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APPLICATION NUMBER:

22-363

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	22-363
Priority or Standard	Standard
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Primary Reviewer	Iffat N. Chowdhury, MD
Efficacy Reviewer	David Gortler, PharmD, FCCP
Review Completion Date	June 10, 2009
Established Name	Pitavastatin
(Proposed) Trade Name	Livalo®
Therapeutic Class	HMG CoA Reductase Inhibitor
Applicant	Kowa Company, Ltd.
Formulation(s)	Oral Tablets
Dosing Regimen	1, 2 and 4 mg
Indication(s)	Lipid-Lowering
Intended Population(s)	Primary Hyperlipidemia and Mixed Dyslipidemia

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LIST OF ABBREVIATIONS AND DEFINITIONS:

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase (ALAT/SGPT)
Alk Phos	Alkaline phosphatase
ANCOVA	Analysis of covariance
Apo-A1	Apolipoprotein A1
Apo-B	Apolipoprotein B
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (ASAT/SGOT)
AUC	Area Under the Curve
AT	Aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
COM	Completer population
CPK	Creatine phosphokinase
CRF	Case Report Form
DILI	Drug-induced liver injury
CVD	Cardiovascular disease
ECG	Electrocardiogram
FAS	Full Analysis Set
GCP	Good Clinical Practice
HbA_{1c}	Glycosylated hemoglobin A_{1c}
HDL	High density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hsCRP	High sensitivity C-reactive protein
IBS	Irritable Bowel Syndrome
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein cholesterol
LFTs	Liver function tests
LOCF	Last observation carried forward
LV	Left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum Recommended Human Dose
NCEP	National cholesterol Education Program
NDA	New Drug Application
NYHA	New York Heart Association

Abbreviation	Definition
PK	Pharmacokinetic
PP	Per protocol
PRBC	Packed Red Blood Cells
PT	Preferred term
PSUR	Periodic safety update report
QD	Once daily
RBC	Red blood cells
RLP-C	Remnant-like particle cholesterol
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SOC	System Organ Class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL	Very low density lipoprotein-C
vs.	Versus
WBC	White blood cells

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that daily doses of 1, 2, and 4 mg of pitavastatin be approved as an adjunctive therapy to diet for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia.

1.2 Benefit-Risk Assessment

The assessment of pitavastatin's efficacy and safety was based on data from five 12-16 week phase 2 clinical trials, five 12-week phase 3 clinical trials, and four long-term extension studies, as well as post-marking data from Japan.

In subjects with primary hypercholesterolemia or mixed dyslipidemia, doses of 1 mg, 2 mg, and 4 mg pitavastatin reduced levels of LDL by approximately 28%, 31%, 41%, respectively, relative to placebo. The reductions in LDL observed with pitavastatin 2 mg and 4 mg were, in general, comparable to the reductions observed with low-to-moderate doses of atorvastatin and simvastatin, and greater than the reductions seen with low-to-moderate doses of pravastatin. The changes in levels of TC, Apo B, TG, and HDL associated with pitavastatin treatment were favorable and comparable to the changes noted with low-to-moderate doses of atorvastatin and simvastatin, and greater than the changes seen with low-to-moderate doses of pravastatin.

Based on a meta-analysis of data from 14 large statin cardiovascular outcomes trials, the average reductions in LDL reported with the 1 mg, 2 mg, and 4 mg doses of pitavastatin would be expected to reduce the risk for major cardiovascular events by approximately 30% to 40% (Cholesterol Treatment Trialists' **Collaborators, Lancet 2005).**

The principal safety concern with statins is myopathy, with rhabdomyolysis representing the most severe form of muscle toxicity. There were nine cases (1.4%) of rhabdomyolysis reported in two phase 2 studies of pitavastatin. All cases occurred in subjects treated with 8 mg or higher. (b) (4)

There were no cases of rhabdomyolysis during the phase 3 trials in subjects treated with doses of 4 mg or less of pitavastatin. This may reflect the minimal overlap in serum pitavastatin levels in subjects treated with the 4 mg and 8 mg doses of pitavastatin. The incidence of serum CPK > 10XULN in the 1 mg, 2 mg, and 4 mg pitavastatin groups was low (0.1%) and similar to the incidence noted in the atorvastatin 20 mg group (0.4%). None of the subjects in the simvastatin or pravastatin groups developed a serum CPK > 10XULN. Myalgia was reported by up to 2% of subjects treated with pitavastatin 1 mg through 4 mg and by up to 3% of subjects treated with low-to-moderate doses of comparator statins.

Statins have long been known to modestly increase levels of hepatic aminotransferases. These increases often resolve with continued statin therapy. Statins have rarely been associated with

severe hepatic injury. The incidence rates of ALT >3XULN in the pitavastatin 1 mg, 2 mg, and 4 mg groups were 0.3%, 0.5%, and 0.1%, respectively. One subject (0.4%) in the simvastatin 40 mg group and two subjects in the atorvastatin 80 mg group (2%) developed an ALT >3XULN. **There were no cases of severe hepatic injury of Hy's Law**[1] reported in subjects treated with pitavastatin 1 mg through 4 mg or with comparator statins. One subject treated long-term with 4 mg pitavastatin, however, did develop an ALT > 3XULN with a total bilirubin > 1.5XULN and a slightly elevated Alk Phos. The transaminitis began to resolve and the bilirubin level normalized within one day of stopping the drug. Pitavastatin was subsequently reintroduced without reoccurrence of transaminitis.

Given concern about proteinuria with high doses of rosuvastatin, Kowa was asked to measure the urine protein/creatinine ratio in a subset of subjects from the phase 3 pitavastatin trials. The frequency of subjects who shifted from a normal baseline ratio to an abnormal on-treatment ratio was 10% for pitavastatin 2 mg, 7% for pitavastatin 4 mg, 8% for atorvastatin 20 mg, 0% for atorvastatin 40 mg, 14% for simvastatin 20 mg, and 7% for simvastatin 40 mg.

In summary, the data provided in this NDA indicate that pitavastatin 1 mg, 2 mg, and 4 mg effectively lower levels of LDL, Apo B, TC, TG, and increase levels of HDL. The safety profile of pitavastatin 1 mg through 4 mg appears to be similar to the safety profiles of low-to-moderate doses of atorvastatin, simvastatin, and pravastatin. The cardiovascular benefits of pitavastatin would be expected to outweigh any risks (e.g., myopathy) associated with this statin.

1.3 Recommendations for Postmarket Risk Management Activities

None

1.4 Recommendations for Postmarket Studies/Clinical Trials

The applicant did not investigate the pharmacokinetics of pitavastatin in patients with severe renal impairment (glomerular filtration rate < 30 mL/min/1.73m^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 ≥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

1 Hy's Law is defined as an ALT or AST > 3XULN accompanied by a bilirubin > 2XULN with a normal alkaline phosphatase level. This constellation of laboratory findings signals potential for severe drug-induced hepatotoxicity.

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.

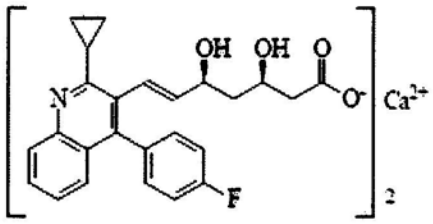
2 Introduction and Regulatory Background

2.1 Product Information

Table 1 Pitavastatin General Information

Proposed Proprietary Name of Drug Product	Livalo
Generic Name of Drug Product	pitavastatin calcium tablets
Common Name of Drug Substance	pitavastatin calcium
NDA Sponsor	Kowa Company Limited
API Manufacturer	(b) (4)
Drug Product Manufacturer	Patheon Inc.
Dosage Form	coated tablet
Strengths	1 mg, 2 mg, and 4 mg
Route of Administration	Oral
Proposed Indication	Livalo is indicated for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), TC/HDL-C, and Apo-B/ Apo-A1 ratio and to increase HDL-C and Apo-A1.

Pitavastatin is a synthetic HMG-Co-A reductase inhibitor or statin. Its chemical name is (+)-monocalcium *bis*{(3*R*, 5*S*, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}. The absolute stereochemical structure of pitavastatin is provided below:



Molecular formula: $C_{50}H_{46}CaF_2N_2O_8$ Molecular weight: 880.98

2.2 Tables of Currently Available Treatments for Proposed Indications

The following is a table of the statins available in the US and the date of approval.

Table 2 Statin US Approval Dates

Statin	Approval Date
Mevacor/Lovastatin	1987
Pravachol/Pravastatin	1991
Zocor/Simvastatin	1991
Lescol/Fluvastatin	1993
Lipitor/Atorvastatin	1996
Baycol/Cerivastatin	1997, withdrawn 2001
Crestor/Rosuvastatin	2003

2.3 Availability of Proposed Active Ingredient in the United States

HMG-CoA reductase inhibitors are anti-hyperlipidemic agents whose development originated with the discovery of mevastatin (Compactin®) in 1976 and mevinolin (lovastatin – Mevacor®) in 1979. Over the last 20 years, a total of 8 statins have come to the market worldwide. Lovastatin was approved in the US in 1987, pravastatin (Pravachol®) was approved in 1991, followed by simvastatin (Zocor®) and fluvastatin (Lescol®). A 'second generation' of more effective and more potent statins followed with the approval of atorvastatin (Liptor®) in 1996 and cerivastatin (Baycol®) in 1997, although this drug was subsequently withdrawn in 2001 due to myotoxicity. In 2003, rosuvastatin (Crestor®) was approved in the US and pitavastatin (Livalo®) was approved in Japan. Pitavastatin has subsequently been approved in South Korea in 2005 and Thailand in 2007.

2.4 Important Safety Issues with Consideration to Related Drugs

As a class of drugs, statins have been associated with elevated liver ATs and rarely hepatitis and liver failure. Asymptomatic liver AT elevations >3XULN are seen in <1% of patients on low and intermediated doses of statins and 2 to 3% at high doses (McKenney 2006). The cause of this elevation in liver AT with statin therapy has not been determined, but in many if not most cases,

statin-related transaminitis does not appear to herald significant liver injury, even with continued statin treatment.

Statins have also been associated with myopathy and rare cases of rhabdomyolysis. According to findings from 21 clinical trials providing 180,000 person years of follow-up in patients treated with a statin or placebo, myopathy (defined as muscle symptoms plus CK >10XULN) occurs in 5 patients per 100,000 person-years and rhabdomyolysis in 1.6 patients per 100,000 person-years (placebo-corrected) (McKenney, 2006).

Proteinuria has been described rarely with statins, but was recently found significantly more frequently in patients receiving rosuvastatin 80 mg than in patients given placebo. The frequency of proteinuria with lower doses of rosuvastatin (5-40 mg), as well as atorvastatin, pravastatin, and simvastatin was no different than placebo (McKenney, 2006). In studies with human renal proximal cell cultures, simvastatin, pravastatin, and rosuvastatin inhibited protein uptake in a dose-dependent manner (Verhulst, 2004). These studies suggest that proteinuria is possible with all statins, but is more likely to be seen with the more potent inhibitors of HMG-CoA reductase (Bays, 2006).

In 2005, the Agency concluded that proteinuria in patients receiving statins is not associated with renal impairment or renal failure (FDA Public Health Advisory on Crestor, 2006).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

- The Agency requested three overnight urine collections for subjects in the Phase 3 program at baseline and endpoint of the core studies. In follow-up discussions, it was agreed that a spot urine protein: creatinine ratio would be adequate; these samples would be on a subset of patients who had not yet had their baseline visit
- The Agency requested translated case report forms on all deaths and discontinuations due to adverse events from the Japanese NDA application
- The Agency agreed to the proposed set of clinical pharmacology studies
- It was suggested that Kowa consider conducting a PK study in African Americans compared to Caucasians to assure that no differences exist in pharmacokinetics
- The firm was asked to consider using the full range of doses of the chosen comparator statins
- The firm was informed that their compound could not be promoted as being comparable to atorvastatin and simvastatin unless they studied the full dose range of these drugs
- The Agency agreed to a deferral of pediatric studies until the post-approval phase
- The Agency commented that a thorough QTc study should be conducted
- The Agency requested that a statistical analysis plan be provided in addition to the core study protocols for the Phase 3 program

- The Agency agreed that the proposed number of patients and exposure duration were sufficient to support an NDA
- (b) (4)
- The Agency requested inclusion of narratives **for serious adverse events judged "related to drug" by the investigator** from Japanese post-marketing reports
- The Agency agreed that a full translation of reports and information from the Japanese NDA was not necessary and that the summary translation described by the applicant would probably be sufficient
- The final study report for extension study 310 would not be included in the NDA

All of the recommendations were implemented with the exception of the designs for studies 301 and 302 and the inclusion of the full dose range for the comparator statins. Studies 301 and 302 were kept as forced titration and two separate studies as originally planned. Atorvastatin 40 mg was used only in Study 310 if patients who did not achieve the targeted LDL-C goals.

2.6 Other Relevant Background Information

The following are important revisions or additions to the Japanese pitavastatin label:

8/2004: [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.

8/2004: [Adverse Reactions (other adverse reactions)] Hypersensitivity: urticaria, erythema; Renal: pollakiuria; muscular: cramp, feeling of weakness; Psychoneurotic: sleep loss

6/2005: [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.

6/2005: [Adverse Reactions (other adverse reactions)] Digestive: nausea/vomiting, anorexia

12/2005: [Adverse Reactions (other adverse reactions)] Digestive: glossitis

12/2006: [Adverse Reactions (other adverse reactions)] Others: dysgeusia

3/2009: [Interactions (precautions for concomitant use)][pharmacokinetics] rifampicin, erythromycin

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Although the submission contained a large amount of data, this clinical reviewer still had a number of requests for patient information. The patient narratives for serious adverse events, adverse events of special interest, and withdrawals were not in a defined section of the ISS, but were scatted throughout the individual 14 studies. Some of the narratives were not included in the studies where they were specified. Furthermore, patient narratives were not constructed to impart the most information.

3.2 Compliance with Good Clinical Practices

The clinical development program in Europe and US was conducted to the standards set out in the current good clinical practice (GCP) guidelines. As certified in the submission, no debarred investigators were used in the conduct of these studies.

There were no specific concerns with any particular investigative site. The ratio of the number of subjects enrolled to the number of subjects screened at any site was taken into account. Sites that enroll a high percent of screened subjects may be randomizing ineligible subjects. The number of subjects discontinued, the number of subjects with **protocol violations, and the sites with "high enrollers" were also considered. The following sites were identified by this reviewer for** inspection:

Table 3 Clinical Sites Recommended for DSI Audit

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site # 1200 Dr. A Blokhin **State Institution "Out-patient** Clinic # 1 of Medical Center of Russian Federation **President's Management Department"** 31, Grokholsky lane, Moscow, 129010, Russia	NK-104-301	76 randomized 100 screened 2 D/C 12 with protocol violations	primary hyperlipidemia and mixed dyslipidemia
Site # 1214 Prof. Svetlana Tchurina St.Petersburg State Medical **Institution "Pokrovskaya City Hospital", Cardiology** Department #2 85, Bolshoy pr. V.O., St.Petersburg, 199106, Russia	NK-104-301	68 randomized 85 screened 0 D/C 16 with protocol violations	primary hyperlipidemia and mixed dyslipidemia
For Study 302, please select any two sites from the four submitted from that study.			

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #2301 Dr. Leiv Ose Rikshospitalet - University Hospital N-0027 Oslo, Norway	NK-104-302	56 randomized 111 screened 6 D/C 12 with protocol violations	primary hyperlipidemia and mixed dyslipidemia
Site # 2501 Dr. Mark Blagden Avondale Surgery 3-5 Avondale Road, Chesterfield, S40 4TP, UK	NK-104-302	33 randomized 52 screened 6 D/C 16 with protocol violations	primary hyperlipidemia and mixed dyslipidemia
Site # 2116 Prof Yury Shvarts Saratov State Medical University 137, Bolshaya Sadovaya str. Saratov, 410054, Russia	NK-104-302	46 randomized 72 screened 3 D/C 5 with protocol violations	primary hyperlipidemia and mixed dyslipidemia
Site # 2106 Prof Victor Gurevich Central Medical Unit #122 4, Prospect Kultury, St.Petersburg, 194291, Russia	NK-104-302	33 randomized 46 screened 1 D/C 3 with protocol violations	primary hyperlipidemia and mixed dyslipidemia

In a consult dated July 9, 2009, the Division of Scientific Investigations concluded that the above six clinical sites adequately adhered to the study protocols and that the data from these sites may be used in support of the proposed indications.

3.3 Financial Disclosures

A signed FDA form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was included in the submission declaring the absence of financial interests and arrangements between the applicant and clinical investigators. The form was appended with a list of investigators who participated in all the Phase 2 and Phase 3 studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Suong T. Tran, Ph.D. reviewed the Chemistry, Manufacturing and Controls (CMC) data. A brief summary of the CMC data is provided below.

Pitavastatin as the calcium salt is formulated as an immediate-release tablet. Although the initial formulation work was conducted in Japan, the formulation marketed in Japan and the proposed formulation for approval in this application differ.

One of the differences is that in the US formulation, a 2 mg tablet contains 2.09 mg pitavastatin calcium, equivalent to 2.00 mg pitavastatin, while the Japanese 2 mg tablet contains 2 mg pitavastatin calcium, equivalent to (b) (4) of pitavastatin. According to the applicant, the significance of this was investigated in study (NK-104-1.35) which showed bioequivalence between the formulations (Japanese formulation [Livalo®] and the Phase 3 formulation for the US new drug applications) in Caucasian subjects.

The Phase 3 studies were conducted with a product manufactured by SkyePharma, France. The formulation that is the subject of this application is made by a different manufacturer, Patheon based in Cincinnati, USA. The same formulation was transferred to Patheon from SkyePharma and the only difference is that the SkyePharma tablets are plain round white biconvex film-coated tablets whereas the Patheon tablets also carry debossing. The proposed product is a conventional immediate-release **round white film-coated tablet debossed on one side with 'KC' and either "1", '2' or '4' on the** reverse containing pitavastatin calcium equivalent to 1 mg, 2 mg or 4 mg pitavastatin respectively.

According to the applicant, the impact of the potential difference in the tablets from the different manufacturing sites has been investigated and shown not to affect dissolution of the tablets (NK-104-1.39US). The pharmacokinetic profile and bioequivalence, following a single dose of the tablets from the different manufacturing sites has been investigated in study NK-104-1.37US; results show that SkyePharma 2 mg tablet vs. Patheon 2mg tablet and SkyePharma 4mg tablet and Patheon 4 mg tablet are bioequivalent.

(b) (4)

4.2 Clinical Microbiology

Not Applicable.

4.3 Preclinical Pharmacology/Toxicology

C. Lee Elmore, Ph.D. and Karen Davis-Bruno, Ph.D. reviewed the pre-clinical data. A brief summary from the pharmacology/toxicology review is provided below.

Preclinical studies were generally adequate to support the proposed dosing regiment.

Acute, subchronic, and chronic toxicology studies were performed in a variety of animal species including mice, rat, dog, and monkey with pitavastatin. Additional studies were performed to explore potential mechanisms of the identified target organ toxicities (lens, kidney, thyroid, liver, skeletal muscle, lung, forestomach), as well as qualification of various metabolites (lactone, 8-hydroxypitavastatin formed in humans) and impurities (b) (4) The

pharmacology/toxicology review discusses in detail these findings; this clinical review will only highlight hepatic, skeletal muscle, and renal toxicities.

Hepatic toxicities

Hepatic effects have been seen in mice, rats and dogs. In the 12-month toxicity study both AST and ALT activity was increased in male dogs given 3 mg/kg/day (24-fold human exposure at 4 mg/day dose). Elevated ATs were not detected upon recovery following drug withdrawal; hepatic histopathologies were not observed.

In a 3-month dog toxicity study with pitavastatin at 10 mg/kg/day, centrilobular dilatation of liver sinusoids where observed, which resolved during recovery. A 3-month dog toxicity study with co-administration of mevalonic acid (100-150 mg/kg/day) and pitavastatin (5 mg/kg/day) resulted in an absence of AT elevations at doses up to 5 mg/kg/day (42-fold human exposure at 4 mg/day based on AUC).

Studies in mice up to 225 mg/kg/day (150-fold human exposure based on AUC) did show the liver histopathology; however, pitavastatin does not appear to induce drug metabolizing enzymes, nor is it associated with the severe necrosis and cellular atypia and cholestasis observed in animals following treatment with other statins. Further support of a lessened biliary toxicity is seen in guinea pigs (3 mg/kg/day for 15 days) and hamsters (1 mg/kg/day for 14 days) where pitavastatin did not show any change in biliary lipids.

Skeletal muscle toxicities

Degeneration and necrosis were observed in the 1- and 3-month rat toxicity studies at 50 mg/kg/day (894-fold human exposure at the 4 mg/day dose). Myopathy was not observed in the chronic rat study at doses up to 10 mg/kg/day (56-fold MHRD based on AUC). Myopathy was observed in the mouse carcinogenicity study at the highest dose (75 mg/kg/day) and in male rats given 25 mg/kg/day in the carcinogenicity study. Doses associated with myopathy in the lifetime carcinogenicity studies in mice and rats represent exposure levels 26 and 295-fold MRHD, respectively, based on AUC.

Renal toxicities

Renal toxicities were seen in male and female monkeys in 1-month and 6-month toxicology studies. Findings consisted of mild swelling of the proximal tubule epithelium with slight desquamation of tubular epithelium at ≥6 mg/kg/day (≥8.7-fold MRHD at a 4 mg/day dose) in conjunction with increased kidney weight. The high-dose findings were recoverable by 2 months post-withdrawal.

Creatinine and blood urea nitrogen or phenolsulphonephthalein clearance were unremarkable. Higher doses of pitavastatin at shorter duration resulted in further exacerbation of renal toxicities, which suggests dose-dependency.

Metabolism studies suggest that monkeys, more so than any other test species, form a greater proportion of 8- hydroxypitavastatin (minor metabolite). This metabolite is observed in monkey urine and feces. A mechanistic study investigated a link between 8-hydroxypitavastatin and renal toxicity. In this study, rats were administered 8-hydroxypitavastatin at 200 mg/kg BID for 2 weeks and 400 mg/kg/day BID for 1 week. All rats were found dead or sacrificed moribund before the study was scheduled for termination. Degeneration of the renal tubules, increased blood urea nitrogen and creatinine were also observed, suggesting a correlation.

Genetic Toxicology

Several studies evaluating mutagenic/genotoxic potential were negative. Pitavastatin was negative for genotoxicity in a chromosomal aberration assay without metabolic activation in CHL cells. Pitavastatin was also negative in an Ames reverse mutation battery, *in vivo* mouse and rat micronucleus assays, an *in vivo/in vitro* single cell gel (Comet assay), and an *in vivo/ in vitro* rat unscheduled DNA synthesis (UDS) assay.

Carcinogenicity

The initial 92-week mouse carcinogenicity study was found to be inadequate by the Executive Carcinogenicity Assessment Committee (ECAC) because of inadequate dosing of male mice and excess deaths in the high-dose group in the first year of the study. The ECAC also requested a peer review of stomach histopathology to determine if the hyperplastic lesions could have progressed over time to a neoplastic response since the carcinogenicity study was not carried out to the complete 104 weeks recommended duration.

A 92-week rat carcinogenicity study was subsequently submitted. The ECAC found the dose selection and survival rates to be adequate. Survival in controls for each gender was similar to the lowest dose group. A high incidence of hypertrophy and hyperplasia of the liver and forestomach and skeletal myofiber atrophy were seen which might have progressed to neoplasia if the study were to have continued for the complete 104 week duration.

ECAC requested a transgenic mouse study to address these inadequacies. Two Tg *rasH2* mouse carcinogenicity studies were submitted. Overall, the carcinogenicity assessment suggests no tumorogenicity in rats at doses up to 25 mg/kg/day (295-fold human exposure at 4 mg/day based on AUC) after 104 weeks treatment and in Tg rasH2 mice up to 150 mg/kg/day (194-fold human exposure at 4 mg/day based on AUC) after 26 weeks.

4.4 Clinical Pharmacology

S.W. Lau, Ph.D., Manoj Kharuna, Ph.D., and Wei Qui, Ph.D. reviewed the PK/PD data. A brief summary of clinically relevant PK/PD information is provided below.

4.4.1 Mechanism of Action

Pitavastatin selectively and competitively inhibits HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals and *in vitro* studies in cultured animal and human cells have shown pitavastatin to have a high uptake into, and selectivity for, the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, pitavastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, pitavastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

4.4.2 Pharmacodynamics

In study PKH/NKN98389N/NK-104.1.01 with healthy volunteers, lipid parameters were assessed along with pharmacokinetic parameters and showed a dose-response for LDL reduction after 7 days of treatment at doses up to 8 mg. In study HPC/NKN00435N/NK-104.1.19, there was not a dose response for LDL reduction with daily doses of 24 to 64 mg.

4.4.3 Pharmacokinetics

The pharmacokinetics of pitavastatin shows a linear profile over 1 mg to 24 mg doses, although the increase in steady state AUC between 2 mg and 4 mg is 2.7 fold. The ratio between the highest and lowest AUC values varies up to 4-fold in the therapeutic range.

For the doses lower than 4 mg, the time to steady state could not be determined due to the large numbers of concentrations below the limit of quantification. For the higher doses, the concentrations showed that steady state was achieved after 6 days of dosing for pitavastatin and after 5 days of dosing for the lactone metabolite.

The half-life of pitavastatin is approximately 8.5 to 12 hours for the 2 mg and 4 mg doses following multiple doses in the fed state.

Pitavastatin is not metabolized by CYP3A4. CYP2C9 and CYP2C8 have minor involvement in the metabolic pathway. The uptake of pitavastatin into hepatocytes is principally by OATP1B1 (organic anion transporting polypeptide) but OATP1B3 and NTCP (sodium-dependent taurocholate co-transporting polypeptide) also play a role (Fujino, 2005). Within the liver pitavastatin is metabolized to pitavastatin lactone by UGT1A3 and UGT2B7. Efflux from the liver is mediated by the transporter BCRP (breast cancer resistance protein).

According to the applicant, the main metabolite for the parent compound is a pitavastatin lactone **that is "inactive". The lactone is reversibly converted back to the parent active moiety. This** suggests that the two molecules exist at equilibrium in blood after drug administration. Although the metabolite may be ineffective in terms of efficacy, it is unknown if the pitavastatin lactone contributes to adverse events such as myalgia. There is both non-clinical and clinical evidence that the lactone moiety of statins plays a part in adverse muscle reactions (Skottheim, 2008).

At the request of the Agency, the applicant submitted limited data available for pitavastatin levels in patients with serious adverse events. Specifically, plasma concentrations for patients receiving 1, 2, 4 or 8 mg of pitavastatin were compared to the plasma samples of patients with serious adverse events from study NKS-104A2204 (12-week Phase 2 study) to determine if an overlap in exposure existed among patients receiving the proposed marketed doses and those with evidence of toxicity.

According to the review by Dr. Manoj Khurana, the average C_{trough} (pitavastatin and lactone) were compared among the following AE categories: 1) no muscle related AE, 2) CPK elevation, 3) myalgia and 4) rhabdomyolysis. The average pitavastatin and lactone exposures were similar among the first three groups and higher than the group with rhabdomyolysis (Figure 1).

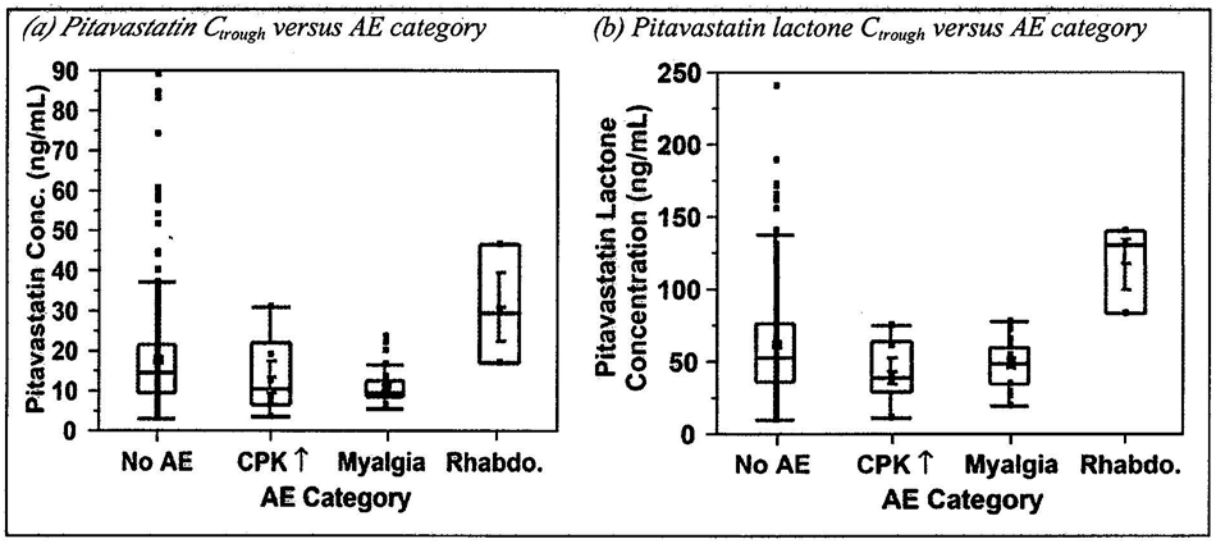


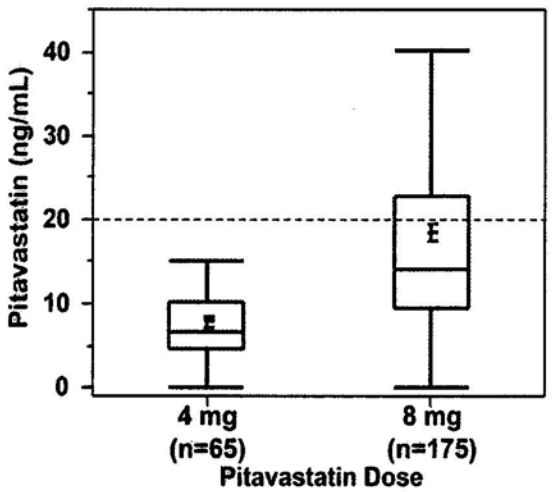
Figure 1 (Left) Pitavastatin and (Right) pitavastatin lactone trough concentrations versus AE categories in 8 mg dose group (Study NKS104A2204)

Source: M. Khurana clinical pharmacology review.

In study 2204, the steady-state concentrations of pitavastatin and its lactone were compared between subjects receiving 4 mg or 8 mg and two patients with rhabdomyolysis to assess if there was overlap in exposure between these three groups (Figure 2). There was no overlap in exposure among subjects in the 25th to 75th percentiles for the 4 mg and the 8 mg groups. None of the subjects in the 4 mg group had pitavastatin or pitavastatin lactone concentrations of greater than 20 ng/mL or 75 ng/mL, respectively, the values measured in the two subjects who developed rhabdomyolysis on 8 mg of pitavastatin.

Figure 2 . Mean(±SE) (blue) and box plots (red) of Week 2 Ctrough for (Left) pitavastatin and (Right) pitavastatin lactone versus pitavastatin dose (Study NKS104A2204)

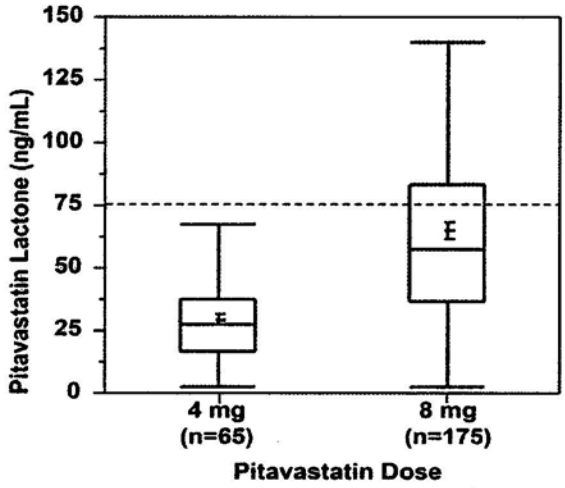
(a) Pitavastatin Week 2 C_{trough} versus dose



(Ɛ) Mean(±SE), box represents the middle 50% of data with the line representing median

(----) represents the lowest C_{trough} of pitavastatin observed in the patients with rhabdomyolysis

(b) Pitavastatin Lactone Week 2 C_{trough} versus dose



(Ɛ) Mean(±SE), box represents the middle 50% of data with the line representing median

(----) represents the lowest C_{trough} of pitavastatin lactone observed in the patients with rhabdomyolysis

Source: M. Khurana clinical pharmacology review.

Descriptions of drug-drug interactions are summarized in Section 7.5.5.

5 Sources of Clinical Data

Overview of Material Consulted in Review

Submission/Cover Letter Date	Documents
October 1, 2008	Original clinical submission including SAS data files, case report forms, and proposed labeling
November 21, 2008	Clinical site information
November 26, 2008	Coding Dictionary, MedDRA version 8.1
January 14, 2009	Subanalysis LIVES
January 26, 2009	Patient Information
February 16, 2009	PSUR #10 from Japan; Interim Report Study 310
March 6, 2009	Patient Information; Ethnicity Analysis
March 11, 2009	Patient Information; Muscle-related Analysis
	Patient Information; Muscle-related Analysis
April 16, 2009	Patient Information; Post-marketing Information
April 30, 2009	Patient Information; Safety Report
	Patient Information
May 5, 2009	Patient Information; Rhabdomyolysis
June 9, 2009	Patient Information; Safety report
June 22, 2009	Patient Information; Creatinine Outliers

5.1 Tables of Studies/Clinical Trials

Table 4 Summary of Clinical Studies

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s): Dosage regimen: Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Clinical Efficacy and Safety – Controlled Clinical Studies Pertinent to Indication (cont.)									
Efficacy/ Safety	[NK-104-209]	[5.3.5.1.3]	Efficacy, safety and tolerability/dose-response	Double-blind, randomised, placebo and open active (atorvastatin) controlled, parallel fixed dose	Pitavastatin 8, 16, 32 or 64 mg QD Atorvastatin 80 mg QD Oral tablets	422 (pita 8 mg 103, pita 16 mg 103, pita 32 mg 34, pita 64 mg 33, ator 80 mg 96, placebo 53)	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia	16 weeks	Complete Abbreviated
Efficacy/ Safety	[NKS104 A2204]	[5.3.5.1.4]	Efficacy, safety and tolerability	Double-blind, randomised, placebo and open active (atorvastatin) controlled, parallel fixed dose	Pitavastatin 4 and 8 mg QD Atorvastatin 10 to 20 to 40 mg QD Oral tablets	357 (pita 4mg 71, pita 8mg 214, ator 10/20/40 mg 36, placebo 36)	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia	12 weeks	Complete Abbreviated
Efficacy/ Safety	[NK-104-210/211]	[5.3.5.1.5]	Efficacy, safety and tolerability	Double-blind, randomised, placebo and open active (atorvastatin) controlled, parallel fixed dose with open label extension, fixed dose.	Pitavastatin 4 or 8 mg QD Atorvastatin 10 or 40 mg QD Pitavastatin 8 mg QD in safety extension study NK-104-211 Oral tablets	135* (pita 4 mg 28, pita 8 mg 58, ator 10 mg 16, ator 40 mg 15, placebo 16), 24 (pita 8 mg) in safety extension	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia	12 weeks and 72 weeks (patients from NK-104-210) Safety extension terminated Jan 2003.	Complete Abbreviated
Clinical Efficacy and Safety – Controlled Clinical Studies Pertinent to Indication									
Efficacy/ Safety	[HEC/NK98 402N/NK-104.2.02]	[5.3.5.1.1]	Efficacy and safety/dose-response	Double-blind, randomised, placebo-controlled, parallel, fixed dose	Pitavastatin 1, 2, 4 or 8 mg QD Oral tablet	261 (pita 1 mg 53, pita 2 mg 50, pita 4 mg 52, pita 8 mg 52, placebo 54)	Primary hyper-cholesterolaemia	12 weeks	Complete Full
Efficacy/ Safety	[HEC/NK98 403N/ NK-104.2.03]	[5.3.5.1.2]	Efficacy and safety/dose-response	Double-blind, randomised, placebo-controlled, parallel, fixed dose	Pitavastatin 1, 2, 4 or 8 mg QD Oral tablet	252 (pita 1 mg 49, pita 2 mg 50, pita 4 mg 51, pita 8 mg 52, placebo 50)	Combined (mixed) dyslipidaemia	12 weeks	Complete Full

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s): Dosage regimen: Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Clinical Efficacy and Safety – Controlled Clinical Studies Pertinent to Indication (cont.)									
Efficacy/ Safety	[NK-104-301]	[5.3.5.1.6]	Non-inferiority of LDL-C lowering effect: pitavastatin vs atorvastatin	Double-blind, active (atorvastatin) controlled, randomised, parallel, fixed dose or forced titration	Pitavastatin 2 mg QD or 2 mg QD (first 4 wks) to 4 mg QD (remaining 8 wks) Atorvastatin 10 mg QD or 10 mg QD (first 4 wks) to 20 mg QD (remaining 8 wks) Oral tablets	830 (pita 2mg 321, pita 4mg 303, ator 10mg 103, ator 20mg 103)	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia	12 weeks	Complete Full
Efficacy/ Safety	[NK-104-302]	[5.3.5.1.7]	Non-inferiority of LDL-C lowering effect: pitavastatin vs simvastatin	Double-blind, active (simvastatin) controlled, randomised, parallel, fixed dose or forced titration	Pitavastatin 2 mg QD or 2 mg QD (first 4 wks) to 4 mg QD (remaining 8 wks) Simvastatin 20 mg QD or 20 mg QD (first 4 wks) to 40 mg QD (remaining 8 wks) Oral tablets	857 (pita 2mg 315, pita 4mg 323, simv 20 mg 108, simv 40mg 111)	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia	12 weeks	Complete Full
Efficacy/ Safety	[NK-104-304]	[5.3.5.1.8]	Non-inferiority of LDL-C lowering effect: pitavastatin vs simvastatin	Double-blind, active (simvastatin) controlled, randomised, parallel, forced titration	Pitavastatin 2 mg QD (first 4 wks) to 4 mg QD (remaining 8 wks) Simvastatin 20 mg QD (first 4 wks) to 40 mg QD (remaining 8 wks) Oral tablets	355 (pita 4mg 236, simv 40mg 119)	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia and two or more risk factors for CHD	12 weeks	Complete Full

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s): Dosage regimen: Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Clinical Efficacy and Safety – Controlled Clinical Studies Pertinent to Indication (cont.)									
Efficacy/ Safety	[NK-104-305]	[5.3.5.1.9]	Non-inferiority of LDL-C lowering effect: pitavastatin vs atorvastatin	Double-blind, active (atorvastatin) controlled, randomised, parallel, forced titration	Pitavastatin 2 mg QD (first 4 wks) to 4 mg QD (remaining 8 wks) Atorvastatin 20 mg QD (first 4 wks) to 40 mg QD (remaining 8 wks) Oral tablets	418 (pita 4 mg 279, ator 20 mg 139)	Type II DM and combined (mixed) dyslipidaemia	12 weeks	Complete Full
Efficacy/ Safety	[NK-104-306]	[5.3.5.1.10]	Non-inferiority of LDL-C lowering effect: pitavastatin vs pravastatin	Double-blind, active (pravastatin) controlled, randomised, parallel, fixed dose or forced titration	Pitavastatin 1, 2 or 2 (first 4 wks) to 4 mg QD (remaining 8 wks) Pravastatin 10, 20 or 20 mg QD (first 4 wks) to 40 mg QD (remaining 8 wks) Oral tablets	962 (pita 1 mg 209, pita 2 mg 226, pita 4 mg 216, prav 10 mg 108, prav 20 mg 99, prav 40 mg 104)	Elderly (> 65 years) patients with primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia	12 weeks	Complete Full
Efficacy/ Safety	[NK-104-309]	[5.3.5.1.11]	Long-term safety and tolerability LDL-C target attainment	Double blind and single blind extension (NK-104-304), active (simvastatin) controlled, fixed or elective titration	Pitavastatin 4 mg QD Simvastatin 40 or 80 mg QD (patients who attained LDL-C target are 40 mg and not attained are 80 mg at wk 0 = wk 12 of NK-104-304) Oral tablets	178 (pita 4 mg 121, simv 40/80 mg 57)	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia and two or more risk factors for CHD (patients from study NK-104-304)	44 weeks (16 weeks DB and 28 weeks SB)	Complete Full

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s): Dosage regimen: Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Clinical Efficacy and Safety - Uncontrolled Clinical Studies									
Efficacy/ Safety	[NKS104 A2204E1]	[5.3.5.2.1]	Long-term safety and tolerability	Open-label extension (NKS104 A2204), fixed dose	Pitavastatin 8 mg QD Oral tablet	53	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia (patients from study NKS104 A2204)	52 weeks (patients from NKS104A2 204) Terminated Dec 2002.	Complete Abbreviated
Efficacy/ Safety	[NK104-307]	[5.3.5.2.2]	Long-term safety and tolerability	Open-label extension (NK-104-301/NK-104-302), fixed dose	Pitavastatin 4 mg QD Oral tablet	1353	Primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia (patients from studies NK-104-301/NK-104-302)	52 weeks	Complete Full
Efficacy/ Safety	[NK-104-308]	[5.3.5.2.3]	Long-term safety and tolerability	Open-label extension (NK-104-306), fixed or elective titration	Pitavastatin 2 mg QD or 2 (first 8 wks) to 4 mg QD (remaining 52 wks if target LDL-C was not attained) Oral tablet	539 (pita 2 mg 449, pita 4 mg 90)	Elderly (> 65 years) patients with primary hyper-cholesterolaemia or combined (mixed) dyslipidaemia (patients from study NK-104-306)	60 weeks	Complete Full

5.2 Review Strategy

Data from individual Phase 2 and 3 trials were reviewed for efficacy. Pooled data from the Phase 2 and Phase 3 trials (and their long-term extensions) were used for integrated assessments of efficacy and safety. Post-marketing safety data from Japan, including PSURs from July 2003-June 2008, and the study report from a 20,000 patient registry entitled LIVES were also reviewed as part of the safety assessment.

5.3 Discussion of Individual Studies/Clinical Trials

See separate document for the review of individual clinical trials.

The integrated review of efficacy provided in section 6 is composed of data from five Phase 2 studies and five Phase 3 studies.

The Phase 2 studies are designated 209, 210, 2204, 202, and 203. Studies 209, 2204, and 209 were randomized, double-blind, placebo-controlled and active open-labeled investigations in subjects with primary hyperlipidemia or mixed dyslipidemia. Study 209 was 16 weeks in duration, whereas studies 2204 and 209 were 12 weeks. The doses of pitavastatin examined were 4 mg, 8 mg, 16 mg, 32 mg, and 64 mg. (b) (4)
(b) (4)
Studies 202 and 203 were randomized, double-blind, placebo-controlled 12-week investigations in subjects with primary hyperlipidemia and mixed dyslipidemia, respectively. Doses of pitavastatin included 1 mg, 2 mg, 4 mg, and 8 mg. All told, approximately 1400 subjects were randomized into the five Phase 2 studies.

The Phase 3 studies were designated 301, 302, 304, 305, and 306. The Phase 3 studies were randomized, double-blind, active-controlled 12-week trials in subjects with primary hyperlipidemia and mixed dyslipidemia. Study 301 included pitavastatin 2 mg and 4 mg, and atorvastatin 10 mg and 20 mg. Studies 302 and 304 included pitavastatin 2 mg and 4 mg, and simvastatin 20 mg and 40 mg. Study 305 included subjects with type II diabetes who were randomized to pitavastatin 2 mg and 4 mg, and atorvastatin 10 mg and 20 mg. Study 306 included subjects > 65 years of age who were randomized to pitavastatin 1 mg, 2 mg, and 4 mg, and pravastatin 10 mg, 20 mg, and 40 mg. A total of approximately 3400 subjects were randomized into the five Phase 3 trials.

6 Review of Efficacy:

6.1 Indication

Pitavastatin is being proposed for the indication, as drug therapy, in addition to dietary restriction for the reduction of elevated total cholesterol, LDL, Apo B, and TG and to increase HDL in subjects with primary hypercholesterolemia or mixed hyperlipidemia.

The purpose of this integrated summary of efficacy is to compare the efficacy of 1, 2 and 4 mg of pitavastatin tablets to atorvastatin, pravastatin and simvastatin, and to incorporate those findings into the product labeling.

6.1.1 Methods

This section reviews the efficacy of two core Phase 2 studies (202 and 203) and five core Phase 3 studies (301, 302, 304, 305 and 306).

There were three phase 2 studies (209, 210, and 2204) in addition to studies 202 and 203 and the data from those studies appear in some of the summary tables. However, these three studies were terminated when it became clear that 8 mg and higher doses of pitavastatin were associated with an increased risk for myopathy.

Integrated efficacy data were summarized for the following treatment groups:

- Pitavastatin 1 mg, 2 mg, and 4 mg;
- Atorvastatin 10 mg and 20 mg;
- Simvastatin 20 mg and 40 mg;
- Pravastatin 10 mg, 20 mg, and 40 mg;
- Placebo

The 1 mg dose of pitavastatin was compared with the 10 mg dose of pravastatin. The 2 mg dose of pitavastatin was compared with the 20 mg dose of pravastatin, the 10 mg dose of atorvastatin, and the 20 mg dose of simvastatin. The 4 mg dose of pitavastatin was compared with the 40 mg dose of pravastatin, the 20 mg dose of atorvastatin, and the 40 mg dose of simvastatin. The dose comparisons were selected based on the pitavastatin Phase 2 studies and on literature values of

percent reduction in LDL observed with the comparators in similar populations of subjects, primary hypercholesterolemia and mixed dyslipidemia.

The pooled efficacy analyses should be interpreted with caution, as not all dose groups were represented in all studies. The pravastatin dose groups comprise only elderly subjects, and the proportion of elderly subjects is much higher in the pitavastatin 1 mg group than in the pitavastatin 2 mg or 4 mg groups. The proportions of subjects with Type II diabetes mellitus and mixed dyslipidemia were higher in the pitavastatin 4 mg group and the atorvastatin 20 mg group than the other treatment groups, as these treatments were used in study 305 conducted in diabetics with dyslipidemia

The Phase 2 core studies tested for superiority of pitavastatin against placebo and active comparators using ANOVA and dose response, and the Phase 3 core studies tested for non-inferiority of pitavastatin to an active comparator using ANCOVA for the primary efficacy variable (mean percent change from baseline to endpoint of LDL) and used descriptive statistics for the secondary efficacy variables.

The following analysis populations were defined for the Phase 2 core studies:

- **The Safety population** was defined as all randomized subjects who received at least one dose of double-blind study medication and who had data after randomization.
- **The ITT population** was defined as all randomized subjects who received double-blind medications 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 PP population** was defined as 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 fulfilled all the criteria for evaluation during the 12 weeks of treatment post-randomization.
- **The Completers population** was defined as all subjects who completed 12 weeks of treatment.

The following analysis populations were defined for the Phase 3 core studies:

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

For the Phase 3 trials, the FAS was the primary population used for the efficacy analyses, while the PP and COM populations were used for conformational analyses.

Data Handling Rules

Baseline:
Lipid baselines in the Phase 2 core studies were defined as the mean values at Week -2 and Week 0 (or one of them if the other was missing). The lipid baselines for the Phase 3 core studies were defined for each patient as the average of the lipid values measured at Week 0, prior to the first dose of study drug, and the lipid values measured at the last two visits prior to Week 0.

Handling of Missing Data:
Endpoint for the core studies was defined as either the last scheduled lipid value for subjects who completed the 12-week double-blind treatment period or as the last available lipid value for subjects who discontinued early. For intermediate visits there was no imputation of missing values.

Study Treatment Exposures:
The duration of study treatment (calculated as the date of last dose - date of first dose +1) during the treatment period was summarized for each treatment. These summaries were based on the FAS, including only subjects who received at least one dose of study drug and had at least one post-baseline lipid evaluation. Subjects in the five Phase 3 core studies who were randomized to 4 mg pitavastatin, 20 mg atorvastatin, 40 mg simvastatin, or 40 mg pravastatin received a lower dose (2 mg pitavastatin, 10 mg atorvastatin, 20 mg simvastatin, 20 mg pravastatin, respectively) for the first 4 weeks of treatment before being up-titrated to their randomized dose.

Statistical Methods: Individual Core Studies:
Analysis of variance (ANOVA) was used for the statistical analysis of the placebo-controlled Phase 2 studies, with factors for center and treatment in all studies with the additions of baseline LDL as a covariate in the model in studies 202 and 203. Treatment groups were compared with placebo using alpha-adjusted contrasts. In Studies 202 and 203, a linear regression model was fitted to assess dose response.

The active-controlled Phase 3 core studies were powered to demonstrate non-inferiority of pitavastatin to the corresponding dose of active comparator. The active-controlled studies all used analysis of covariance (ANCOVA) with treatment and country as factors and baseline LDL as a covariate. Adjusted means for the treatment differences and the corresponding 95% CIs on the differences were constructed. **For each comparison, non-inferiority of pitavastatin was confirmed if the lower bound of the 95% CI was greater than -6%.** The non-inferiority margin was chosen at 6% because use of this value has precedent in a number of published statin studies.

Secondary efficacy lipid variables were evaluated using ANCOVA and 95% CIs on the mean differences between the pitavastatin groups and the corresponding comparator groups in terms of

percent change from baseline values. Non-inferiority margins for secondary variables were not defined.
The LDL targets were calculated using baseline data collected prior to randomization, based on the NCEP ATP III Guidelines. Target attainment, using the NCEP criteria, was determined **using the LDL value from the last visit ('endpoint' for FAS or Week 12 for the PP population).** The proportion of subjects who reached their LDL target was analyzed using a linear probability model, which assumes the identity link and binomial distribution including treatment, country, risk categories (high, medium or low risk as defined in the NCEP guidelines), and baseline LDL as factors in the model. Point estimates (and 95% CI) on the differences between the pitavastatin groups and the corresponding comparator groups are presented.

6.1.2 Demographics

The demographic characteristics of the study subjects were similar across the core studies. Mean age ranged from 50 to 60 years, with the exception of Study 306 (carried out in elderly subjects) where the mean age was approximately 70 years. The majority of subjects in each treatment and dose group were Caucasian (>75%). In studies 202 and 203, where there were higher proportions of males to females in each group (60-76% vs. 24-40%, respectively). In study 304, there was a higher proportion of males than females (68-69% vs. 31-32%, respectively), and in study 302, there was a higher proportion of females than males in the pitavastatin groups (61-63% vs. 37-39%, respectively).

There did not appear to be any clinically meaningful differences in demographic characteristics between treatment groups within each individual study, as shown in the following table.

Table 5 Phase 2 Core Studies: Demographic Characteristics by Study and Dose

Study Treatment	N	Age		Sex n (%)		Race n (%)			
		Mean (SD)	Range	Male	Female	Caucasian	Black	Asian/ Indian	Hispanic/ Other
NK-104-2.02 (ITT)									
Pitavastatin									
1 mg	52	54.5 (11.3)	29, 73	35 (67.3)	17 (32.7)	52 (100)	0	0	0
2 mg	49	52.7 (9.6)	25, 75	37 (75.5)	12 (24.5)	49 (100)	0	0	0
4 mg	50	53.1 (11.8)	22, 75	38 (76.0)	12 (24.0)	49 (98.0)	0	1 (2.0)	0
Placebo	51	52.4 (12.3)	21, 74	36 (70.6)	15 (29.4)	50 (98.0)	0	1 (2.0)	0
NK-104-2.03 (ITT)									
Pitavastatin									
1 mg	49	51.6 (9.4)	23, 70	33 (67.4)	16 (32.7)	49 (100)	0	0	0
2 mg	50	51.9 (9.5)	22, 73	35 (70.0)	15 (30.0)	47 (94.0)	1 (2.0)	1 (2.0)	1 (2.0)
4 mg	48	53.3 (9.4)	30, 74	29 (60.4)	19 (39.6)	44 (91.7)	1 (2.1)	3 (6.3)	0

Study Treatment	N	Age		Sex n (%)		Race n (%)			
		Mean (SD)	Range	Male	Female	Caucasian	Black	Asian/ Indian	Hispanic/ Other
Placebo	50	51.2 (11.6)	27, 75	34 (68.0)	16 (32.0)	50 (100)	0	0	0

Table 6 Phase 3 Core Studies: Demographic Characteristics by Study and Dose

Study Treatment	N	Age		Sex n (%)		Race n (%)			
		Mean (SD)	Range	Male	Female	Caucasian	Black	Asian/ Indian	Hispanic/ Other
NK-104-301									
Pitavastatin									
2 mg	316	58.4 (9.51)	23, 75	142 (44.9)	174 (55.1)	238 (75.3)	0	78 (24.7)	0
4 mg	300	57.9 (10.10)	18, 74	136 (45.3)	164 (54.7)	232 (77.3)	0	68 (22.7)	0
Atorvastatin									
10 mg	102	59.2 (8.63)	28, 74	52 (51.0)	50 (49.0)	79 (77.5)	0	23 (22.5)	0
20 mg	103	58.0 (9.14)	35, 73	48 (46.6)	55 (53.4)	79 (76.7)	0	24 (23.3)	0
NK-104-302									
Pitavastatin									
2 mg	311	58.7 (8.83)	30, 75	115 (37.0)	196 (63.0)	310 (99.7)	1 (0.3)	0	0
4 mg	320	57.7 (8.97)	29, 75	125 (39.1)	195 (60.9)	318 (99.4)	0	1 (0.3)	1 (0.3)
Simvastatin									
20 mg	107	58.6 (9.64)	34, 74	44 (41.1)	63 (58.9)	106 (99.1)	0	0	1 (0.9)
40 mg	110	58.4 (9.54)	25, 74	48 (43.6)	62 (56.4)	110 (100)	0	0	0
NK-104-304									
Pitavastatin 4 mg	233	60.1 (6.82)	35, 75	158 (67.8)	75 (32.2)	233 (100)	0	0	0
Simvastatin 40 mg	119	60.9 (6.78)	40, 74	82 (68.9)	37 (31.1)	118 (99.2)	1 (0.8)	0	0
NK-104-305									
Pitavastatin 4 mg	275	59.1 (9.21)	24, 75	155 (56.4)	120 (43.6)	243 (88.4)	0	32 (11.6)	0
Atorvastatin 20 mg	137	59.8 (9.06)	36, 75	78 (56.9)	59 (43.1)	118 (86.1)	0	19 (13.9)	0
NK-104-306									
Pitavastatin									
1 mg	207	70.0 (4.60)	65, 89	89 (43.0)	118 (57.0)	207 (100)	0	0	0
2 mg	224	70.5 (4.49)	65, 87	100 (44.6)	124 (55.4)	222 (99.1)	1 (0.4)	0	1 (0.4)

Study Treatment	N	Age		Sex n (%)		Race n (%)			
		Mean (SD)	Range	Male	Female	Caucasian	Black	Asian/ Indian	Hispanic/ Other
4 mg	210	70.2 (4.10)	65, 82	89 (42.4)	121 (57.6)	207 (98.6)	0	0	3 (1.4)
Pravastatin									
10 mg	103	70.5 (4.61)	65, 82	49 (47.6)	54 (52.4)	103 (100)	0	0	0
20 mg	96	69.9 (4.51)	65, 86	48 (50.0)	48 (50.0)	94 (97.9)	0	2 (2.1)	0
40 mg	102	70.2 (4.94)	65, 89	42 (41.2)	60 (58.8)	102 (100)	0	0	0

Source: Individual clinical study reports

Primary Diagnosis:
The primary diagnosis for the majority of subjects was primary hypercholesterolemia (>74%) with the exception of subjects who were randomized into study 305 (diagnosed with combined or mixed dyslipidemia).

The baseline characteristics based on subjects' primary lipid diagnosis are detailed in the following table.

Table 7 Baseline Diagnostic Characteristics by Target Dose (FAS Population) - Integrated Phase 2 and 3 Core Studies

Treatment	N	Diagnosis, n (%)		
		Primary hypercholesterolemia	Combined/Mixed dyslipidemia	Heterozygous FH
Pitavastatin				
1 mg	309	240 (77.7)	68 (22.0)	1 (0.3)
2 mg	945	743 (78.6)	196 (20.7)	6 (0.6)
4 mg	1533	967 (63.1)	557 (36.3)	9 (0.6)
Atorvastatin				
10 mg	118	96 (81.4)	21 (17.8)	1 (0.8)
20 mg	238	80 (33.6)	158 (66.4)	0
Simvastatin				
20 mg	107	80 (74.8)	26 (24.3)	1 (0.9)
40 mg	228	195 (85.5)	28 (12.3)	5 (2.2)
Pravastatin				
10 mg	103	90 (87.4)	13 (12.6)	0
20 mg	96	84 (87.5)	11 (11.5)	1 (1.0)
40 mg	102	89 (87.3)	12 (11.8)	1 (1.0)
Placebo	154	82 (53.2)	72 (46.8)	0

Source: End-of-Text Table 3

Within each study, there were no meaningful differences between the treatment arms with respect to NCEP risk categories, as shown in the following table.

Table 8 Baseline NCEP Risk Category by Study and Dose – Phase 2 and 3 Core Studies

Study Treatment	N	NCEP Risk Category, n (%)		
		High	Moderate	Low
NK-104-2.02		NA		
NK-104-2.03		NA		
NK-104-301 (Safety)				
Pitavastatin				
2 mg	316	160 (50.6)	77 (24.4)	79 (25.0)
4 mg	300	133 (44.3)	52 (17.3)	115 (38.3)
Atorvastatin				
10 mg	102	46 (45.1)	27 (26.5)	29 (28.4)
20 mg	103	50 (48.5)	21 (20.4)	32 (31.1)
NK-104-302 (Safety)				
Pitavastatin				
2 mg	311	108 (34.7)	91 (29.3)	112 (36.0)
4 mg	320	84 (26.3)	108 (33.8)	128 (40.0)
Simvastatin				
20 mg	107	38 (35.5)	35 (32.7)	34 (31.8)
40 mg	110	26 (23.6)	49 (44.5)	35 (31.8)
NK-104-304 (Safety)				
Pitavastatin 4 mg	233	59 (25.3)	165 (70.8)	9 (3.9)
Simvastatin 40 mg	119	35 (29.4)	79 (66.4)	5 (4.2)
NK-104-305 (Safety)				
Pitavastatin 4 mg	275	275 (100)	0	0
Atorvastatin 20 mg	137	137 (100)	0	0
NK-104-306 (Safety)				
Pitavastatin				
1 mg	207	32 (15.5)	50 (24.2)	125 (60.4)
2 mg	224	36 (16.1)	65 (29.0)	123 (54.9)
4 mg	210	32 (15.2)	67 (31.9)	111 (52.9)
Pravastatin				
10 mg	103	16 (15.5)	29 (28.2)	58 (56.3)
20 mg	96	15 (15.6)	25 (26.0)	56 (58.3)
40 mg	102	12 (11.8)	25 (24.5)	65 (63.7)

Source: Individual clinical study reports

Hypertension:

Generally, the prevalence of hypertension was similar among treatment groups and was highest in studies 301, 302, and 305 (approximately 60-78% of subjects).

Diabetes was less common, reported for 0% to 14% of subjects in the non-diabetic studies, and for 100% of subjects in study 305, as planned by the protocol. Within each study, the proportions of subjects with risk factors were regarded as similar across the treatment arms.

The breakdown of hypertensive and diabetic subjects in the core studies is shown in the following table.

Table 9 Incidence of Hypertension and Diabetes – Phase 2 and 3 Core Studies

Study Treatment	N	Hypertension, n (%)	Diabetes, n (%)
NK-104-2.02		NA	
NK-104-2.03		NA	
NK-104-301			
Pitavastatin			
2 mg	316	208 (65.8)	26 (8.2)
4 mg	300	188 (62.7)	14 (4.7)
Atorvastatin			
10 mg	102	67 (65.7)	12 (11.8)
20 mg	103	65 (63.1)	14 (13.6)
NK-104-302			
Pitavastatin			
2 mg	311	200 (64.3)	18 (5.8)
4 mg	320	188 (59.1)	21 (6.6)
Simvastatin			
20 mg	107	76 (71.0)	9 (8.4)
40 mg	110	72 (65.5)	6 (5.5)
NK-104-304			
Pitavastatin 4 mg	233	123 (52.8)	15 (6.4)
Simvastatin 40 mg	119	70 (58.8)	8 (6.7)
NK-104-305			
Pitavastatin 4 mg	275	215 (78.2)	275 (100)
Atorvastatin 20 mg	137	104 (75.9)	137 (100)
NK-104-306			
Pitavastatin			
1 mg	207	97 (46.9)	11 (5.3)
2 mg	224	113 (50.4)	16 (7.1)
4 mg	210	108 (51.4)	17 (8.1)
Pravastatin			
10 mg	103	54 (52.4)	6 (5.8)
20 mg	96	48 (50.0)	4 (4.2)
40 mg	102	48 (47.1)	3 (2.9)

Source: Individual clinical study reports

Baseline Cholesterol/Lipid Values:

Baseline lipid profiles were as expected for the populations recruited into the core studies, and there were no imbalances within any study considered likely to have affected the outcome or interpretation of the study. Where the baseline LDL, HDL, and TG values differed across the studies, it was generally attributable to the differing entrance criteria with respect to lipid parameters.

The baseline lipid values relative to study and dose are shown in the following table.

Table 10 Baseline Lipid Values by Study and Dose – Phase 2 and 3 Core Studies

Study Treatment	N	Mean values (SD)			
		LDL-C	HDL-C	TC	TG
		mg/dL	mg/dL	mg/dL	mg/dL
NK-104-2.02					
Pitavastatin					
1 mg	52	196.9 (27.03)	54.1 (11.58)	281.9 (30.89)	159.3 (61.95)
2 mg	50	200.8 (19.31)	57.9 (11.58)	285.7 (27.03)	159.3 (61.95)
4 mg	50	196.9 (27.03)	54.1 (15.44)	285.7 (30.89)	159.3 (61.95)
Placebo	51	196.9 (27.03)	57.9 (15.44)	285.7 (27.03)	141.6 (53.10)
NK-104-2.03					
Pitavastatin					
1 mg	49	177.6 (34.75)	50.2 (7.72)	281.9 (42.47)	274.3 (88.50)
2 mg	50	177.6 (30.89)	50.2 (11.58)	281.9 (38.61)	274.3 (79.65)
4 mg	48	181.5 (38.61)	54.1 (15.44)	289.6 (46.33)	274.3 (70.80)
Placebo	50	181.5 (34.75)	46.3 (7.72)	281.9 (34.75)	265.5 (88.50)
NK-104-301					
Pitavastatin					
2 mg	316	183.49 (16.78)	48.50 (11.35)	263.50 (22.71)	157.70 (56.03)
4 mg	300	181.81 (16.82)	49.92 (12.23)	263.26 (22.12)	157.36 (57.98)
Atorvastatin					
10 mg	102	179.76 (16.85)	50.16 (11.69)	261.30 (22.62)	156.84 (60.67)
20 mg	103	181.81 (16.69)	48.65 (12.93)	262.63 (22.46)	161.03 (66.35)
NK-104-302					
Pitavastatin					
2 mg	311	183.59 (16.99)	51.28 (12.76)	267.64 (22.19)	163.66 (60.91)
4 mg	320	183.99 (16.45)	52.78 (12.91)	268.03 (20.76)	156.40 (61.86)
Atorvastatin					
10 mg	107	184.07 (17.15)	50.99 (11.83)	268.38 (22.67)	166.70 (56.83)
20 mg	110	184.00 (15.66)	52.26 (10.69)	267.03 (20.31)	153.86 (55.39)
NK-104-304					
Pitavastatin 4 mg	233	166.09 (20.31)	47.52 (11.39)	246.35 (25.47)	164.01 (67.87)
Simvastatin 40 mg	119	166.68 (23.46)	46.04 (8.18)	245.43 (30.26)	163.71 (66.09)
NK-104-305					

Study Treatment	N	Mean values (SD)			
		LDL-C	HDL-C	TC	TG
		mg/dL	mg/dL	mg/dL	mg/dL
Pitavastatin 4 mg	275	143.00 (27.49)	41.79 (9.24)	233.23 (32.62)	244.15 (77.90)
Atorvastatin 20 mg	137	145.87 (26.94)	40.88 (7.48)	235.57 (31.37)	244.75 (88.82)
NK-104-306					
Pitavastatin					
1 mg	209	164.36 (22.91)	60.80 (15.27)	253.41 (29.16)	141.21 (53.91)
2 mg	226	162.83 (20.50)	60.24 (15.45)	250.48 (25.35)	137.20 (48.70)
4 mg	216	163.48 (21.86)	58.08 (14.62)	250.65 (25.53)	145.42 (55.84)
Pravastatin					
10 mg	108	163.57 (22.29)	57.70 (15.35)	249.66 (28.15)	142.03 (54.04)
20 mg	99	163.71 (19.32)	59.68 (14.19)	252.89 (25.76)	147.91 (61.45)
40 mg	104	166.58 (21.89)	59.39 (15.19)	253.77 (24.51)	139.07 (53.66)

Source: Individual clinical study reports

6.1.3 Subject Disposition

The majority of subjects (>94%) in each treatment group were included in the FAS/ITT population. Generally, the proportion of subjects included in the FAS/ITT population from the pitavastatin dose groups was similar to the proportion of subjects in the comparator/placebo groups for each study.

At least 88% of subjects receiving pitavastatin completed treatment in each study. Mean duration of exposure was, in general, similar among the pitavastatin doses (78.4 to 88.3 days) and the comparators (37.7 to 87.0 days).

A total of 3933 subjects were included in the FAS/ITT population for the integrated core studies: 2832 subjects who received pitavastatin doses (1 mg, 2 mg, and 4 mg), with just over a third of these subjects receiving pitavastatin 4 mg, and 1101 subjects in the comparator groups.

Subject disposition from Phase 2 and Phase 3 studies is shown in the following tables.

Table 11 Phase 2 Core Studies: Patient Disposition by Study and Dose

Study Treatment	N	Safety n (%)	FAS/ITT n(%)	Completers n (%)	Per Protocol n (%)
NK-104-2.02					
Pitavastatin					
1 mg	53	53 (100)	52 (98.1)	NA	48 (90.6)
2 mg	50	50 (100)	49 (98.0)	NA	41 (82.0)
4 mg	52	52 (100)	50 (96.2)	NA	42 (80.8)
Placebo	54	54 (100)	51 (94.4)	NA	45 (83.3)
NK-104-2.03					
Pitavastatin					
1 mg	49	49 (100)	49 (100)	NA	40 (81.6)
2 mg	50	50 (100)	50 (100)	NA	39 (78.0)
4 mg	51	51 (100)	48 (94.1)	NA	46 (90.2)
Placebo	50	50 (100)	50 (100)	NA	45 (90.0)

Table 12 Phase 3 Core Studies: Patient Disposition by Study and Dose

Study Treatment	N	Safety n (%)	FAS/ITT n(%)	Completers n (%)	Per Protocol n (%)
NK-104-301					
Pitavastatin					
2 mg	321	316 (98.4)	315 (98.1)	301 (93.8)	236 (73.5)
4 mg	303	300 (99.0)	298 (98.3)	288 (95.0)	250 (82.5)
Atorvastatin					
10 mg	103	102 (99.0)	102 (99.0)	98 (95.1)	82 (79.6)
20 mg	103	103 (100)	102 (99.0)	100 (97.1)	82 (79.6)
NK-104-302					
Pitavastatin					
2 mg	315	311 (98.7)	307 (97.5)	295 (93.7)	266 (84.4)
4 mg	323	320 (99.1)	319 (98.8)	304 (94.1)	282 (97.3)
Simvastatin					
20 mg	108	107 (99.1)	107 (99.1)	99 (91.7)	87 (80.6)
40 mg	111	110 (99.1)	110 (99.1)	107 (96.4)	95 (85.6)
NK-104-304					
Pitavastatin 4 mg	236	233 (98.7)	233 (98.7)	223 (94.5)	182 (77.1)
Simvastatin 40 mg	119	119 (100)	118 (99.2)	107 (89.9)	84 (70.6)
NK-104-305					
Pitavastatin 4 mg	279	275 (98.6)	274 (98.2)	248 (88.9)	214 (76.7)
Atorvastatin 20 mg	139	137 (98.6)	136 (97.8)	124 (89.2)	107 (77.0)
NK-104-306					
Pitavastatin					

Study Treatment	N	Safety n (%)	FAS/ITT n(%)	Completers n (%)	Per Protocol n (%)
1 mg	209	207 (99.0)	207 (99.0)	188 (90.0)	171 (81.8)
2 mg	226	224 (99.1)	224 (99.1)	208 (92.0)	179 (79.2)
4 mg	216	210 (97.2)	210 (97.2)	194 (89.8)	170 (78.7)
Pravastatin					
10 mg	108	103 (95.4)	103 (95.4)	89 (82.4)	82 (75.9)
20 mg	99	96 (97.0)	96 (97.0)	88 (88.9)	76 (76.8)
40 mg	104	102 (98.1)	102 (98.1)	95 (91.3)	82 (78.8)

Source: Individual clinical study reports

6.1.4 Analysis of Primary Endpoint

The primary efficacy variable in the core studies was the percent change from baseline LDL at the end of 12 weeks of treatment (or at endpoint for subjects who did not complete 12 weeks of treatment). The efficacy population included all randomized subjects who received at least one dose of study drug and had at least one post-baseline lipid assessment.

For the Phase 3 studies, pitavastatin was considered non-inferior to the comparator statin if the lower bound of the 95% confidence interval for the difference between groups in the mean percent change in LDL from baseline to endpoint was above -6%.
The mean percent change in LDL from baseline to endpoint by study and dose is shown in the following table.

Table 13 Mean Percent Change in LDL (mg/dL) from Baseline to Endpoint by Study and Dose - Core Phase 2 and 3 Studies (ITT/FAS Population)

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-2.02							
Pitavastatin							
1 mg	52	196.9 (27.03)	NA	-32.4 (8.6)	NA	0.000	Placebo
2 mg	49	200.8 (19.31)	NA	-36.5 (12.7)	NA	0.000	Placebo
4 mg	50	196.9 (27.03)	NA	-44.7 (10.1)	NA	0.000	Placebo
Placebo	51	196.9 (27.03)	NA	-2.3 (14.5)	NA	NA	NA
NK-104-2.03							
Pitavastatin							
1 mg	49	177.6 (34.75)	NA	-27.3 (15.5)	NA	0.000	Placebo
2 mg	50	177.6 (30.89)	NA	-31.4 (12.7)	NA	0.000	Placebo
4 mg	48	181.5 (38.61)	NA	-41.9 (16.0)	NA	0.000	Placebo
Placebo	50	181.5 (34.75)	NA	-1.9 (13.0)	NA	NA	NA
NK-104-301							
Pitavastatin							
2 mg	315	183.6 (16.76)	113.9 (27.96)	-37.91	-0.15 (-3.42,	0.926	Atorvastatin

Study Treatment	**N**	**Baseline (mg/dL)**	**Week 12 LOCF (mg/dL)**	**% change Week 12 LOCF**	**Mean difference (95% CI)**	**p-value**	**vs.**
		Mean (SD)	**Mean (SD)**	**Mean (SD)**			
				(13.969)	3.11)*		10 mg
4 mg	298	182.0 (16.72)	100.3 (26.86)	-44.61 (14.983)	0.96 (-2.32, 4.24)*	0.565	Atorvastatin 20 mg
Atorvastatin							
10 mg	102	179.8 (16.85)	111.5 (28.21)	-37.81 (15.604)	NA	NA	NA
20 mg	102	181.9 (16.73)	102.5 (31.00)	-43.53 (16.153)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	307	183.6 (16.98)	111.9 (28.44)	-38.99 (14.573)	4.08 (0.82, 7.34)*	0.014	Simvastatin 20 mg
4 mg	319	184.1 (16.45)	103.0 (27.58)	-43.97 (14.494)	1.08 (-2.13, 4.29)*	0.509	Simvastatin 40 mg
Simvastatin							
20 mg	107	184.1 (17.15)	119.1 (27.65)	-34.97 (15.528)	NA	NA	NA
40 mg	110	184.0 (15.66)	104.6 (27.49)	-42.84 (15.769)	NA	NA	NA
NK-104-304							
Pitavastatin 4 mg	233	166.1 (20.31)	92.9 (23.51)	-43.96 (12.770)	0.31 (-2.47, 3.09)*	0.829	Simvastatin 40 mg
Simvastatin 40 mg	118	166.9 (23.47)	93.3 (24.67)	-43.77 (14.416)	NA	NA	NA
NK-104-305							
Pitavastatin 4 mg	274	142.8 (27.41)	84.3 (31.01)	-40.78 (19.599)	-2.33 (-6.18, 1.52)	0.235	Atorvastatin 20 mg
Atorvastatin 20 mg	136	146.0 (26.98)	82.4 (27.45)	-43.25 (16.378)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	164.4 (22.91)	112.2 (22.35)	-31.43 (11.83)	8.79 (5.76, 11.81)*	<0.001	Pravastatin 10 mg
2 mg	224	162.8 (20.50)	99.2 (24.03)	-38.99 (13.07)	10.23 (7.17, 13.29)*	<0.001	Pravastatin 20 mg
4 mg	210	163.5 (21.86)	90.7 (23.58)	-44.31 (13.70)	10.46 (7.43, 13.49)*	<0.001	Pravastatin 40 mg
Pravastatin							
10 mg	103	163.6 (22.29)	126.7 (28.59)	-22.41 (14.05)	NA	NA	NA
20 mg	96	163.7 (19.32)	116.2 (20.85)	-28.83 (11.05)	NA	NA	NA
40 mg	102	166.6 (21.89)	109.5 (25.34)	-33.98 (14.30)	NA	NA	NA

* Satisfied -6% non-inferiority criterion
Source: Individual clinical study reports

The mean percent change in LDL from baseline to endpoint for the integrated core studies is presented in the following table.

Table 14 Mean Percent Change in LDL (mg/dL) from Baseline to Endpoint (FAS Population) - Integrated Core Studies

Treatment	N	Baseline (mg/dL)		Week 12 Endpoint (mg/dL)		% change Week 12 Endpoint	
		Mean	SD	Mean	SD	%	SD
Pitavastatin							
1 mg	309	173.39	28.790	119.40	27.416	-30.79	12.251
2 mg	945	179.32	21.514	111.12	28.455	-37.98	14.062
4 mg	1533	171.50	27.208	97.02	28.615	-43.17	15.333
Atorvastatin							
10 mg	118	180.82	17.621	112.34	27.119	-37.74	14.796
20 mg	238	161.42	29.168	91.05	30.649	-43.37	16.248
Simvastatin							
20 mg	107	184.07	17.152	119.07	27.647	-34.97	15.528
40 mg	228	175.13	21.801	98.75	26.608	-43.32	15.058
Pravastatin							
10 mg	103	163.57	22.285	126.68	28.594	-22.41	14.051
20 mg	96	163.71	19.321	116.24	20.851	-28.83	11.054
40 mg	102	166.58	21.893	109.47	25.342	-33.98	14.299
Placebo	154	189.55	29.744	184.32	34.730	-2.35	12.991

Table includes limited data from phase 2 studies 2204 and 210.
Source: End-of-Text-Tables 5.2.1 and 5.2.2

The two core Phase 2 studies demonstrated that pitavastatin 1 mg through 4 mg lowers LDL in a dose-related manner and to a statistically significantly greater extent than placebo.

The results of the individual Phase 3 core studies showed that, with the exception of Study 305 (study of type II diabetics), the mean percent decrease from baseline to endpoint in LDL for pitavastatin 2 mg was non-inferior to atorvastatin 10 mg and simvastatin 20 mg. The mean percent decrease from baseline to endpoint in LDL for pitavastatin 4 mg was non-inferior to atorvastatin 20 mg and simvastatin 40 mg.

In study 305, the lower bound of the 95% confidence interval for the difference in the mean percent change in LDL from baseline to endpoint was just over the -6% criterion. Thus the 4 mg dose of pitavastatin was considered **"inferior" to the 20 mg dose of atorvastatin in subjects with** type II diabetes.

In study 306, all three pitavastatin doses (1 mg, 2 mg, and 4 mg) showed statistically significantly greater mean percent reductions in LDL from baseline to endpoint when compared with the three corresponding doses of pravastatin (10 mg, 20 mg, and 40 mg). A statistically

significant reduction in LDL was also achieved with pitavastatin 2 mg compared with simvastatin 20 mg in study 302.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints included the percent change from baseline to endpoint in HDL, TC, TG, non-HDL, Apo-A1, and Apo-B, and the proportion of subjects achieving target LDL values according to NCEP criteria. Additional secondary variables assessed in some of the clinical studies were changes in the levels of hs-CRP, small-dense-LDL, and adiponectin.

Non-inferiority criteria were not used to assess the efficacy of pitavastatin relative to placebo or the comparator statins.

HDL Cholesterol

Subjects in studies 202 and 203 showed statistically significant increases in HDL from baseline to endpoint for all pitavastatin doses compared with subjects who received placebo. The levels of HDL, however, did not increase in a dose-related fashion.

The results of the Phase 3 core studies showed that the increases from baseline to endpoint in HDL were either comparable to or greater in the pitavastatin groups (2 mg to 4 mg) vs. the comparators, but the differences were generally not statistically significant for between-group comparisons. The exception was study 306, where the increases in HDL in the pitavastatin 2 and 4 mg groups were statistically significantly larger compared with the changes in the 20 mg and 40 mg pravastatin groups.

The following table presents the mean percent change in HDL from baseline to endpoint by study and dose.

Table 15 Mean Percent Change in HDL (mg/dL) from Baseline to Endpoint by Study and Dose – Core Phase 2 and 3 Studies (ITT/FAS Population)

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean Difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-2.02							
Pitavastatin							
1 mg	52	54.1 (11.58)	NA	9.5 (8.6)	NA	0.003	Placebo
2 mg	49	57.9 (11.58)	NA	8.4 (11.9)	NA	0.004	Placebo
4 mg	50	54.1 (15.44)	NA	7.9 (11.7)	NA	0.011	Placebo
Placebo	51	57.9 (15.44)	NA	1.6 (12.0)	NA	NA	NA
NK-104-2.03							
Pitavastatin							

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean Difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
1 mg	49	50.2 (7.72)	NA	8.0 (12.0)	NA	0.064	Placebo
2 mg	50	50.2 (11.58)	NA	9.4 (9.9)	NA	0.018	Placebo
4 mg	48	54.1 (15.44)	NA	9.5 (14.6)	NA	0.006	Placebo
Placebo	50	46.3 (7.72)	NA	3.5 (9.3)	NA	NA	NA
NK-104-301							
Pitavastatin							
2 mg	315	48.5 (11.37)	50.0 (12.74)	4.03 (16.528)	-0.36 (-3.86, 3.14)	0.840	Atorvastatin 10 mg
4 mg	298	49.9 (12.27)	52.0 (13.41)	5.04 (16.664)	-2.98 (-6.51, 0.54)	0.097	Atorvastatin 20 mg
Atorvastatin							
10 mg	102	50.2 (11.69)	51.2 (13.12)	3.04 (16.876)	NA	NA	NA
20 mg	102	48.4 (12.81)	49.3 (13.19)	2.47 (13.722)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	307	51.3 (12.81)	54.0 (14.09)	5.98 (16.095)	-0.46 (-3.74, 2.81)	0.782	Simvastatin 20 mg
4 mg	319	52.8 (12.91)	55.5 (13.33)	6.16 (14.674)	0.44 (-2.79, 3.67)	0.791	Simvastatin 40 mg
Simvastatin							
20 mg	107	51.0 (11.83)	53.2 (12.51)	5.54 (18.091)	NA	NA	NA
40 mg	110	52.3 (10.69)	55.5 (11.38)	6.83 (12.846)	NA	NA	NA
NK-104-304							
Pitavastatin 4 mg	233	47.5 (11.39)	50.5 (12.22)	6.81 (12.553)	-2.30 (-4.91, 0.30)	0.083	Simvastatin 40 mg
Simvastatin 40 mg	118	46.0 (8.21)	47.9 (9.10)	4.50 (12.067)	NA	NA	NA
NK-104-305							
Pitavastatin 4 mg	274	41.7 (9.18)	44.4 (9.84)	7.34 (15.818)	0.22 (-2.94, 3.37)	0.893	Atorvastatin 20 mg
Atorvastatin 20 mg	136	40.8 (7.50)	43.9 (9.17)	8.20 (16.175)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	60.8 (15.27)	60.9 (15.61)	0.63 (10.94)	1.07 (-3.72, 1.57)	0.425	Pravastatin 10 mg
2 mg	224	60.2 (15.45)	61.2 (15.82)	2.14 (11.49)	-3.37 (-6.04, -0.70)	0.013	Pravastatin 20 mg
4 mg	210	58.1 (14.62)	60.2 (15.66)	4.13 (11.32)	-3.07 (-5.71, -0.42)	0.023	Pravastatin 40 mg

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean Difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
Pravastatin							
10 mg	103	57.7 (15.35)	57.3 (15.62)	-0.14 (12.17)	NA	NA	NA
20 mg	96	59.7 (14.19)	58.7 (14.00)	-1.15 (10.31)	NA	NA	NA
40 mg	102	59.4 (15.19)	59.6 (15.67)	0.80 (11.85)	NA	NA	NA

Source: Individual clinical study reports

As seen in the pooled data shown below, with each increasing pitavastatin dose, subjects experienced a mean percent increase from baseline to endpoint in HDL (3.4% at the 1 mg dose to 6.4% at the 4 mg dose). The mean percent increase in HDL at endpoint for subjects treated with pitavastatin 2 mg (4.7%) was similar to that for subjects treated with atorvastatin 10 mg and simvastatin 20 mg (3.8% and 5.5%, respectively) and greater than that for subjects treated with pravastatin 20 mg (-1.2%). For subjects treated with pitavastatin 4 mg, the mean percent increase in HDL at endpoint (6.4%) was similar to treatment with atorvastatin 20 mg and simvastatin 40 mg (5.7% and 5.6%, respectively), but greater than for subjects treated with pravastatin 40 mg (0.8%)

The pooled HDL data from the core studies are shown in the following table.

Table 16 Mean Percent Change in HDL (mg/dL) from Baseline to Endpoint (FAS Population) - Integrated Core Phase 2 and 3 Studies

Treatment	N	Baseline (mg/dL)		Week 12 Endpoint (mg/dL)		% Change Week 12 Endpoint	
		Mean	SD	Mean	SD	Mean	SD
Pitavastatin							
1 mg	309	57.86	14.86	59.30	15.07	3.35	11.49
2 mg	945	52.63	13.75	54.72	14.72	4.72	14.87
4 mg	1533	50.19	13.38	52.92	13.97	6.42	14.50
Atorvastatin							
10 mg	118	49.85	11.43	51.23	12.58	3.82	16.64
20 mg	238	44.10	10.78	46.20	11.37	5.74	15.41
Simvastatin							
20 mg	107	50.99	11.83	53.18	12.52	5.54	18.09
40 mg	228	49.03	9.97	51.53	10.93	5.62	12.48

Pravastatin							
10 mg	103	57.70	15.35	57.26	15.62	-0.14	12.17
20 mg	96	59.68	14.19	58.69	14.00	-1.15	10.31
40 mg	102	59.39	15.19	59.62	15.68	0.80	11.85
Placebo	154	53.27	13.96	54.05	14.92	1.81	11.50

Table includes limited data from phase 2 study 210.
Source: End-of-Text Tables 8.2.1 and 8.2.2

Triglycerides

Subjects in the Phase 2 core studies showed statistically significant reductions in TG from baseline to endpoint with all pitavastatin doses compared with placebo.

The results of the Phase 3 core studies showed that the decreases from baseline to endpoint in TG were either comparable to or greater in the pitavastatin groups (2 mg to 4 mg) compared with the active comparators, but the differences for between-group comparisons were only statistically significant for Study 304 (pitavastatin 4 mg vs. simvastatin 40 mg). For study 305, the decrease from baseline to endpoint in TG was 20.1% in the pitavastatin 4 mg group and 27.2% in the atorvastatin 20 mg group and differences for between-group comparisons were statistically significant in favor of atorvastatin 20 mg. For Study 306, the decreases in levels of TG in the pitavastatin 1 mg and 4 mg groups were statistically significantly greater compared with the changes observed in the pravastatin 10 mg and 40 mg groups.

The following table presents the mean percent change in TG from baseline to endpoint by study and dose.

Table 17 Mean Percent Change in Triglycerides (mg/dL) from Baseline to Endpoint by Study and Dose - Core Phase 2 and 3 Studies (ITT/FAS Population)

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-2.02							
Pitavastatin							
1 mg	52	159.3 (61.9)	NA	-14.2 (28.4)	NA	0.001	Placebo
2 mg	49	159.3 (61.9)	NA	-18.2 (24.9)	NA	0.000	Placebo
4 mg	50	159.3 (61.9)	NA	-21.7 (21.7)	NA	0.000	Placebo
Placebo	51	141.6 (53.10)	NA	3.7 (31.1)	NA	NA	NA
NK-104-2.03							
Pitavastatin							
1 mg	49	274.3 (88.50)	NA	-13.8 (29.7)	NA	0.000	Placebo
2 mg	50	274.3 (79.65)	NA	-21.6 (21.8)	NA	0.000	Placebo
4 mg	48	274.3 (70.80)	NA	-24.8 (17.5)	NA	0.000	Placebo
Placebo	50	265.5 (88.50)	NA	7.9 (48.5)	NA	NA	NA
NK-104-301							

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
Pitavastatin							
2 mg	315	157.8 (56.10)	132.0 (59.35)	-14.09 (28.771)	-3.57 (-9.47, 2.33)	0.236	Atorvastatin 10 mg
4 mg	298	156.8 (57.29)	125.4 (65.11)	-19.05 (24.598)	-2.83 (-8.77, 3.12)	0.351	Atorvastatin 20 mg
Atorvastatin							
10 mg	102	156.8 (60.67)	125.2 (60.54)	-17.70 (29.912)	NA	NA	NA
20 mg	102	161.9 (66.13)	122.7 (58.99)	-22.25 (23.971)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	307	163.8 (60.97)	135.3 (61.22)	-15.95 (24.49)	0.66 (-5.08, 6.39)	0.822	Simvastatin 20 mg
4 mg	319	155.4 (59.49)	124.6 (55.67)	-16.85 (27.32)	0.48 (-5.17, 6.13)	0.866	Simvastatin 40 mg
Simvastatin							
20 mg	107	166.7 (56.83)	137.3 (58.53)	-15.58 (28.08)	NA	NA	NA
40 mg	110	153.9 (55.39)	125.5 (56.91)	-16.13 (29.19)	NA	NA	NA
NK-104-304							
Pitavastatin 4 mg	233	164.0 (67.87)	126.7 (53.08)	-19.76 (21.313)	5.23 (0.15, 10.30)	0.044	Simvastatin 40 mg
Simvastatin 40 mg	118	163.9 (66.34)	136.6 (72.18)	-14.81 (29.691)	NA	NA	NA
NK-104-305							
Pitavastatin 4 mg	274	244.5 (77.93)	195.9 (118.63)	-20.11 (29.487)	-6.75 (-12.79, -0.71)	0.029	Atorvastatin 20 mg
Atorvastatin 20 mg	136	245.2 (88.97)	174.3 (82.78)	-27.16 (29.086)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	141.2 (53.91)	118.8 (43.75)	-13.38 (20.851)	8.72 (3.70, 13.75)	0.001	Pravastatin 10 mg
2 mg	224	137.2 (48.70)	114.3 (46.21)	-14.62 (22.862)	4.81 (-0.27, 9.90)	0.063	Pravastatin 20 mg
4 mg	210	145.4 (55.83)	110.6 (44.04)	-21.52 (18.640)	6.20 (1.17, 11.23)	0.016	Pravastatin 40 mg
Pravastatin							
10 mg	103	142.0 (54.04)	134.9 (70.36)	-4.72 (27.822)	NA	NA	NA
20 mg	96	147.9 (61.45)	127.6 (51.71)	-11.00 (23.859)	NA	NA	NA
40 mg	102	139.1 (53.66)	115.0 (44.27)	-14.61 (20.705)	NA	NA	NA

Source: Individual clinical study reports

As seen in the individual studies, the integrated data showed that with each increasing pitavastatin dose subjects experienced a mean percent decrease from baseline to endpoint in TG (13.4% at the 1 mg dose to 19.4% at the 4 mg dose)(Table below). The mean percent decrease in TG at endpoint for subjects treated with pitavastatin 2 mg (15.3%) was slightly lower compared with subjects treated with atorvastatin 10 mg (17.5%), similar to subjects treated with simvastatin 20 mg (15.6%) and slightly greater than for subjects treated with pravastatin 20 mg (11.0%). For subjects treated with pitavastatin 4 mg, the mean percent decrease (19.4%) was lower compared with subjects treated with atorvastatin 20 mg (25.1%) but higher than compared with subjects treated with simvastatin 40 mg (15.5%) and pravastatin 40 mg (14.6%).

The following table presents the mean percent change in TG from baseline to endpoint in the integrated core studies.

Table 18 Mean Percent Change in Triglycerides from Baseline to Endpoint (FAS Population) - Integrated Phase 2 and 3 Core Studies

Treatment	N	Baseline (mg/dL)		Week 12 Endpoint (mg/dL)		% Change Week 12 Endpoint	
		Mean	SD	Mean	SD	Mean	SD
Pitavastatin							
1 mg	309	163.78	77.024	137.28	66.094	-13.39	23.56
2 mg	945	160.91	64.53	133.09	62.50	-15.30	25.39
4 mg	1533	178.02	77.24	139.38	77.22	-19.35	25.46
Atorvastatin							
10 mg	118	160.11	63.43	127.04	59.44	-17.49	29.79
20 mg	238	209.50	89.90	152.21	77.72	-25.05	27.07
Simvastatin							
20 mg	107	166.70	56.83	137.33	58.53	-15.58	28.08
40 mg	228	159.06	61.38	131.20	65.36	-15.45	29.39
Pravastatin							
10 mg	103	142.03	54.04	134.91	70.36	-4.72	27.82
20 mg	96	147.91	61.45	127.65	51.71	-11.00	23.86
40 mg	102	139.07	53.657	114.95	44.275	-14.61	20.705
Placebo	154	188.02	85.84	192.24	104.57	5.81	43.59

Table includes limited data from phase 2 study 2204.
Source: End-of-Text Tables 7.2.1 and 7.2.2

Total Cholesterol

Subjects in the Phase 2 core studies showed a statistically significant reduction in TC from baseline to endpoint at all pitavastatin doses when compared with subjects receiving placebo.

The results of the Phase 3 core studies showed that the decreases from baseline to endpoint in TC were either comparable to or greater in the pitavastatin groups (2 mg to 4 mg) vs. the comparators. In study 302, the mean percent decrease in TC in the pitavastatin 2 mg group was statistically significantly greater than the decrease in the simvastatin 20 mg group. For study 305, the decrease from baseline in TC was 28.2% in the pitavastatin 4 mg group and 31.6% in the atorvastatin 20 mg group and the difference for between-group comparison was statistically significant in favor of atorvastatin 20 mg. For Study 306, the reductions in TC in the three pitavastatin groups were statistically significantly greater compared with the changes in the corresponding three pravastatin groups.

The following table presents the mean percent change in TC from baseline to endpoint by study and dose.

Table 19 Mean Percent Change in Total Cholesterol (mg/dL) from Baseline to Endpoint by Study and Dose - Core Phase 2 and 3 Studies (ITT/FAS Population)

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-2.02							
Pitavastatin							
1 mg	52	281.85 (30.89)	NA	-22.8 (6.4)	NA	0.000	Placebo
2 mg	49	285.71 (27.03)	NA	-26.1 (9.4)	NA	0.000	Placebo
4 mg	50	285.71 (30.89)	NA	-32.5 (7.8)	NA	0.000	Placebo
Placebo	51	285.71 (27.03)	NA	-1.3 (10.7)	NA	NA	NA
NK-104-2.03							
Pitavastatin							
1 mg	49	281.85 (42.47)	NA	-19.4 (11.0)	NA	0.000	Placebo
2 mg	50	281.85 (38.61)	NA	-23.0 (9.2)	NA	0.000	Placebo
4 mg	48	289.58 (46.33)	NA	-31.0 (11.6)	NA	0.000	Placebo
Placebo	50	281.85 (34.75)	NA	-2.5 (10.7)	NA	NA	NA

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-301							
Pitavastatin							
2 mg	315	263.6 (22.70)	190.4 (30.85)	-27.68 (10.47)	-0.52 (-3.02, 1.98)	0.684	Atorvastatin 10 mg
4 mg	298	263.3 (22.18)	177.2 (29.98)	-32.42 (11.50)	-0.37 (-2.88, 2.14)	0.773	Atorvastatin 20 mg
Atorvastatin							
10 mg	102	261.3 (22.62)	187.7 (34.53)	-28.08 (12.48)	NA	NA	NA
20 mg	102	262.7 (22.56)	176.4 (33.11)	-32.69 (12.32)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	307	267.7 (22.13)	192.9 (33.28)	-27.90 (11.21)	2.59 (0.10, 5.07)	0.041	Simvastatin 20 mg
4 mg	319	268.0 (20.76)	183.4 (31.88)	-31.50 (10.94)	0.88 (-1.56, 3.33)	0.479	Simvastatin 40 mg
Simvastatin							
20 mg	107	268.4 (22.67)	199.7 (31.46)	-25.37 (11.52)	NA	NA	NA
40 mg	110	267.0 (20.31)	185.1 (33.13)	-30.53 (12.35)	NA	NA	NA
NK-104-304							
Pitavastatin 4 mg	233	246.3 (25.47)	168.8 (27.47)	-31.39 (9.44)	0.28 (-1.79, 2.34)	0.793	Simvastatin 40 mg
Simvastatin 40 mg	118	245.6 (30.31)	168.3 (29.01)	-31.16 (11.11)	NA	NA	NA
NK-104-305							
Pitavastatin 4 mg	274	233.1 (32.56)	166.9 (37.38)	-28.21 (13.46)	-3.14 (-5.79, -0.49)	0.020	Atorvastatin 20 mg
Atorvastatin 20 mg	136	235.8 (31.39)	160.9 (32.94)	-31.56 (11.82)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	253.4 (29.16)	196.8 (29.55)	-22.19 (8.90)	6.52 (4.25, 8.79)	<0.001	Pravastatin 10 mg
2 mg	224	250.5 (23.35)	183.3 (27.49)	-26.68 (9.43)	6.23 (3.93, 8.52)	<0.001	Pravastatin 20 mg
4 mg	210	250.7 (25.53)	173.1 (28.21)	-30.75 (10.46)	6.84 (4.56, 9.11)	<0.001	Pravastatin 40 mg
Pravastatin							
10 mg	103	249.7 (28.15)	211.0 (34.87)	-15.34 (11.04)	NA	NA	NA
20 mg	96	252.9 (25.76)	200.5 (26.83)	-20.61 (8.43)	NA	NA	NA
40 mg	102	253.8 (24.51)	192.1 (28.96)	-24.07 (10.91)	NA	NA	NA

Source: Individual clinical study reports

As seen in the individual studies above, the integrated data showed that with each increasing pitavastatin dose subjects experienced a mean percent decrease in TC (21.6% at the 1 mg dose to 30.8% at the 4 mg dose)(Table below). The mean percent decreases in TC at endpoint were slightly greater for the pitavastatin 2 mg and atorvastatin 10 mg groups (27.1% and 28.1%, respectively) compared with the simvastatin 20 mg and pravastatin 20 mg groups (25.4% and 20.6%, respectively). For subjects treated with pitavastatin 4 mg, the mean percent decrease in TC (30.8%) was similar to treatment with atorvastatin 20 mg (32.1%) and simvastatin 40 mg (30.9%) and slightly greater than for subjects treated with pravastatin 40 mg (24.1%).

The following table presents the mean percent change in TC from baseline to endpoint in the integrated for the Phase 2 and 3 core studies.

Table 20 Mean Percent Change in Total Cholesterol (mg/dL) from Baseline to Endpoint (FAS Population) - Integrated Phase 2 and 3 Core Studies

Treatment	N	Baseline (mg/dL)		Week 12 Endpoint (mg/dL)		% Change Week 12 Endpoint	
		Mean	SD	Mean	SD	Mean	SD
Pitavastatin							
1 mg	309	263.03	34.99	205.40	33.90	-21.64	9.196
2 mg	945	263.89	26.00	192.13	32.51	-27.11	10.50
4 mg	1533	256.96	30.90	177.33	33.08	-30.77	11.30
Atorvastatin							
10 mg	118	262.27	22.98	188.26	32.90	-28.13	11.83
20 mg	238	247.32	30.92	167.55	33.83	-32.05	12.03
Simvastatin							
20 mg	107	268.38	22.668	199.72	31.464	-25.37	11.519
40 mg	228	255.96	28.039	176.40	32.128	-30.86	11.705
Pravastatin							
10 mg	103	249.66	28.15	210.98	34.87	-15.34	11.04
20 mg	96	252.89	25.76	200.47	26.83	-20.61	8.42
40 mg	102	253.77	24.51	192.10	28.96	-24.07	10.91
Placebo	154	278.30	32.11	277.87	42.20	-0.01	10.49

Table includes limited data from phase 2 study 2204.
Source: End-of-Text Tables 6.2.1 and 6.2.2

Non-HDL Cholesterol

Non-HDL levels were not reported in studies 202 and 203.

The results from studies 301, 302, and 304 showed that the decreases from baseline to endpoint in non-HDL were either comparable to or greater in the pitavastatin groups (2 mg to 4 mg) vs. the comparator groups but the differences were only statistically significantly in favor of pitavastatin (pitavastatin 2 mg vs. simvastatin 20 mg) in Study 302. For the 305 study, the decrease from baseline to endpoint in non-HDL was 35.7% in the pitavastatin 4 mg group and 39.7% in the atorvastatin 20 mg group and difference for between-group comparisons was statistically significant in favor of atorvastatin 20 mg. For study 306, pitavastatin was statistically significantly superior to pravastatin in all three dose group comparisons.

The following table presents the mean percent change in non-HDL from baseline to endpoint by study and dose for the core Phase 3 studies.

Table 21 Mean Percent Change in Non-HDL (mg/dL) from Baseline to Endpoint by Study and Dose - Core Phase 3 Studies (FAS Population)

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-301							
Pitavastatin							
2 mg	315	215.1 (21.17)	140.4 (31.07)	-34.67 (13.02)	-0.63 (-3.71, 2.45)	0.688	Atorvastatin 10 mg
4 mg	298	213.3 (21.02)	125.3 (31.20)	-41.10 (14.16)	0.47 (-2.62, 3.56)	0.766	Atorvastatin 20 mg
Atorvastatin							
10 mg	102	211.1 (22.55)	136.5 (32.85)	-35.16 (15.16)	NA	NA	NA
20 mg	102	214.3 (22.86)	127.1 (34.57)	-40.57 (15.14)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	307	216.4 (21.29)	138.9 (32.69)	-35.81 (13.73)	3.60 (0.54, 6.66)	0.021	Simvastatin 20 mg
4 mg	319	215.1 (19.94)	127.9 (30.64)	-40.53 (13.26)	1.04 (-1.98, 4.05)	0.499	Simvastatin 40 mg
Simvastatin							

Study Treatment	N	Baseline (mg/dL)	Week 12 LOCF (mg/dL)	% Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
20 mg	107	217.4 (21.93)	146.5 (31.01)	-32.26 (14.63)	NA	NA	NA
40 mg	110	214.8 (18.84)	129.7 (32.57)	-39.44 (15.29)	NA	NA	NA
NK-104-304							
Pitavastatin 4mg	233	198.8 (25.22)	118.3 (26.76)	-40.44 (11.67)	1.35 (-1.17, 3.87)	0.293	Simvastatin 40 mg
Simvastatin 40mg	118	199.6 (29.33)	120.4 (27.62)	-39.24 (13.45)	NA	NA	NA
NK-104-305							
Pitavastatin 4mg	274	191.3 (30.62)	122.6 (36.86)	-35.73 (17.16)	-3.72 (-7.12, -0.32)	0.032	Atorvastatin 20 mg
Atorvastatin 20mg	136	195.0 (30.54)	117.1 (33.06)	-39.72 (15.26)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	192.6 (26.43)	135.9 (24.95)	-29.11 (11.03)	9.01 (6.19, 11.82)	<0.001	Pravastatin 10 mg
2 mg	224	190.3 (23.74)	122.0 (26.18)	-35.70 (11.99)	9.41 (6.56, 12.26)	<0.001	Pravastatin 20 mg
4 mg	210	192.6 (26.09)	112.8 (25.66)	-41.13 (12.66)	9.62 (6.81, 12.44)	<0.001	Pravastatin 40 mg
Pravastatin							
10 mg	103	192.0 (27.32)	153.7 (34.70)	-19.89 (13.65)	NA	NA	NA
20 mg	96	193.2 (23.74)	141.8 (24.85)	-26.51 (10.47)	NA	NA	NA
40 mg	102	194.4 (25.53)	132.5 (28.21)	-31.54 (13.43)	NA	NA	NA

Source: Individual clinical study reports

As seen in the individual studies above, the integrated data showed that with each increasing pitavastatin dose subjects experienced a mean percent decrease in non-HDL (28.5% at the 1 mg dose to 39.6% at the 4 mg dose)(Table below). The mean decrease in non-HDL at endpoint was similar for the pitavastatin 2 mg, atorvastatin 10 mg, and simvastatin 20 mg groups (34.9%, 35.3%, and 32.3%, respectively) and notably greater than for the pravastatin 20 mg group (26.5%). For subjects treated with pitavastatin 4 mg, the mean percent decrease (39.6%) was similar to treatment with atorvastatin 20 mg (40.1%) and simvastatin 40 mg (39.3%) and greater than for subjects treated with pravastatin 40 mg (31.5%).

The following table presents the mean percent change in non-HDL from baseline to endpoint integrated for the Phase 3 core studies.

Table 22 Mean Percent Change in Non-HDL (mg/dL) from Baseline to Endpoint (FAS Population) - Integrated Core Phase 3 Studies

Treatment	N	Baseline (mg/dL)		Week 12 Endpoint (mg/dL)		% Change Week 12 Endpoint	
		Mean	SD	Mean	SD	Mean	SD
Pitavastatin							
1 mg	309	205.16	35.08	146.10	32.09	-28.48	11.20
2 mg	945	211.26	25.96	137.42	32.50	-34.94	12.98
4 mg	1533	206.77	28.93	124.42	32.33	-39.64	14.02
Atorvastatin							
10 mg	118	212.41	22.50	137.03	31.13	-35.30	14.36
20 mg	238	203.23	29.08	121.38	34.01	-40.09	15.18
Simvastatin							
20 mg	107	217.39	21.93	146.54	31.01	-32.26	14.63
40 mg	228	206.92	25.91	124.87	30.40	-39.34	14.33
Pravastatin							
10 mg	103	191.96	27.32	153.72	34.70	-19.89	13.65
20 mg	96	193.21	23.74	141.78	24.85	-26.51	10.47
40 mg	102	194.39	25.53	132.48	28.21	-31.54	13.43

Source: End-of-Text Tables 9.2.1 and 9.2.2

Apolipoprotein A1

Subjects in the Phase 2 core studies showed an increase in Apo-A1 from baseline to endpoint at all pitavastatin doses when compared with subjects receiving placebo, but the differences were only statistically significant for pitavastatin 1 mg compared with placebo in study 202, and for pitavastatin 4 mg compared with placebo in study 203.

The results of the Phase 3 core studies showed that the increases from baseline in Apo-A1 were either comparable to or greater in the pitavastatin groups (2 mg to 4 mg) vs. the respective active comparator groups, but the differences were not statistically significant for between-group comparisons.

The following table presents the mean percent change in Apo-A1 from baseline to endpoint by study and dose:

Table 23 Mean Percent Change in Apolipoprotein A1 (mg/dL) from Baseline to Endpoint by Study and Dose – Core Phase 2 and 3 Studies (ITT/FAS Population)

Study Treatment	N	Baseline (mg/dL)	Week 12 (mg/dL)	% Change Week 12	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-2.02							
Pitavastatin							
1 mg	52	147.1 (27.0)	NA	9.2 (12.6)	NA	0.044	Placebo

Study Treatment	N	Baseline (mg/dL)	Week 12 (mg/dL)	% Change Week 12	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
2 mg	49	151.6 (24.2)	NA	5.6 (12.4)	NA	0.369	Placebo
4 mg	50	148.0 (28.0)	NA	5.0 (12.7)	NA	0.582	Placebo
Placebo	51	155.4 (27.1)	NA	1.7 (11.1)	NA	NA	NA
NK-104-2.03							
Pitavastatin							
1 mg	49	142.7 (25.2)	NA	2.9 (12.2)	NA	0.615	Placebo
2 mg	50	141.8 (25.1)	NA	5.4 (10.5)	NA	0.188	Placebo
4 mg	48	147.4 (33.3)	NA	6.9 (14.0)	NA	0.014	Placebo
Placebo	50	140.0 (22.3)	NA	1.9 (11.9)	NA	NA	NA
NK-104-301							
Pitavastatin							
2 mg	315	155.2 (26.10)	164.0 (28.97)	6.48 (14.356)	0.20 (-2.71, 3.11)	0.894	Atorvastatin 10 mg
4 mg	298	158.5 (26.48)	166.2 (27.94)	5.59 (13.707)	-1.97 (-4.90, 0.96)	0.188	Atorvastatin 20 mg
Atorvastatin							
10 mg	102	157.9 (25.64)	165.6 (26.49)	6.37 (14.000)	NA	NA	NA
20 mg	102	154.6 (26.38)	160.0 (26.98)	4.51 (13.915)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	305	161.8 (25.65)	171.9 (28.67)	6.73 (13.520)	0.76 (-2.08, 3.60)	0.598	Simvastatin 20 mg
4 mg	316	163.3 (26.45)	173.0 (26.77)	6.82 (13.420)	0.29 (-2.49, 3.07)	0.838	Simvastatin 40 mg
Simvastatin							
20 mg	107	162.7 (27.32)	172.0 (26.13)	7.38 (16.953)	NA	NA	NA
40 mg	110	164.1 (20.36)	174.4 (23.55)	6.92 (13.331)	NA	NA	NA
NK-104-304							
Pitavastatin 4 mg	233	158.4 (26.06)	169.3 (27.06)	7.62 (12.725)	-1.28 (-3.86, 1.30)	0.330	Simvastatin 40 mg
Simvastatin 40 mg	118	155.5 (20.77)	165.4 (21.90)	6.86 (12.078)	NA	NA	NA
NK-104-305							
Pitavastatin 4 mg	274	155.9 (26.35)	163.4 (27.20)	5.92 (13.599)	-1.92 (-4.52, 0.69)	0.149	Atorvastatin 20 mg
Atorvastatin 20 mg	136	153.3 (23.80)	158.3 (24.17)	4.46 (13.622)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	173.5 (26.00)	176.7 (29.01)	2.40 (13.17)	0.32 (-2.26, 2.89)	0.810	Pravastatin 10 mg
2 mg	224	173.6 (28.03)	177.6 (28.70)	2.84 (10.86)	-2.04 (-4.69,	0.131	Pravastatin 20

Study Treatment	N	Baseline (mg/dL)	Week 12 (mg/dL)	% Change Week 12	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
					0.61)		mg
4 mg	210	170.3 (25.88)	174.6 (27.49)	2.81 (10.18)	-2.49 (-5.08, 0.11)	0.061	Pravastatin 40 mg
Pravastatin							
10 mg	103	167.7 (26.65)	171.3 (27.57)	3.30 (11.01)	NA	NA	NA
20 mg	96	173.9 (27.53)	174.8 (26.15)	0.82 (10.40)	NA	NA	NA
40 mg	102	171.7 (26.87)	173.0 (30.36)	0.18 (9.82)	NA	NA	NA

Source: Individual clinical study reports

As seen in the individual studies above, the integrated data showed that with each increasing pitavastatin dose subjects experience a mean percent increase in Apo-A1 (3.6% at the 1 mg dose to 6.0% at the 4 mg dose)(Table below). The mean percent increase in Apo-A1 at endpoint for the pitavastatin 2 mg group (5.7%) was similar to that for the atorvastatin 10 mg group (6.1%), slightly lower than that for the simvastatin 20 mg group (7.4%), and notably greater than for the pravastatin 20 mg group (0.8%). For subjects treated with pitavastatin 4 mg, the mean percent increase (6.0%) was slightly higher than treatment with atorvastatin 20 mg (4.5%), lower than for treatment with simvastatin 40 mg (6.9%), and notably greater than for subjects treated with pravastatin 40 mg.

The following table presents the mean percent change in Apo-A1 from baseline to endpoint integrated for the core studies.

Table 24 Mean Percent Change in Apolipoprotein A1 from Baseline to Endpoint (FAS Population) - Integrated Core Phase 2 and 3 Studies

Treatment	N	Baseline (mg/dL)		Week 12 Endpoint (mg/dL)		% Change Week 12 Endpoint	
		Mean	SD	Mean	SD	Mean	SD
Pitavastatin							
1 mg	309	164.23	29.61	168.87	30.18	3.62	13.07
2 mg	945	160.67	27.55	168.81	29.44	5.66	13.17
4 mg	1533	160.34	27.31	168.58	28.09	5.99	13.06
Atorvastatin							
10 mg	118	156.69	25.22	163.96	25.81	6.05	13.81
20 mg	238	153.87	24.91	159.03	25.36	4.48	13.72
Simvastatin							
20 mg	107	162.73	27.32	171.95	26.13	7.38	16.95
40 mg	228	159.66	20.97	169.74	23.07	6.90	12.65
Pravastatin							
10 mg	103	167.71	26.65	171.34	27.57	3.30	11.01
20 mg	96	173.89	27.527	174.77	26.152	0.82	10.400
40 mg	102	171.67	26.87	173.01	30.36	0.18	9.82
Placebo	154	153.35	27.99	155.23	32.55	1.50	11.67

Table includes limited data from phase 2 study 2204.
Source: End-of-Text Tables 10.2.1 and 10.2.2

Apolipoprotein B

Subjects in the Phase 2 core studies showed statistically significant reductions in Apo-B from baseline to endpoint at all pitavastatin doses when compared with placebo.

The results of studies 301, 302, 304, and 305 indicated that the decreases from baseline to endpoint in Apo-B were either comparable to or greater in the pitavastatin groups vs. the comparators (2 mg to 4 mg), but the differences were not statistically significant for between-group comparisons. For the 306 study, all doses of pitavastatin were associated with statistically significantly larger reductions in Apo-B vs. the corresponding pravastatin groups.

The following table presents the mean percent change in Apo-B from baseline to endpoint by study and dose.

Table 25 Mean Percent Change in Apolipoprotein B (mg/dL) from Baseline to Endpoint by Study and Dose - Core Phase 2 and 3 Studies (ITT/FAS Population)

Study Treatment	N	Baseline (mg/dL)	Week 12 (mg/dL)	% Change Week 12	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-2.02							
Pitavastatin							
1 mg	52	127.4 (27.3)	NA	-25.5 (8.9)	NA	0.000	Placebo
2 mg	49	126.5 (20.7)	NA	-30.8 (10.4)	NA	0.000	Placebo
4 mg	50	128.8 (26.4)	NA	-37.0 (8.9)	NA	0.000	Placebo
Placebo	51	128.6 (23.0)	NA	0.3 (17.0)	NA	NA	NA
NK-104-2.03							
Pitavastatin							
1 mg	49	135.3 (29.8)	NA	-22.9 (17.8)	NA	0.000	Placebo
2 mg	50	130.5 (30.4)	NA	-22.8 (16.4)	NA	0.000	Placebo
4 mg	48	137.7 (30.2)	NA	-32.3 (14.6)	NA	0.000	Placebo
Placebo	50	133.3 (22.3)	NA	4.6 (13.0)	NA	NA	NA
NK-104-301							
Pitavastatin							
2 mg	315	164.1 (21.59)	114.4 (23.30)	-29.76 (13.755)	0.18 (-2.98, 3.34)	0.912	Atorvastatin 10 mg
4 mg	298	162.3 (22.23)	103.7 (23.47)	-35.33 (14.959)	-0.08 (-3.26, 3.10)	0.961	Atorvastatin 20 mg
Atorvastatin							
10 mg	102	161.3 (22.34)	112.8 (26.71)	-29.13 (17.555)	NA	NA	NA
20 mg	102	162.9 (25.65)	103.9 (24.28)	-35.54 (14.522)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	305	161.2 (22.46)	112.9 (24.84)	-29.81 (13.696)	2.99 (-0.07, 6.04)	0.055	Simvastatin 20 mg
4 mg	316	160.3 (20.27)	104.6 (23.35)	-34.59 (13.305)	0.52 (-2.47, 3.51)	0.732	Simvastatin 40 mg
Simvastatin							
20 mg	107	163.4 (21.06)	117.7 (22.71)	-27.06 (15.268)	NA	NA	NA
40 mg	110	161.9 (18.33)	105.9 (25.39)	-34.24 (15.664)	NA	NA	NA
NK-104-304							
Pitavastatin 4 mg	233	152.5 (20.90)	100.7 (21.79)	-33.73 (12.326)	0.46 (-2.15, 3.07)	0.730	Simvastatin 40 mg
Simvastatin 40 mg	118	153.3 (24.61)	100.9 (21.30)	-33.78 (12.874)	NA	NA	NA

Study Treatment	N	Baseline (mg/dL)	Week 12 (mg/dL)	% Change Week 12	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-305							
Pitavastatin 4 mg	274	149.2 (26.61)	101.0 (27.16)	-31.69 (18.489)	-1.59 (-5.17, 1.99)	0.384	Atorvastatin 20 mg
Atorvastatin 20 mg	136	150.0 (24.04)	100.0 (24.96)	-33.56 (15.455)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	147.1 (21.61)	109.2 (19.70)	-25.35 (10.91)	8.07 (5.37, 10.77)	<0.001	Pravastatin 10 mg
2 mg	224	146.0 (20.31)	100.4 (18.69)	-30.93 (11.57)	9.03 (6.25, 11.80)	<0.001	Pravastatin 20 mg
4 mg	210	149.1 (22.23)	94.0 (18.82)	-36.58 (12.17)	9.11 (6.39, 11.84)	<0.001	Pravastatin 40 mg
Pravastatin							
10 mg	103	145.9 (23.13)	121.3 (25.99)	-16.96 (13.33)	NA	NA	NA
20 mg	96	149.1 (19.66)	114.2 (18.74)	-22.31 (10.19)	NA	NA	NA
40 mg	102	150.1 (21.94)	108.4 (20.70)	-27.51 (11.85)	NA	NA	NA

Source: Individual clinical study reports

As seen in the individual studies above, the integrated data showed that with each increasing pitavastatin dose subjects experienced a mean percent decrease in Apo-B (24.7% at the 1 mg dose to 34.2% at the 4 mg dose)(Table below). The mean percent decrease in Apo-B from baseline to endpoint for the pitavastatin 2 mg group (29.6%) was similar to that for the atorvastatin 10 mg group (29.7%), but slightly higher than for the simvastatin 20 mg and pravastatin 20 mg groups (27.1% and 22.3%, respectively). For subjects treated with pitavastatin 4 mg, the mean decrease (34.2%) was similar to that for subjects treated with atorvastatin 20 mg and simvastatin 40 mg (34.4% and 34.0%, respectively) and greater than for subjects treated with pravastatin 40 mg (27.5%).

The following table presents the mean percent change in Apo-B from baseline to endpoint in the integrated core studies.

Table 26 Mean Percent Change in Apolipoprotein B (mg/dL) from Baseline to Endpoint (FAS Population) - Integrated Core Phase 2 and 3 Studies

Treatment	N	Baseline (mg/dL)		Week 12 Endpoint (mg/dL)		% Change Week 12 Endpoint	
		Mean	SD	Mean	SD	Mean	SD
Pitavastatin							
1 mg	309	141.81	25.25	106.12	22.51	-24.66	12.22
2 mg	945	155.27	24.90	108.43	23.82	-29.62	13.45
4 mg	1533	155.04	24.69	101.33	24.22	-34.21	14.32
Atorvastatin							
10 mg	118	162.37	21.81	112.75	25.51	-29.70	16.69
20 mg	238	155.66	25.52	101.63	24.70	-34.42	15.06
Simvastatin							
20 mg	107	163.36	21.07	117.74	22.71	-27.06	15.27
40 mg	228	157.46	22.18	103.20	23.53	-34.01	14.25
Pravastatin							
10 mg	103	145.85	23.13	121.31	25.98	-16.96	13.33
20 mg	96	149.08	19.66	114.23	18.74	-22.31	10.20
40 mg	102	150.14	21.94	108.39	20.70	-27.51	11.86
Placebo	154	142.10	27.72	141.84	32.42	1.01	14.05

Table includes limited data from phase 2 study 2204.
Source: End-of-Text Tables 11.2.1 and 11.2.2

LDL NCEP Target Attainment

LDL NCEP target attainment was determined for the Phase 3 studies, but not the Phase 2 studies.

The results of studies 302, 304, and 305 showed that the proportions of subjects attaining NCEP LDL targets at endpoint were either comparable to or greater in the pitavastatin groups (2 mg and 4 mg) compared with the respective active comparator groups, although none of the differences were statistically significant. For study 301, the proportion of subjects attaining their LDL target at endpoint was greater with atorvastatin 10 mg treatment compared with pitavastatin 2 mg (65.7% vs. 56.8%) but the difference was not statistically significant. For the 306 study, pitavastatin was statistically significantly superior to pravastatin at the respective low doses but not for the higher-dose groups.

The following table presents a summary of the number and percentage of subjects who attained their NCEP LDL target at endpoint by study and dose.

Table 27 Subjects with LDL NCEP Target Attainment by Study and Dose – Core Phase 3 Studies (FAS Population)

Study Treatment	N	Achieved NCEP Target at Endpoint (%)	p-value	vs.	Mean difference (95% CI)
NK-104-2.02	NA				
NK-104-2.03	NA				
NK-104-301					
Pitavastatin					
2 mg	315	179 (56.8%)	0.105	Atorvastatin 10 mg	8.9 (-1.9, 19.6)
4 mg	298	232 (77.9%)	0.155	Atorvastatin 20 mg	-7.3 (-17.3, 2.8)
Atorvastatin					
10 mg	102	67 (65.7%)	NA	NA	NA
40 mg	102	72 (70.6%)	NA	NA	NA
NK-104-302					
Pitavastatin					
2 mg	307	215 (70.0%)	0.297	Simvastatin 20 mg	-5.5 (-16.0, 4.9)
4 mg	319	253 (79.6%)	0.762	Simvastatin 40 mg	-1.4 (-10.3, 7.5)
Simvastatin					
20 mg	107	69 (64.5%)	NA	NA	NA
40 mg	110	86 (78.2%)	NA	NA	NA
NK-104-304					
Pitavastatin 4 mg	233	203 (87.1%)	0.695	Simvastatin 40 mg	-1.5 (-9.2, 6.1)
Simvastatin 40 mg	118	101 (85.6%)	NA	NA	NA
NK-104-305					
Pitavastatin 4 mg	274	212 (77.4)	0.242	Atorvastatin 20 mg	4.8 (-3.3, 13.0)
Atorvastatin 20 mg	136	111 (82.2)	NA	NA	NA
NK-104-306					
Pitavastatin					
1 mg	207	172 (83.1%)	0.001	Pravastatin 10 mg	-18.0 (-28.6, -7.5)
2 mg	224	199 (88.8%)	0.092	Pravastatin 20 mg	-7.6 (-16.4, 1.2)
4 mg	210	191 (91.0%)	0.469	Pravastatin 40 mg	-2.7 (-10.1, 4.6)
Pravastatin					
10 mg	103	67 (65.0%)	NA	NA	NA
20 mg	96	78 (81.3%)	NA	NA	NA
40 mg	102	90 (88.2%)	NA	NA	NA

Source: Individual clinical study reports

The following table presents a summary of the number and percentage of subjects who attained their NCEP LDL target at endpoint in the integrated core studies.

Table 28 Subjects with LDL NCEP Target Attainment (FAS Population) - Integrated Core Studies

Treatment	n (%) Attained NCEP Target at Endpoint
Pitavastatin	
1 mg	172 (83.1%)
2 mg	593 (70.1%)
4 mg	1171 (81.8%)
Atorvastatin	
10 mg	81 (68.6%)
20 mg	183 (77.2%)
Simvastatin	
20 mg	69 (64.5%)
40 mg	187 (82.0%)
Pravastatin	
10 mg	67 (65.0%)
20 mg	78 (81.3%)
40 mg	90 (88.2%)
Placebo	6 (11.8%)

Table includes limited data from phase 2 study 2204.
Source: End-of-Text Table 15.1.2

6.1.6 Other Endpoints

High Sensitivity C-Reactive Protein

The mean changes in hsCRP observed in the pitavastatin groups were small and inconsistent, as were the changes in the comparator groups.

The following table presents the mean changes in hsCRP from baseline to endpoint by study and dose.

Table 29 Mean Change in hsCRP (mg/L) from Baseline to Endpoint by Study and Dose – Core Phase 3 Studies (FAS Population)

Study Treatment	N	Baseline (mg/L)	Week 12 LOCF (mg/L)	Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
NK-104-2.02	NA						
NK-104-2.03	NA						
NK-104-301							
Pitavastatin							
2 mg	315	3.47 (5.40)	3.14 (7.43)	-0.32 (7.92)	-0.99 (-2.24, 0.26)	0.0121	Atorvastatin 10 mg
4 mg	298	3.04 (4.12)	3.12 (5.14)	0.09 (5.41)	-0.57 (-1.82,	0.038	Atorvastatin

Study Treatment	N	Baseline (mg/L)	Week 12 LOCF (mg/L)	Change Week 12 LOCF	Mean difference (95% CI)	p-value	vs.
		Mean (SD)	Mean (SD)	Mean (SD)			
					0.69)		20 mg
Atorvastatin							
10 mg	102	3.95 (6.79)	2.32 (3.02)	-1.65 (6.74)	NA	NA	NA
20 mg	102	3.14 (3.63)	2.59 (2.96)	-0.53 (3.52)	NA	NA	NA
NK-104-302							
Pitavastatin							
2 mg	307	3.33 (8.47)	2.39 (2.91)	-0.94 (8.54)	1.06 (0.15, 1.7)	0.002	Simvastatin 20 mg
4 mg	316	2.7 (3.8)	2.0 (4.6)	0.23 (4.5)	-0.57 (-1.6, 0.33)	0.021	Simvastatin 40 mg
Simvastatin							
10 mg	107	3.33 (4.04)	3.46 (6.81)	0.09 (6.92)	NA	NA	NA
20 mg	110	3.16 (4.24)	2.33 (3.20)	-0.83 (4.37)	NA	NA	NA
NK-104-304							
Pitavastatin 4 mg	233	3.21 (4.89)	2.85 (4.54)	-0.36 (6.04)	0.48 (-0.81, 1.78)	0.046	Simvastatin 40 mg
Simvastatin 40 mg	118	3.77 (7.93)	3.88 (1.13)	0.05 (5.46)	NA	NA	NA
NK-104-305							
Pitavastatin 4 mg	274	4.08 (6.60)	3.93 (9.03)	-0.14 (1.05)	-0.86 (-2.44, 0.73)	0.029	Atorvastatin 20 mg
Atorvastatin 20 mg	136	3.11 (4.06)	2.85 (3.99)	-0.26 (4.28)	NA	NA	NA
NK-104-306							
Pitavastatin							
1 mg	207	2.78 (7.30)	3.14 (7.51)	-0.07 (7.95)	0.85 (-1.69, 3.39)	0.051	Pravastatin 10 mg
2 mg	224	3.82 (5.30)	3.88 (1.04)	0.21 (1.16)	-0.39 (-2.98, 2.20)	0.077	Pravastatin 20 mg
4 mg	210	5.00 (1.27)	4.05 (1.19)	-0.92 (1.64)	0.35 (-2.21, 2.91)	0.079	Pravastatin 40 mg
Pravastatin							
10 mg	103	4.59 (1.19)	4.01 (1.02)	-0.83 (0.15)	NA	NA	NA
20 mg	96	2.70 (3.31)	3.49 (5.22)	0.80 (4.92)	NA	NA	NA
40 mg	102	3.64 (6.03)	4.24 (1.71)	0.62 (1.82)	NA	NA	NA

Source: Individual clinical study reports

Small-Dense-LDL

Recent studies have shown that the presence of small, dense LDL particles are associated with an increase in the risk of CHD. In Study 305, mean small-dense-LDL decreased by 425.6 nmol/L

in the pitavastatin 4 mg group and by 526.9 nmol/L in the atorvastatin 20 mg group (p=0.02). The clinical significance of these findings is unknown.

Small-dense-LDL was not assessed in any of the other core studies.

Adiponectin

Low levels of adiponectin have been shown to be an independent risk factor for diabetes mellitus and metabolic syndrome. In study 305, the levels of adiponectin increased by 1.2 ug/mL in the atorvastatin 20 mg group and decreased by 0.3 ug/mL in the pitavastatin 4 mg group (p=0.04). The clinical significance of these findings is unknown.

Adiponectin was not assessed in any of the other core studies.

6.1.7 Subpopulations

Subgroup Analyses for LDL

Age

Treatment with pitavastatin, atorvastatin, and simvastatin showed a trend of greater efficacy in elderly subjects (≥65 years) vs. younger subjects (<65 years). In the pitavastatin groups, the mean percent decreases from baseline to endpoint in LDL were 31% to 45% in older subjects compared to 29% to 42% in younger subjects. In the simvastatin groups, the mean percent decreases from baseline to endpoint in LDL were 38% to 48% in older subjects and 33% to 42% in younger subjects. In the atorvastatin groups, the mean percent decreases from baseline to endpoint in LDL were 40% to 46% in older subjects and 36% to 43% in younger subjects.

The following table presents mean percent change from baseline to endpoint LDL by age in the integrated core studies.

Table 30 Mean Percent Change in LDL (mg/dL) from Baseline to Endpoint by Age (FAS Population) - Integrated Core Phase 2 and 3 Studies

Treatment	<65 Years		≥65 Years	
	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)
Pitavastatin				
1 mg	86	-29.25 (13.29)	222	-31.39 (11.80)
2 mg	519	-36.71 (13.98)	426	-39.52 (14.03)
4 mg	974	-42.10 (15.52)	558	-45.03 (14.84)
Atorvastatin				
10 mg	88	-36.79 (15.82)	30	-40.51 (11.05)
20 mg	163	-42.22 (16.53)	74	-45.89 (15.42)
Simvastatin				
20 mg	72	-33.45 (13.95)	35	-38.10 (18.17)
40 mg	163	-41.45 (16.22)	65	-48.02 (10.36)
Pravastatin				
10 mg	NA	NA	103	-22.41 (14.05)
20 mg	NA	NA	96	-28.83 (11.05)
40 mg	NA	NA	102	-33.98 (14.30)
Placebo	127	-0.96 (12.63)	27	-8.89 (12.90)

Table includes limited data from phase 2 study 2204.
Source: End-of-Text-Table 5.3

Gender

Treatment with pitavastatin (and simvastatin) showed a trend towards greater LDL lowering in females than in males. For females the percent decrease in LDL from baseline to endpoint ranged from 32% to 45%, while for males it ranged from 30% to 41% across all doses. This trend was not observed with atorvastatin or pravastatin treatment.

The following table presents the mean percent change from baseline to endpoint LDL by gender in the integrated core studies.

Table 31 Mean Percent Change in LDL (mg/dL) from Baseline to Endpoint by Sex (FAS Population) - Integrated Core Phase 2 and 3 Studies

Treatment	Male		Female	
	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)
Pitavastatin				
1 mg	157	-29.74 (12.20)	151	-31.88 (12.25)
2 mg	427	-35.85 (13.61)	518	-39.73 (14.20)
4 mg	773	-40.95 (15.64)	759	-45.43 (14.69)
Atorvastatin				
10 mg	63	-38.28 (14.80)	55	-37.11 (14.90)
20 mg	126	-44.07 (15.39)	111	-42.57 (17.20)
Simvastatin				
20 mg	44	-33.40 (12.62)	63	-36.07 (17.29)
40 mg	129	-42.35 (14.44)	99	-44.59 (15.81)
Pravastatin				
10 mg	49	-20.54 (13.13)	54	-24.11 (14.75)
20 mg	48	-28.98 (11.96)	48	-28.68 (10.19)
40 mg	42	-33.17 (14.21)	60	-34.55 (14.45)
Placebo	94	-2.91 (13.76)	60	-1.48 (11.75)

Source: End-of-Text-Table 5.4

Age and Gender

Consistent with the greater mean decreases in LDL seen in females than males, and the greater decreases in LDL in elderly vs. younger subjects receiving pitavastatin, the elderly females showed the greatest decreases in LDL (32% to 46%) when the two factors were examined together. The smallest reductions were observed in younger males (28% to 40%)

The following table shows the mean percent change from baseline to endpoint LDL by age and gender in the integrated core studies.

Table 32 Mean Percent Change in LDL (mg/dL) from Baseline to Endpoint by Age and Gender (FAS Population) - Integrated Core Phase 2 and 3 Studies

Treatment	Male <65 Years		Male ≥65 Years		Female <65 Years		Female ≥65 Years	
	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)
Pitavastatin								
1 mg	58	-28.16 (12.26)	99	-30.67 (12.13)	28	-31.52 (15.21)	123	-31.96 (11.54)
2 mg	259	-34.08 (13.17)	168	-38.58 (13.87)	260	-39.34 (14.29)	258	-40.13 (14.12)
4 mg	543	-40.00 (15.37)	230	-43.20 (16.07)	431	-44.75 (15.31)	328	-46.32 (13.79)
Atorvastatin								
10 mg	48	-37.60 (15.21)	15	-40.46 (13.66)	40	-35.82 (16.66)	15	-40.56 (8.13)
20 mg	81	-43.30 (15.52)	45	-45.46 (15.23)	82	-41.16 (17.50)	29	-46.56 (15.95)
Simvastatin								
20 mg	35	-33.81 (11.80)	9	-31.79 (16.14)	37	-33.11 (15.89)	26	-40.28 (18.61)
40 mg	101	-41.75 (15.37)	28	-44.51 (10.36)	62	-40.96 (17.62)	37	-50.68 (9.66)
Pravastatin								
10 mg	-	-	49	-20.54 (13.13)	-	-	54	-24.11 (14.75)
20 mg	-	-	48	-28.98 (11.96)	-	-	48	-28.68 (10.19)
40 mg	-	-	42	-33.17 (14.21)	-	-	60	-34.55 (14.45)
Placebo	80	-1.98 (13.665)	14	-8.20 (13.54)	47	0.77 (10.55)	13	-9.63 (12.67)

Source: End-of-Text-Table 5.5

Race:
There were very small proportions of Black, Hispanic, and other non-Caucasian subjects enrolled in the studies. Therefore, no meaningful comparisons can be made with respect to reductions in lipid variables in these subgroups.

BMI:
There were no obvious trends in the changes in LDL by baseline BMI.

NCEP Risk Category:
No apparent trend was seen in the mean percent reduction of LDL from baseline to endpoint across the low, medium, and high NCEP risk categories. For the pitavastatin groups, the decreases in LDL for the low-risk subgroup ranged from 30.9% to 43.8%, for the medium-risk subgroup it ranged from 34.0% to 43.9%, and for the high-risk subgroup from 29.3% to 42.5%.

Baseline LDL

With respect to baseline LDL, treatment with pitavastatin was generally more effective in the subgroups with baseline LDL ≥160 mg/dL than in the groups with baseline LDL <160 mg/dL. No obvious difference was seen between groups with baseline LDL values of 160-<190 mg/dL and LDL 190-<220 mg/dL. For the pitavastatin subgroups, the decreases in LDL for the LDL

<160 mg/dL subgroup ranged from 27.7% to 40.8%, for the LDL 160-<190 mg/dL subgroup it ranged from 32.5% to 43.7%, for the LDL 190-<220 mg/dL subgroup it ranged from 32.6% to 45.3% and for the LDL ≥220 mg/dL subgroup from 30.6% to 44.6%.

The mean percent changes in LDL by baseline LDL for the pitavastatin and comparators are shown in the following table.

Table 33 Mean Percent Change in LDL (mg/dL) from Baseline to Endpoint by Baseline LDL Category (FAS Population) - Integrated Core Phase 2 and 3 Studies

Treatment	LDL <160 mg/dL		LDL 160-<190 mg/dL		LDL 190-<220 mg/dL		LDL ≥220 mg/dL	
	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)	N	% Change Week 12 Endpoint Mean (SD)
Pitavastatin								
1 mg	103	-27.68 (13.26)	123	-32.52 (11.19)	62	-32.58 (11.29)	20	-30.62 (13.65)
2 mg	162	-36.61 (13.81)	485	-38.29 (13.85)	274	-38.46 (14.41)	24	-35.45 (15.99)
4 mg	462	-40.75 (17.94)	693	-43.65 (14.38)	340	-45.31 (12.97)	37	-44.59 (13.97)
Atorvastatin								
10 mg	9	-29.92 (18.43)	77	-37.64 (15.64)	27	-39.27 (10.18)	5	-44.95 (13.61)
20 mg	107	-43.13 (14.90)	95	-43.08 (16.42)	33	-46.12 (19.14)	2	-24.07 (26.43)
Simvastatin								
20 mg	8	-32.21 (18.94)	59	-32.25 (15.81)	37	-38.35 (13.31)	3	-54.19 (8.26)
40 mg	54	-41.82 (17.09)	112	-42.25 (15.13)	59	-46.20 (12.72)	3	-54.02 (8.26)
Pravastatin								
10 mg	55	-21.28 (12.72)	34	-23.60 (12.99)	14	-23.99 (20.90)	0	-
20 mg	43	-26.40 (12.96)	42	-30.84 (9.45)	11	-30.63 (6.59)	0	-
40 mg	41	-32.32 (15.99)	45	-33.45 (13.52)	15	-39.87 (11.07)	1	-37.85 (0)
Placebo	24	2.71 (13.66)	67	-1.71 (13.36)	39	-4.25 (12.23)	24	-6.14 (11.30)

Table includes limited data from phase 2 studies 2204 and 210.
Source: End-of-Text-Table 5.9

Diabetes

For the pitavastatin groups, the decreases in LDL for subjects with diabetes ranged from 25.0% to 41.4% and for subjects without diabetes the decreases ranged from 31.0% to 43.7%.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The 1 mg, 2 mg, and 4 mg doses of pitavastatin are associated with reductions in LDL and favorable changes in secondary lipid parameters.

6.1.9 Persistence of Efficacy and/or Tolerance Effects

The absolute changes in LDL and other lipid parameters observed with pitavastatin in the 12-week Phase 3 trials appear to persist with long-term treatment. Based on long-term data with other statins, there is no reason to believe that the changes in lipid levels observed within 6-8 weeks of starting pitavastatin would not persist with chronic therapy.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

As a class the statins have been associated with elevated liver ATs and rarely hepatitis and liver failure. The clinical data presented by the applicant in this NDA show a frequency of AT elevations for pitavastatin which is similar to that seen for currently approved statins. No cases of **Hy's Law or liver failure were seen in the pitavastatin clinical trials.**

Statins have also been associated with myopathy and rare cases of rhabdomyolysis, which can lead to acute renal failure and death. Nine of 648 (1.38%) subjects treated with pitavastatin doses of 8 mg and higher developed rhabdomyolysis (defined as CPK>10XULN and myoglobinemia with/without myoglobinuria) in Phase 2 studies. The rhabdomyolysis occurred within 3 weeks of administration of the higher doses.(b) (4)

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. The mechanism for the proteinuria is unclear, although there have been postulations of inhibition of protein uptake by renal tubular cells via the statin effect on HMG-CoA reductase activity in the kidney (Gotto, 2003). Thus, the clinical relevance of statin-associated proteinuria is debatable. The Renal Expert Panel of the **National Lipid Association's Safe**ty Task Force found no evidence that statins cause acute renal failure or renal insufficiency. The Renal Expert Panel also found no convincing evidence of an association between statins and hematuria (Kasiske, 2006).

There were a number of problems with the assessment of proteinuria and hematuria in the pitavastatin NDA. The applicant did not provide pooled dipstick urinalysis data from the Phase 3 trials. 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 of proteinuria was not examined in the long-term extension trials with spot urine protein/creatinine ratios.

In the data presented to this clinical reviewer, the frequency of patients with worsened proteinuria was similar with pitavastatin, atorvastatin, and simvastatin. However, the number of

subjects examined with spot urine protein/creatinine ratios was small and persistence or reversibility of the proteinuria was not assessed in the extension trials.

This clinical reviewer requested the mean change in creatinine levels in the subgroup that had the protein/creatinine ratios from baseline to end of treatment to correlate renal function changes with proteinuria. According to the applicant, serum creatinine was measured only at screening for the core Phase 3 trial. Thus, end of treatment creatinine values were not available to assess renal function in those subjects with changes in spot urine protein/creatinine ratios.

7.1 Methods

The materials submitted by the sponsor for this review are summarized in section 5. The review involved analysis of the files submitted electronically as part of the sponsor's original submission, the 4-month safety update, and patient/study information as requested by this clinical reviewer during the review process.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The submitted integrated safety summary focused on five Phase 2 studies, five Phase 3 studies and four Phase 3 extension Studies. The applicant categorized these 14 studies into four different groups as described below (section 7.1.3).

For the safety analysis, this reviewer focused on Group 1, which comprised 12-week Phase 2 and Phase 3 studies. The subgroup analyses for race, gender, and age were conducted with Group 3.

7.1.2 Categorization of Adverse Events

AEs were coded according to Medical Dictionary for Regulatory Activities (Version 8.1) (MedDRA) terminology. According to the applicant, where changes in severity were recorded in the CRF, the most severe incidence of the AE was reported in the tables and listings. AEs that occurred intermittently were reported as separate events. Treatment emergent AEs (TEAEs) were summarized by treatment, severity and relationship to the study drug. In addition, the frequency (the number of AEs and the number of subjects experiencing an AE) of TEAEs were summarized by MedDRA body system and preferred term.

Standardized MedDRA Queries (SMQs) categories (Acute Renal Failure [SMQ], Possible Drug-Related Hepatic Disorders [SMQ] and Rhabdomyolysis/Myopathy [SMQ]) were used for the subgroup and time dependency analyses. A full list of terms included in these categories is provided in the Appendix.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooled safety analysis included five Phase 2 studies, five Phase 3 studies and four extension studies. See Table 4 for key characteristics of the Phase 2 and 3 trials. A brief description of the four extension studies follows. Study 309 was an extension of Study 304 and included 178 subjects treated with pitavastatin 4 mg or simvastatin 40 or 80 mg. The study was double-blind

for 16 weeks and single-blind for up to an additional 28 weeks. Study 2204E1 was an extension of Study 2204 and included 53 subjects treated with 8 mg of pitavastatin. This study was terminated due to concern over myopathy with doses of pitavastatin greater than 4 mg. Study 307 was an extension of Study 302 and included 1353 subjects treated with 4 mg open-label pitavastatin for up to 52 weeks. Study 308 was an extension of Study 306 and included 539 subjects treated with 4 mg of open-label pitavastatin for up to 60 weeks.

The applicant chose to pool data from the fourteen studies into four different groupings.

Group 1 contains safety data from the 12 to 16-week Phase 2 and 3 placebo and active-controlled studies. Adverse events are presented by the randomized dose and each patient is counted once. Ten of the 14 studies comprise this grouping. There are no data from the extension studies in Group 1.

Groups 2, 3, and 4 contain data from the 12 to 16-week Phase 2 and 3 trials and the extension studies.

The Group 2 analyses examined the longest period of therapy from randomization and include safety data for each subject until they had a gap in treatment of > 2 weeks. Data are presented by actual dose taken at the time of an adverse event and may count a patient more than once.

The Group 3 analyses examined all the safety data collected while each subject was on study and ignores any gaps in treatment. Adverse events are presented by the dose that patients were actually taking at the time of the event. Group 3 data was examined further by subgroup evaluations.

The Group 4 analyses examined only the safety data from the longest continuous exposure period for each subject, but presents adverse events by the drug that the patient was taking at the time of the event and is not split by dose.

As used in this review, "short-term trial" is synonymous with 12 weeks of exposure to pitavastatin or comparator statin **and "long-term trial" is** synonymous with exposure to pitavastatin of up to 52 weeks.

It should be noted that the analyses of safety data from Groups 2, 3, and 4 include up to 60 weeks of exposure to pitavastatin but almost no long-term exposure with the comparator statins. **Therefore, valid assessments of pitavastatin's safety relative to low-to-moderate doses of** atorvastatin, simvastatin, and pravastatin are limited to data analyses from Group 1.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

According to ICH guidelines, the total number of patients exposed to an investigational drug for long-term treatment of non-life threatening conditions should be at least 1500 patients, with 300 to 600 exposed at 6 months and at least 100 patients exposed at one year. Table 34 summarizes the longest continuous exposure to pitavastatin by dose.

Table 34 Duration of Pitavastatin Exposure by Dose at End of Longest Continuous Exposure (Group 4)

	Dose at End of Continuous Exposure		
Duration of Exposure (weeks)	**Pitavastatin 1 mg (N=192)**	**Pitavastatin 2 mg (N=819)**	**Pitavastatin 4 mg (N=2280)**
< 8 weeks	20	92	40
8 to <12 weeks	39	84	134
12 to <24 weeks	133	232	502
24 to <36 weeks	0	17	180
36 to <52 weeks	0	15	331
52 to <76 weeks	0	379	1093
Source: Pitavastatin Study Report, Table 2.7.4.13, pg. 62.			

The total patient exposure in this NDA is adequate for 2 and 4 mg daily oral dosages. Although the 1 mg dose does not have adequate safety exposure at one year, this is not an issue as the higher doses fulfill the exposure criteria.

Table 35 presents a summary of the duration of exposure for each dose of pitavastatin, comparator, and placebo in Group 1. Mean duration of exposure for 1 mg to 4 mg pitavastatin ranged from 11.6 to 12.0 weeks. For atorvastatin 10 mg to 40 mg, mean duration of exposure ranged from 11.1 to 12.2 weeks. Mean duration of exposure for 20 mg to 40 mg of simvastatin was approximately 11.9 weeks and for pravastatin 10 mg to 40 mg mean duration of exposure was 11.2 weeks. Mean duration of exposure to placebo treatment was 10.2 weeks.

Mean exposure to doses of 8 mg pitavastatin and above were lower than 1 mg, 2 mg, and 4 mg pitavastatin due to the early termination of high-dose treatment arms or studies with doses higher than 4 mg (studies 209, 2204 and 210).

Table 35 Duration of Exposure to Study Drug-Group 1

Treatment Groups Randomised Dose	N	Duration of Exposure (weeks)		No. (%) of Subjects				
		Mean ± SD	Range	<1 week	1 to <4 weeks	4 to <8 weeks	8 to <12 weeks	≥12 weeks
Placebo	208	10.2 ± 3.7	0-16	3 (1.4)	14 (6.7)	39 (18.8)	32 (15.4)	120 (57.7)
Pitavastatin								
Pita 1 mg	309	11.6 ± 2.4	0-15	5 (1.6)	9 (2.9)	6 (1.9)	79 (25.6)	210 (68.0)
Pita 2 mg	951	12.0 ± 2.1	0-21	7 (0.7)	16 (1.7)	20 (2.1)	199 (20.9)	709 (74.6)
Pita 4 mg	1540	11.9 ± 2.1	0-27	8 (0.5)	34 (2.2)	26 (1.7)	321 (20.8)	1151 (74.7)
Pita 8 mg	479	7.4 ± 4.2	0-20	12 (2.5)	122 (25.5)	130 (27.1)	87 (18.2)	128 (26.7)
Pita 16 mg	102	4.9 ± 2.2	0-9	3 (2.9)	33 (32.4)	48 (47.1)	18 (17.6)	0
Pita 32 mg	34	1.9 ± 1.1	0-4	6 (17.6)	28 (82.4)	0	0	0
Pita 64 mg	33	1.6 ± 0.9	0-3	8 (24.2)	25 (75.8)	0	0	0
Pita Total	3448	10.9 ± 3.4	0-27	49 (1.4)	267 (7.7)	230 (6.7)	704 (20.4)	2198 (63.7)
Atorvastatin								
Ator 10 mg	118	12.2 ± 2.4	2-17	0	3 (2.5)	3 (2.5)	14 (11.9)	98 (83.1)
Ator 20 mg	240	12.1 ± 2.3	0-16	4 (1.7)	6 (2.5)	0	31 (12.9)	199 (82.9)
Ator 40 mg	51	11.1 ± 2.4	3-13	0	1 (2.0)	5 (9.8)	14 (27.5)	31 (60.8)
Ator 80 mg	96	5.4 ± 2.2	1-10	0	27 (28.1)	49 (51.0)	20 (20.8)	0
Ator Total	505	10.8 ± 3.5	0-17	4 (0.8)	37 (7.3)	57 (11.3)	79 (15.6)	328 (65.0)
Simvastatin								
Simv 20 mg	107	11.9 ± 2.3	1-15	1 (0.9)	3 (2.8)	3 (2.8)	12 (11.2)	88 (82.2)
Simv 40 mg	229	11.8 ± 2.4	0-16	2 (0.9)	6 (2.6)	5 (2.2)	41 (17.9)	175 (76.4)
Simv Total	336	11.9 ± 2.4	0-16	3 (0.9)	9 (2.7)	8 (2.4)	53 (15.8)	263 (78.3)
Pravastatin								
Prav 10 mg	103	10.9 ± 3.1	1-14	0	9 (8.7)	4 (3.9)	35 (34.0)	55 (53.4)
Prav 20 mg	96	11.4 ± 2.4	1-15	1 (1.0)	3 (3.1)	4 (4.2)	26 (27.1)	62 (64.6)
Prav 40 mg	102	11.4 ±2.3	1-14	0	3 (2.9)	4 (3.9)	27 (26.5)	68 (66.7)
Prav Total	301	11.2 ±2.6	1-15	1 (0.3)	15 (5.0)	12 (4.0)	88 (29.2)	185 (61.5)

Source: Pitavastatin Study Report, Table 2.7.4.17.

Table 36 summarizes the exposure data for pitavastatin and other statins in the clinical trials by total years of patient exposure for Group 3. Pitavastatin 4 mg had the highest patient-years of exposure at 1,728 years, 2 mg of pitavastatin had 823 patient-years, and pitavastatin 1 mg had 68 patient-years. Atorvastatin, simvastatin, and pravastatin had fewer patient-years of exposure, ranging from 14 patient-years for pravastatin 40 mg to 74 patient-years for simvastatin 40 mg.

Table 36 Pitavastatin and Comparator Drug Exposures by Patient Years - Group 3

	Pita 1 mg N=309	Pita 2 mg N=2562	Pita 4 mg N=2406	Ator 10 mg N=394	Ator 20 mg N=264	Ator 40mg N=54	Simv 20 mg N=336	Simv 40 mg N=219	Prav 10 mg N=103	Prav 20 mg N=198	Prav 40mg N=96
No. of Weeks of Exposure	11.56	16.71	37.36	6.54	11.59	7.39	6.57	17.69	10.86	7.57	7.88
Total Pt. Years of Exposure	68.68	823.47	1728.64	49.53	58.87	7.68	42.44	74.48	21.51	28.81	14.55

Source: Pitavastatin Study Report

7.2.2 Explorations for Dose Response

Summaries of subjects exposed at different doses and durations in the pitavastatin development program are shown in section 7.2.1.

7.2.3 Special Animal and/or In Vitro Testing

The adequacy of preclinical carcinogenicity testing is addressed by Dr. Lee Elmore, the Pharmacology/Toxicology reviewer.

7.2.4 Routine Clinical Testing

The methods and frequency of monitoring laboratory parameters were, in general, adequate. The applicant initially did not report persistent, defined as two consecutive measurements for ALT and/or AST ≥3XULN elevations. The NDA submission reported only single occurrences of AT elevations. Since patients can have random isolated elevations which turn out to be nonspecific and unrelated to the study drug, it can be informative to report persistent elevations to try to identify patients who are more likely to have clinically significant and drug-related elevations. The applicant submitted an analysis of persistently elevated ATs during the review process. These data were reviewed and found not to be different from the original data submitted by the applicant.

The applicant did not pool the dipstick urinalysis data in the Integrated Summary of Safety. This would have been helpful to the analysis of hematuria and proteinuria as it relates to pitavastatin. Although the applicant examined spot urine protein/creatinine ratios in the short-term trials, proteinuria was not examined in the extension trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant has adequately addressed enzymatic pathways responsible for clearance of pitavastatin. See Section 8.2 for an overview of **drug-drug interactions; please refer to Dr. Lau's** review for a more detailed analysis.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant has conducted appropriate evaluations to detect known class associations with myopathy/rhabdomyolysis and liver AT elevations. Although the applicant complied with the **Division's request for proteinuria** assessment in the short-term studies, the estimate for the persistence of proteinuria identified in these trials was not investigated in the extension trials to determine if there were changes or further worsening in the level of proteinuria.

7.3 Major Safety Results

7.3.1 Deaths

There were six deaths in subjects taking pitavastatin and one death in a subject taking simvastatin. There was one additional death due to subarachnoid hemorrhage in a patient taking (b) (4) pitavastatin in the open-label extension to study 104A220. This death is not listed in the table below. (b) (4) There is no imbalance in deaths when considered in terms of the number of patients exposed to pitavastatin vs. each comparator statin.

Table 37 Listing of All Deaths in the Safety Population

Treatment/ Study No.	Subject ID Grp	Age (yrs)	Gender	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
Pitavastatin 2mg NK-104-308 (extension)	**6201004**	**75**	F	**218**	**262**	**Non-Hodgkin's** Lymphoma	**Non-Hodgkin's** Lymphoma	Same
Pitavastatin 2 mg NK-104-308 (extension)	6516069	76	F	329	329	Broncho-pneumonia and cerebrovascular accident	Broncho-pneumonia and cerebrovascular accident	Same
Pitavastatin 4 mg NK-104-305 (core)	5110042	62	F	57	59	Myocardial infarction	Myocardial infarction	Same
Pitavastatin 4 mg NK-104-307 (Extension)	1108015	58	M	69	174	Hypoxic Encephalopathy	Hypoxic Encephalopathy	Same, ?Myocardial infarction
Pitavastatin 4 mg NK-104-307 (Extension)	2109026	72	M	312	312	Cardiac death	Cardiac death	Same
Pitavastatin 4 mg NK-104-309 (Extension)	4504013	61	M	301	301	Myocardial Ischemia	Myocardial Ischemia	Same
Simvastatin 20 mg NK-104-302 (core)	2116059	64	M	41	41	Sudden cardiac death	Sudden cardiac death	Same

Of the six deaths in subjects taking pitavastatin, three were associated with ongoing cardiovascular/cerebrovascular disease. In the opinion of this reviewer, one death on pitavastatin attributed to hypoxic encephalopathy could have been due to an underlying cardiovascular event. All case narratives were reviewed and none appear to cause undue concern.

7.3.2 Serious Adverse Events

A serious adverse event (SAE), according to the applicant, was any adverse experience that resulted in any of the following: death, life-threatening adverse event, persistent or significant disability, in-patient hospitalization, congenital anomaly or birth defect, or was medically significant in that it may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed.

The incidence of nonfatal SAEs was 1.1% (32/2800) for the 1 mg to 4 mg doses of pitavastatin in the Phase 2 and 3 trials (Group 1). This is similar to the incidence of SAEs for atorvastatin (1.6%) and pravastatin (1.3%) and slightly lower than simvastatin (3.0%) in these clinical trials. Most of the SAEs were related to ongoing cardiovascular disease and are unlikely to be drug-related. There were no cases of CPK, AST, or ALT elevations which were considered serious for pitavastatin 1 mg to 4 mg. The following table includes all SAEs with pitavastatin 1 mg to 4 mg in Group 1.

Table 38 Summary of All Treatment-Emergent Serious Adverse Events Pitavastatin 1 mg to 4 mg Group 1 Analysis

System Organ Class/Preferred Term	Placebo (N=208)	Pitavastatin 1 mg (N=309)	Pitavastatin 2 mg (N=951)	Pitavastatin 4 mg (N=1540)
Number (%) of Patients with any Serious Treatment Emergent Adverse Event	**1 (0.5)**	**1 (0.3)**	**10 (1.1)**	**21 (1.4)**
Cardiac Disorders	**1 (0.5)**	**0**	**3 (0.3)**	**8 (0.5)**
Acute Coronary Syndrome	0	0	0	1 (0.1)
Acute Myocardial Infarction	0	0	1 (0.1)	1 (0.1)
Angina Pectoris	0	0	0	0
Angina Unstable	0	0	0	0
Atrial Fibrillation	0	0	0	0
Myocardial Infarction	1 (0.5)	0	1 (0.1)	5 (0.3)
Pleuropericarditis	0	0	1(0.1)	0
Tachycardia paroxysmal	0	0	0	1 (0.1)
Gastrointestinal Disorders	**0**	**0**	**1 (0.1)**	**1 (0.1)**
Gastritis	0	0	0	1 (0.1)
Pancreatitis	0	0	1 (0.1)	0 (0.1)
General Disorders and	**0**	**0**	**1 (0.1)**	**1 (0.1)**

System Organ Class/Preferred Term	Placebo (N=208)	Pitavastatin 1 mg (N=309)	Pitavastatin 2 mg (N=951)	Pitavastatin 4 mg (N=1540)
Administrative Site Conditions				
Chest pain	0	0	1 (0.1)	0
Non-cardiac chest pain	0	0	0	1 (0.1)
Sudden Cardiac Death	0	0	0	0
Hepatobiliary Disorders	**0**	**0**	**0**	**0**
Cholecystitis	0	0	0	0
Cholelithiasis	0	0	0	0
Immune System Disorders	**0**	**0**	**1 (0.1)**	**0**
Anaphylactic Reaction	0	0	1 (0.1)	0
Infections and Infestations	**0**	**0**	**0**	**2**
Cystitis	0	0	0	0
Erysipelas	0	0	0	0
Gastroenteritis	0	0	0	1 (0.1)
Peritonsillar abscess	0	0	0	1 (0.1)
Injury, Poisonings, and Procedural Complications	**0**	**0**	**1 (0.1)**	**1 (0.1)**
Alcohol Poisoning	0	0	0	0
Concussion	0	0	1 (0.1)	0
Femoral Neck Fractures	0	0	0	1 (0.1)
Humerus Fracture	0	0	0	
Joint Dislocation	0	0	0	0
Lower Limb Fracture	0	0	0	0
Skin Injury	0	0	0	0
Investigations	**0**	**0**	**0**	**2 (0.1)**
Alanine Aminotransferase Increased	0	0	0	0
Arteriogram Coronary	0	0	0	1 (0.1)
Aspartate Aminotransferase Increased	0	0	0	0
Blood Creatine Phosphokinase Increased	0	0	0	0

System Organ Class/Preferred Term	Placebo (N=208)	Pitavastatin 1 mg (N=309)	Pitavastatin 2 mg (N=951)	Pitavastatin 4 mg (N=1540)
Blood Creatinine Increased	0	0	0	1 (0.1)
Blood Urine Present	0	0	0	0
Myoglobin Blood Increased	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**0**	**1 (0.1)**
Arthralgia	0	0	0	0
Intervertebral Disc Degeneration	0	0	0	1 (0.1)
Intervertebral Disc Disorder	0	0	0	0
Lumbar Spinal Stenosis	0	0	0	0
Myalgia	0	0	0	0
Myopathy	0	0	0	0
Pain in Extremity	0	0	0	0
Rhabdomyolysis	0	0	0	0
Spinal Column Stenosis	0	0	0	1 (0.1)
Neoplasms Benign, Malignant, and Unspecified (incl. cysts and polyps)	**0**	**0**	**0**	**1 (0.1)**
Breast Cancer	0	0	0	1 (0.1)
Prostate Cancer	0	0	0	0
Nervous System Disorders	**0**	**1 (0.3)**	**1 (0.1)**	**2 (0.1)**
Burning Sensation	0	0	1 (0.1)	0
Cerebral Thrombosis	0	1 (0.3)	0	0
Convulsion	0	0	0	1 (0.1)
Encephalopathy	0	0	0	0
Syncope	0	0	0	0
Transient Ischaemic Attack	0	0	0	1 (0.1)
Pregnancy, Puerperium, and Perinatal Conditions	**0**	**0**	**1 (0.1)**	**0**
Abortion Spontaneous	0	0	1 (0.1)	0
Renal and Urinary	**0**	**0**	**1 (0.1)**	**0**

System Organ Class/Preferred Term	Placebo (N=208)	Pitavastatin 1 mg (N=309)	Pitavastatin 2 mg (N=951)	Pitavastatin 4 mg (N=1540)
Disorders				
Myoglobinuria	0	0	0	0
Proteinuria	0	0	0	0
Renal Failure	0	0	0	0
Urinary incontinence			1 (0.1)	
Reproductive System and Breast Disorders	**0**	**0**	**0**	**2 (0.1)**
Benign Prostatic Hyperplasia	0	0	0	1 (0.1)
Vaginal Prolapse	0	0	0	1 (0.1)
Skin and Subcutaneous Disorders	**0**	**0**	**1 (0.1)**	**0**
Pruritus generalized	0	0	1 (0.1)	0
Vascular Disorders	**0**	**0**	**0**	**0**
Aortic Aneurysm	0	0	0	0
Bleeding Varicose Vein	0	0	0	0
Hypertensive Crisis	0	0	0	0

Source: Pitavastatin Study Report, Table 1.9, beg pg 458.

* One additional SAE noted for 8 mg pitavastatin in NKS104A2204 in ISS for Subject 112-015, who was originally excluded from CSR safety population

At doses $\leq$4 mg of pitavastatin, there was no clear association with the dose of pitavastatin and the development of any SAE. However, as summarized in the table below, the frequency of SAEs increased at the doses $\geq$ 8 mg of pitavastatin.

Table 39 Summary of All Treatment Emergent Serious Adverse Events, Pitavastatin 8 mg to 64 mg- Group 1

System Organ Class/Preferred Term	Pitavastatin 8 mg N=479	Pitavastatin 16 mg (N=102)	Pitavastatin 32 mg (N=34)	Pitavastatin 64 mg (N=33)	Pitavastatin 1mg-64mg (N=3448)
Number (%) of Patients with any Serious Treatment Emergent Adverse Event	**6 (1.3)**	**1 (1.0)**	**3 (8.8)**	**3 (9.1)**	**45 (1.3)**
Blood and Lymphatic System Disorders	**0**	**0**	**0**	**0**	**0**
Lymphadenopathy	0	0	0	0	0

System Organ Class/Preferred Term	Pitavastatin 8 mg N=479	Pitavastatin 16 mg (N=102)	Pitavastatin 32 mg (N=34)	Pitavastatin 64 mg (N=33)	Pitavastatin 1mg-64mg (N=3448)
Cardiac Disorders	**2 (0.4)**	**0**	**0**	**0**	**13 (0.4)**
Acute Coronary Syndrome	0	0	0	0	1 (0.0)
Acute Myocardial Infarction	0	0	0	0	2 (0.1)
Angina Pectoris	1 (0.2)	0	0	0	1 (0.0)
Angina Unstable	0	0	0	0	0
Atrial Fibrillation	0	0	0	0	0
Myocardial Infarction	1 (0.2)	0	0	0	7 (0.2)
Pleuropericarditis	0	0	0	0	1 (0.0)
Tachycardia paroxysmal	0	0	0	0	1 (0.0)
Ear and Labyrinth Disorders	**0**	**0**	**0**	**0**	**0**
Deafness Neurosensory	0	0	0	0	0
	0				
Gastrointestinal Disorders	**0**	**0**	**0**	**0**	**2 (0.1)**
Gastritis	0	0	0	0	1 (0.0)
Pancreatitis	0	0	0	0	1 (0.0)
General Disorders and Administrative Site Conditions	**0**	**0**	**0**	**0**	**2 (0.1)**
Chest pain	0	0	0	0	1 (0.0)
Non-cardiac chest pain	0	0	0	0	1 (0.0)
Sudden Cardiac Death	0	0	0	0	0
Hepatobiliary Disorders	**0**	**0**	**0**	**0**	**0**
Cholecystitis	0	0	0	0	0
Cholelithiasis	0	0	0	0	0
Immune System Disorders	**0**	**0**	**0**	**0**	**1 (0.0)**
Anaphylactic Reaction	0	0	0	0	1 (0.0)
Infections and Infestations	**0**	**0**	**0**	**2**	**2 (0.1)**
Cystitis	0	0	0	0	0
Erysipelas	0	0	0	0	0

System Organ Class/Preferred Term	Pitavastatin 8 mg N=479	Pitavastatin 16 mg (N=102)	Pitavastatin 32 mg (N=34)	Pitavastatin 64 mg (N=33)	Pitavastatin 1mg-64mg (N=3448)
Gastroenteritis	0	0	0	0	1 (0.0)
Peritonsillar abscess	0	0	0	0	1 (0.0)
Injury, Poisonings, and Procedural Complications	**2 (0.4)**	**0**	**0**	**0**	**4 (0.1)**
Alcohol Poisoning	0	0	0	0	0
Concussion	0	0	0	0	1 (0.0)
Femoral Neck Fractures	0	0	0	0	1 (0.0)
Humerus Fracture	0	0	0	0	0
Joint Dislocation	1 (0.2)	0	0	0	1 (0.0)
Lower Limb Fracture	1 (0.2)	0	0	0	1 (0.0)
Skin Injury	1 (0.2)	0	0	0	1 (0.0)
Investigations	**1 (0.2)**	**0**	**2 (5.9)**	**2 (6.1)**	**7 (0.2)**
Alanine Aminotransferase Increased	0	0	1 (2.9)	1 (3.0)	2 (0.1)
Arteriogram Coronary	0	0	0	1 (0.1)	0
Aspartate Aminotransferase Increased	0	0	1 (2.9)	1 (3.0)	2 (0.1)
Blood Creatine Phosphokinase Increased	0	0	1 (2.9)	1 (3.0)	2 (0.1)
Blood Creatinine Increased	0	0	0	0	1 (0.0)
Blood Urine Present	0	0	0	1 (3.0)	1 (0.0)
Myoglobin Blood Increased	1 (0.2)	0	0	0	1 (0.0)
Metabolism and Nutrition Disorders	**0**	**0**	**0**	**1 (3.0)**	**1 (0.0)**
Hypokalemia	0	0	0	1 (3.0)	1 (0.0)
Musculoskeletal and Connective Tissue Disorders	**2 (0.4)**	**2 (1.9)**	**3 (8.9)**	**3 (9.1)**	**10 (0.3)**
Arthralgia	0	1 (1.0)	0	0	1 (0.0)
Intervertebral Disc Degeneration	0	0	0	0	1 (0.0)
Intervertebral Disc Disorder	0	0	0	0	0

System Organ Class/Preferred Term	Pitavastatin 8 mg N=479	Pitavastatin 16 mg (N=102)	Pitavastatin 32 mg (N=34)	Pitavastatin 64 mg (N=33)	Pitavastatin 1mg-64mg (N=3448)
Lumbar Spinal Stenosis	0	0	0	0	0
Myalgia	0	0	1 (2.9)	1 (3.0)	2 (0.1)
Myopathy	0	0	0	1 (3.0)	1 (0.0)
Pain in Extremity	1 (0.2)	0	0	0	1 (0.0)
Rhabdomyolysis	2 (0.4)	1 (1.0)	3 (8.8)	3 (9.1)	9 (0.2)
Spinal Column Stenosis	0	0	0	0	1 (0.0)
Neoplasms Benign, Malignant, and Unspecified (incl. cysts and polyps)	**0**	**0**	**0**	**0**	**1 (0.0)**
Breast Cancer	0	0	0	0	1 (0.0)
Prostate Cancer	0	0	0	0	0
Nervous System Disorders	**0**	**0**	**1 (2.9)**	**0**	**5 (0.1)**
Burning Sensation	0	0	1 (2.9)	0	2 (0.1)
Cerebral Thrombosis	0	0	0	0	1 (0.0)
Convulsion	0	0	0	0	1 (0.0)
Encephalopathy	0	0	0	0	0
Syncope	0	0	0	0	0
Transient Ischaemic Attack	0	0	0	0	1 (0.0)
Pregnancy, Puerperium, and Perinatal Conditions	**0**	**0**	**0**	**0**	**1 (0.0)**
Abortion Spontaneous	0	0	0	0	1 (0.0)
Renal and Urinary Disorders	**0**	**0**	**1 (2.9)**	**2 (6.1)**	**4 (0.1)**
Myoglobinuria	0	0	1 (2.9)	0	1 (0.0)
Proteinuria	0	0	0	1 (3.0)	1 (0.0)
Renal Failure	0	0	0	1 (3.0)	1 (0.0)
Urinary Incontinence	0	0	0	0	1 (0.0)
Reproductive System and Breast Disorders	**0**	**0**	**0**	**0**	**2 (0.1)**
Benign Prostatic Hyperplasia	0	0	0	0	1 (0.0)
Vaginal Prolapse	0	0	0	0	1 (0.0)

System Organ Class/Preferred Term	Pitavastatin 8 mg N=479	Pitavastatin 16 mg (N=102)	Pitavastatin 32 mg (N=34)	Pitavastatin 64 mg (N=33)	Pitavastatin 1mg-64mg (N=3448)
Skin and Subcutaneous Disorders	**0**	**0**	**0**	**0**	**1 (0.0)**
Pruritus generalized	0	0	0	0	1 (0.0)
Vascular Disorders	**0**	**0**	**0**	**0**	**0**
Aortic Aneurysm	0	0	0	0	0
Bleeding Varicose Vein	0	0	0	0	0
Hypertensive Crisis	0	0	0	0	0
Source: Pitavastatin Study Report, Table 1.9, beg pg 458.					

For pitavastatin, SAEs occurred most frequently for the following disorders: rhabdomyolysis (nine subjects at doses ≥ 8 mg), myocardial infarction (seven subjects), ALT increased (two subjects at 32 mg and 64 mg), AST increased (two subjects at 32 mg and 64 mg), blood CPK increased (two subjects at 32 mg and 64 mg), myalgia (two subjects at 32 mg and 64 mg), and burning sensation (two subjects at 2 mg and 32 mg). Overall, there were few SAEs for pitavastatin 1 mg to 4 mg. Most SAEs clustered at the higher doses of pitavastatin. The incidence of myocardial infarctions was 0.2% or seven events out of 3,448 subjects; this is not unexpected given the background risk factors present in these trials.

Rhabdomyolysis occurred with pitavastatin 8 mg and higher: two patients at 8 mg, one patient at 16 mg, three patients at 32 mg, and three patients at 64 mg. (b) (4)

(b) (4)

(b) (4) Section 7.3.4 describes in more detail rhabdomyolysis and other muscle-related disorders.

No elevations of ALT, AST, or CPK were reported as a SAE for pitavastatin 1 mg to 4 mg. There were increases in ALT (0.3%), AST (0.3%) and CPK (0.3%) for pitavastatin 8 mg to 64 mg which were reported as serious.

SAEs which occurred in greater than 0.1 % subjects in 1-64 mg pitavastatin as compared to atorvastatin, simvastatin, or pravastatin are further summarized in Table 40 below.

Table 40 Serious Adverse Events Which Occurred in > 0.1% More Patients in the Pitavastatin Overall Group than Comparators by Event

System Organ Class/Preferred Term	Atorvastatin Overall (N=505)	Simvastatin Overall (N=336)	Pravastatin Overall (N=301)	Pitavastatin 1-64 mg (N=3448)
Number (%) of	**8 (1.6)**	**10 (3.0)**	**4 (1.3)**	**45 (1.3)**

System Organ Class/Preferred Term	Atorvastatin Overall (N=505)	Simvastatin Overall (N=336)	Pravastatin Overall (N=301)	Pitavastatin 1-64 mg (N=3448)
Patients with any Serious Treatment Emergent Adverse Event				
Cardiac Disorders	**2 (0.4)**	**1 (0.3)**	**1 (0.3)**	**13 (0.4)**
Acute Myocardial Infarction	0	0	1 (0.3)	2 (0.1)
Myocardial Infarction	0	0	0	7 (0.2)
Gastrointestinal Disorders	**0**	**0**	**0**	**2 (0.1)**
Gastritis	0	0	0	1 (0.0)
Pancreatitis	0	0	0	1 (0.0)
Investigations	**0**	**0**	**0**	**7 (0.2)**
Alanine Aminotransferase Increased	0	0	0	2 (0.1)
Aspartate Aminotransferase Increased	0	0	0	2 (0.1)
Blood Creatine Phosphokinase Increased	0	0	0	2 (0.1)
Musculoskeletal and Connective Tissue Disorders	**1 (0.2)**	**1 (0.3)**	**0**	**10 (0.3)**
Myalgia	0	0	0	2 (0.1)
Myopathy	0	0	0	1 (0.0)
Rhabdomyolysis	0	0	0	9 (0.2)
Nervous System Disorders	**1 (0.2)**	**1 (0.3)**	**0**	**5 (0.1)**
Burning Sensation	0	0	0	2 (0.1)
Renal and Urinary Disorders	**0**	**0**	**0**	**4 (0.1)**
Myoglobinuria	0	0	0	1 (0.0)
Proteinuria	0	0	0	1 (0.0)
Renal Failure	0	0	0	1 (0.0)
Urinary Incontinence	0	0	0	1 (0.0)
Reproductive System and Breast Disorders	**0**	**0**	**0**	**2 (0.1)**
Benign Prostatic Hyperplasia	0	0	0	1 (0.0)
Vaginal Prolapse	0	0	0	1 (0.0)

System Organ Class/Preferred Term	Atorvastatin Overall (N=505)	Simvastatin Overall (N=336)	Pravastatin Overall (N=301)	Pitavastatin 1-64 mg (N=3448)
Source: Table above.				

There were no cases of serious myalgia, myopathy, renal disorders or rhabdomyolysis for atorvastatin, simvastatin, or pravastatin. In contrast, these SAEs occurred in subjects taking pitavastatin, but only with higher doses (> 8 mg).

Table 41 Most Frequent SAEs for Pitavastatin in Group 1 and Group 3

SOC/PT	Group 1			Group 3	
No. (%) of Pts.	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
Mean Exposure (Weeks)	11.6	12.0	11.9	16.7	37.4
No. (%) of Subjects with any SAE	1 (0.3)	10 (1.1)	21 (1.4)	66 (2.6)	73 (3.0)
Cardiac Disorders	0	3 (0.3)	8 (0.5)	12 (0.5)	25 (1.0)
Myocardial Infarction	0	1 (0.1)	5 (0.3)	3 (0.1)	10 (0.4)
Gastrointestinal Disorders	0	1 (0.1)	1 (0.1)	6 (0.2)	9 (0.4)
Musculoskeletal and CT Disorders	0	0	1 (0.1)	11 (0.4)	5 (0.2)
Neoplasms Benign, Malignant & Unspecified (inc Cysts &Polyps)	0	0	1 (0.1)	15 (0.6)	6 (0.2)
Source: Pitavastatin Study Report, Table 2.7.4.87					

More SAEs occurred with longer duration of exposure to pitavastatin. From the table above, the incidence of SAEs in Group 3 was 2.8% (139/4968) for pitavastatin 2 mg and 4 mg. This was slightly higher than the 1.2% (31/2491) for pitavastatin 2 mg and 4 mg in Group 1. Most of the SAEs in Group 3 continued to be related to ongoing cardiovascular disease. However, the incidence of SAEs in musculoskeletal and connective tissue disorders was higher in Group 3 (0.3% or 16/4968) as compared to Group 1 (0.04% or 1/2491). Given the longer duration of exposure in Group 3 as compared to Group 1, it is not unexpected there is a higher incidence of serious musculoskeletal and connective tissues disorders in Group 3.

7.3.3 Dropouts and/or Discontinuations

Group 3 Analysis

Table 42 summarizes discontinuations from Group 3. The proportion of withdrawals for pitavastatin was the highest (9.4%) for the 4 mg dose, whereas the 2 mg pitavastatin had a withdrawal rate of 7.0% and 1 mg pitavastatin had a rate of 7.8%. Overall, there were 429 subjects, or 12.3%, who discontinued on 1-4 mg of pitavastatin.

Table 42 Summary of All Discontinuations in Group 3

Treatment Dose at Time of Discontinuation	N	No. (%) of Subjects					
		All Subjects who Discontinued	Reason for Discontinuation				
			AE/Lab Abnormality/Death§	Consent Withdrawn/Lost to Follow-up	Protocol Violation	Termination of Study or Withdrawal of Subject by Sponsor/Investigator Judgment	Other*
Pita 1 mg	309	24 (7.8)	11 (3.6)	8 (2.6)	5 (1.6)	0	0
Pita 2 mg	2562	179 (7.0)	87 (3.4)	50 (2.0)	31 (1.2)	0	11 (0.4)
Pita 4 mg	2406	226 (9.4)	103 (4.3)	83 (3.5)	35 (1.5)	1 (0.0)	4 (0.2)
Ator 10 mg	394	19 (4.8)	6 (1.5)	7 (1.8)	2 (0.5)	2 (0.5)	2 (0.5)
Ator 20 mg	264	5 (1.9)	3 (1.1)	2 (0.8)	0	0	0
Ator 40 mg	54	4 (7.4)	1 (1.9)	0	2 (3.7)	1 (1.9)	0
Simv 20 mg	336	19 (5.7)	7 (2.1)	9 (2.7)	3 (0.9)	0	0
Simv 40 mg	219	14 (6.4)	10 (4.6)	3 (1.4)	1 (0.5)	0	0
Simv 80 mg	5	1 (20.0)	0	1 (20.0)	0	0	0
Prav 10 mg	103	16 (15.5)	8 (7.8)	4 (3.9)	3 (2.9)	0	1 (1.0)
Prav 20 mg	198	14 (7.1)	6 (3.0)	4 (2.0)	4 (2.0)	0	0
Prav 40 mg	96	3 (3.1)	2 (2.1)	1 (1.0)	0	0	0

Source: Pitavastatin Study Report, Table 2.7.4.32,pg. 83.

*administration problems; § death was given as reason for discontinuation in two subjects on 2 mg pitavastatin, four subjects on 4 mg pitavastatin and one subject on 20 mg simvastatin; AE: adverse event

Group 1 Analysis

Table 43 summarizes the discontinuations across the short-term Phase 2 and Phase 3 clinical trials. The proportion of withdrawals for pitavastatin was the highest (7.1%) for the 1 mg dose, whereas the 2 mg and 4 mg doses were similar at around 5.8%. Overall, there were 611 subjects, or 17.7%, who discontinued on 1-64 mg of pitavastatin.

Table 43 Summary of All Discontinuations in Group 1

Treatment Randomized Dose	N	No. (%) of Subjects	
		All Subjects who Discontinued	Reason for Discontinuation

			AE/Lab Abnormality/Death§	Consent Withdrawn/Lost to Follow-up	Protocol Violation	Termination of Study or Withdrawal of Subject by Sponsor/Investigator Judgment	Other*
Placebo	208	53 (25.5)	4 (1.9)	8 (3.8)	0	41 (19.7)	0
Pita 1 mg	309	22 (7.1)	10 (3.2)	7 (2.3)	5 (1.6)	0	0
Pita 2 mg	951	56 (5.9)	32 (3.4)	12 (1.3)	10 (1.1)	0	2 (0.2)
Pita 4 mg	1540	88 (5.7)	44 (2.9)	26 (1.7)	14 (0.9)	1 (0.1)	3 (0.2)
Pita 8 mg	479	298 (62.2)	19 (4.0)	11 (2.3)	6 (1.3)	113 (23.6)	149 (31.1)
Pita 16 mg	102	80 (78.4)	20 (19.6)	4 (3.9)	2 (2.0)	54 (52.9)	0
Pita 32 mg	34	34 (100)	4 (11.8)	1 (2.9)	0	29 (85.3)	0
Pita 64 mg	33	33 (100)	12 (36.4)	0	0	21 (63.6)	0
Pita Overall	3448	611 (17.7)	141 (4.1)	61 (1.8)	37 (1.1)	218 (6.3)	154 (4.5)
Ator 10 mg	118	7 (5.9)	0	5 (4.2)	0	2 (1.7)	0
Ator 20 mg	240	11 (4.6)	6 (2.5)	3 (1.3)	2 (0.8)	0	0
Ator 40 mg	51	8 (15.7)	2 (3.9)	1 (2.0)	2 (3.9)	1 (2.0)	2 (3.9)
Ator 80 mg	96	69 (71.9)	12 (12.5)	2 (2.1)	1 (1.0)	54 (56.3)	0
Ator Overall	505	95 (18.8)	20 (4.0)	11 (2.2)	5 (1.0)	57 (11.3)	2 (0.4)
Simv 20 mg	107	8 (7.5)	3 (2.8)	5 (4.7)	0	0	0
Simv 40 mg	229	15 (6.6)	7 (3.1)	5 (2.2)	3 (1.3)	0	0
Simv Overall	336	23 (6.8)	10 (3.0)	10 (3.0)	3 (0.9)	0	0
Prav 10 mg	103	15 (14.6)	8 (7.8)	4 (3.9)	2 (1.9)	0	1(1.0)
Prav 20 mg	96	8 (8.3)	3 (3.1)	4 (4.2)	1 (1.0)	0	0
Prav 40 mg	102	9 (8.8)	5 (4.9)	1 (1.0)	3 (2.9)	0	0
Prav Overall	301	32 (10.6)	16 (5.3)	9 (3.0)	6 (2.0)	0	1(0.3)

Source: Pitavastatin Study Report, Table 2.7.4.31.
*administration problems; § death was given as reason for discontinuation in two subjects on 2 mg pitavastatin, four subjects on 4 mg pitavastatin and one subject on 20 mg simvastatin; AE: adverse event

The proportion of subjects discontinuing due to withdrawal of consent or lost to follow-up was also highest for the 1 mg dose of pitavastatin (2.3%) compared to the 2 mg and 4 mg doses of pitavastatin (1.3 and 1.7%, respectively). For any dose of pitavastatin, 1.8% of discontinuations were due to withdrawal of consent or lost to follow-up.

Pitavastatin 8 mg and higher doses had rates of discontinuation from 62.2 % to 100% due to a combination of adverse events or the applicant stopping randomization and/or terminating the study due to an inordinately high incidence of myopathy.

The discontinuation rates for atorvastatin 10 mg (5.9%), atorvastatin 20 mg (4.6%), simvastatin 20 mg (7.5%), and simvastatin 40 mg (6.6%) were comparable to the discontinuation rates for the 2 mg (5.9%) and 4 mg (5.7%) doses of pitavastatin.

The following table summarizes adverse events leading to withdrawal of subjects in Group 1.

Table 44 Adverse Events Leading to Withdrawal in > 1% of Subjects (and > 1 Subject in any Group) by Randomized Dose of Pitavastatin- 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 1-64 mg (N=3448)
No. (%) of Subjects with any TEAEs that led to Withdrawal	4 (1.9)	12 (3.9)	31 (3.3)	48 (3.1)	22 (4.6)	20 (19.6)	4 (11.8)	12 (36.4))	149 (4.3)
Gastrointestinal Disorders	**0**	**6 (1.9)**	**9 (0.9)**	**14 (0.9)**	**4 (0.8)**	**2 (2.0)**	**1 (2.9)**	**1 (3.0)**	**37 (1.1)**
General Disorders & Admin. Site Conditions	**1 (0.5)**	**2 (0.6)**	**5 (0.5)**	**3 (0.2)**	**2 (0.4)**	**5 (4.9)**	**2 (5.9)**	**4 (12.1)**	**23 (0.7)**
Fatigue	0	1 (0.3)	3 (0.3)	1 (0.1)	1 (0.2)	3 (2.9)	0	3 (9.1)	12 (0.3)
Pyrexia	0	0	0	0	0	2 (2.0)	0	0	2 (0.1)
Investigations	**0**	**0**	**2(0.2)**	**2 (0.1)**	**2 (0.4)**	**12 (11.8)**	**4 (11.8)**	**8 (24.2)**	**30 (0.9)**
ALT increased	0	0	1(0.1)	0	0	6 (5.9)	4 (11.8)	3 (9.1)	14 (0.4)
AST abnormal	0	0	0	0	0	0	0	2 (6.1)	2 (0.1)
AST increased	0	0	0	0	0	5 (4.9)	4 (11.8)	3 (9.1)	12 (0.3)
Blood CPK abnormal	0	0	0	0	0	0	1 (2.9)	2 (6.1)	3 (0.1)
Blood CPK increased	0	0	0	1 (0.1)	2 (0.4)	11 (10.8)	2 (5.9)	4 (12.1)	20 (0.6)
Musculoskeletal and Connective Tissue Disorders	**2 (1.0)**	**2 (0.6)**	**12 (1.3)**	**10 (0.6)**	**8 (1.7)**	**13 (12.7)**	**3 (8.8)**	**10 (30.3)**	**58 (1.7)**
Back Pain	1 (0.5)	0	1 (0.1)	1 (0.1)	0	2 (2.0)	0	0	4 (0.1)
Myalgia	1 (0.5)	1 (0.3)	7 (0.7)	8 (0.5)	4 (0.8)	6 (5.9)	3 (8.8)	6 (18.2)	35 (1.0)
Myopathy	0	0	0	0	0	1 (1.0)	0	2 (6.1)	3 (0.1)
Pain in extremity	0	1 (0.3)	3 (0.3)	0	2 (0.4)	3 (2.9)	0	1 (3.0)	10 (0.3)
Rhabodomyolysis	0	0	0	0	2 (0.4)	1 (1.0)	2 (5.9)	3 (9.1)	**8 (0.2)**
Nervous System Disorders	**0**	**2 (0.6)**	**3 (0.3)**	**5 (0.3)**	**4 (0.8)**	**4 (3.9)**	**1 (2.9)**	**0**	**19 (0.6)**
Renal and Urinary Disorders	**0**	**0**	**1 (0.1)**	**1 (0.1)**	**0**	**1 (1.0)**	**1 (2.9)**	**2 (6.1)**	**6 (0.2)**
Myoglobinuria	**0**	**0**	**0**	**0**	**0**	**1 (1.0)**	**1 (2.9)**	**0**	**1 (0.2)**
Pollakiuria	**0**	**0**	**0**	**1 (0.1)**	**0**	**0**		**0**	**2 (0.1)**
Proteinuria	**0**	**0**	**0**	**0**	**0**	**1 (1.0)**		**1 (3.0)**	**1 (0.0)**
Renal Failure	**0**	**0**	**0**	**0**	**0**	**0**		**1 (3.0)**	**1 (0.0)**
Urinary retention	**0**	**0**	**1 (0.1)**	**0**	**0**	**0**		**0**	**1 (0.1)**

Source: Pitavastatin Study Report, Table 2.7.4.90 and ISS Table 1.8
According to an email from the sponsor on 2/09 both "abnormal" and "increased" have the same meaning and merely reflect the choice term of the reporting physician. Both are judged to reflect reported values higher than the upper limit of the normal range.

In Group 1, adverse events leading to withdrawal of subjects were similar for pitavastatin 1 mg (3.9%), 2 mg (3.3%), and 4 mg (3.1%). Adverse events leading to withdrawal of subjects increased almost dose proportionally with pitavastatin 8 mg-64mg (4.6% to 36.4%). Withdrawals due to AEs for atorvastatin, simvastatin, and pravastatin ranged from 2.1% to 11.5% in these trials.

Myalgia was the most common adverse event leading to withdrawal in subjects given pitavastatin in Group 1. Withdrawals due to myalgia were similar for 1mg-4mg (0.3 to 0.7%), but increased in a dose-related manner for > 8 mg pitavastatin. For example, with pitavastatin 16 mg, withdrawal due to myalgia occurred in 5.9% and increased to 18.2% in subjects given 64 mg pitavastatin. Discontinuations due to rhabdomyolysis, pain in extremity, and myopathy also occurred in a dose-related manner at doses ≥ 8mg.

Withdrawals due to increased/abnormal CPK also occurred with > 8 mg pitavastatin in a dose-related manner. For example, for pitavastatin 16 mg, blood CPK increased occurred at a rate of 10.8%. For pitavastatin 64 mg the incidence was as high as 17.2% (combined blood CPK abnormal and blood CPK increased). Withdrawals due to blood CPK increased occurred in 1 patient on pitavastatin 4 mg and no patients on 1 mg or 2 mg pitavastatin. Withdrawals due to increased CPK were not seen with atorvastatin, simvastatin, or pravastatin.

In Group 1, withdrawals due to ALT increased occurred at a rate of 5.9% with 16 mg, 11.8% with 32 mg, and 9.1% with 64 mg. According to the applicant, one withdrawal occurred in pitavastatin 2 mg secondary to increased ALT. There were two patients on atorvastatin 80 mg who withdrew from the study due to ALT elevations. Otherwise there were no withdrawals with lower doses of pitavastatin or comparators due to increased ALT in Group 1.

No withdrawals occurred with AST abnormal/increased in patients administered pitavastatin 1 mg to 8 mg. With pitavastatin ≥ 16 mg, withdrawals occurred from 4.9% to 11.8% due to abnormal/increased AST. There was one patient on atorvastatin 80 mg who withdrew due to increased AST. Withdrawals due to abnormal/increased AST were not seen with simvastatin or pravastatin.

There were six subjects who withdrew from the clinical trials due to renal and urinary disorders in Group 1: one subject in the 2 mg pitavastatin group (0.1%, urinary retention), one subject in the 4 mg pitavastatin group (0.1%, pollakiuria), one subject in the 16 mg pitavastatin group (1.0%, pollakiuria), one subject in the 32 mg pitavastatin group (2.9%, myoglobinuria) and two subjects in the 64 mg pitavastatin group (6.1%; renal failure and proteinuria). Withdrawals due to renal and urinary disorders were not seen with placebo or the comparator statins.

Table 45 : Adverse Events Leading to Withdrawal Reported by ≥0.5% of Subjects (and >1 Subject in any Group) by Number (%) of Subjects for Pitavastatin by Dose at Onset - Group 3

	Group 3	
SOC/PT	Pita 2 mg (N=2562)	Pita 4 mg (N=2406)

	Group 3	
SOC/PT	**Pita 2 mg (N=2562)**	**Pita 4 mg (N=2406)**
Mean Exposure (Wks)	16.7	37.4
No. (%) of Subjects with any TEAE leading to Withdrawal	85 (3.3)	88 (3.7)
Cardiac Disorders	11 (0.4)	6 (0.2)
Gastrointestinal Disorders	22 (0.9)	17 (0.7)
General Disorders & Admin. Site Conditions	7 (0.3)	2 (0.1)
Investigations	10 (0.4)	23 (1.0)
Blood CK increased	5 (0.2)	14 (0.6)
Musculoskeletal & Connective Tissue Disorders	21 (0.8)	17 (0.7)
Myalgia	13 (0.5)	13 (0.5)
Nervous System Disorders	9 (0.4)	6 (0.2)
Source: ISS, Table 3.9, pg. 1639 Values for pita 1 mg are the same for Group 1 and 3 analyses		

In Group 3, the incidence of subjects who had an adverse event that led to withdrawal was similar for 2 mg (3.3%) and 4 mg (3.7%) pitavastatin and was similar to the withdrawal rates when compared to Group 1.

In Group 3, subjects on 4 mg pitavastatin withdrew due to blood CK increased (0.6%) slightly more than for myalgia (0.5%). Myalgia continued to be the most common reason for withdrawal in subjects on 2 mg pitavastatin (0.5%).

7.3.4 Significant Adverse Events

Muscle-Related Events: Rhabdomyolysis

Myopathy and rhabdomyolysis have been reported in the post-marketing period for all currently approved statins. For pitavastatin, there have been cases of severe myopathy and rhabdomyolysis in clinical trials with doses from 8 mg to 64 mg [redacted]

The sponsor defined rhabdomyolysis in two of its Phase 2 studies as follows:

- In study 209 - An increase in CK > 10,000 mIU/mL associated with muscle aches (myalgia), a positive test for hemoglobin in urine in the absence of red blood cells in the urinary sediment, and/or myoglobinuria and myoglobinemia
- In study 2204 - characterized by myalgia, marked CK elevations and myoglobinemia with/without myoglobinuria. Measurement of myoglobin was triggered by CK value >10XULN or if any muscle events were experienced

The ACC/AHA/NHLBI (Pasternak, 2002) defined myopathy, myalgia, myositis, and rhabdomyolysis as follows:

- Myopathy - a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
- Myalgia - muscle ache or weakness without CK elevation.
- Myositis - muscle symptoms with increased CK levels
- **Rhabdomyolysis—muscle symptoms with marked** CK elevation (typically substantially greater than 10XULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)

The FDA usually defines rhabdomyolysis as follows:

- CK level >50XULN (or >10,000 IU/L) with organ damage, usually renal compromise

Nine subjects (1.4%) were reported as having rhabdomyolysis after immediate-release pitavastatin, two (0.4%) with 8 mg pitavastatin, one (1.0%) with 16 mg pitavastatin, three (8.8%) with 32 mg pitavastatin and three (9.1%) with 64 mg pitavastatin. A tenth case of rhabdomyolysis was reported with an (b) (4) formulation of pitavastatin at a dose of 16 mg. (b) (4)

All nine cases of rhabdomyolysis in the immediate-release formulation occurred in the Phase 2 trials. The average length of time on the current drug dose prior to the development of rhabdomyolysis was 22 days. The median was 21 days with a range of 11 to 30 days. Thus, 8 to 64 mg doses were clearly myotoxic and produced muscle symptoms in an unacceptably high number of healthy individuals within 3 weeks after starting therapy.

Brief descriptions of the rhabdomyolysis cases in the clinical trials are provided in Table 46.