Table 46 Summary of Rhabdomyolysis Cases in Pitavastatin Phase 2 Trials

Subject No.	Description of Event	MedDRA Preferred Term	Age	Sex	Duration of Treatment (Days)	Reaction Onset (Days on Study)	Serious Y/N	Pita Dose (mg)	Other Details Including Laboratory Values (CK ULN = 120 IU/L)	Does Event Meet Definition or Condition Set? - Y/N					
										Study Rhabdo-myolysis Definition	Hosp.	CK levels (IU/L)			ACC/ AHA & NLA Definition
												>1,000	>5,000	>10,000	
Study NKS104/A2204															
0002/ 00013	pain in limb, blood CK increased, myoglobinaemia	rhabdo-myolysis	58	F	30	27	Y	8	CK: 2540 IU/L (22 fold ULN), plasma myoglobin: 698 mcg/L (ULN 90), urine myoglobin: 7.1 mcg/L (ULN 1.0), AST 69 U/L (ULN 22) and ALT 74 U/L (ULN 25). BUN and creatinine in normal range. Recovered.	Y	N	Y	N	N	N
0070/ 00013	myalgia suspicious of rhabdomyolysis, blood CK increased, liver function tests NOS abnormal	rhabdo-myolysis	74	F	31	30	Y	8	CK 1986 IU/L (16 fold ULN), plasma myoglobin 91 mcg/L (ULN 90), urine myoglobin not measured. AST and ALT elevated no values. Treated with silymarin and Hepa-Merz, used for liver protection. BUN and creatinine in normal range. Recovered.	N	N	Y	N	N	N
Study NK-104-209															
24 005	pain in limbs, elevation in CK	rhabdo-myolysis	70	M	25	25	N	16	Peak CK 26,360 IU/L (220 fold ULN), myoglobin 7888 ng/mL sample Day 26, peak ALT 250 U/L and AST 683 U/L. BUN and creatinine were high at baseline and creatinine did not increase. Recovered	Y	N	Y	Y	Y	N

Subject No.	Description of Event	MedDRA Preferred Term	Age	Sex	Duration of Treatment (Days)	Reaction Onset (Days on Study)	Serious Y/N	Pita Dose (mg)	Other Details Including Laboratory Values (CK ULN = 120 IU/L)	Does Event Meet Definition or Condition Set? - Y/N					
										Study Rhabdo-myolysis Definition	Hosp.	CK levels (IU/L)			ACC/ AHA & NLA Definition
												>1,000	>5,000	>10,000	
Study NK-104-209 cont.															
23 004	myalgia aggravated, rhabdomyolysis, myoglobulinuria, AST and ALT increased	rhabdo-myolysis	63	F	15	11	Y	32	CK 3821 IU/L (32 fold ULN) and myoglobin 7812 ng/mL, creatinine increase from 1.4 to 1.7, AST 74 U/L (ULN 22) and ALT 56 U/L (ULN 25). Recovered.	N	Y	Y	N	N	Y
26 002	myalgia, rhabdo-myolysis, blood CK increased, AST and ALT increased	rhabdo-myolysis	75	M	26	26	Y	32	CK 80,000 IU/L (666 fold ULN), AST 1151 U/L (ULN 22) and ALT 459 U/L (ULN 25). Fatigue and brownish coloured urine. Recovered.	Y	Y	Y	Y	Y	N
37 001	muscle pain and weakness	rhabdo-myolysis	58	F	21	21	Y	32	Peak CK 62,496 IU/L (522 fold ULN) on day 26, AST 944 U/L (ULN 22) and ALT 308 U/L (ULN 25). Treated with i.v. hydration and ciprofloxacin for concurrent urinary tract infection. Recovered.	Y	Y	Y	Y	Y	N

Subject No.	Description of Event	MedDRA Preferred Term	Age	Sex	Duration of Treatment (Days)	Reaction Onset (Days on Study)	Serious Y/N	Pita Dose (mg)	Other Details Including Laboratory Values (CK ULN = 120 IU/L)	Does Event Meet Definition or Condition Set? - Y/N					
										Study Rhabdo-myolysis Definition	Hosp.	CK levels (IU/L)			ACC/ AHA & NLA Definition
												>1,000	>5,000	>10,000	
02 008	muscle aches, rhabdomyolysis, blood CK increased, AST and ALT increased, renal failure NOS	rhabdo-myolysis	58	F	19	16	Y	64	Peak CK 21210 IU/L (176 fold ULN) on day 23, AST 988 U/L (ULN 22) and ALT 549 U/L (ULN 25). Peak BUN 70 mg/dL and creatinine 6.2 mg/dL on Day 25. BUN returned to 18 mg/dL and creatinine to 1.4 mg/dL. Recovered.	Y	Y	Y	Y	Y	Y
Study NK-104-209															
45 008	muscle pain in limbs and myalgia in hands, haematuria and proteinuria	rhabdo-myolysis	56	M	23	21	Y	64	CK 65,800 IU/L (548 fold ULN), AST 836 U/L (ULN 22) and ALT 763 U/L (ULN 25). No evidence of renal dysfunction. Recovered.	Y	Y	Y	Y	Y	N
45 018	myopathy, fatigue	rhabdo-myolysis	42	F	21	21	Y	64	CK 31,997 IU/L (266 fold ULN), AST 445 U/L (ULN 22) and ALT 635 U/L (ULN 25). Greenish urine. Treated with forced hydration and furosemide. Recovered.	Y	Y	Y	Y	Y	N

Source: [Module 5.3.5.1.3, CSR] and [Module 5.3.5.1.4, CSR]
MedDRA: Medical Dictionary for Regulatory Activities; No.: number; CK: creatine kinase; AST aspartate transaminase; ALT: alanine transaminase; ULN: upper limit of normal; BUN: blood urea nitrogen; Hosp: hospitalisation, ACC/AHA & NLA: American College of Cardiology/ American Heart Association and National Lipid Association; Y/N: yes/no, NOS: not otherwise specified.

Upon request by this clinical reviewer, on January 26, 2009, and March 11, 2009, the applicant submitted additional data on subjects who had rhabdomyolysis in the development program.

Table 47 Demographics of Nine Subjects with Rhabdomyolysis- Group 1

	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)
Rhabdomyolysis	0	0	0	2	1	3	3
Sex							
Males	0	0	0	0	1	1	1
Females	0	0	0	2	0	2	2
Age							
Mean (SD)	0	0	0	66 (11.3)	70	69(8.5)	52 (8.7)
Median	0	0	0	66	-	69	56
Range	0	0	0	58, 74	70, 70	63, 75	42, 58
Hypertension							
Yes	0	0	0	1	0	2	1
No	0	0	0	1	1	1	2
Diabetes							
Yes	0	0	0	0	1	0	0
No	0	0	0	2	0	3	3
Baseline Creatinine							

	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)
Mean (SD)	0	0	0	1.05 mg/dL (0.07)	1.05 mg/dL (-)	1.23 mg/dL (0.25)	1.03 mg/dL (0.231)
Median	0	0	0	1.05 mg/dL	1.5 mg/dL	1.20 mg/dL	0.90 mg/dL
Range	0	0	0	1.0, 1.1	1.5, 1.5	1.0, 1.5	0.93,1.3

Source: Pitavastatin Study Report, Table 1.3.1.

There were slightly more women than men with rhabdomyolysis. Otherwise, the patients who developed rhabdomyolysis were similar to the overall randomized population in terms of age, history of hypertension, and diabetes (see demographics of all randomized patients, section 6.1.2). Mean baseline creatinine was within the normal laboratory parameters; however the maximum value was slightly elevated at 1.5 mg/dL. Creatinine clearance values were not collected by the applicant.

From the clinical trial data the frequency of rhabdomyolysis appears to be dose-related at doses ≥8 mg. It may be as important to identify a plasma concentration of pitavastatin and/or its lactone metabolite above which the likelihood of rhabdomyolysis increases. Furthermore, the risks of myopathy may be increased in special populations in which patients are exposed to higher levels of drug (drug-drug interactions, renal impairment). Analyses of plasma concentrations of pitavastatin in patients with rhabdomyolysis and other serious adverse events were conducted by the clinical pharmacology reviewers (See Section 4).

CPK Elevations

Mild CPK elevations, such as those present after vigorous exertion, may not predict who is at risk of developing rhabdomyolysis, but CPK >10XULN is a useful marker to compare potentially myotoxic drugs. For example, cerivastatin 0.4 mg and 0.8 mg had an incidence of CPK >10XULN of 1.6% and 2.1%, respectively in clinical trials.(b) (4) Eventually cerivastatin was removed from the market due to rhabdomyolysis(b) (4) The incidence of CPK >10XULN for pitavastatin 1-4 mg was well below the incidence seen in clinical trials for cerivastatin and rosuvastatin.

Table 48 summarizes CPK elevations for pitavastatin in the clinical trials for Groups 1 and 3.

Table 48 CPK >1X, 3X, 5X and 10X ULN for Pitavastatin 1-4 mg -Groups 1 & 3

	Group 1			Group 3	
CPK Elevations	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 2 mg (N=2562)	Pita 4 mg (N=2406)
>1X ULN	66 (21.4)	207 (21.8)	332 (21.6)	440 (17.2)	677 (28.1)
>3X ULN	4 (1.3)	16 (1.7)	17 (1.1)	22 (0.9)	42 (1.7)
>5X ULN	2 (0.6)	1 (0.1)	7 (0.5)	3 (0.1)	20 (0.8)

>10X ULN	0	1 (0.1)	1 (0.1)	1 (0.0)	3 (0.1)

Source: Pitavastatin Study Report, Table 2.7.4.125.

In Group 1, there was one subject (0.4%) in the atorvastatin 20 mg group who had a CPK > 10XULN. There were no subjects on simvastatin of pravastatin with CPK >10XULN.

In Group 3 there was an increase in CPK elevation >5XULN with pitavastatin 4 mg (0.8%) as compared to pitavastatin 2 mg (0.1%). This is consistent with Group 1 pitavastatin 4 mg (0.5%) as compared to pitavastatin 2 mg (0.1%) CPK > 5XULN. However, it is difficult to describe elevations in CPK in the range of 1 to 4 mg as dose-related, as pitavastatin 1 mg had a slightly greater incidence of CPK elevations over 2 mg and 4 mg in Group 1. Furthermore, >10XULN elevations in CPK seemed to be similar in 1 mg, 2 mg and 4 mg doses. However, CPK >10XULN was dose-related with pitavastatin >8 mg.

In order to look for potential patient populations who might be at higher risk of CPK elevations, this clinical reviewer requested further analyses of patients who developed CPK ≥10XULN for any dose of pitavastatin. Data were analyzed to see if there was an association with CPK **elevations and patients' age, sex, baseline c**reatinine level, or past medical history of hypertension or diabetes.

Table 49 Demographics of Patients with CPK> 10XULN on Any Dose of Pitavastatin-Group 1

	Pita 1 mg (N=309)	**Pita 2 mg (N=951)**	**Pita 4 mg (N=1540)**	**Pita 8 mg (N=479)**	**Pita 16 mg (N=102)**	**Pita 32 mg (N=34)**	**Pita 64 mg (N=33)**
Number of subjects with >10XULN	0	2	1	3	8	9	7
Sex							
Males	0	1	1	1	2	3	3
Females	0	1	0	2	6	6	4
Age							
Mean (SD)	0	53 (21)	67	60 (13)	60 (10)	69 (6)	54 (9)
Median	0	53	67	58	60	67	56
Range	0	38-68	67	48-74	44-72	59-76	47-68
Hypertension							
Yes	0	2	1	1	4	4	4
No	0	0	0	2	4	5	3
Diabetes							
Yes	0	0	1	0	2	0	0
No	0	2	0	3	6	9	7
Baseline Creatinine							
Mean (SD)	0	1.10 mg/dL (0.141)	0.80 mg/dL (-)	1.07 mg/dL (0.058)	1.06 mg/dL (0.256)	1.10 mg/dL (0.200)	1.13 mg/dL (0.206)

	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)
Median	0	1.10 mg/dL	0.8 mg/dL	1.10 mg/dL	1.00 mg/dL	1.00 mg/dL	1.10 mg/dL
Range	0	1.0- 1.2	0.8-0.8	1.0-1.1	0.8-1.5	0.9-1.5	0.9-1.4

Source: Pitavastatin Study Report, Table 1.3.1.

Of the 30 patients with CPK >10XULN for any dose of pitavastatin, 11 (37%) were men and 19 (64%) were women. Average age was around 60 years. Only 3 out of 30 were diabetic and 16 (53%) had history of hypertension. Mean baseline creatinine was within normal laboratory parameters; however the maximum value was slightly elevated at 1.5 mg/dL. Subjects with serum creatinine values greater than 1.5XULN were not included in the clinical trials per the exclusion criteria.

Table 50 summarizes the individual preferred terms under the musculoskeletal and connective tissue disorders reported by greater than 1 patient for Group 1. Adverse events in this category seem to be dose-related, particularly at doses >8 mg and include: pain in extremity, arthralgia, and muscle spasms. Myalgia was reported by 1.4% of subjects in the placebo group, compared to 1.9% for 1 mg, 2.8% for 2 mg, and 3.1% of subjects on 4 mg pitavastatin. For doses 1-4 mg pitavastatin combined, the incidence of myalgia was 3.8%. Pitavastatin 8 mg had an incidence of myalgia of 5.2%. The incidence rates for myalgia were 9.8%, 14.7%, and 30% for the pitavastatin 16 mg, 32 mg, and 64 mg groups, respectively.

Table 50 shows a sharp demarcation in the incidence of increased CPK between the 1-4 mg and 8-64 mg dose groups. Pitavastatin 1-4 mg had an incidence (1.3-0.8%) similar to placebo (1.0%) for increased CPK. The frequency of elevated CPK jumped to 2.3% with pitavastatin 8 mg and 13.7% with 16 mg and was overall more frequent with higher doses of pitavastatin.

Table 50 TEAEs Reported in >1 Subject in Musculoskeletal and Connective Tissue Disorders and CK TEAEs Reported in Investigation by Number (%)-Group 1

MedDRA SOC/Preferred Term - No. (%) of Subjects	Placebo (N=203)	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)	Pita Overall (N=3448)
Musculoskeletal & Connective Tissue Disorders	28 (13.5)	41 (13.3)	82 (8.6)	123 (8.0)	62 (12.9)	31 (30.4)	8 (23.5)	17 (51.5)	364 (10.6)
Arthralgia	6 (2.9)	8 (2.6)	14 (1.5)	18 (1.2)	6 (1.3)	5 (4.9)	0	1 (3.0)	52 (1.5)
Arthritis	0	0	0	4 (0.3)	1 (0.2)	1 (1.0)	0	0	6 (0.2)
Back pain	6 (2.9)	12 (3.9)	17 (1.8)	21 (1.4)	11 (2.3)	5 (4.9)	0	0	66 (1.9)
Buttock pain	0	0	1 (0.1)	1 (0.1)	0	1 (1.0)	0	0	3 (0.1)
Chest wall pain	0	0	1 (0.1)	1 (0.1)	0	0	0	0	2 (0.1)
Joint stiffness	0	2 (0.6)	2 (0.2)	0	1 (0.2)	1 (1.0)	0	0	6 (0.2)
Joint swelling	0	0	1 (0.1)	1 (0.1)	1 (0.2)	2 (2.0)	0	0	5 (0.1)
Muscle spasms	1 (0.5)	2 (0.6)	7 (0.7)	8 (0.5)	7 (1.5)	2 (2.0)	1 (2.9)	0	27 (0.8)
Muscle tightness	0	0	1 (0.1)	1 (0.1)	1 (0.2)	0	0	0	3 (0.1)
Muscular weakness	0	0	0	0	2 (0.4)	0	0	4 (12.1)	6 (0.2)
Musculoskeletal chest pain	0	1 (0.3)	3 (0.3)	4 (0.3)	0	0	0	0	8 (0.2)
Musculoskeletal discomfort	2 (1.0)	0	2 (0.2)	0	2 (0.4)	0	0	0	4 (0.1)
Musculoskeletal pain	1 (0.5)	0	1 (0.1)	2 (0.1)	1 (0.2)	1 (1.0)	0	0	5 (0.1)
Musculoskeletal stiffness	3 (1.4)	2 (0.6)	3 (0.3)	1 (0.1)	2 (0.4)	3 (2.9)	0	0	11 (0.3)
Myalgia	3 (1.4)	6 (1.9)	27 (2.8)	47 (3.1)	25 (5.2)	10 (9.8)	5 (14.7)	10 (30.3)	130 (3.8)
Myopathy	0	0	0	0	0	1 (1.0)	0	2 (6.1)	3 (0.1)
Neck pain	1 (0.5)	4 (1.3)	0	1 (0.1)	1 (0.2)	1 (1.0)	1 (2.9)	0	8 (0.2)
Osteoarthritis	0	3 (1.0)	4 (0.4)	14 (0.9)	2 (0.4)	0	0	0	23 (0.7)
Osteochondrosis	0	0	0	2 (0.1)	0	0	0	0	2 (0.1)
Pain in extremity	4 (1.9)	7 (2.3)	6 (0.6)	14 (0.9)	8 (1.7)	3 (2.9)	1 (2.9)	2 (6.1)	41 (1.2)
Periarthritis	0	1 (0.3)	1 (0.1)	0	0	0	0	0	2 (0.1)
Rhabdomyolysis	0	0	0	0	2 (0.4)	1 (1.0)	3 (8.8)	3 (9.1)	9 (0.3)
Shoulder pain	1 (0.5)	5 (1.6)	3 (0.3)	8 (0.5)	3 (0.6)	1 (1.0)	0	1 (3.0)	21 (0.6)
Tendonitis	1 (0.5)	2 (0.6)	0	2 (0.1)	0	0	0	0	4 (0.1)
Investigations									
Blood CK	0	0	0	0	0	0	1 (2.9)	2 (6.1)	3 (0.1)
Blood CK abnormal	0	0	0	0	0	1 (1.0)	1 (2.9)	0	2 (0.1)
Blood CK increased	2 (1.0)	4 (1.3)	8 (0.8)	11 (0.7)	11 (2.3)	14 (13.7)	3 (8.8)	7 (21.2)	58 (1.7)

Source: ISS, Table 1.6; Clinical Summary 2.7.4.96

Thus, there is a clear demarcation between pitavastatin 1-4 mg and pitavastatin 8-64 mg in terms of muscle-related events. Pitavastatin 1-4 mg had similar incidence rates of CPK elevations, myalgia, and no cases of rhabdomyolysis in the clinical trials. Pitavastatin 8-64 mg had dose-related increases in CPK elevations, myalgia, and nine cases of rhabdomyolysis.

Time to first occurrence of rhabdomyolysis/myopathy is summarized in Section 7.5.2.

Liver-Related Events

Serum AT levels have been used to screen statins for potential hepatotoxicity. According to the Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (October 2007), many drugs, including both significant hepatotoxins and drugs that do not cause severe liver injury, can cause laboratory evidence of hepatic injury, with leakage of liver enzymes and elevations in serum ALT/AST $\geq$ 3-5XULN. The finding of a higher rate of such elevations in drug-treated vs. placebo-treated subjects is a potential signal for DILI. A more specific signal of such potential is a higher rate of marked AT elevations (10-20XULN), with absolute increases >1,000 IU/L of particular concern.

The Agency's Liver Injury Guidance also recommends identifying any cases of altered liver function that satisfy Hy's Law, which if met would suggest the drug is likely to be capable of causing severe DILI. Possible Hy's Law cases are identified as subjects with AST or ALT >3XULN, total bilirubin ≥2XULN, and normal Alk Phos levels.

This clinical reviewer noted that the applicant reported only single occurrences of elevated ATs during the clinical trials. Therefore, the following tables only include single occurrences of elevated ATs.

Table 51 ALT elevations for Pitavastatin 1-8 mg and comparators in Group 1

	Pitavastatin				Atorvastatin				Simvastatin		Pravastatin			
No.(%) Subjects Abnormal Results	**1mg N=309**	**2mg N=951**	**4mg N=1540**	**8mg N=479**	**10mg N=118**	**20mg N=240**	**40mg N=51**	**80mg N=96**	**20mg N=107**	**40mg N=229**	**10mg N=103**	**20mg N=96**	**40mg N=102**	**Placebo N=108**
>3XULN	1 (0.3)	5 (0.5)	1 (0.1)	4 (0.8)	0	0	0	0	0	1 (0.4)	0	0	0	0
>5XULN	0	2 (0.2)	2 (0.1)	1 (0.2)	0	0	0	0	0	0	0	0	0	0
>10XULN	1 (0.3)	0	0	0	0	0	0	1(1.0)	0	0	0	0	0	0
>20XULN	0	0	0	0	0	0	0	1(1.0)	0	0	0	0	0	0
ALT >3XULN with TB >1.5XULN	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ALT >3XULN with TB >2XULN	0	0	0	0	0	0	0	1(1.0)	0	0	0	0	0	0

Source: ISS, Table 1, page 16. If a patient had more than one ALT value above ULN, then the highest value observed was counted.

As shown in the table above, in Group 1, the percentage of subjects who reported an elevation in ALT >3XULN was between 0.1 and 0.5 % for 1 mg to 4 mg pitavastatin and could not be quite described as dose-related. While the frequency of transaminitis in these pitavastatin groups was low, it was higher than the incidence observed in the low-to-moderate dose atorvastatin, simvastatin, and pravastatin comparators.

There was one patient on 1 mg pitavastatin who had an ALT >10XULN (Subject 6507-022) who was diagnosed with acute cholecystitis (described below). However, there were no other reports of ALT/AST elevations >10XULN for 2-8 mg pitavastatin in the 12-16 week clinical trials. In these clinical trials, the comparator statins had relatively infrequent ALT/AST elevations > 3XULN, while the placebo group had no elevations. There was one patient on atorvastatin 80 mg with concurrent ALT/AST >3XULN and TB >2XULN, who was diagnosed with hepatitis C.

In Group 1 the higher doses of pitavastatin had a greater incidence of elevated liver enzymes than pitavastatin 1-4 mg. The frequencies of ALT or AST > 3XULN with pitavastatin 16 mg, 32 mg, and 64 mg were 8/102 (7.8%), 6/34 (17.7%), and 5/33 (15.2%), respectively (Table 52).

According to the applicant, there was a high correlation between elevation of >3XULN ALT/AST and CPK >10XULN (only one subject did not have concurrent elevations in ALT/AST and CPK). The applicant proposes that the increased levels of AST/ALT with the higher doses of pitavastatin therefore may represent muscle rather than liver injury.

Table 52 ALT elevations for Pitavastatin 16-64 mg - Group 1

No.(%) Subjects Abnormal Results	**Pitavastatin 16 mg (N=102)**	**Pitavastatin 32 mg (N=34)**	**Pitavastatin 64 mg (N=33)**

>3XULN	5 (4.9)	2 (5.9)	2 (6.1)
>5XULN	3 (2.9)	3 (8.8)	2 (6.1)
>10XULN	0	1 (2.9)	1 (3.0)
>20XULN	0	0	0
Source, ISS, 1.12.4 If a patient had more than one ALT value above ULN, then the highest value observed was counted.			

When considering Group 3, the incidence of subjects with mild ALT elevations (>3XULN) with doses of 1 mg to 4 mg was between 0.3 to 0.7% and was similar to Group 1 (Table below). In Group 3, the mild to moderate ALT elevations were dose- related, but the same dose-relationship did not extend to >10XULN. However, the longer duration of exposure did result in a slightly higher incidence of ALT elevations >5XULN and >10XULN as compared to Group 1 (Table 51). There was one subject on simvastatin 20 mg (0.3%) with ALT >3XULN, but no other subjects in Group 3 had ALT >3XULN for atorvastatin or pravastatin.

Table 53 ALT elevations for Pitavastatin 1-4 mg and Comparators Group 3

	Pitavastatin			Atorvastatin			Simvastatin			Pravastatin		
No.(%) Subjects Abnormal Results	**1mg N=309**	**2mg N=2562**	**4mg N=2406**	**10mg N=394**	**20mg N=264**	**40mg N=54**	**20mg N=336**	**40mg N=219**	**80mg N=5**	**10mg N=103**	**20mg N=198**	**40mg N=96**
>3XULN	1 (0.3)	7 (0.3)	17(0.7)	0	0	0	1 (0.3)	0	0	0	0	0
>5XULN	0	3 (0.1)	9 (0.4)	0	0	0	0	0	0	0	0	0
>10XULN	1 (0.3)	1 (0.0)	2 (0.1)	0	0	0	0	0	0	0	0	0
>20XULN	0	0	0	0	0	0	0	0	0	0	0	0
ALT >3XULN with TB >1.5XULN	0	0	1 (0.0)	0	0	0	0	0	0	0	0	0
ALT >3XULN with TB >2XULN	0	0	0	0	0	0	0	0	0	0	0	0
Source: ISS, Table 3. If a patient had more than one ALT value above ULN, then the highest value observed was counted.												

There were four subjects, one subject each on 1 mg and 2 mg pitavastatin and 2 subjects on pitavastatin 4 mg, with ALT >10XULN in Group 3. Subject #6507-022 (same subject cited in Group 1) on pitavastatin 1 mg, was diagnosed with acute cholecystitis on study day 28. Pertinent labs were as follows: ALT=326 U/L, AST= 282 U/L, total bilirubin=0.34 mg/dL, and alkaline phosphatase= 121 U/L.

Subject #6105-034 was a 71-year-old woman on pitavastatin 2 mg who on study day 279 had ALT= 341 U/L (>10XULN), AST= 180 U/L (>5XULN), total bilirubin= 0.91, and alkaline phosphatase=129 U/L (>1.5XULN). Subject was withdrawn from study secondary to her laboratory elevations, but had an ALT= 31 U/L and AST=21 U/L at the withdrawal visit.

Subject # 1211-019 was a 53-year-old woman on 4 mg pitavastatin who on study day 227 had ALT=455 U/L (>10XULN), AST=182 U/L (>5XULN), TB=1.56 mg/dL, and alkaline phosphatase= 172 U/L (>2XULN). Subject was admitted to the hospital and a diagnosis of acute cholecystitis with mechanical jaundice was made. On study day 232, a cholecystectomy was performed with drainage of the bile duct. Laboratory values returned to normal by study day 266.

The subject subsequently discontinued the study. From the data available from the CRF, this patient did not meet the **criteria for Hy's Law.**

Subject #5108-047 was a 67-year-old woman with type II diabetes who received pitavastatin 4 mg from October 2006 to January 2007 during Study 305. She entered an extension study immediately following participation in Study 305 and remained on pitavastatin 4 mg. Concomitant medications included metformin, metoprolol, molsidomine, cilazapril, and amlodipine. One April 25, 2007, 113 days after starting in the extension study, the subject had an ALT=363 U/L (>10XULN), an AST 455 U/L (>20XULN), a bilirubin=2.07 mg/dL (>1.5XULN), and an Alk Phos=96 (slightly higher than normal). At this time, the patient reported a single episode of diarrhea. Pitavastatin was discontinued from the study drug on April **26, 2007. On the following day, the subject's ALT was 253 U/L, her AST was 131 U/L, and** bilirubin was 0.6 mg/dL. CPK was reported to be 516 U/L (normal <145 U/L). An abdominal ultrasound was unremarkable. HBs antigen was negative, as were antibodies to MCV. Over the **next week, the subject's laboratory values dec**lined. Pitavastatin was re-introduced on May 11, 2007. Subject was able to resume the study drug and had normal ALT, AST, and TB on the study drug with follow-up. On Study Day 402 (last visit) her ALT = 16 U/L, AST = 18 U/L, CPK =64 U/L, TB= 0.52 mg/dL. The investigator considered a viral infection of the gastrointestinal tract as the cause of the transaminitis and elevated bilirubin.

It is possible that pitavastatin caused this subject's laboratory abnormalities. However, the fact that the ALT and AST values decreased and the bilirubin concentration normalized within one day of stopping pitavastatin, which has a half-life of 8 to 12 hours, and there was a negative re-challenge to pitavastatin argue against drug causality.

Bilirubin and Transaminase Elevations

With pitavastatin doses from 1 mg to 4 mg in short-term trials, there were no Hy's Law cases or patients with concurrent bilirubin elevations >1.5XULN and ALT or AST >3xULN. In the Group 3 analysis, there was one patient in the 4 mg pitavastatin group with ALT and AST >3XULN with TB >1.5XULN (Subject #5108-047). This patient was not considered to meet the **criteria for Hy's Law as discussed above.**

There was one patient in the atorvastatin 80 mg group with concurrent elevation of both ALT and AST >3XULN and TB >2XULN. Subject #9053-008 was a 64-year-old woman who on study day 29 had an ALT=264 U/L (>10XULN), AST=179 U/L (>5XULN), TB= 2.64 mg/dL (>2XULN) and an initial alkaline phosphatase= 362 U/L. According to the applicant, this patient **was diagnosed with hepatitis C and therefore did not meet Hy's Law.**

Isolated Elevations of Bilirubin/Alkaline phosphatase

There were isolated total bilirubin values >2XULN reported in three subjects (0.3%) in the 2 mg pitavastatin group, and one subject each in the 1 mg (0.3%), 4 mg (0.1%), and 8 mg (0.2%) pitavastatin groups.

There were isolated alkaline phosphatase values >1.5XULN in 1(0.3%) patient on 1 mg pitavastatin and 3(0.3%) patients on 2 mg pitavastatin. Two patients (0.2%) in the 2 mg pitavastatin group reported an elevated ALP >2XULN, but this magnitude of increase was not observed in the higher pitavastatin groups. One subject (0.5%) in the placebo group reported an elevated ALP >1.5XULN.

Demographic Analysis of Patients with Transaminase Elevations

In order to investigate potential patient populations who might be at a higher risk of AT elevations, data were analyzed to see if there was an association with AT elevations and the **patient's age, sex, presence of hypertension,** or diabetes, baseline creatinine or baseline AT levels.

Table 54 Demographics of Patients with ALT/AST Elevations in Clinical Trials

	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)
Number of subjects with >3XULN ALT or AST	2	8	4	6	9	8	5
Sex							
Males	0	3	1	4	2	3	3
Females	2	5	3	2	7	5	2
Age							
Mean (SD)	67 (1.41)	54.5 (9.9)	49.8 (14.4)	50.3 (16.6)	62.4 (10.4)	68.8 (6.94)	61.0 (8.40)
Median	67	53.5	45.5	48	64.5	70.0	56.0
Range	66-68	35-67	35-69	34-74	44- 73	59- 76	53- 72
Hypertension							
Yes	2	6	1	4	5	4	3
No	0	2	3	2	4	4	2
Diabetes							
Yes	0	1	1	0	2	0	0
No	2	7	3	6	7	8	5
Baseline Creatinine							
Mean (SD)	0.70 (0.0)	0.88 (0.116)	0.80 (0.115)	34.72 (52.32)	1.04 (0.25)	1.10 (0.21)	1.28 (0.11)
Median	0.70	0.8	0.8	1.05	0.90	1.00	1.30
Range	0.7- 0.7	0.8- 1.1	0.7- 0.9	1.0- 107.8	0.8- 1.5	0.9- 1.5	1.1- 1.4
Baseline ALT >1XULN							
Yes	1	5	0	1	1	0	0
No	1	3	4	5	8	8	5

Source: Pitavastatin Study Report, Table 1.3.1.

Of the 42 patients with elevated ATs, 16 (38%) were men and 26 (62%) were women. Pitavastatin 1 to 4 mg doses had 6 patients with baseline ALT elevations and 7 patients with

normal liver tests who subsequently had elevations in ALT or AST. Only 2/28 subjects on pitavastatin 8 mg to 64 mg had elevated AT at baseline who subsequently had elevations of AT on pitavastatin. Hypertension (60%) was more prevalent than diabetes (9.5%).
Of the 42 patients with elevated liver enzymes on pitavastatin, 13 subjects had the drug withdrawn. Data are not available on the remaining subjects as to how many had the dose lowered or how many had pitavastatin withheld temporarily. However, at least 2/3 of the patients with elevated liver enzymes were able to continue on treatment despite ALT elevations.

Renal-Related Events

In addition to the known association of statins with rhabdomyolysis and liver AT elevations, the development of proteinuria with and without hematuria has been observed with all the statins (Bays, 2006). However, it has been suggested that the proteinuria found in humans treated with statins may not be a toxic effect, but a physiologic response. Thus, the clinical relevance of statin-associated proteinuria is debatable with the Renal Expert Panel of the National Lipid **Association's Safety Task Force finding no evidence** that statins cause acute renal failure or renal insufficiency (not associated with rhabdomyolysis) (Kasiske, 2006). The Renal Expert Panel also found no convincing evidence of an association between statins and hematuria. In fact, there are also studies suggesting that statins have a renal protective effect (Fried, 2001).

Preclinical pharmacology/toxicology data in rats suggest a possible role for 8-hydoxypitavastatin and renal toxicity (see Section 4.3). The plasma and urine concentrations of 8-hydroxypitavastatin was investigated in clinical study 15. Seven healthy Japanese male volunteers were administered 4 mg pitavastatin once daily under fed conditions for seven days in an open-label study conducted to investigate the pharmacokinetics of plasma pitavastatin, lactone and 8-hydroxy pitavastatin metabolites. Blood and urine samples for determination of pitavastatin and its metabolites plasma concentrations and urinary excretion were obtained at specified intervals over Days 1 to 9. Safety was assessed by clinical laboratory tests (hematology, biochemistry, urinalysis and serum lipids), ophthalmology, vital signs, physical examination and adverse events. According to the applicant, a trace amount of 8-hydroxypitavastatin (0.6 ng/mL) was detected in the plasma of two subjects. The cumulative excretion was less than 1% for 8-hydroxypitavastatin and its conjugate.

This clinical reviewer recommends the inclusion of 8-hydroxypitavastatin assessment in the post-marketing required pharmacokinetic study in severe renal impairment.

There were a number of problems with the assessment of proteinuria and hematuria in the pitavastatin NDA. The applicant did not provide pooled data from the Phase 3 trials of the dipstick urinalysis. The applicant only conducted spot urine protein/creatinine ratios on 334 subjects in four Phase 3 trials (55 on 2 mg pitavastatin, 175 on 4 mg pitavastatin, 7 on 20 mg simvastatin, 30 on 40 mg simvastatin, 13 on 10 mg atorvastatin, and 54 on 20 mg atorvastatin). Furthermore, persistence or reversibility of proteinuria was not examined in the extension trials with spot urine protein/creatinine ratios. A correlation of creatinine changes from baseline to end of treatment to the changes in proteinuria could not be made because the applicant did not collect serum creatinine at end of treatment.

This clinical reviewer requested the rationale for not pooling the dipstick urinalysis data for hematuria and proteinuria. The applicant responded on 29 May 2009 with the following **justification: "The urine dipstick data in the** phase 3 EU program was performed locally by the investigators and therefore may have a subjective interpretive component. Dipstick values are subject to high sensitivity and therefore are good for screening of positive findings but also can produce false positives due to interfering medications or failure to read and record various analytes at their appropriate time intervals, which vary from 30 seconds to 2 minutes, depending on the analyte. Therefore, pooled results of investigator-obtained urine dipsticks for groups 1 and 3 were not performed.

In the event of a positive dipstick value on any of the tested analytes (specific gravity, pH, blood, protein, nitrite, bilirubin, ketones, glucose, leukocytes, urobilinogen), an aliquot of urine was sent to the central laboratory for analysis. This algorithm resulted in a small subset of patients undergoing central laboratory urinalysis either at baseline or endpoint of the studies. Many of the samples submitted to the central laboratory were submitted for analytes other than blood or protein, so the total pool of positive blood or protein samp**les was minimal."**

This clinical reviewer believes that since the dipstick urinalysis was confirmed with microscopic detection of RBCs in the urine, pooling the results of the microscopic data would have been a valid assessment of hematuria.

The Division requested that the applicant conduct 24-hour urine collections to investigate if pitavastatin causes proteinuria. The applicant agreed to conduct a spot urine protein/ creatinine ratio in four short-term trials on a subset of patients. A value of <0.2 mg/mg for protein/creatinine ratio was determined to be normal. The lower limit of 0.26 mg/mg was decided to be the clinical threshold for new proteinuria. Table 55 summarizes the spot urine protein/creatinine ratios from a subgroup of subjects from studies 301, 302, 304, and 305.

The spot urine protein/creatinine ratio was measured in 334 subjects (55 on 2 mg pitavastatin, 175 on 4 mg pitavastatin, 7 on 20 mg simvastatin, 30 on 40 mg simvastatin, 13 on 10 mg atorvastatin, and 54 on 20 mg atorvastatin).

Table 55 Spot Urine Protein/ Creatinine Ratio Subset of Patients from Four Phase 3 Studies

Mean Urine Protein: Creatinine Ratio (mg/mg)	**Pita 2 mg (n=55)**	**Pita 4 mg (n=175)**	**Simv 20 mg (n=7)**	**Simv 40 mg (n=30)**	**Ator 10 mg (n=13)**	**Ator 20 mg (n=54)**
Baseline Mean (SD)	0.14 (0.32)	0.10 (0.14)	0.08 (0.07)	0.07 (0.06)	0.07 (0.11)	0.09 (0.17)
Last Visit# Mean (SD)	0.31 (1.43) **(n=55)**	0.27 (1.59) **(n=175)**	0.20 (0.36) **(n=7)**	0.07 (0.09) **(n=30)**	0.17 (0.32) **(n=13)**	0.14 (0.33) **(n=54)**
Mean Change from	0.17	0.18	0.12	0.001	0.11	0.05

Baseline (SD)	(1.47) (n=55)	(1.59) (n=175)	(0.36) (n=7)	(0.08) (n=30)	(0.33) (n=13)	(0.36) (n=54)
Source: Table 2.7.4.141.						

Table 56 Spot Urine Protein/ Creatinine Ratio Subset of Patients from Four Phase 3 Studies

Mean Urine Protein: Creatinine Ratio (mg/mg)	**Pitavastatin Overall (N=230)**	**Atorvastatin Overall** (N=67)	**Simvastatin Overall (N=37)**
Baseline Mean (SD)	0.108 (0.19)	0.087 (0.16)	0.075 (0.07)
95% Confidence Interval	0.082-0.134	0.049-0.124	0.054- 0.097
Range	0.01 to 1.73	0.01 to 1.12	0.02 to 0.26
Last Visit# Mean (SD)	0.283 (1.54)	0.149 (0.3226)	0.098 (0.175)
95% Confidence Interval	0.082-0.484	0.070- 0.227	0.040-0.156
Range	0.01 to 16.20	0.01 to 2.33	0.01 to 1.02
Mean Change from Baseline (SD)	0.176 (1.56)	0.062 (0.35)	0.023 (0.17)
Source: ISS, Table 1.15.2			

The mean change from baseline in spot urine protein/creatinine values worsened to a greater degree in the pitavastatin 2 mg and 4 mg groups compared with the comparator statin groups. Mean change from baseline to last visit for pitavastatin was 0.176, compared to 0.062 for atorvastatin and 0.023 for simvastatin. Subjects randomized to pitavastatin had baseline proteinuria values that were numerically higher than subjects on comparator statins. It is unclear if this may have affected the changes from baseline.

The following tables show the number of patients who shifted from normal to abnormal results in spot urine protein/creatinine ratios from baseline to the end of 12-weeks treatment. Normal spot urine protein/creatinine ratio is considered <0.26 mg/mg; levels of 0.26 to <0.5 mg/mg are indicative of moderate proteinuria; and values >0.5 mg/mg correspond to a urine protein excretion > 3XULN.

Table 57 Shift Tables for Spot Urine Protein/Creatinine Ratios for Pitavastatin

	Pitavastatin 2 mg (N=951) Week 12 or Last Visit				Pitavastatin 4 mg (N=1540) Week 12 or Last Visit			
Number of Patients	<0.26	0.26-<0.5	>=0.5	Total	<0.26	0.26-<0.5	>=0.5	Total
Baseline								
<0.26	44	1	3	49	151	10	2	163
0.26-<0.5	1	1	0	2	5	1	1	7
>=0.5	3	1	0	4	1	2	2	5
Total	48	4	3	55	157	13	5	175

	Atorvastatin 20 mg (N=240) Week 12 or Last Visit				Atorvastatin 40 mg (N=51) Week 12 or Last Visit			
Number of Patients	<0.26	0.26-<0.5	>=0.5	Total	<0.26	0.26-<0.5	>=0.5	Total
Baseline								
<0.26	47	2	2	51	0	0	0	0
0.26-<0.5	1	1	0	2	0	0	0	0
>=0.5	1	0	0	1	0	0	0	0
Total	49	3	2	54	0	0	0	0

	Simvastatin 20 mg (N=107) Week 12 or Last Visit				Simvastatin 40 mg (N=219) Week 12 or Last Visit			
Number of Patients	<0.26	0.26-<0.5	>=0.5	Total	<0.26	0.26-<0.5	>=0.5	Total
Baseline								
<0.26	6	0	1	7	27	2	0	29
0.26-<0.5	0	0	0	0	1	0	0	1
>=0.5	0	0	0	0	0	0	0	0
Total	6	0	1	7	28	2	0	30

Source: Pitavastatin ISS.

The data in the shift tables indicate that the majority of patients treated with pitavastatin and the comparator statins had baseline and on-treatment spot urine protein/creatinine ratios less than 0.26 mg/mg. The frequency of subjects who shifted from a normal baseline spot urine protein/creatinine ratio to an abnormal ratio was 5/49 (10%) for pitavastatin 2 mg, 12/163 (7%) for pitavastatin 4 mg, 4/51 (8%) for atorvastatin 20 mg, 0% for atorvastatin 40 mg, 1/7 (14%) for simvastatin 20 mg, and 2/29 (7%) for simvastatin 40 mg. Thus, the relative frequency of patients with proteinuria was similar among subjects in the pitavastatin, atorvastatin, and simvastatin groups.

This clinical reviewer requested the mean change in creatinine levels in the subgroup that had the protein/ creatinine ratios measured to correlate renal function changes with proteinuria. According to the applicant, serum creatinine was measured only at screening for the 12-week studies. Thus, end-of-treatment creatinine values were not available to assess renal function in the subjects with changes in spot urine protein/creatinine ratios.

This clinical reviewer requested the narratives on the patients who had <.2 mg/mg to >.5 mg/mg change in protein/creatinine ratios for pitavastatin and other comparator statins to see if the change in proteinuria was reversible with drug withdrawal or reoccurred with rechallenge. However, the case report forms were not readily available from the applicant, as these subjects had not been identified previously with serious adverse events.

In Group 1,there were two subjects coded with renal failure (one on 4 mg and one on 64 mg pitavastatin); one subject was coded with chronic renal failure (2 mg pitavastatin ; and one subject reported with renal impairment (2 mg pitavastatin). Only one subject out of these four identified withdrew from the study (Subject # 9002008 on 64 mg). No patients on placebo, atorvastatin, or pravastatin were reported to have renal failure or renal impairment.

In Group 3, a total of 12 subjects on pitavastatin were identified with renal failure (two subjects on 2 mg; two subjects on 4 mg), chronic renal failure (two subjects on 2 mg; five subjects on 4 mg), and renal impairment (one subject on 2 mg). Of these 12 subjects, seven were > 65 years old, four had diabetes, and 11 had hypertension. The applicant characterized four subjects with mild renal failure, six with mild chronic renal failure, and one with moderate renal failure.

This clinical reviewer examined the CRFs for the 12 subjects identified with renal failure, chronic renal failure, or renal insufficiency. It should be noted that subjects with baseline serum creatinine values within 1.5XULN were allowed to enroll into the studies. Almost all of the 12 subjects in question had baseline serum creatinine values in the high-normal range with very little change on-treatment. For 6/12 subjects, the highest recorded serum creatinine values ranged from 0.8 mg/dL to 1.2 mg/dL. Of the other six subjects, one subject (#002008) was on 64 mg pitavastatin and had definite drug-associated rhabdomyolysis and renal failure; this subject had a CPK of 21,210 IU/L, serum creatinine of 6.2 mg/dL and BUN of 70 mg/dL. The five remaining **subjects' baseline and peak creatinine/end of visit serum creatinine values are tabulated below.**

Table 58 Change in Serum Creatinine in Subgroup of Renal Failure Patients

Subject Identifier	Baseline Creatinine	Peak Creatinine Level	Change in Creatinine
#6201054	1.3 mg/dL	1.5 mg/dL	+0.2 mg/dL
#6206035	1.2 mg/dL	2.1 mg/dL	+0.9 mg/dL
#6207005	1.9 mg/dL	1.9 mg/dL	0
#6403024	1.8 mg/dL	1.8 mg/dL	0
#5110043	1.5 mg/dL	4.1 mg/dL	+2.6 mg/dL

Two of the five patients had a change in serum creatinine > 0.5 mg/dL from baseline and are described below.

Patient #5110043 on 2 mg pitavastatin was discontinued from the study after a hospitalization for **"acute hemorrhage into digestive tract" requiring transfusion of PRBC. His acute renal failure** with a serum creatinine of 4.1 mg/dL and BUN of 67 mg/dL was likely complicated by the gastrointestinal bleeding.

Patient #6206035 on 2 mg pitavastatin had a peak serum creatinine of 2.1 mg/dL, which decreased to 1.8 mg/dL at the last patient visit. The patient discontinued from the study due to femoral neck fracture which required hospitalization. According to the CRF, she had a history of renal insufficiency at baseline. Other co-morbidities included hypertension, anemia, diverticulum, restless leg syndrome, and hyperuricemia. It is difficult to determine causality of the worsening renal function from the information provided in the CRF.

In summary, most of the 12 subjects coded as having renal failure or renal impairment had high-normal serum creatinine values at baseline, and developed small, and in some cases transient, increases in serum creatinine on-treatment. Excluding patients #5110043 and #002008, this reviewer would not categorize the above cases as renal failure.

7.3.5 Submission Specific Primary Safety Concerns

Musculoskeletal-related adverse events, liver-related adverse events, and renal-related adverse events are described in Section 7.2.5.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table summarizes the adverse events which occurred in ≥1% of subjects and > 1 subject in any group by randomized dose of pitavastatin. The placebo group is listed for comparison of adverse events.

Table 59 TEAEs Reported by > 1% of Subjects (and >1 Subject in any Group) by Randomized Doses of Pitavastatin in Group 1

SOC/PT No. (%) of Subjects	Placebo N=208	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)	Pita Overall N=3448
No. (%) of Subjects with any TEAEs	113 (54.3)	156 (50.5)	336 (35.3)	607 (39.4)	229 (47.8)	62 (60.8)	17 (50.0)	25 (75.8)	1432 (41.5)
Cardiac Disorders	**4 (1.9)**	**3 (1.0)**	**12 (1.3)**	**26 (1.7)**	**7 (1.5)**	**1 (1.0)**	**0**	**1 (3.0)**	**50 (1.5)**
Palpitations	2 (1.0)	1 (0.3)	2 (0.2)	3 (0.2)	0	1 (1.0)	0	1 (3.0)	8 (0.2)
Ear & Labyrinth Disorders	**5 (2.4)**	**0**	**8 (0.8)**	**14 (0.9)**	**3 (0.6)**	**0**	**0**	**1 (3.0)**	**26 (0.8)**
Ear Pain	2 (1.0)	0	0	2 (0.1)	0	0	0	0	2 (0.1)
Eye Disorders	**3 (1.4)**	**2 (0.6)**	**6 (0.6)**	**11 (0.7)**	**5 (1.0)**	**1 (1.0)**	**0**	**0**	**25 (0.7)**
Gastrointestinal Disorders	**31 (14.9)**	**46 (14.9)**	**82 (8.6)**	**180 (11.7)**	**56 (11.7)**	**15 (14.7)**	**3 (8.8)**	**12 (36.4)**	**394 (11.4)**
Abdominal Pain	2 (1.0)	0	2 (0.2)	13 (0.8)	6 (1.3)	2 (2.0)	0	1 (3.0)	24 (0.7)

SOC/PT No. (%) of Subjects	Placebo N=208	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)	Pita Overall N=3448
Abdominal Pain Upper	6 (2.9)	3 (1.0)	10 (1.1)	13 (0.8)	9 (1.9)	0	0	1 (3.0)	36 (1.0)
Constipation	4 (1.9)	11 (3.6)	14 (1.5)	34 (2.2)	9 (1.9)	5 (4.9)	1 (2.9)	2 (6.1)	76 (2.2)
Diarrhoea	4 (1.9)	8 (2.6)	14 (1.5)	29 (1.9)	6 (1.3)	6 (5.9)	1 (2.9)	2 (6.1)	66 (1.9)
Dry Mouth	1 (0.5)	3 (1.0)	5 (0.5)	14 (0.9)	0	0	0	0	22 (0.6)
Dyspepsia	3 (1.4)	6 (1.9)	11 (1.2)	19 (1.2)	5 (1.0)	2 (2.0)	0	0	43 (1.2)
Flatulence	2 (1.0)	5 (1.6)	7 (0.7)	16 (1.0)	6 (1.3)	1 (1.0)	0	0	35 (1.0)
Nausea	5 (2.4)	5 (1.6)	13 (1.4)	22 (1.4)	8 (1.7)	2 (2.0)	1 (2.9)	5 (15.2)	56 (1.6)
Stomach Discomfort	1 (0.5)	0	3 (0.3)	2 (0.1)	1 (0.2)	1 (1.0)	0	2 (6.1)	9 (0.3)
Vomiting	1 (0.5)	1 (0.3)	7 (0.7)	10 (0.6)	4 (0.8)	0	0	2 (6.1)	24 (0.7)
General Disorders & Admin. Site Conditions	**11 (5.3)**	**10 (3.2)**	**27 (2.8)**	**49 (3.2)**	**22 (4.6)**	**8 (7.8)**	**3 (8.8)**	**11 (33.3)**	**130 (3.8)**
Chest Pain	2 (1.0)	0	2 (0.2)	3 (0.2)	2 (0.4)	0	0	0	7 (0.2)
Fatigue	5 (2.4)	3 (1.0)	7 (0.7)	16 (1.0)	12 (2.5)	5 (4.9)	0	10 (30.3)	53 (1.5)
Pyrexia	0	1 (0.3)	4 (0.4)	4 (0.3)	1 (0.2)	2 (2.0)	1 (2.9)	1 (3.0)	14 (0.4)
Immune System Disorders	**3 (1.4)**	**2 (0.6)**	**3 (0.3)**	**5 (0.3)**	**2 (0.4)**	**0**	**0**	**0**	**12 (0.3)**
Hypersensitivity	2 (1.0)	0	0	2 (0.1)	1 (0.2)	0	0	0	3 (0.1)
Infections & Infestations	**47 (22.6)**	**60 (19.4)**	**104 (10.9)**	**186 (12.1)**	**78 (16.3)**	**6 (5.9)**	**2 (5.9)**	**1 (3.0)**	**437 (12.7)**
Bronchitis	6 (2.9)	3 (1.0)	3 (0.3)	7 (0.5)	8 (1.7)	0	0	0	21 (0.6)
Cystitis	1 (0.5)	6 (1.9)	5 (0.5)	8 (0.5)	1 (0.2)	0	0	0	20 (0.6)
Gastroenteritis	1 (0.5)	3 (1.0)	0	8 (0.5)	4 (0.8)	0	0	0	15 (0.4)
Herpes Simplex	2 (1.0)	2 (0.6)	2 (0.2)	4 (0.3)	3 (0.6)	0	0	0	11 (0.3)
Influenza	7 (3.4)	10 (3.2)	15 (1.6)	20 (1.3)	8 (1.7)	0	1 2.9)	0	54 (1.6)
Nasopharyngitis	14 (6.7)	21 (6.8)	36 (3.8)	66 (4.3)	17 (3.5)	3 (2.9)	0	0	143 (4.1)
Sinusitis	2 (1.0)	5 (1.6)	2 (0.2)	10 (0.6)	3 (0.6)	1 (1.0)	0	0	21 (0.6)
Upper Respiratory Tract Infection	6 (2.9)	4 (1.3)	11 (1.2)	10 (0.6)	14 (2.9)	0	0	0	39 (1.1)
Urinary Tract Infection	1 (0.5)	1 (0.3)	9 (0.9)	16 (1.0)	8 (1.7)	1 (1.0)	0	1 (3.0)	36 (1.0)
Viral Infection	0	3 (1.0)	2 (0.2)	8 (0.5)	1 (0.2)	0	1 (2.9)	0	15 (0.4)
Injury, Poisoning & Procedural Complications	**4 (1.9)**	**3 (1.0)**	**20 (2.1)**	**22 (1.4)**	**16 (3.3)**	**5 (4.9)**	**0**	**0**	**66 (1.9)**
Investigations	**10 (4.8)**	**13 (4.2)**	**28 (2.9)**	**35 (2.3)**	**31 (6.5)**	**18 (17.6)**	**9 (26.5)**	**13 (39.4)**	**147 (4.3)**
ALT increased	1 (0.5)	1 (0.3)	10 (1.1)	5 (0.3)	2 (0.4)	9 (8.8)	5 (14.7)	5 (15.2)	37 (1.1)
AST abnormal	0	0	0	0	0	0	0	2 (6.1)	2 (0.1)
AST increased	0	1 (0.3)	3 (0.3)	3 (0.2)	0	7 (6.9)	5 (14.7)	5 (15.2)	24 (0.7)
Blood CPK abnormal	0	0	0	0	0	0	1 (2.9)	2 (6.1)	3 (0.1)
Blood CPK increased	2 (1.0)	4 (1.3)	8 (0.8)	11 (0.7)	11 (2.3)	14 (13.7)	3 (8.8)	7 (21.2)	58 (1.7)
Blood urine present	0	1 (0.3)	1 (0.1)	0	2 (0.4)	0	2 (5.9)	2 (6.1)	8 (0.2)
Cardiac murmur	2 (1.0)	0	0	1 (0.1)	0	0	0	0	1 (0.0)
ECG QT corrected	2 (1.0)	0	0	0	0	0	0	0	0
Metabolism & Nutritional Disorders	**0**	**0**	**9 (0.9)**	**17 (1.1)**	**2 (0.4)**	**2 (2.0)**	**0**	**2 (6.1)**	**32 (0.9)**

SOC/PT No. (%) of Subjects	Placebo N=208	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)	Pita Overall N=3448
Hypokalemia	0	0	1 (0.1)	0	0	0	0	2 (6.1)	3 (0.1)
Musculoskeletal and Connective Tissue Disorders	**28 (13.5)**	**41 (13.3)**	**82 (8.6)**	**123 (8.0)**	**62 (12.9)**	**31 (30.4)**	**8 (23.5)**	**17 (51.5)**	**364 (10.6)**
Arthralgia	6 (2.9)	8 (2.6)	14 (1.5)	18 (1.2)	6 (1.3)	5 (4.9)	0	1 (3.0)	52 (1.5)
Back Pain	6 (2.9)	12 (3.9)	17 (1.8)	21 (1.4)	11 (2.3)	5 (4.9)	0	0	66 (1.9)
Joint swelling	0	0	1 (0.1)	1 (0.1)	1 (0.2)	2 (2.0)	0	0	5 (0.1)
Muscle spasms	1 (0.5)	2 (0.6)	7 (0.7)	8 (0.5)	7 (1.5)	2 (2.0)	1 (2.9)	0	27 (0.8)
Musculoskeletal discomfort	2 (1.0)	0	2 (0.2)	0	2 (0.4)	0	0	0	4 (0.1)
Musculoskeletal stiffness	3 (1.4)	2 (0.6)	3 (0.3)	1 (0.1)	2 (0.4)	3 (2.9)	0	0	11 (0.3)
Musculoskeletal weakness	0	0	0	0	2 (0.4)	0	0	4 (12.1)	6 (0.2)
Myalgia	3 (1.4)	6 (1.9)	27 (2.8)	47 (3.1)	25 (5.2)	10 (9.8)	5 (14.7)	10 (30.3)	130 (3.8)
Myopathy	0	0	0	0	0	1 (1.0)	0	2 (6.1)	3 (0.1)
Neck pain	1 (0.5)	4 (1.3)	0	1 (0.1)	1 (0.2)	1 (1.0)	1 (2.9)	0	8 (0.2)
Osteoarthritis	0	3 (1.0)	4 (0.4)	14 (0.9)	2 (0.4)	0	0	0	23 (0.7)
Pain in extremity	4 (1.9)	7 (2.3)	6 (0.6)	14 (0.9)	8 (1.7)	3 (2.9)	1 (2.9)	2 (6.1)	41 (1.2)
Rhabdomyolysis	0	0	0	0	2 (0.4)	1 (1.0)	3 (8.8)	3 (9.1)	**9 (0.3)**
Shoulder pain	1 (0.5)	5 (1.6)	3 (0.3)	8 (0.5)	3 (0.6)	1 (1.0)	0	1 (3.0)	21 (0.6)
Neoplasms Benign, Malignant & Unspecified	**2 (1.0)**	**0**	**1 (0.1)**	**1 (0.1)**	**0**	**0**	**0**	**0**	**2 (0.1)**
Nervous System Disorders	**25 (12.0)**	**23 (7.4)**	**48 (5.0)**	**90 (5.8)**	**38 (7.9)**	**9 (8.8)**	**3 (8.8)**	**10 (30.3)**	**221 (6.4)**
Dizziness	2 (1.0)	4 (1.3)	6 (0.6)	16 (1.0)	4 (0.8)	2 (2.0)	0	1 (3.0)	33 (1.0)
Headache	14 (6.7)	13 (4.2)	27 (2.8)	45 (2.9)	23 (4.8)	3 (2.9)	1 (2.9)	7 (21.2)	119 (3.5)
Hypoaesthesia	1 (0.5)	0	1 (0.1)	2 (0.1)	1 (0.2)	2 (2.0)	1 (2.9)	0	7 (0.2)
Migraine	2 (1.0)	0	1 (0.1)	8 (0.5)	1 (0.2)	1 (1.0)	0	1 (3.0)	12 (0.3)
Psychiatric Disorders	**9 (4.3)**	**11 (3.6)**	**16 (1.7)**	**23 (1.5)**	**8 (1.7)**	**0**	**0**	**2 (6.1)**	**60 (1.7)**
Insomnia	5 (2.4)	4 (1.3)	10 (1.1)	8 (0.5)	1 (0.2)	0	0	1 (3.0)	24 (0.7)
Renal and Urinary Disorders	**3 (1.4)**	**5 (1.6)**	**12 (1.3)**	**16 (1.0)**	**5 (1.0)**	**3 (2.9)**	**1 (2.9)**	**2 (6.1)**	**44 (1.3)**
Leukocyturia	2 (1.0)	2 (0.6)	0	1 (0.1)	0	0	0	0	3 (0.1)
Pollakiuria	0	1 (0.3)	2 (0.2)	2 (0.1)	2 (0.4)	2 (2.0)	0	0	9 (0.3)
Reproductive System & Breast Disorders	**1 (0.5)**	**3 (1.0)**	**3 (0.3)**	**15 (1.0)**	**5 (1.0)**	**2 (2.0)**	**0**	**0**	**28 (0.8)**
Respiratory, Thoracic & Mediastinal Disorders	**9 (4.3)**	**10 (3.2)**	**17 (1.8)**	**50 (3.2)**	**9 (1.9)**	**1 (1.0)**	**2 (5.9)**	**2 (6.1)**	**91 (2.6)**
Cough	1 (0.5)	4 (1.3)	7 (0.7)	16 (1.0)	5 (1.0)	0	0	1 (3.0)	33 (1.0)
Epitaxis	2 (1.0	2 (0.6)	3 (0.3)	4 (0.3)	0	0	1 (2.9)	0	10 (0.3)
Pharyngolaryngeal pain	4 (1.9)	2 (0.6)	3 (0.3)	15 (1.0)	3 (0.6)	1 (1.0)	0	0	24 (0.7)
Sinus congestion	2 (1.0)	0	1 (0.1)	0	2 (0.4)	0	0	1 (3.0)	4 (0.1)
Skin & Subcutaneous Tissue Disorders	**4 (1.9)**	**9 (2.9)**	**33 (3.5)**	**38 (2.5)**	**10 (2.1)**	**2 (2.0)**	**4 (11.8)**	**2 (6.1)**	**98 (2.8)**
Pruritus	1 (0.5)	2 (0.6)	8 (0.8)	9 (0.6)	0	0	0	2 (6.1)	21 (0.6)

SOC/PT No. (%) of Subjects	Placebo N=208	Pita 1 mg (N=309)	Pita 2 mg (N=951)	Pita 4 mg (N=1540)	Pita 8 mg (N=479)	Pita 16 mg (N=102)	Pita 32 mg (N=34)	Pita 64 mg (N=33)	Pita Overall N=3448
Rash	2 (1.0)	1 (0.3)	5 (0.5)	8 (0.5)	3 (0.6)	0	2 (5.9)	0	19 (0.6)
Surgical & Medical Procedures	**3 (1.4)**	**1 (0.3)**	**2 (0.2)**	**3 (0.2)**	**2 (0.4)**	**1 (1.0)**	**0**	**0**	**9 (0.3)**
Vascular Disorders	**4 (1.9)**	**5 (1.6)**	**10 (1.1)**	**31 (2.0)**	**5 (1.0)**	**2 (2.0)**	**0**	**1 (3.0)**	**54 (1.6)**
Hypertension	2 (1.0)	4 (1.3)	6 (0.6)	20 (1.3)	2 (0.4)	1 (1.0)	0	0	33 (1.0)

Source: Clinical Summary, Table 2.7.4.55, ISS, Table 1.6.

The incidence of cardiac disorders was similar in placebo (1.9%), pitavastatin 1 mg (1%), 2 mg (1.3%), and 4 mg (1.7%). Pitavastatin 1-4 mg was also similar to placebo for reported gastrointestinal disorders and renal and urinary disorders. Nervous system disorders occurred less frequently on 1 mg pitavastatin (7.4%), 2 mg pitavastatin (5%), and 4 mg pitavastatin (5.8%) than compared to placebo (12%).

However, there was a distinct difference between placebo (1.4%) and 4 mg pitavastatin (3.1%) for myalgia. Myalgia also occurred with higher frequency in 1 mg pitavastatin (1.9%) and 2 mg pitavastatin (2.8%) as compared to placebo. Increases in blood CPK for 1 mg pitavastatin (1.3%), 2 mg pitavastatin (0.8%), and 4 mg pitavastatin (0.7%) were not too different from placebo (1%).

Increases in ALT ranged between 0.3% and 1.1% for pitavastatin 1 to 4 mg as compared to placebo (0.5%).

7.4.2 Laboratory Findings

Overview of laboratory testing in the development program

Generally a full blood chemistry and hematology analysis was conducted prior to the start of treatment phase (Week 0) and at the end of treatment (Week 12) or upon early termination for all Phase 2 and Phase 3 core studies, except for studies 209 and 210, where samples were taken every 4 or 8 weeks. For all the extension studies (except for study 211), a full blood chemistry assessment was made every 2, 4 or 6 weeks for the first 8-12 weeks, and then every 8 weeks until the second to last and final assessments which had a 4-week interval.

The monitoring of liver (AST and ALT) and muscle enzymes (CK) occurred every 2 weeks up to Week 4, and then every 4 weeks. The exceptions were study 210 where monitoring occurred every 2 weeks and study 202 and study 203 where monitoring occurred every 4 weeks.

Hepatic Biochemistry

Liver-related laboratory results (ALT, AST, ALP, and TB) in the clinical trials are discussed in Section 7.3.4

Muscle Biochemistry

Muscle-related laboratory results (CPK) in the clinical trials are discussed in Section 7.3.4.

Renal Biochemistry

According to the applicant, no change in mean serum creatinine was seen in Group 3 for pitavastatin. Analysis of creatinine changes could not be made of subjects with spot urine protein/creatinine ratios because only a baseline serum creatinine was measured in these patients.

The following table summarizes the serum creatinine at baseline, end of treatment and the mean change from baseline in creatinine for Group 3.

Table 60 Mean Serum Creatinine in Group 3

Treatment at Measurement	Time Point 1 = Baseline 2 = Endpoint		N	Serum Creatinine	SD
Pitavastatin 1mg	1	Mean	100	0.992	0.197
	2	Mean	100	1.016	0.189
		Mean Change from Baseline	100	0.023	0.067
Pitavastatin 2mg	1	Mean	540	0.966	0.176
	2	Mean	540	0.944	0.184
		Mean Change from Baseline	540	-0.022	0.103
Pitavastatin 4mg	1	Mean	1887	0.943	0.172
	2	Mean	1889	0.919	0.171
		Mean Change from Baseline	1887	-0.024	0.119
Atorvastatin 10mg	1	Mean	18	1.033	0.157
	2	Mean	18	1	0.168
		Mean Change from Baseline	18	-0.033	0.103
Atorvastatin 20mg	1	Mean	67	0.925	0.162
	2	Mean	67	0.904	0.164
		Mean Change from Baseline	67	-0.021	0.093
Atorvastatin 40mg	1	Mean	54	1.011	0.153
	2	Mean	54	1.006	0.157
		Mean Change from Baseline	54	-0.006	0.092

Source: NDA amendment #0031. Baseline: Screening or Week 0 of the 12-week core studies
Endpoint: Last measurement

According to the applicant, there was little change in serum creatinine from baseline to end of treatment. In fact, pitavastatin 2 mg and 4 mg showed a mean negative change in serum creatinine of -0.022 and -0.024, respectively.

This clinical reviewer requested further information on subjects with extreme changes in serum creatinine. The following table summarizes the creatinine outliers changes in Group 3.

Table 61 Summary of Creatinine Outliers by Dose at Onset – Group 3

Creatinine Outliers	Pitavastatin 1 mg (N=309)	Pitavastatin 2 mg (N=2562)	Pitavastatin 4 mg (N=2406)	Atorvastatin 10 mg (N=394)	Atorvastatin 20 mg (N=264)	Atorvastatin 40 mg (N=54)
Normal at baseline and change>1.5mg/dL						
No	102 (100.0)	543 (100.0)	1831 (99.95)	18 (100.0)	64 (100.0)	53 (100.0)
Yes	0	0	1 (0.1)	0	0	0
Change from baseline >0.5mg/dL						
No	102 (100.0)	557 (100.0)	1884 (99.95)	18 (100.0)	66 (100.0)	54 (100.0)
Yes	0	0	1 (0.1)	0	0	0

Creatinine Outliers	Simvastatin 20 mg (N=336)	Simvastatin 40 mg (N=219)	Simvastatin 80 mg (N=5)	Pravastatin 10 mg (N=103)	Pravastatin 20 mg (N=198)	Pravastatin 40 mg (N=96)
Normal at baseline and change>1.5mg/dL						
No	1 (100.0)	53 (100.0)	4 (100.0)	1 (100.0)	0	0
Yes	0	0	0	0	0	0
Change from baseline >0.5mg/dL						
No	1 (100.0)	54 (100.0)	5 (100.0)	1 (100.0)	0	0
Yes	0	0	0	0	0	0

Source: NDA submission #0034

In Group 3, there was one patient on 4 mg pitavastatin who had a change from baseline >0.5 mg/dL and value greater than 1.5 mg/dL recorded as 10 mg/dL at Week 32. According to the applicant, this patient had an immediate follow-up creatinine value of 0.9 mg/dL and all other creatinine values were within normal range. Thus, the reported value of 10 mg/dL is most like a laboratory error.

Hematology

The incidence of shifts in platelet counts from normal to low was (10/3448, 0.3%) for pitavastatin compared to placebo (2/208, 0.9%) in Group 1. Atorvastatin (1/505, 0.2%), simvastatin (1/336, 0.3%) and pravastatin (0/301, 0%) also had incidences of normal to low platelet shifts that were lower than placebo.

Further breakdown of pitavastatin by dose of shifts in platelet counts from normal to low is as follows: 1 mg= 1/309 (0.3%), 2 mg= 0/951 (0%), 4 mg= 8/1540, (0.5%), 8 mg= 1/479, (0.2%).

Other Biochemistry Parameters

The incidence of clinically significant abnormalities with 1 mg, 2 mg and 4 mg pitavastatin in the Group 3 analysis was very low, ranging from 0% to 0.5% for all parameters except for glucose (1.3%) in the 4 mg pitavastatin treatment group. The table below summarizes the shifts from not clinically significant to clinically significant laboratory values.

Table 62 Shifts from Not Clinically Significant to Clinically Significant Laboratory Values – Group 3

Laboratory variable	Pita 1 mg (N=309)		Pita 2 mg (N=2562)		Pita 4 mg (N=2406)	
Haematology						
Erythrocytes (RBCs)	-		-		4	(0.2)
Haemoglobin	-		6	(0.2)	9	(0.4)
Haematocrit	-		4	(0.2)	5	(0.2)
Leukocytes (WBCs)	-		2	(0.1)	4	(0.2)
Platelet count	-		-		7	(0.3)
Biochemistry						
Albumin	-		-		-	
Alkaline phosphatase	-		1	(0.0)	4	(0.2)
Bilirubin (total)	1	(0.3)	1	(0.0)	5	(0.2)
Blood urea nitrogen	-		-		6	(0.2)
Creatinine	-		1	(0.0)	1	(0.0)
Glucose	1	(0.3)	5	(0.2)	32	(1.3)
Inorganic phosphorus	-		-		-	
Lactate dehydrogenase (LDH)	-		1	(0.0)	2	(0.1)
Potassium	-		10	(0.4)	12	(0.5)
Sodium	-		1	(0.0)	1	(0.0)
Total protein	-		-		1	(0.0)
Uric acid	-		2	(0.1)	10	(0.4)

Source: Clinical Summary, Table 2.7.4.139.

The mean plasma glucose values in Group 1 are summarized below. Both pitavastatin and its comparator statins showed increases in mean serum glucose.

Table 63 Mean Plasma Glucose- Group 1

Assigned Treatment	Time Point 1 = Baseline 2 = Endpoint		N	Plasma Glucose	SD
Placebo	1	Mean	**208**	**51.014**	**47.314**
	2	Mean	**200**	**51.205**	**46.951**
		Mean Change from Baseline	**200**	**-0.282**	**9.769**
Pitavastatin 1mg	1	Mean	**308**	**66.411**	**44.452**
	2	Mean	**302**	**67.619**	**46.499**

Assigned Treatment	Time Point 1 = Baseline 2 = Endpoint		N	Plasma Glucose	SD
		Mean Change from Baseline	**301**	**1.081**	**11.265**
Pitavastatin 2mg	1	Mean	**950**	**88.508**	**33.826**
	2	Mean	**909**	**89.192**	**34.173**
		Mean Change from Baseline	**909**	**0.14**	**14.753**
Pitavastatin 4mg	1	Mean	**1538**	**95.462**	**31.335**
	2	Mean	**1494**	**96.549**	**33.414**
		Mean Change from Baseline	**1492**	**0.977**	**15.397**
Pitavastatin 8mg	1	Mean	**479**	**77.593**	**41.159**
	2	Mean	**450**	**77.327**	**42.25**
		Mean Change from Baseline	**450**	**0.409**	**11.114**
Pitavastatin 16mg	1	Mean	**102**	**97.206**	**14.109**
	2	Mean	**101**	**97.386**	**13.493**
		Mean Change from Baseline	**101**	**0.119**	**12.675**
Pitavastatin 32mg	1	Mean	**34**	**92.882**	**8.879**
	2	Mean	**34**	**97**	**11.824**
		Mean Change from Baseline	**34**	**4.118**	**8.738**
Pitavastatin 64mg	1	Mean	**33**	**97.121**	**11.937**
	2	Mean	**31**	**100.52**	**9.733**
		Mean Change from Baseline	**31**	**2.484**	**10.334**
Atorvastatin 10mg	1	Mean	**118**	**97.322**	**16.027**
	2	Mean	**114**	**99.833**	**24.584**
		Mean Change from Baseline	**114**	**2.211**	**16.702**
Atorvastatin 20mg	1	Mean	**240**	**114.57**	**27.808**
	2	Mean	**230**	**121.54**	**37.829**
		Mean Change from Baseline	**230**	**6.37**	**30.332**
Atorvastatin 40mg	1	Mean	**51**	**93.059**	**8.305**
	2	Mean	**51**	**94.314**	**12.782**
		Mean Change from Baseline	**51**	**1.255**	**9.593**
Atorvastatin 80mg	1	Mean	**96**	**95.24**	**12.79**
	2	Mean	**96**	**96.667**	**13.154**
		Mean Change from Baseline	**96**	**1.427**	**11.069**
Simvastatin 20mg	1	Mean	**107**	**100.13**	**17.576**
	2	Mean	**102**	**99.382**	**17.889**

Assigned Treatment	Time Point 1 = Baseline 2 = Endpoint		N	Plasma Glucose	SD
		Mean Change from Baseline	**102**	**-0.5**	**14.034**
Simvastatin 40mg	1	Mean	**229**	**99.533**	**18.698**
	2	Mean	**222**	**99.104**	**17.353**
		Mean Change from Baseline	**222**	**-0.59**	**12.066**
Pravastatin 10mg	1	Mean	**103**	**95.01**	**11.288**
	2	Mean	**101**	**96.218**	**12.739**
		Mean Change from Baseline	**101**	**0.98**	**8.499**
Pravastatin 20mg	1	Mean	**96**	**96.479**	**15.835**
	2	Mean	**94**	**97.872**	**18.572**
		Mean Change from Baseline	**94**	**1.394**	**10.883**
Pravastatin 40mg	1	Mean	**102**	**96.216**	**12.302**
	2	Mean	**101**	**97.089**	**15.352**
		Mean Change from Baseline	**101**	**0.99**	**8.895**

Source: NDA submission amendment # 0031

7.4.3 Vital Signs

Generally vital signs were assessed prior to the start of treatment phase (Week 0) and at the end of treatment (Week 12) or upon early termination for all Phase 2 and Phase 3 core studies, except for studies 209 and 210, where assessments were made every 2 or 4 weeks and for studies 202 and 203 at Weeks 4 and 8. For study 209, weight was measured at screening, visits 2 and 10 and at early termination. For all the extension studies vital signs were assessed according to schedule described for the full set of blood chemistry parameters (see Section 7.4.2).

There were no differences between the treatment groups and no changes over time in mean vital signs (SBP, DBP, pulse rate, and body weight) for the Phase 3 core and extension studies.

7.4.4 Electrocardiograms (ECGs)

For all Phase 2 and Phase 3 core studies a 12-lead electrocardiogram (ECG) was conducted prior to the start of treatment phase (Week 0) and/or at screening or during placebo or dietary run-ins, and at the end of treatment (Week 12 or 16) or upon early termination. For the extension studies ECG evaluations were conducted according to the schedule described for the full set of blood chemistry parameters (see Section 7.4.3) except for study 2204E1, where the Week 8 ECG assessment was followed by a 12-week interval, and then ECG assessments every 8 weeks.

Shifts in ECG from normal to abnormal not clinically significant (NCS) ranged from 4.2% to 14.6% of subjects across all the active-treatment groups, and in general the incidence was comparable to placebo (5.8%), except for the higher doses of each treatment where the incidence

tended to be slightly higher than placebo: 32 mg pitavastatin (11.8%), 64 mg pitavastatin (9.1%), 40 mg simvastatin (9.6%), 80 mg atorvastatin (14.6%) and 40 mg pravastatin (10.8%).

The incidence of shifts from normal (or from abnormal NCS) to abnormal clinically significant (CS) ECG values was low ranging from 0 to 1% for 1 mg to 8 mg pitavastatin; ECG shifts from normal to abnormal CS were observed in one subject with 10 mg atorvastatin (0.8%) and one subject with 20 mg atorvastatin (0.4%), and shifts from abnormal NCS to abnormal CS for one subject with 10 mg pravastatin (1%). There were no clinically significant shifts in ECG values for the higher doses of pitavastatin (16 mg, 32 mg and 64 mg).

7.4.5 Special Safety Studies/Clinical Trials

The QT-IRT reviewed protocol NK-104-1.34US which was conducted to determine the effect of pitavastatin on ECG parameters with a focus on cardiac repolarization (QTc duration) at steady state at 2 dose levels (therapeutic [4mg] and supratherapeutic [16 mg]) compared with placebo in healthy adult subjects.

According to the QT-IRT the applicant's choice of 16 mg as a supratherapeutic 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 the 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 co-administered with cyclosporine, a potent organic anion transporting polypeptides (OATP) OATP1B1 inhibitor, compared with administration of pitavastatin alone.

The QT-IRT confirmed the applicant**'s conclusions of lack of QT**c effect for pitavastatin and establishment of assay sensitivity in independent analyses.

No significant QT prolongation effect of pitavastatin (4 mg and 16 mg) was detected in this thorough QT 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 ΔQTc for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that the assay sensitivity was established in the study.

7.4.6 Immunogenicity

Repeat dose toxicity studies in animals did not indicate any effect of pitavastatin on parameters **associated with the immune response – white cell numbers, spleen or thymus – except at high** doses in some studies. As such, the applicant did not conduct specific immunotoxicity studies. Further details are described in the pharmacology/toxicology review.

7.5 Other Safety Explorations

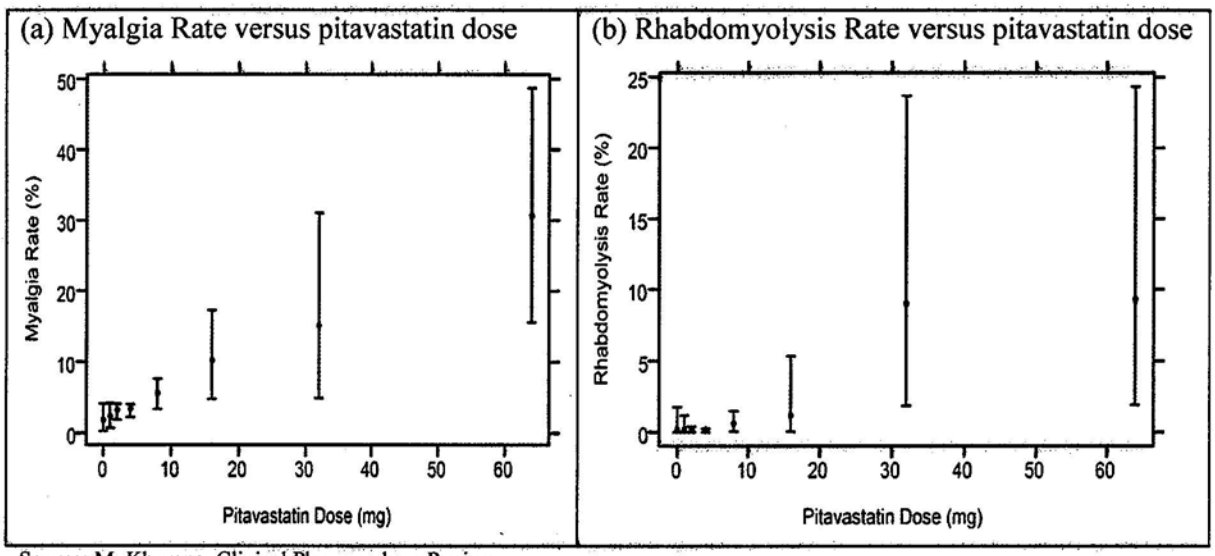
7.5.1 Dose Dependency for Adverse Events

Pitavastatin was studied at single daily oral doses of 1, 2, 4, 8, 16, 32, and 64 mg. The applicant has proposed a starting dose of 2 mg daily with a dose range of 1 to 4 mg once daily for patients with primary hypercholesterolemia and mixed dyslipidemia.

(b) (4)

Based on data from the Phase 2 and Phase 3 trials, the incidence of myalgia increased with pitavastatin dose most notably with doses ≥ 8 mg. Rhabdomyolysis occurred only with pitavastatin doses of 8 mg and higher in the clinical trials (Figure 3).

Figure 3 Myalgia (a) and Rhabdomyolysis (b) rates (95% CI) versus pitavastatin dose



Source: M. Khurana, Clinical Pharmacology Review.

7.5.2 Time Dependency for Adverse Events

Table 64 summarizes the time to first occurrence of adverse events of interest with pitavastatin. Most subjects with adverse events in the rhabdomyolysis/myopathy (SMQ) on pitavastatin presented within the first 4 weeks after start of therapy and then less commonly thereafter.

Table 64 Time to Onset of Selected Adverse Events by Study Drug at Onset

	0 to < 4 weeks	4 to <12 weeks	12 to <24 weeks	24 to <52 weeks
Rhabdomyolysis/myopathy (SMQ)				

	0 to < 4 weeks	4 to <12 weeks	12 to <24 weeks	24 to <52 weeks
Rhabdomyolysis/myopathy (SMQ)				
Subjects with events/total for interval	57/3291	74/3161	47/2783	86/1909
% subjects with event per week in interval	0.433	0.293	0.141	0.161
CPK >1XULN	**0 to < 4 weeks**	**4 to <12 weeks**	**12 to <24 weeks**	**24 to <52 weeks**
Subjects with events/total for interval	253/3291	378/960	126/2337	212/1585
% subjects with event per week in interval	1.922	1.596	0.449	0.478
Possible Drug Related Hepatic Disorder (SMQ)	**0 to < 4 weeks**	**4 to <12 weeks**	**12 to <24 weeks**	**24 to <52 weeks**
Subjects with events/total for interval	7/3291	14/3201	13/2868	19/2000
% subjects with event per week in interval	0.053	0.055	0.038	0.034
Source: Pitavastatin Study Report, Tables 2.7.4.69, 70, 71, 72.				

7.5.3 Drug-Demographic Interactions

Age

Among the elderly (> 65 years old), the adverse events on pitavastatin were similar at 1 mg (53.6%), 2 mg (50.9%) and 4 mg (50.4%). Adverse events leading to discontinuations for those > 65 years were also similar between the pitavastatin doses (Table 65). Thus, there was not a dose-dependent relationship for adverse events or withdrawals due to adverse events in the elderly with pitavastatin 1-4 mg.

In contrast, the elderly had higher adverse events, discontinuations from adverse events, and serious adverse events when compared to the non-elderly (<65 years old). For example, pitavastatin 2 mg had the most notable difference between the elderly and non-elderly (Table 65).

Table 65 Overview of Adverse Events by Age and by Dose at Onset of Pitavastatin- Group 3 Analysis

No. (%) of Subjects with	< 65 years old			>65 years old		
	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)
TEAEs Leading to Discontinuations	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)

No. (%) of Subjects with	< 65 years old			>65 years old		
	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)
Deaths	0	0	3 (0.2)	0	1 (0.1)	1 (0.1)
Source: Pitavastatin Study Report, Table 2.7.4.147, pg 323.						

The differences in adverse events between the elderly and non-elderly, particularly for the 2 mg pitavastatin dose, were driven by higher incidences of Rhabdomyolysis/Myopathy SMQ and additional muscular events of interest (Table 66). For example, subjects >65 years old had an incidence of 6.6% vs. 2.3% for those under 65 years for the SMQ Rhabdomyolysis/Myopathy. Myalgia as a preferred term under the Rhabdomyolysis/Myopathy SMQ accounted for the greatest difference between the two age groups.

Table 66 Selected Adverse Events of Interest by SMQ and Preferred Term (> 1%) of Subjects by Age, Number (%) of Subjects and by Dose at Onset -Group 3

SMQ/Preferred Term No. (%) of Subjects with	<65 years old			>65 years old		
	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)
Blood creatinine increased	0	0	0	0	0	1 (0.1)
Chromaturia	0	0	1 (0.1)	0	0	0
Muscle fatigue	0	0	0	0	3 (0.2)	0
Muscle weakness	0	0	1 (0.1)	0	1 (0.1)	0
Musculoskeletal discomfort	0	1 (0.1)	0	0	1 (0.1)	0
Musculoskeletal pain	0	1 (0.1)	0	0	3 (0.2)	1 (0.1)
Myalgia	3 (3.4)	22 (1.6)	68 (4.4)	3 (1.4)	62 (5.1)	31 (3.6)
Myalgia intercostal	0	0	1 (0.1)	0	1 (0.1)	0
Myoglobin blood increased	0	0	1 (0.1)	0	0	0
Myositis	0	0	0	0	0	0
Renal failure	0	0	1 (0.1)	0	2 (0.2)	1(0.1)
Renal failure chronic	0	0	4 (0.3)	0	2 (0.2)	1 (0.1)
Renal impairment	0	0	0	0	1 (0.1)	0
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)**
Blood creatinine increased	**0**	**0**	**0**	**1 (0.5)**	**4 (0.3)**	**2 (0.2)**
Blood urea increased	**0**	**0**	1 (0.1)	**0**	**0**	**1 (0.1)**
Protein urine present	**0**	**0**	0	**0**	**2 (0.2)**	**0**
Proteinuria	**0**	**0**	1 (0.1)	**1 (0.5)**	**1 (0.1)**	**0**
Additional Renal Events of Interest	**0**	**0**	**4 (0.3)**	**0**	**2 (0.2)**	**1 (0.1)**
Renal failure chronic	**0**	**0**	4 (0.3)	**0**	**2 (0.2)**	**1 (0.1)**

SMQ/Preferred Term No. (%) of Subjects with	<65 years old			>65 years old		
	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)
Possible Drug Related Hepatic Disorders (SMQ)	**3 (3.4)**	**11 (0.8)**	**33 (2.1)**	**3 (1.4)**	**9 (0.7)**	**10 (1.2)**
Alanine aminotransferase increased	1 (1.1)	8 (0.6)	21 (1.4)	0	5 (0.4)	5 (0.6)
Aspartate aminotransferase increased	1 (1.1)	3 (0.2)	12 (0.8)	0	4 (0.3)	5 (0.6)
Blood alkaline phosphatase increased	0	0	3 (0.2)	0	1 (0.1)	1 (0.1)
Blood bilirubin increased	0	0	1 (0.1)	0	1 (0.1)	0
Hepatic enzyme increased	1 (1.1)	0	0	1(0.5)	0	1 (0.1)
Hepatic steatosis	0	0	3 (0.2)	0	0	0
Hepatomegaly	0	0	0	0	0	0
Hyperbilirubinaemia	0	0	1 (0.1)	0	0	0
Jaundice cholestatic	0	0	0	1 (0.5)	0	0
Liver function test abnormal	0	1 (0.1)	0	0	0	0
Transaminase increased	0	1 (0.1)	1 (0.1)	1 (0.5)	2 (.2)	1 (0.1)
Source: Pitavastatin Study Report, Table 2.7.4.148, pg.323.						

According to the applicant, the difference in adverse events for pitavastatin 2 mg between the elderly and the non-elderly is explained by more long-term data in the elderly for 2 mg pitavastatin than in the non-elderly group. This clinical reviewer requested the exposure data for the two age groups.

Table 67 Duration of Exposure to Pitavastatin for Subjects > 65 Years Old – Group 3

	Pitavastatin 1 mg N=222	Pitavastatin 2 mg N=1225	Pitavastatin 4 mg N=865
Patients with total exposure			
<4 weeks	14 (6.3)	105 (8.6)	17 (2.0)
4 <12 weeks	67 (30.2)	426 (34.8)	277 (32.0)
12 <24 weeks	141 (63.5)	254 (20.7)	54 (6.2)
24 <36 weeks	0	28 (2.3)	54 (6.2)
36 <52 weeks	0	22 (1.8)	108 (12.5)
>52 weeks	0	390 (31.8)	355 (41.0)
Source: Table 3.1 Safety Summary.			

Table 68 Duration of Exposure to Pitavastatin for Subjects < 65 Years Old- Group 3

	Pitavastatin 1 mg N=87	Pitavastatin 2 mg N=1337	Pitavastatin 4 mg N=1541
Patients with total exposure			
<4 weeks	0	15.7 (11.7)	15 (1.0)
4 <12 weeks	18 (20.7)	757 (56.6)	297 (19.3)
12 <24 weeks	69 (79.3)	423 (31.6)	180 (11.7)
24 <36 weeks	0	0	100 (6.5)
36 <52 weeks	0	0	174 (11.3)
>52 weeks	0	0	775 (50.3)

	Pitavastatin 1 mg N=87	Pitavastatin 2 mg N=1337	Pitavastatin 4 mg N=1541
Source: Table 3.1 Safety Summary.			

There were no subjects <65 years old on pitavastatin 2 mg for greater than 24 weeks. In comparison, there were 390 on pitavastatin 2 mg who were >65 years old for greater than 52 weeks. Therefore, the higher incidence of myalgias and other additional muscular events of interest could have been due to the greater number of elderly in long-term trials with pitavastatin 2 mg. Although no overall difference in safety was observed between older and younger subjects, greater sensitivity of some older individuals cannot be ruled out.

Ethnicity

The total number of subjects in the ethnic subgroups given pitavastatin was too small (Black, N=8; Hispanic, N=14, Asian + Indian, N=386) to adequately compare the overall incidence and profile of adverse events relative to Caucasians (N=2,372). However, there is suggestion in the pooled short- and long-term trials (Group 3) that myalgia may be more common in the Asian+Indian subgroup (8.3%) vs. Caucasians (3.3%) on pitavastatin 4 mg. In the short-term trials (Group 1), the incidence of myalgia with 4 mg pitavastatin was 3.7% in Asian +Indian vs. 2.8% in Caucasians vs. 1.5% on placebo. Liver-related events were similar in Asian +Indian as compared to Caucasians.

In order to further investigate the possibility of increased myalgia in the Asian/Indian population, this clinical reviewer requested that the applicant conduct a subgroup analysis of adverse drug reactions of patients on 4 mg pitavastatin in the 20,000 patient post-marketing registry (LIVES) in Japan. Only 186 patients out of 20,000 were on 4 mg in this study. The incidence of myalgia was 1.1% (CI= 0.1-3.8) which was less frequent than the clinical trial data which showed an incidence of 3.1% for 4 mg pitavastatin. However, the number of subjects in the LIVES trial on 4 mg is too small to meaningfully describe the myalgia potential in Asian/Indian populations.

The applicant did study the PK differences for pitavastatin between Japanese and Caucasian men (NK-104-1.35). This ethnic comparison study showed that C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of pitavastatin in Caucasian men after the EU formulation were slightly lower than those in Japanese subjects after the JP formulation, even though the EU formulation contains 5% more of the active ingredient than does the JP formulation. According to the applicant, adjustments for age and body weight yielded results that allow the conclusion of equivalence of C_{max} and AUC_{0-t} in Caucasian men dosed with the EU formulation of pitavastatin and Japanese men dosed with the JP formulation of pitavastatin. The ratio for $AUC_{0-\infty}$ was distinctly lower than 100%, and the LCL was below the threshold of 80%, so equivalence cannot be concluded.

Gender

Adverse events occurred more frequently in women < 65 years old on pitavastatin 1 mg (51.7%) than in men (37.9%). This difference was driven **by 2 events of "AST increased" and "Hepatic enzymes increased" in a small group of 29 women.** The difference in liver-related events was not seen with pitavastatin 2 mg or 4 mg for younger women as compared to younger men. Women

>65 on 1 mg pitavastatin had an incidence of any adverse events (56.9%) similar to men >65 on pitavastatin 1 mg (49.5%). Except for 1 mg pitavastatin, the overall incidence and profile of adverse events, between men and women were similar.

Table 69 Overview of Adverse Events by Gender and Age for Pitavastatin- Group 3

No. (%) of Subjects with:	Male <65 years						Female <65 years					
	Pita 1 mg (N=58)		Pita 2 mg (N=707)		Pita 4 mg (N=800)		Pita 1 mg (N=29)		Pita 2 mg (N=630)		Pita 4 mg (N=741)	
Any TEAE	22	(37.9)	170	(24.0)	425	(53.1)	15	(51.7)	154	(24.4)	382	(51.6)
Mild	11	(19.0)	107	(15.1)	238	(29.8)	6	(20.7)	98	(15.6)	188	(25.4)
Moderate	11	(19.0)	62	(8.8)	165	(20.6)	8	(27.6)	53	(8.4)	178	(24.0)
Severe	0		1	(0.1)	22	(2.8)	1	(3.4)	3	(0.5)	16	(2.2)
Treatment-Related TEAE	11	(19.0)	67	(9.5)	87	(10.9)	4	(13.8)	57	(9.0)	86	(11.6)
TEAEs Leading to Discontinuation	1	(1.7)	13	(1.8)	27	(3.4)	1	(3.4)	9	(1.4)	24	(3.2)
Serious TEAEs	0		4	(0.6)	23	(2.9)	0		3	(0.5)	18	(2.4)
Deaths	0		0		2	(0.3)	0		0		1	(0.1)

No. (%) of Subjects with:	Males ≥65 years						Female ≥65 years					
	Pita 1 mg (N=99)		Pita 2 mg (N=516)		Pita 4 mg (N=352)		Pita 1 mg (N=123)		Pita 2 mg (N=709)		Pita 4 mg (N=513)	
Any TEAE	49	(49.5)	268	(51.9)	182	(51.7)	70	(56.9)	355	(50.1)	254	(49.5)
Mild	31	(31.3)	129	(25.0)	94	(26.7)	37	(30.1)	138	(19.5)	117	(22.8)
Moderate	17	(17.2)	116	(22.5)	80	(22.7)	27	(22.0)	186	(26.2)	116	(22.6)
Severe	1	(1.0)	23	(4.5)	8	(2.3)	6	(4.9)	31	(4.4)	19	(3.7)
Treatment-Related TEAE	15	(15.2)	74	(14.3)	40	(11.4)	21	(17.1)	101	(14.2)	46	(9.0)
TEAEs Leading to Discontinuation	4	(4.0)	28	(5.4)	19	(5.4)	6	(4.9)	35	(4.9)	18	(3.5)
Serious TEAEs	1	(1.0)	25	(4.8)	10	(2.8)	0		34	(4.8)	22	(4.3)
Deaths	0		0		1	(0.3)	0		1	(0.1)	0	

Source: Clinical Summary, Table 2.7.4.149.

7.5.4 Drug-Disease Interactions

Renal Impairment

Subjects with moderate renal impairment (baseline Clcr 30-50 mL/min/1.73 m^2), as well as subjects on hemodialysis, had an 80% increase in AUC compared to healthy subjects treated with a single 4 mg dose of pitavastatin. Except for a small trial for 7 days with 2 mg of pitavastatin in patients with moderate renal impairment, subjects with serum creatinine > 1.5XULN were excluded from the clinical trials. Therefore, there are inadequate data to know if subjects with severe renal impairment were more likely to have CPK elevations, or more likely to complain of myalgia or have other drug related adverse effects. Furthermore, there are no long-term safety data from the clinical studies for use of pitavastatin in subjects with severely impaired renal function.

The applicant did not investigate the pharmacokinetics of pitavastatin in patients with severe renal impairment (glomerular filtration rate < 30 mL/min/1.73 m^2, not on hemodialysis) and therefore does not recommend dose adjustment in these patients. This clinical reviewer believes

a PK study in patients with severe renal insufficiency is necessary for patient safety. Clinically, patients requiring statins for cardiovascular benefit often overlap with patients with renal insufficiency and dose adjustment information would be helpful guidance for physicians.

Rosuvastatin serves as an example highlighting the importance of investigating the PK in patients with severe renal insufficiency. Patients with mild to moderate renal impairment (Clcr $\geq$30 mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin. Patients on hemodialysis had a steady-state plasma concentration of rosuvastatin that was approximately 50% greater compared with healthy subjects. However, patients with severe renal impairment (Clcr <30 mL/min/1.73 m^2) not on hemodialysis had plasma concentrations of rosuvastatin 3-fold increased as compared to healthy individuals. Dose adjustment for rosuvastatin is in the current labeling of the product as a starting dose of 5 mg, not to exceed 10 mg of rosuvastatin in patients with severe renal insufficiency, not on hemodialysis.

Impaired Liver Function

Subjects with mild (Child-Pugh A) hepatic impairment had a mean C_{max} and AUC $_{0-t}$ after a single 2 mg dose of pitavastatin that was 1.34 and 1.60-fold greater than healthy subjects. Subjects with moderate (Child-Pugh B) hepatic impairment had mean C_{max} and AUC $_{0-t}$ after a single 2 mg dose of pitavastatin that was 2.69 and 3.93-fold greater than healthy subjects. The mean clearance values (CL/F) of pitavastatin decreased in relation to the severity of the hepatic impairment.

7.5.5 Drug-Drug Interactions

Heart transplant patients on cyclosporine receiving daily doses of pitavastatin 2 mg had a 6.6-fold increase in Cmax and a 4.6-fold increase in AUC $_{0-24}$ compared to values obtained in healthy subjects. The clinical pharmacology reviewer recommends a contraindication for the co-administration of pitavastatin and cyclosporine. The PK of pitavastatin lactone was not affected by the co-administration of pitavastatin and cyclosporine.

Healthy subjects receiving 600 mg twice daily of gemfibrozil and 4 mg of pitavastatin daily had an increase of 31% in Cmax and 45% in AUC $_{0-24}$ for pitavastatin when compared to placebo. Fenofibrate co-administration with pitavastatin increased the pitavastatin steady state AUC $_{0-24}$ by 18%.

An open-label, cross-over study in which subjects received warfarin 2 mg to 7 mg on days 1-21 and pitavastatin 4 mg on days 14-21 showed no clinically relevant changes in AUC or C_{max} for pitavastatin.

Erythromycin, a CYP3A4 inhibitor, co-administered with pitavastatin produced almost a 3-fold increase in AUC. The clinical pharmacology reviewer recommends a maximum dose of 1 mg pitavastatin to be co-administered with erythromycin to prevent exceeding the exposure for the 4 mg pitavastatin dose. The combination of rifampin and pitavastatin increases pitavastatin Cmax by 2 fold. Consequently, the clinical pharmacology reviewer recommends a maximum dose of 2 mg pitavastatin to be used concurrently with rifampin.

Additional drug- drug interactions are summarized in Table 71. The enalapril exposure claim is pending submission of two bioanalytical reports from the applicant for review by clinical pharmacology.

Table 70 Summary of Drug-Drug Interaction Studies (ratio of C_{max} and AUC for Pitavastatin and/or Co-administered Drugs)

Co-administered drug	Dose regimen		Change in AUC&*	Change in C_{max}&*
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6		↑4.6 fold†	↑6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days		↑2.82 fold †	↑3.62 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	(b) (4)	(b) (4)	
		Rifampin	↓15%	↓ 18%
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days		↑45%	↑31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days		↑18%	↑11%
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice for 4 days		↑ 15%	↓12%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	(b) (4)	(b) (4)	
		Ezetimibe	↑9%	↑ 2%
Warfarin	Individualized maintenance dose of warfarin (2_-_7 mg) for 8 days + pitavastatin 4 mg QD for 9 days	R-warfarin	↑7%	↑3%
		S-warfarin	↑ 6%	↑ 3%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days			(b) (4)
		Digoxin	↓3%	↓4%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days		(b) (4)	
		Enalapril	↑12%	↑12%
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	(b) (4)		
		Atazanavir	↑6%	↑13%
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days		↓23%	↓22%

Data given as x-fold change represent a simple ratio between co-administration and pitavastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to pitavastatin alone (i.e., 0% = no change).

† **Clinically Significant** *[see Dosage and Administration (2) and Warnings and Precautions (5)]*

* Values are for pitavastatin unless otherwise noted

Source: Dr. Lau's clinical pharmacology review.

This clinical reviewer suggested three other medications that are used in the management of patients with cardiovascular disease that may need to have a DDI study with pitavastatin: diltiazem, verapamil, and amiodarone. According to the clinical pharmacology reviewer, verapamil and diltiazem's R values are 1.02 and <1.03, respectively. Thus, the DDI potential **would be low. Amiodarone's potential DDI is unknown.**

The clinical pharmacology reviewer recommends an additional pitavastatin DDI study with lopinavir/ritonavir due to the in**crease in rosuvastatin exposure – a statin with a PK profile similar to pitavastatin's.**

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please see the pharmacology/toxicology report by Dr. Elmore for further details.

Carcinogenicity studies showed forestomach thickening with hyperkeratosis and hyperplasia in mice and rats in both repeat dose toxicity and carcinogenicity studies. Similar findings have been observed with other statins, but not after subcutaneous dosing, suggesting the effects were caused by a local effect in the forestomach. The occurrence of papillomas and carcinomas can be concluded to be the natural progression of these changes when prolonged over the duration of dosing used in these carcinogenicity studies. Forestomach papillomas have also been reported for fluvastatin, lovastatin, pravastatin and simvastatin in the mouse and for fluvastatin in the rat. The mechanisms underlying this effect on the forestomach are recognized and understood not to pose a risk to humans.

Pitavastatin induced thyroid tumors in the carcinogenicity study in rats. In studies designed to understand the mechanism(s) underlying this effect, pitavastatin was shown to increase thyroid weight, decrease thyroxine (T_4) and increase thyroid stimulating hormone (TSH) concentrations in rats dosed for up to 28 days with 25 or 50 mg/kg/day; these effects correlated with an increase in UDP-GT activity in liver microsomes.

A subsequent study showed that these effects were not seen in animals receiving 5 mg/kg/day. Clearance of exogenously administered ^{125}I-T4 was increased, with a consequent fall in circulating plasma levels, in rats administered 25 and 50 mg/kg/day for 8 days. Together, these data provide an explanation for the histological **changes in the thyroid – decreased T4 with a** feedback increase in TSH which provides constant stimulation of the thyroid resulting in hypertrophy and ultimately to hyperplasia and tumors. Similar events have been described for simvastatin and have been shown to be a rat-specific phenomenon.

7.6.2 Human Reproduction and Pregnancy Data

Pitavastatin is contraindicated in women who are pregnant or breast feeding. In these clinical trials, there were 2 pregnancies in the healthy volunteer studies which resulted in spontaneous

abortions. In study 123US, patient #038, a 22-year-old Caucasian woman, experienced an SAE of abortion spontaneous. Her pregnancy tests at Screening, Check-in, and Day (b) (6) (check-in the period 2) were negative. She was randomly assigned to treatment sequence BA (pitavastatin 4 mg for 14 days taken in the evening and pitavastatin 4 mg for 14 days taken in the morning after 30-day washout) completed Day (b) (6) she had a spontaneous abortion. No action was required, and the event was considered resolved (b) (6) The subject completed the study.

Subject 015, [Study 109] exhibited a positive serum pregnancy test on the Day 16 post study assessment following gemfibrozil + pitavastatin treatment. The subject had a spontaneous abortion a month later.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pitavastatin has not been studied in children or adolescents. A pediatric waiver was granted by the Agency, as pitavastatin does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound
There is no prior history of drug abuse potential or withdrawal with other members of the statin drug group. No specific trials to test for drug abuse potential were performed. There have been no reports of significant overdose in the post-marketing data from Japan. In case of overdose, the applicant directs that patients be treated symptomatically with supportive measures. As pitavastatin is highly protein bound, hemodialysis is not expected to be of benefit.

7.7 Additional Submissions

Kowa did not submit a 120-day Safety Update since no additional clinical trials were conducted after the original NDA submission. In lieu of the traditional Safety Update the applicant submitted the tenth periodic safety update report from Japan and the final study report for extension study NK-104-310.

The periodic safety update report (PSUR) #10 from Japan included updates from various sources including spontaneous reports, clinical investigational researches, and published references that the applicant had received from 17 January 2008 to 16 July 2009. There were three spontaneous reports of rhabdomyolysis; two patients on 2 mg pitavastatin and 1 patient on 4 mg pitavastatin. There were five spontaneous reports of hepatic **–related events. As these were spontaneous** reports, no CRFs were available for review.

The applicant submitted a final study report for extension study NK-104-310; however the applicant did not intend to use this extension study as support of safety or efficacy for the NDA. The dataset for this study was not submitted.

In brief, Study NK-104-10 was a 44-week, multicenter, double-dummy, parallel group, active-controlled, follow-on study in patients from the core study NK-104-305 program. The study consisted of a 16 week double-blind phase followed by a 28 week single-blind phase. Visit 1

(Week 0) was the same day as the last visit (Week 12) of the core study. Patients assigned to pitavastatin 4 mg in study NK-104-305 continued treatment with pitavastatin 4 mg in this study. Patients assigned to atorvastatin 20 mg in study NK-104-305 either continued treatment with atorvastatin 20 mg or could be up-titrated to atorvastatin 40 mg at Visit 1 if they did not achieve their target LDL-C level at Visit 7 of the core study. Treatment was administered according to a double-blind, double-dummy design with each patient dose consisting of one tablet and two capsules.

Male and female patients (age 18-75 years), with type II DM (HbA1c $\leq$7.5%) and combined dyslipidemia as defined by elevated plasma LDL-C (LDL-C $\geq$ 100 mg/dL and $\leq$ 220 mg/dL) despite dietary therapy, and elevated TG of $\geq$ 150 mg/dL, who satisfied the inclusion/exclusion criteria of the previous core study, NK-104-305, and completed the core study.

Approximately half of the safety population (52% of the pitavastatin 4 mg treatment group and 58% of the atorvastatin 20 mg/40 mg treatment group) was male. The mean age of the patients was 59.3 years in the pitavastatin 4 mg treatment group and 60.0 years in the atorvastatin 20 mg/40 mg treatment group. Patients who up-titrated to atorvastatin 40 mg were slightly younger on average than those who remained on atorvastatin 20 mg (54.7 years vs. 60.5 years). Most patients (93% pitavastatin 4 mg and 90.1% atorvastatin 20 mg/40 mg) were Caucasian, the other patients in the study were Indian. Mean duration of combined dyslipidemia was 4.6 years in the pitavastatin 4 mg treatment group and 5.3 years in the atorvastatin 20 mg/40 mg treatment group. All patients had type II DM. Mean duration of type II DM was 6.05 years in the pitavastatin 4 mg treatment group and 6.43 years in the atorvastatin 20 mg/40 mg treatment group. Patients who up-titrated to 40 mg atorvastatin had a shorter mean duration of type II DM (2.71 years) than those who remained on 20 mg atorvastatin (6.83 years). Seven atorvastatin 20 mg treated patients failed to meet the LDL-C target at Week 8 of the core study and were up-titrated to the 40 mg dose at Visit 1 of the extension study.

The most commonly reported adverse events (in order of incidence) for the pitavastatin 4 mg treatment group were nasopharyngitis, myalgia/myalgia intercostal, and spinal osteoarthritis. The most common adverse events in order of incidence for the atorvastatin 20 mg/40 mg treatment group were myalgia/myalgia intercostal, arteriosclerosis and inadequate control of diabetes mellitus.

The overall proportion of patients who reported TEAEs during the extension study was similar in the pitavastatin 4 mg treatment group (49.7%) and in the atorvastatin 20 mg/40 mg treatment group (46.5%). Treatment related TEAEs were reported for fewer patients in the atorvastatin 20 mg/40 mg treatment group (2.8%) than in the pitavastatin 4 mg treatment group (3.5%) although as numbers were small it is difficult to draw any meaningful conclusions. A total of 13 patients had serious TEAEs: 8 (5.6%) in the pitavastatin 4 mg group and 5 (7.0%) in the atorvastatin 20 mg/40 mg treatment group. There were no reports of myopathy or rhabdomyolysis.

Myalgia/myalgia intercostal was reported by 11 patients in total: 6 (4.2%) patients in the pitavastatin 4 mg treatment group and 5 (7.0%) in the atorvastatin 20 mg/40 mg treatment group. One patient in each treatment group had reports of myalgia with elevated CK during the

treatment period. The patient in the pitavastatin 4 mg treatment group had two episodes of mild myalgia, both considered unrelated to study treatment by the investigator; and neither episode was temporally related to the CK elevations reported for this patient. The patient in the atorvastatin 20 mg/40 mg treatment group had mild myalgia with a concurrent increase in CK, both considered possibly related to study treatment. The patient was temporarily discontinued, but due to an error did not restart study drug and was considered discontinued because of administrative problems.

One patient (in the pitavastatin 4 mg treatment group) showed clinically significant abnormalities in liver enzyme values (>10XULN), but no specific safety concerns were raised.
Clinically significant abnormalities in CPK values were reported for 3 patients from the pitavastatin 4 mg treatment group (one patient at >5XULN, and two patients at >1XULN but <2X ULN) and one patient from the atorvastatin 20 mg/40 mg treatment group (>2XULN but <3XULN).

There were no significant findings in blood glucose, HbA1c analysis, urinalysis, vital signs or 12-lead ECG interpretations.

The following shift table summarizes the change from baseline to end of study for blood glucose. The incidence of normal to high blood glucose values was similar in the pitavastatin group and in the atorvastatin group.

Table 71 Change in Blood Glucose Study NK-104-310

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Table 29.5.1
Laboratory Data
Blood Chemistry - Glucose (mg/dL): Shift Tables
Safety Population:Part A

Relationship to Normal Range	Pitavastatin 4 mg (N=143)					Atorvastatin 20mg/40mg (N=71)				
	Week 44 Endpoint					Week 44 Endpoint				
Number of Patients	L	N	H	Missing (-)	Total	L	N	H	Missing (-)	Total
Baseline*										
Low (L)	0	0	0	0	0	0	0	0	0	0
Normal (N)	0	31	27	0	58	0	18	12	1	31
High (H)	0	19	65	1	85	0	6	34	0	40
Total	0	50	92	1	143	0	24	46	1	71

Source: NDA Submission –Safety Update

8 Post-market Experience

Pitavastatin 1 mg, 2 mg, and 4 mg doses were approved in Japan for the treatment of dyslipidemia in 2003. Per routine Japanese regulations, Kowa was required to conduct an open-label, single-arm 2-year post-approval study of pitavastatin in approximately 20,000 patients (LIVES)(Kurihara, 2007). Nearly all subjects were treated with 1 mg or 2 mg of pitavastatin. The most commonly reported reactions were increased CPK (2.7%), increased ALT (1.8%), and increased AST (1.5%). Rhabdomyolysis was reported in 2 subjects (0.01%), although the diagnosis in one case is questionable as **the subject's CPK value was below 10XULN.** Proteinuria was reported for 5 subjects (0.03%) and renal failure in 1 subject (0.01%). Hepatic

function abnormal was recorded for 6 subjects (0.03%), liver disorder for 4 subjects (0.02%), and jaundice in 1 subject (0.01%). There were no cases of liver failure or transplant reported. Although uncontrolled, these data do not raise concern about the safety of the 1 mg and 2 mg doses of pitavastatin.

The Office of Surveillance and Epidemiology (OSE) reviewed 49 cases of Japanese post-marketing reports of possible liver injury associated with pitavastatin including elevations in transaminases, alkaline phosphatase, and bilirubin levels. According to the OSE reviewer, the cases were of poor quality and the reason for these elevations could not be elucidated. No case described an outcome of liver transplant or liver failure. It was recommended that the sponsor submit all possible liver injury reports in an expedited manner for three years post-approval.

In April 2009, the Division requested that the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), a consulting organization that works for the Ministry of Health, Labour and Welfare, identify any post-marketing adverse events of concern for pitavastatin. The PMDA submitted a list of revisions to the Japanese pitavastatin label (Table 72).

In a second correspondence dated June 24, 2009, the Division again asked the PMDA if they had **any concerns regarding pitavastatin's safety – in particular its muscle and hepatic safety profiles – relative to other marketed statins in Japan.** Statins approved in Japan include fluvastatin, simvastatin, atorvastatin, pravastatin, pitavastatin, and rosuvastatin. In a response dated July 16, 2009, the PMDA stated that they do not have any **concerns regarding pitavastatin's safety** relative to other marketed statins in Japan.

Table 72 Japanese Pitavastatin Label Revisions

Date of Revision	Details of Revision
2004. 8.	[Adverse Reactions(clinically significant adverse reactions)] Hepatic function disorder, jaundice: Hepatic function disorder with significant elevations of AST (GOT) and ALT (GPT), etc. and jaundice may occur. Patients should be carefully monitored through periodic hepatic function tests, etc., and if abnormalities are observed, discontinue administration and take appropriate measures.
2004. 8.	[Adverse Reactions(other adverse reactions)] hypersensitivity : urticaria, erythema renal : pollakiuria muscular : cramp,feeling of weakness Psychoneurotic:sleep loss
2005. 6.	[Adverse Reactions(clinically significant adverse reactions)] Platelets decreased: Platelets decreased may occur. Patients should be carefully monitored through blood tests etc. If abnormalities are observed, discontinue administration and take appropriate measures.
2005. 6.	[Adverse Reactions(other adverse reactions)] Digestive organ:nausea/vomiting,anorexia
2005. 12.	[Adverse Reactions(other adverse reactions)]

	Digestive organ:glossitis
2006. 12.	[Adverse Reactions(other adverse reactions)] others:dysgeusia
2009. 3.	[Interactions (precautions for concomitant use)] [pharmacokinetics] rifampicin, erythromycin

Post-marketing Rhabdomyolysis in Japan

The company reported 37 post marketing (spontaneously reported) cases of rhabdomyolysis in Japan from July 2003 to January 2008. To help us understand the significance of that number, the Division asked the Japanese regulatory authorities to provide prescription use data for pitavastatin in Japan. They responded that they did not track that data, but confirmed that they had the same number of reports of rhabdomyolysis as submitted in the NDA by the sponsor.

The company submitted an estimate for the number of prescriptions in Japan based on the number of tablets distributed and the prescribing information from 1,600 physicians. Specifically, the prescribing information was used to break down the numbers of shipped tablets into the number of prescriptions for each dose.

Kowa believes that 13/37 cases met the definition of rhabdomyolysis. The definition Kowa used was CPK >10,000 IU/L, signs and symptoms (myalgia, weakness), and the clinical diagnosis of rhabdomyolysis. The estimated total number of prescriptions for all doses in Japan was (b) (4). If there were 13 cases of rhabdomyolysis, then the incidence of rhabdomyolysis would be 0.06 per (b) (4) prescriptions. Kowa claims that pitavastatin is comparable in the incidence of rhabdomyolysis with other statins and is well below the incidence of cerivastatin for rhabdomyolysis.

Post Marketing Liver-Related Events in Japan

There were 49 pitavastatin post-market reports from Japan of possible liver injury evaluated by OSE. OSE estimates these 49 cases occurred in about 2,000,000 patient-years of exposure in Japan.

There were no deaths secondary to liver injury or liver transplantation reported in the 49 cases from Japan. There was one death in an 88 year old woman with CHF on 1 mg pitavastatin. The OSE reviewer reported that the death was unlikely related to pitavastatin.

According to the "Liver Injury Case Definitions" where a severity score of 4 or 5 are the most severe cases, there were no cases that met those criteria. In the hospitalized cases, 38 patients received a severity score of 3(moderate to severe). The median time to event was <6 months in 24/38 cases. Further breakdown:

- 18/38 of cases had an ALT >20XULN
- 11/38 cases had TB >2.5XULN (11 others had unknown TB)
- 26/38 cases had Alk Phos > 2XULN

- 11/38 had concurrent AT > 3XULN and TB >2 XULN

The "R" score which is calculated as "Peak ALT/ULN / Peak Alk Phos/ ULN" indicates the type of liver-related injury. A score > 5 indicates hepatocellular injury; 5 > R > 2 indicates a mixed picture; and <2 indicates cholestatic injury. In these 38 hospitalized patients:

- 8 patients had a R score >5 (hepatocellular)
- 10 patients had a R score between 2 and 5 (mixed)
- **10 patients had a R score < 2 – (cholestatic)**

The presence of possible alternative causes for liver injury in these cases are: viral hepatitis A, B, or C; autoimmune hepatitis; alcoholic hepatitis; hepatobiliary disease; congestive heart failure; medications; other.

The OSE review is complicated by submission **of "un-synthesized" re**ports from Japan (the narratives are not processed, but seem to be directly transmitted from the physician reports). OSE recommends that the sponsor submit all possible liver injury reports in an expedited fashion for three years post-approval.

9 Appendices

9.1 Literature References

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9.2 Labeling Recommendations

See final approved labeling

9.3 Advisory Committee Meeting

Given that pitavastatin is the 8th statin evaluated for approval by the Agency and there were no significant safety issues identified with pitavastatin relative to marketed statins, an Advisory Committee meeting was not considered necessary.

Appendix A

The following lists of preferred terms for "adverse events of interest" were identified by the applicant using three MedDRA Version 8.1 SMQs : 1)Rhabdomyolysis/myopathy (SMQ), 2) Acute renal failure (SMQ), and 3) a subset of **Hepatic Disorders (SMQ) – "Possible drug related hepatic disorders – comprehensive search". T**here is another list of preferred terms for **"Symptomatic Myopathy" complied by the applicant to follow definitions according to National** Lipid Association. Two lists of **"additional" AE preferred terms** were selected for muscular and renal AEs.

MedDRA Version 8.1
RHABDOMYOLYSIS/MYOPATHY (SMQ)
Preferred Terms
Anuria
Biopsy muscle abnormal
Blood calcium decreased
Blood creatine phosphokinase abnormal
Blood creatine phosphokinase increased
Blood creatine phosphokinase MM increased
Blood creatinine abnormal
Blood creatinine increased
Chromaturia
Compartment syndrome
Creatinine renal clearance decreased
Diaphragm muscle weakness
Electromyogram abnormal
Glomerular filtration rate abnormal
Glomerular filtration rate decreased
Hypercreatininaemia
Hypocalcaemia
Muscle disorder
Muscle enzyme increased
Muscle fatigue

Muscle haemorrhage
Muscle necrosis
Muscle rupture
Muscular weakness
Musculoskeletal discomfort
Musculoskeletal disorder
Musculoskeletal pain
Myalgia
Myalgia intercostal
Myoglobin blood increased
Myoglobin blood present
Myoglobin urine present
Myoglobinaemia
Myoglobinuria
Myopathy
Myopathy toxic
Myositis
Oliguria
Polymyalgia
Renal failure
Renal failure acute
Renal failure chronic
Renal impairment
Renal tubular necrosis
Rhabdomyolysis
Additional Muscle AEs of Interest - Symptomatic myopathy terms not in the SMQ
Preferred Terms
Back disorder
Back pain
Buttock pain
Chest wall pain
Fibromyalgia
Flank pain
Groin pain
Limb discomfort
Muscle atrophy
Muscle spasms
Muscle tightness
Muscle twitching
Musculoskeletal chest pain
Musculoskeletal stiffness
Myofascial spasm
Neck pain
Pain in extremity
Pain in jaw
Polymyalgia rheumatica

Sensation of heaviness
Shoulder pain
Torticollis
NLA Symptomatic Myopathy - muscle symptoms
Preferred Terms
Back disorder
Back pain
Buttock pain
Chest wall pain
Compartment syndrome
Fibromyalgia
Flank pain
Groin pain
Limb discomfort
Muscle atrophy
Muscle disorder
Muscle fatigue
Muscle haemorrhage
Muscle necrosis
Muscle rupture
Muscle spasms
Muscle tightness
Muscle twitching
Muscular weakness
Musculoskeletal chest pain
Musculoskeletal discomfort
Musculoskeletal disorder
Musculoskeletal pain
Musculoskeletal stiffness
Myalgia
Myalgia intercostals
Myofascial spasm
Myopathy
Myopathy toxic
Myositis
Neck pain
Pain in extremity
Pain in jaw
Polymyalgia
Polymyalgia rheumatica
Rhabdomyolysis
Sensation of heaviness
Shoulder pain
Torticollis

MedDRA Version 8.1

ACUTE RENAL FAILURE (SMQ)
Preferred Terms

Acute nephritic syndrome
Acute prerenal failure
Albuminuria
Anuria
Azotaemia
Blood creatinine abnormal
Blood creatinine increased
Blood urea abnormal
Blood urea increased
Blood urea nitrogen/creatinine ratio increased
Creatinine renal clearance decreased
Dialysis
Glomerular filtration rate abnormal
Glomerular filtration rate decreased
Haemodialysis
Hypercreatininaemia
Neonatal anuria
Nephritis
Nephritis interstitial
Nephropathy toxic
Oedema due to renal disease
Oliguria
Peritoneal dialysis
Protein urine present
Proteinuria
Renal failure acute
Renal failure neonatal
Renal function test abnormal
Renal impairment
Renal impairment neonatal
Renal transplant
Renal tubular disorder
Renal tubular necrosis
Tubulointerstitial nephritis
Urea renal clearance decreased
Urine output decreased
Additional Renal AEs of Interest
Preferred Terms
Nephritis allergic
Nephrotic syndrome
Renal failure chronic

MedDRA Version 8.1

Hepatic Disorders (SMQ) - Possible drug related hepatic disorders – comprehensive search.
Preferred Terms
LIVER RELATED INVESTIGATIONS, SIGNS AND SYMPTOMS (SMQ)

5'nucleotidase increased
Alanine aminotransferase abnormal
Alanine aminotransferase increased
Ammonia abnormal
Ammonia increased
Ascites
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
Bile output abnormal
Bile output decreased
Bilirubin conjugated increased
Biopsy liver abnormal
Blood alkaline phosphatase abnormal
Blood alkaline phosphatase increased
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Blood cholinesterase abnormal
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Blood cholinesterase decreased
Bromosulphthalein test abnormal
Caput medusae
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased
Guanase increased
Haemorrhagic ascites
Hepaplastin abnormal
Hepaplastin decreased
Hepatic congestion
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic function abnormal
Hepatic mass
Hepatic pain
Hepatomegaly

Hepatosplenomegaly
Hyperammonaemia
Hyperbilirubinaemia
Hypercholia
Hypoalbuminaemia
Kayser-Fleischer ring
Leucine aminopeptidase increased
Liver function test abnormal
Liver induration
Liver palpable subcostal
Liver scan abnormal
Liver tenderness
Mitochondrial aspartate aminotransferase increased
Oedema due to hepatic disease
Perihepatic discomfort
Portal vein pressure increased
Retinol binding protein decreased
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
Urobilin urine present
X-ray hepatobiliary abnormal

CHOLESTASIS AND JAUNDICE OF HEPATIC ORIGIN (SMQ)

Bilirubin excretion disorder
Cholaemia
Cholestasis
Cholestatic pruritus
Hepatitis cholestatic
Hyperbilirubinaemia
Icterus index increased
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Ocular icterus
Yellow skin

HEPATITIS, NON-INFECTIOUS (SMQ)
Autoimmune hepatitis
Chronic hepatitis
Cytolytic hepatitis

Graft versus host disease in liver
Granulomatous liver disease
Hepatitis
Hepatitis acute
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis toxic
Ischaemic hepatitis
Radiation hepatitis

LIVER NEOPLASMS, MALIGNANT AND UNSPECIFIED (SMQ)

Hepatic cancer metastatic
Hepatic cancer stage I
Hepatic cancer stage II
Hepatic cancer stage III
Hepatic cancer stage IV
Hepatic neoplasm
Hepatic neoplasm malignant
Hepatic neoplasm malignant non-resectable
Hepatic neoplasm malignant recurrent
Hepatic neoplasm malignant resectable
Hepatobiliary carcinoma in situ
Hepatobiliary neoplasm
Hepatoblastoma
Hepatoblastoma recurrent
Liver carcinoma ruptured
Malignant hepatobiliary neoplasm
Mixed hepatocellular cholangiocarcinoma

LIVER NEOPLASMS, BENIGN (SMQ)
Benign hepatic neoplasm
Focal nodular hyperplasia
Haemangioma of liver
Hepatic adenoma
Hepatic cyst
Hepatic cyst ruptured
Hepatic haemangioma rupture

HEPATIC FAILURE, FIBROSIS AND CIRRHOSIS AND OTHER LIVER DAMAGE-RELATED CONDITIONS (SMQ)

Ascites
Asterixis
Biliary cirrhosis
Biliary cirrhosis primary
Biliary fibrosis
Coma hepatic
Cryptogenic cirrhosis
Hepatectomy
Hepatic atrophy
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic failure
Hepatic fibrosis
Hepatic infiltration eosinophilic
Hepatic lesion
Hepatic necrosis
Hepatic steatosis
Hepatobiliary disease
Hepatocellular damage
Hepatocellular foamy cell syndrome
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatotoxicity
Liver and small intestine transplant
Liver disorder
Liver operation
Liver transplant
Lupoid hepatic cirrhosis
Nodular regenerative hyperplasia
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Portal hypertension
Portal triaditis
Renal and liver transplant
Reye's syndrome
Spider naevus
Varices oesophageal

POSSIBLE LIVER-RELATED COAGULATION AND BLEEDING DISTURBANCES (SMQ)

Blood fibrinogen abnormal
Blood fibrinogen decreased
Blood thrombin abnormal
Blood thrombin decreased

Blood thromboplastin abnormal
Blood thromboplastin decreased
Coagulation factor IX level abnormal
Coagulation factor IX level decreased
Coagulation factor V level abnormal
Coagulation factor V level decreased
Coagulation factor VII level abnormal
Coagulation factor VII level decreased
Coagulation factor X level abnormal
Coagulation factor X level decreased
Coagulation factor decreased
International normalised ratio abnormal
International normalised ratio decreased
Protein C decreased
Protein S abnormal
Protein S decreased
Prothrombin level abnormal
Prothrombin level decreased
Prothrombin time abnormal
Prothrombin time prolonged
Prothrombin time ratio abnormal
Prothrombin time ratio decreased
Thrombin time abnormal
Thrombin time prolong

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22363	ORIG 1		LIVALO TABLETS

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/s/

IFFAT N CHOWDHURY
08/03/2009

ERIC C COLMAN
08/03/2009

8/3/09

INDIVIDUAL EFFICACY STUDY REVIEWS

Application Type	NDA
Submission Number	22-363
PDUFA Goal Date	August 3rd 2009
Reviewer Name	David Gortler, PharmD, FCCP
Established Name	Pitavastatin
(Proposed) Trade Name	**Livalo ™**
Therapeutic Class	HMG-CoA Reductase Inhibitor
Applicant	Kowa Company Ltd (KCL)
Formulation	Oral tablets
Dosing Regimen	1, 2 and 4 mg
Indication	Lipid-lowering agent
Intended Population	Primary hyperlipidemia and mixed lipidemia populations

Table of Contents

LIST OF ABBREVIATIONS AND DEFINITIONS:

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
Apo-A1	Apolipoprotein A1
Apo-B	Apolipoprotein B
ASAT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (ASAT/SGOT)
BUN	Blood urea nitrogen
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
COM	Completer population
CVD	Cardiovascular Disease
FAS	Full Analysis Set
HbA_{1c}	Glycosylated hemoglobin A_{1c}
HDL	High density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hsCRP	High sensitivity C-reactive protein
ID	Identification
LDL	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
NCEP	National cholesterol Education Program
PP	Per protocol
QD	Once daily
RBC	Red blood cells
RLP-C	Remnant-like particle cholesterol
SD	Standard deviation
TC	Total cholesterol
TG	Triglycerides
VLDL	Very low density lipoprotein-C
vs.	Versus

1 Review of Efficacy: Discussion of Individual Studies

2 Phase 2 individual Study Reviews

2.1 Efficacy and Dose Response in 261 subjects with Primary Hypercholesterolemia [HEC/NK98402N/NK-104.202]

Study initiation date: 19 June 1999
Study completion date: 06 July 2000

2.1.1.1 General Discussion of Study Objectives, Endpoints and Methods

Primary objective:

- To compare the efficacy of th (b) (4) doses of pitavastatin (1, 2, 4(b) (4) ; mg) and placebo in reducing serum LDL. The primary efficacy parameter was the percentage change in calculated LDL between baseline and endpoint in subjects with primary hypercholesterolemia.

Secondary objectives:

- To assess the efficacy of pitavastatin on other lipid parameters including total cholesterol, high density lipoprotein-cholesterol (HDL), triglycerides, Apo A1 and Apo B as percentage change
- To compare the safety of the four doses of pitavastatin with placebo for AE rates and changes in laboratory parameters.

Study Design:
HEC/NK98402N/NK-104.2.02 was a double blind, Phase 2 placebo-controlled dose-ranging study designed to determine the appropriate dose of pitavastatin.

This study included male and female subjects who were between 18 and 75 years of age. Subjects needed to have primary hypercholesterolemia (Fredrickson Type IIa), with LDL levels ≥160 but ≤250 mg/dL and TG ≤300 mg/dL. LDL values were calculated using the Friedewald formula.

The duration of the treatment phase was 16 weeks, which consisted of 4 weeks of placebo treatment before randomization and 12 weeks of active double-blind treatment. The study was divided into 2 periods designated A and B as specified in the study design schematic below.

Period A		Randomization	Period B
Wash-out	Placebo run-in		Treatment period

Screening visit (enrolment)			Baseline visit				Final visit
Visit 1	Visit 2	Visit 1/2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Week -8 to -10	Week -4	Week -4	Week -2	Week 0	Week 4	Week 8	Week 12

At their first visit, subjects were instructed to discontinue their current lipid-lowering treatment (four week wash-out period for subjects on statins and resins and six week wash-out period for subjects on fibrates).

Following the washout period, subjects were to take two tablets once daily at bedtime during the single-blind and double-blind treatment periods.

Period A: placebo run-in period (Visit 2 to Visit 4)
All subjects received two tablets of placebo in a single-blind manner for four weeks.

Period B: treatment period (Visit 4 to Visit 7)
Upon completion of the placebo run-in, subjects who were >80% compliant with placebo treatment and still in accordance with the inclusion and exclusion criteria were randomized to one of the five treatment groups shown below. Each subject received one of these regimens for 12 weeks under double-blind conditions:

- pitavastatin 1 mg arm: 1 tablet of active pitavastatin 1 mg and 1 tablet of pitavastatin placebo
- pitavastatin 2 mg arm: 1 tablet of active pitavastatin 2 mg and 1 tablet of pitavastatin placebo
- pitavastatin 4 mg arm: 2 tablets of active pitavastatin 2 mg
- (b) (4) [redacted]
- pitavastatin placebo arm: two tablets of placebo

Inclusion criteria:

- Provision of written informed consent to participate in the study
- Age between 18 years and 75 years inclusive at study entry
- Ambulatory males or females
- For female subjects of childbearing potential, a negative pregnancy test at Visit 2, and the use of oral contraceptives for ≥3 months before study entry and throughout the study period
- LDL level at Visit 3 ≥ 160 mg/dL, but ≤ 250 mg/dL, and triglyceride level ≤300 mg/dL

- Willing to adhere to the recommended diet (NCEP Step-1 or equivalent diet) throughout the whole study period

Exclusion Criteria

- Pregnant females
- Females of childbearing potential not taking oral contraceptives for greater than three months before study entry, or intending to stop contraception during the study period
- Body Mass Index (BMI) > 30 kg/m^2
- Alcohol abuse, defined by a current' intake of > 14 standard drinks each week. A standard drink was defined as one glass of wine (200mL at 11% alcohol) or one bottle of beer (500 mL at 5%) or 30 mL of spirits
- History of hypersensitivity to HMG-CoA reductase inhibitors
- Any other disease or condition which in the opinion of the investigator might pose a risk to the subject or confound the results of the study (e.g. other endocrine diseases or acute or chronic infections)
- Use of one or more of the following concomitant drugs: immunosuppressive drugs (e.g., cyclosporin), systemic antifungal agents of the azole class [e.g., itraconazole or ketoconazole), warfarin or warfarin-like anticoagulants, mibefradil, vitamins containing niacin, erythromycin or erythromycin-like drugs (e.g. clarithromycin and azithromycin), corticosteroids including inhalation formulation, androgens (estrogen and progesterone as replacement therapy for post-menopausal females were permitted if the dose was unchanged for at least eight weeks before enrolment at Visit 1 and was not intended to change throughout the whole duration of the study]
- Treatment with any other investigational drug within 30 days before the enrolment visit (Visit 1)
- Compliance < 80% during the placebo run-in period
- For subjects with known Type I or Type I1 diabetes mellitus, the fasting serum glucose level had to be < 126 mg/dL at Visit 2
- Subjects with significant renal impairment, defined by serum creatinine > 1.8 mg/dL at Visit 2, or known nephrotic syndrome
- Uncontrolled hypertension (treated or untreated), defined as diastolic blood pressure ≥110mmHg and/or systolic blood pressure ≥180 mmHg. Subjects receiving beta-blockers or diuretics could be enrolled only if their treatment had been unchanged for at least 8 weeks before enrollment (Visit I), and if it was not intended to change during the study
- History of myocardial infarction, unstable angina, stroke, transient ischemic attack, percutaneous transluminal coronary angioplasty or coronary artery bypass surgery
- Congestive heart failure NYHA Class 3 or 4
- Subjects with known active liver disease and/or elevated serum transaminase (AST or ALT) > 2x ULN at Visit 3
- Subjects with known muscular or neuromuscular disease and/or CK > 3x ULN at Visit 3 with no obvious explanation (e.g. muscular trauma, massage or strenuous exercise)
- Any malignant tumor which required any treatment within the past 10 years.
- Subjects with known cataracts, however, subjects whose lenses have been removed could be enrolled

- Subject with known HIV infection, known severe depression, poor mental function and/or suicidal tendencies
- **Diagnosis of (Fredrickson's) Types I, IIb, III, IV, V hyperlipidemia**
- Known heterozygous or homozygous forms of familial hypercholesterolemia or subjects with a LDL level > 250 mg/dL at Visit 3
- Secondary hypercholesterolemia due to hypothyroidism TSH > ULN at Visit 3. Subjects with a history of hypothyroidism who were on a stable dose of thyroxine six months before Visit 2 with normalized plasma thyroxine and TSH could be included

Treatment Phase:
A centralized randomization system was used to ensure an optimal balance of subjects among treatment groups by center and by country. When contacted by the investigator, the system indicated a 6-digit treatment identification number that was allocated to a dose level; treatment packages and blister strips were then labeled accordingly along with sealed envelopes containing the randomization codes.

Dose selection:
The following doses of pitavastatin were used in this study: 1 mg, 2 mg, 4 mg, (b) (4) These doses were selected on the basis of data obtained from previous Phase 1 and 2 studies of pitavastatin in humans.

Blinding
During the run-in period (Period A), placebo was given according to a single-blind procedure.

During the treatment period (Period B), neither the investigator nor the subject was aware of the treatment assignment. The investigator was not to receive lipid values from the treatment period (Period B) until after the study was completed.

Prior and Concomitant Therapy
Subjects were not permitted to receive the following prescribed medications during the study:

- Immunosuppressive drugs (e.g. cyclosporin)
- Systemic antifungal agents of the azole class (e.g. itraconazole or ketoconazole)
- Warfarin or warfarin-like anticoagulants
- Mibefradil
- Vitamins containing niacin (< 50 mg/day)
- Erythromycin or erythromycin-like drugs (e.g. clarithromycin and azithromycin)
- Corticosteroids including inhalation formulation
- Androgens (estrogen and progesterone as replacement therapy for post-menopausal females were permitted if the dose was unchanged for at least 8 weeks before enrolment at Visit 1 and was not intended to change throughout the whole duration of the study)

Efficacy and Safety Measurements Assessed
Each subject signed a subject consent form at the screening visit (Visit 1) before any study-related procedures were conducted. Eligible subjects were randomized at the baseline visit (Visit 4) after the wash-out and placebo run-in period (Period A). Follow-up visits were conducted

during the double-blind treatment period (Period B), at Visit 5 (Week 4), Visit 6 (Week 8) and Visit 7 (Week 12, final visit).

Sample Size Calculation:
The sample size was calculated in order to detect a difference in the main efficacy criterion. The primary efficacy criterion was the percentage change in calculated LDL between baseline (mean of the calculated LDL at Visits 3 and 4) to the end-point (final visit, Visit 7) of 7% between the two nearest doses with a standard deviation of 10%.

This calculation was based on a power of at least 80% (P=0.2) and a risk error of 5% (a=0.05) for rejecting the null hypothesis in a two-tailed test. This allowed 43 subjects in each of the five groups with a total of 225 subjects. The number of subjects was increased by 10% to allow for variability between centers and countries, and increased by 5% to take into account randomized subjects not evaluable for the ITT analysis. To correct for final non-eligibility at Visit 4 the number of subjects was increased by 30%, therefore the total number of subjects required during Period A was at least 325 subjects.

Statistical analyses
The dose-response relationship was analyzed in two steps:

- The smallest dose with which a difference to placebo occurred was identified using step-down contrasts;
- Using all doses different from placebo, an estimate regression of log-dose against log-percent change was made, with tests on linear and quadratic components.

The dose with 40% LDL change was identified with either 2nd degree regression or with linear regression.

Modification to the statistical procedure:
The preliminary analysis revealed the requirements of ANOVA were not met. It was found that an arcsinus transformation appeared to be appropriate (for applying ANOVA). ANOVA with treatment center as fixed effect and baseline LDL were used for the primary efficacy assessment.

Data sets analyzed
In total, 261 subjects entered the randomized phase of the study, of which the following 10 subjects were not included in the ITT population (two subjects had a problem with treatment compliance, and 8 subjects did not have any measurements after Visit 4).

Three subject populations were defined in the protocol for the efficacy analysis.

- Intent-To-Treat (ITT) population: all randomized subjects who received double-blind medication and had at least one baseline value of plasma LDL at Week -2 or 0 (Visit 3 or Visit 4) and at least one post-randomization value of plasma LDL . The primary efficacy analysis used the ITT population.
- Valid for efficacy (VFE) population: all randomized subjects valid for the ITT analysis who complied with the major inclusion/exclusion criteria, who had two baseline values of plasma LDL (measured at Weeks -2 and 0), who had at least one valid plasma LDL

measurement at least four weeks after randomization, who had a level of compliance of greater than 80%, and whose randomization code had not been broken.

- Per-protocol (PP) population: all randomized subjects who received double blind medication, who fulfilled the randomization criteria and other major inclusion/exclusion criteria, who had two baseline values of plasma LDL (measured at Weeks -2 and 0), and who fulfilled all the criteria for evaluation during the 12 weeks of treatment post-randomization.

Withdrawals:
A total of 13 subjects withdrew from the study prematurely with a total of 248 subjects completing the study. The percentage of subjects who withdrew prematurely was similar between treatment groups.

Protocol violations:
A total of 251 subjects were included in the intent-to-treat (ITT) population. Of these, 33 subjects had major protocol violations, leaving a total of 218 subjects in the per-protocol (PP) population.

The most frequent major protocol **deviation was "no valid measurement at Visit 7." There were** no important differences between the treatment groups with respect to the type or frequency of major protocol deviations.

As shown in the following table, the majority of subjects in the study were male (181 subjects [72.1%] overall). The majority of subjects were Caucasian (98.8%). The mean age of the subjects was 53.3 years (range; 21 years to 75 years), with the majority of subjects aged between 45 years to 64 years.

Demographic Characteristics (ITT population; N = 251)							(b) (4)		
	1 mg n=49		2 mg N=50		4 mg N=48			Placebo N=50	
	n	%	n	%	n	%		n	%
Gender:									
Male	35	67.3	37	75.5	38	76.0		36	70.6
Female	17	32.7	12	24.5	12	24.0		15	29.4
Race:									
Caucasian	52	100.0	49	100.0	49	98.0		50	98.0
Asian	0	0.0	0	0.0	1	2.0		1	2.0
Age (years):									
Mean	54.5		52.7		53.1			54.2	
Std Deviation	11.3		9.6		11.8			12.3	
Median	56.0		52.0		55.0			54.0	
Min, max	29.0	73.0	25.0	75.0	22.0	75.0		21.0	74.0

In general, there was an even age distribution between groups, however, there was a slightly greater percentage of subjects aged ≥65 years in the pitavastatin 1 mg group (11 subjects [21.2%]), pitavastatin 4 mg group (8 subjects, 16.0%), and placebo group (9 subjects [17.7%]), compared to the pitavastatin 2 mg (b) (4) groups (5 subjects [10.2%]).

Approximately half of the subjects in the ITT population were smokers (126 subjects [50.2%]); the mean duration of smoking history was 25.6 years (range: 1 year to 52.4 years). The proportion of smokers in the placebo group (60.8%) was slightly greater than in the pitavastatin treatment groups (53.1% or less). The majority of subjects consumed alcohol (209 subjects [83.3%]), with a mean number of four alcoholic drinks per week. There were no important differences between the groups with regard to alcohol consumption.

As shown in the below table, a total of 227 subjects (90.4%) in the ITT population had at least one clinical risk factor for coronary heart disease (CHD). The majority of subjects (186 subjects [74.1%]) had 1 or 2 clinical risk factors for CHD. The distribution of clinical risk factors (1 to 3 risk factors) was similar in each treatment group.

Protocol Amendment:
There was one amendment which was made to the protocol on November 26, 1999. The purpose of this amendment was to exclude all subjects with a history of percutaneous transluminal angioplasty or coronary bypass surgery to improve the safety of subjects taking part in the study.

Number of clinical risk factors for Coronary Heart Disease (ITT population; N = 251)							(b) (4)		
	1 mg n=49		2 mg N=50		4 mg N=48			Placebo N=50	
	n	%	n	%	n	%		n	%
At least one risk factor:									
No	2	16.3	6	12.2	7	14.0		5	9.8
Yes	50	96.2	43	87.8	43	86.0		46	90.2
Number of clinical risk factors:									
0	2	3.9	6	12.2	7	14.0		5	9.8
1	26	50.0	18	36.7	19	38.0		18	35.3
2	20	38.5	14	28.6	17	34.0		21	41.2
3	4	7.7	11	22.5	7	14.0		7	13.8
4	0	0.0	0	0.0	0	0.0		0	0.0

The baseline serum lipid profiles were similar among the treatment groups and conformed to a population of subjects with Type IIa hyperlipidemia. The descriptions of the baseline serum lipid profiles are shown in the following table:

	NK-104			(b) (4)	Placebo
	1 mg n=52	2 mg n=49	4 mg n=50		n=51
Total cholesterol (mg/dL)					
Mean (SD)	281.9 (30.9)	285.7 (27.0)	285.7 (30.9)		285.7 (27.0)
Median	278.0	285.7	278.0		281.9
Q1-Q3	262.5, 301.2	266.4, 305.0	262.5, 301.2		262.5, 301.2
Min, Max	216.2, 366.8	239.4, 339.8	235.5, 351.4		243.2, 351.4
MD	0	0	0		0
Triglycerides (mg/dL)					
Mean (SD)	159.3 (61.9)	159.3 (61.9)	159.3 (61.9)		141.6 (53.1)
Median	141.6	150.4	150.4		141.6
Q1-Q3	106.2, 185.8	106.2, 185.8	115.0, 194.7		106.2, 185.8
Min, Max	70.8, 336.3	70.8, 336.3	61.9, 300.9		61.9, 274.3
MD	0	0	0		0
HDL (mg/dL)					
Mean (SD)	54.1 (11.6)	57.9 (11.6)	54.1 (15.4)		57.9 (15.4)
Median	54.1	54.1	54.1		54.1
Q1-Q3	46.3, 61.8	50.2, 69.5	46.3, 61.8		50.2, 69.5
Min, Max	30.9, 81.1	38.6, 84.9	34.7, 96.5		38.6, 92.7
MD	0	0	0		0
LDL (mg/dL)					
Mean (SD)	196.9 (27.0)	200.8 (19.3)	196.9 (27.0)		196.9 (27.0)
Median	200.8	196.9	189.2		189.2
Q1-Q3	177.6, 216.2	181.5, 216.2	177.6, 208.5		177.6, 216.2
Min, Max	139.0, 262.5	158.3, 247.1	162.2, 274.1		142.9, 262.5
MD	0	0	0		0
ApoA1 (mg/dL)					
Mean (SD)	147.1 (27.0)	151.6 (24.2)	148.0 (28.0)		155.4 (27.1)
Median	143.5	150.0	142.0		148.5
Q1-Q3	131.0, 161.5	131.0, 169.0	127.0, 165.0		139.0, 178.0
Min, Max	81.0, 222.0	108.0, 198.0	107.0, 224.0		110.0, 216.0
MD	0	0	1		1
ApoB (mg/dL)					
Mean (SD)	127.4 (27.3)	126.5 (20.7)	128.8 (26.4)		128.6 (23.0)
Median	123.5	122.0	124.0		126.5
Q1-Q3	111.5, 139.0	114.0, 136.0	111.0, 138.0		113.0, 146.0
Min, Max	67.6, 205.0	96.2, 204.0	89.1, 231.0		89.6, 194.0
MD	0	0	1		1

The majority of subjects (192 subjects [76.5%]) had a significant family medical history of lipid and cardiovascular pathology. The most common of these conditions were myocardial infarction (1 14 subjects [59.4%]) and hypercholesterolemia (105 subjects [54.7%]). There were no clinically significant differences between treatment groups.

Resting pulse and blood pressure were similar in all treatment groups at baseline. Eight subjects (3.2%) had a significant abnormality in ECG measurement at baseline.

One hundred and eighty-nine subjects (72.7%) received at least one concomitant medication. There were no differences between the treatment groups with respect to the number of subjects receiving concomitant medication during the study.

The most common hypolipidemic drug treatments previously taken were: simvastatin (53 subjects [24.1%]), cholesterol and triglyceride reducers (39 subjects [17.7%]), pravastatin (1.9 subjects [8.6%]), and atorvastatin (17 subjects [7.7%]). All other statin therapy was taken by less than 5% of the population.

Primary Endpoint (changes in LDL measurements):
The primary efficacy variable for the ITT population was the percentage change in LDL between baseline and endpoint. There were statistically significant differences in the adjusted mean percent change in LDL between each pitavastatin group and placebo ($p<0.001$) as shown in the following table:

Percent Change from Baseline LDL at Week 12 in Study:

ITT population LDL (mg/dL)	Placebo	Pitavastatin (QD)			(b) (4)
		1 mg	2 mg	4 mg	
Week 12, LOCF					
N	51	52	49	50	(b) (4)
Baseline mean (SD)	196.9 (27.0)	196.9 (27.0)	200.8 (19.3)	196.9 (27.0)	
Adjusted mean % change	-4.0	-33.3	-38.2	-46.5	
p-value for diff vs placebo		<0.001	<0.001	<0.001	

The adjusted mean percent changes from baseline in LDL were -33.3%, -38.2%, -46.5%, (b) (4) (b) (4) for the pitavastatin 1 mg, 2 mg, 4 mg, (b) (4) doses, respectively, compared with -4.0% for placebo ($p=0.000$ all active doses vs. placebo). The differences in the changes in LDL between each active treatment group were also statistically significant ($p\leq 0.027$).

Results for the PP population were comparable with the ITT population.

Secondary Efficacy Endpoints:
Secondary Efficacy Endpoint: Total cholesterol (TC)
Mean percent changes in TC at endpoint for pitavastatin 1, 2, 4 (b) (4) mg were statistically significant compared with placebo ($p<0.001$) and the pairwise comparisons between the individual active-treatments were all statistically significant ($p\leq 0.032$) as shown in the following table:

ITT population Week 12, LOCF	Placebo	Pitavastatin (QD)			(b) (4)
		1 mg	2 mg	4 mg	
TC (mg/dL)					
N	51	52	49	50	(b) (4)
Baseline mean (SD)	285.7 (27.0)	281.9 (30.9)	285.7 (27.0)	285.7 (30.9)	
Mean % change[a]	-1.3	-22.8	-26.1	-32.5	
p-value for diff vs placebo		<0.001	<0.001	<0.001	

Secondary Efficacy Endpoint: Triglyceride (TG)

Mean percent changes in TG at endpoint for pitavastatin 1, 2, 4(b) (4) mg were significantly different vs. placebo ($p \leq 0.001$), and the differences between the 1 and(b) (4) mg and the 2 and(b) mg pitavastatin groups were statistically significant ((b) (4)
Differences are shown in the following table:

ITT population Week 12, LOCF	Placebo	Pitavastatin (QD)			(b) (4)
		1 mg	2 mg	4 mg	
TG (mg/dL)					
N	51	52	49	50	(b) (4)
Baseline mean (SD)	141.6 (53.1)	159.3 (61.9)	159.3 (61.9)	159.3 (61.9)	
Adjusted mean % change	-2.1	-14.8	-17.4	-21.2	
p-value for diff vs placebo		0.001	<0.001	<0.001	

Secondary Efficacy Endpoint: HDL:

Each dose of pitavastatin increased HDL concentrations by a statistically significant amount (range; 7.6% to 9.4%) compared with placebo (2.5%) ($p \leq 0.026$), with an inverse relationship to dose. There were no statistically significant differences in mean increases in HDL among the active-treatment groups. Differences are shown in the following table:

ITT population Week 12, LOCF	Placebo	Pitavastatin (QD)			(b) (4)
		1 mg	2 mg	4 mg	
HDL (mg/dL)					
N	51	52	49	50	(b) (4)
Baseline mean (SD)	57.9 (15.4)	54.1 (11.6)	57.9 (11.6)	54.1 (15.4)	
Adjusted mean % change	2.5	9.4	9.0	8.3	
p-value for diff vs placebo		0.003	0.004	0.011	

Secondary Efficacy Endpoint: Apo B

As expected, give the results for LDL, pitavastatin lowered levels of Apo-B in a dose-related manner (as detailed in the table above) with statistically significant differences between all active-treatment arms compared with placebo.($p \leq 0.001$), as shown in the following table:

	NK-104			(b) (4)	Placebo
	1 mg n=52	2 mg n=49	4 mg n=50		n=51
Apo B (mg/100mL) at Visit 4					
Mean (SD)	127.4 (27.3)	126.5 (20.7)	128.8 (26.4)		128.6 (23.0)
% change from baseline to last valid value					
Adjusted mean*	-24.1	-30.4	-36.1		0.3
Mean (SD)	-25.5 (8.9)	-30.8 (10.4)	-37.0 (8.9)		0.3 (17.0)

Secondary Efficacy Endpoint: Apo A1

All doses of pitavastatin increased Apo A1 concentrations in an inverse dose-dependent manner and were greater than that obtained with placebo. Comparison between treatment groups indicated a statistically significant difference in Apo A1 concentration between pitavastatin 1 mg and placebo (p=0.044), and pitavastatin 1 mg and(b) (4) Differences are shown in the following table:

	NK-104			(b) (4)	Placebo
	1 mg n=52	2 mg n=49	4 mg n=50		n=51
Apo-A1 (mg/100mL) at Visit 4					
Mean (SD)	147.1 (27.0)	151.6 (24.2)	148.0 (28.0)		155.4 (27.1)
% change from baseline to last valid value					
Adjusted mean*	8.5	5.6	4.7		3.2
Mean (SD)	9.2 (12.6)	5.6 (12.4)	5.0 (12.7)		1.7 (11.1)

Efficacy Conclusions:

Pitavastatin produced clinically and statistically significant dose-related reductions in LDL compared to placebo. Further analyses showed that compared to placebo all doses of pitavastatin increased HDL levels and decreased TG levels regardless of baseline HDL and TG levels.

2.2 Efficacy and Dose Response in 252 subjects with Primary Mixed or Combined Hyperlipidemia [HEC/NK98402N/NK-104.203]

Study initiation date: 19 June 1999
Study completion date: 21 August 2000

2.2.1.1 General Discussion of Study Objectives, Endpoints and Methods

Primary objective:

- To compare the efficacy of four doses of pitavastatin (1 mg, 2 mg, 4 mg,(b) (4)) and placebo in reducing serum LDL. The primary efficacy parameter was the percentage change of measured LDL between baseline and endpoint.

Secondary objectives:

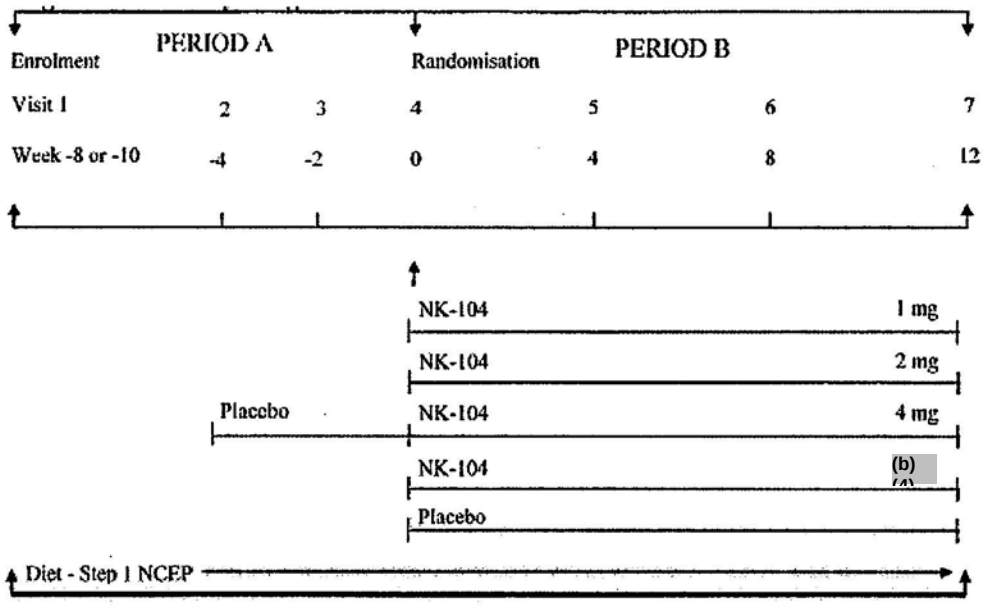
- To assess the efficacy of pitavastatin and placebo on other lipid parameters including TC, HDL, TG, Apo Al, and Apo B (percentage changes between baseline and endpoint);
- To compare the safety of the four doses of pitavastatin with placebo for adverse event rates and changes in laboratory parameters.

Study Design:

This was a multinational, multicentre, randomized, double-blind, placebo-controlled, dose-ranging study with four parallel pitavastatin groups (1 mg, 2 mg, 4 mg,(b) (4)) in subjects with primary mixed or combined hyperlipidemia (LDL ≥135mg/dL and ≤300 mg/dL, TG ≥175mg/dL and ≤ 500 mg/dL).

A total of 44 centers in Europe (France, Italy, Finland, Norway, Germany, Sweden, UK, and the Netherlands), Israel, and Canada participated. The protocol planned for the enrollment of approximately 375 subjects with primary mixed or combined hyperlipidemia in Period A to ensure at least 250 evaluable subjects.

The duration of the treatment phase was 16 weeks, and consisted of four weeks of placebo treatment before randomization and 12 weeks of active double-blind treatment. The study was divided into two periods designated A and B as specified in the study design schematic following:



Period A (Visits 1 to 4)
Subjects with a diagnosis of primary mixed or combined hyperlipidemia were enrolled at Visit 1 if no exclusion criteria applied.

- Concomitant use of hypolipidemic drugs was discontinued at enrollment (Visit 1)
- Statins or bile acid sequestrants could not have been taken within 4 weeks prior to the beginning of the placebo run-in period at Visit 2
- Prior to Visit 2, fibrate treatment was to have been discontinued for 6 weeks and probucol treatment was to have been discontinued for one year
- Subjects had to have maintained an appropriate diet (NCEP Step-1 or equivalent for at least four weeks before they could start single-blind placebo treatment at Visit 2. This diet was to be continued throughout the study
- Visits 1 and 2 could take place on the same day for subjects who had adhered to a stable diet for at least four weeks prior to enrolment and who were not taking lipid-lowering drugs (4 weeks for statins and 6 weeks for fibrates)
- The duration of the single-blind treatment period was four weeks (Visits 2 to 4)

Period A: placebo run-in period (Visit 2 to Visit 4)
All subjects received two tablets of placebo in a single-blind manner for four weeks.

Period B: treatment period (Visit 4 to Visit 7)
At the completion of the placebo run-in (Visit 4), subjects who were in accordance with the inclusion and exclusion criteria were randomized to one of the five treatment groups shown below for 12 weeks under double-blind conditions:

- NK- 104 1 mg arm: one tablet of active NK- 104 1 mg and one tablet of NK- 104 placebo
- NK- 104 2 mg arm: one tablet of active NK- 104 2 mg and one tablet of NK- 104 placebo
- NK- 104 4 mg arm: two tablets of active NK- 104 2 mg

(b) (4)

- Placebo arm: two tablets of NK- 104 placebo

Subject safety was monitored by incidence of reported AEs, vital signs, 12-lead ECG, physical examination and laboratory investigations (biochemistry, hematology, urinalysis). The diet was continued throughout Period B.

Dose Selection:
The following doses of pitavastatin were used in this study: 1 mg, 2 mg, 4 mg, (b) (4) These doses were selected based on data obtained from previous Phase 1 and 2 studies of pitavastatin in humans. The dose range 1 mg to (b) (4) g has been shown to be well tolerated and below the maximal tolerated dose; the range 1 mg to 4 mg has been shown to decrease the levels of TC and LDL.

Blinding
During the run-in period (Period A), placebo was given according to a single-blind procedure.

During the double-blind treatment period (Period B), neither the investigator nor the subject were aware of the treatment assignment. The investigator was not to receive lipid values from the treatment period (Period B) until after the study was completed.

- Inclusion Criteria
- Subjects had to be aged 18 to 75 (inclusive)
- Ambulatory males and females were eligible for the study. Women of childbearing potential had to have taken oral contraceptives for at least 3 months prior to study entry and have to maintain this throughout the study period. A negative pregnancy test was required at Visit 2
- Subjects had to be willing to adhere to the recommended diet (NCEP Step-1 or equivalent diet) throughout the whole study period
- LDL and TG levels had to be within the following ranges at Visit 3:
  1. LDL $\geq$135mg/dL and $\leq$300 mg/dL;
  2. TG $\geq$175mg/dL and $\leq$500 mg/dL.
- Written informed consent had to be given before participation in the study.

Exclusion Criteria
- Pregnant women
- Women of childbearing potential who had not taken oral contraceptives for greater than 3 months prior to study entry or who were intending to stop contraception during the study period
- Body Mass Index (BMI) of greater than 33 kg/m^2
- Alcohol abuse defined by a current intake of more than 14 standard drinks per week. A standard drink was defined as 1 glass of wine (200mL at 11% alcohol content) or one bottle of beer (500 mL at 5% alcohol content) or 30 mL of spirit
- A history of hypersensitivity to HMG-CoA reductase inhibitors.

- Any other disease or condition that, in the opinion of the investigator, might have posed a risk to the subject or have confounded the results of the study (e.g. other endocrine disease, acute or chronic infections)
- Concomitant use of the following drugs:
    1. Immunosuppressive drugs, including cyclosporin
    2. Systemic antifungal agents of the azole class, e.g. itraconazole or ketoconazole
    3. Warfarin or warfarin-like anticoagulant
    4. Mibefradil
    5. Vitamins that contained niacin (≤50 mg/dL)
    6. Erythromycin or erythromycin-like drugs such as clarithromycin and azithromycin
    7. Corticosteroids including inhalation formulation, androgens (estrogen and progesterone as replacement therapy to post-menopausal women were permitted if the dose had been unchanged for at least 8 weeks prior to the enrolment visit [Visit 1] and was not intended to change throughout the whole duration of the study)
    8. Any other pre-existing medication therapy was to be continued unmodified throughout the study.
    9. Concomitant medication was documented on study entry. If, for any reason, changes of concomitant medication were necessary, the new therapeutic regimen and the new medication were documented.
- Treatment with any other investigational drug within 30 days before the enrollment visit (Visit 1)
- Compliance < 80% during the placebo run-in period
- For subjects with known type 1 or type 2 diabetes mellitus the fasting serum glucose had to have been < (126 mg/dL) at Visit 2
- Significant renal impairment, defined by serum creatinine > 1.8 mg/dL at Visit 2 or known nephrotic syndrome
- Uncontrolled hypertension (treated or untreated) defined as diastolic blood pressure ≥110 mm Hg and/or systolic blood pressure ≥180 mm Hg. Subjects on B-blockers or diuretics could be enrolled only if their treatment had been unchanged for at least eight weeks prior to enrollment (Visit 1) and there was no intention that it would be changed during the study
- History of myocardial infarction, unstable angina, stroke, transient ischemic attack, percutaneous transluminal coronary angioplasty or coronary bypass surgery
- Congestive heart failure (New York Heart Association Class 3 or 4)
- Subjects with known active liver disease and/or elevated serum transaminases AST or ALT greater than two times the upper limit of normal (ULN) at Visit 3
- Subjects with known muscular or neuromuscular disease and/or serum CK greater than three times the ULN at Visit 3 that did not have an obvious explanation (e.g. muscle trauma, massage, or strenuous exercise)
- Any malignant tumor that had required any treatment in the past 10 years
- Subjects with a known cataract. However, subjects whose lenses had been removed could be enrolled
- Subjects with known HIV infection, known severe depression, poor mental function, and/or suicidal ideas

Exclusion criteria with regards to hyperlipidemia

- A diagnosis of Types I, III, IV or V hyperlipidemia
- Known heterozygous or homozygous forms of familial hypercholesterolemia
- Subject with LDL level > 300 mg/dL at Visit 3
- Secondary hypercholesterolemia due to hypothyroidism TSH greater than ULN at Visit 2). Subjects with a history of hypothyroidism who were on a stable dose of thyroxine six months before Visit 2 with normalized plasma thyroxine and TSH could be included

Israeli centers: subjects at Israeli centers with a history of cardiovascular disease or prior treatment with statins were excluded from the trial

Removal of subjects from Therapy or Assessment:
As far as possible, it was the responsibility of the investigator to maintain the subject in the study. However, the subject could be withdrawn from the study at any time for the following reasons:

- Withdrawal of consent by the subject
- Any medical condition or personal circumstance that exposed the subject to substantial risk by continuing in the trial or that prevented the subject from adhering to the requirements of the protocol
- Any clinically significant AE or SAE
- If the subjects required chronic (greater than two weeks) treatment with systemic corticosteroids, immunosuppressants, antifungal therapy with agents in the azole class, erythromycin-like drugs
- Secondary occurrence of major exclusion criteria
- Severe laboratory abnormality after randomization (this had to be confirmed by repeat testing before a decision to withdraw could be made):
  - elevation of serum transaminase (ALT and/or AST) by greater than 3x ULN,
  - serum CK greater than l0x ULN with or without symptoms, or greater than 5x ULN with muscle symptoms. Subjects at Israeli centers were to be withdrawn from the trial if their serum CK was greater than 5x ULN with or without symptoms
  - serum LDL less than 50 mg/dL

Repeat laboratory tests were to be done within 1 week with the exception of serum LDL which could be repeated after four weeks (at the next visit). These events were considered as clinically important AEs.

The most frequent major protocol **deviation was "no valid measurement at Visit 7."**

Treatments:
Subjects were to take two tablets once daily at bedtime during the single-blind and double-blind treatment periods.

Statistical analyses planned in the protocol
Analysis of the dose-response relationship was to be done in two steps:

- Identification of the smallest dose different from placebo using step-down contrasts.

- Then, using all doses different from placebo, regression of log-dose against log percent change, with tests on linear and quadratic components, to be estimated.

The dose with 40% LDL change was then to be identified with the 2nd degree regression if the quadratic term was not significant, or with linear regression if otherwise.

Analysis Carried Out:
The primary criterion was to be compared between treatment groups using an analysis of variance with random variable (ANOVA with random effect or mixed model) using contrasts, to test each dose against placebo and each dose of the active drug against the other, and adjusted means.

The analysis was to be performed using two covariates: centre as qualitative random variable and baseline LDL as a quantitative fixed variable.

Determination of Sample Size
The sample size was calculated to enable the detection of a difference of 7.0% between the two nearest doses with a standard deviation of 10% in the main efficacy criteria (the percentage reduction of LDL from baseline [mean of the measured LDL at Visits 3 and 41 to the final Visit [Visit 7 at 12 weeks]. This calculation assumed a power of at least 80% (β= 0.2) and a risk error of 5% (a = 0.05) for rejecting the null hypothesis in a two-tailed test. Forty-three subjects per arm were required for a total of 225 subjects in the five treatment groups. This number was increased by 10% to account for variability between centers and countries, and 5.0% to account for any randomized subjects who would not be evaluable for ITT analysis, giving a total of 250 subjects for the 5 groups. To correct for final non-eligibility at Visit 4, this total number was increased by 50% to result in the enrolment of at least 375 subjects in Period A of the study. It was planned in the protocol that approximately 60 centers in Europe, Israel, and Canada would participate in the study; the mean planned accrual per center was six subjects.

Three subject populations were defined in the protocol for the efficacy analysis:

- Intent-To-Treat (ITT) population: All randomized subjects who received double-blind medication and having at least one baseline value of plasma LDL at week (-2) or 0 (V3 or V4) and at least one value of plasma LDL post-randomization.
- Valid for efficacy (VFE) population: All randomized subjects valid for ITT who, in addition, comply with major inclusion/exclusion criteria, have two baseline values of plasma LDL (calculated at weeks (-2) and 0) and at least one valid plasma LDL measurement after at least 4 weeks treatment post randomization, whose random code has not been broken and with a compliance > 80%.
- Per-protocol population: All randomized subjects who receive double blind medication, fulfill the randomization criteria and other major inclusion/exclusion criteria, have two baseline values of plasma LDL (calculated at weeks (-2) and 0) and fulfill all the criteria for evaluation during the 12 weeks treatment post randomization.

Assessment of Efficacy:
The primary efficacy assessment criterion was the percentage change in LDL between baseline and endpoint.

The secondary efficacy assessment criteria were the percentage change between baseline and endpoint in other lipid parameters: TC, HDL, TG, and Apo A1 and Apo B.

Withdrawals:
A total of six subjects (2.4%) withdrew from the study prematurely and 246 subjects (97.6%) completed the study. In general, the percentage of subjects who withdrew prematurely was similar among treatment groups. Subject withdrawals from the study after enrollment are presented by treatment group, as shown below:

Study withdrawal by primary reason				(b) (4)		
	NK- 104				Placebo	Total
	1 mg n=49	2 mg n=50	4 mg n=51		n=50	n=252
Completed study	48 (98.0%)	.49 (98.0%)	48 (94.1%)		50 (100.0%)	246 (97.6%)
Premature withdrawal	1 (2.0%)	1 (2.0%)	3 (5.9%)		0 (0.0%)	6 (2.4%)
Withdrawal of consent	1*	1	2		0	5
Clinically significant or SAE	0	0	1		0	1

Protocol amendments:
Amendment 1 (dated 26 November 1999): this amendment was designed to improve the safety of subjects participating in the trial by excluding all subjects with a history of percutaneous transluminal angioplasty or coronary bypass surgery.

Amendment 2 (dated 8 December 1999): this amendment was designed to ensure that the study complied with the conditions requested by the Israeli Ministry of Health and, therefore, only applied to Israel. Only subjects without any history of cardiovascular disease and without a history of prior treatment with statins were to be enrolled into the study. The CK value that was the trigger for withdrawal of subjects from the study was reduced from 10x the upper limit of normal to 5x the upper limit of normal.

Protocol violations:
In total, 252 subjects entered the randomized phase of the study. Three of the 252 randomized subjects were not included in the ITT population. Of these 249 subjects, 32 had major protocol deviations and were not included in the PP population, giving a total of 217 subjects in the PP population.

Demographic and Other Baseline Characteristics
The majority of the subjects in the ITT population were male (male: 167 subjects [67.1 %]); this proportion was similar in all treatment groups. The mean age of the subjects was 51.7 years (range, 19 to 75 years), with most subjects aged between 45 to 64 years (177 subjects [71.1 %]). The majority of subjects were Caucasian (241 subjects [96.8%]).

Approximately half of the subjects in the ITT population were smokers (135 subjects [54.2%]); the mean duration of smoking history was 25.2 years (range, 2.4 to 102.0 years). There were no

clinically significant differences between treatment groups with regard to tobacco consumption. The majority of subjects consumed alcohol (167 subjects [67.1 %]); the mean consumption was 5.3 alcoholic drinks per week. The proportion of subjects who consumed alcohol was greater in the pitavastatin 1 mg, 2 mg, (b) (4) groups as compared to the pitavastatin 4 mg and placebo groups.

A total of 217 subjects (87.2%) had at least one clinical risk factor for CHD.

Demographic characteristics (ITT population; N = 249)

	NK-104						Placebo	
	1 mg n=49		2 mg n=50		4 mg n=48		n=50	
	n	%	n	%	n	%	n	%
Gender:								
Male	33	67.4	35	70.0	29	60.4	34	68.0
Female	16	32.7	15	30.0	19	39.6	16	32.0
Race:								
Caucasian	49	100.0	47	94.0	44	91.7	50	100.0
Asian	0	0.0	1	2.0	3	6.3	0	0.0
Black	0	0.0	1	2.0	1	2.1	0	0.0
Other*	0	0.0	1	2.0	0	0.0	0	0.0
Age (years):								
Mean	51.6		51.9		53.3		51.2	
Std Deviation	9.4		9.5		9.4		11.6	
Median	53.0		52.0		53.5		50.0	
Min, Max	23.0, 70.0		22.0, 73.0		30.0, 74.0		27.0, 75.0	

Clinical risk factors for CHD:

The majority of subjects in the ITT population (68.3%) had one or two clinical risk factors for CHD. All treatment groups were broadly similar with respect to the proportion of subjects with clinical risk factors. Details of the number of clinical risk factors for coronary heart disease are presented in the following table:

Number of clinical risk factors for CHD (ITT population; N = 249)							(b) (4)		
	1 mg n=49		2 mg N=50		4 mg N=48			Placebo N=50	
	n	%	n	%	n	%		n	%
At least one risk factor:									
No	8	16.3	6	12.0	5	10.4		8	16.0
Yes	41	83.7	44	88.0	43	89.6		42	84.0

Number of clinical risk factors:							(b) (4)		
(-1)	1	2.0	1	2.0	0	0.0		0	0.0
0	7	14.3	5	10.0	5	10.4		8	16.0
1	17	34.7	16	32.0	26	54.2		14	28.0
2	17	34.7	17	34.0	11	22.9		15	30.0
3	7	14.3	10	20.0	6	12.5		13	26.0
4	0	0.0	1	2.0	0	0.0		0	0.0

*In case of baseline value of HDL ≥1.54 mmol/L, 1 clinical risk factor was removed (-1 was added to the number of clinical risk factors). Two patients did not have any risk factor for coronary heart diseases and as their baseline value of HDL was ≥1.54 mmol/L, their number of clinical risk factors was negative.

The differences between baseline characteristics of the various lipid parameters are shown in the following table:

	NK-104			(b) (4)	Placebo
	1 mg n=49	2 mg n=50	4 mg n=48		n=50
Total cholesterol (mg/dL)					
Mean (SD)	281.9 (42.5)	281.9 (38.6)	289.6 (46.3)		281.9 (34.7)
Median	266.4	278.0	285.7		281.9
Q1-Q3	251.0, 305.0	262.5, 297.3	251.0, 312.7		254.8, 301.2
Min, Max	227.8, 459.5	220.1, 390.0	204.6, 420.8		223.9, 401.5
MD	0	0	0		0
Triglycerides (mg/dL)					
Mean (SD)	274.3 (88.5)	274.3 (79.6)	274.3 (70.8)		265.5 (88.5)
Median	265.5	247.8	256.6		247.8
Q1-Q3	212.4, 300.9	221.2, 336.3	238.9, 309.7		194.7, 309.7
Min, Max	159.3, 522.1	141.6, 469.0	150.4, 486.7		150.4, 531.0
MD	0	0	0		0
HDL (mg/dL)					
Mean (SD)	50.2 (7.7)	50.2 (11.6)	54.1 (15.4)		46.3 (7.7)
Median	46.3	46.3	50.2		50.2
Q1-Q3	42.5, 54.1	42.5, 57.9	46.3, 57.9		42.5, 54.1
Min, Max	30.9, 69.5	30.9, 73.4	30.9, 119.7		30.9, 69.5
MD	0	0	0		0
LDL (mg/dL)					
Mean (SD)	177.6 (34.7)	177.6 (30.9)	181.5 (38.6)		181.5 (34.7)
Median	169.9	177.6	177.6		177.6
Q1-Q3	154.4, 200.8	154.4, 200.8	154.4, 196.9		158.3, 200.8
Min, Max	115.8, 312.7	131.3, 251.0	123.6, 335.9		119.7, 308.9
MD	0	0	0		0
ApoA1 (mg/dL)					
Mean (SD)	142.7 (25.2)	141.8 (25.1)	147.4 (33.3)		140.0 (22.3)
Median	138.0	134.0	142.0		139.5
Q1-Q3	132.0, 153.0	124.0, 152.0	127.0, 162.0		120.0, 157.0
Min, Max	98.8, 213.0	102.0, 212.0	82.1, 282.0		99.5, 199.0
MD	0	1	0		0

ApoB (mg/dL)				(b) (4)	
Mean (SD)	135.3 (29.8)	130.5 (30.4)	137.7 (30.2)		133.3 (22.3)
Median	131.0	125.0	132.5		131.0
Q1-Q3	114.0, 147.0	106.0, 145.0	110.5, 157.5		114.0, 153.0
Min, Max	92.3, 247.0	75.1, 199.0	85.2, 215.0		85.2, 177.0
MD	0	1	0		0

The majority of subjects (79.1%) had a significant family medical history of lipid and cardiovascular pathology. The most common of these conditions were myocardial infarction (57.4%) and hypercholesterolemia (48.7%). There were no clinically important differences between the treatment groups with the exception of hypercholesterolemia, which was less frequent in the pitavastatin 2 mg group than in the other treatment groups, and hypertension, which was less frequent in the pitavastatin 2 mg and placebo groups than in the other treatment groups.

Significant medical history (ITT population; N = 249)							(b) (4)		
	pitavastatin 1 mg n=49		pitavastatin 2 mg N=50		pitavastatin 4 mg N=48			Placebo N=50	
	n	%	n	%	n	%		n	%
Myocardial infarction	19	52.8	26	61.9	14	42.4		27	62.8
Hypercholesterolemia	20	55.6	12	28.6	23	69.7		21	48.8
Hypertension	18	50	12	28.6	16	48.5		12	27.9
Hyperlipidemia	13	36.1	15	35.7	15	45.5		17	39.5
Angina	10	27.8	13	31.0	10	30.3		14	32.6

There were no clinically significant differences between the treatment groups with regard to height, weight, or BMI.

In general, there was an even distribution between groups with respect to the number of subjects receiving concomitant medication.

The majority of subjects (72.6%) received at least one concomitant medication. The most common hypolipidemic drug treatments previously taken were: atorvastatin (18.1 %), **simvastatin (15.4%), "Bezalip" (8.4%), pravastatin (6.5%), and gemfibrozil (6.1%). All other** hypolipidemic medication was taken by less than 6% of the population.

The most common concomitant medication taken by subjects during the placebo run-in period included Premarin (3.2%), Tylenol (2.5%), aspirin "Bayer" (2.5%), and Vitamin E (2.0%).