age (years)						
Mean (SD)	70.0 (4.60)	70.5 (4.61)	70.5 (4.49)	69.9 (4.51)	70.2 (4.10)	70.2 (4.94)
Range	65 - 89	65 - 82	65 - 87	65 - 86	65 - 82	65 - 89
Age group n (%)						
65-69 years	118 (57.0)	51 (49.5)	108 (48.2)	52 (54.2)	108 (51.4)	56 (54.9)
70-74 years	56 (27.1)	33 (32.0)	73 (32.6)	27 (28.1)	67 (31.9)	28 (27.5)
≥75 years	33 (15.9)	19 (18.4)	43 (19.2)	17 (17.7)	35 (16.7)	18 (17.6)
Race n (%)						
Caucasian	207 (100.0)	103 (100.0)	222 (99.1)	94 (97.9)	207 (98.6)	102 (100.0)
Black	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)
Hispanic	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	0 (0.0)
Diagnosis n (%)						
Primary hypercholesterolemia	187 (90.3)	90 (87.4)	206 (92.0)	84 (87.5)	194 (92.4)	89 (87.3)
Combined dyslipidemia	19 (9.2)	13 (12.6)	16 (7.1)	11 (11.5)	15 (7.1)	12 (11.8)
Familial hypercholesterolemia ¹	1 (0.5)	0 (0.0)	2 (0.9)	1 (1.0)	1 (0.5)	1 (1.0)
Duration of current disease (years)						
Mean (SD)	3.99 (6.723)	3.14 (5.576)	3.17 (4.748)	4.03 (6.634)	3.54 (5.708)	3.09 (5.325)
Range	-0.1 - 45.9	-0.0 - 30.8	-0.1 - 24.8	-0.1 - 30.7	-0.1 - 31.3	-0.1 - 29.4
Height (m)						
Mean (SD)	1.67 (0.095)	1.67 (0.095)	1.67 (0.089)	1.67 (0.088)	1.67 (0.093)	1.66 (0.089)
Range	1.4 - 1.9	1.5 - 1.9	1.4 - 1.9	1.4 - 1.9	1.4 - 2.0	1.5 - 1.9
Weight (Kg)						
Mean (SD)	74.87 (12.091)	75.81 (11.975)	74.72 (11.403)	75.74 (11.688)	75.80 (12.047)	74.57 (11.722)
Range	46.5 - 115.2	49.0 - 121.5	45.2 - 104.2	46.2 - 103.8	46.0 - 114.0	45.0 - 105.0
BMI (kg/m²)						
Mean (SD)	26.93 (3.760)	27.05 (3.354)	26.76 (3.591)	27.10 (3.536)	27.24 (3.607)	26.95 (3.493)
Range	17.0 - 34.9	17.0 - 35.0	18.6 - 35.7	18.5 - 35.3	19.1 - 35.1	18.2 - 34.2

(continued) Demographic and Other Baseline Characteristics (Safety Population)

Demographic Characteristic	Pitavastatin 1 mg QD (N=207)	Pravastatin 10 mg QD (N=103)	Pitavastatin 2 mg QD (N=224)	Pravastatin 20 mg QD (N=96)	Pitavastatin 4 mg QD (N=210)	Pravastatin 40 mg QD (N=102)
NCEP risk category n (%)						
High	32 (15.5)	16 (15.5)	36 (16.1)	15 (15.6)	32 (15.2)	12 (11.8)
Moderate	50 (24.2)	29 (28.2)	65 (29.0)	25 (26.0)	67 (31.9)	25 (24.5)
Low	125 (60.4)	58 (56.3)	123 (54.9)	56 (58.3)	111 (52.9)	65 (63.7)
Diabetes n (%)						
Present	11 (5.3)	6 (5.8)	16 (7.1)	4 (4.2)	17 (8.1)	3 (2.9)
Hypertension n (%)						
Present	97 (46.9)	54 (52.4)	113 (50.4)	48 (50.0)	108 (51.4)	48 (47.1)

[†] Heterozygous familial hypercholesterolemia.

The Safety population included 525 (55.7%) females and 417 (44.3%) males. The mean age of the subjects was approximately 70 years in each treatment group and ranged between 65 and 89 years. All except seven subjects were Caucasian.

The treatment groups were relatively well matched in terms of diagnosis and duration of disease. Approximately 90% of subjects in each treatment group had primary hypercholesterolemia and most of the remainder had combined dyslipidemia. Six subjects in total had heterozygous familial hypercholesterolemia. Mean duration of disease ranged between 3.09 years and 4.03 years across the treatment groups. At least one patient in each group was not diagnosed with hypercholesterolemia until after the screening visit.

NCEP risk categories for major coronary events were similar across the treatment groups. Between 15.2% and 16.1% of subjects across the treatment groups were at high risk of CVD, except for the pravastatin 40 mg group in which 11.8% of subjects were in the high risk category.

The prevalence of diabetes ranged between 2.9% and 8.1% across all treatment groups, whilst approximately 50% of subjects in each group were hypertensive. The highest proportion of subjects with diabetes was in the pitavastatin 4 mg group, and the lowest proportion was in the pravastatin 40 mg group.

There were no differences between the groups in height, weight and BMI.

There were no apparent treatment group differences in the demographic summaries of either the FAS or Safety populations.

Baseline Lipid Characteristics:

The treatment groups were well matched in terms of baseline LDL values as shown in the following table:

Baseline Lipids (Safety Population)						
Demographic Characteristic	Pitavastatin 1 mg QD (N=207)	Pravastatin 10 mg QD (N=103)	Pitavastatin 2 mg QD (N=224)	Pravastatin 20 mg QD (N=96)	Pitavastatin 4 mg QD (N=210)	Pravastatin 40 mg QD (N=102)
LDL (mg/dL)						
Mean (SD)	164.36 (22.91)	163.57 (22.29)	162.83 (20.50)	163.71 (19.32)	163.48 (21.86)	166.58 (21.89)
Range	118.0 - 262.0	124.5 - 218.7	127.3 - 212.7	132.7 - 212.3	107.0 - 220.7	118.7 - 223.7
HDL cholesterol (mg/dL)						
Mean (SD)	60.80 (15.27)	57.70 (15.35)	60.24 (15.45)	59.68 (14.19)	58.08 (14.62)	59.39 (15.19)
Range	28.0 - 128.0	28.0 - 107.7	34.7 - 124.7	32.7 - 103.7	28.3 - 113.3	36.0 - 115.0
TC (mg/dL)						
Mean (SD)	253.41 (29.16)	249.66 (28.15)	250.48 (25.35)	252.89 (25.76)	250.65 (25.53)	253.77 (24.51)
Range	176.0 - 370.3	177.5 - 324.7	195.3 - 338.0	198.7 - 322.0	170.0 - 322.3	202.3 - 308.7
TG (mg/dL)						
Mean (SD)	141.21 (53.91)	142.03 (54.04)	137.20 (48.70)	147.91 (61.45)	145.42 (55.84)	139.07 (53.66)
Range	53.3 - 375.7	68.3 - 337.0	56.7 - 298.7	74.7 - 397.0	53.7 - 351.3	56.0 - 320.0

Baseline mean LDL ranged between 162.8 mg/dL and 166.6 mg/dL across the treatment groups. Similarly, there were no meaningful differences between the groups in mean baseline HDL cholesterol, TC and TG. Baseline mean HDL cholesterol ranged between 57.70 mg/dL and 60.8 mg/dL across the treatment groups, TC ranged between 249.7 mg/dL and 253.8 mg/dL across the treatment groups, and TG ranged between 137.2 mg/dL and 147.9mg/dL.

Approximately 10% of subjects (range 8.7% to 12.5% across all treatment groups) were smokers at baseline. There were no differences between the groups in the proportion of subjects who were current smokers.

Approximately two-thirds of subjects were sporadic consumers of alcohol (range 58.4% to 68.8% across all treatment groups). Eight subjects were excessive consumers of alcohol, (i.e., >3 glasses of wine or beer per day or >20 drinks per week).

The treatment groups were balanced at baseline with respect to risk factors and mean lipid values. There were a few categories of note:

- The proportion of subjects with LDL in the category 130 to <160 mg/dL ranged between 37.3% and 52.4% across all treatment groups, and the proportion of subjects with LDL in the category 160 to <190 mg/dL ranged between 33.0% and 44.1%.
- The proportion of subjects with HDL cholesterol in the category \geq 60 mg/dL ranged between 36.9% and 48.8% across all treatment groups.
- The proportion of subjects with TC in the category 240 to <280 mg/dL ranged between 41.7% and 58.8% across all treatment groups, and the proportion of subjects with TC in the category 200 to <240 mg/dL ranged between 28.4% and 38.8%.
- The proportion of subjects with treated hypertension ranged between 30.4% and 41.0% across all treatment groups.

Between 94.7% and 99.0% of subjects in each treatment group had one or more items of medical history. The most common organ systems with medical history were musculoskeletal and cardiovascular with between 52.1% and 60.4% of subjects in each group having medical history in these categories.

The number of subjects in each treatment group who were taking lipid-lowering medications prior to enrolment ranged between 10.7% and 20.8% across all treatment groups. The most common prior lipid-lowering medication was simvastatin, with 117 subjects (between 5.8% and 15.5% of subjects in any treatment group) taking this medication. The second most common lipid-lowering medication was atorvastatin, which was taken by 20 subjects (approximately 2%) overall, although the proportion of subjects in the pravastatin 20 mg group was 4.2%.

Treatment Compliance:

The percent treatment compliance by treatment group is summarized in the following table:

Treatment Compliance (Safety Population)						
	Pitavastatin 1 mg QD (N=207)	Pravastatin 10 mg QD (N=103)	Pitavastatin 2 mg QD (N=224)	Pravastatin 20 mg QD (N=96)	Pitavastatin 4 mg QD (N=210)	Pravastatin 40 mg QD (N=102)
Overall % compliance						
N	205	103	223	96	209	102
Mean (SD)	98.3 (4.49)	98.2 (3.88)	99.1 (3.00)	98.3 (4.17)	98.7 (3.31)	98.4 (3.36)
Median	100.0	100.0	100.0	100.0	100.0	100.0
Quartiles	97.9 - 100.0	97.6 - 100.0	98.8 - 100.0	98.8 - 100.0	98.5 - 100.0	97.7 - 100.0
Range	63 - 104	68 - 101	90 - 120	76 - 102	78 - 117	78 - 104

Compliance was generally good and comparable across treatment groups, with median compliance being 100.0% in all treatment groups and the quartiles differing from the median by not more than 2.4 percentage points. A few subjects were poorly compliant (<80% or >120%) and 20 (2.1%) subjects were excluded from the PP population for this reason.

Analysis of Efficacy:

Primary Efficacy Variable: Mean Percent Change from Baseline in LDL:

The mean percent change in LDL from baseline to endpoint, is presented in the following table:

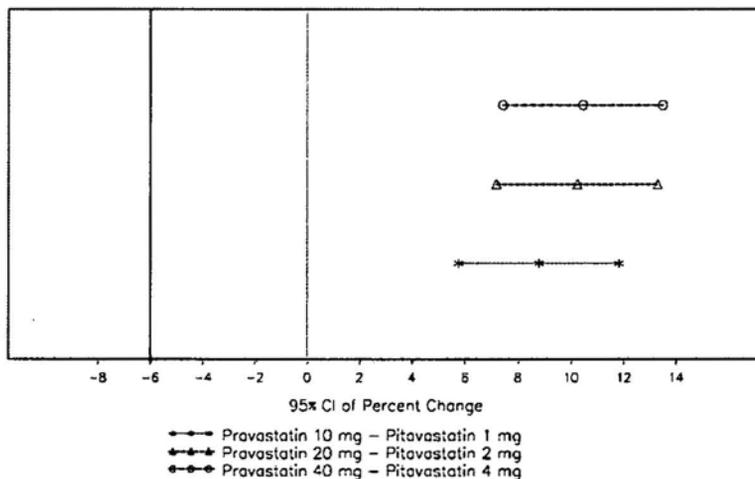
Mean values at baseline and at endpoint are also presented in the tables for orientation.

Change from Baseline to Endpoint or Week 12 in LDL (mg/dL) (FAS Population)						
	Pitavastatin 1 mg QD	Pravastatin 10 mg QD	Pitavastatin 2 mg QD	Pravastatin 20 mg QD	Pitavastatin 4 mg QD	Pravastatin 40 mg QD
FAS						
N	207	103	224	96	210	102
Baseline LDL						
Mean (SD)	164.4 (21.91)	163.6 (22.29)	162.8 (20.50)	163.7 (19.32)	163.5 (21.86)	166.6 (21.89)
Endpoint LDL						
Mean (SD)	112.1 (21.19)	126.7 (28.59)	99.2 (24.03)	116.2 (20.85)	90.7 (23.58)	109.5 (25.34)
% change from baseline to endpoint						
Mean (SD)	-31.43 (11.85)	-22.41 (14.05)	-38.99 (13.07)	-28.83 (11.05)	-44.31 (13.70)	-33.98 (14.30)
Adjusted Mean Difference (95% CI)	5.75 (5.76; 11.81)		10.23 (7.17; 13.29)		10.46 (7.43; 13.49)	
P-value (test for difference)	<0.001		<0.001		<0.001	

Changes in the PP and COM Populations were similar.

95% CI on Treatment Difference in Adjusted Mean Percent Change in LDL (FAS):

The 95% CIs for the treatment differences in LDL are illustrated in the following diagram:



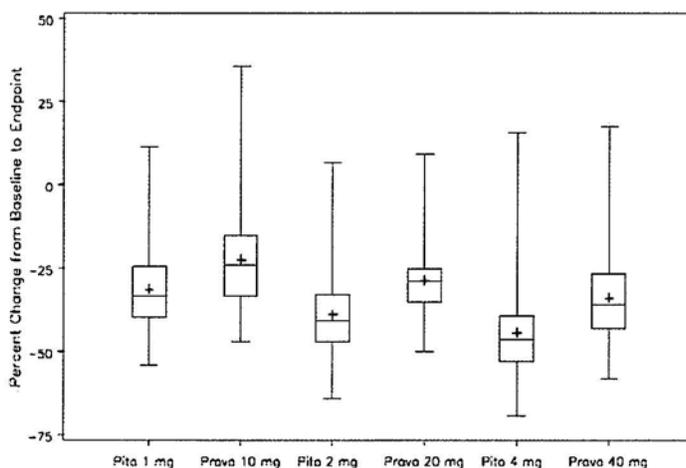
Mean LDL concentrations fell from baseline to endpoint in all treatment groups, and there was a greater decrease with increasing doses for both drugs. For the mean percent change from baseline to endpoint in LDL in the FAS, pitavastatin was non-inferior to pravastatin for all three dose group comparisons: pitavastatin 1 mg vs. pravastatin 10 mg, pitavastatin 2 mg vs. pravastatin 20 mg and pitavastatin 4 mg vs. pravastatin 40 mg. Furthermore, pitavastatin was statistically significantly superior to pravastatin for all three dose group comparisons (P<0.001).

The mean percent decrease in LDL values from baseline to endpoint was approximately 10% greater in all pitavastatin groups compared with each of the pravastatin groups. The lowest difference between the groups was in the pitavastatin 1 mg vs. pravastatin 10 mg comparison

where the adjusted mean difference was 8.79% (95% CI [5.76; 11.81], $P < 0.001$). For both the medium and high-dose groups, the lower limit for the 95% CI of the difference between pitavastatin and pravastatin was greater than 6%. The analysis of this endpoint in both the COM and PP populations supported the findings in the FAS population. There were no meaningful differences between the baseline, endpoint (or Week 12), or changes from baseline values in both the COM and PP populations compared with the FAS.

Box Plot of Percent Change from Baseline in LDL (mg/dL) (FAS)

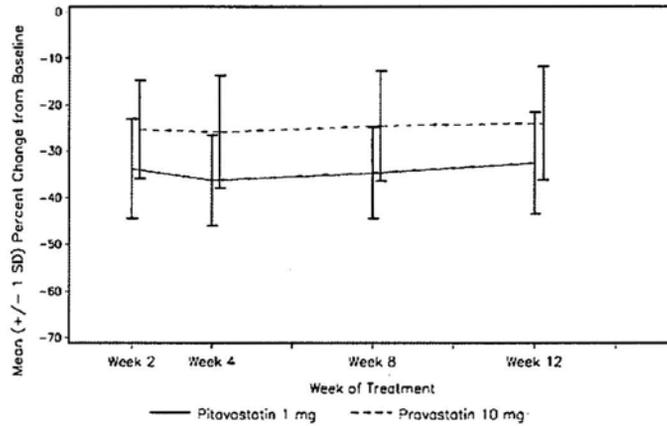
The mean percentage change in LDL from baseline to endpoint is illustrated in the following figure:



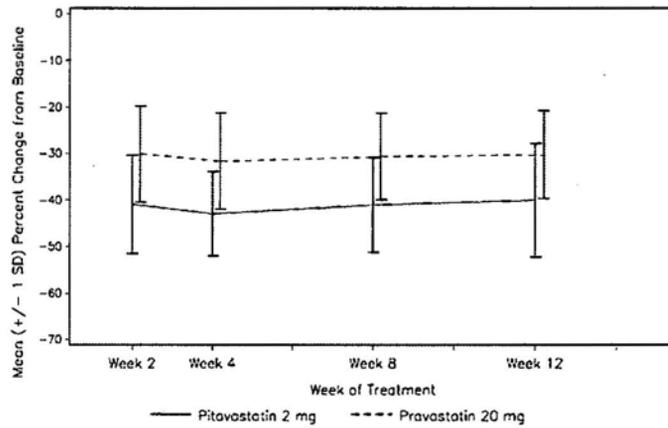
There appeared to be a dose-response relationship for LDL lowering for both pitavastatin 1 mg, 2 mg and 4 mg, and pravastatin.

Mean Percent Change from Baseline in LDL (mg/dL) (FAS)

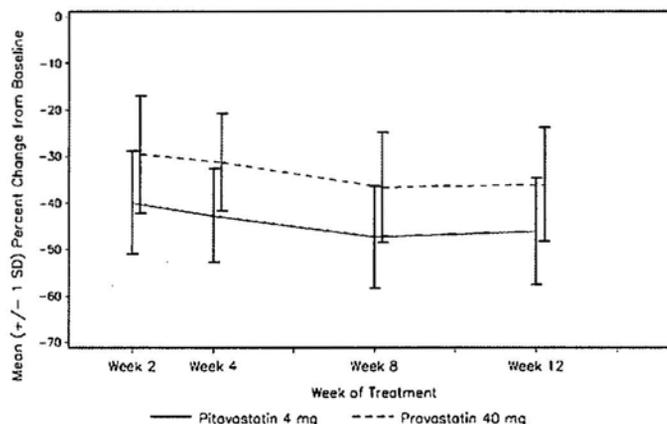
A: Pitavastatin 1 mg and Pravastatin 10 mg



B: Pitavastatin 2 mg and Pravastatin 20 mg



C: Pitavastatin 4 mg and Pravastatin 40 mg



Decreases in LDL were apparent across the treatment groups after 2 weeks and were sustained throughout the 12-week treatment period. In the highest dose groups studied, LDL continued to decrease over a period of 8 weeks and the decrease was sustained until the end of the 12-week treatment period.

Secondary Efficacy Variables:

LDL Target Attainment:

A summary of the number of subjects who attained the LDL target is provided in the following table:

Subjects With LDL Target Attainment (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Number (percent) of subjects with target attained according to NCEP criteria						
Unadjusted proportion achieving target results	172 (83.1%)	67 (65.0%)	199 (88.8%)	78 (81.3%)	191 (91.0%)	90 (88.2%)
Mean Difference	-18.0		-7.6		-2.7	
(95% CI)	(-28.6; -7.5)		(-16.4; 1.2)		(-10.1; 4.6)	
P-value	0.001		0.092		0.469	

LDL target attainment was achieved in more subjects in the pitavastatin groups than in the pravastatin groups for all dose comparisons.

Overall, the difference between the treatments in the proportion of subjects with target attainment was greater between the lower dose groups compared with the higher dose groups. Using the NCEP criteria, the proportion of subjects who attained target LDL in the pitavastatin vs. pravastatin groups, respectively, was 83.1% vs. 65.0% for the low-dose groups, 88.8% vs. 81.3% for the medium dose groups, and 91.0% vs. 88.2% for the high-dose groups. The difference was statistically significant (P<0.05) for the low-dose group comparison.

LDL Sub-Group Analyses

LDL by Country:

**Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Country
Subgroup (FAS)**

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Denmark						
N	56	24	54	25	53	26
Baseline	165.43	164.18	164.83	171.01	166.20	169.23
% change to endpoint	-32.72 (10.74)	-21.75 (15.14)	-39.44 (12.01)	-32.95 (7.12)	-47.12 (8.63)	-38.54 (10.27)
Germany						
N	45	21	50	22	45	20
Baseline	170.37	170.67	166.87	164.61	162.67	163.50
% change to endpoint	-30.35 (11.84)	-22.12 (12.90)	-35.60 (13.18)	-26.01 (11.18)	-42.70 (15.95)	-32.59 (14.89)
Israel						
N	10	8	10	4	11	8
Baseline	149.87	157.10	163.03	142.42	158.36	170.63
% change to endpoint	-18.63 (12.33)	-18.35 (17.43)	-40.07 (11.10)	-20.85 (5.51)	-38.40 (8.31)	-22.60 (19.13)
Netherlands						
N	32	15	35	15	32	14
Baseline	171.32	174.56	163.95	167.22	175.93	177.02
% change to endpoint	-30.90 (9.76)	-24.66 (12.93)	-37.81 (13.25)	-27.47 (12.36)	-45.69 (11.72)	-33.30 (9.53)
UK						
N	64	35	75	30	69	34
Baseline	157.98	155.65	158.15	158.04	156.95	161.13
% change to endpoint	-33.32 (12.60)	-23.01 (14.18)	-41.32 (13.65)	-29.20 (12.66)	-43.49 (16.34)	-34.27 (16.00)

The mean percent decrease in LDL was lower in the subjects in Israel compared with the other countries for some, though not all, dose groups. However, mean baseline LDL was lower in the Israeli subjects compared with the other countries, particularly in the pitavastatin 1 mg and pravastatin 20 mg groups. In addition, very few subjects were recruited in Israel compared with the other countries.

LDL by Age:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by age in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Age Subgroup (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
65-69 years						
N	118	51	108	52	108	56
Baseline	165.85	163.35	162.57	163.74	165.70	169.46
% change to endpoint	-31.20 (11.81)	-21.79 (13.03)	-37.55 (14.16)	-29.09 (11.06)	-45.77 (12.19)	-36.03 (12.34)
70-74 years						
N	56	33	73	27	67	28
Baseline	162.81	168.22	163.41	161.23	159.05	165.30
% change to endpoint	-31.69 (11.82)	-23.05 (16.10)	-39.16 (11.24)	-27.47 (12.30)	-42.58 (14.80)	-26.58 (17.06)
≥75 years						
N	33	19	43	17	35	18
Baseline	161.67	156.05	162.51	167.53	165.09	159.63
% change to endpoint	-31.80 (12.29)	-22.98 (13.58)	-42.31 (12.77)	-30.17 (9.17)	-43.10 (15.67)	-39.15 (11.30)

With the exception of an apparent age effect in the pitavastatin 2 mg group, there were no systematic differences between the age groups 65-69 years, 70-74 years, and ≥75 years in mean percent decrease from baseline to endpoint in LDL.

LDL by Sex:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by sex in the following table.

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Sex Subgroup (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Male						
N	89	49	100	48	89	42
Baseline	158.81	156.76	160.39	161.57	163.62	167.73
% change to endpoint	-31.09 (12.20)	-20.54 (13.13)	-37.92 (13.00)	-28.98 (11.96)	-42.51 (15.76)	-33.17 (14.21)
Female						
N	118	54	124	48	121	60
Baseline	168.54	169.75	164.81	165.84	163.37	165.78
% change to endpoint	-31.68 (11.60)	-24.11 (14.75)	-39.85 (13.19)	-28.68 (10.19)	-45.62 (11.85)	-34.55 (14.45)

There were no differences between males and females in mean percent decrease from baseline to endpoint in LDL.

LDL by Race

Only seven of the 942 subjects in the FAS were not Caucasian: two subjects in the pitavastatin 2 mg dose group, two subjects in the pravastatin 20 mg dose group and three subjects in the pitavastatin 4 mg dose group. Therefore, no meaningful comparisons can be made between the responses of the non-Caucasians compared with Caucasians in percent change from baseline to endpoint in LDL.

LDL by BMI Category:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by BMI category in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by BMI Subgroup (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
<25 kg/m²						
N	69	28	77	27	58	30
Baseline	163.65	161.56	162.13	162.99	163.06	168.89
% change to endpoint	-31.49 (10.95)	-22.18 (16.75)	-39.15 (13.16)	-30.08 (10.16)	-40.64 (14.12)	-35.39 (11.91)
25-<30 kg/m²						
N	89	55	101	47	110	46
Baseline	166.59	163.52	161.95	164.55	164.74	166.18
% change to endpoint	-31.41 (12.07)	-23.70 (11.48)	-38.10 (13.73)	-29.16 (12.24)	-46.44 (11.67)	-34.59 (16.07)
≥30 kg/m²						
N	49	20	46	22	42	26
Baseline	161.31	166.50	165.96	162.79	160.75	164.64
% change to endpoint	-31.37 (12.80)	-19.19 (16.46)	-40.66 (11.42)	-26.59 (9.44)	-43.79 (16.89)	-31.28 (13.64)

There were no apparent differences between subjects in BMI categories <25 kg/m², 25-<30 kg/m², and ≥30 kg/m² in mean percent decrease from baseline to endpoint in LDL.

LDL by NCEP CHD Risk Category:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by NCEP CHD risk category in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by NCEP CHD Risk Category Subgroup (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Low risk						
N	125	58	123	56	111	65
Baseline	163.35	159.86	163.33	163.98	162.02	167.50
% change to endpoint	-30.93 (12.04)	-24.26 (14.27)	-38.30 (12.95)	-28.97 (11.46)	-45.04 (13.70)	-33.50 (14.48)
Moderate risk						
N	50	29	65	25	67	25
Baseline	168.80	168.87	161.36	159.74	164.68	160.55
% change to endpoint	-34.01 (10.74)	-20.79 (12.99)	-39.84 (13.43)	-29.86 (10.90)	-42.57 (15.14)	-37.96 (11.31)
High risk						
N	32	16	36	15	32	12
Baseline	161.35	167.37	163.82	169.29	166.00	174.22
% change to endpoint	-29.34 (12.34)	-18.64 (14.84)	-39.80 (13.03)	-26.59 (10.12)	-45.40 (10.05)	-28.29 (17.49)

There were no apparent differences between subjects in low, moderate or high risk categories in mean percent decrease from baseline to endpoint in LDL.

LDL by Baseline LDL Category:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by categorized baseline LDL in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Baseline LDL Category Subgroup (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
<160 mg/dL						
N	88	55	113	43	101	41
Baseline	143.35	147.02	146.15	146.91	145.13	145.89
% change to endpoint	-27.83 (12.84)	-21.28 (12.72)	-37.87 (13.20)	-26.40 (12.96)	-41.87 (16.41)	-32.32 (16.00)
160-190 mg/dL						
N	91	34	82	42	80	45
Baseline	172.53	172.90	172.58	171.43	172.92	172.48
% change to endpoint	-34.58 (9.71)	-23.60 (12.99)	-40.61 (12.84)	-30.84 (9.45)	-47.11 (9.31)	-33.45 (13.52)
≥190 mg/dL						
N	28	14	29	11	29	16
Baseline	203.83	205.88	200.26	199.88	201.32	203.02
% change to endpoint	-32.47 (12.09)	-23.99 (20.90)	-38.75 (13.17)	-30.63 (6.59)	-45.08 (12.22)	-39.74 (10.70)

The mean percent decrease in LDL was not influenced by baseline LDL. When the percent change from baseline was grouped by baseline LDL, the mean percent change from baseline to endpoint in all three categories was similar to that of the overall FAS analysis.

LDL by Diabetes:

The mean percent change from baseline to endpoint in LDL for the FAS is presented by subjects with and without a diagnosis of diabetes in the following table:

Mean (SD) Percent Change from Baseline to Endpoint in LDL (mg/dL) by Diabetes Subgroup (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Diabetic						
N	11	6	16	4	17	3
Baseline	158.30	168.50	160.79	154.33	159.55	172.44
% change to endpoint	-25.01 (16.929)	-16.69 (15.877)	-39.62 (10.965)	-22.10 (16.604)	-42.37 (10.021)	-34.74 (8.270)
Not diabetic						
N	196	97	208	92	193	99
Baseline	164.70	163.26	162.99	164.11	163.82	166.41
% change to endpoint	-31.79 (11.44)	-22.77 (13.95)	-38.94 (13.24)	-29.12 (10.79)	-44.48 (13.98)	-33.96 (14.47)

There were no differences between subjects with and without diabetes in mean percent decrease from baseline to endpoint in LDL. However, there were relatively few subjects with diabetes (57 of the 942 subjects in the FAS).

Secondary Efficacy Lipid Variables:

Total cholesterol (TC):

Change from baseline in TC is summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables (mg/dL): TC (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	253.4 (29.16)	249.7 (28.15)	250.5 (25.35)	252.9 (25.76)	250.7 (25.53)	253.8 (24.51)
Endpoint mean (SD)	196.8 (29.55)	211.0 (34.87)	183.3 (27.49)	200.5 (26.83)	173.1 (28.21)	192.1 (28.96)
Mean % change (SD)	-22.19 (8.90)	-15.34 (11.04)	-26.68 (9.43)	-20.61 (8.43)	-30.75 (10.46)	-24.07 (10.91)
Adjusted Mean	6.52		6.23		6.84	
Difference (95% CI)	(4.25; 8.79)		(3.93; 8.52)		(4.56; 9.11)	
P-value	<0.001		<0.001		<0.001	

Total cholesterol decreased by between 15.34% and 30.75% across all treatment groups, with the greatest decrease being in the pitavastatin 4 mg group. The mean percent decrease in TC from baseline to endpoint in the FAS was statistically significantly greater in all pitavastatin groups compared with each of the pravastatin groups (P<0.001). The adjusted mean differences for the dose group comparisons low, medium, and high were: 6.52%, 6.23% and 6.84%, respectively.

High Density Lipoprotein cholesterol (HDL cholesterol):

Change from baseline in HDL cholesterol is summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables (mg/dL): HDL cholesterol (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	60.8 (15.27)	57.7 (15.35)	60.2 (15.45)	59.7 (14.19)	58.1 (14.62)	59.4 (15.19)
Endpoint mean (SD)	60.9 (15.61)	57.3 (15.62)	61.2 (15.82)	58.7 (14.00)	60.2 (15.66)	59.6 (15.67)
Mean % change (SD)	0.63 (10.94)	-0.14 (12.17)	2.14 (11.49)	-1.15 (10.31)	4.13 (11.32)	0.80 (11.85)
Adjusted Mean	-1.07		-3.37		-3.07	
Difference (95% CI)	(-3.72; 1.57)		(-6.04; -0.70)		(-5.71; -0.42)	
P-value	0.425		0.013		0.023	

There was an increase in HDL cholesterol values in the pitavastatin 1 mg (0.63%), pitavastatin 2 mg (2.14%) and pitavastatin 4 mg (4.13%) groups whereas there was a decrease in HDL in the pravastatin 10 mg group (-0.14%) and the pravastatin 20 mg group (-1.15%) and an increase of 0.80% in the pravastatin 40 mg group. The adjusted mean differences were statistically significantly different: -3.37% (P=0.013) for the medium dose group comparison and -3.07% (P=0.023) for the high-dose group comparison.

Triglycerides (TG):

Change from baseline in TG is summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables (mg/dL): TG (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	141.2 (53.91)	142.0 (54.04)	137.2 (48.70)	147.9 (61.45)	145.4 (55.83)	139.1 (53.66)
Endpoint mean (SD)	118.8 (43.75)	134.9 (70.36)	114.3 (46.21)	127.6 (51.71)	110.6 (44.04)	115.0 (44.27)
Mean % change (SD)	-13.38 (20.851)	-4.72 (27.822)	-14.62 (22.857)	-11.00 (23.859)	-21.52 (18.640)	-14.61 (20.705)
Adjusted Mean	8.72		4.81		6.20	
Difference (95% CI)	(3.70; 13.75)		(-0.27; 9.90)		(1.17; 11.23)	
P-value	0.001		0.063		0.016	

Triglycerides decreased in all treatment groups, and the magnitude of the change was dose-related both in the pitavastatin and pravastatin treatment groups. The decrease was statistically significantly greater in the pitavastatin 1 mg and 4 mg groups compared with the corresponding pravastatin groups; the adjusted mean differences for the low and high-dose group comparisons, respectively, were 8.72% (P=0.001) and 6.20% (P=0.016). However, the adjusted mean difference in the medium dose group comparison, 4.81%, was not statistically significant (P=0.063).

Apolipoprotein-B (Apo-B):

Change from baseline in Apo-B is summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables (mg/dL): Apo-B (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	147.1 (21.61) (N=201)	145.9 (23.13) (N=100)	146.0 (20.31) (N=212)	149.1 (19.66) (N=90)	149.1 (22.23) (N=201)	150.1 (21.94) (N=98)
Endpoint mean (SD)	109.2 (19.70) (N=207)	121.3 (25.99) (N=103)	100.4 (18.69) (N=223)	114.2 (18.74) (N=96)	94.0 (18.82) (N=208)	108.4 (20.70) (N=102)
Mean % change (SD)	-25.35 (10.905) (N=201)	-16.96 (13.325) (N=100)	-30.93 (11.572) (N=211)	-22.31 (10.191) (N=90)	-36.58 (12.171) (N=199)	-27.51 (11.852) (N=98)
Adjusted Mean	8.07		9.03		9.11	
Difference (95% CI)	(5.37; 10.77)		(6.25; 11.80)		(6.39; 11.84)	
P-value	<0.001		<0.001		<0.001	

Apo-B decreased in all treatment groups but more so in the pitavastatin groups compared with the pravastatin groups, and the differences were statistically significantly different (P<0.001 for all three comparisons). The magnitude of the changes was dose-related in both the pitavastatin and pravastatin treatment groups. The adjusted mean differences for the dose group comparisons increased slightly with increasing dose: 8.07% (low), 9.03% (medium) and 9.11% (high).

Non-HDL cholesterol:

Changes from baseline in Non-HDL cholesterol are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables (mg/dL): Non-HDL cholesterol (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	192.6 (26.43)	192.0 (27.32)	190.3 (23.74)	193.2 (23.74)	192.6 (26.09)	194.4 (25.53)
Endpoint mean (SD)	135.9 (24.95)	153.7 (34.70)	122.0 (26.18)	141.8 (24.85)	112.8 (25.66)	132.5 (28.21)
Mean % change (SD)	-29.11 (11.03)	-19.89 (13.65)	-35.70 (12.00)	-26.51 (10.47)	-41.13 (12.66)	-31.54 (13.43)
Adjusted Mean	9.01		9.41		9.62	
Difference (95% CI)	(6.19; 11.82)		(6.56; 12.26)		(6.81; 12.44)	
P-value	<0.001		<0.001		<0.001	

At endpoint, mean Non-HDL cholesterol was lower in all of the treatment groups and the decrease was statistically significantly greater (P<0.001) in all three pitavastatin groups compared with their corresponding pravastatin groups. The magnitude of the changes were dose-related both in the pitavastatin and pravastatin treatment groups and the adjusted mean differences for the dose group comparisons increased slightly with increasing dose: 9.01% (low), 9.41% (medium) and 9.62% (high).

Non-HDL cholesterol:HDL cholesterol ratio:

Changes from baseline in Non-HDL cholesterol:HDL cholesterol ratio are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Non-HDL cholesterol:HDL cholesterol ratio (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	3.38 (0.99)	3.59 (1.11)	3.37 (0.95)	3.43 (0.92)	3.55 (1.07)	3.52 (1.08)
Endpoint mean (SD)	2.371 (0.71)	2.907 (1.11)	2.139 (0.76)	2.55 (0.75)	2.01 (0.71)	2.40 (0.911)
Mean change (SD)	-1.01 (0.58)	-0.68 (0.66)	-1.23 (0.65)	-0.88 (0.52)	-1.55 (0.71)	-1.12 (0.67)
Adjusted Mean	0.402		0.380		0.410	
Difference (95% CI)	(0.284; 0.521)		(0.261; 0.500)		(0.292; 0.529)	
P-value	<0.001		<0.001		<0.001	

The ratio of Non-HDL cholesterol:HDL cholesterol was similar across all treatment groups at baseline (between 3.37 and 3.59). At endpoint, mean Non-HDL cholesterol:HDL cholesterol ratio was lower in all of the treatment groups and the decrease was statistically significantly greater (P<0.001) in all three pitavastatin groups compared to their corresponding pravastatin groups. The adjusted mean differences for the dose group comparisons were: 0.40 (low), 0.38 (medium) and 0.41 (high).

TC:HDL cholesterol Ratio:

Changes from baseline in TC:HDL cholesterol ratio are summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: TC:HDL cholesterol ratio (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	4.38 (0.99)	4.59 (1.11)	4.37 (0.95)	4.432 (0.92)	4.55 (1.07)	4.52 (1.08)
Endpoint mean (SD)	3.37 (0.71)	3.907 (1.11)	3.139 (0.76)	3.554 (0.75)	3.006 (0.71)	3.403 (0.912)
Mean change (SD)	-1.011 (0.58)	-0.679 (0.66)	-1.23 (0.65)	-0.878 (0.51)	-1.547 (0.71)	-1.12 (0.67)
Adjusted Mean	0.402		0.380		0.410	
Difference (95% CI)	(0.284; 0.521)		(0.261; 0.500)		(0.292; 0.529)	
P-value	<0.001		<0.001		<0.001	

Total cholesterol:HDL cholesterol ratio was similar across all treatment groups at baseline (between 4.372 and 4.586). At endpoint, mean TC:HDL cholesterol ratio was lower in all of the treatment groups and the decrease was statistically significantly greater (P<0.001) in all three pitavastatin groups compared with their corresponding pravastatin groups. The adjusted mean differences for the dose group comparisons were: 0.402 (low), 0.380 (medium) and 0.410 (high).

Apolipoprotein A1 (Apo-A1):

Change from baseline in Apo-A1 is summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables (mg/dL): Apo-A1 (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	173.5 (26.00)	167.7 (26.65)	173.6 (28.03)	173.9 (27.53)	170.3 (25.88)	171.7 (26.9)
Endpoint mean (SD)	176.7 (29.01)	171.3 (27.57)	177.6 (28.70)	174.8 (26.15)	174.6 (27.49)	173.0 (30.36)
Mean % change (SD)	2.40 (13.17)	3.30 (11.01)	2.84 (10.86)	0.82 (10.40)	2.81 (10.18)	0.18 (9.82)
Adjusted Mean	0.32		-2.04		-2.49	
Difference (95% CI)	(-2.26; 2.89)		(-4.69; 0.61)		(-5.08; 0.11)	
P-value	0.810		0.131		0.061	

For Apo-A1, the mean percent change from baseline to endpoint ranged between 2.40% and 2.84% in the pitavastatin groups and from 0.18% to 3.30% in the pravastatin groups, with no apparent dose relationship. The adjusted mean differences for the dose group comparisons were: 0.32% (low), -2.04% (medium) and -2.49% (high), and were not statistically significant.

Apo-B:Apo-A1 Ratio

Change from baseline in Apo-B:Apo-A1 ratio is summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables: Apo-B:Apo-A1 Ratio (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	0.87 (0.19)	0.89 (0.20)	0.86 (0.19)	0.87 (0.17)	0.90 (0.21)	0.90 (0.22)
Endpoint mean (SD)	0.64 (0.16)	0.73 (0.19)	0.58 (0.15)	0.66 (0.15)	0.55 (0.15)	0.65 (0.19)
Mean change (SD)	-0.23 (0.15)	-0.18 (0.14)	-0.28 (0.15)	-0.20 (0.13)	-0.35 (0.15)	-0.25 (0.15)
Adjusted Mean	0.07		0.08		0.10	
Difference (95% CI)	(0.04; 0.10)		(0.06; 0.11)		(0.07; 0.13)	
P-value	<0.001		<0.001		<0.001	

The Apo-B:Apo-A1 ratio at baseline ranged between 0.86 and 0.90. The mean decreases from baseline to endpoint were consistently greater in the pitavastatin treatment groups compared with the pravastatin treatment groups. The decreases appeared to be dose related in both treatments. All three treatment group differences were statistically significant (P<0.001). The adjusted mean differences for the dose group comparisons were: 0.07 (low), 0.08 (medium) and 0.10 (high).

High Sensitivity C-Reactive Protein (hsCRP):

Change from baseline in hsCRP is summarized for the FAS in the following table:

Change from Baseline in Secondary Efficacy Lipid Variables (mg/L): hsCRP (FAS)

	Pitavastatin 1 mg QD N=207	Pravastatin 10 mg QD N=103	Pitavastatin 2 mg QD N=224	Pravastatin 20 mg QD N=96	Pitavastatin 4 mg QD N=210	Pravastatin 40 mg QD N=102
Baseline mean (SD)	2.78 (7.30)	4.59 (11.85)	3.82 (5.30)	2.70 (3.31)	5.00 (12.68)	3.64 (6.03)
Endpoint mean (SD)	3.14 (7.51)	4.01 (10.19)	3.88 (10.44)	3.49 (5.21)	4.05 (11.88)	4.24 (17.07)
Mean change (SD)	-0.36 (7.95)	-0.58 (15.18)	0.06 (11.61)	0.21 (4.92)	-0.95 (16.39)	0.40 (18.18)
Adjusted Mean	0.85		-0.39		0.35	
Difference (95% CI)			(-2.98; 2.20)		(-2.21; 2.91)	
P-value	0.511		0.768		0.786	

There was wide variability in hsCRP values with mean values at baseline between 2.70 and 5.00 mg/L. At endpoint, there was little change in hsCRP and no consistency in the direction of change, ranging between -9.2 and +8.0 mg/L. There was no apparent dose response in either group and none of the comparisons were statistically significant.

Efficacy Conclusions:

- Pitavastatin was non-inferior to pravastatin for the comparisons pitavastatin 1 mg vs. pravastatin 10 mg, pitavastatin 2 mg vs. pravastatin 20 mg and pitavastatin 4 mg vs. pravastatin 40 mg for percent change from baseline to endpoint or Week 12 in change from baseline in LDL in both the FAS and PP population.
- Pitavastatin was statistically significantly superior to pravastatin for all three dose group comparisons of percent change from baseline in LDL (P<0.001) in both the FAS and the PP population.
- LDL target attainment was achieved in more subjects in the pitavastatin groups than in the pravastatin groups for all three dose group comparisons using NCEP criteria. The proportion of subjects who attained target LDL ranged between 83% and 91% in the pitavastatin groups and between 65% and 88% in the pravastatin groups.
- Pitavastatin was statistically significantly superior to pravastatin for all three dose group comparisons of the secondary lipid measures for TC and Apo-B, in the medium and high-dose group comparisons for HDL cholesterol, and in the low and high-dose group comparisons for TG.
- There were no discernible differences between the subgroups (age, sex, race, BMI, risk category, baseline LDL, presence of hypertension, presence of diabetes and primary diagnosis) in mean percent change from baseline in LDL.

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/s/

DAVID S GORTLER

08/03/2009

David Gortler Final Draft of Pitavastatin Individual Efficacy Reviews

ERIC C COLMAN

08/03/2009

12/3/08

Memorandum

Filing Meeting: December 1, 2008

NDA 22-363

Pitavastatin 1 mg, 2 mg, 4 mg

Proposed Trade Name: Livalo®

Kowa Co, Ltd.

Letter date: October 1, 2008

Date received: October 1, 2008

PDUFA date: August 8, 2009

Primary Clinical Reviewer: Iffat N. Chowdhury, MD

Background

In NDA 22-363, the applicant has requested approval of Pitavastatin (a competitive inhibitor of HMG-CoA reductase) for use in patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total cholesterol, LDL-C, Apo B, non-HDL-C, TG, and increase HDL-C.

Since September 2003, Pitavastatin has been available in Japan under the brand name Livalo® in 1 mg, 2 mg, and 4 mg dosages. It has also been approved in Korea and Thailand.

During the Japanese drug development phase, Kowa Co., Ltd sub-licensed Pitavastatin to Negma (later acquired by Novartis) for development in Europe and Sankyo US for development in the United States. (b) (4)

(b) (4)

Novartis and Sankyo returned the rights for Pitavastatin to Kowa Co., in 2005. Thereafter, Kowa Research Europe and Kowa Research Institute initiated a new Phase 3 program with 1, 2, and 4 mg doses. Kowa Research Institute opened IND 60,492 with the Agency in April 2005.

An End-of-Phase 2 meeting was held between the firm and the Agency on September, 20, 2005 and a pre-NDA meeting on January 28, 2008. At these meetings and in related correspondence, the following agreements were reached:

- The Agency requested 3 overnight urine collections for subjects in the Phase 3 program at baseline and endpoint of the core studies. In follow-up discussions, it was agreed that a spot urine protein: creatinine ratio would be adequate; these samples would be on a subset of patients who had not passed the baseline visit.
- The Agency requested translated case report forms on all deaths and discontinuations due to adverse events from the Japanese NDA application.
- The Agency agreed to the proposed set of clinical pharmacology studies.

- It was suggested that Kowa consider conducting a PK study in African Americans compared to Caucasians to assure that no differences exist in pharmacokinetics
- The Agency recommend that comparative doses of atorvastatin to 40 mg be included in studies to permit a reasonable evaluation of efficacy/safety and also suggested alternative designs such as a parallel design and combining Study 301 and 302.
- The Agency agreed to a deferral of pediatric studies until the post-approval phase.
- The Agency commented that a thorough QTc study should be conducted.
- The Agency requested that a statistical analysis plan be provided in addition to the core study protocols for the Phase 3 program.
- The Agency agreed that the proposed number of patients and exposure duration were sufficient to support an NDA.
- (b) (4) 1
- The Agency requested inclusion of narratives for serious adverse events judged “related to drug” by the investigator from Japanese post-marketing reports
- The Agency agreed that a full translation of reports and information from the Japanese NDA was not necessary and that the summary translation described by KRI would probably be sufficient.
- The final study report for extension study NK-104-310 would not be included in the NDA

All of the recommendations were implemented with the exception of the design for Study NK-104-301 and 302. These two studies were kept as forced titration and two separate studies as originally planned. Atorvastatin 40 mg was used only in Study 310 if patients did not achieve the targeted LDL-C goals.

Pharmacokinetic studies have been conducted in special populations (elderly, renal impairment, hepatic impairment and fatty liver) and the impact of race, gender, and time of dosing on pharmacokinetics has also been studied. A total of 12 drug-drug interaction studies have been conducted.

A thorough QT study has been conducted with Pitavastatin 4 mg and 16 mg; the applicant concludes there is no tendency to QT prolongation.

Phase 3 Clinical Trials

This original NDA is an electronic submission containing 5 Phase 3 clinical trials and 4 extension trials. The following is a list of the Phase 3 trials.

Study No.	Objective
301	Pitavastatin 2 mg vs. atorvastatin 10mg Pitavastatin 4 mg vs. atorvastatin 20 mg in patients with primary hypercholesterolemia or combined dyslipidemia

Study No.	Objective
302	Pitavastatin 2 mg vs. simvastatin 20 mg Pitavastatin 4 mg vs. simvastatin 20 mg in patients with primary hypercholesterolemia or combined dyslipidemia
304	Pitavastatin 4 mg vs. simvastatin 40 mg in patients with high cardiovascular risk
305	Pitavastatin 4 mg vs. atorvastatin 20 mg in patients with diabetes
306	Pitavastatin 1 mg vs. pravastatin 10 mg Pitavastatin 2 mg vs. pravastatin 20 mg Pitavastatin 4 mg vs. pravastatin 40 mg in elderly patients
307	Extension of study 301 and 302
308	Extension of study 306
309	Extension of study 304
310	Extension of study 305

Studies 301 and 302 represent the pivotal studies, whereas studies 304, 305, 306 are special population studies.

In Study 301, after completion of a 6 to 8 week washout/dietary lead-in period, subjects were randomized to 1 of 4 treatment groups: Pitavastatin 2 mg QD, Pitavastatin 4 mg QD (2 mg, titrated to 4 mg QD), atorvastatin 10 mg QD or atorvastatin 20 mg QD (10 mg, titrated to 20 mg QD). The primary efficacy variable was the percent change in LDL-C from baseline to Week 12 endpoint.

In Study 302, after completion of a 6 to 8 week washout/dietary lead-in period, subjects were randomized to 1 of 4 treatment groups: Pitavastatin 2 mg QD, Pitavastatin 4 mg QD (2 mg, titrated to 4 mg QD), simvastatin 20 mg QD or simvastatin 40 mg QD (20 mg, titrated to 40 mg QD). The primary efficacy variable was the percent change in LDL-C from baseline to Week 12 endpoint.

Pitavastatin exposure by dose

	Pitavastatin 1 mg N=309	Pitavastatin 2 mg N=2562	Pitavastatin 4 mg N=2406
No. of Weeks of Exposure (Mean)	11.56	16.71	37.36
Total Patient Years of Exposure	68.68	823.47	1728.64

Efficacy Data (LDL-C)

The five Phase 3 trials were all non-inferiority trials. The non-inferiority criterion was met in all comparisons except in the comparison of Pitavastatin 4 mg to Atorvastatin 20

mg in study 305 in diabetics. However, in study 301, Pitavastatin 4 mg was non-inferior to Atorvastatin 20 mg. See Table 2.5.1.7 from the NDA submission cited below.

Table 2.5.17: Summary of Effects of Pitavastatin and Comparators on LDL-C in the Phase III Core Studies at Week 12

Week 12, LOCF (FAS) NK104-301	Pitavastatin 1 mg QD	Atorvastatin 10 mg QD	Pitavastatin 2 mg QD	Atorvastatin 20 mg QD	Pitavastatin 4 mg QD	Atorvastatin 40 mg QD
N	Not included	102	315	102	298	Not included
Mean % change (SD)		-37.8 (15.60)	-37.9 (13.97)	-43.5 (16.15)	-44.6 (14.98)	
Week 12, LOCF (FAS) NK104-302	Pitavastatin 1 mg QD	Simvastatin 10 mg QD	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	Not included	Not included	307	107	319	110
Mean % change (SD)			-39.0 (14.57)	-35.0 (15.53)	-44.0 (14.49)	-42.8 (15.77)
Week 12, LOCF (FAS) NK104-304	Pitavastatin 1 mg QD	Simvastatin 10 mg QD	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	Not included	Not included	Not included	Not included	233	118
Mean % change (SD)					-44.0 (12.77)	-43.8 (14.42)
Week 12, LOCF (FAS) NK104-305	Pitavastatin 1 mg QD	Atorvastatin 10 mg QD	Pitavastatin 2 mg QD	Atorvastatin 20 mg QD	Pitavastatin 4 mg QD	Atorvastatin 40 mg QD
N	Not included	Not included	Not included	136	274	Not included
Mean % change (SD)				-43.3 (16.4)	-40.8 (19.6)	
Week 12, LOCF (FAS) NK104-306	Pitavastatin 1 mg QD	Pravastatin 10 mg QD	Pitavastatin 2 mg QD	Pravastatin 20 mg QD	Pitavastatin 4 mg QD	Pravastatin 40 mg QD
N	207	103	224	96	210	102
Mean % change (SD)	-31.4 (11.83)	-22.41 (14.05)	-39.0 (13.07)	-28.8 (11.05)	-44.31 (13.70)	-34.0 (1430)

Source: NK-104-301 CSR Table 8; NK-104-302 CSR Table 8; NK-104-304 CSR Table 10; NK-104-305 CSR Table 10; NK-104-306 CSR Table 9

Safety Data

There were seven deaths in the Phase 3 studies; six deaths on Pitavastatin (two deaths on 2mg Pitavastatin, four deaths on 4 mg Pitavastatin) and one death on simvastatin 20 mg. The causes of death for the six subjects on Pitavastatin (Subjects 6201004, 6516069, 5110042, 1108015, 2109026, 4504013) were Non-Hodgkin's lymphoma, bronchopneumonia and cerebrovascular accident, myocardial infarction, hypoxic encephalopathy, cardiac death, and myocardial ischemia. The death of the patient taking 20 mg simvastatin was a sudden cardiac death (Subject 2116059).

One additional death occurred with 16 mg (b) (4) formulation of Pitavastatin during [CNKS104A2205E1], the one-year open-label extension study to [NKS104A2205]. Subject GBR/0122/00036 died on Day 30 of the study extension due to a subarachnoid haemorrhage.

Treatment-emergent adverse events in Phase 3 studies

The summary table shown below lists adverse events from the Phase 3 studies.

Table 2.7.4.43 Overview of TEAEs Reported in Phase III Core and Extension Studies

Treatment Randomised Dose	N*	No. (%) of Subjects							
		Any TEAE	Mild TEAEs	Mod TEAEs	Severe TEAEs	Treatment related TEAEs†	Serious TEAEs	Dis-continuation due to TEAEs	
Core Studies									
Study NK-104-301									
Pita 2 mg	316	60 (19.0)	34 (10.8)	21 (6.6)	5 (1.6)	20 (6.3)	3 (0.9)	5 (1.6)	
Pita 4 mg	300	50 (16.7)	28 (9.3)	20 (6.7)	2 (0.7)	16 (5.3)	1 (0.3)	6 (2.0)	
Ator 10 mg	102	17 (16.7)	8 (7.8)	9 (8.8)	0	3 (2.9)	1 (1.0)	0	
Ator 20 mg	103	23 (22.3)	9 (8.7)	12 (11.7)	2 (1.9)	2 (1.9)	2 (1.9)	0	
Study NK-104-302									
Pita 2 mg	311	110 (35.4)	57 (18.3)	50 (16.1)	3 (1.0)	52 (16.7)	3 (1.0)	13 (4.2)	
Pita 4 mg	320	103 (32.2)	52 (16.3)	49 (15.3)	2 (0.6)	42 (13.1)	4 (1.3)	8 (2.5)	
Simv 20 mg	107	36 (33.6)	13 (12.1)	21 (19.6)	2 (1.9)	15 (14.0)	2 (1.9)	3 (2.8)	
Simv 40 mg	110	30 (27.3)	14 (12.7)	15 (13.6)	1 (0.9)	9 (8.2)	2 (1.8)	1 (0.9)	
Study NK-104-304									
Pita 4 mg	233	119 (51.1)	81 (34.8)	34 (14.6)	4 (1.7)	33 (14.2)	4 (1.7)	9 (3.9)	
Simv 40 mg	119	60 (50.4)	34 (28.6)	25 (21.0)	1 (0.8)	26 (21.8)	5 (4.2)	6 (5.0)	
Study NK-104-305									
Pita 4 mg	275	100 (36.4)	71 (25.8)	24 (8.7)	4 (1.5)	32 (11.6)	4 (1.5)	7 (2.5)	
Ator 20 mg	137	54 (39.4)	31 (22.6)	21 (15.3)	2 (1.5)	15 (10.9)	4 (2.9)	5 (3.6)	
Study NK-104-306									
Pita 1 mg	207	113 (54.6)	64 (30.9)	42 (20.3)	7 (3.4)	33 (15.9)	1 (0.5)	9 (4.3)	
Pita 2 mg	224	115 (51.3)	73 (32.6)	38 (17.0)	4 (1.8)	37 (16.5)	2 (0.9)	11 (4.9)	
Pita 4 mg	210	110 (52.4)	63 (30.0)	42 (20.0)	5 (2.4)	27 (12.9)	3 (1.4)	8 (3.8)	
Prav 10 mg	103	57 (55.3)	32 (31.1)	24 (23.3)	1 (1.0)	24 (23.3)	0	8 (7.8)	
Prav 20 mg	96	47 (49.0)	26 (27.1)	17 (17.7)	4 (4.2)	14 (14.6)	1 (1.0)	2 (2.1)	
Prav 40 mg	102	54 (52.9)	32 (31.4)	20 (19.6)	2 (2.0)	15 (14.7)	3 (2.9)	4 (3.9)	
Extension Studies									
Study NK-104-307									
Pita 4 mg	1353	741 (54.8)	368 (27.2)	337 (24.9)	36 (2.7)	162 (12.0)	49 (3.6)	55 (4.1)	
Study NK-104-308									
Pita 2 mg	539	408 (75.7)	152 (28.2)	216 (40.1)	40 (7.4)	73 (13.5)	51 (9.5)	30 (5.6)	
Pita 4 mg	95	57 (60.0)	23 (24.2)	28 (29.5)	6 (6.3)	4 (4.2)	7 (7.4)	7 (7.4)	
Pita 2 mg/ 4 mg	539	442 (82.0)	160 (29.7)	237 (44.0)	45 (8.3)	77 (14.3)	56 (10.4)	37 (6.9)	
Study NK-104-309									
Pita 4 mg	121	92 (76.0)	38 (31.4)	45 (37.2)	9 (7.4)	13 (10.7)	4 (3.3)	7 (5.8)	
Simv 40 mg/ 80 mg	57	45 (78.9)	19 (33.3)	21 (36.8)	5 (8.8)	10 (17.5)	7 (12.3)	6 (10.5)	
Study NK-104-310 (16-Week Interim Report)									
Pita 4 mg	143	56 (39.2)	35 (24.5)	20 (14.0)	1 (0.7)	4 (2.8)	4 (2.8)	2 (1.4)	
Ator 20 mg/ 40 mg	71	21 (29.6)	10 (14.1)	8 (11.3)	3 (4.2)	1 (1.4)	5 (7.0)	1 (1.4)	

Source: [Module 5.3.5]

† Treatment-related as assessed by the investigator; * Safety population; TEAE: treatment-emergent adverse event; No.: number

Subgroup Analysis

Subgroup analysis including gender, age, renal impairment, and liver impairment will be an important component of the safety review. For this memorandum, this clinical reviewer has found potential issues with two subgroups: the elderly and Asians.

Age

Table 2.7.4.147 Overview of TEAEs by Age (<65 Years and ≥65 Years) and by Dose at Onset of Pitavastatin in Phase II/III Core and Extension Studies (Group 3)

No. (%) of Subjects with:	<65 years			≥65 years		
	Pita 1 mg (N=87)	Pita 2 mg† (N=1337)	Pita 4 mg (N=1541)	Pita 1 mg (N=222)	Pita 2 mg* (N=1225)	Pita 4 mg (N=865)
Any TEAE	37 (42.5)	324 (24.2)	807 (52.4)	119 (53.6)	623 (50.9)	436 (50.4)
Mild	17 (19.5)	205 (15.3)	426 (27.6)	68 (30.6)	267 (21.8)	211 (24.4)
Moderate	19 (21.8)	115 (8.6)	343 (22.3)	44 (19.8)	302 (24.7)	196 (22.7)
Severe	1 (1.1)	4 (0.3)	38 (2.5)	7 (3.2)	54 (4.4)	27 (3.1)
Treatment-Related TEAE	15 (17.2)	124 (9.3)	173 (11.2)	36 (16.2)	175 (14.3)	86 (9.9)
TEAEs Leading to Discontinuation	2 (2.3)	22 (1.6)	51 (3.3)	10 (4.5)	63 (5.1)	37 (4.3)
Serious TEAEs	0	7 (0.5)	41 (2.7)	1 (0.5)	59 (4.8)	32 (3.7)
Deaths	0	0	3 (0.2)	0	1 (0.1)	1 (0.1)

Source: [Module 5.3.5.3.2b ISS Tables 3.12.1]

† Many subjects in this group had 4 weeks at 2 mg before escalating to 4 mg; * 539 subjects received 2 mg in long-term extension study NK-104-308 (mean duration of approximately 48 weeks); TEAE: Treatment-emergent adverse event; No.: number.

From the brief overview for this memorandum, it appears the elderly who received 2 mg of Pitavastatin reported TEAEs of interest more frequently than non-elderly subjects receiving the same dose.

Table 2.7.4.148 Selected TEAEs of Interest by SMQ and Preferred Term ($\geq 1\%$ of Subjects), by Age, by Number (%) of Subjects and by Dose at Onset of Pitavastatin (Target Doses) in Phase II/III Core and Extension Studies (Group 3)

SMQ/Preferred Term No. (%) of Subjects with	<65 years			≥ 65 years		
	Pita 1 mg (N=87)	Pita 2 mg (N=1337)	Pita 4 mg (N=1541)	Pita 1 mg (N=222)	Pita 2 mg (N=1225)	Pita 4 mg (N=865)
Any Selected TEAE	12 (13.8)	72 (5.4)	212 (13.8)	29 (13.1)	159 (13.0)	94 (10.9)
Rhabdomyolysis/Myopathy (SMQ)	5 (5.7)	31 (2.3)	136 (8.8)	4 (1.8)	81 (6.6)	58 (6.7)
Blood CK increased	3 (3.4)	8 (0.6)	64 (4.2)	1 (0.5)	12 (1.0)	25 (2.9)
Myalgia	3 (3.4)	22 (1.6)	68 (4.4)	3 (1.4)	62 (5.1)	31 (3.6)
Additional Muscular Events of Interest	5 (5.7)	36 (2.7)	62 (4.0)	23 (10.4)	82 (6.7)	32 (3.7)
Back pain	5 (5.7)	12 (0.9)	28 (1.8)	7 (3.2)	39 (3.2)	14 (1.6)
Neck pain	0	0	3 (0.2)	4 (1.8)	6 (0.5)	0
Pain in extremity	1 (1.1)	9 (0.7)	11 (0.7)	6 (2.7)	16 (1.3)	5 (0.6)
Shoulder pain	0	4 (0.3)	7 (0.5)	5 (2.3)	9 (0.7)	4 (0.5)
Acute Renal Failure (SMQ)	0	0	2 (0.1)	1 (0.5)	4 (0.3)	2 (0.2)
Additional Renal Events of Interest	0	0	4 (0.3)	0	2 (0.2)	1 (0.1)
Possible Drug Related Hepatic Disorders (SMQ)	3 (3.4)	11 (0.8)	33 (2.1)	3 (1.4)	9 (0.7)	10 (1.2)

Source: [Module 5.3.5.3.2b ISS Table 3.12.2.1 and 3.12.2.2]

SMQ Standardised MedDRA Query; CK: creatine kinase; TEAE: treatment-emergent adverse event; No.: number.

Race

Asian patients reported similar incidence of myalgia as compared with Caucasians at the 2 mg Pitavastatin dose. However, at the 4 mg dose, Asians reported more than double the incidence of Caucasians, 8.3% vs. 3.7%.

Table 2.7.4.151 Overview of TEAEs by Race by Dose at Onset of Pitavastatin in Phase II/III Core and Extension Studies (Group 3)

No. (%) of Subjects with:	Caucasian			Asian + Indian	
	Pita 1 mg (N=309)	Pita 2 mg (N=2372)	Pita 4 mg (N=2188)	Pita 2 mg (N=181)	Pita 4 mg (N=205)
Any TEAE	156 (50.5)	919 (38.7)	1140 (52.1)	23 (12.7)	96 (46.8)
Mild	85 (27.5)	457 (19.3)	560 (25.6)	14 (7.7)	76 (37.1)
Moderate	63 (20.4)	406 (17.1)	515 (23.5)	7 (3.9)	18 (8.8)
Severe	8 (2.6)	56 (2.4)	63 (2.9)	2 (1.1)	2 (1.0)
Treatment-Related TEAE	51 (16.5)	282 (11.9)	248 (11.3)	15 (8.3)	9 (4.4)
TEAEs Leading to Discontinuation	12 (3.9)	80 (3.4)	85 (3.9)	4 (2.2)	3 (1.5)
Serious TEAEs	1 (0.3)	64 (2.7)	72 (3.3)	2 (1.1)	1 (0.5)
Deaths	0	1 (0.0)	3 (0.1)	0	1 (0.5)

No. (%) of Subjects with:	Black		Hispanic + Other	
	Pita 2 mg (N=3)	Pita 4 mg (N=5)	Pita 2 mg (N=6)	Pita 4 mg (N=8)
Any TEAE	1 (33.3)	3 (60.0)	4 (66.7)	4 (50.0)
Mild	0	0	1 (16.7)	1 (12.5)
Moderate	1 (33.3)	3 (60.0)	3 (50.0)	3 (37.5)
Severe	0	0	0	0
Treatment-Related TEAE	1 (33.3)	1 (20.0)	1 (16.7)	1 (12.5)
TEAEs Leading to Discontinuation	0	0	1 (16.7)	0

Source: [Module 5.3.5.3.2b ISS Tables 3.15.1]

Only Caucasian subjects received 1 mg pitavastatin; there were no deaths or serious TEAEs reported by Black, Hispanic or subjects of other ethnic origins; TEAE: Treatment-emergent adverse event; No.: number.

Table 2.7.4.152 Selected TEAEs of Interest by SMQ and Preferred Term (>1% of Subjects), by Race, by Number (%) of Subjects and by Dose at Onset of Pitavastatin (Target Doses) in Phase II/III Core and Extension Studies (Group 3)

SMQ/Preferred Term No. (%) of Subjects with	Caucasian			Asian + Indian	
	Pita 1 mg (N=309)	Pita 2 mg (N=2372)	Pita 4 mg (N=2188)	Pita 2 mg (N=181)	Pita 4 mg (N=205)
Any Selected TEAE	41 (13.3)	221 (9.3)	277 (12.7)	7 (3.9)	25 (12.2)
Rhabdomyolysis/Myopathy (SMQ)	9 (2.9)	106 (4.5)	171 (7.8)	5 (2.8)	19 (9.3)
Blood CK increased	4 (1.3)	19 (0.8)	86 (3.9)	1 (0.6)	2 (1.0)
Myalgia	6 (1.9)	78 (3.3)	80 (3.7)	5 (2.8)	17 (8.3)
Additional Muscular Events of Interest	28 (9.1)	114 (4.8)	89 (4.1)	1 (0.6)	5 (2.4)
Back pain	12 (3.9)	50 (2.1)	41 (1.9)	0	1 (0.5)
Musculoskeletal chest pain	1 (0.3)	7 (0.3)	10 (0.5)	0	2 (1.0)
Neck pain	4 (1.3)	6 (0.3)	3 (0.1)	0	0
Pain in extremity	7 (2.3)	23 (1.0)	15 (0.7)	1 (0.6)	1 (0.5)
Shoulder pain	5 (1.6)	12 (0.5)	10 (0.5)	0	1 (0.5)
Acute Renal Failure (SMQ)	1 (0.3)	4 (0.2)	4 (0.2)	0	0
Additional Renal Events of Interest	0	2 (0.1)	4 (0.2)	0	0
Possible Drug Related Hepatic Disorders (SMQ)	6 (1.9)	19 (0.8)	41 (1.9)	1 (0.6)	2 (1.0)
ALT increased	1 (0.3)	13 (0.5)	24 (1.1)	0	2 (1.0)

Source: [Module 5.3.5.3.2b ISS Table 3.15.2.1 and 3.15.2.3]

Only Caucasian subjects received 1 mg pitavastatin; Results from Black, Hispanic and subjects of other ethnic origin are not shown since the numbers in these groups were very small (see text); SMQ Standardised MedDRA Query; CK: creatine kinase; ALT: alanine transaminase; No.: number.

In addition to the clinical studies sponsored by the applicant, the applicant has submitted a post-marketing registry surveillance study of Pitavastatin. This study has been conducted in Japan from 2003 to 2007. A total of 20,270 subjects were recruited of whom 19,925 subjects were included in the safety database.

The applicant has also submitted Periodic Safety Update Reports for Pitavastatin from January 2004 to January 2008 from Japan.

Applicant requests included in NDA

Kowa Co., Ltd requests 5 year marketing exclusivity under 21 CFR 314.108(b)(2).

Labeling

The applicant submitted both clean and annotated draft Package Insert and draft Patient Package Insert labeling for Pitavastatin with clean Word and pdf versions.

Pediatric waiver

Kowa Co., Ltd requests a deferral of pediatric studies based upon discussions at the End-of-Phase 2 Meeting on September 20, 2005.

User Fee

The User Fee payment is for NDA 223-363 is \$1,247,200.00

Site Inspections

All clinical trial sites were in locations outside the United States. A request for information on the foreign sites was requested from the applicant. This data will help determine the DSI consultation.

Financial Disclosures

FDA Form 3454 was submitted with this application.

Assessment

Fileability: From a clinical standpoint, this NDA is fileable. (See Filing Checklist for Pitavastatin)

Requests

1. A request has been made to the applicant to submit data regarding the number of patients screened, enrolled and discontinued by site/investigator. This data will help determine the sites inspected.
2. A request has been made to the applicant to clarify the location in the NDA or submit a rationale for assuming the applicability of foreign data in the submission to the US population.
3. A request has been made to submit or show the location of the "coding dictionary".
4. A request has been made to the applicant to submit data regarding the rhabdomyolysis/myopathy cases seen with higher doses of Pitavastatin (8 mg through 64 mg).

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/s/

Iffat N Chowdhury
12/2/2008 02:28:24 PM
MEDICAL OFFICER

Eric Colman
12/3/2008 08:30:48 AM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Requested from the applicant
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		Requested from applicant
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes ____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Iffat N. Chowdhury, MD	11/20/08
Reviewing Medical Officer	Date
Eric Colman	11/20/08
Clinical Team Leader	Date

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this page is the manifestation of the electronic signature.**

/s/

Iffat N Chowdhury
12/2/2008 02:36:21 PM
MEDICAL OFFICER

Eric Colman
12/3/2008 08:31:05 AM
MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22-363
Generic Name	Livalo (Pitavastatin or NK-104)
Sponsor	Kowa Research Institute, Inc.
Indication	Treatment of Primary Hypercholesterolemia and Mixed Dyslipidemia
Dosage Form	Tablets
Drug Class	Hydroxy methylglutaryl coenzyme A reductase inhibitor (HMGRI) or "Statin"
Therapeutic Dose	4 mg QD
Duration of Therapeutic Use	chronic
Maximum Tolerated Dose	Not reported
Application Submission Date	20 January 2009
Review Classification	Standard
Date Consult Received	30 January 2009
Clinical Division	DMEP / HFD 510

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of pitavastatin (4 mg and 16 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between pitavastatin (4 mg and 16 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guideline. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTcI$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that the assay sensitivity was established in the study.

The supratherapeutic dose (16 mg qd) produces mean C_{max} values of 4.4-fold higher than the mean C_{max} for the therapeutic dose (4 mg qd). At these concentrations, there was no detectable prolongation of the QTc interval. However, these concentrations do not cover the worst case scenario where C_{max} increased 6.6-fold due to metabolic inhibition with cyclosporine. The Agency had previously recommended that doses higher than 16 mg should be evaluated in the TQT study during the protocol review (see section 1.2). To account for the increase in exposure with co-administration with cyclosporine, (b) (4)

(b) (4)

In this randomized, double-blinded, four-arm parallel study, One hundred and seventy-four (174) subjects were enrolled and randomly assigned to 1 of 4 treatment groups, the placebo group, the pitavastatin 4-mg group, the pitavastatin 16-mg group, or the moxifloxacin 400-mg group; 171 subjects were included in the PD population and ECG analysis. The overall summary of findings are presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Pitavastatin (4 mg and 16 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
Pitavastatin 4 mg qd	16	2.6	(-0.4, 5.5)
Pitavastatin 16 mg qd	16	2.9	(-0.0, 5.9)
Moxifloxacin 400 mg*	3	11.3	(8.6, 14.1)

*Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 6 time points (Hours 1, 1.5, 2, 3, 4 and 5) is 7.4 ms.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

When we reviewed the protocol for this study in May 2007, we asked the sponsor to evaluate doses higher than 16 mg because we knew at that time that metabolic inhibition with cyclosporine increased C_{max} by 6.6-fold. It is not clear why the sponsor did not evaluate higher doses.

From QT-IRT Review of Protocol (22-May-2007):

“The proposed supratherapeutic dose is 16 mg qd. At steady state, this dose is expected to provide a 4-fold increase in plasma concentrations compared to the highest therapeutic dose of 4 mg qd. This increase in plasma concentrations covers increases due to moderate hepatic impairment (2.7-fold increase in C_{max}); Coadministration with a high-fat meal (65-80% increase in C_{max}); and gender differences (60% increase in C_{max} for females). This dose will not cover the increase due to metabolic inhibition with cyclosporine, where C_{max} increased 6.6-fold.

Doses higher than 16 mg have been administered safely to healthy volunteers and patients. We recommend you consider using a higher dose (e.g., 32 mg) for the supratherapeutic dose in your ‘thorough QT study’.”

2 PROPOSED LABEL

The sponsor proposed the following description of study results in the label. Our recommendations are shown using red strikeout font for deletions and blue font for insertions. We defer all final labeling decisions to the review division.

12.2 Pharmacodynamics

(b) (4)

[Redacted content]

3 BACKGROUND

3.1 MARKET APPROVAL STATUS

Kowa has obtained a marketing authorisation for pitavastatin in Japan, where it was launched onto the market as Livalo® Tablets in 2003. A marketing authorisation has subsequently also been obtained in Korea in 2005. Pitavastatin is regarded as an investigational medical product in Europe, North America, and China, where it is in phase III clinical development.

3.2 PRECLINICAL INFORMATION

From the IB

“The effects of pitavastatin on the cardiovascular and respiratory systems were examined in male dogs. Systolic, diastolic and mean blood pressure values were unchanged in all groups. However, heart rate (HR) was increased at 3 and 6 hours after dosing in the 10.0mg/kg group. No significant changes were observed in ECG parameters and arrhythmic events were not noted at any of the dose levels, no drug-induced changes in respiratory function were noted. HR was increased following treatment with pitavastatin at 10.0mg/kg, which represents a dose safety margin (body weight basis) of approximately 149-fold over a clinical dose of 4mg/day for a 60kg patient, and provides systemic exposure (C_{max}) 58 to 199 times that seen with a clinical dose of 4mg/day. Therefore, the relevance of this effect to the intended clinical dose of pitavastatin was considered minimal. In conclusion, pitavastatin had no clinically significant effects on electrocardiograms, blood pressure, respiratory function or clinical observations in dogs at dose levels of 0.1, 1.0, and 10mg/kg.

“The effects of pitavastatin and its main metabolite, pitavastatin lactone, on the hERG current were studied in the human ether-a-go-go-related gene transfected human embryonic kidney 293 cells (hERG-transfected HEK293 cells) using a whole-cell patch-clamp technique. The results indicated that pitavastatin and its main metabolite, pitavastatin lactone, do not affect the hERG current at concentrations up to 1×10^{-5} and 3×10^{-7} mol/L, respectively, which are approximately 80- and 4-fold greater, respectively, than the maximum exposures at the clinical dose of 4mg/day. Safety margins based upon the free fraction of pitavastatin and pitavastatin lactone were 16000- and 270-fold respectively, (assuming 0.5% and 1.38% free fraction values, respectively) greater than the maximum exposures at the clinical dose of 4mg/day.

“The effects of pitavastatin lactone on the action potential in isolated guinea pig papillary muscles were studied using a glass-electrode recording technique. No effects of pitavastatin lactone on the action-potential duration (APD) were observed at concentrations of 1×10^{-7} , 3×10^{-7} , or 1×10^{-6} mol/L. However, the high concentration of 3×10^{-6} mol/L significantly prolonged APD₆₀ and APD₉₀ (4.7% and 4.0%, from their pre-treatment values, respectively) without affecting APD₃₀, relative to vehicle group ($p < 0.01$). These results indicate that pitavastatin lactone had no effect on the action potentials of isolated guinea pig papillary muscles at concentrations up to 1×10^{-6} mol/L, which compared to clinical dosing at 4mg/day

represents a 13-fold greater concentration. The safety margin based on the free form of pitavastatin lactone is approximately 900-fold (assuming 1.38% free fraction value) greater than the maximum exposure at the clinical dose of 4mg/day. Pitavastatin lactone and E-4031 did not affect the resting membrane potential, action-potential amplitude, or dV/dt max at any concentration.”

Reviewer's comments: in vitro and in vivo data suggest that pitavastatin may not affect QT duration at the proposed therapeutic dose.

3.3 PREVIOUS CLINICAL EXPERIENCE

From the IB

“The safety, tolerability, and pharmacokinetics in plasma and urine of pitavastatin and its lactone have been investigated in four studies in Japanese (n=49) and Caucasian (n=80) healthy subjects. Pitavastatin 0.5 to 8mg were administered to Japanese and 1 to 64mg to Caucasian healthy subjects [1 to 4]. In studies in both Japanese and Caucasian healthy subjects, tablets were used with matching placebos.

“In 8 Japanese studies conducted in patients with hyperlipidemia, clinical adverse events occurred in 368 of 886 patients (42%) evaluated for safety. The studies comprised the phase II and phase III trials submitted for Japanese NDA approval. These adverse events were considered to be not drug-related in 318 patients. The most common individual adverse events were common cold (8.5%), abdominal pain (4.4%), pharyngitis (4.0%), coughing (4.0%), headache (2.8%), and back pain (2.8%). The most frequently reported laboratory events were increases in γ -GTP (12.2%), CK (10.2%), ALT (9.1%), AST (7.2%), and LDH (5.4%).

“Overall, 43 patients (4.9%) discontinued treatment because of adverse events; these were considered drug-related in 25 patients (2.8%). There were 21 serious adverse events; all were deemed unrelated to drug administration. In all cases, the serious events resolved or improved except for two patients, one with bladder carcinoma and one with cerebral infarction. No deaths occurred.

“Multiple once-daily administrations of pitavastatin 1 to 64mg for 2 weeks were well tolerated. No SAEs were reported. In the low dose ranging study general tolerability of pitavastatin 1, 2, 4, and 8mg was good. No SAEs were reported. Thirty AEs were reported in 11 subjects, 26 (in 8 subjects) on pitavastatin and 4 (in 3 subjects) on placebo. AEs were mainly gastrointestinal events (14/30 in 5 subjects) and headaches (8/30). There was no relationship between the occurrence/frequency of AEs and dose of pitavastatin. Relationship of AEs with pitavastatin was assessed either possible (23/30) or unlikely (7/30). Although pitavastatin was clinically well tolerated, some subjects had one or more out of range transaminase values considered not significant, except for two subjects receiving 1 and 8mg, respectively. These two subjects presented with transaminase increases (mainly ALAT) of 2.0- and 3.7-fold the upper limit of normal (ULN), respectively, both after seven days of multiple administrations. Subjects were not discontinued from the study but continued treatment and were followed up; the transaminase elevations resolved spontaneously.”

Reviewer's comments: No syncope, seizures, sudden death or ventricular arrhythmias were reported in these trials. There were no clinically relevant ECG changes reported.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Pitavastatin's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT had reviewed the protocol (under IND 60493 N104PN) prior to conducting this study. The sponsor submitted the study report for pitavastatin including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Randomized, Parallel Trial to Define the Electrocardiogram Effects of Pitavastatin Using a Clinical and a Supratherapeutic Dose Compared With Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough Corrected QT Interval Trial

4.2.2 Protocol Number

NK-104-1.34US

4.2.3 Study Dates

First volunteer enrolled: 15 June 2007

Last volunteer completed: 06 August 2007

4.2.4 Objectives

To determine the effect of pitavastatin on electrocardiogram (ECG) parameters with a focus on cardiac repolarization (QTc duration) at steady state at 2 dose levels (therapeutic [4 mg] and supratherapeutic [16 mg]) compared with placebo in healthy adult subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a double-blind, double-dummy, placebo-controlled, randomized, single-center, 4-arm, parallel study of healthy subjects. One hundred and seventy-four (174) subjects were enrolled and randomly assigned to 1 of 4 treatment groups: the placebo group, the pitavastatin 4-mg group, the pitavastatin 16-mg group, or the moxifloxacin 400-mg group.

On the morning of Days 1 through 4, all subjects received 4 tablets and 1 capsule, such that all tablets looked identical and all capsules looked identical. Subjects randomly assigned to receive pitavastatin or moxifloxacin received the required number of tablets and capsules to deliver active treatment, and the rest of the tablets and capsules were placebo. Subjects randomly assigned to receive placebo received all placebo tablets and

capsules. A combination of tablets, capsules, and overencapsulated tablets ensured blinding.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

This was a double-blind study. The placebo for pitavastatin was provided as a negative control and was identical to pitavastatin tablets. Capsules containing inactive material were provided as a placebo to the over-encapsulated moxifloxacin. The placebo capsule and the over-encapsulated moxifloxacin tablets were made to appear identical when prepared by the pharmacist.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were randomly assigned to 1 of 4 treatment groups and receive the following dose levels:

- Placebo group: No active ingredient
- Pitavastatin 4-mg group: One 4-mg dose of pitavastatin daily for 4 days
- Pitavastatin 16-mg group: One 16-mg dose of pitavastatin daily for 4 days
- Moxifloxacin 400-mg group: One 400-mg dose of moxifloxacin for 1 day.

Moxifloxacin were provided as one over-encapsulated moxifloxacin 400-mg tablet for one day. The placebo capsules were identical in appearance to the over-encapsulated moxifloxacin tablets. The dosing scheme is provided in Table 2.

Table 2: Dosing Scheme

Dosing Group	Day 1	Day 2	Day 3	Day 4
Placebo Group				
Placebo tablet	4	4	4	4
Pitavastatin tablet (4 mg)	0	0	0	0
Placebo capsule	1	1	1	1
Moxifloxacin-tablet-containing capsule	0	0	0	0
Pitavastatin 4 mg Group				
Placebo tablet	3	3	3	3
Pitavastatin tablet (4 mg)	1	1	1	1
Placebo capsule	1	1	1	1
Moxifloxacin-tablet-containing capsule	0	0	0	0
Pitavastatin 16 mg Group				
Placebo tablet	0	0	0	0
Pitavastatin tablet (4 mg)	4	4	4	4
Placebo capsule	1	1	1	1
Moxifloxacin-tablet-containing capsule	0	0	0	0
Moxifloxacin 400 mg Group				
Placebo tablet	4	4	4	4
Pitavastatin tablet (4 mg)	0	0	0	0
Placebo capsule	1	1	1	0
Moxifloxacin-tablet-containing capsule	0	0	0	1

Source: CSR Table 1 on Page 34.

4.2.6.2 Sponsor's Justification for Doses

Rationale for Pitavastatin Doses: The clinical dose of pitavastatin chosen for this study is 4 mg. A suprathreshold dose of pitavastatin is required to mimic the exposure in healthy subjects that may occur in the target population under the worst of circumstances (e.g., concomitant liver disease, presence of heart disease, taking more than the clinical dose prescribed) and to eliminate variables known to change ECG parameters (e.g., concomitant drugs, diseases). A 16 mg suprathreshold dose of pitavastatin per day was selected, which should have a very low probability of any AEs in healthy subjects receiving only 4 days of treatment. There is a low probability of AEs related to myotoxicity at this dosing level. In previous trials described above using doses up to 64 mg/day, no signs of myotoxicity were seen before 2 weeks of pitavastatin administration. It is therefore predicted that a 4-day course of pitavastatin at doses of 16 mg/day should provide a low risk of myotoxicity.

Rationale for Moxifloxacin Positive Control Dose: Oral moxifloxacin (400 mg) was chosen as the positive control to demonstrate assay sensitivity since this drug is known to prolong the duration of the QTc by approximately 5 to 10 milliseconds (ms), an effect that is close to that which represents the threshold of regulatory concern. Under the current study conditions, the 400 mg moxifloxacin dose is expected to produce a placebo-corrected change from Baseline in the QTc of 5 to 10 ms using a time-matched analysis."

(Source: Page 434 of CSR NK-104-1.34US)

Reviewer's comment: Sponsor's choice of 16 mg as a suprathreshold dose did not appear to cover the highest expected exposure of pitavastatin. It is expected that the highest exposure of pitavastatin (i.e., worst-case scenario) would be through metabolic

inhibition by cyclosporine or presence of significant hepatic compromise. In Study NK-104-20, steady-state C_{max} and AUC_{0-24} rose significantly by 6.6-times and 4.6-times, respectively, when pitavastatin was coadministered with cyclosporine, a potent organic anion transporting polypeptides (OATP) OATP1B1 inhibitors, compared with administration of pitavastatin alone. However, cyclosporine will be contraindicated in the presence of pitavastatin. Increased exposures were also observed in subjects with hepatic impairment. The increase in subjects with Child-Pugh B was more than twice but less than 4-fold. Increased exposures were also observed in subjects with moderate renal impairment and subjects on hemodialysis. However, the increases were less than twice.

The proposed clinical dosing regimen is 1, 2, and 4 mg QD. Currently, the maximum tested dose is 64 mg after single dose (study 1.19) and 64 mg QD for 14 days (study 2.09) in phase 1 trials with no SAEs related to drug reported. In phase 2 trials with the dose range of 1 mg to 64 mg daily, myalgia or severe myotoxicity were observed at doses of 8 mg and above. Linear pharmacokinetics is established over the dose range of 1 to 64 mg QD.

4.2.6.3 Instructions with Regard to Meals

The meal schedule was kept constant throughout the trial relative to the ECG (extracted) time points. The first meal began after the 4-hour blood draw (12:00 noon, 4 hours after dosing) and was completed within 30 minutes to allow 1.5 hours before collection of the 6-hour ECG. The ECGs were extracted from 15 minutes after dosing for 10 minutes. The evening meal was scheduled for 10 hours after dosing (6:00 in the evening) and was completed in 30 minutes to allow 1.5 hours before the 12-hour ECG.
(Source: Page 453 of CSR NK-104-1.34US)

4.2.6.4 ECG and PK Assessments

The table of study assessments is shown in Appendix 6.2.

Reviewer's comments: Based on the median T_{max} of 1-1.8 hour for pitavastatin and 2.5 hour for pitavastatin lactone, and the terminal half-life of ~8 hours for both pitavastatin and pitavastatin lactone, the sampling schedules for ECGs and PK are adequate.

4.2.6.5 Baseline

Time-matched baselines were used in the study.

4.2.7 ECG Collection

All ECG measurements were made by cardiologists blinded to study medication of the subjects. All QT intervals were measured using the median representative beat of the entire 10-second recordings. The RR interval employed was the average of all the RR intervals contained within the same time frame. All the QT and RR intervals were recognized by computer and adjusted appropriately by certified cardiovascular technologists and 100% visually validated or manually adjusted by US Board Certified cardiologists. The primary lead for the ECG evaluations was lead II. The secondary choice was lead V5. Lead III was used in the cases of limb lead reversal since in that instance it was the same as lead II. Interpretation included the gambit of morphological repolarization patterns of the T-U wave complex with special attention to the categories

of early after depolarizations. T-U wave morphological changes were reported and described in a detailed manner so that they could be characterized as belonging to 1 of 4 categories ranging from a normal U-wave variant to an early after depolarization. The number and percentage of tracings that fell into each of the categories were reported with an assessment of severity.

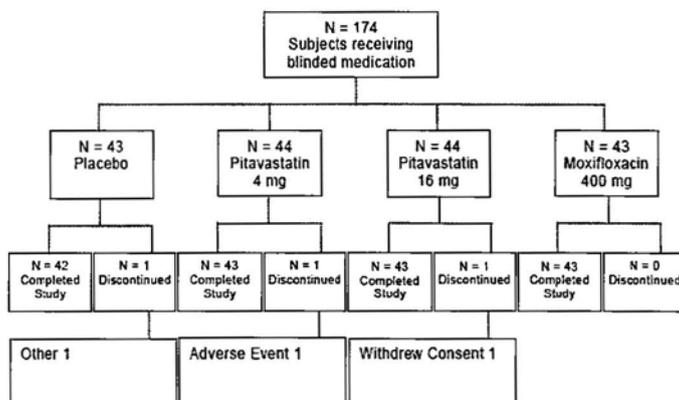
4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

The study enrolled 174 subjects, between 18-45 years of age, 80 males and 94 females with a mean BMI of 18-30 kg/m² in the study; 171 subjects were included in the PD population and ECG analysis.

There were no deaths or SAEs in the study. One subject in the pitavastatin 4-mg group discontinued because of the AE of conjunctivitis.

Disposition of study subjects



4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the time-matched change from baseline in QTc based on an individually corrected QT interval (QTcI). The individual correction factors for the calculations of QTcIs were obtained through a linear regression of QT on RR in log scales using baseline data. The primary endpoint was analyzed by the analysis of covariance that included the effects of treatment group and the corresponding baseline. A separate analysis was performed for each scheduled ECG time and included data from all 4 treatment groups. A one-sided 95% upper confidence bound was placed on the difference between each pitavastatin treatment group mean and the placebo mean for each scheduled ECG time.

Analysis comparing moxifloxacin with placebo was performed to assess assay sensitivity at hours 1 to 6 only. A one-sided 95% lower confidence bound was placed on the difference between the moxifloxacin 400-mg group and placebo group in time-matched difference from baseline for each scheduled ECG time point.

Sponsor's results are presented in Table 3. The largest mean difference from the placebo group in the QTcI for the pitavastatin 4-mg group was 2.57 ms at 16 hours after dosing, and the largest upper limit of the one-sided 95% CI was 5.52 ms (16 hours after dosing). The largest mean difference from the placebo group in the QTcI for the pitavastatin 16-mg group was 2.93 ms (16 hours after dosing), and the largest upper limit of the CI was 5.87 ms (16 hours after dosing). All one-sided upper limits of the 95% CI of mean difference from placebo were well below 10 ms. The null hypothesis was rejected for the primary analysis, and it was concluded that the mean increase in QTcI over placebo was less than 10 ms.

Assay sensitivity analysis results are presented in Table 4. In the positive-control group (moxifloxacin 400-mg group), the one-sided lower limit of the 95% CI of the mean difference from the placebo group in the QTcI was greater than 5 ms at 1.5 to 4 hours after dosing.

Reviewer's comments: We confirmed the sponsor's conclusions of lack of QTc effect for the study drug and establishment of assay sensitivity in our independent analyses presented in Section 5.2.

Table 3: Mean Difference from Placebo in Time-Matched Difference from Baseline in QTcI for Each Pitavastatin Dose Adjusted for Baseline QTcI

Hours After Dosing	Pitavastatin 4 mg - Placebo Difference	Pitavastatin 4 mg - Placebo (95% Upper Confidence Boundary)	Pitavastatin 16 mg - Placebo Difference	Pitavastatin 16 mg - Placebo (95% Upper Confidence Boundary)
0.25	0.29	3.22	0.11	3.04
0.5	-0.99	1.81	1.17	3.97
1	-1.55	1.15	-1.27	1.44
1.5	0.73	3.76	0.64	3.67
2	0.42	3.13	0.46	3.17
3	1.04	3.75	1.78	4.49
4	2.47	5.43	0.56	3.53
6	0.50	3.59	-0.05	3.05
8	-1.13	1.92	-0.01	3.06
10	0.28	3.37	-0.24	2.89
12	1.34	4.12	2.60	5.41
16	2.57	5.52	2.93	5.87
24	1.26	3.82	0.21	2.75

Source: Sponsor's CSR Table 7 on Page 61.

Table 4: Time-Matched Difference from Baseline in QTcI for Moxifloxacin vs. Placebo and Mean Difference from Placebo Adjusted for Baseline QTcI

Hours After Dosing	Moxifloxacin 400 mg			Placebo			Difference	95% Lower Confidence Boundary
	n	Mean	Standard Error	n	Mean	Standard Error		
1	43	-0.76	1.14	41	-6.16	1.17	5.39	2.68
1.5	43	1.85	1.28	41	-7.13	1.31	8.98	5.95
2	43	5.48	1.15	42	-5.68	1.16	11.16	8.46
3	43	5.06	1.15	42	-6.28	1.16	11.34	8.63
4	43	6.37	1.25	41	-4.83	1.28	11.20	8.24
6	43	4.15	1.31	42	-3.10	1.33	7.25	4.16

Source: Sponsor's CSR Table 9 on Page 63.

4.2.8.2.2 Categorical Analysis

The categorical analyses were done using descriptive methods. The categories of the ECG intervals exceeding predefined upper limits were as follows:

- Absolute QTc interval prolongation
 - QTc interval >450 ms
 - QTc interval >480 ms
 - QTc interval >500 ms
- Change from baseline in QTc interval
 - QTc interval increases from baseline >30 ms
 - QTc interval increases from baseline >60 ms

Table 5 presents the number of subjects with QTcI greater than 450 ms. One subject in the pitavastatin 4-mg group and 2 subjects in the pitavastatin 16-group had a QTcI of greater than 450 ms, while 2 subjects in the placebo group had a QTcI greater than 450 ms. Six subjects in the moxifloxacin 400-mg group had a QTcI greater than 450 ms. No subject had a QTcI of greater than 480 ms.

Table 5: Number of Subjects with a QTcI Greater Than 450 Milliseconds

Hours After Dosing	Placebo			Pitavastatin 4 mg			Pitavastatin 16 mg			Moxifloxacin 400 mg		
	N	n	%	N	n	%	N	n	%	N	n	%
0.25	42	0	0.0	43	1	2.3	43	1	2.3	43	0	0.0
0.5	42	0	0.0	43	0	0.0	43	0	0.0	43	0	0.0
1	42	0	0.0	43	1	2.3	43	0	0.0	43	1	2.3
1.5	42	0	0.0	43	1	2.3	43	0	0.0	43	1	2.3
2	42	0	0.0	43	1	2.3	43	1	2.3	43	3	7.0
3	42	0	0.0	43	1	2.3	43	1	2.3	43	4	9.3
4	42	1	2.4	43	1	2.3	43	0	0.0	43	4	9.3
6	42	0	0.0	43	1	2.3	43	0	0.0	43	0	0.0
8	42	0	0.0	43	1	2.3	42	0	0.0	41	2	4.9
10	42	0	0.0	43	1	2.3	42	1	2.4	43	2	4.7
12	42	1	2.4	43	1	2.3	43	0	0.0	43	1	2.3
16	42	1	2.4	43	1	2.3	43	1	2.3	43	1	2.3
24	42	0	0.0	43	0	0.0	43	0	0.0	43	0	0.0
Anytime	42	2	4.8	43	1	2.3	43	2	4.7	43	6	14.0

Source: Sponsor's CSR Table 10 on Page 65.

No subject had an increase in the time-matched difference from baseline in the QTcI of greater than 30 ms.

4.2.8.3 Safety Analysis

A total 36 subjects (20.7%) reported treatment-related AEs (i.e., considered possibly or probably treatment related). The pitavastatin 16-mg group had a higher percentage of subjects with treatment-related AEs (27.3%) than either the placebo group (18.6%) or the pitavastatin 4-mg group (15.9%). In the moxifloxacin 400-mg group, 20.9% of subjects reported treatment-related AEs.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK population included 86 subjects with sufficient plasma concentration data. Mean plasma concentrations of pitavastatin and pitavastatin lactone versus time on Day 4 by treatment group are presented in Figure 1 and Figure 1, respectively.

Figure 1: Mean Plasma Concentration of Pitavastatin versus Time

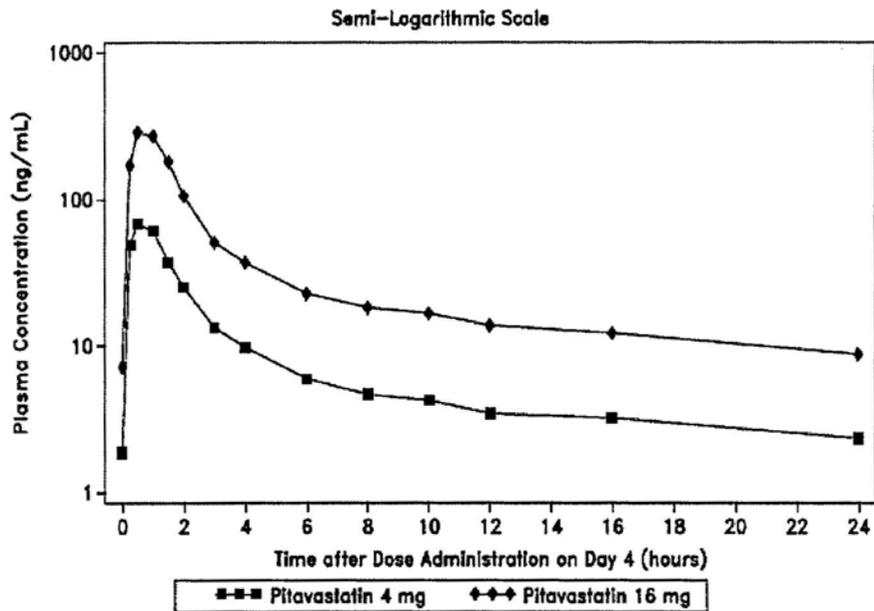
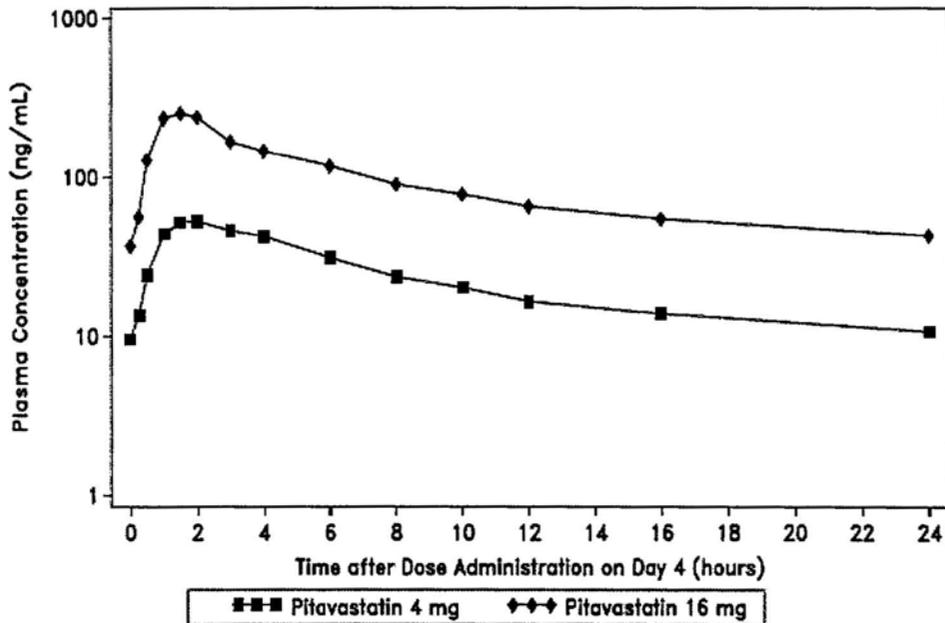


Figure 2: Mean Plasma Concentration of Pitavastatin Lactone versus Time



The plasma pitavastatin lactone concentrations in both the pitavastatin 4-mg and 16-mg groups were observed to reach their 2 highest concentrations at 1.5 and 2 hours and gradually declined from 3 to 24 hours. At 24 hours, there were measurable concentrations of pitavastatin lactone in samples from all subjects. Summaries of the PK parameters for pitavastatin and pitavastatin lactone by treatment group are presented in Table 6 and Table 7, respectively.

Table 6: Pitavastatin Pharmacokinetic Parameters by Treatment Group.

Pharmacokinetic Parameter Mean (SD)	Treatment Group	
	Pitavastatin 4 mg N = 43	Pitavastatin 16 mg N = 43
AUC _{0-τ} (ng·h/mL)	204.701 (77.6669)	839.913 (372.7108)
C _{max} (ng/mL)	86.732 (45.0277)	371.319 (166.0392)
T _{max} (h) ^a	0.580 (0.33, 2.08)	0.580 (0.33, 1.67)
K _{el} (1/h)	0.04162 (0.018817) ^b	0.04521 (0.013706) ^c
t _{1/2} (h)	22.517 (16.5861) ^b	17.536 (8.4326) ^c
V _d /F (L)	630.802 (385.7460) ^b	522.417 (257.5533) ^c
CL/F (L/h)	22.367 (8.3227)	22.146 (8.0184)

^a Median (minimum, maximum)^b N = 23^c N = 30**Table 7: Pitavastatin Lactone Pharmacokinetic Parameters by Treatment Group.**

Pharmacokinetic Parameter Mean (SD)	Treatment Group	
	Pitavastatin 4 mg N = 43	Pitavastatin 16 mg N = 43
AUC _{0-τ} (ng·h/mL)	540.498 (164.8471)	2170.388 (744.9316)
C _{max} (ng/mL)	58.429 (16.6621)	290.290 (139.2213)
T _{max} (h) ^a	2.080 (1.08, 4.12)	1.580 (0.58, 2.28)
K _{el} (1/h)	0.04013 (0.014312) ^b	0.04095 (0.011894) ^c
t _{1/2} (h)	20.691 (12.4423) ^b	18.527 (6.0951) ^c

^a Median (minimum, maximum)^b N = 28^c N = 34

Total and peak exposure to pitavastatin lactone also increased proportionally with increased dose between the 4-mg and 16-mg groups. The exposures increased approximately 4-fold with the 4-fold increase in dose. The median T_{max} for pitavastatin lactone was similar in the 2 treatment groups, 2.1 hours and 1.6 hours for the pitavastatin 4-mg and 16-mg groups, respectively. As with pitavastatin, the t_{1/2} of pitavastatin lactone was estimated for only those subjects where the correlation coefficient (r²) of the regression analysis of the elimination phase was 0.9000 or greater. The mean t_{1/2} for pitavastatin lactone was similar in the 2 treatment groups, approximately 20.7 hours and 18.5 hours for the pitavastatin 4-mg (28 subjects) and 16-mg (34 subjects) groups, respectively.

The pitavastatin lactone AUC_{0-τ} was approximately 2.5-fold that of the AUC_{0-τ} of pitavastatin in both the pitavastatin 4-mg and 16-mg groups. The C_{max} was slightly lower for pitavastatin lactone than for pitavastatin in both the pitavastatin 4-mg and 16-mg

groups. The T_{max} of pitavastatin lactone was longer by approximately 1 to 1.5 hours when compared with pitavastatin in both the pitavastatin 4-mg and 16-mg groups. The K_{el} and $t_{1/2}$ for pitavastatin and pitavastatin lactone were similar in both the pitavastatin 4-mg and 16-mg groups.”

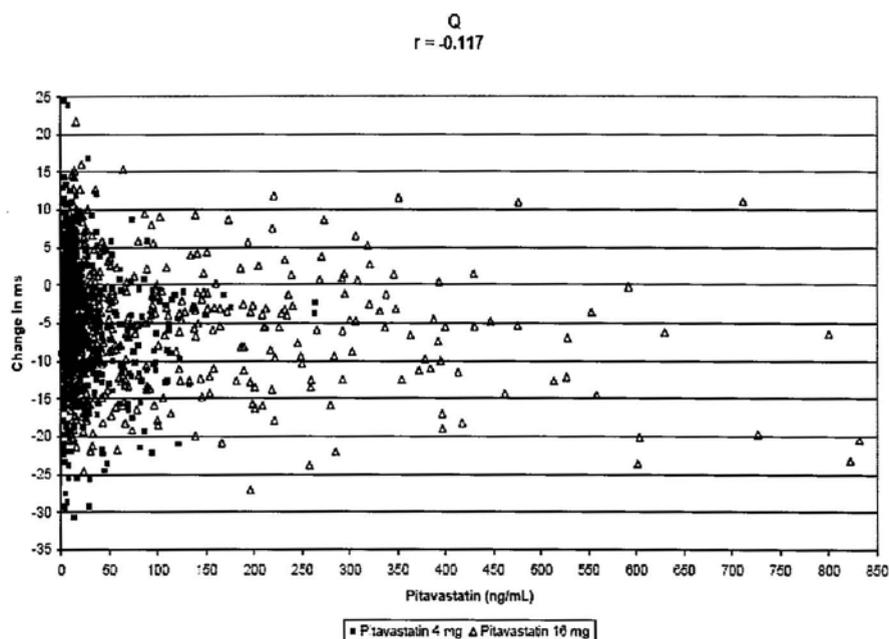
(Source: Section 11.4 in CSR NK-10401.34US)

Reviewer’s comments: The exposure in terms of both C_{max} and AUC_{tau} is approximately dose-proportional for both pitavastatin and pitavastatin lactone over the dose range of 4 and 16 mg of pitavastatin.

4.2.8.4.2 Exposure-Response Analysis

The PD (ECG) population included the 171 subjects with available ECG data at Baseline and Day 4.

Figure 3: Time-Matched Difference from Baseline in QTcI versus Plasma Pitavastatin Concentration.



The correlation coefficient (r) for the linear regression of the time-matched difference from Baseline in QTcI versus plasma pitavastatin concentration was -0.117 . Correlation coefficients of the linear regression of the time-matched difference from Baseline in the QTcI, QTcB, and QTcF versus the plasma concentration of pitavastatin ranged from -0.155 to -0.114 and the correlation coefficients of the time-matched difference from Baseline in the QTcI, QTcB, and QTcF versus plasma concentration of pitavastatin lactone ranged from -0.044 to -0.041 , indicating little to no relationship between the difference from time-matched Baseline in the QTc and plasma concentration for either pitavastatin or pitavastatin lactone.

Reviewer’s comments: The sponsor did not use placebo correction in the analysis. The plots of $\Delta\Delta QTc$ vs. drug concentrations are presented in section 5.

5 REVIEWERS' ASSESSMENT

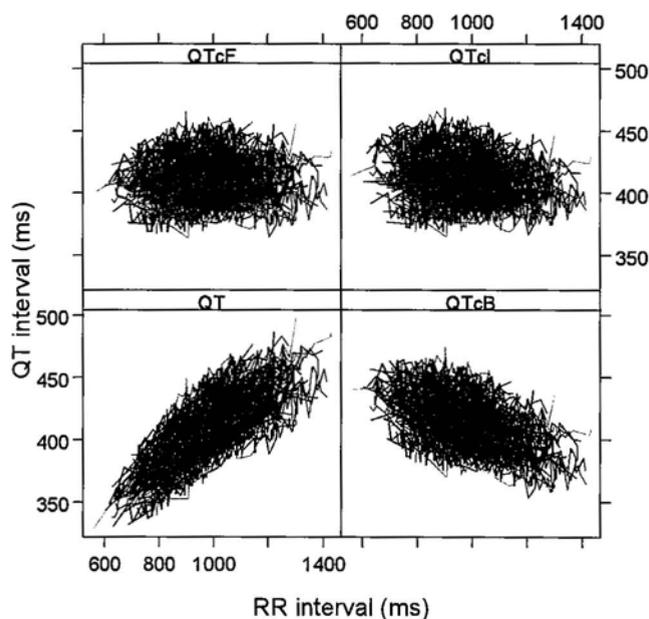
5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcI) and RR. We used the mean sum of squared slopes (MSSS) as the criterion based on the post-dose data. Baseline values were excluded in the validation. The smaller this value is, the better the correction. Based on the results listed in Table 8 and Figure 4, it appears that QTcI is the best correction method. Therefore, we used QTcI as the correction method for our analysis.

Table 8: Mean Sum of Squared Slopes for Different QT Correction Methods (Post Dose Only)

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Pitavastatin 4 mg	43	0.0043	43	0.0011	43	0.0010
Pitavastatin 16 mg	43	0.0057	43	0.0017	43	0.0011
Moxifloxacin 400 mg	43	0.0051	43	0.0013	43	0.0012
Placebo	42	0.0050	42	0.0009	42	0.0011
All	171	0.0050	171	0.0013	171	0.0011

Figure 4: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 Analysis of Study Drug Effect and Assay Sensitivity

We used mixed model to analyze the Δ QTcI effect for each time point. The model includes treatment and baseline values as covariates. The analysis results are presented in Table 9. The largest upper bounds of the 2-sided 90% CI for the mean difference between 4 mg pitavastatin and placebo, and between 16 mg pitavastatin and placebo are 5.5 ms and 9.9 ms, respectively. The results agree with the sponsor's findings of lack of effect on QTc prolongation for the study drug.

For the moxifloxacin group, the largest lower bound of the unadjusted 90% confidence interval is 11.3 ms. By considering Bonferroni multiple endpoint adjustment for 6 time points (Hours 1, 1.5, 2, 3, 4, and 5), the largest lower bound is 7.4 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI at Each Time Point by Treatment

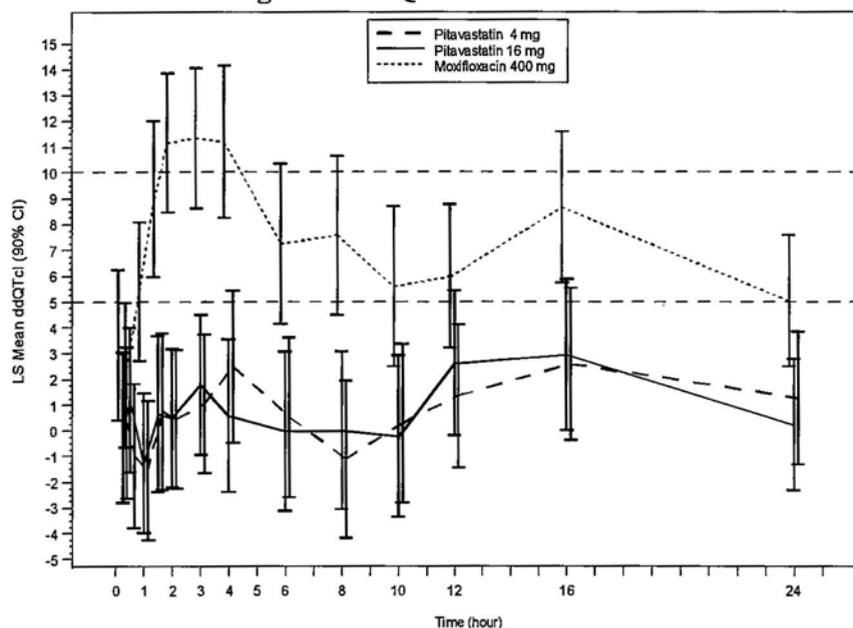
Time (hrs)	Treatment Group									
	Placebo	Pitavastatin 4 mg			Pitavastatin 16 mg			Moxifloxacin 400 mg		
		Δ QTcI	$\Delta\Delta$ QTcI		Δ QTcI	$\Delta\Delta$ QTcI		Δ QTcI	$\Delta\Delta$ QTcI	
LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	
0.25	-6.0	-5.7	0.3	(-2.6, 3.2)	-5.9	0.1	(-2.8, 3.0)	-2.7	3.3	(0.4, 6.2)
0.5	-7.2	-8.2	-1.0	(-3.8, 1.8)	-6.0	1.2	(-1.6, 4.0)	-5.1	2.2	(-0.7, 5.0)
1	-6.2	-7.7	-1.6	(-4.3, 1.2)	-7.4	-1.3	(-4.0, 1.4)	-0.8	5.4	(2.7, 8.1)
1.5	-7.1	-6.4	0.7	(-2.3, 3.8)	-6.5	0.6	(-2.4, 3.7)	1.8	9.0	(6.0, 12.0)
2	-5.7	-5.3	0.4	(-2.3, 3.1)	-5.2	0.5	(-2.2, 3.2)	5.5	11.2	(8.5, 13.9)
3	-6.3	-5.2	1.0	(-1.7, 3.7)	-4.5	1.8	(-0.9, 4.5)	5.1	11.3*	(8.6, 14.1)
4	-4.8	-2.4	2.5	(-0.5, 5.4)	-4.3	0.6	(-2.4, 3.5)	6.4	11.2	(8.2, 14.2)
6	-3.1	-2.6	0.5	(-2.6, 3.6)	-3.1	-0.0	(-3.1, 3.1)	4.2	7.3	(4.2, 10.3)
8	-4.1	-5.2	-1.1	(-4.2, 1.9)	-4.1	-0.0	(-3.1, 3.1)	3.5	7.6	(4.5, 10.7)
10	-3.9	-3.6	0.3	(-2.8, 3.4)	-4.1	-0.2	(-3.4, 2.9)	1.7	5.6	(2.5, 8.7)
12	-3.3	-2.0	1.3	(-1.4, 4.1)	-0.7	2.6	(-0.2, 5.4)	2.7	6.0	(3.2, 8.8)
16	-7.5	-4.9	2.6	(-0.4, 5.5)	-4.6	2.9	(-0.0, 5.9)	1.2	8.6	(5.7, 11.6)
24	-4.3	-3.1	1.3	(-1.3, 3.8)	-4.1	0.2	(-2.3, 2.8)	0.7	5.0	(2.5, 7.6)

*The lower bound of the 90% CI is 7.4 ms after Bonferroni adjustment for 6 time points (Hours 1, 1.5, 2, 3, 4, and 5).

5.2.1.2 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcI for different treatment groups.

Figure 5: $\Delta\Delta$ QTcI Time Course



5.2.1.3 Categorical Analysis

Table 10 presents the categorical analysis results for QTcI. No subjects had a QTcI above 480 ms. None of the subjects had a QTcI change from baseline that was above 30 ms.

Table 10: Categorical Analysis of QTcI

Treatment Group	N	QTcI ≤ 450 ms	450 ms < QTcI ≤ 480 ms
Baseline	171	156 (91.2%)	15 (8.8%)
Pitavastatin 4 mg	43	42 (97.7%)	1 (2.3%)
Pitavastatin 16 mg	43	41 (95.3%)	2 (4.7%)
Moxifloxacin 400 mg	43	37 (86.0%)	6 (14.0%)
Placebo	42	40 (95.2%)	2 (4.8%)

5.2.2 PR Analysis

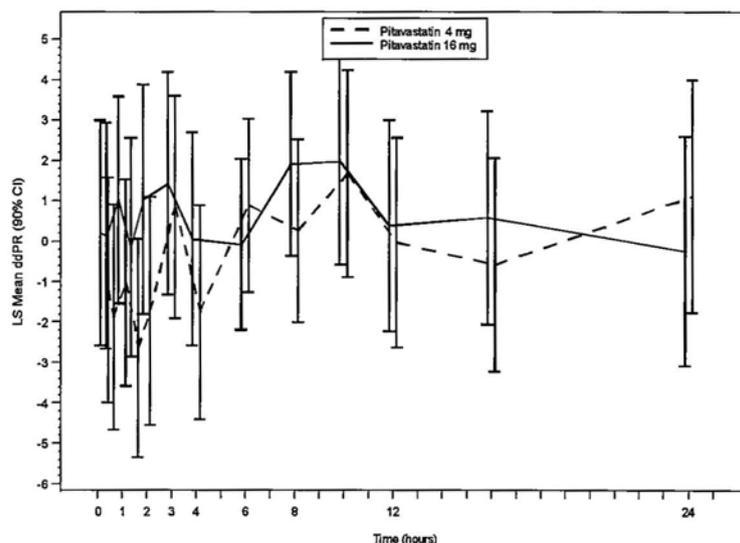
The same statistical analysis used for QTcI was performed for PR intervals. The point estimates and the 90% confidence intervals are presented in Table 11 and also shown in

Figure 6. The largest upper limits of 90% CI for the PR mean differences between 4 mg pitavastatin and placebo, and between 16 mg pitavastatin and placebo are 4.2 ms and 4.6 ms, respectively.

Table 11: Analysis Results of Δ PR and $\Delta\Delta$ PR for Study Drug

Time (hrs.)	Treatment Group						
	Placebo	Pitavastatin 4 mg			Pitavastatin 16 mg		
		Δ PR	$\Delta\Delta$ PR		Δ PR	$\Delta\Delta$ PR	
LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	
0.25	0.2	-1.0	-1.2	(-4.0, 1.6)	0.4	0.2	(-2.6, 3.0)
0.5	1.1	-0.7	-1.9	(-4.7, 0.9)	1.3	0.1	(-2.7, 2.9)
1	0.0	-1.0	-1.0	(-3.6, 1.5)	1.0	1.0	(-1.5, 3.6)
1.5	-0.4	-3.0	-2.7	(-5.3, 0.0)	-0.5	-0.2	(-2.9, 2.5)
2	-0.3	-2.1	-1.7	(-4.5, 1.1)	0.7	1.0	(-1.8, 3.9)
3	-1.0	-0.2	0.8	(-1.9, 3.6)	0.4	1.4	(-1.3, 4.2)
4	-0.4	-2.2	-1.8	(-4.4, 0.9)	-0.4	0.0	(-2.6, 2.7)
6	0.2	1.0	0.9	(-1.3, 3.0)	0.1	-0.1	(-2.2, 2.0)
8	-2.2	-1.9	0.3	(-2.0, 2.5)	-0.3	1.9	(-0.4, 4.2)
10	-2.3	-0.7	1.7	(-0.9, 4.2)	-0.4	2.0	(-0.6, 4.6)
12	-1.4	-1.4	-0.0	(-2.6, 2.6)	-1.0	0.4	(-2.2, 3.0)
16	-0.3	-0.9	-0.6	(-3.2, 2.0)	0.3	0.6	(-2.1, 3.2)
24	-0.1	1.0	1.1	(-1.8, 4.0)	-0.3	-0.2	(-3.1, 2.6)

Figure 6: $\Delta\Delta$ PR Time Course



Categorical analysis results of PR intervals are presented in Table 12. Only one subject (Subject 2027) in the study drug group (pitavastatin 4 mg) had a PR of marginally above 200 ms (201.6 ms) at 3 hours post-dose. This subject's time-matched baseline was 188.6 ms.

Table 12: Categorical Analysis of PR

Treatment Group	N	PR < 200 ms	PR ≥200 ms
Baseline	171	169 (98.8%)	2 (1.2%)
Pitavastatin 4 mg	43	42 (97.7%)	1 (2.3%)
Pitavastatin 16 mg	43	43 (100%)	0 (0.0%)
Moxifloxacin 400 mg	43	42 (97.7%)	1 (2.3%)
Placebo	42	40 (95.2%)	2 (4.8%)

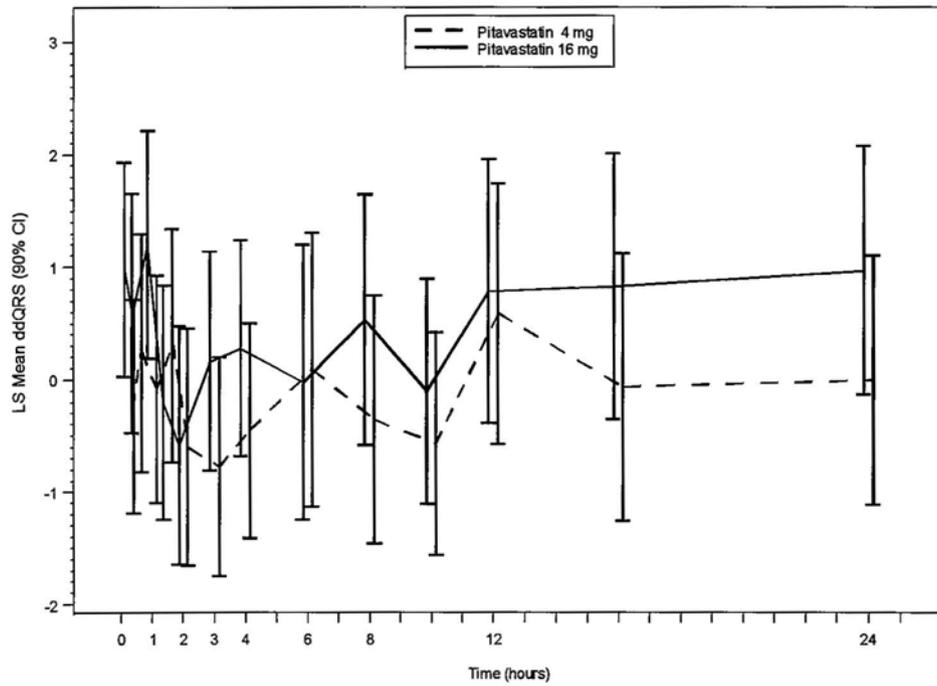
5.2.3 QRS Analysis

The same statistical analysis used for QTcI was performed for QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 13 and also shown in Figure 7. The largest upper limits of 90% CI for the QRS mean differences between 4 mg pitavastatin and placebo, and between 16 mg pitavastatin and placebo are 1.7 ms and 2.2 ms, respectively. There were no subjects whose QRS intervals were 120 ms or above.

Table 13: Analysis Results of ΔQRS and ΔΔQRS for Study Drug

Time (hrs.)	Treatment Group						
	Placebo	Pitavastatin 4 mg			Pitavastatin 16 mg		
		ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS	
	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0.25	-0.3	-0.5	-0.2	(-1.2, 0.7)	0.7	1.0	(0.0, 1.9)
0.5	-0.3	-0.1	0.2	(-0.8, 1.3)	0.3	0.6	(-0.5, 1.6)
1	0.1	0.0	-0.1	(-1.1, 0.9)	1.3	1.2	(0.2, 2.2)
1.5	-0.2	0.1	0.3	(-0.7, 1.3)	-0.4	-0.2	(-1.3, 0.8)
2	0.0	-0.6	-0.6	(-1.7, 0.5)	-0.5	-0.6	(-1.6, 0.5)
3	0.2	-0.6	-0.8	(-1.7, 0.2)	0.4	0.2	(-0.8, 1.1)
4	0.4	-0.1	-0.4	(-1.4, 0.5)	0.6	0.3	(-0.7, 1.2)
6	0.7	0.7	0.1	(-1.1, 1.3)	0.6	-0.0	(-1.3, 1.2)
8	-0.1	-0.5	-0.4	(-1.5, 0.7)	0.4	0.5	(-0.6, 1.6)
10	-0.2	-0.8	-0.6	(-1.6, 0.4)	-0.3	-0.1	(-1.1, 0.9)
12	-0.4	0.2	0.6	(-0.6, 1.7)	0.4	0.8	(-0.4, 2.0)
16	-0.6	-0.7	-0.1	(-1.3, 1.1)	0.2	0.8	(-0.4, 2.0)
24	0.3	0.3	-0.0	(-1.1, 1.1)	1.2	1.0	(-0.1, 2.1)

Figure 7: $\Delta\Delta$ QRS Time Course



The categorical analysis results of QRS intervals are presented in Table 14. Only one subject (Subject 1009) in the study drug group (pitavastatin 16 mg) had at least a QRS of marginally above 120 ms. The time points when this subject's QRS intervals were above 120 and his/her corresponding baselines are presented in Table 15.

Table 14: Categorical Analysis of QRS Intervals

Treatment Group	N	QRS < 120 ms	QRS \geq 120 ms
Baseline	171	170 (99.4%)	1 (0.6%)
Pitavastatin 4 mg	43	43 (100%)	0 (0.0%)
Pitavastatin 16 mg	43	42 (97.7%)	1 (2.3%)
Moxifloxacin 400 mg	43	43 (100%)	0 (0.0%)
Placebo	42	42 (100%)	0 (0.0%)

Table 15: Listing of Subjects Whose QRS Intervals Were Above 120 ms

Subject ID	Treatment	Time (hrs)	QRS at Baseline	QRS at Post-Dose	QRS Change
(b) (4)	Pitavastatin 16 mg	(b) (4)			
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				
	Pitavastatin 16 mg				

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta\text{QTcF}$ and pitavastatin concentrations is visualized in Figure 8 with no evident exposure-response relationship. The relationship between $\Delta\Delta\text{QTcF}$ and pitavastatin lactone concentrations is visualized in Figure 9 with no evident exposure-response relationship.

Figure 8: $\Delta\Delta\text{QTcF}$ versus Pitavastatin Concentration

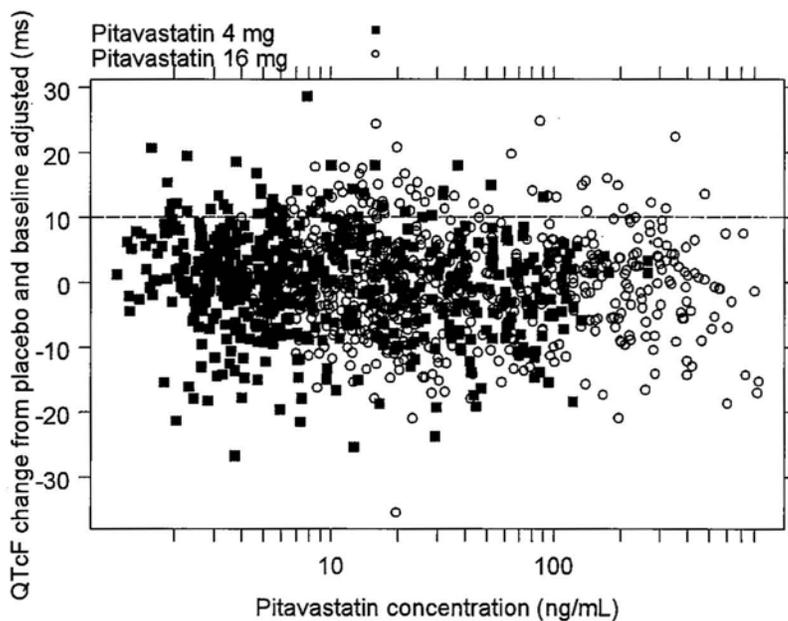
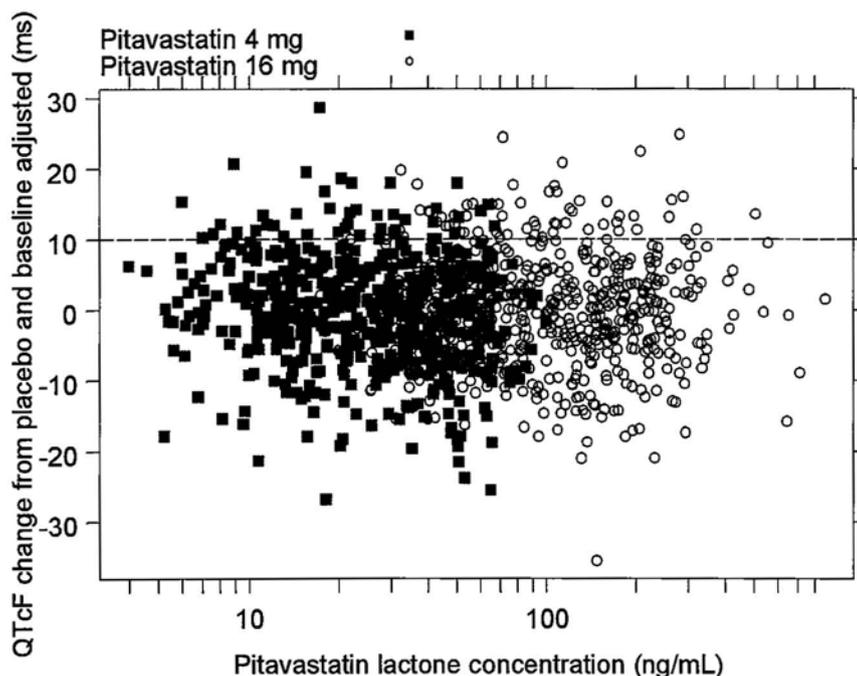


Figure 9: $\Delta\Delta$ QTcF versus Pitavastatin Lactone Concentration



5.4 CLINICAL ASSESSMENTS

Safety Assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study

ECG Assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 100% of the ECGs were annotated in the primary lead II, with less than 0.04% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable. Neither pitavastatin 4 mg nor 16 mg changed QTc duration.

PR and QRS Interval

Pitavastatin did not change significantly PR and QRS intervals. The largest upper limits of 90% CI for the PR mean differences between aleglitazar 4 mg and placebo and pitavastatin 16 mg and placebo are 4.2 ms and 4.6 ms, respectively. The largest upper limits of 90% CI for the QRS mean differences between pitavastatin 4 mg and placebo and pitavastatin 16 mg and placebo are 1.7 ms and 2.2 ms, respectively. Only one subject (Subject 2027) in the study drug group (pitavastatin 4 mg) had a PR of marginally above 200 ms (201.6 ms) at 3 hours post-dose. There are no subjects who experienced absolute QRS interval greater than 120 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	1mg, 2mg and 4mg once a day																																																																																																																																																																																																							
Maximum tolerated dose	<p>MTD or NOAEL levels in humans have not been rigorously evaluated.</p> <p>In the NK-104-1.01 trial, doses of 1-24 mg were administered daily for up to 14 days with no SAEs reported. In the 1.19 trial, doses of 24-64 mg/day were administered with a single SAE of hepatitis, deemed unrelated to study drug. There were a number of minor increases in LFTs and CPK, none of which were clinically significant or non-reversible.</p> <p>There are 5 Phase 2 trials with the dose range of 1 mg to 64 mg daily. Two of them (HEC-NK98402N-NK-104.2.02 and HEC-NKN98403N-NK-104.2.03) investigated the dose response from 1 mg to 8 mg daily and confirmed a good tolerability. In Phase 2 trial (NK-104-2.09) with doses of pitavastatin higher than the therapeutic dose of 4 mg (8, 16, 32 and 64 mg once daily), 7 cases of severe myotoxicity were observed (characterized by myalgia, marked elevations in CK of greater than 10 times the ULN, myoglobinemia, and myoglobinuria) and were considered related to the study drug (1 of 103 patients [16 mg], 3 of 34 patients [32 mg], and 3 of 33 patients [64 mg]). The events occurred within 2 to 4 weeks of treatment and occurred when high doses of pitavastatin were administered without titration from lower dose levels. While CK elevations with or without symptoms were not seen at the 8 mg dose in 206 patients treated for up to 12 weeks in the fore-mentioned Phase 2 trials, 2 of 214 patients taking 8 mg pitavastatin in another Phase 2 study conducted in Europe and Canada reported myalgia with CK elevations above 10 times the ULN and myoglobinemia 2 to 4 weeks after randomization. The trial medication in these patients was discontinued and the patients fully recovered within 2 weeks.</p>																																																																																																																																																																																																							
Principal adverse events	<p>Principal adverse events are liver function test elevations such as elevated ALT and AST and muscle-related adverse events such as myalgia and CK elevation. These are common adverse events among statins.</p> <p>TEAEs Reported by $\geq 1\%$ of Subjects (and More Than one Subject) assessed as Treatment-Related by the investigator are summarized by number (%) and by randomized dose in 2 pivotal Phase 3 trials (NK-104-301 and NK-104-302) and its extension study (NK-104-307)</p> <table border="1"> <thead> <tr> <th rowspan="2">MedDRA SOC/Preferred Term No. (%) of Subjects</th> <th colspan="4">NK-104-301 (Core)</th> <th colspan="4">NK-104-302 (Core)</th> <th>NK-104-307 (Extension)</th> </tr> <tr> <th>Pita 2mg (N=110)</th> <th>Ator 10 mg (N=102)</th> <th>Pita 4 mg (N=100)</th> <th>Ator 20 mg (N=103)</th> <th>Pita 2 mg (N=111)</th> <th>Simv 20 mg (N=197)</th> <th>Pita 4 mg (N=320)</th> <th>Simv 40 mg (N=118)</th> <th>Pita 4 mg (N=155)</th> </tr> </thead> <tbody> <tr> <td>No. of Days Exposure (Mean)</td> <td>86.4</td> <td>87.2</td> <td>85.7</td> <td>86.6</td> <td>83.4</td> <td>81.8</td> <td>83.8</td> <td>84.0</td> <td>141.5</td> </tr> <tr> <td>No. (%) of Subjects with any Treatment-related TEAE</td> <td>20 (18.2)</td> <td>3 (2.9)</td> <td>16 (15.5)</td> <td>2 (1.9)</td> <td>52 (46.7)</td> <td>15 (14.0)</td> <td>42 (13.1)</td> <td>9 (8.2)</td> <td>162 (12.0)</td> </tr> <tr> <td>Cardiac Disorders</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>3 (2.7)</td> <td>1 (0.9)</td> <td>1 (0.3)</td> <td>0</td> <td>1 (0.6)</td> </tr> <tr> <td>Gastrointestinal Disorders</td> <td>6 (5.5)</td> <td>1 (1.0)</td> <td>6 (6.0)</td> <td>0</td> <td>17 (15.3)</td> <td>6 (5.6)</td> <td>10 (3.1)</td> <td>4 (3.4)</td> <td>43 (32.6)</td> </tr> <tr> <td>Constipation</td> <td>4 (3.6)</td> <td>1 (1.0)</td> <td>3 (3.0)</td> <td>0</td> <td>1 (0.9)</td> <td>1 (0.9)</td> <td>3 (0.9)</td> <td>0</td> <td>4 (3.1)</td> </tr> <tr> <td>Nausea</td> <td>1 (0.9)</td> <td>0</td> <td>0</td> <td>0</td> <td>1 (0.9)</td> <td>2 (1.9)</td> <td>1 (0.3)</td> <td>1 (0.9)</td> <td>12 (9.0)</td> </tr> <tr> <td>Diarrhea</td> <td>0</td> <td>0</td> <td>1 (1.0)</td> <td>0</td> <td>4 (3.6)</td> <td>1 (0.9)</td> <td>2 (0.6)</td> <td>1 (0.9)</td> <td>4 (3.1)</td> </tr> <tr> <td>General Disorders & Admin. 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Site Conditions	0	1 (1.0)	2 (2.0)	0	9 (8.1)	6 (5.6)	1 (0.3)	0	6 (4.5)	Fatigue	0	0	0	0	6 (5.4)	0	1 (0.3)	0	1 (0.8)	Investigations	6 (5.5)	0	3 (3.0)	0	6 (5.4)	1 (0.9)	4 (1.3)	1 (0.9)	62 (46.6)	ALT increased	1 (0.9)	0	1 (1.0)	0	4 (3.6)	0	2 (0.6)	1 (0.9)	17 (12.9)	Blood CK increased	3 (2.7)	0	0	0	1 (0.9)	1 (0.9)	1 (0.3)	0	40 (30.3)	Musculoskeletal & Connective Tissue Disorders	6 (5.5)	0	5 (5.0)	2 (1.9)	14 (12.6)	5 (4.7)	7 (2.2)	2 (1.8)	32 (24.5)	Myalgia	5 (4.5)	0	5 (5.0)	1 (1.0)	7 (6.3)	2 (1.9)	4 (1.3)	2 (1.8)	21 (16.0)	Nervous System Disorders	5 (4.5)	0	4 (4.0)	0	7 (6.3)	3 (2.8)	9 (2.8)	1 (0.9)	14 (10.7)	Headache	2 (1.8)	0	2 (2.0)	0	4 (3.6)	2 (1.9)	5 (1.6)	0	6 (4.5)	Psychiatric Disorders	3 (2.7)	1 (1.0)	0	0	3 (2.7)	1 (0.9)	2 (0.6)	0	9 (6.8)	Skin & Subcutaneous Tissue Disorders	1 (0.9)	0	0	0	10 (9.0)	0	2 (0.6)	0	16 (12.2)
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Highlights of Clinical Pharmacology

	Single Dose	64mg					
	Multiple Dose	64mg once a day for 14 days in Phase I studies					
Maximum dose tested	In the 2.09 study referenced above in the MTD section, the durations of exposure by suprathreshold dose are noted in the table below:						
		Placebo (N = 53)	NK-104 (QD)				Atorva 80 mg (N = 96)
			8 mg (N = 103)	16 mg (N = 103)	32 mg (N = 34)	64 mg (N = 33)	
	Exposure (Days) ^a	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	1	0	0	0	2 (5.9)	1 (3.0)	0
	2 – 14	2 (3.8)	5 (4.9)	9 (8.7)	17 (50.0)	23 (69.7)	3 (3.1)
	15 – 28	13 (24.5)	31 (30.1)	30 (29.1)	15 (44.1)	9 (27.3)	30 (31.3)
	29 – 42	16 (30.2)	24 (23.3)	31 (30.1)	0	0	22 (22.9)
	43 – 56	18 (34.0)	34 (33.0)	26 (25.2)	0	0	28 (29.2)
	57 – 70	4 (7.5)	9 (8.7)	7 (6.8)	0	0	12 (12.5)
N	53	103	103	34	33	95	
Mean (SD)	37.7 (14.1)	37.2 (15.1)	34.0 (15.8)	13.2 (7.8)	11.0 (6.4)	38.1 (15.4)	
Median	36.0	35.0	31.0	12.5	10.0	37.0	
Range	6 to 61	4 to 65	2 to 64	1 to 27	1 to 23	7 to 69	
^a Date of the Last Dose – Date of the First Dose +1							
Atorva = atorvastatin (QD); QD = once daily.							

Highlights of Clinical Pharmacology

Exposures Achieved at Maximum Tested Dose	Single Dose	NK-104: C _{max} : 785.08 ng/ml (42.2), AUC _{0-inf} : 2030.10 ng.h/ml (41.5) NK-104 lactone: C _{max} : 415.71 ng/ml (25.9), AUC _{0-inf} : 4059.10 ng.h/ml (25.6) ^{CLN018} (%CV)																			
	Multiple Dose	After 14-day multiple dose: NK-104: C _{max} : 807.65 ng/ml (37.9), AUC ₀₋₂₄ : 2547.30 ng.h/ml (42.5) NK-104 lactone: C _{max} : 446.50 ng/ml (33.1), AUC ₀₋₂₄ : 4420 ng.h/ml (33.1) ^{CLN018} (%CV)																			
Range of linear PK	1 mg once a day – 64mg once a day ^{CLN017, CLN018}																				
Accumulation at steady state	Accumulation after 14-day multiple dose is summarized below																				
	<table border="1"> <thead> <tr> <th>Daily dose (qd)</th> <th>AUC₀₋₂₄ Day 14/AUC₀₋₂₄ Day 1</th> </tr> </thead> <tbody> <tr> <td>1mg¹⁾</td> <td>1</td> </tr> <tr> <td>2mg¹⁾</td> <td>1.3</td> </tr> <tr> <td>4mg¹⁾</td> <td>1.5</td> </tr> <tr> <td>8mg¹⁾</td> <td>1.3</td> </tr> <tr> <td>16mg¹⁾</td> <td>1.3</td> </tr> <tr> <td>24mg¹⁾</td> <td>1.3</td> </tr> <tr> <td>32mg²⁾</td> <td>1.2</td> </tr> <tr> <td>48mg²⁾</td> <td>1.3</td> </tr> <tr> <td>64mg²⁾</td> <td>1.3</td> </tr> </tbody> </table>		Daily dose (qd)	AUC ₀₋₂₄ Day 14/AUC ₀₋₂₄ Day 1	1mg ¹⁾	1	2mg ¹⁾	1.3	4mg ¹⁾	1.5	8mg ¹⁾	1.3	16mg ¹⁾	1.3	24mg ¹⁾	1.3	32mg ²⁾	1.2	48mg ²⁾	1.3	64mg ²⁾
Daily dose (qd)	AUC ₀₋₂₄ Day 14/AUC ₀₋₂₄ Day 1																				
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1) CLN017, 2) CLN018																					
%CV was not calculated																					

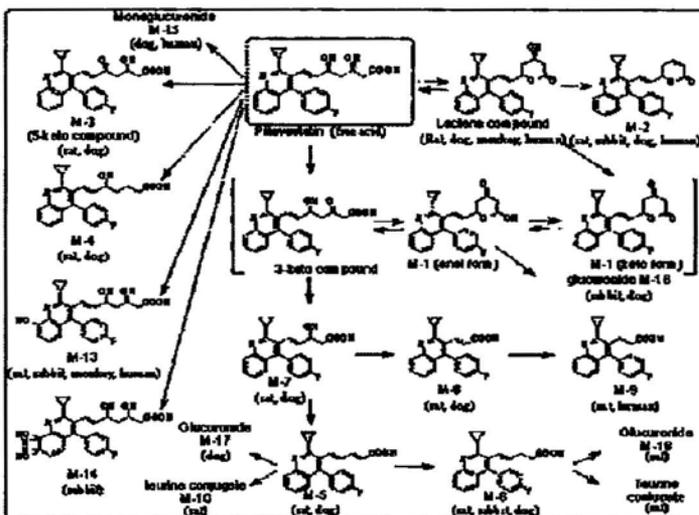
Highlights of Clinical Pharmacology

Summary of ^{14}C study of NK-104 32mg single dose was conducted. The major metabolite of NK-104 in plasma was its lactone. M-13 was speculated as one of metabolites from in vitro microsome study and measured in this study but M-13 was a minor metabolite. In vitro studies suggested some other metabolites but one investigational study which analyzed human plasma samples showed that the plasma level of the other metabolites are also marginal compared to the parent and its lactone.

Parameter	Radioactivity	NK-104	NK-104 lactone	8-OH-NK-104 (M-13)
C_{max} (ng/ml) ¹⁾	1189	857.7	274.2	2.99
T_{max} (hr) ¹⁾	0.5	0.5	0.75	1.25
AUC_0-t (ng.hr/ml) ¹⁾	10288	2991	1818	12
k_z (hr ⁻¹) ¹⁾	0.0103	0.0485	0.0428	0.1782
$t_{1/2}$ (hr) ¹⁾	87.8	14.3	16.2	3.9
AUC (ng.hr/ml) ¹⁾	12289	3175	2074	16
CL/F (ml/min) ¹⁾	-	183	-	-
V_d/F (litres) ¹⁾	-	228	-	-
IC 50 of HMG-CoA inhibition (nM) ^{2),3)}	-	6.8	12	3.5

1) CLN027, 2) PHAD01, 3) PHAD26

Metabolites



Highlights of Clinical Pharmacology

Absorption	Absolute/Relative Bioavailability	Absolute bioavailability is 51% CLN042 %CV was not calculated for this study																																																					
	Tmax	<p>Tmax (hr) on Day 14 in the 14-day multiple dose studies are below.</p> <table border="1" data-bbox="607 442 1096 753"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">NK-104</th> <th colspan="2">NK-104 lactone</th> </tr> <tr> <th>median</th> <th>min-max</th> <th>median</th> <th>min-max</th> </tr> </thead> <tbody> <tr> <td>1mg¹⁾</td> <td>1.8</td> <td>1.0-2.0</td> <td>2.5</td> <td>2.0-4.0</td> </tr> <tr> <td>2mg¹⁾</td> <td>1.5</td> <td>1.0-2.0</td> <td>1.8</td> <td>1.5-4.0</td> </tr> <tr> <td>4mg¹⁾</td> <td>1</td> <td>0.5-2.0</td> <td>2.5</td> <td>1.0-4.0</td> </tr> <tr> <td>8mg¹⁾</td> <td>1.3</td> <td>0.5-3.0</td> <td>2.5</td> <td>1.0-3.0</td> </tr> <tr> <td>16mg¹⁾</td> <td>1.8</td> <td>1.0-2.0</td> <td>2.5</td> <td>1.5-4.0</td> </tr> <tr> <td>24mg¹⁾</td> <td>1.5</td> <td>1.0-3.0</td> <td>2.5</td> <td>1.0-4.0</td> </tr> <tr> <td>32mg²⁾</td> <td>1.25</td> <td>1.00-3.00</td> <td>2</td> <td>1.00-4.00</td> </tr> <tr> <td>48mg²⁾</td> <td>1.25</td> <td>1.00-2.00</td> <td>3</td> <td>2.00-4.00</td> </tr> <tr> <td>64mg²⁾</td> <td>1</td> <td>1.00-1.50</td> <td>3</td> <td>1.50-4.00</td> </tr> </tbody> </table> <p>1) CLN017, 2) CLN018</p>		NK-104		NK-104 lactone		median	min-max	median	min-max	1mg ¹⁾	1.8	1.0-2.0	2.5	2.0-4.0	2mg ¹⁾	1.5	1.0-2.0	1.8	1.5-4.0	4mg ¹⁾	1	0.5-2.0	2.5	1.0-4.0	8mg ¹⁾	1.3	0.5-3.0	2.5	1.0-3.0	16mg ¹⁾	1.8	1.0-2.0	2.5	1.5-4.0	24mg ¹⁾	1.5	1.0-3.0	2.5	1.0-4.0	32mg ²⁾	1.25	1.00-3.00	2	1.00-4.00	48mg ²⁾	1.25	1.00-2.00	3	2.00-4.00	64mg ²⁾	1	1.00-1.50	3
	NK-104			NK-104 lactone																																																			
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C _{max} (ng/mL)	30	73.3733	1.4045	0.9464, 2.0552	33	64.10	1.5668	1.0758, 2.8705	52.5765																																																																																	
AUC _{0-∞} (ng·h/mL)	30	190.2320	1.7337	1.2333, 2.4173	33	109.5627	1.7514	1.2640, 2.5391	105.7229																																																																																	
AUC _{0-t} (ng·h/mL)	24	232.7430	1.8625	1.1987, 2.8940	24	124.2897	1.7549	1.1867, 2.7148	124.9619																																																																																	
CL _F (mL/min)	24	286.4590	0.5359	0.3455, 0.8343	24	297.2346	0.5571	0.3654, 0.8427	533.4959																																																																																	

Highlights of Clinical Pharmacology

		Ref.: CLN049																																																																						
Extrinsic Factors	Drug interactions	<p>Summary of drug-drug interaction of pitavastatin</p> <table border="1"> <thead> <tr> <th>Co-administered drug</th> <th>Dose regimen</th> <th>Change in AUC^{0-∞}</th> <th>Change in C_{max}^{0-∞}</th> </tr> </thead> <tbody> <tr> <td>Fenofibrate</td> <td>Pitavastatin 4 mg QD - fenofibrate 160 mg QD for 7 days</td> <td>*1.18</td> <td>†1.11</td> </tr> <tr> <td>Gemfibrozil</td> <td>Pitavastatin 4 mg QD - gemfibrozil 600 mg BID for 7 days</td> <td>*1.45</td> <td>†1.31</td> </tr> <tr> <td>Cyclosporine</td> <td>Pitavastatin 2 mg QD for 6 days - cyclosporine 2 mg/kg on Day 6</td> <td>†4.67</td> <td>†6.61</td> </tr> <tr> <td>Grapefruit Juice</td> <td>Pitavastatin 2 mg single dose on Day 3 - grapefruit juice for 4 days</td> <td>*1.15</td> <td>†0.88</td> </tr> <tr> <td rowspan="2">Ezetimibe</td> <td rowspan="2">Pitavastatin 2 mg QD - ezetimibe 10 mg for 7 days</td> <td>pitavastatin</td> <td>0.98</td> <td>1.00</td> </tr> <tr> <td>ezetimibe</td> <td>*1.09</td> <td>†1.02</td> </tr> <tr> <td rowspan="2">Warfarin</td> <td rowspan="2">Individualized maintenance dose of warfarin (2-7 mg) + pitavastatin 4 mg QD for 9 days</td> <td>R-warfarin</td> <td>1.07</td> <td>1.03</td> </tr> <tr> <td>S-warfarin</td> <td>1.06</td> <td>1.03</td> </tr> <tr> <td>Digoxin</td> <td>Pitavastatin 4 mg QD - digoxin 0.25 mg for 7 days</td> <td>pitavastatin</td> <td>*1.04</td> <td>†0.91</td> </tr> <tr> <td rowspan="2">Rifampicin</td> <td rowspan="2">Pitavastatin 4 mg QD - rifampicin 600 mg QD for 5 days</td> <td>pitavastatin</td> <td>*1.29</td> <td>†2.00</td> </tr> <tr> <td>rifampicin</td> <td>0.85</td> <td>0.82</td> </tr> <tr> <td>Enalapril</td> <td>Pitavastatin 4 mg QD - enalapril 20 mg daily for 5 days</td> <td>pitavastatin</td> <td>*1.06</td> <td>†0.93</td> </tr> <tr> <td rowspan="2">Atazanavir</td> <td rowspan="2">Pitavastatin 4 mg QD - atazanavir 300 mg daily for 5 days</td> <td>pitavastatin</td> <td>*1.31</td> <td>†1.60</td> </tr> <tr> <td>atazanavir</td> <td>1.06</td> <td>1.13</td> </tr> <tr> <td>Itraconazole</td> <td>Pitavastatin 4 mg single dose on Day 4 - itraconazole 200 mg daily for 5 days</td> <td>*0.77</td> <td>†0.75</td> </tr> <tr> <td>Erythromycin</td> <td>Pitavastatin 4 mg single dose on Day 4 - erythromycin 500 mg 4 times daily for 6 days</td> <td>†2.82†</td> <td>†3.62†</td> </tr> </tbody> </table> <p>† Clinically Significant [see Dosage and Administration (2) and Warnings and Precautions (5)] * Values are for pitavastatin unless otherwise noted</p>	Co-administered drug	Dose regimen	Change in AUC ^{0-∞}	Change in C _{max} ^{0-∞}	Fenofibrate	Pitavastatin 4 mg QD - fenofibrate 160 mg QD for 7 days	*1.18	†1.11	Gemfibrozil	Pitavastatin 4 mg QD - gemfibrozil 600 mg BID for 7 days	*1.45	†1.31	Cyclosporine	Pitavastatin 2 mg QD for 6 days - cyclosporine 2 mg/kg on Day 6	†4.67	†6.61	Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 - grapefruit juice for 4 days	*1.15	†0.88	Ezetimibe	Pitavastatin 2 mg QD - ezetimibe 10 mg for 7 days	pitavastatin	0.98	1.00	ezetimibe	*1.09	†1.02	Warfarin	Individualized maintenance dose of warfarin (2-7 mg) + pitavastatin 4 mg QD for 9 days	R-warfarin	1.07	1.03	S-warfarin	1.06	1.03	Digoxin	Pitavastatin 4 mg QD - digoxin 0.25 mg for 7 days	pitavastatin	*1.04	†0.91	Rifampicin	Pitavastatin 4 mg QD - rifampicin 600 mg QD for 5 days	pitavastatin	*1.29	†2.00	rifampicin	0.85	0.82	Enalapril	Pitavastatin 4 mg QD - enalapril 20 mg daily for 5 days	pitavastatin	*1.06	†0.93	Atazanavir	Pitavastatin 4 mg QD - atazanavir 300 mg daily for 5 days	pitavastatin	*1.31	†1.60	atazanavir	1.06	1.13	Itraconazole	Pitavastatin 4 mg single dose on Day 4 - itraconazole 200 mg daily for 5 days	*0.77	†0.75	Erythromycin	Pitavastatin 4 mg single dose on Day 4 - erythromycin 500 mg 4 times daily for 6 days	†2.82†	†3.62†
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Highlights of Clinical Pharmacology

Expected High Clinical Exposure Scenario	<p>With the exception of coadministration of cyclosporine or presence of significant hepatic compromise, it is anticipated that a four fold increase in C_{max} or AUC would be predictive of the maximum exposure. This will take into account accidental double-dosing by a patient, and variation in inter-patient bioavailability. Linear pharmacokinetics have been demonstrated for NK-104, and therefore no additional accumulation is expected at higher doses. The investigated supratherapeutic dose of 4X highest clinical dose was in line with the E14 recommendations.</p> <p>In the submitted draft labeling in NDA, a concomitant therapy with cyclosporine is a contraindication.</p>
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6.2 TABLE OF STUDY ASSESSMENTS

ASSESSMENTS PERFORMED	STUDY PERIOD																	
	Screening		Baseline		Single-Dose Double-Blind Treatment													
	Days -30 to -3	Day -2	Day -1	Days 1 to 3	Day 4													Day 5
					Time after drug administration (hours)													
				0	0.25	0.5	1	1.5	2	3	4	6	8	10	12	16	24	
Informed consent	X																	
Physical examination	X	X																X ^a
Medical history	X	X																
Baseline signs and symptoms	X																	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication history	X																	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements	X		X	X	X								X				X	X
Height and weight	X	X ^b																X ^b
Safety ECG at site	X		X	X ^c														X
PD 12-lead ECG ^d			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests/Urinalysis	X	X																X ^e
Serum pregnancy test	X	X																X
Urine drug screen	X	X																
PK blood draw ^f					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization ^g				X														

ASSESSMENTS PERFORMED	STUDY PERIOD																	
	Screening		Baseline		Single-Dose Double-Blind Treatment													
	Days -30 to -3	Day -2	Day -1	Days 1 to 3	Day 4													Day 5
					Time after drug administration (hours)													
				0	0.25	0.5	1	1.5	2	3	4	6	8	10	12	16	24	
Dose administration (fasted) ^h				X	X													
Admission/Discharge		X																X ⁱ

ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic

^a The physical examination was performed anytime after the ECG on Day 5.

^b Only weight was measured.

^c On Days 1, 2, and 3, the safety ECGs were obtained 2 to 3 hours after dosing.

^d The PD 12-lead ECGs were retrieved from H-12 (digital flash card placed in on the morning of on Days -1 and 4). The PD 12-lead ECGs were collected at approximately 2-minute intervals within a 10-minute window (i.e., 5 ECGs were collected for each time point) at 13 selected time points on Day -1 (Baseline) and on Day 4. The PD ECGs were collected at the following time points: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8, 10, 12, 16, and 24 hours, starting at approximately 7:30 to 10:00 in the morning of Day -1. The PD ECGs were collected again at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing on Day 4.

^e The clinical laboratory tests and urinalysis were collected anytime after the safety ECG on Day 5. If a subject withdrew from the study before Day 5, clinical laboratory tests and urinalysis were collected at the time of discontinuation.

^f The PK blood samples were collected before dosing (trough level) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing on Day 4. Blood samples were collected from all subjects on all treatments to maintain comparable study conditions and the study blind, but were only analyzed for the active pitavastatin groups.

^g Randomization was performed at the end of Day -1, or on Day 1 immediately before dosing.

^h Doses were administered according to the assigned dosing group. The following 4 dosing groups were used:

Placebo group: 4 placebo tablets and 1 placebo capsule on Days 1 to Day 4

Pitavastatin 4 mg group: 3 placebo tablets, one 4 mg pitavastatin tablet, and 1 placebo capsule on Days 1 to Day 4

Pitavastatin 16 mg group: four 4 mg pitavastatin tablets and 1 placebo capsule on Day 1 to Day 4

Moxifloxacin 400 mg group: 4 placebo tablets and 1 placebo capsule on Days 1 to 3, and 4 placebo tablets and one 400 mg moxifloxacin capsule on Day 4.

ⁱ Subjects were discharged any time after all study procedures had been completed on Day 5.

Source: Protocol NK-104-1.34US

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/s/

Joanne Zhang
5/14/2009 01:59:30 PM
BIOMETRICS

Lihan K Yan
5/14/2009 02:01:39 PM
BIOMETRICS

Monica Fiszman
5/15/2009 10:05:24 AM
PHARMACOLOGIST

Ping Ji
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UNKNOWN

Christine Garnett
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Norman Stockbridge
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