

Primary Efficacy Variable

The primary efficacy variable was the percentage change in LDL between baseline and endpoint. Summary statistics for the percentage decrease in LDL during the treatment period are presented below.

Percentage decrease between baseline and last valid value for LDL (ITT population; N = 249):

	NK-104			(b) (4)	Placebo
	1 mg n=49	2 mg n=50	4 mg n=48		n=50
LDL (mg/dL) at Visit 4					
Mean	177.6	177.6	181.5		181.5
SD	34.7	30.9	38.6		34.7
Min, Max	115.8, 312.7	131.3, 251.0	123.6, 335.9		119.7, 308.9
Percentage decrease between baseline and last valid value					
Adjusted mean*	27.0	31.4	41.5		1.6
Mean	27.3	31.4	41.9		1.9
SD	15.5	12.7	16.0		13.0
Min, Max	1.2, 56.7	-0.4, 54.4	-30.8, 62.6		-28.2, 38.3

All doses of pitavastatin significantly lowered LDL, with the adjusted mean percentage change from baseline being -27.0%, -31.4%, -41.5%, (b) (4) in the NK- 104 1 mg, 2 mg, 4 mg, (b) (4) (b) (4) groups, respectively, compared with placebo (-1.6%). The result of the global effect of treatment test using ANOVA showed a significant variation in the adjusted LDL concentration during treatment (P<0.001). The reduction in LDL occurred in a dose-dependent manner with the greatest reduction being observed in the pitavastatin (b) (4) group (b) (4).

The comparisons between the pitavastatin treatment groups and placebo showed a statistically significant difference (P = 0.000). A statistically significant difference was also observed for each of the pitavastatin treatment group comparisons (P = 0.000) with the exception of pitavastatin 4 mg versus the pitavastatin (b) (4) group (b) (4) and the pitavastatin 1 mg versus the pitavastatin 2 mg group (P=0.112); the dose-related effect of pitavastatin was shown by the results of the linear regression analysis. Calculation of the dose-response log linear relationship (Ln transformation of percent change) using the linear equation was significant, but not significant using quadratic equation. Linear regression relationships (percent change) were significant when calculated with the quadratic equation for the linear term but not for the square term, and for the linear term with the linear equation.

Secondary Efficacy Variables:

The secondary efficacy variables were the percentage decrease of the following parameters during the treatment period: TC, HDL, TG, Apo A1, and Apo B. Data for the secondary efficacy variables are presented in the following table:

Percentage change between baseline and last valid value for total cholesterol, HDL, triglyceride, Apo A1, and Apo B (ITT population; N = 249)

Percentage change between baseline and last valid value	NK-104			(b) (4)	Placebo
	1 mg n=49	2 mg n=50	4 mg n=48		n=50
TC (mg/dL) at Visit 4					
Mean	281.9	281.9	289.6		281.9
SD	42.5	38.6	46.3		34.7
% change from baseline to last valid value					
Adjusted mean*	-19.3	-23.0	-30.7		-2.6
Mean	-19.4	-23.0	-31.0		-2.5
SD	11.0	9.2	11.6		10.7
HDL (mg/dL) at Visit 4					
Mean	50.2	50.2	54.1		46.3
SD	7.7	11.6	15.4		7.7
% change from baseline to last valid value					
Adjusted mean*	8.0	9.3	10.5		3.2
Mean	8.0	9.4	9.5		3.5
SD	12.0	9.9	14.6		9.3
TG (mg/dL) at Visit 4:					
Mean	274.3	274.3	274.3		265.5
SD	88.5	79.6	70.8		88.5
% change from baseline to Visit 6*					
Adjusted mean*	-16.9	-21.9	-22.0		0.8
Mean	-16.6	-22.5	-21.6		1.3
SD	20.3	20.8	22.5		28.9
% change from baseline to Visit 7					
Mean	-13.8	-21.6	-24.8		7.9
SD	29.7	21.8	17.5		48.5
Apo A1 (mg/dL) at Visit 4					
Mean	142.7	141.8	147.4		140.0
SD	25.2	25.1	33.3		22.3
% change from baseline to last valid value					
Adjusted mean*	2.9	5.2	8.1		1.6
Mean	2.9	5.4	6.9		1.9
SD	12.2	10.5	14.0		11.9
Apo B (mg/dL) at Visit 4					
Mean	135.3	130.5	137.7		133.3
SD	29.8	30.4	30.2		22.3
% change from baseline to last valid value					
Adjusted mean*	-22.6	-23.0	-32.0		4.7
Mean	-22.9	-22.8	-32.3		4.6
SD	17.8	16.4	14.6		13.0

Pitavastatin-treated subjects had a reduction in TC, TG, and Apo B that generally increased in magnitude with increasing dose. The greatest reduction for each of these parameters occurred with the (b) (4) dose (b) (4) with the exception of TG at Visit 7 (greatest reduction occurred with the 4 mg dose [-24.8%]).

The global treatment effects for TC, TG, and ApoB were statistically significant ($P < 0.001$). The comparison between all doses of pitavastatin and placebo for TC, TG, and ApoB showed a statistically significant difference ($P \leq 0.004$). For TC and ApoB, statistically significant differences were also observed between all pitavastatin treatment groups ($P \leq 0.004$) with the exception of pitavastatin 1 mg versus NK- 104 2 mg, and pitavastatin 4 mg versus pitavastatin (b) (4). For TG, on the other hand, no statistically significant differences were observed between the NK- 104 treatment groups with the exception of NK- 104 1 mg versus NK- 104 (b) (4) at Visit 6 (b) (4) and pitavastatin 1 mg versus pitavastatin 4 mg at Visit 7 ($P = 0.045$).

Percentage change between baseline and last valid value	NK-104			(b) (4)	Placebo n=50
	1 mg n=49	2 mg n=50	4 mg n=48		
TC (mg/dL) at Visit 4					
Mean	281.9	281.9	289.6		281.9
SD	42.5	38.6	46.3		34.7
% change from baseline to last valid value					
Adjusted mean*	-19.3	-23.0	-30.7		-2.6
Mean	-19.4	-23.0	-31.0		-2.5
SD	11.0	9.2	11.6		10.7
TG (mg/dL) at Visit 4:					
Mean	274.3	274.3	274.3		265.5
SD	88.5	79.6	70.8		88.5
% change from baseline to Visit 6*					
Adjusted mean*	-16.9	-21.9	-22.0		0.8
Mean	-16.6	-22.5	-21.6		1.3
SD	20.3	20.8	22.5		28.9
% change from baseline to Visit 7					
Mean	-13.8	-21.6	-24.8		7.9
SD	29.7	21.8	17.5		48.5
Apo B (mg/dL) at Visit 4					
Mean	135.3	130.5	137.7		133.3
SD	29.8	30.4	30.2		22.3
% change from baseline to last valid value					
Adjusted mean*	-22.6	-23.0	-32.0		4.7
Mean	-22.9	-22.8	-32.3		4.6
SD	17.8	16.4	14.6		13.0

Secondary Efficacy Variable: HDL

An increase in HDL concentration was observed in all pitavastatin treatment groups regardless of baseline HDL concentration (range 6.8% to 10.5%) and the placebo group (3.2%), with the greatest increase being observed at 4 mg. The global treatment effect, however, was not statistically significant ($P = 0.057$). Differences between the placebo and pitavastatin treatment groups and between each pitavastatin dose group were not statistically significant except for the pitavastatin 2 mg and 4 mg comparisons with placebo ($P \leq 0.018$).

Percentage change between baseline and last valid value	NK-104			(b) (4)	Placebo
	1 mg n=49	2 mg n=50	4 mg n=48		n=50
HDL (mg/dL) at Visit 4					
Mean	50.2	50.2	54.1		46.3
SD	7.7	11.6	15.4		7.7
% change from baseline to last valid value					
Adjusted mean*	8.0	9.3	10.5		3.2
Mean	8.0	9.4	9.5		3.5
SD	12.0	9.9	14.6		9.3

Secondary Efficacy Variable: Apo A1

All doses of pitavastatin increased Apo A1 concentrations (range, 2.9% to 8.1%) and were greater than that obtained with placebo (1.6%). The greatest increase in Apo A1 was seen with the pitavastatin 4 mg dose (8.1%). The global treatment effect was not statistically significant (P = 0.062). No statistically significant differences were observed between the pitavastatin treatment groups and placebo with the exception of the comparisons between placebo and the pitavastatin 4 mg and (b) (4) groups (b) (4), or between each pitavastatin dose group (P≥0.052).

Percentage change between baseline and last valid value	NK-104			(b) (4)	Placebo
	1 mg n=49	2 mg n=50	4 mg n=48		n=50
Apo A1 (mg/dL) at Visit 4					
Mean	142.7	141.8	147.4		140.0
SD	25.2	25.1	33.3		22.3
% change from baseline to last valid value					
Adjusted mean*	2.9	5.2	8.1		1.6
Mean	2.9	5.4	6.9		1.9
SD	12.2	10.5	14.0		11.9

The dose-response log linear relationship was only statistically significant for TC and ApoB with the linear equation and the linear term.

Similar Apo A1 results were shown for the PP population.

Efficacy Conclusions:

- All doses of pitavastatin lowered LDL by statistically significant amounts compared with placebo.
- The reduction in LDL occurred in a dose-dependent manner with the greatest reduction being observed in the pitavastatin^{(b) (4)} group^{(b) (4)}
- Pitavastatin-treated subjects had statistically significant ($P < 0.001$) reductions in TC, TG, and Apo B that generally increased with increasing dose. The greatest reduction for each of these parameters was also seen in the ^{(b) (4)} dose group, and these effects were statistically significant.
- A non-linear increase in HDL concentration was observed over treatment groups, with the greatest increase being observed at 4 mg. This effect was not statistically significant ($P = 0.057$).

3 Phase 3 Individual Study reviews:

3.1 Study of Pitavastatin 2 mg vs. Atorvastatin 10 mg and Pitavastatin 4 mg vs. Atorvastatin 20 mg (following up-titration) in subjects with Primary Hypercholesterolemia or Combined Dyslipidemia [NK-104-301]

Study initiation date: 4 October 2005

Study completion date: 8 November 2006

3.1.1.1 General Discussion of Study Objectives, Endpoints and Methods

Primary Objective:

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

Secondary Objectives:

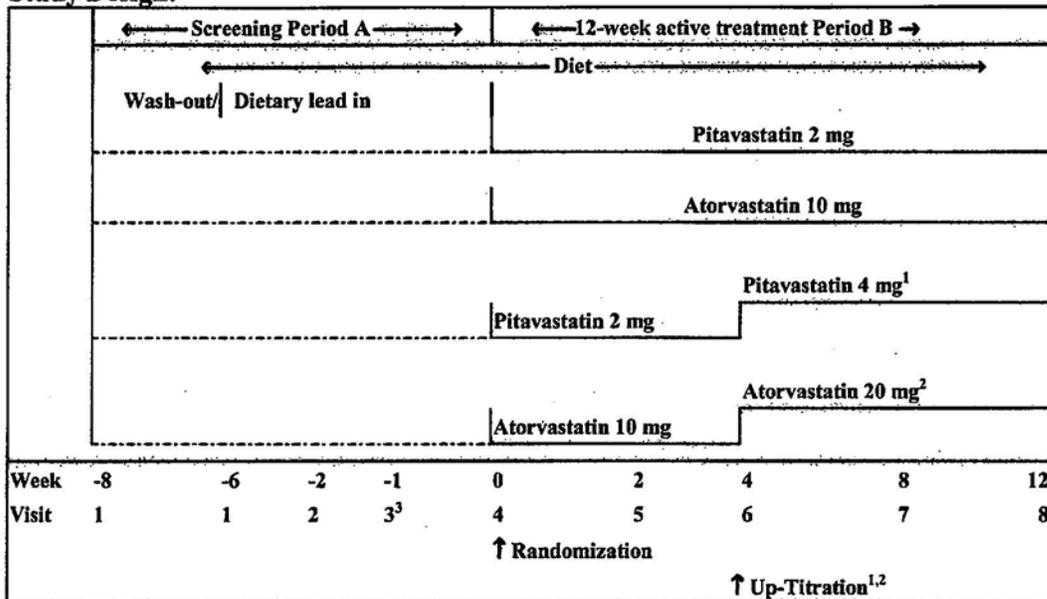
- To compare the efficacy of pitavastatin 2 mg daily vs. atorvastatin 10 mg daily and pitavastatin 4 mg daily vs. atorvastatin 20 mg daily with respect to changes from baseline in other lipid and lipoprotein fractions (TC, HDL, non-HDL, TC:HDL ratio, TG, non-HDL:HDL ratio, Apo-B, and Apo-A1, Apo-B:Apo-A1 ratio, hsCRP, and LDL target attainment of the NCEP).
- To compare the safety and tolerability of pitavastatin 2 mg daily vs. atorvastatin 10 mg daily and pitavastatin 4 mg daily vs. atorvastatin 20 mg daily when administered for 12 weeks using an up-titration regimen for the higher dose (i.e. 4 mg pitavastatin or 20 mg atorvastatin).

Study Design:

This was an 18 to 20 week, randomized, multicenter, double-blind, double-dummy, active-controlled non-inferiority Phase 3 study, conducted at 39 sites in India, Russia, Spain, and Denmark, which recruited approximately 800 subjects with primary hypercholesterolemia or combined dyslipidemia. Subjects who qualified entered a 6 to 8 week washout/dietary lead-in period followed by a 12-week treatment period. The 12-week treatment period involved an up-titration in the pitavastatin 4 mg group and the atorvastatin 20 mg groups. Subjects in the pitavastatin 4 mg group received pitavastatin 2 mg from Week 0 to Week 4, and 4 mg from Week 4 to 12. Subjects in the atorvastatin 20 mg group received atorvastatin 10 mg from Week 0 to Week 4, and 20 mg from Week 4 to 12.

Treatment was administered according to a double-dummy design. A schematic of the overall study plan is detailed in the study design schematic following:

Study Design:



1: subjects in the pitavastatin 4 mg group received pitavastatin 2 mg from Week 0 to Week 4, and 4 mg from Week 4 to 12
 2: subjects in the atorvastatin 20 mg group received atorvastatin 10 mg from Week 0 to Week 4, and 20 mg from Week 4 to 12

A dietary lead-in period of six weeks for statin naive subjects and eight weeks for subjects on previous statin therapy was included to ensure adequate washout of prior therapy where applicable and stable baseline lipid values. The treatment duration of 12 weeks was chosen based on past clinical trial design.

Dose selection:

Atorvastatin was chosen as the comparator since it is one of the most commonly used and well-studied statins.

In the European Phase 2 dose ranging studies in subjects with primary hypercholesterolemia and combined hyperlipidemia, doses of 1, 2, 4, — mg of pitavastatin were well tolerated, and the 4 mg dose has been shown to lower LDL, TC, TG, Apo-B, as well as increase HDL. Since pitavastatin was well tolerated at these doses, a favorable risk-benefit ratio was expected in this study.

b(4)

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

Selection of Study Population:

Subjects to be included in this study were male and female subjects (aged 18 to 75 years) with primary hypercholesterolemia or combined dyslipidemia.

Inclusion criteria:

- Males and non-pregnant, non-lactating females (age 18-75 years);
- Women of child bearing potential were allowed to enter the study ONLY if they used sustained contraceptive preparations (e.g., implants or IM injections) or complied with an approved mechanical contraceptive method. Women were considered to be of childbearing potential unless they were post-hysterectomy or at least one year post-menopausal or post-tubal ligation. All women of child bearing potential were tested and only those with a negative result from a pregnancy test at the beginning of the dietary lead-in period (Visit 1/Week -8/-6), and before initiating active treatment (Visit 4/Week 0) were included;
- Subjects who were eligible and able to participate in the study and who had given informed consent after the purpose and nature of the investigation had been explained to them;
- In order to have qualified for randomization, subjects must have been following a fat and cholesterol restrictive diet during the dietary stabilization period (i.e. for at least eight weeks for those subjects previously taking lipid-lowering medication and at least six weeks for those not previously taking lipid-lowering medication). Subjects also agreed not to eat grapefruit or drink grapefruit juice during the study;
- In order to have qualified for randomization at Visit 4 (Week 0), subjects must have presented with primary hypercholesterolemia or combined dyslipidemia, as defined by elevated plasma LDL (mean LDL ≥ 160 mg/dL and ≤ 220 mg/dL) with a lower qualifying value being within 15% of the higher qualifying measurement despite dietary therapy and
- TG levels of ≤ 400 mg/dL at both consecutive visits (Visits 2 and 3 or Visits 3 and 3A as applicable) during the dietary lead-in period. When required Visit 3A was scheduled one week after Visit 3 for collecting the additional lipid sample; and
- Subjects who, at the start of the study, agreed to be available for every clinic visit.

Exclusion criteria:

- Homozygous familial hypercholesterolemia (heterozygous component of familial hypercholesterolemia was acceptable for inclusion) or familial hypoalphalipoproteinemia;
- Any conditions which may have caused secondary dyslipidemia. This included, but was not restricted to alcoholism; auto-immune disease; nephrotic syndrome; uremia; any viral or non viral hepatitis clinically active within 12 months from study entry; obstructive hepatic or biliary disease; dys- or macroglobulinemia; multiple myeloma; glycogen storage disease; chronic pancreatitis; porphyria; and uncontrolled hypothyroidism or hyperthyroidism (controlled hypo- or hyperthyroidism [i.e., condition presenting with normal baseline serum TSH and treatment stable during at least the last two months prior to study entry] was permitted);

- Uncontrolled diabetes mellitus as defined by $HbA_{1c} > 8\%$. Subjects with controlled Type II diabetes were allowed, provided the disease had been stable at least three months prior to study entry;
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug. The investigator looked for evidence of any of the following: history of major gastrointestinal tract surgery (e.g. gastrectomy, gastroenterostomy, or small bowel resection), gastritis, current active ulcers, gastrointestinal, or rectal bleeding. Current active or recurrent irritable bowel syndrome (IBS) or history of inflammatory bowel syndrome. Subjects with a past history of IBS without symptoms for at least six months prior to the study start were allowed to enter the study;
- Any history of pancreatic injury or pancreatitis, or impaired pancreatic function/injury as indicated by abnormal lipase or amylase;
- Liver injury as indicated by serum transaminase levels [ALAT/SGPT] or [ASAT/SGOT] $> 1.5 \times$ ULRR over the lead-in period. The ALAT and ASAT levels must have been $\leq 1.5 \times$ ULRR on at least two of the three evaluations between Visit 1 (Week -8/-6) and Visit 3 (Week -1) for the subject to be eligible for further study participation. If ALAT and/or ASAT was $> 2 \times$ ULRR at any time point between Visit 1 (Week -8/-6) and Visit 3 (Week -1), the subject was immediately excluded from further study participation;
- Impaired renal function as indicated by serum creatinine levels $> 1.5 \times$ ULRR at Visit 1 (Week -8/-6). However, if creatinine was between 1.5 and $2 \times$ ULRR, one retest was permitted at Visit 2 (Week -2), provided all other criteria were fulfilled. Only subjects with serum creatinine of $\leq 1.5 \times$ ULRR at the retest were eligible for further study participation. If serum creatinine was $> 2 \times$ ULRR at Visit 1 (Week -8/-6), the subject was immediately excluded from further study participation;
- Current obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions, which was likely to require intervention during the course of the study or was regarded as clinically meaningful by the investigator;
- Serum CK $> 5 \times$ ULRR. However, if at Visit 1 (Week -8/-6) serum CK was $> 5 \times$ ULRR without a clinical explanation, one re-test was allowed. If the repeat CK was $> 5 \times$ ULRR in the absence of conditions explaining the CK elevation the subject was immediately excluded from further study participation;
- Uncontrolled hypothyroidism defined as TSH $> ULRR$. Subjects with TSH $> ULRR$ at Visit 1 were permitted to have a retest at Visit 2 and if TSH was also $> ULRR$ at Visit 2 the subject was excluded from the study;
- Any severe acute illness or severe trauma in the last three months prior to Visit 1 (Week -8/-6);
- Major surgery, during the three months prior to Visit 1 (Week -8/-6);
- Significant CVD prior to randomization, such as myocardial infarction, coronary or peripheral artery angioplasty, bypass graft surgery or severe or unstable angina pectoris within the last three months;

- Evidence of symptomatic heart failure NYHA class III or IV, gross cardiac enlargement (cardiothoracic ratio >0.5); significant heart block or cardiac arrhythmias. History of uncontrolled complex ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardias with a ventricular response rate of >100 beats per minute at rest. Subjects whose electrophysiological instability are controlled with a pacemaker or implantable cardiac device were eligible;
- Left ventricular (LV) ejection fraction <0.25;
- History of symptomatic cerebrovascular disease including cerebrovascular hemorrhage or ischemia, transient ischemic attack, or carotid endarterectomy within one month prior to randomization;
- Any other medical or surgical conditions at the discretion of the investigator which placed the subject at higher risk derived from his/her participation in the study, could confound the result of the study, or were likely to prevent the subject from complying with the requirements of the study or completing the study period;
- Known HIV infection;
- Poorly controlled or uncontrolled hypertension. Only subjects with SBP ≤160 mm Hg and DBP ≤90 mm Hg with or without antihypertensive therapy;
- Prior or current known muscular or neuromuscular disease of any type;
- Current active neoplastic disease or subjects who may require antineoplastic treatment during the course of the study. History of prior malignancy except those subjects who had been cancer free for >10 years. Subjects with prior history of basal cell carcinoma or squamous cell carcinoma of the skin remained eligible if they had been cancer free for >5 the past years;
- Within the last two years, a history of drug abuse or continuous consumption of more than 65 mL pure alcohol per day (e.g., more than 4 x 125-mL glasses of wine or three glasses of spirits per day);
- Exposure to any investigational new drug within 30 days of study entry (Visit 1/Week -8/-6) or ingestion of any drug known to be toxic to a major organ system (such as those producing blood dyscrasias, nephrotoxicity, hepatotoxicity or neurotoxicity) 12 weeks prior to the study entry (Visit 1/Week -8/-6);
- Current or recent (within four weeks of Visit 1/Week -8/-6) use of supplements known to alter lipid metabolism e.g. soluble fibers (including >2 teaspoons Metamucil or psyllium containing supplement per day), or other dietary fiber supplements, fish oils, or other products at the discretion of the investigator;
- History of hypersensitivity reactions to other HMG-CoA reductase inhibitors;
- Any of the following concomitant medications:
 1. All agents used for or under investigation for lowering or modifying plasma lipid levels, including statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors (including ezetimibe), and nicotinic acid >500 mg per day.

Subjects on these medications could participate in the study, provided treatment was interrupted at least 8 weeks prior to randomization;

2. Oral contraceptives or any systemic steroid hormones (including estrogens, progestins, androgens or glucocorticoids) for any condition, except for noncyclic (continuous) administration of estrogen/progesterone replacement therapy or sustained contraceptive preparations (e.g., implants or IM injections) which must have been constant for at least the last three months prior to study entry (Visit 1/Week -8/-6) and were anticipated to remain unchanged for the duration of the study. Subjects on systemic steroidal treatment could enter the study if the treatment was discontinued at least four weeks prior to Visit 1 (Week -8/-6). Steroid hormones administered topically or as inhalers were permitted. NSAIDs were allowed, provided dosing was stable for at least four weeks prior to entry into the study but were disallowed if used for immunosuppressive therapy;
 3. Anticoagulants and antiplatelet drugs, other than aspirin or ticlopidine in stable doses. Use of aspirin for pain relief, when required, was allowed;
 4. HIV protease inhibitors;
 5. Cyclosporine;
 6. Systemic azole antifungal agents (e.g., itraconazole or ketoconazole);
 7. Nefazodone (antidepressant);
 8. Continuous systemic erythromycin, clarithromycin and telithromycin. Brief systemic or topical courses of these macrolides for sporadic infections/illness did not result in exclusion;
 9. Danazol (gonadotropin inhibitor);
 10. Grapefruit and grapefruit juice; and
 11. Glitazones/thiazolidinediones (pioglitazone, rosiglitazone).
- History of resistance to lipid-lowering medications. Known hypersensitivity or intolerance to any lipid-lowering agent, i.e., elevated transaminases, myositis;
 - Excessive obesity defined as BMI above 35 kg/m². BMI values were rounded to the nearest whole number: down at <0.5 and up at ≥0.5;
 - Any factor which made regular clinic attendance in the morning impractical (e.g., shift and/or night work); and/or
 - Any signs of mental dysfunction or other factors (including language problems) likely to limit the ability of the subject to cooperate with the performance of the study.

Exceptions to the exclusion criteria:

Subjects using the following medications were permitted to enter the study provided the therapy had been stable before study entry (Visit 1/Week -8/-6) for the time indicated below and a change in dose or treatment were unlikely during the course of the study:

1. Therapy for hyperthyroidism or hypothyroidism stable for at least two months prior to **Visit 1 (week -8/-6), provided subject's baseline (Visit 1 or retest at Visit 2) serum TSH** was within the normal range (i.e., subjects presents controlled hypo- or hyperthyroidism);
2. Antihypertensive therapy stable for at least the last two months prior to Visit 1 (Week -8/-6);
3. Estrogen receptor modulators (e.g., raloxifene) for prevention of osteoporosis stable for at least three months prior to Visit 1 (Week -8/-6);
4. Non-cyclic (continuous) estrogen/progesterone preparations for hormone replacement therapy or sustained contraceptive preparations (e.g., implants or IM injections) stable for at least the three months prior to Visit 1 (Week -8/-6); and/or

Hypoglycemic agents excluding thiazolidinediones (glitazones) if subjects with stable Type II diabetes were enrolled. Subjects must have been instructed to inform the investigator before taking any new medication for the duration of the study, including over-the-counter medications and natural products. Any permitted concomitant medications should have been kept as stable as possible for the duration of the study.

Removal of subjects from therapy or assessment:

The investigator was to document whether or not each subject completed the clinical study. Subjects who, after randomization, discontinued prematurely from the study were not replaced. All subjects who discontinued early were encouraged to complete all efficacy and safety evaluations corresponding to Visit 8 /Week 12 as soon as possible after discontinuation from study treatment.

If for any reason either study treatment or observations were discontinued, the reason was to be recorded. Reasons that a subject may have discontinued participation in a clinical study were considered to constitute one of the following:

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

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

Treatment:

Treatment was administered according to a double-dummy design. Each subject dose consisted of one small tablet, one large tablet, and one capsule taken orally once daily before bedtime with approximately 200mL of water. Either one of the tablets or the capsule was the active dose. The others were placebos.

Study Populations:

- **The Safety Population** was defined as all randomized subjects who received at least one dose of the study drug.
- **The Full Analysis Set** 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. In this study, the ITT population was referred to as the FAS.
- **The Per Protocol Population** was defined as all subjects in the FAS, who had no major protocol violations, and who had an on-treatment lipid assessment at Week 12 (Visit 8).
- **The Completers** population was defined as all subjects, irrespective of protocol violations, who had a Week 12 (last week of measurement) measurements, whether or not on drug.

The FAS was the primary population used for the efficacy analyses, and the PP and COM populations were used for confirmation analysis of the efficacy endpoints.

Sample Size Justification

A sample size of 800 randomized subjects was planned, with 300 subjects in the pitavastatin 2 mg and pitavastatin 4 mg groups and 100 subjects in the atorvastatin 10 mg and atorvastatin 20 mg groups. Assuming a SD of 12 (for percent reduction from baseline LDL), a non-inferiority limit of 6% for the treatment difference and a 1-tailed test at 2.5% significance level, this sample size would provide 99% power to reject the null hypothesis that the mean percent decrease from baseline LDL was at least 6% greater in the atorvastatin groups than in the pitavastatin groups vs. the alternative that any advantage in the atorvastatin groups is less than the non-inferiority limit.

Statistical Analysis of the Primary Efficacy Variable:

The percent change in LDL from baseline to 'endpoint' for the FAS and the percent change in LDL from baseline to Week 12 (Visit 8) for the PP and COM Population were analyzed ANCOVA including treatment and country as factors and the baseline LDL as a covariate.

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

In order to test the assumptions of the ANCOVA, the different treatment covariate slopes were compared by including the treatment × covariate term in the model. In addition, normality was assessed.

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

- Age (<65 years, ≥ 65 years);
- Sex (Male, Female);
- Race (Caucasian, Non-Caucasian);
- BMI (<25 kg/m², 25 - <30 kg/m², ≥30 kg/m²);
- Risk Category (Low, Moderate, High [as defined by NCEP Guidelines]);
- Baseline LDL (<160 mg/dL, 160-<190 mg/dL, ≥190 mg/dL);
- Hypertension (Yes, No);
- Diabetes (Yes, No);
- Primary Diagnosis (Primary Hypercholesterolemia, Combined dyslipidemia, Heterozygous familial hypercholesterolemia).

Treatment × subgroup interactions were tested within the ANCOVA for those subgroups where all levels of the subgroup included ≥ 5% of subjects. The analysis was also performed using logistic regression, including treatment, country and risk categories as factors and baseline LDL as a covariate, using the two models. If iterative calculations met the convergence criteria with the linear probability model, the results of these analyses were to be presented.

Summary statistics of the percent change in LDL from baseline to endpoint were presented by treatment for each level of each subgroup. The interaction of treatments and levels of the subgroups was tested.

Statistical Analysis of the Secondary Efficacy Variable:

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

The LDL targets were calculated using data collected prior to randomization, based on the NCEP 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 (categorized as defined in the NCEP guidelines), as factors in the model. Point estimates (and 95% CI) on the differences between the pitavastatin groups and the corresponding atorvastatin groups are presented.

Protocol Amendments:

There were two amendments to Protocol NK-104-301:

Amendment 1:

The following change was made throughout the protocol:

1. The eligible LDL level of ≥ 130 mg/dl was changed to ≥ 160 mg/dl.

Amendment 2 was generated to address the potential gap between the core study and the follow-up study, the potential effect of glitazones, and additional proteinuria evaluation. The resultant changes were:

1. Provided guidance on the procedure to be followed during the gap between the core study and the follow-up study.
2. Excluded glitazones as an allowed concomitant medication for diabetes.
3. Allowed glitazones/thiazolidinediones (pioglitazone, rosiglitazone) as prohibited concomitant medications.
4. Additional urine protein assessments were to be performed at baseline (Visit 4, Week 0) and at end of treatment (Visit 8, Week 12) to investigate if statin treatment may cause proteinuria.
5. Addition of notification/clarification changes.

Changes in the Planned Analyses:

The final SAP was issued prior to unblinding (26 March 2007) and was amended twice (4 July 2007 and 11 July 2007) after unblinding in order to modify the intervals of baseline LDL (i.e., <160 , 160 - <190 and ≥ 190 mg/dL) used in the linear probability model for the analysis of target LDL attainment and to include analyses of the quantitative assessment of urine protein:creatinine ratio. The following changes were made to the planned analyses prior to unblinding .

The protocol specified that baseline lipid values would be calculated as the mean of the values obtained at Week -2 (Visit 2) and Week -1 (Visit 3). However, for LDL, TC, HDL, non-HDL, TG, TC:HDL ratio and non-HDL:HDL ratio, the baseline was calculated as the mean of the lipid measurements from Week -2 (Visit 2), Week -1 (Visit 3) and Week 0 (Visit 4). If Visit 3A was required, the baseline value was the mean from Week -1 (Visit 3), Week -1 Repeat (Visit 3A) and Week 0 (Visit 4). **If the subject's Visit 4 (Week 0) blood sample was taken after the first dose of study drug, baseline was calculated as the mean of Week -2 (Visit 2) and Week -1 (Visit 3) or Week -1 (Visit 3) and Week 1 Repeat (Visit 3A) as applicable.**

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

Protocol Violations and Deviations:

A total of 180 subjects (22%) were excluded from the per protocol population, 47 (6%) due to not having a Week 12 lipid assessment.

The most frequently reported violations that resulted in the exclusion of subjects from the PP population were lack of compliance, taking lipid-lowering drugs, or other prohibited medications

during the run-in or treatment period, and Week 12 fell outside of the +/- 14 day window. Protocol violations were proportional in all four groups.

Disposition of subjects:

Subject Disposition

	Pitavastatin 2 mg QD	Atorvastatin 10 mg QD	Pitavastatin 4 mg QD	Atorvastatin 20 mg QD
Number (%) of subjects Randomized	321 (100.0)	103 (100.0)	303 (100.0)	103 (100.0)
Safety Population	316 (98.4)	102 (99.0)	300 (99.0)	103 (100.0)
Full Analysis Set (FAS)	315 (98.1)	102 (99.0)	298 (98.3)	102 (99.0)
Completers (COM) Population	301 (93.8)	98 (95.1)	288 (95.0)	100 (97.1)
Per Protocol Population (PP)	236 (73.5)	82 (79.6)	250 (82.5)	82 (79.6)
Prematurely Discontinued From Study During Active Treatment	15 (4.7)	4 (3.9)	13 (4.3)	4 (3.9)
Reason for Discontinuation - Active Treatment:				
Adverse event	5 (1.6)	0	5 (1.7)	0
Abnormal laboratory value(s)	1 (0.3)	0	1 (0.3)	0
Protocol violation	3 (0.9)	0	2 (0.7)	1 (1.0)
Subject withdrew consent	4 (1.2)	2 (1.9)	1 (0.3)	1 (1.0)
Subject lost to follow up	1 (0.3)	2 (1.9)	3 (1.0)	2 (1.9)
Administrative problems	1 (0.3)	0	1 (0.3)	0

Investigators at 39 centers randomized a total of 830 subjects: 624 subjects were randomized to treatment with pitavastatin, and 206 to atorvastatin. Of the 830 subjects randomized, 821 received at least one dose of study drug (Safety Population), 616 took pitavastatin and 205 took atorvastatin. Nine subjects were randomized but did not participate in the study and did not receive study drug, primarily due to protocol violations. Overall, 58% of subjects were randomized at 15 centers in Russia, 24% at 12 centers in India, 10% at nine centers in Spain, and 8% at three centers in Denmark. The greatest percentage of subjects randomized at a single center was 8% of all subjects, at Center 1214 in Russia.

Demographic and Other Baseline Characteristics:

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

Demographic and Other Baseline Characteristics (Safety Population)				
Demographic Characteristic	Pitavastatin 2 mg QD (N=316)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=300)	Atorvastatin 20 mg QD (N=103)
Sex (n, %)				
Male	142 (44.9)	52 (51.0)	136 (45.3)	48 (46.6)
Female	174 (55.1)	50 (49.0)	164 (54.7)	55 (53.4)
Age (years)				
Mean (SD)	58.4 (9.51)	59.2 (8.63)	57.9 (10.10)	58.0 (9.14)
Range	23 - 75	28 - 74	18 - 74	35 - 73
Age group (n, %)				
<35 years	5 (1.6)	1 (1.0)	7 (2.3)	0
35-39 years	6 (1.9)	0	12 (4.0)	5 (4.9)
40-44 years	12 (3.8)	5 (4.9)	16 (5.3)	4 (3.9)
45-49 years	32 (10.1)	6 (5.9)	20 (6.7)	5 (4.9)
50-54 years	49 (15.5)	17 (16.7)	42 (14.0)	20 (19.4)
55-59 years	58 (18.4)	25 (24.5)	50 (16.7)	24 (23.3)
60-64 years	57 (18.0)	21 (20.6)	60 (20.0)	15 (14.6)
65-69 years	61 (19.3)	17 (16.7)	70 (23.3)	20 (19.4)
70-74 years	34 (10.8)	10 (9.8)	23 (7.7)	10 (9.7)
≥75 years	2 (0.6)	0	0	0
Race (n, %)				
Caucasian	238 (75.3)	79 (77.5)	232 (77.3)	79 (76.7)
Black	0	0	0	0
Asian	1 (0.3)	0	0	0
Hispanic	0	0	0	0
Indian	77 (24.4)	23 (22.5)	68 (22.7)	24 (23.3)
Other	0	0	0	0
Diagnosis (n, %)				
Primary hypercholesterolemia	250 (79.1)	80 (78.4)	236 (78.7)	81 (78.6)
Combined dyslipidemia	65 (20.6)	21 (20.6)	62 (20.7)	22 (21.4)
Familial hypercholesterolemia ¹	1 (0.3)	1 (1.0)	2 (0.7)	0
Duration of current disease (years)				
Mean (SD)	3.352 (3.94)	3.400 (3.95)	3.021 (4.29)	3.366 (3.66)
Range	-0.03 - 22.92	0.00 - 16.04	-0.08 - 29.14	0.00 - 15.02
Height (m)				
Mean (SD)	1.65 (0.09)	1.66 (0.09)	1.65 (0.09)	1.66 (0.09)
Range	1.4 - 2.0	1.4 - 1.9	1.4 - 1.9	1.4 - 1.9
Weight (Kg)				
Mean (SD)	74.75 (11.4)	75.92 (12.9)	75.03 (12.58)	75.50 (12.28)
Range	40.0 - 108.0	31.5 - 111.0	45.0 - 124.3	48.0 - 102.8
BMI (kg/m²)				
Mean (SD)	27.32 (3.38)	27.49 (3.66)	27.46 (3.54)	27.30 (3.78)
Range	17.0 - 35.3	13.1 - 34.9	19.4 - 34.9	18.1 - 34.9
Baseline lipids				
LDL (mg/dL)				
Mean (SD)	183.49 (16.79)	179.76 (16.85)	181.81 (16.82)	181.81 (16.69)
Range	148.7 - 232.3	152.7 - 229.7	136.0 - 224.0	146.0 - 225.3
HDL (mg/dL)				
Mean (SD)	48.50 (11.4)	50.16 (11.7)	49.92 (12.2)	48.65 (12.9)
Range	26.0 - 85.3	31.3 - 89.7	26.0 - 89.0	25.0 - 90.0
TC (mg/dL)				
Mean (SD)	263.50 (22.7)	261.30 (22.6)	263.26 (22.1)	262.63 (22.5)
Range	213.3 - 356.3	222.0 - 337.7	201.7 - 326.0	208.3 - 318.0

(Continued) Demographic and Other Baseline Characteristics (Safety Population)				
Demographic Characteristic	Pitavastatin 2 mg QD (N=316)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=300)	Atorvastatin 20 mg QD (N=103)
TG (mg/dL)				
Mean (SD)	157.70 (56.0)	156.84 (60.7)	157.36 (58.0)	161.03 (66.4)
Range	60.0 - 352.7	68.7 - 360.0	52.3 - 374.0	49.0 - 386.0
NCEP Risk category² (n, %)				
High	160 (50.6)	46 (45.1)	133 (44.3)	50 (48.5)
Moderate	77 (24.4)	27 (26.5)	52 (17.3)	21 (20.4)
Low	79 (25.0)	29 (28.4)	115 (38.3)	32 (31.1)
Diabetes (n, %)				
Present	26 (8.2)	12 (11.8)	14 (4.7)	14 (13.6)
Hypertension (n, %)				
Present	208 (65.8)	67 (65.7)	188 (62.7)	65 (63.1)
Smoking Status (n, %)				
Current Smoker	47 (14.9)	12 (11.8)	35 (11.7)	14 (13.6)
Ex-Smoker	39 (12.3)	16 (15.7)	30 (10.0)	12 (11.7)
Alcohol Consumption (n, %)				
Regular	9 (2.8)	3 (2.9)	6 (2.0)	4 (3.9)
Excessive	0	0	1 (0.3)	0
CHD or CHD Risk Equivalents at Screening (n, %)				
Clinical coronary heart disease	124 (39.2)	38 (37.3)	118 (39.3)	38 (36.9)
Symptomatic carotid artery disease	2 (0.6)	1 (1.0)	6 (2.0)	2 (1.9)
Peripheral arterial disease	11 (3.5)	2 (2.0)	5 (1.7)	4 (3.9)
Abdominal aortic aneurysm	1 (0.3)	0	0	0
Diabetes	26 (8.2)	12 (11.8)	14 (4.7)	14 (13.6)
Major Cardiovascular Risk Factors at Week 0 (n, %)				
Hypertension - treated	199 (63.0)	60 (58.8)	175 (58.3)	65 (63.1)
Hypertension - untreated	9 (2.8)	7 (6.9)	13 (4.3)	0
Family history of premature CHD	37 (11.7)	11 (10.8)	22 (7.3)	9 (8.7)
Systolic Blood Pressure at Week 0 (n, %)				
≥ 160 mmHg	2 (0.6)	1 (1.0)	0	0

A total of 46% of subjects in the Safety Population were male and this balance was reflected across the treatment groups. The mean age of the subjects was approximately 58 years in each treatment group and ages ranged from 18 to 75 years across groups. The majority of subjects 76% were Caucasian; 23% were Indian, and one subject was Asian.

The treatment groups were well matched in terms of baseline LDL values. Baseline mean LDL ranged from 179.8 mg/dL to 183.5mg/dL across the treatment groups. Similarly, there were no meaningful differences between the groups in mean baseline HDL, TC and TG. Baseline mean HDL from between 48.5mg/dL to 50.2 mg/dL, TC ranged from 261.3 mg/dL to 263.5mg/dL, and TG ranged from 156.8 mg/dL to 161.0 mg/dL across the treatment groups.

The treatment groups were well matched in terms of diagnosis and duration of disease. Approximately 79% of subjects in each treatment group had primary hypercholesterolemia, ranging from 78.4% to 79.1% and most of the remainder had combined dyslipidemia. Mean duration of disease was similar across the treatment groups.

There was a statistically significant difference among treatment groups in the distribution of subjects in the three NCEP risk categories for major coronary events ($P=0.018$) and in the proportion of subjects with diabetes ($P=0.013$).

The presence of hypertension was balanced across groups; it ranged from 63% to 66%.

There were no differences between the groups in vital statistics (height, weight and BMI).

Baseline Characteristics:

Approximately 13% of subjects (range 12% to 15% across all treatment groups) were smokers at baseline. The majority of subjects ($\geq 73\%$) in all treatment groups were non-smokers or ex-smokers. More than half of subjects did not consume alcohol (range 60% to 63% across all treatment groups). The risk of CHD was balanced across the treatment groups, ranging between 37% and 39%. The treatment groups were balanced at baseline with respect to mean lipid values. There were a few categories of note:

- The proportion of subjects with LDL in the category 160 to <190 mg/dL ranged between 60% and 69% across all treatment groups, and the proportion of subjects with LDL in the category ≥ 190 mg/dL ranged between 25% and 36%.
- The proportion of subjects with HDL in the category ≥ 60 mg/dL ranged between 17% and 22% across all treatment groups.
- The proportion of subjects with TC in the category 240 to <280 mg/dL ranged between 62% and 65% across all treatment groups, and the proportion of subjects with TC in the category 200 to <240 mg/dL ranged between 13% and 18%.
- The proportion of subjects with treated hypertension ranged between 58% and 63% across all treatment groups.

Between 87% and 91% of subjects in each treatment group had one or more diagnoses on their medical history. The most common organ systems with medical history were cardiovascular (ranged between 71% and 75%) and endocrine (ranged between 29% and 42%).

The number of subjects in each treatment group who were taking lipid-lowering medications prior to enrollment ranged between 39% and 46% across all treatment groups. The most common prior lipid-lowering medication was simvastatin, with 178 subjects (between 17% and 24% of subjects in any treatment group) taking this medication. The second most common lipid-lowering medication was atorvastatin, which was taken by 146 subjects (between 17% and 21% of subjects in any treatment group).

Treatment Compliance:

No subjects were noncompliant with the dietary restrictions. The percent drug treatment compliance by treatment group is summarized in the following table:

Treatment Compliance (Safety Population)

	Pitavastatin 2 mg QD (N=316)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=300)	Atorvastatin 20 mg QD (N=103)
Overall %Compliance				
N=	316	102	299	103
Mean (SD)	97.9 (4.79)	97.5 (6.91)	97.7 (5.34)	97.8 (8.29)
Median	100.0	100.0	100.0	100.0
Quartiles	97.6, 100.0	96.8, 100.0	97.6, 100.0	98.0, 100.0
Range	54 - 107	39 - 107	67 - 110	22 - 108

Analysis of Efficacy:

Primary Efficacy Analysis - Mean Percent Change From Baseline in LDL :

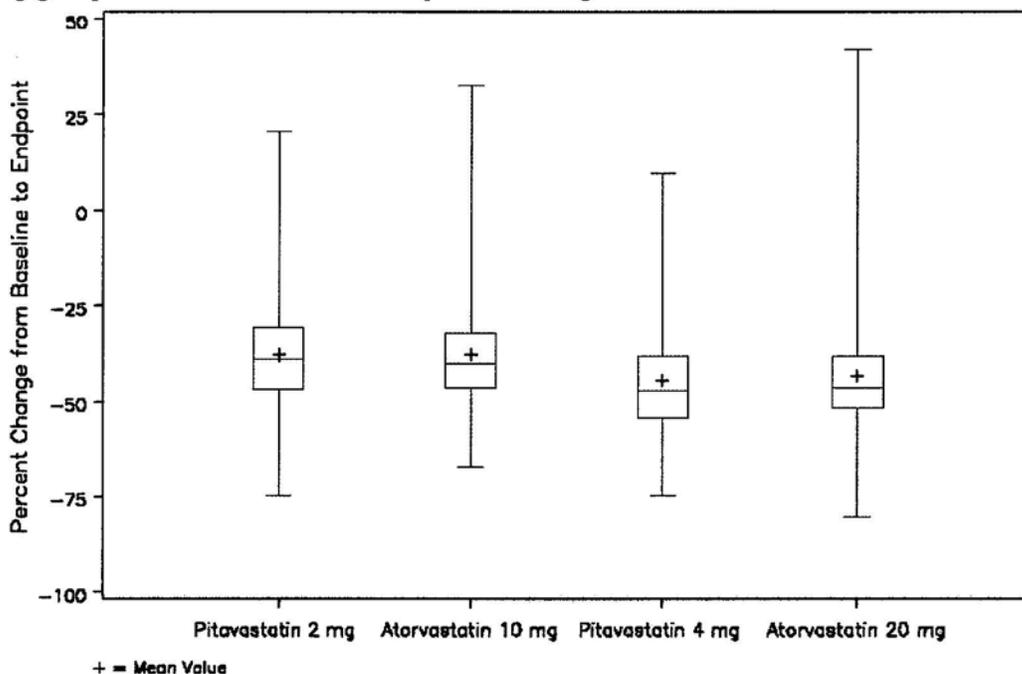
The percent change in LDL from baseline to endpoint (i.e., Week 12 or the last on treatment assessment) for the FAS, and to Week 12 for the PP and COM Populations, is presented in the following table.

Change from Baseline to Endpoint or Week 12 in LDL (mg/dL) FAS population

	Pitavastatin 2 mg QD	Atorvastatin 10 mg QD	Pitavastatin 4 mg QD	Atorvastatin 20 mg QD
N	315	102	298	102
Baseline LDL				
Mean (SD)	183.6 (16.76)	179.8 (16.85)	182.0 (16.72)	181.9 (16.73)
Endpoint LDL				
Mean (SD)	113.9 (27.96)	111.5 (28.21)	100.3 (26.86)	102.5 (31.00)
% change from baseline to endpoint				
Mean (SD)	-37.91 (13.97)	-37.81 (15.60)	-44.61 (14.98)	-43.53 (16.15)
Adjusted Mean Difference (95% CI)	-0.15 (-3.42; 3.11)		0.96 (-2.32; 4.24)	
P-value	0.926		0.565	

The values for the PP and COM populations were similar.

The percent change from baseline in LDL at the study endpoint in the FAS population in all four dosing groups are illustrated in the box plot following:



For the change from baseline to endpoint in LDL, pitavastatin was non-inferior to atorvastatin for both the low (pitavastatin 2 mg vs. atorvastatin 10 mg) and high (pitavastatin 4 mg vs. atorvastatin 20 mg) dose group comparisons in the FAS, PP, and COM populations.

In the two high-dose groups (pitavastatin 4 mg and atorvastatin 20 mg) the reductions in LDL increased through Week 8 of treatment and then leveled off at Week 12.

Secondary Efficacy Variables:

Secondary Efficacy Variable: LDL Target Attainment:

Target LDL goals were met in a higher percentage of subjects taking the pitavastatin 4 mg and atorvastatin 20 mg doses as compared to the pitavastatin 2 mg and atorvastatin 20 mg doses. However, using goals as defined by NCEP criteria showed that the lower dose group seemed to show an advantage for atorvastatin 10 mg while the high-dose comparison showed an apparent advantage for pitavastatin 4 mg, as shown in the tables below:

Subjects With LDL Target Attainment (FAS)

	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
Target attained according to NCEP criteria (n, %)				
Yes	179 (56.8)	67 (65.7)	232 (77.9)	72 (70.6)
No	136 (43.2)	35 (34.3)	66 (22.1)	30 (29.4)
Difference ¹	8.9		-7.3	
(95% CI)	(-1.9; 19.6)		(-17.3; 2.8)	
P-value	0.105		0.155	
Adjusted proportion achieving target ²	66.4%	73.8%	85.3%	81.3%
Adjusted Mean Difference	7.4		-4.0	
(95% CI)	(-2.8; 17.5)		(-14.2; 6.2)	
P-value	0.156		0.438	
Adjusted proportion achieving target ³	66.6%	71.2%	78.2%	76.4%
Adjusted Mean Difference	4.6		-1.7	
(95% CI)	(-4.8; 14.1)		(-9.1; 5.7)	
P-value	0.336		0.648	

LDL Sub-Group Analyses:

There were no subgroups with markedly different outcomes from the overall FAS analysis, and no significant treatment by subgroup interactions, although some minor differences were noted.

With respect to age (<65, ≥65 years), there tended to be greater reductions in LDL among the elderly. There were no apparent gender differences in the low-dose groups. However, the reductions in LDL were greater in females in both high-dose groups. Caucasians tended to have higher baseline LDL values and greater reductions in LDL than the non-Caucasians (primarily Indians).

No effect was observed in the sub-group analyses by CHD risk category. There did seem to be greater reductions in LDL in subjects with a diagnosis of primary hypercholesterolemia than in subjects with combined dyslipidemia.

Secondary Efficacy Lipid Variable: Total cholesterol (TC):

The secondary efficacy lipid variable TC for the FAS is summarized in the following table:

Percent Change from Baseline in Total cholesterol (FAS)				
	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
TC (mg/dL)				
Baseline Mean (SD)	263.6 (22.70)	261.3 (22.62)	263.3 (22.18)	262.7 (22.56)
Mean % Change (SD)	-27.68 (10.47)	-28.08 (12.48)	-32.42 (11.50)	-32.69 (12.32)
Adjusted Mean Difference	-0.52		-0.37	
(95% CI)	(-3.02; 1.98)		(-2.88; 2.14)	
P-value	0.684		0.773	

Total cholesterol decreased 27.7% in the pitavastatin 2 mg group and 28.1% in the atorvastatin 10 mg group. In the high-dose groups, TC decreased 32.4% in pitavastatin 4 mg and 32.7% in atorvastatin 20 mg. The adjusted mean differences were not statistically significant for the low or high-dose group comparisons (P=0.684 and P=0.773, respectively).

Secondary Efficacy Lipid Variable: HDL:

The secondary efficacy lipid variable HDL for the FAS is summarized in the following table:

Change from Baseline in HDL (FAS)				
	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
HDL (mg/dL)				
Baseline Mean (SD)	48.5 (11.37)	50.2 (11.69)	49.9 (12.27)	48.4 (12.81)
Mean % Change (SD)	4.03 (16.53)	3.04 (16.88)	5.04 (16.66)	2.47 (13.72)
Adjusted Mean Difference (95% CI)	-0.36 (-3.86; 3.14)		-2.98 (-6.51; 0.54)	
P-value	0.840		0.097	

HDL increased 4.03% in the pitavastatin 2 mg group and 3.04% in the atorvastatin 10 mg group and 5.04% in the pitavastatin 4 mg group and 2.47% in the atorvastatin 20 mg group. Although the adjusted mean differences favored pitavastatin, they were not statistically significant for either comparison (P=0.840 and 0.097, respectively).

Secondary Efficacy Lipid Variables: Non-HDL cholesterol:

The secondary efficacy lipid variable non-HDL cholesterol for the FAS is summarized in the following table:

Percent Change from Baseline in Non-HDL cholesterol (FAS)				
	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
Non-HDL (mg/dL)				
Baseline Mean (SD)	215.1 (21.17)	211.1 (22.55)	213.3 (21.02)	214.3 (22.86)
Mean % Change (SD)	-34.67 (13.020)	-35.16 (15.158)	-41.10 (14.16)	-40.57 (15.137)
Adjusted Mean Difference (95% CI)	-0.63 (-3.71; 2.45)		0.47 (-2.62; 3.56)	
P-value	0.688		0.766	

Non-HDL cholesterol values decreased 34.67% from baseline in the pitavastatin 2 mg group and 35.16% in the atorvastatin 10 mg group. The adjusted mean differences were not statistically significantly different (P=0.688). In the pitavastatin 4 mg and atorvastatin 20 mg groups the decreases were 41.10% and 40.57%, respectively, and the adjusted mean differences were not statistically significantly different (P=0.766).

Secondary Efficacy Lipid Variables: Triglycerides:

The secondary efficacy lipid variable TG is summarized for the FAS in the following table:

Percent Change from Baseline in Triglycerides (FAS)				
	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
TG (mg/dL)				
Baseline Mean (SD)	157.8 (56.1)	156.8 (60.7)	156.8 (57.3)	161.9 (66.1)
Mean % Change (SD)	-14.09 (28.8)	-17.70 (29.9)	-19.05 (24.6)	-22.25 (24.0)
Adjusted Mean Difference (95% CI)	-3.57 (-9.47; 2.33)		-2.83 (-8.77; 3.12)	
P-value	0.236		0.351	

Triglycerides decreased in all treatment groups. In the pitavastatin 2 mg group and the atorvastatin 10 mg group, the decreases from baseline were 14.09% and 17.70%, respectively. In the pitavastatin 4 mg group and the atorvastatin 20 mg group, the decreases from baseline were 19.05% and 22.25%, respectively. The adjusted mean differences were not statistically significant in the comparison of either the low or high-dose groups (P=0.236 and P=0.351, respectively).

Secondary Efficacy Lipid Variable: TC:HDL Ratio:

The secondary efficacy lipid variable TC:HDL ratio for the FAS is summarized in the following table:

Change from Baseline in TC:HDL Ratio (FAS)				
	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
TC:HDL Ratio				
Baseline Mean (SD)	5.73 (1.23)	5.48 (1.19)	5.59 (1.30)	5.81 (1.42)
Mean Change (SD)	-1.71 (0.98)	-1.64 (1.06)	-1.97 (1.03)	-1.99 (1.12)
Adjusted Mean Difference (95% CI)	-0.048 (-0.239; 0.143)		0.072 (-0.120; 0.264)	
P-value	0.625		0.461	

The TC:HDL ratio decreased approximately 1.71 in the pitavastatin 2 mg dose group and 1.64 in the atorvastatin 10 mg group and 1.92 for pitavastatin 4 mg and 1.982 for atorvastatin 20 mg. The adjusted mean differences were not statistically significant for either comparison (P=0.625 and P=0.461, respectively).

Secondary Efficacy Lipid Variables: Apolipoproteins:

The secondary efficacy lipid variables Apo-B, Apo-A1, and Apo-B:Apo-A1 ratio from the FAS are summarized in the following table:

Percent Change from Baseline in Apolipoproteins (FAS)				
	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
Apo-B (mg/dL)				
Baseline Mean (SD)	164.1 (21.59)	161.3 (22.34)	162.3 (22.26)	162.9 (25.65)
Mean % Change (SD)	-29.76 (13.76)	-29.13 (17.56)	-35.33 (14.96)	-35.54 (14.52)
Adjusted Mean Difference (95% CI)	0.18 (-2.98; 3.34)		-0.08 (-3.26; 3.10)	
P-value	0.912		0.961	
Apo-A1 (mg/dL)				
Baseline Mean (SD)	155.2 (26.10)	157.9 (25.64)	158.5 (26.48)	154.6 (26.38)
Mean % Change (SD)	6.48 (14.36)	6.37 (14.00)	5.59 (13.71)	4.51 (13.92)
Adjusted Mean Difference (95% CI)	0.20 (-2.71; 3.11)		-1.97 (-4.90; 0.96)	
P-value	0.894		0.188	
Apo-B:Apo-A1 Ratio				
Baseline Mean (SD)	1.09 (0.23)	1.05 (0.23)	1.06 (0.243)	1.10 (0.28)
Mean Change (SD)	-0.37 (0.22)	-0.36 (0.22)	-0.41 (0.22)	-0.42 (0.22)
Adjusted Mean Difference (95% CI)	-0.01 (-0.05; 0.03)		0.01 (-0.03; 0.05)	
P-value	0.648		0.551	

Apo-B decreased in the low-dose group (29.8% in the pitavastatin 2 mg group and 29.1% in the atorvastatin 10 mg group) and in the high-dose group (35.3% in the pitavastatin 4 mg group and 35.5% in the atorvastatin 20 mg group). The adjusted mean differences were not statistically significant (P=0.912 and P=0.961, respectively) in either comparison. Apo-A1 increased 6.5% from baseline in the pitavastatin 2 mg group, 6.37% in the atorvastatin 10 mg group, 5.6% in the pitavastatin 4 mg group, and 4.5% in the atorvastatin 20 mg group. The adjusted mean differences were not statistically significant for the comparisons of the low and high-dose groups (P=0.894 and P=0.188, respectively). The Apo-B:Apo-A1 ratio decreased from baseline for all treatment groups: 0.37 in the pitavastatin 2 mg group, 0.36 in the atorvastatin 10 mg group, 0.41 in the pitavastatin 4 mg group, and 0.42 for the atorvastatin 20 mg group. The adjusted mean differences were not statistically significant for the comparison of the low or high-dose groups (P=0.648 and P=0.551, respectively).

Secondary Efficacy Lipid Variables: hsCRP:

The secondary efficacy lipid variable hsCRP in the FAS is summarized in the following table:

Change from Baseline in hsCRP (FAS)				
	Pitavastatin 2 mg QD (N=315)	Atorvastatin 10 mg QD (N=102)	Pitavastatin 4 mg QD (N=298)	Atorvastatin 20 mg QD (N=102)
hsCRP (mg/L)				
Baseline Mean (SD)	3.47 (5.40)	3.95 (6.79)	3.04 (4.12)	3.14 (3.63)
Mean % Change (SD)	-0.32 (7.92)	-1.65 (6.74)	0.09 (5.41)	-0.53 (3.52)
Adjusted Mean Difference (95% CI)	-0.99 (-2.24; 0.26)		-0.57 (-1.82; 0.69)	
P-value	0.0121		0.0377	

Mean hsCRP decreased from baseline in the low-dose group (0.32% in the pitavastatin 2 mg group and 1.65% in the atorvastatin 10 mg group). In the high-dose group, a mean increase from baseline was seen for pitavastatin 4 mg of 0.09%, and a mean decrease of 0.53% was seen for atorvastatin 20 mg. The adjusted mean differences were not statistically significant (P=0.121 and P=0.377, respectively) for either comparison.

Efficacy Conclusions:

- For the percent change from baseline to endpoint in LDL, pitavastatin was non-inferior to atorvastatin for both the low-dose (pitavastatin 2 mg vs. atorvastatin 10 mg) and high-dose (pitavastatin 4 mg vs. atorvastatin 20 mg) comparisons in the FAS population. The analysis of the percent change from baseline to Week 12 in the PP and COM populations supported the findings in the FAS population as shown in the summary following table:

LDL (mg/dL) Week 12, (FAS)	Pitavastatin 2 mg QD	Atorvastatin 10 mg QD	Pitavastatin 4 mg QD	Atorvastatin 20 mg QD
n=	315	102	298	102
Baseline mean (SD)	183.6 (16.8)	179.8 (16.9)	182.0 (16.7)	181.9 (16.7)
Mean % change (SD)	-37.9 (14.0)	-37.8 (15.6)	-44.6 (15.0)	-43.5 (16.2)
Adjusted Mean Difference (95% CI) p-value	-0.15 (-3.42; 3.1) 0.926		0.96 (-2.32; 4.2) 0.565	

- LDL target attainment was achieved in a higher percentage of subjects at the higher doses of pitavastatin and atorvastatin for the NCEP criteria.
- Using the NCEP criteria, the high-dose comparison showed an apparent advantage for pitavastatin 4 mg; while the low-dose comparison seemed to show an advantage for atorvastatin 10 mg; neither comparison was statistically significant.
- Pitavastatin 2 mg was comparable to atorvastatin 10 mg, and pitavastatin 4 mg was comparable to atorvastatin 20 mg, for the comparisons of the secondary lipid measures. No statistically significant differences in the adjusted means were observed.
- Decreases from baseline in TC, TG, non-HDL, TC:HDL ratio, Apo-B:Apo-A1 ratio and non-HDL:HDL ratio were comparable between the pitavastatin and atorvastatin low and high-dose groups, with no significant differences observed. Similarly, increases from baseline for Apo-A were comparable in the low and high-dose groups. Increases from baseline in HDL were somewhat greater in the pitavastatin groups but the differences were not statistically significant. Decreases from baseline in Apo-B were comparable within the low and high-dose groups. Treatment group differences in mean changes from baseline in hsCRP were not statistically significant.
- There were no subgroups with markedly different outcomes from the overall FAS analysis, and no significant treatment by subgroup interactions, although some minor differences were noted.
- In the analysis of change from baseline in LDL by subgroups, no statistically significant treatment by subgroup interactions were observed.

3.2 Study of Pitavastatin 2 mg vs. Simvastatin 20 mg and Pitavastatin 4 mg vs. Simvastatin 40 mg (Following Up-Titration) in subjects with Primary Hypercholesterolemia or Combined Dyslipidemia [NK-104-302]

Study initiation date: 13 September 2005

Study completion date: 4 October 2006

3.2.1.1 General Discussion of Study Objectives, Endpoints and Methods

Primary Objective:

To demonstrate the non-inferiority of pitavastatin 2 mg QD vs. simvastatin 20 mg QD and pitavastatin 4 mg QD vs. simvastatin 40 mg QD, with respect to the reduction of LDL, when administered for 12 weeks using an up-titration regimen for the higher doses (i.e., 4 mg pitavastatin and 40 mg simvastatin) in subjects with primary hypercholesterolemia or combined dyslipidemia.

Secondary Objective:

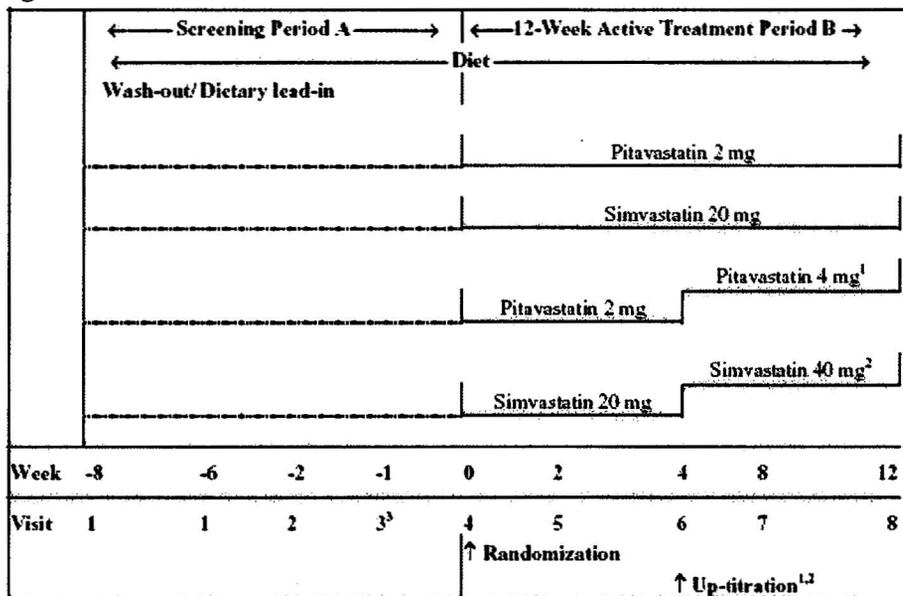
- To compare the efficacy of pitavastatin 2 mg QD vs. simvastatin 20 mg QD and pitavastatin 4 mg QD vs. simvastatin 40 mg QD with respect to LDL target attainment NCEP goals and changes in other lipid and lipoprotein fractions TC, HDL, TC:HDL ratio, non-HDL:HDL ratio, TG, Apo-B and Apo-A1, Apo-B:Apo-A1 ratio, hsCRP, and
- To assess the safety and tolerability of pitavastatin 2 mg QD vs. simvastatin 20 mg QD and pitavastatin 4 mg QD vs. simvastatin 40 mg QD when administered for 12 weeks using an up-titration regimen for the higher dose.

Study Design:

This was an 18 to 20 week, randomized, multicenter, double-blind, double-dummy, active-controlled study in subjects with primary hypercholesterolemia or combined dyslipidemia. Subjects who qualified entered a 6 to 8 week wash-out/dietary lead-in period followed by a 12-week treatment period. Subjects were randomized to 1 of 4 treatment groups: pitavastatin 2 mg QD, pitavastatin 4 mg QD (2 mg, titrated to 4 mg QD), simvastatin 20 mg QD or simvastatin 40 mg QD (20 mg, titrated to 40 mg QD). Subjects in the pitavastatin 4 mg group received pitavastatin 2 mg from Week 0 to Week 4, and 4 mg from Week 4 to 12. Subjects in the simvastatin 40 mg group received simvastatin 20 mg from Week 0 to Week 4, and 20 mg from Week 4 to 12.

Treatment was administered according to a double-dummy design consisting of one small tablet, one large tablet, and one capsule taken orally QD before bedtime as detailed in the Study Design schematic which follows:

Study Design:



1: Patients in the pitavastatin 4 mg group received pitavastatin 2 mg from Week 0 to Week 4, and 4 mg from Week 4 to 12.
 2: Patients in the simvastatin 40 mg group received simvastatin 20 mg from Week 0 to Week 4, and 40 mg from Week 4 to 12.
 3: Lipid panel may have been repeated (Visit 3A) 1 week after Visit 3 as required for qualification.

A dietary lead-in period of 6 weeks for subjects not taking lipid-lowering agents and eight weeks for subjects on previous lipid-lowering therapy was included to ensure adequate washout of prior therapy, and stable baseline lipid values. The treatment duration of 12 weeks was chosen based on past clinical trial design.

Dose selection:

Simvastatin was chosen as the comparator since it is one of the most commonly used and well-studied statins in clinical use.

At therapeutic doses of 5 to 80 mg once daily, simvastatin reduces mean LDL concentrations by approximately 26-47%. The doses of simvastatin selected for this study are those recommended by the manufacturers of the product and assessed in the Scandinavian Simvastatin Survival Study, although simvastatin may be given at doses as low as 5mg QD and as high as 80 mg QD. Therefore, the 20 mg and 40 mg doses selected for use and compared to the pitavastatin 2 mg and 4 mg in this study were reasonable.

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

Selection of Study Population:

Subjects to be included in this study were male and female subjects (aged 18-75 years) with primary hypercholesterolemia or combined dyslipidemia.

Inclusion Criteria:

- Males and non-pregnant, non-lactating females (age 18-75 years).

- Women of child bearing potential were allowed to enter the study only if they used sustained contraceptive preparations (e.g., implants or IM injections) or complied with an approved mechanical contraceptive method. A woman was considered to be of childbearing potential unless she was post-hysterectomy or at least one year post-menopausal or post-tubal ligation. All women of child bearing potential had a negative pregnancy test at the beginning of the dietary lead-in period (Visit 1/Week -8/-6), and before initiating active treatment (Visit 4/Week 0);
- Subjects who were eligible and able to participate in the study and who had given informed consent after the purpose and nature of the investigation had been explained to them;
- In order to qualify for randomization, subjects must have been following a fat and cholesterol restrictive diet as advised by the EAS during the dietary stabilization lead-in period (i.e., for at least eight weeks for those subjects previously taking lipid-lowering medication and at least six weeks for those not previously taking lipid-lowering medication). Subjects also had to agree not to eat grapefruit or drink grapefruit juice for the duration of the study;
- In order to qualify for randomization at Visit 4 (Week 0), subjects presented with primary hypercholesterolemia or combined dyslipidemia, as defined by elevated plasma LDL [mean LDL ≥ 160 mg/dL and ≤ 220 mg/dL with the lower qualifying value being within 15% of the higher qualifying measurement] despite dietary therapy and TG levels of ≤ 400 mg/dL at both consecutive visits (Visits 2 and 3 or Visits 3 and 3A as applicable) during the dietary lead-in period. When required, Visit 3A was scheduled one week after Visit 3, for collecting the additional lipid sample to enable the subject to qualify for randomization; and
- Subjects who agreed to be available for every clinic visit, which occurred in the morning.

Exclusion criteria:

- Homozygous familial hypercholesterolemia (heterozygous component of familial hypercholesterolemia was acceptable for inclusion) or familial hypoalphalipoproteinemia;
- Any conditions which may cause secondary dyslipidemia. This included, but was not restricted to, alcoholism, auto-immune disease, nephrotic syndrome, uremia, any viral or non viral hepatitis clinically active within 12 months from study entry, obstructive hepatic or biliary disease, dys- or macroglobulinemia, multiple myeloma, glycogen storage disease, chronic pancreatitis, porphyria, and uncontrolled hypothyroidism or hyperthyroidism (controlled hypo- or hyperthyroidism, [i.e., condition presenting with normal baseline serum TSH and treatment stable during at least the last two months prior to study entry] were permitted);
- Uncontrolled diabetes mellitus as defined by $HbA_{1c} > 8\%$. Subjects with controlled Type II diabetes were allowed, provided the disease had been stable during at least the last three months prior to study entry;
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of any drug. The investigator was guided by the

evidence of any of the following: history of major gastrointestinal tract surgery e.g., gastrectomy, gastroenterostomy, or small bowel resection, gastritis, current active ulcers, gastrointestinal, or rectal bleeding. Current active or recurrent IBS or history of IBS. Subjects with a past history of IBS without symptoms for at least the last six months prior to the study start were allowed to enter the study;

- Any history of pancreatic injury or pancreatitis, or impaired pancreatic function/injury as indicated by abnormal lipase or amylase;
- Liver injury as indicated by serum transaminase levels ALAT/SGPT or ASAT/SGOT $>1.5 \times$ ULRR over the lead-in period. The ALAT and ASAT levels must have been $\leq 1.5 \times$ ULRR on at least two of the three evaluations between Visit 1 (Week -8/-6) and Visit 3 (Week -1) for the subject to have been eligible for further study participation. If ALAT and/or ASAT was $>2 \times$ ULRR at any time point between Visit 1 (Week -8/-6) and Visit 3 (Week -1), the subject was immediately excluded from further study participation;
- Impaired renal function as indicated by serum creatinine levels $>1.5 \times$ ULRR at Visit 1 (Week -8/-6). However, if creatinine was between 1.5 and $2 \times$ ULRR, one retest was permitted at Visit 2 (Week -2), provided all other criteria were fulfilled. Serum creatinine had to have been $\leq 1.5 \times$ ULRR at the retest for the subject to be eligible for further study participation. If serum creatinine was $>2 \times$ ULRR at Visit 1 (Week -8/-6), the subject was immediately excluded from further study participation;
- Current obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions, which was likely to require intervention during the course of the study or was regarded as clinically meaningful by the investigator;
- Serum creatine kinase (CK) $>5 \times$ ULRR without clinical explanation. However, if at Visit 1 (Week -8/-6) serum CK was $>5 \times$ ULRR without a clinical explanation, one retest was allowed. If the repeat CK was $>5 \times$ ULRR in the absence of conditions explaining the CK elevation, the subject was immediately excluded from further study participation;
- Uncontrolled hypothyroidism defined as TSH $>$ ULRR. Subjects with TSH $>$ ULRR at Visit 1 were permitted to have a retest at Visit 2 and if TSH was also $>$ ULRR at Visit 2 the subject was excluded from the study;
- Any severe acute illness or severe trauma in the last three months prior to Visit 1 (Week -8/-6);
- Major surgery, during the three months prior to Visit 1 (Week -8/-6);
- Significant CVD prior to randomization, such as myocardial infarction, coronary or peripheral artery angioplasty, bypass graft surgery, or severe or unstable angina pectoris;
- Evidence of symptomatic heart failure (NYHA class III or IV), gross cardiac enlargement (cardiothoracic ratio >0.5); significant heart block or cardiac arrhythmia. History of uncontrolled complex ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardia with a ventricular response rate of > 100 beats per minute at rest. Subjects whose electrophysiological instability was controlled with a pacemaker or implantable cardiac device were eligible;
- Left ventricular ejection fraction < 0.25 ;

- History of symptomatic cerebrovascular disease including cerebrovascular hemorrhage, transient ischemic attack, or carotid endarterectomy within one month prior to randomization;
- Any other medical or surgical conditions at the discretion of the investigator which placed the subject at higher risk derived from his/her participation in the study, which could have confounded the result of the study, or were likely to prevent the subject from complying with the requirements of the study or completing the study period;
- Known HIV infection;
- Poorly controlled or uncontrolled hypertension. Subjects were to have had SBP ≤ 160 mm Hg and DBP ≤ 90 mm Hg with or without antihypertensive therapy;
- Prior or current known muscular or neuromuscular disease of any type;
- Current active neoplastic disease or subjects who required antineoplastic treatment during the course of the study. History of prior malignancy except those subjects who had been cancer free for >10 years. Subjects with prior history of basal cell carcinoma or squamous cell carcinoma of the skin remained eligible if they had been cancer free for >5 the past years;
- Within the last two years, a history of drug abuse or continuous consumption of more than 65mL pure alcohol per day (e.g., more than 4 \times 125-mL glasses of wine or three glasses of spirits per day);
- Exposure to any investigational new drug within 30 days of study entry (Visit 1/Week -8/-6) or ingestion of any drug known to be toxic to a major organ system (such as those producing blood dyscrasias, nephrotoxicity, hepatotoxicity or neurotoxicity) within 12 weeks prior to the study entry (Visit 1/Week -8/-6);
- Current or recent (within four weeks of Visit 1/Week -8/-6) use of supplements known to alter lipid metabolism; e.g., soluble fibers (including >2 teaspoons Metamucil or psyllium containing supplement per day), or other dietary fiber supplements, fish oils, or other products at the discretion of the investigator;
- History of hypersensitivity reactions to other HMG-CoA reductase inhibitors;
- Any of the following concomitant medications:
 1. All agents used for or under investigation for lowering or modifying plasma lipid levels, including statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors (including ezetimibe) and nicotinic acid >500 mg per day. Subjects on these medications could participate in the study, provided treatment was interrupted at least eight weeks prior to randomization;
 2. Oral contraceptives or any systemic steroid hormones (including estrogens, progestins, androgens or glucocorticoids) for any condition, except for noncyclic (continuous) administration of estrogen/progesterone replacement therapy or sustained contraceptive preparations (e.g., implants or IM injections) which must have been constant for at least the last three months prior to study entry (Visit 1/Week -8/-6) and were anticipated to remain unchanged for the duration of the study. Subjects on systemic steroidal treatment might enter the study if the

treatment had been discontinued at least four weeks prior to Visit 1 (Week -8/-6). Steroid hormones administered topically or as inhalers were permitted. Non-steroidal anti-inflammatory agents were allowed provided dosing was stable for at least four weeks prior to entry into the study, but were disallowed if they had been used for immunosuppressive therapy;

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

Exceptions to the exclusion criteria:

Subjects using the following medications were permitted to enter the study provided the therapy had been stable before study entry (Visit 1/Week -8/-6) for the time indicated below and a change in dose or treatment were unlikely during the course of the study:

1. Therapy for hyperthyroidism or hypothyroidism stable for at least two months prior to **Visit 1 (week -8/-6), provided subject's baseline (Visit 1 or retest at Visit 2) serum TSH** was within the normal range (i.e., subjects presents controlled hypo- or hyperthyroidism);
2. Antihypertensive therapy stable for at least the last two months prior to Visit 1 (Week -8/-6);
3. Estrogen receptor modulators (e.g., raloxifene) for prevention of osteoporosis stable for at least 3 months prior to Visit 1 (Week -8/-6);
4. Noncyclic (continuous) estrogen/progesterone preparations for hormone replacement therapy or sustained contraceptive preparations (e.g., implants or IM injections) stable for at least the three months prior to Visit 1 (Week -8/-6); and/or

Hypoglycemic agents excluding thiazolidinediones (glitazones) if subjects with stable Type II diabetes were enrolled.

Subjects must have been instructed to inform the investigator before taking any new medication for the duration of the study, including over-the-counter medications and natural products. Any permitted concomitant medications should have been kept as stable as possible for the duration of the study.

Removal of subjects from therapy or assessment:

The investigator was to document whether or not each subject completed the clinical study. Subjects who, after randomization, discontinued prematurely from the study were not replaced. All subjects who discontinued early were encouraged to complete all efficacy and safety evaluations corresponding to Visit 8 /Week 12 as soon as possible after discontinuation from study treatment.

If for any reason either study treatment or observations were discontinued, the reason was to be recorded. Reasons that a subject may have discontinued participation in a clinical study were considered to constitute one of the following:

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

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

Treatment:

Treatment was administered according to a double-dummy design. Each subject dose consisted of one small tablet, one large tablet, and one capsule taken orally at bedtime with approximately 200mL of water. Either one of the tablets or the capsule was the active dose. The others were placebos.

Study population:

The following analysis populations were defined:

- **The Safety Population** was defined as all randomized subjects who receive at least one dose of the study drug.
- **The FAS (Full Analysis Set) Population** included all randomized subjects who received at least one dose of study drug and who had at least one on-treatment lipid assessment. (In this protocol, the ITT population was referred to as the FAS population)
- **The PP Population** included all subjects in the FAS who had no major protocol violations, and who had an on-treatment lipid assessment at Week 12 (Visit 8).
- **The COM Population** included all subjects, irrespective of protocol violations, who had Week 12 (last week of measurement) measurements whether on drug or not.

Analysis Population:

The final protocol only stipulated the use of the ITT and Safety populations. The ITT population defined in the protocol was renamed and referred to as the FAS.

Sample Size Justification

A sample size of 800 subjects was planned, with 300 subjects in each of the pitavastatin 2 mg and 4 mg groups and 100 subjects in each of the simvastatin 20 mg and 40 mg groups. Assuming an SD of 12 for percent reduction from baseline LDL, a non-inferiority limit of 6% for the treatment differences, and a one-tailed test at the 2.5% significance level, this sample size provided 99% power to reject the null hypothesis, that the mean percent decrease from baseline LDL was at least 6% greater in the simvastatin groups than in the pitavastatin groups, versus the alternative that any advantage in the simvastatin groups was less than the non-inferiority limit.

Statistical analysis of the primary efficacy variable:

The percent change in LDL from baseline to 'endpoint' for the FAS and the percent change in LDL from baseline to Week 12 (Visit 8) for the PP population were analyzed using ANCOVA with treatment and country as factors and the baseline LDL as a covariate. The analysis was performed using a logistic regression model. If the iterative calculation met the convergence criteria with the linear probability model, then the result of the linear probability model was used.

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

In order to test the assumptions of the ANCOVA, the different treatment covariate slopes were compared by including the treatment × covariate term in the model. In addition, normality was assessed.

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

- Age (< 65 years, ≥65 years);
- Sex;
- Race (Caucasian, Non-Caucasian);

- BMI (< 25 kg/m², 25 - <30 kg/m², ≥ 30 kg/m²);
- NCEP Risk Category (Low, Moderate, High);
- Baseline LDL (< 160 mg/dL, 160 - < 190 mg/dL, ≥ 190 mg/dL);
- Hypertension (Yes, No);
- Diabetes (Yes, No);
- Primary Diagnosis (Primary hypercholesterolemia, Combined dyslipidemia, Heterozygous familial hypercholesterolemia).

For those subgroups where each level of the subgroup included ≥5% of subjects, treatment × subgroup interactions were tested by including them in the original ANCOVA model.

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

Statistical analysis of the secondary efficacy variable:

Secondary efficacy lipid variables were also evaluated using ANCOVA and 95% CIs on the mean differences between the pitavastatin groups and the corresponding simvastatin groups. Non-inferiority margins for secondary variables were not explicitly defined.

The LDL targets were calculated for each subject using 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 (categorized as defined in the NCEP guidelines), as factors. Point estimates (and 95% CIs) of the differences between the pitavastatin groups and the corresponding simvastatin groups were presented.

Protocol Amendment:

There was one amendment to Protocol NK-104-302.

Amendment 1 was generated to address the potential gap between the core study and the follow-up study, the potential effect of glitazones, and additional proteinuria evaluation. The resultant changes were:

1. Provided guidance on the procedure to be followed during the gap between the core study and the follow-up study.
2. Excluded glitazones/thiazolidinediones (pioglitazone, rosiglitazone) as concomitant medications.
3. Additional urine protein assessments were to be performed at baseline (Visit 4, Week 0) and at end of treatment (Visit 8, Week 12) to investigate if statin treatment may cause proteinuria.
4. Addition of notification/clarification changes.

Changes in the Planned Analysis:

The following changes have been made from the analysis of baseline lipid values planned in the protocol:

The protocol specified that baseline lipid values would be calculated as the mean of the values obtained at Week -2 (Visit 2) and Week -1 (Visit 3). However, for LDL, TC, HDL, TG, TC:HDL ratio and non-HDL:HDL ratio, the baseline was calculated as the mean of the lipid measurements from Week -2 (Visit 2), Week -1 (Visit 3) and Week 0 (Visit 4). If Visit 3A was completed, the baseline value was the mean from Week -1 (Visit 3), Week -1 Repeat (Visit 3A) and Week 0 (Visit 4). The result at Week 0 (Visit 4) was included in the calculation of baseline as this was the last measurement before study treatment commenced.

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

Protocol violations and deviations:

Subjects with major protocol violations were identified programmatically prior to unblinding to determine who should be excluded from the PP population. A total of 127 subjects (15%) were excluded from the PP population, 52 due to not having a Week 12 lipid assessment.

The most frequently reported violations that resulted in the exclusion of subjects from the PP population were lack of compliance, taking lipid-lowering drugs or other prohibited medications during the run-in or treatment period, Week 12 visit outside of visit window, and failure to meet hyperlipidemia requirements. A number of individual data points were excluded for visits which occurred outside of defined visit windows.

Disposition of subjects:

Investigators at 45 centers randomized a total of 857 subjects: 638 subjects were randomized to treatment with pitavastatin, and 219 to simvastatin. Of the 857 subjects randomized, 848 received at least one dose of study drug (Safety Population; nine subjects were not dosed primarily due to protocol violations), 631 took pitavastatin and 217 took simvastatin. Overall, 479 (56%) of the subjects were randomized at 19 centers in Russia, 142 (17%) were randomized at five centers in Norway, 129 (15%) were randomized at 10 centers in the UK, 82 (10%) were randomized at five centers in Finland, and 25 (3%) were randomized at six centers in Italy. The greatest number of subjects randomized at a single center was 56 (7% of all subjects), at Center 2301 in Norway.

	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
Number of subjects Randomized	315 (100.0)	108 (100.0)	323 (100.0)	111 (100.0)
Safety Population	311 (98.7)	107 (99.1)	320 (99.1)	110 (99.1)
Full Analysis Set (FAS)	307 (97.5)	107 (99.1)	319 (98.8) ¹	110 (99.1)
Completers (COM) Population	295 (93.7)	99 (91.7)	304 (94.1)	107 (96.4)
Per-Protocol Population (PP)	266 (84.4)	87 (80.6)	282 (87.3)	95 (85.6)
Discontinued Study Drug	23 (7.3)	9 (8.3)	19 (5.9)	4 (3.6)
Reason for Discontinuation from Study				
Adverse event	13 (4.1)	2 (1.9)	8 (2.5)	1 (0.9)
Protocol violation	4 (1.3)	1 (0.9)	3 (0.9)	1 (0.9)
Subject withdrew consent	6 (1.9)	5 (4.6)	7 (2.2)	2 (1.8)
Subject lost to follow up	0	0	1 (0.3)	0
Death	0	1 (0.9)	0	0

Demographic and Other Baseline Characteristics:

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

Demographic and Other Baseline Characteristics (Safety Population)

Demographic Characteristic	Pitavastatin 2 mg QD (N=311)	Simvastatin 20 mg QD (N=107)	Pitavastatin 4 mg QD (N=320)	Simvastatin 40 mg QD (N=110)
Sex (n, %)				
Male	115 (37.0)	44 (41.1)	125 (39.1)	48 (43.6)
Female	196 (63.0)	63 (58.9)	195 (60.9)	62 (56.4)
Age (years)				
Mean (SD)	58.7 (8.83)	58.6 (9.64)	57.7 (8.97)	58.4 (9.54)
Range	30 - 75	34 - 74	29 - 75	25 - 74
Age group (n,%)				
<35 years	1 (0.3)	1 (0.9)	4 (1.3)	2 (1.8)
35-39 years	6 (1.9)	4 (3.7)	3 (0.9)	3 (2.7)
40-44 years	16 (5.1)	5 (4.7)	20 (6.3)	3 (2.7)
45-49 years	22 (7.1)	9 (8.4)	29 (9.1)	6 (5.5)
50-54 years	50 (16.1)	13 (12.1)	58 (18.1)	19 (17.3)
55-59 years	68 (21.9)	25 (23.4)	72 (22.5)	29 (26.4)
60-64 years	51 (16.4)	15 (14.0)	45 (14.1)	14 (12.7)
65-69 years	71 (22.8)	20 (18.7)	63 (19.7)	22 (20.0)
70-74 years	25 (8.0)	15 (14.0)	25 (7.8)	12 (10.9)
≥75 years	1 (0.3)	0	1 (0.3)	0
Race (n,%)				
Caucasian	310 (99.7)	106 (99.1)	318 (99.4)	110 (100.0)
Black	1 (0.3)	0	0	0
Asian	0	0	1 (0.3)	0
Hispanic	0	1 (0.9)	0	0
Other	0	0	1 (0.3)	0
Diagnosis (n,%)				
Primary hypercholesterolemia	241 (77.5)	80 (74.8)	244 (76.3)	94 (85.5)
Combined dyslipidemia	66 (21.2)	26 (24.3)	74 (23.1)	14 (12.7)
Familial hypercholesterolemia	4 (1.3)	1 (0.9)	2 (0.6)	2 (1.8)
Duration of current disease (years)				
Mean (SD)	4.02 (5.65)	4.16 (5.46)	3.85 (5.03)	3.96 (4.64)
Range	-0.011 - 36.11	0.003 - 30.14	-0.126 - 44.22	0.003 - 18.55
Height (m)				
Mean (SD)	1.67 (0.09)	1.68 (0.10)	1.68 (0.09)	1.68 (0.09)
Range	1.4 - 1.9	1.4 - 1.9	1.5 - 2.0	1.5 - 1.9

Table (cont'd) Demographic and Other Baseline Characteristics (Safety Population)

Demographic Characteristic	Pitavastatin 2 mg QD (N=311)	Simvastatin 20 mg QD (N=107)	Pitavastatin 4 mg QD (N=320)	Simvastatin 40 mg QD (N=110)
Weight (Kg)				
Mean (SD)	78.01 (12.43)	78.45 (13.78)	77.08 (12.00)	78.32 (12.40)
Range	44.0 - 121.3	54.0 - 116.0	49.0 - 109.0	52.0 - 113.3
BMI (kg/m²)				
Mean (SD)	27.97 (3.40)	27.87 (3.75)	27.36 (3.26)	27.69 (3.49)
Range	19.3 - 35.0	19.8 - 34.8	19.0 - 34.8	18.9 - 34.8
Baseline lipids				
LDL (mg/dL)				
Mean (SD)	183.59 (17.00)	184.07 (17.15)	183.99 (16.45)	184.00 (15.66)
Range	130.3 - 221.3	148.7 - 228.3	148.0 - 225.3	155.7 - 223.7
HDL (mg/dL)				
Mean (SD)	51.28 (12.76)	50.99 (11.83)	52.78 (12.91)	52.26 (10.69)
Range	27.3 - 95.3	30.3 - 90.3	26.0 - 121.0	33.3 - 85.3
TC (mg/dL)				
Mean (SD)	267.64 (22.19)	268.38 (22.67)	268.03 (20.76)	267.03 (20.31)
Range	192.0 - 322.7	223.3 - 326.7	224.7 - 336.7	219.7 - 332.0
TG (mg/dL)				
Mean (SD)	163.66 (60.91)	166.70 (56.83)	156.40 (61.86)	153.86 (55.39)
Range	57.3 - 385.3	70.3 - 363.0	49.7 - 464.7	76.0 - 370.3
NCEP Risk category (n,%)				
High	108 (34.7)	38 (35.5)	84 (26.3)	26 (23.6)
Moderate	91 (29.3)	35 (32.7)	108 (33.8)	49 (44.5)
Low	112 (36.0)	34 (31.8)	128 (40.0)	35 (31.8)
Diabetes (n,%)				
Present	18 (5.8)	9 (8.4)	21 (6.6)	6 (5.5)
Hypertension (n,%)				
Present	200 (64.3)	76 (71.0)	188 (59.1)	72 (65.5)

The four treatment groups were similar in terms of demographic characteristics of sex, age and race. There were more females than males in the study: overall, 516 (61%) subjects in the Safety Population were female. The mean age of the subjects was approximately 58 years in each treatment group and ranged between 25 and 75 years. All except four subjects were Caucasian.

The treatment groups were well matched in terms of baseline LDL values. Baseline mean LDL ranged between 183.6 mg/dL and 184.1 mg/dL across the treatment groups. Similarly, there were no meaningful differences between the groups in mean baseline HDL, TC and TG. Baseline mean HDL ranged between 51.0 mg/dL and 52.8 mg/dL, TC ranged between 267.0 mg/dL and 268.4 mg/dL. Baseline TG tended to be somewhat higher in the two low-dose groups, but the differences were not statistically significant (P=0.189).

The treatment groups were well matched in terms of diagnosis and duration of disease. Approximately 80% of subjects had primary hypercholesterolemia (with the highest percentage (85.5%) in the simvastatin 40 mg group) and most of the remainder had combined dyslipidemia. Nine subjects in total had heterozygous familial hypercholesterolemia. Mean duration of the clinical diagnosis of hypercholesterolemia ranged between 3.85 years and 4.16 years across the treatment groups.

NCEP risk categories for major coronary events were similar across the low-dose groups (35% and 36%, respectively, for pitavastatin 2 mg and simvastatin 20 mg) and across the high-dose groups (26% and 24%, respectively, for pitavastatin 4 mg and simvastatin 40 mg) in the Safety Population.

The prevalence of diabetes ranged between 6% (pitavastatin 2 mg) and 8% (simvastatin 20 mg) across all treatment groups. The presence of hypertension ranged from 59% (pitavastatin 4 mg) to 71% (simvastatin 20 mg).

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

Baseline Characteristics:

Between 13% and 18% of subjects across all treatment groups were smokers at baseline. The majority of subjects (≥69%) in all treatment groups were non-smokers or ex-smokers.

More than half of subjects were sporadic (i.e., occasional) consumers of alcohol (range 59% to 64% across all treatment groups).

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

- The proportion of subjects with LDL in the category 160 to <190 mg/dL ranged between 55% and 61% across all treatment groups, and the proportion of subjects with LDL in the category ≥190 mg/dL ranged between 34% and 37%.
- The proportion of subjects with HDL in the category ≥60 mg/dL ranged between 21% and 26% across treatment groups while the proportion of subjects with HDL <40 mg/dL ranged between 7% and 18 %.
- The proportion of subjects with treated hypertension ranged between 54% and 67% across all treatment groups.

Between 90% and 96% of subjects in each treatment group had one or more diagnoses listed on their medical history. The most common organ systems with medical history were cardiovascular (ranged between 67% and 79%) and musculoskeletal (ranged between 33% and 40%).

The number of subjects who were taking lipid-lowering medications prior to enrollment ranged between 18% and 36% across treatment groups. Lower percentages were observed in the two pitavastatin groups. The most common prior lipid-lowering medication was simvastatin, with between 10% and 24% of subjects across treatment groups taking this medication. The second most common lipid-lowering medication was atorvastatin, which was taken by between 3% and 8% of subjects in any treatment group.

In summary, with the exception of risk category, there were no apparent treatment group differences in the demographic summaries of the Safety Population.

Treatment Compliance:

Compliance was generally good and comparable across treatment groups, with median compliance close to 100% in all four treatment groups. However, approximately 4% of subjects in all four groups were poorly compliant (<80% or >120%) and were excluded from the PP population for this reason.

Treatment Compliance (Safety Population)

	Pitavastatin 2 mg QD (N=311)	Simvastatin 20 mg QD (N=107)	Pitavastatin 4 mg QD (N=320)	Simvastatin 40 mg QD (N=110)
Overall %Compliance				
N	307	106	318	109
Median	100.0	100.0	100.0	98.9
Mean (SD)	98.2 (4.94)	97.2 (6.92)	97.4 (7.58)	98.4 (3.17)
Range	47 - 108	53 - 102	6 - 105	82 - 106

Analysis of efficacy:

The percent change in LDL from baseline to endpoint (Week 12 or the last treatment assessment) for the FAS, is presented in the following table:

Change from Baseline to Endpoint or Week 12 in LDL (mg/dL) in the FAS population.

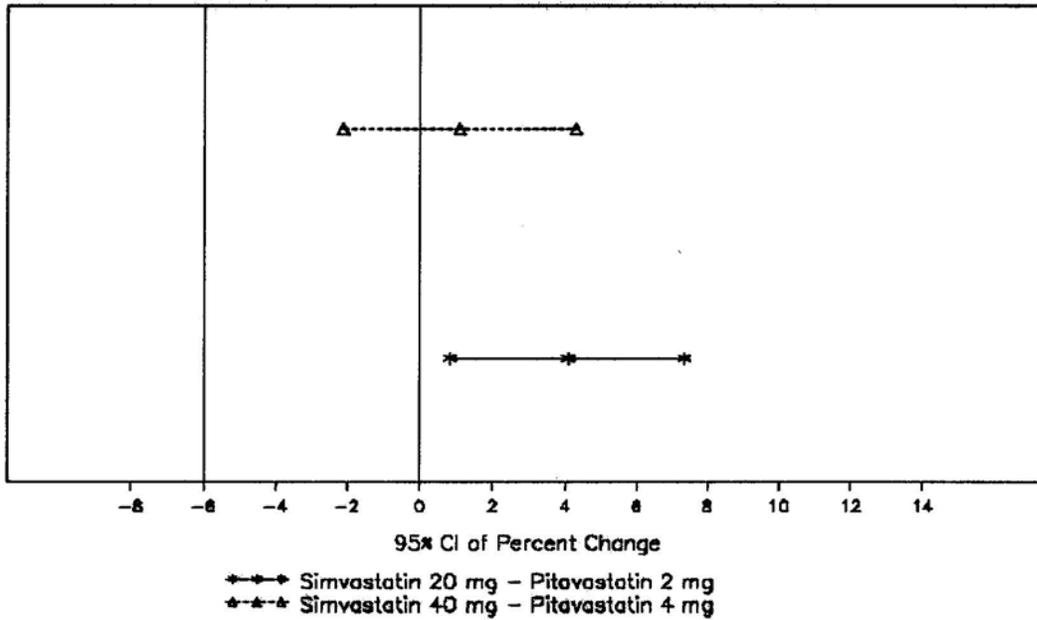
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	319	110
Baseline LDL				
Mean (SD)	183.6 (16.98)	184.1 (17.15)	184.1 (16.45)	184.0 (15.66)
Endpoint LDL				
Mean (SD)	111.9 (28.44)	119.1 (27.65)	103.0 (27.58)	104.6 (27.49)
Percent Change from Baseline				
Mean (SD)	-38.99 (14.57)	-34.97 (15.53)	-43.97 (14.49)	-42.84 (15.77)
Adjusted Mean Difference		4.08		1.08
(95% CI)		(0.82; 7.34)		(-2.13; 4.29)
P-value		0.014		0.509

The table above shows that the mean percent decrease in LDL values from baseline to endpoint was approximately 4% greater in the low-dose pitavastatin group (39%) compared with the low-dose simvastatin group (35%).

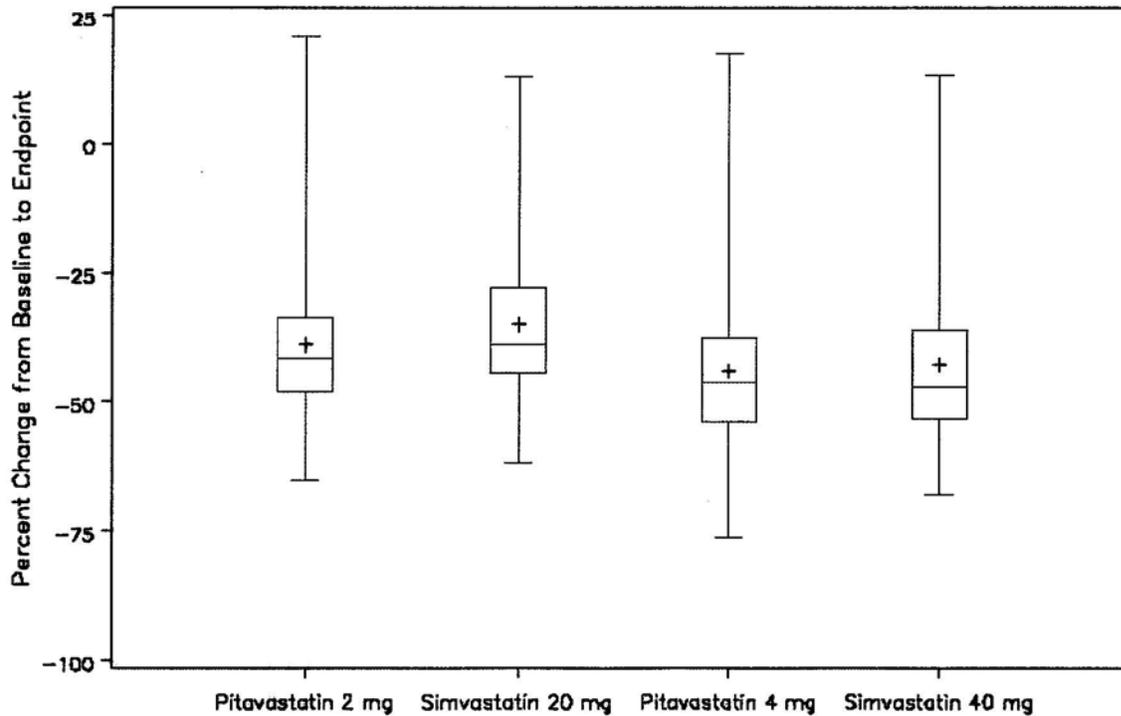
The adjusted mean difference was 4.1% (95% CI [0.82; 7.34]) P=0.014. The analysis of this endpoint in the COM population (39.3% decrease from baseline for pitavastatin 2 mg and 35.6% decrease for simvastatin 20 mg; P=0.025) and the PP population (40% decrease from baseline for pitavastatin 2 mg and 36.1% decrease for simvastatin 20 mg; P=0.023) were comparable and supported the findings in the FAS population.

For the high-dose groups, the mean percent decreases in LDL values from baseline to endpoint were slightly higher for pitavastatin 4 mg (44%) compared to simvastatin 40 mg (43%) and the non-inferiority of pitavastatin was confirmed. In this comparison the difference was not statistically significant: the adjusted mean difference was 1.08% (95% CI [-2.13; 4.29]) P=0.509. The analysis of this endpoint in the COM and PP populations were comparable and supported the findings in the FAS population.

Adjusted Mean Percent Difference LDL as applied to the 95% Confidence Intervals on Treatment Difference in (FAS).



The percent change from baseline in LDL at the study endpoint in the FAS population in all four dosing groups are illustrated in the following box plot:



In summary, for the change from baseline to endpoint in LDL, pitavastatin was non-inferior to simvastatin for both the low-dose groups (pitavastatin 2 mg vs. simvastatin 20 mg) and high-dose groups (pitavastatin 4 mg vs. simvastatin 40 mg) comparisons in the FAS, PP, and COM populations. Furthermore, pitavastatin 2 mg was statistically significantly superior to simvastatin 20 mg ($P \leq 0.025$) in all three populations.

Reductions in LDL for both the low and high-dose groups occurred within eight weeks following initiation of treatment. For the low-dose groups, the LDL levels decreased within 2 to 4 weeks, while in the high-dose groups, LDL reductions continued until Week 8 and then tended to remain stable.

Secondary Efficacy Variables:

LDL Target Attainment

Using the NCEP criteria, the proportion of subjects who attained target LDL in the pitavastatin vs. simvastatin low-dose groups was 70% vs. 65%, respectively, and 80% vs. 78%, respectively, for the high-dose groups. The differences were not statistically significant for the low-dose (-5.5; $P=0.297$) or the high-dose (-1.4; $P=0.762$) comparisons.

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

Subjects With LDL Target Attainment (FAS):

	Pitavastatin 2 mg QD (N=307)	Simvastatin 20 mg QD (N=107)	Pitavastatin 4 mg QD (N=319)	Simvastatin 40 mg QD (N=110)
Target attained according to NCEP criteria (n,%)				
Yes	215 (70.0%)	69 (64.5%)	253 (79.6%)	86 (78.2%)
Difference (95% CI)	-5.5 (-16.0; 4.9)		-1.4 (-10.3; 7.5)	
P-value	0.297		0.762	
Adjusted proportion achieving target	78.4%	73.2%	87.2%	86.0%
Adjusted Mean Difference (95% CI)	-5.2 (-15.3; 5.0)		-1.2 (-10.0; 7.6)	
P-value	0.316		0.788	
Adjusted proportion achieving target	69.3%	65.3%	73.6%	72.7%
Adjusted Mean Difference (95% CI)	-4.0 (-14.7; 6.7)		-1.0 (-10.0; 8.1)	
P-value	0.461		0.836	

LDL Sub-Group Analysis by Baseline Characteristics:

The mean percent decrease in LDL did not appear to be influenced by baseline LDL, nor by BMI category, presence/absence of hypertension or diabetes. No apparent effect of CHD risk category on LDL reduction in the pitavastatin dose groups was observed.

Total cholesterol:

The secondary efficacy lipid variable TC for the FAS is summarized in the following table:

Mean Percent Change from Baseline to Endpoint in Total cholesterol (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	319	110
Baseline Mean (SD)	267.7 (22.13)	268.4 (22.67)	268.0 (20.76)	267.0 (20.31)
Endpoint Mean (SD)	192.9 (33.28)	199.7 (31.46)	183.4 (31.88)	185.1 (33.13)
Percent Change (SD)	-27.90 (11.21)	-25.37 (11.52)	-31.50 (10.92)	-30.53 (12.35)
Adjusted Mean Difference (95% CI)	2.59 (0.10; 5.07)		0.88 (-1.56; 3.33)	
P-value	0.041		0.479	

Total cholesterol decreased 27.9% from baseline in the pitavastatin 2 mg group and 25.3% in the simvastatin 20 mg group. The adjusted mean difference, 2.6% was statistically significant (P=0.041). In the pitavastatin 4 mg and simvastatin 40 mg treatment groups the decreases were 31.5% and 30.5%, respectively and were not significantly different.

HDL:

The secondary efficacy lipid variable HDL for the FAS is summarized in the following table:

Mean Percent Change from Baseline to Endpoint in HDL (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	319	110
Baseline Mean (SD)	51.3 (12.81)	51.0 (11.83)	52.8 (12.91)	52.3 (10.69)
Endpoint Mean (SD)	54.0 (14.09)	53.2 (12.51)	55.5 (13.33)	55.5 (11.38)
Percent Change (SD)	5.98 (16.1)	5.54 (18.09)	6.16 (14.67)	6.83 (12.85)
Adjusted Mean Difference (95% CI)	-0.46 (-3.74; 2.81)		0.44 (-2.79; 3.67)	
P-value	0.782		0.791	

HDL increased 6% from baseline in the pitavastatin 2 mg group and 5.5% in the simvastatin 20 mg group. In the pitavastatin 4 mg and simvastatin 40 mg groups the increases were 6.2% and 6.8%, respectively. The adjusted mean differences were not statistically significant for either comparison.

Non-HDL:

The secondary efficacy lipid variable Non-HDL cholesterol for the FAS is summarized in the following table:

Mean Percent Change from Baseline to Endpoint in Non-HDL cholesterol (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	319	110
Baseline Mean (SD)	216.4 (21.29)	217.4 (21.93)	215.1 (19.94)	214.8 (18.84)
Endpoint Mean (SD)	138.9 (32.69)	146.5 (31.01)	127.9 (30.64)	129.7 (32.57)
Percent Change (SD)	-35.81 (13.73)	-32.26 (14.63)	-40.53 (13.26)	-39.44 (15.29)
Adjusted Mean Difference (95% CI)	3.60 (0.54; 6.66)		1.04 (-1.98; 4.05)	
P-value	0.021		0.499	

Non-HDL cholesterol values decreased 35.8% from baseline in the pitavastatin 2 mg group and 32.3% in the simvastatin 20 mg group. The adjusted mean differences were statistically significant (P=0.021). In the pitavastatin 4 mg and simvastatin 40 mg groups the decreases were 40.5% and 39.4%, respectively. The adjusted mean differences were not statistically significantly different (P=0.499).

Triglycerides:

The secondary efficacy lipid variable triglycerides for the FAS is summarized in the following table:

Mean Percent Change from Baseline to Endpoint in Triglycerides (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	319	110
Baseline Mean (SD)	163.8 (60.97)	166.7 (56.83)	155.4 (59.49)	153.9 (55.39)
Endpoint Mean (SD)	135.3 (61.22)	137.3 (58.53)	124.6 (55.67)	125.5 (56.91)
Percent Change (SD)	-15.95 (24.49)	-15.58 (28.08)	-16.85 (27.32)	-16.13 (29.19)
Adjusted Mean Difference (95% CI)	0.66 (-5.08; 6.39)		0.48 (-5.17; 6.13)	
P-value	0.822		0.866	

In the pitavastatin 2 mg and simvastatin 20 mg groups the decreases from baseline in TG were 16% and 15.6%, respectively. In the pitavastatin 4 mg and simvastatin 40 mg groups the decreases from baseline were 16.9% and 16.1%, respectively. The adjusted mean differences were not statistically significant in the comparison of either the low (P=0.822) or high (P=0.866) dose groups.

TC:HDL Ratio:

The secondary efficacy lipid variable TC:HDL ratio for the FAS is summarized in the following table:

Mean Change from Baseline to Endpoint in TC:HDL Ratio (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	319	110
Baseline Mean (SD)	5.518 (1.29)	5.511 (1.16)	5.346 (1.20)	5.288 (0.94)
Endpoint Mean (SD)	3.781 (1.10)	3.924 (0.98)	3.446 (0.86)	3.446 (0.84)
Mean Change (SD)	-1.74 (0.93)	-1.587 (1.10)	-1.902 (0.91)	-1.843 (0.92)
Adjusted Mean Difference (95% CI)	0.145 (-0.018; 0.309)		0.031 (-0.131; 0.192)	
P-value	0.082		0.710	

The TC:HDL ratio decreased 1.7 in the pitavastatin 2 mg group and 1.6 in the simvastatin 20 mg group. In the pitavastatin 4 mg and simvastatin 40 mg groups the decreases were 1.9 and 1.8, respectively. The adjusted mean differences were not statistically significant.

Non-HDL:HDL Ratio:

The secondary efficacy lipid variable Non-HDL:HDL ratio for the FAS is summarized in the following table:

Mean Change from Baseline to Endpoint in Non-HDL:HDL Ratio (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	319	110
Baseline Mean (SD)	4.52 (1.29)	4.511 (1.16)	4.346 (1.20)	4.288 (0.94)
Endpoint Mean (SD)	2.78 (1.10)	2.924 (0.98)	2.446 (0.86)	2.446 (0.84)
Mean Change (SD)	-1.74 (0.93)	-1.587 (1.10)	-1.902 (0.91)	-1.843 (0.92)
Adjusted Mean Difference (95% CI)	0.145 (-0.018; 0.309)		0.031 (-0.131; 0.192)	
P-value	0.082		0.710	

The non-HDL:HDL values decreased 1.73 from baseline in the pitavastatin 2 mg group, 1.59 in the simvastatin 20 mg group, 1.90 in the pitavastatin 4 mg group, and 1.84 in the simvastatin 40 mg group. The adjusted mean differences were not statistically significant.

Apolipoprotein B:

The secondary efficacy lipid variable Apo-B for the FAS is summarized in the following table:

Mean Percent Change from Baseline to Endpoint in Apolipoprotein B (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	305	107	316	110
Baseline Mean (SD)	161.2 (22.46)	163.4 (21.06)	160.3 (20.27)	161.9 (18.33)
Endpoint Mean (SD)	112.9 (24.84)	117.7 (22.71)	104.6 (23.35)	105.9 (25.39)
Percent Change (SD)	-29.81 (13.70)	-27.06 (15.27)	-34.59 (13.31)	-34.24 (15.67)
Adjusted Mean Difference (95% CI)	2.99 (-0.07; 6.04)		0.52 (-2.47; 3.51)	
P-value	0.055		0.732	

Apo-B decreased 29.8% in the pitavastatin 2 mg group and 27.1% in the simvastatin 20 mg group. The difference was marginally statistically significant (P=0.055). The Apo-B reduction was 34.6% in the pitavastatin 4 mg group and 34.2% in the simvastatin 40 mg group. The difference between groups was not statistically significant.

Apolipoprotein A1:

The secondary efficacy lipid variable Apo-A1 for the FAS is summarized in the following table:

Mean Percent Change from Baseline to Endpoint in Apolipoprotein A1 (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	305	107	316	110
Baseline Mean (SD)	161.8 (25.65)	162.7 (27.32)	163.3 (26.45)	164.1 (20.36)
Endpoint Mean (SD)	171.9 (28.67)	172.0 (26.13)	173.0 (26.77)	174.4 (23.55)
% change from baseline to Week 12				
Mean (SD)	6.73 (13.52)	7.38 (16.95)	6.82 (13.42)	6.92 (13.33)
Adjusted Mean Difference (95% CI)	0.76 (-2.08; 3.60)		0.29 (-2.49; 3.07)	
P-value	0.598		0.838	

Apo-A1 increased 6.7% from baseline in the pitavastatin 2 mg group, 7.4% in the simvastatin 20 mg group, 6.8% in the pitavastatin 4 mg group, and 6.9% in the simvastatin 40 mg group. The

adjusted mean differences were not statistically significant for the comparison of the low (P=0.598) or high (P=0.838) dose comparison.

Apo-A:Apo-B Ratio:

The secondary efficacy lipid variable Apo-A:Apo-B ratio for the FAS is summarized in the following table:

Mean Change from Baseline to Endpoint in Apo-B:Apo-A1 Ratio (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	305	107	316	110
Baseline Mean (SD)	1.02 (0.22)	1.04 (0.22)	1.01 (0.22)	1.00 (0.16)
Endpoint Mean (SD)	0.67 (0.20)	0.70 (0.19)	0.62 (0.17)	0.62 (0.17)
Mean (SD)	-0.35 (0.18)	-0.34 (0.21)	-0.39 (0.19)	-0.38 (0.19)
Adjusted Mean Difference (95% CI)	0.02 (-0.01; 0.05)		0.00 (-0.03; 0.03)	
P-value	0.250		0.954	

The Apo-B:Apo-A1 ratio decreased from baseline for all treatment groups: 0.35 in the pitavastatin 2 mg group, 0.34 in the simvastatin 20 mg group, 0.39 in the pitavastatin 4 mg group, and 0.38 for the simvastatin 40 mg group. The adjusted mean differences were not statistically significant.

hsCRP:

The secondary efficacy lipid variable hsCRP for the FAS is summarized in the following table:

Mean Change from Baseline to Endpoint in hsCRP (mg/L) (FAS)				
	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
N	307	107	316	110
Baseline Mean (SD)	3.33 (8.47)	3.33 (4.04)	2.57 (3.38)	3.16 (4.24)
Endpoint Mean (SD)	2.39 (2.91)	3.46 (6.81)	2.80 (4.36)	2.33 (3.20)
Mean (SD)	-0.94 (8.54)	0.09 (6.92)	0.23 (4.45)	-0.83 (4.37)
Adjusted Mean Difference (95% CI)	1.06 (0.15; 1.97)		-0.57 (-1.46; 0.33)	
P-value	0.0022		0.0213	

Values for hsCRP decreased from baseline for the pitavastatin 2 mg dose group (0.94) and increased for the simvastatin 20 mg (0.09) group. The adjusted mean difference for the comparison of the low-dose groups (1.06) was statistically significant (P=0.022). For the pitavastatin 4 mg dose, an increase from baseline of 0.23 was observed, and a decrease was observed for simvastatin 40 mg (0.83). The adjusted mean difference for the comparison of the high-dose groups (-0.57) was not statistically significant (P=0.213).

Efficacy Conclusions:

- Pitavastatin was non-inferior to simvastatin for both the low (pitavastatin 2 mg vs. simvastatin 20 mg) and high (pitavastatin 4 mg vs. simvastatin 40 mg) dose group comparisons of the percent change from baseline to endpoint or Week 12 for LDL in the FAS population, as well as in the PP, and COM populations.

LDL (mg/dL) Week 12, (FAS)	Pitavastatin 2 mg QD	Simvastatin 20 mg QD	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
n=	307	107	319	110
Baseline mean (SD)	183.6 (16.98)	184.1 (17.15)	184.1 (16.45)	184.0 (15.66)
Mean % change (SD)	-38.99 (14.57)	-34.97 (15.53)	-43.97 (14.50)	-42.84 (15.77)
Adjusted Mean Difference (95% CI) p-value	4.08 (0.82, 7.34) 0.014		1.08 (-2.13, 4.29) 0.509	

- Pitavastatin 2 mg was statistically significantly superior to simvastatin 20 mg in percent decrease from baseline in LDL (P<0.05) in the FAS population, as well as in the PP, and COM populations.
- NCEP LDL target attainment was achieved in a higher proportion of subjects in the pitavastatin 2 mg group than in the simvastatin 20 mg group. The proportion of subjects who attained target LDL ranged was 70% in the pitavastatin 2 mg group to 65% in the simvastatin 20 mg group.
- The proportion of subjects who attained target LDL, according to the NCEP, in the pitavastatin vs. simvastatin high-dose groups was 79% vs. 78%, respectively.
- Pitavastatin 2 mg was statistically significantly superior to simvastatin 20 mg in the mean percent reduction of Non-HDL cholesterol and TC. Apo-B decreased to a marginally significant extent for pitavastatin 2 mg. Decreases from baseline in TG, TC:HDL ratio, non-HDL:HDL ratio and Apo-B:Apo-A1 ratio were comparable between the pitavastatin and simvastatin low and high-dose groups, with no significant differences observed. Similarly, increases from baseline for HDL and Apo-A1 were somewhat greater in the pitavastatin groups but the differences were not statistically significant.
- For hsCRP, treatment group differences were favored by the high-dose simvastatin group but not the low-dose simvastatin group. Both the high-dose and low-dose groups changes from baseline were statistically significant.

3.3 Study of Pitavastatin 4 mg vs. Simvastatin 40 mg (Following Up-Titration) in subjects with Primary Hypercholesterolemia or Combined Dyslipidemia and Two or More Risk Factors for Coronary Heart Disease [NK-104-304]

Study initiation date: 27 September 2005

Study completion date: 2 October 2006

3.3.1.1 General Discussion of Study Objectives, Endpoints and Methods

Primary Objective:

- To demonstrate the non-inferiority of pitavastatin 4 mg QD vs. simvastatin 40 mg QD, with respect to the reduction of LDL when administered for 12 weeks using an up-titration regimen in subjects with primary hypercholesterolemia or combined dyslipidemia.

Secondary Objectives:

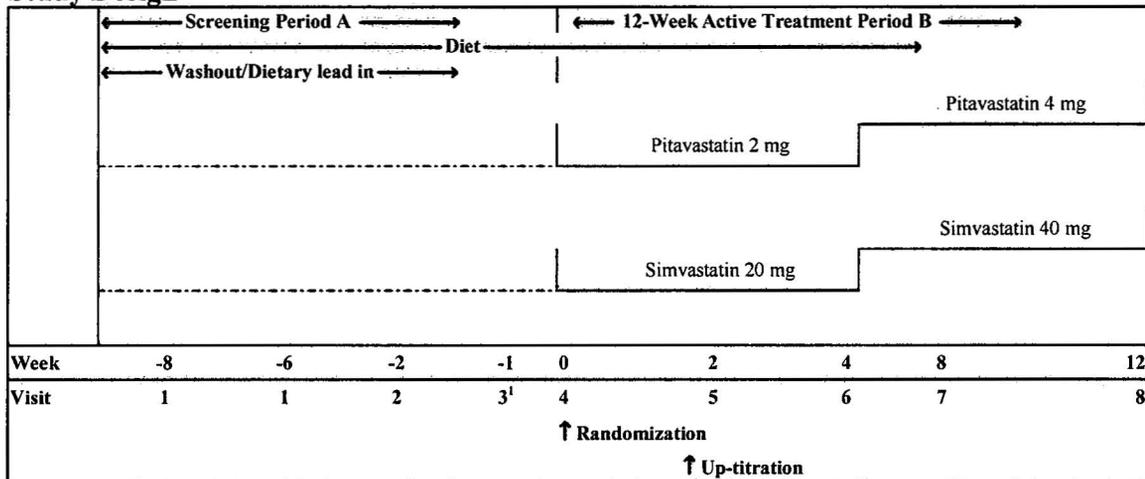
- To compare the efficacy of pitavastatin 4 mg QD vs. simvastatin 40 mg QD with respect to changes from baseline in other lipid and lipoprotein fractions TC, HDL, TC:HDL ratio, non-HDL, non-HDL:HDL ratio, TG, Apo-B and Apo-A1, Apo-B:Apo-A1 ratio, hsCRP, and LDL target attainment of NCEP goals
- To assess the safety and tolerability of pitavastatin 4 mg QD when administered for 12 weeks using an up-titration regimen

Study Design:

This was an 18 to 20-week, randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled study. Subjects who qualified entered a 6 to 8-week wash-out/dietary lead-in period followed by a 12-week treatment period. Subjects were randomly assigned to one of the two treatment groups: pitavastatin 4 mg QD, or simvastatin 40 mg QD in a ratio of 2:1. Subjects assigned to pitavastatin 4 mg started dosing with pitavastatin 2 mg at Visit 4 (Week 0) and had their dose titrated to 4 mg at Visit 6 (Week 4). Similarly, subjects assigned to simvastatin 40 mg started dosing with simvastatin 20 mg at Visit 4 (Week 0) and had their dose titrated to 40 mg at Visit 6 (Week 4). Treatment was administered according to a double-blind, double-dummy design and each subject dose consisted of one small tablet, one large tablet, and one capsule.

The study planned to recruit approximately 300 randomized subjects from the special population of subjects with primary hypercholesterolemia or combined dyslipidemia and two or more risk factors for coronary heart disease. Subjects who qualified entered a 6- to 8-week wash-out/dietary lead-in period followed by a 12-week treatment period as shown in the following study design schematic:

Study Design



Dose selection:

Simvastatin was chosen as the comparator since it is one of the most commonly used and well-studied statins in clinical use in Europe. At therapeutic doses of 5 to 80 mg QD, simvastatin reduces mean LDL concentrations by approximately 26-47%. The doses of simvastatin selected for this study are those recommended by the manufacturers of the product and assessed in the Scandinavian Simvastatin Survival Study, although simvastatin may be given at doses as low as 5mg QD and as high as 80 mg QD.

The 6% non-inferiority margin for the percent change in LDL from baseline to endpoint was chosen because this has precedent in a number of published statin non-inferiority studies.

Selection of study population:

Subjects included in this study were males or females with primary hypercholesterolemia or combined dyslipidemia with two or more risk factors for coronary heart disease and elevated plasma LDL (≥ 130 mg/dL and ≤ 220 mg/dL). This study randomized 355 subjects at 43 centers in Spain, Sweden, Denmark, The Netherlands and the UK in order to assure 300 completers.

Inclusion Criteria:

- Males and females (age range 18-75 years);
- Non-pregnant, non-lactating females. Women of child bearing potential were allowed to enter the study only if they use sustained contraceptive preparations (e.g., implants or intramuscular injections) or complied with an approved mechanical contraceptive method. A woman was considered to be of childbearing potential unless she was post-hysterectomy or at least one year post-menopausal or post-tubal ligation. All women of child bearing potential were required to have a negative pregnancy test at the beginning of the dietary lead-in period (Visit 1 [Week -8/-6]), and before initiating active treatment (Visit 4 [Week 0]);
- Presence of at least two of the following CVD risk factors:
 - Cigarette smoking;

- Hypertension (blood pressure $\geq 140/90$ mmHg or on antihypertensive medication);
- Low HDL (<40 mg/dL);
- Family history of premature CHD (CHD in male first-degree relative <55 years of age or CHD in female first-degree relative <65 years of age).
- Age (men ≥ 45 years, women ≥ 55 years);
- If HDL was >60 mg/dL at Visit 3 (Week -1) or Visit 3A (if applicable), the number of risk factors was reduced by one;
- Subjects who were eligible and able to participate in the study and who gave informed consent after the purpose and nature of the investigation was explained to them;
- To qualify for randomization at Visit 4 (Week 0), subjects were required to follow a fat and cholesterol restrictive diet in accordance with EAS guidelines during the dietary stabilization lead-in period (i.e., for at least 8 weeks for those subjects previously taking lipid-lowering medication and at least 6 weeks for those not previously taking lipid-lowering medication). subjects also agreed not to eat grapefruit or drink grapefruit juice for the duration of the study;
- To qualify for randomization at Visit 4 (Week 0), subjects presented with primary hypercholesterolemia or combined dyslipidemia, as defined by elevated plasma LDL (LDL ≥ 130 mg/dL and ≤ 220 mg/dL) despite dietary therapy and TG levels of ≤ 400 mg/dL at two visits during the dietary lead-in period. If these criteria were not satisfied at both Visit 2 (Week -2) and Visit 3 (Week -1), or if the LDL concentration of the lower qualifying specimen differed by $\geq 15\%$ from the higher qualifying specimen, one additional lipid sample was permitted for both variables one week after Visit 3 (Visit 3A) to enable the subject to qualify for randomization; and
- Subjects who agreed to be available for every clinic visit, which occurred in the morning.

Exclusion Criteria:

- Homozygous familial hypercholesterolemia (heterozygous component of familial hypercholesterolemia was acceptable for inclusion);
- Any conditions that could have caused secondary dyslipidemia. This included, but was not restricted to, alcoholism, auto-immune disease, nephrotic syndrome, uremia, any viral or non viral hepatitis clinically active within 12 months from study entry, obstructive hepatic or biliary disease, dys- or macroglobulinemia, multiple myeloma, glycogen storage disease, chronic pancreatitis, porphyria, and uncontrolled hypothyroidism or hyperthyroidism (controlled hypo- or hyperthyroidism [i.e., condition presenting with normal baseline serum TSH and treatment stable for at least the last two months prior to study entry] were permitted);
- Any surgical or medical condition that might have significantly altered the absorption, distribution, metabolism, or excretion of any drug. The investigator was guided by the evidence of any of the following: history of major gastrointestinal tract surgery (e.g., gastrectomy, gastroenterostomy, or small bowel resection), gastritis requiring active treatment, current active ulcers, gastrointestinal or rectal bleeding. Current active or

recurrent IBS or history of inflammatory bowel syndrome. Subjects with a past history of IBS without symptoms for at least the six months prior to the study start were allowed to enter the study;

- Uncontrolled diabetes mellitus as defined by glycosylated HbA_{1c} >8%. Subjects with controlled diabetes Type II were allowed, provided the disease was stable for at least the three months prior to study entry;
- Any history of pancreatic injury or pancreatitis, or impaired pancreatic function/injury as indicated by abnormal lipase or amylase;
- Liver injury as indicated by serum transaminase levels ALAT/SGPT, or ASAT/SGOT >1.5 x ULRR over the lead-in period. The ALAT/SGPT and ASAT/SGOT levels were required to be ≤1.5 x ULRR on at least 2 of the 3 evaluations between Visit 1 (Week -8/-6) and Visit 3 (Week -1) for the subject to be eligible for further study participation. If ALAT/SGPT and/or ASAT/SGOT was >2 x ULRR at any time point between Visit 1 (Week -8/-6) and Visit 3 (Week -1), the subject was immediately excluded from further study participation;
- Impaired renal function as indicated by serum creatinine levels >1.5 x ULRR at Visit 1 (Week -8/-6). However, if creatinine was between 1.5 and 2 x ULRR, one retest was permitted at Visit 2 (Week -2), provided all other criteria were fulfilled. Serum creatinine was required to be ≤1.5 x ULRR at the retest for the subject to be eligible for further study participation. If serum creatinine was >2 x ULRR at Visit 1 (Week -8/-6), the subject was immediately excluded from further study participation;
- Current obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions that were likely to require intervention during the course of the study or were regarded as clinically meaningful by the investigator;
- Serum creatine kinase (CK) >5 x ULRR. However, if at Visit 1 (Week-8/-6) serum CK was >5 x ULRR without a clinical explanation, one re-test was allowed. If the repeat CK was >5 x ULRR in the absence of conditions explaining the CK elevation, the subject was immediately excluded from further study participation;
- Uncontrolled hypothyroidism defined as TSH >ULRR. Subjects with TSH >ULRR at Visit 1 were permitted to have a retest at Visit 2 and if TSH was also >ULRR at Visit 2, the subject was excluded from the study;
- Any severe acute illness or severe trauma in the three months prior to Visit 1 (Week -8/-6);
- Major surgery three months prior to Visit 1 (Week -8/-6);
- Significant CVD prior to randomization, such as myocardial infarction, coronary or peripheral artery angioplasty, bypass graft surgery or severe or unstable angina pectoris within the previous three months;
- Evidence of symptomatic heart failure (as defined by NYHA class III or IV), gross cardiac enlargement (cardiothoracic ratio >0.5); significant heart block or cardiac arrhythmias. History of uncontrolled complex ventricular arrhythmias, uncontrolled atrial fibrillation/flutter, or uncontrolled supraventricular tachycardia with a ventricular response

rate of >100 beats per minute at rest. Subjects whose electrophysiological instability was controlled with a pacemaker or implantable cardiac device were eligible;

- Left ventricular ejection fraction <0.25;
- History of symptomatic cerebrovascular disease including cerebrovascular hemorrhage, transient ischemic attack or carotid endarterectomy within one month prior to randomization;
- **Any other medical or surgical conditions, which, in the investigator's opinion, placed the subject at higher risk derived from his or her participation in the study, which could confound the result of the study, or were likely to prevent the subject from complying with the requirements of the study or completing the study period;**
- Known HIV infection;
- Poorly controlled or uncontrolled hypertension;
- Prior or current known muscular or neuromuscular disease of any type;
- Current active neoplastic disease or subjects who were anticipated to require antineoplastic treatment during the course of the study. History of prior malignancy, except subjects who had been cancer free for >10 years. Subjects with a history of basal cell carcinoma or squamous cell carcinoma of the skin were eligible if they had been cancer free for >5 years prior to screening;
- History of drug abuse or continuous consumption of more than 65mL pure alcohol per day (e.g., more than 4 x 125 mL glasses of wine or three glasses of spirits per day) within the previous two years;
- Exposure to any investigational new drug within 30 days of study entry (Visit 1/Week -8/-6) or ingestion of any drug known to be toxic to a major organ system (such as those producing blood dyscrasias, nephrotoxicity, hepatotoxicity or neurotoxicity) within 12 weeks prior to the study entry (Visit 1/Week -8/-6);
- Current or recent (within four weeks of Visit 1 [Weeks -8/-6]) use of supplements known to alter lipid metabolism (e.g., soluble fibers [including >2 teaspoons Metamucil or psyllium containing supplement per day]), or other dietary fiber supplements, fish oils, or other products, at the discretion of the investigator;
- History of hypersensitivity reactions to other HMG-CoA reductase inhibitors;
- Concomitant medications listed below:

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

1. All agents used for or under investigation for lowering or modifying plasma lipid levels, including statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors (including ezetimibe), and nicotinic acid >500 mg per day. Subjects on these medications could participate in the study provided treatment was interrupted at least 8 weeks prior to randomization;
 2. Oral contraceptives or any systemic steroid hormones (including estrogens, progestins, androgens or glucocorticoids) for any condition, except for noncyclic (continuous) administration of estrogen/progesterone replacement therapy or sustained contraceptive preparations (e.g., implants or intramuscular injections) that must have been constant for at least the three months prior to study entry (Visit 1/Week -8/-6) and were anticipated to remain unchanged for the duration of the study. Subjects on systemic steroidal treatment were permitted to enter the study if the treatment was discontinued at least 4 weeks prior to Visit 1 (Week -8/-6). Steroid hormones administered topically or as inhalers were permitted. Non-steroidal anti-inflammatory agents were allowed provided dosing was stable for at least four weeks prior to entry into the study but were disallowed if used for immunosuppressive therapy;
 3. Anticoagulants and antiplatelet drugs, other than aspirin or ticlopidine in stable doses. Use of aspirin for pain relief, when required, was allowed;
 4. HIV protease inhibitors;
 5. Cyclosporine;
 6. Systemic azole antifungal agents (e.g., itraconazole or ketoconazole);
 7. Nefazodone (antidepressant);
 8. Continuous systemic erythromycin, clarithromycin, and telithromycin;
 9. Digoxin;
 10. Amiodarone and verapamil (calcium antagonists);
 11. Danazol (gonadotropin inhibitor);
 12. Grapefruit and grapefruit juice; and
 13. Glitazones/thiazolidinediones (pioglitazone, rosiglitazone).
- History of resistance to lipid-lowering medications.
 - Known hypersensitivity or intolerance to any lipid-lowering agent (i.e., elevated serum transaminases, myositis);
 - Excessive obesity defined as BMI above 35 kg/m². BMI values were to be rounded to the nearest whole number: down at <0.5 and up at ≥0.5;

- Any factor that made regular clinic attendance in the morning impractical (e.g., shift and/or night work); and/or
- Any signs of mental dysfunction or other factors (including language problems) likely to limit the ability of the subject to cooperate with the performance of the study.

Removal of subjects form therapy or assessment:

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

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

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

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

Treatment:

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

Study Populations:

The following analysis populations were defined:

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

Analysis Population:

The final protocol only stipulated the use of the ITT and Safety populations. The ITT population defined in the protocol was renamed and referred to as the FAS.

Sample Size Justification:

A sample size of 300 randomized subjects was planned, with 200 subjects in the pitavastatin 4 mg group and 100 subjects in the simvastatin 40 mg group. Assuming an SD of 12 (for percent reduction from baseline LDL), a non-inferiority limit of 6% for the treatment difference, and a one-tailed test at the 2.5% significance level, this sample size provided 99% power to reject the null hypothesis that the mean percent decrease from baseline LDL was at least 6% greater in the simvastatin group than in the pitavastatin group, vs. the alternative that any advantage in the simvastatin group was less than the non-inferiority limit.

Statistical analysis of the primary efficacy variable:

The percent change in LDL from baseline to 'endpoint' for the FAS and the percent change in LDL from baseline to Week 12 (Visit 8) for the PP and COM populations were analyzed using analysis of covariance (ANCOVA) including treatment and country as factors and the baseline LDL as a covariate.

A two-sided 95% CI was constructed for the adjusted mean difference between treatment groups (i.e., simvastatin 40 mg minus pitavastatin 4 mg). Pitavastatin was considered equivalent (non inferior) to simvastatin at the doses tested if the lowest bound on the 95% CI was greater than -6% for the comparison between treatment groups.

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

The primary efficacy variable (LDL lowering) was also analyzed within the following subgroups:

- Age (<65 years, ≥65 years);
- Sex;
- Race (Caucasian, Non-Caucasian);
- BMI (<25 kg/m², 25-<30 kg/m², 30+ kg/m²);

- Risk Category (Low, Moderate, High [as defined by NCEP Guidelines]);
- Baseline LDL (<160 mg/dL, 160-190 mg/dL, >190 mg/dL);
- Hypertension (Yes, No);
- Diabetes (Yes, No);
- Primary diagnosis (primary hypercholesterolemia, combined dyslipidemia, heterozygous familial hypercholesterolemia).

Treatment by subgroup interactions were tested (ANCOVA) for those subgroups where each level of the subgroup included $\geq 5\%$ of subjects. Summary statistics of the percent change in LDL from baseline to endpoint were presented by treatment for each level of each subgroup.

Statistical analysis of the secondary efficacy variable:

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

The LDL targets were calculated using data collected prior to randomization, based on the NCEP Adult Treatment Panel III Guidelines. Target attainment, using the NCEP criteria was determined using the LDL value from the last visit (endpoint for FAS or Week 12 for the PP population). The proportion of subjects who reached their LDL target was analyzed using a linear probability model, which assumes the identity link and binomial distribution including treatment, country, risk categories (high, medium or low risk as defined in the NCEP guidelines) and baseline LDL (categorized as defined in the NCEP guidelines), as factors. Point estimates (and 95% CIs) of the differences between the pitavastatin group and the simvastatin group were presented.

Protocol Amendments:

There were two amendments to Protocol NK-104-304:

Amendment 1:

- The central laboratory had the lipid results for each visit and informed the site as to whether or not the subjects were eligible to take part in the study.
- Lipid results were only revealed for those subjects who did not meet the inclusion criteria during the dietary lead-in phase and who were, therefore, discontinued from further participation in the study.
- Following each visit during the dietary lead-in period, investigators were informed by the central laboratory as to whether or not a **specific subject's lipid and blood chemistry profiles** were within the qualifying range for continued participation in the study

Amendment 2:

- Glitazones were excluded from allowed concomitant medication, to exclude any potential influence on the measurement of TG, HDL and LDL.
- Proteinuria assessments were added at baseline (randomization visit) and end of treatment.

- Inclusion criterion #3 (risk factors) was clarified by the statement that elevated HDL had to be documented at Visit 3 (Week -1) or Visit 3A (if applicable).
- Exclusion criterion #19 (poorly controlled or uncontrolled hypertension) was modified by deleting specified maximum blood pressure values.
- Minor errors in the protocol were corrected and some administrative changes were made.

Changes in the Planned Analysis:

The following changes from the analysis planned in the protocol were included in the amended SAP:

Baseline Lipid Values:

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

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

Protocol violations:

Overall, of the 236 subjects randomized to the pitavastatin 4 mg group, 54 (22.9%) were excluded from the PP population and of the 119 subjects randomized to the simvastatin 40 mg group, n=35 (29.4%) were excluded from the PP population. The reasons for exclusion from the PP population were generally balanced between the two treatment groups, although the proportion of subjects excluded from the PP population in the simvastatin 40 mg group was **almost double the proportion excluded in the pitavastatin 4 mg group for the reasons: “No Week 12 lipid assessment” (10.9% vs. 5.9%, respectively), “Lipid-lowering or other prohibited medications” (11.8% vs. 5.9% respectively).**

Disposition of subjects:

A summary of subject disposition by treatment group and analysis population is presented in the following table:

Subject Disposition		
	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
Number of subjects Randomized	236	119
Safety Population	233 (98.7%)	119 (100.0%)
Full Analysis Set (FAS)	233 (98.7%)	118 (99.2%)
Per Protocol Population (PP)	182 (77.1%)	84 (70.6%)
Completers (COM)	223 (94.5%)	107 (89.9%)
Discontinued Study Drug	13 (5.5%)	12 (10.1%)
Reason for Discontinuation from Study		
Adverse Event	9 (3.8%)	6 (5.0%)
Protocol violation	1 (0.4%)	2 (1.7%)
Withdrew consent	3 (1.3%)	3 (2.5%)
Lost to follow-up	0 (0.0%)	1 (0.8%)

Investigators at 37 centers randomized a total of 355 subjects: 236 subjects were randomized to treatment with pitavastatin 4 mg and 119 to simvastatin 40 mg. Of the 355 subjects randomized, 352 received at least one dose of study drug (Safety population), 233 took pitavastatin 4 mg and 119 took simvastatin 40 mg. Overall, 141 (39.7%) were randomized at five centers in Denmark, 70 (19.7%) were randomized at eight centers in the Netherlands, 62 (17.5%) were randomized at nine centers in Spain, 46 (13.0%) were randomized at eight centers in Sweden, and 36 (10.1%) of the subjects were randomized at seven centers in the UK. The greatest number of subjects randomized at a single center was 46 (13.0% of all subjects), at Center 4302 in Denmark.

Demographic and Other Baseline Characteristics:

The demographic data are summarized in the following table:

Demographic and Other Baseline Characteristics		
Demographic Characteristic	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=119
Sex (n, %)		
Male	158 (67.8%)	82 (68.9%)
Female	75 (32.2%)	37 (31.1%)
Age (years)		
Mean (SD)	60.1 (6.82)	60.9 (6.78)
Range	35-75	40-74
Age group (n,%)		
<35 years	0 (0.0%)	0 (0.0%)
35-39 years	2 (0.9%)	0 (0.0%)
40-44 years	3 (1.3%)	4 (3.4%)
45-49 years	9 (3.9%)	5 (4.2%)
50-54 years	24 (10.3%)	5 (4.2%)
55-59 years	73 (31.3%)	31 (26.1%)
60-64 years	73 (31.3%)	43 (36.1%)
65-69 years	30 (12.9%)	18 (15.1%)
70-74 years	17 (7.3%)	13 (10.9%)
≥75 years	2 (0.9%)	0 (0.0%)
Race (n,%)		
Caucasian	233 (100.0%)	118 (99.2%)
Black	0 (0.0%)	1 (0.8%)

Demographic and Other Baseline Characteristics		
Demographic Characteristic	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=119
Primary diagnosis (n,%)		
Primary hypercholesterolemia	194 (83.3%)	102 (85.7%)
Combined dyslipidemia	35 (15.0%)	14 (11.8%)
Heterozygous familial hypercholesterolemia	4 (1.7%)	3 (2.5%)
Duration of current disease (years)		
Mean (SD)	3.65 (5.38)	4.47 (6.03)
Range	-0.11-26.08	-0.12-27.12
Height (m)		
Mean (SD)	1.71 (0.10)	1.71 (0.10)
Range	1.4-2.0	1.5-1.9
Weight (Kg)		
Mean (SD)	80.78 (13.53)	80.94 (12.83)
Range	46.5-120.0	50.4-122.7
BMI (Kg/m²)		
Mean (SD)	27.57 (3.52)	27.57 (3.25)
Range	19.2-35.0	19.4-34.8
NCEP risk category (n,%)		
High risk	59 (25.3%)	35 (29.4%)
Moderate risk	165 (70.8%)	79 (66.4%)
Low risk	9 (3.9%)	5 (4.2%)
Diabetes (n,%)		
Present	15 (6.4%)	8 (6.7%)
Hypertension (n,%)		
Present	123 (52.8%)	70 (58.8%)
Number (%) of subjects with any Prior Lipid Modifying Medication		
Cholesterol and triglyceride reducers:	81 (34.8%)	47 (39.5%)
Atorvastatin and atorvastatin calcium	19 (8.2%)	12 (10.1%)
Ezetimibe	2 (0.9%)	1 (0.8%)
Fenofibrate	1 (0.4%)	1 (0.8%)
Fluvastatin	4 (1.7%)	6 (5.0%)
Pravastatin and pravastatin sodium	1 (0.4%)	1 (0.8%)
Rosuvastatin	2 (0.9%)	0 (0.0%)
Simvastatin	56 (24.0%)	27 (22.7%)

Approximately two-thirds (240/352 subjects) were male and one-third were female, with the proportions of males and females being similar in both treatment groups (67.8% vs. 32.2% pitavastatin 4 mg; 68.9% vs. 31.1% simvastatin 40 mg). The mean age of the subjects was approximately 60 years in each treatment group, with the highest numbers of subjects falling into the age categories 55-59 years and 60-64 years. All subjects except one in the simvastatin group was Caucasian.

The treatment groups were well matched in terms of diagnosis and duration of disease. Most subjects in each treatment group had primary hypercholesterolemia (194 [83.3%] pitavastatin 4 mg; 102 [85.7%] simvastatin 40 mg) and most of the remainder had combined dyslipidemia (35 [15.0%] pitavastatin 4 mg; 14 [11.8%] simvastatin 40 mg). Seven subjects in total had heterozygous familial hypercholesterolemia. Mean time since diagnosis of dyslipidemia was 3.7 years in the pitavastatin 4 mg group and 4.5 years in the simvastatin 40 mg group.

Diabetes was present in 6.4% of subjects in the pitavastatin 4 mg group and 6.7% of subjects in the simvastatin 40 mg group. The prevalence of hypertension was 52.8% and 58.8% in the pitavastatin 4 mg and simvastatin 40 mg groups, respectively.

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

In summary, there were no apparent treatment group differences in baseline demographic characteristics.

Risk Factor Demographics for Coronary Heart Disease:

The prevalence of risk factors for coronary heart disease in the study population are summarized in the following table:

Risk Factors for Coronary Heart Disease (Safety Population)		
CHD Risk Factor	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=119
CHD or CHD risk equivalents at screening; n (%)		
Clinical CHD	16 (6.9%)	11 (9.2%)
Symptomatic carotid artery disease	1 (0.4%)	0 (0.0%)
Peripheral arterial disease	5 (2.1%)	2 (1.7%)
Abdominal aortic aneurysm	0 (0.0%)	1 (0.8%)
Diabetes	15 (6.4%)	8 (6.7%)
Major cardiovascular risk factors at Week 0; n (%)		
Hypertension - treated	108 (46.4%)	64 (53.8%)
Hypertension - untreated	15 (6.4%)	6 (5.0%)
Family history of premature CHD	104 (44.6%)	52 (43.7%)
Smoking status; n (%)		
Smoker	106 (45.5%)	52 (43.7%)
Non-smoker	127 (54.5%)	67 (56.3%)
TC at baseline; n (%)		
<160 mg/dL	0 (0.0%)	0 (0.0%)
160 - <200 mg/dL	5 (2.1%)	4 (3.4%)
200 - <240 mg/dL	95 (40.8%)	53 (44.5%)
240 - <280 mg/dL	110 (47.2%)	43 (36.1%)
≥280 mg/dL	23 (9.9%)	19 (16.0%)
HDL at baseline; n (%)		
≥60 mg/dL	29 (12.4%)	6 (5.0%)
50 - <60 mg/dL	54 (23.2%)	29 (24.4%)
40 - <50 mg/dL	87 (37.3%)	53 (44.5%)
<40 mg/dL	63 (27.0%)	31 (26.1%)
LDL at baseline; n (%)		
<160 mg/dL	97 (41.6%)	50 (42.0%)
160 - <190 mg/dL	102 (43.8%)	48 (40.3%)
≥190 mg/dL	34 (14.6%)	21 (17.6%)
Systolic blood pressure at Week 0; n (%)		
<120 mmHg	53 (22.7%)	22 (18.5%)
120 - 129 mmHg	63 (27.0%)	27 (22.7%)
130 - 139 mmHg	80 (34.3%)	51 (42.9%)
140 - 159 mmHg	37 (15.9%)	19 (16.0%)
≥160 mmHg	0 (0.0%)	0 (0.0%)

The two treatment groups were balanced with respect to CHD risk factors, although the proportion of subjects in the pitavastatin 4 mg group with treated hypertension was slightly lower compared with the simvastatin 40 mg group (46.4% vs. 53.8%, respectively).

Overall, NCEP risk categories for major coronary events were similar in both of the treatment groups: 25.3% of subjects in the pitavastatin 4 mg group and 29.4% of subjects in the simvastatin 40 mg group were at high risk of CVD.

Baseline lipid characteristics:

The baseline lipid characteristics are presented in the following table:

Baseline Lipids		
	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=119
LDL (mg/dL)		
Mean (SD)	166.1 (20.3)	166.68 (23.5)
Range	123.7-226.7	128.3-223.0
HDL (mg/dL)		
Mean (SD)	47.52 (11.4)	46.04 (8.2)
Range	25.3-100.3	29.0-63.3
TC (mg/dL)		
Mean (SD)	246.35 (25.5)	245.4 (30.3)
Range	187.7-307.7	194.7-334.7
TG (mg/dL)		
Mean (SD)	164.0 (67.87)	163.7 (66.1)
Range	53.7-412.3	67.3-364.3

The two groups were well matched for mean lipid values at baseline. Baseline mean values in the two treatment groups were: LDL approximately 166 mg/dL, HDL 46-47 mg/dL, TC 245-246 mg/dL, and TG approximately 164 mg/dL.

Most subjects had one or more medical history diagnoses at baseline: 218 (93.6%) subjects in the pitavastatin 4 mg group; 109 (91.6%) subjects in the simvastatin 40 mg group. The most common organ systems with medical history were cardiovascular (139 [59.7%] subjects in the pitavastatin 4 mg group; 78 [65.5%] subjects in the simvastatin 40 mg group) and musculoskeletal (109 [46.8%] subjects in the pitavastatin 4 mg group; 52 [43.7%] subjects in the simvastatin 40 mg group).

The proportion of subjects who were taking lipid-lowering medications prior to enrollment was similar in each treatment group, and was 81 (34.8%) in the pitavastatin 4 mg group and 47 (39.5%) in the simvastatin 40 mg group. The most common prior lipid-lowering medications were simvastatin and atorvastatin.

Less than half of subjects were smokers at baseline (106 [45.5%] subjects taking pitavastatin 4 mg; 52 [43.7%] subjects taking simvastatin 40 mg).

The majority of subjects were sporadic consumers of alcohol in both treatment groups (143 [61.4%] subjects taking pitavastatin 4 mg; 87 [73.1%] subjects taking simvastatin 40 mg). Three subjects (all in the pitavastatin 4 mg group) were excessive consumers of alcohol, (i.e., >3 glasses of wine or beer per day or >20 drinks per week).

Treatment Compliance:

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

Treatment Compliance (Safety Population)		
	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=119
Overall % compliance		
N	231 ¹	119
Mean (SD)	97.8 (5.05)	96.9 (8.07)
Median	99.6	98.9
Quartiles	97.6-100.0	96.4-100.0
Range	53-104	29-111

¹ Two subjects did not have compliance data

Analysis of Efficacy:

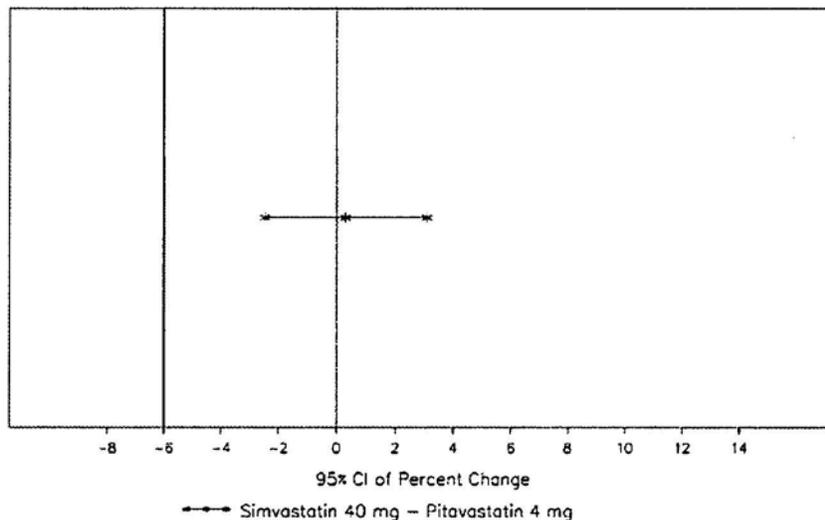
Primary Efficacy Variable: Mean Percent Change from Baseline in LDL:

The percent changes in LDL from baseline to endpoint for the FAS population is presented in the following table:

Change from Baseline to Endpoint or Week 12 in LDL (mg/dL) (FAS Population)		
	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
	FAS	
N	233	118
Baseline LDL		
Mean (SD)	166.1 (20.3)	166.9 (23.5)
Endpoint LDL		
Mean (SD)	92.9 (23.5)	93.3 (24.7)
% change from baseline to endpoint		
Mean (SD)	-43.96 (12.8)	-43.77 (14.4)
Adjusted Mean Difference (95% CI)	0.31 (-2.47; 3.09)	
P-value (test for difference)	0.829	

Changes in LDL in the PP and COM populations were similar.

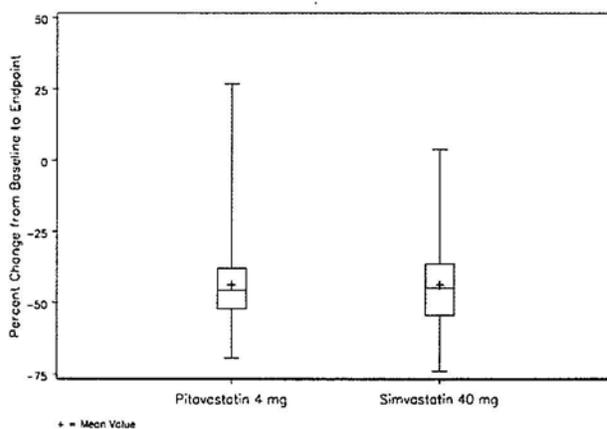
The 95% CIs for the treatment differences in the FAS are illustrated in the following table:



The mean change from baseline to endpoint in LDL in the FAS was -44.0% in the pitavastatin 4 mg group and -43.8% in the simvastatin 40 mg group. The adjusted mean difference between the treatments was 0.31%. The lower bound on the 95% CI, -2.5% was greater than -6%. Therefore, it was concluded that pitavastatin 4 mg was non-inferior to simvastatin 40 mg.

The analysis of this variable in both the PP and COM populations supported the findings in the FAS population.

Box plots of the percentage change from baseline to endpoint for each treatment are illustrated in the box plot following:

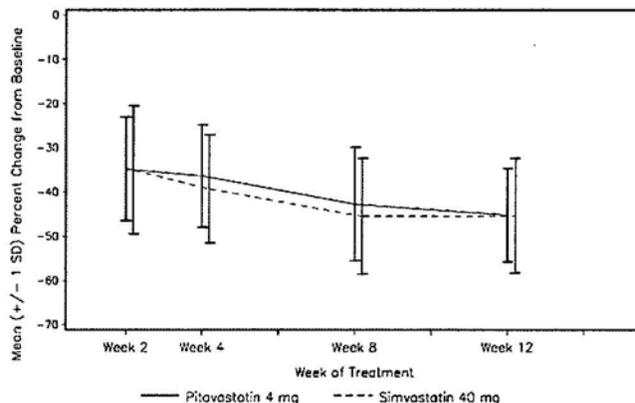


Horizontal lines on the boxes represent the median values and the 25th and 75th percentiles; vertical lines indicate the range of values.

The box plots illustrate the similarity in mean and median effect of two treatments.

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

The percent change from baseline of LDL over time is illustrated in the figure following



The mean percent reduction in LDL was approximately 35% in both treatment groups after 2 weeks of dosing. LDL levels continued to decrease throughout the 12-week treatment period in the pitavastatin 4 mg group until they had decreased by approximately 45% at Week 12. In the simvastatin 40 mg group, LDL levels decreased by approximately 45% during the first 8 weeks of treatment, then remained stable between Week 8 and Week 12.

Secondary Efficacy Variables:

LDL Target Attainment:

A summary of the number (percent) of subjects who attained the LDL target at endpoint as defined by NCEP criteria is shown in the following table:

Subjects With LDL Target Attainment (FAS)

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Number (%) of subjects with target attained according to NCEP criteria		
Unadjusted proportion achieving target results	203 (87.1%)	101 (85.6%)
Difference	-1.5	
(95% CI)	(-9.2; 6.1)	
P-value	0.695	

The proportion of subjects with LDL target attainment using NCEP criteria was 87.1% in the pitavastatin 4 mg group and 85.6% of subjects in the simvastatin 40 mg group. The difference between the groups was -1.5% and was not statistically significant (P=0.695). Linear probability models supported these analyses.

LDL Sub-Group Analyses:

LDL by Country:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Sweden		
N	27	19
Baseline	169.1	169.5
% change to endpoint	-44.1 (9.22)	-43.0 (10.6)
Spain		
N	42	20
Baseline	174.7	173.8
% change to endpoint	-35.2 (14.7)	-33.0 (15.3)
Denmark		
N	93	47
Baseline	165.0	167.5
% change to endpoint	-46.53 (11.85)	-46.29 (14.6)
Netherlands		
N	45	23
Baseline	161.2	158.7
% change to endpoint	-47.15 (10.5)	-46.24 (13.2)
UK		
N	26	9
Baseline	161.9	163.6
% change to endpoint	-43.3 (13.8)	-50.04 (11.2)

Subjects who were enrolled in Spain appeared to have higher mean LDL values at baseline, although the percent change from baseline to endpoint was less than in other countries. Across other countries, there was no discernible effect of country on the change from baseline in mean LDL. The mean percent decrease in LDL ranged between 43.3% and 47.2% in the pitavastatin 4 mg group, and between 43.0% and 50.0% in the simvastatin 40 mg group. The mean percent decrease in LDL in each country was generally similar in the two treatment groups, with the exception of the UK, where the mean percent decrease in LDL was greater for the simvastatin 40 mg group compared with the pitavastatin 4 mg group (50.0% vs. 43.3%, respectively). However, a total of only 35 subjects were included in the FAS in the UK with just nine of them receiving simvastatin.

LDL by Age:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
<65 years		
N	184	87
Baseline	166.7	169.4
% change to endpoint	-44.2 (11.5)	-42.30 (15.5)
≥65 years		
N	49	31
Baseline	163.9	159.8
% change to endpoint	-42.9 (16.7)	-47.9 (9.9)

In contrast to the simvastatin group, the mean percent decrease from baseline to endpoint in LDL was slightly higher in the younger subjects as compared to the pitavastatin group. This difference resulted in a statistically significant treatment-by-age group interaction (P=0.024).

LDL by BMI Category:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
<25 kg/m²		
N	56	24
Baseline	166.3	165.0
% change to endpoint	-46.1 (12.1)	-45.56 (14.2)
25-<30 kg/m²		
N	120	69
Baseline	165.4	166.7
% change to endpoint	-43.8 (13.1)	-43.37 (14.8)
≥30 kg/m²		
N	57	25
Baseline	167.4	169.1
% change to endpoint	-42.3 (12.6)	-43.2 (14.1)

There was a slightly greater mean percent decrease in LDL observed in both treatment groups in subjects with a BMI of <25 kg/m² compared with subjects with higher BMIs. The p-value for the interaction between treatment and BMI category was P=0.870.

LDL by NCEP CHD Risk Category:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Low risk		
N	9	5
Baseline	163.1	173.7
% change to endpoint	-39.81 (22.1)	-37.05 (23.6)
Moderate risk		
N	165	78
Baseline	165.9	163.7
% change to endpoint	-44.5 (12.5)	-43.22 (14.8)
High risk		
N	59	35
Baseline	167.0	172.9
% change to endpoint	-43.1 (11.9)	-46.0 (11.8)

Subjects in the low risk category of both treatment groups had slightly lower reductions from baseline in LDL compared with the moderate and high risk categories. However only 14 of the 351 subjects in the FAS were in the low risk category and so this observation should be interpreted with caution. The p-value for the interaction between treatment and risk category was P=0.673.

LDL by Baseline LDL Category:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
<160 mg/dL		
N	97	49
Baseline	146.2	144.7
% change to endpoint	-42.71 (13.7)	-42.8 (16.)
160-190 mg/dL		
N	102	48
Baseline	174.4	173.3
% change to endpoint	-44.39 (12.8)	-43.90 (13.9)
≥190 mg/dL		
N	34	21
Baseline	197.9	203.8
% change to endpoint	-46.2 (9.1)	-45.8 (10.5)

The mean percent decrease from baseline in LDL was similar in the two treatment groups within each baseline LDL category. However, there were somewhat greater mean percent decreases in LDL with increasing baseline LDL levels on both treatment groups. The p-value for the interaction between treatment and baseline LDL was P=0.792.

Secondary Efficacy Lipid Variables:

Total cholesterol (TC)

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	246.3 (25.5)	245.6 (30.3)
Endpoint mean (SD)	168.8 (27.5)	168.3 (29.0)
Mean % change (SD)	-31.4 (9.5)	-31.16 (11.1)
Adjusted Mean Difference (95% CI)	0.28 (-1.8; 2.3)	
P-value	0.793	

There was no difference between the two groups in mean percent decrease in TC (31.4% pitavastatin 4 mg group; 31.2% simvastatin 40 mg group). The adjusted mean difference for the treatment group comparison was 0.3%, and was not statistically significant (P=0.793).

High Density Lipoprotein cholesterol (HDL):

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	47.5 (11.4)	46.0 (8.2)
Endpoint mean (SD)	50.5 (12.2)	47.9 (9.1)
Mean % change (SD)	6.81 (12.6)	4.50 (12.1)
Adjusted Mean Difference (95% CI)	-2.3 (-4.91; 0.30)	
P-value	0.083	

There was an increase in HDL values of 6.8% in the pitavastatin 4 mg group and 4.5% in the simvastatin 40 mg group. The adjusted mean difference for the treatment group comparison was -2.30%, and was not statistically significant in the FAS (P=0.083). However, in the PP population, the adjusted mean difference for the treatment group comparison was -3.4% (95% CI -6.3; -0.50) and was statistically significant (P=0.021).

Triglycerides (TG):

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	164.0 (67.9)	163.9 (66.3)
Endpoint mean (SD)	126.7 (53.1)	136.6 (72.2)
Mean % change (SD)	-19.76 (21.3)	-14.81 (29.7)
Adjusted Mean Difference (95% CI)	5.23 (0.15; 10.3)	
P-value	0.044	

Triglycerides decreased by 19.8% in the pitavastatin 4 mg group and by 14.8% in the simvastatin 40 mg group. The adjusted mean difference for the treatment group comparison was 5.2%, and was statistically significant (P=0.044).

Apolipoprotein B (Apo-B):

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	152.5 (20.9)	153.3 (24.6)
Endpoint mean (SD)	100.7 (21.8)	100.9 (21.3)
Mean % change (SD)	-33.7 (12.3)	-33.8 (12.9)
Adjusted Mean Difference (95% CI)	0.46 (-2.15; 3.07)	
P-value	0.730	

Apo-B decreased by almost 34% in both treatment groups. The adjusted mean difference for the treatment group comparison was 0.5%, which was not statistically significant (P=0.730).

Apolipoprotein A1 (Apo-A1):

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	158.4 (26.1)	155.5 (20.8)
Endpoint mean (SD)	169.3 (27.1)	165.4 (21.9)
Mean % change (SD)	7.62 (12.7)	6.86 (12.1)
Adjusted Mean Difference (95% CI)	-1.28 (-3.86; 1.30)	
P-value	0.330	

Apolipoprotein A1 values were similar in both treatment groups at baseline. At endpoint, Apo-A1 increased by 7.6% in the pitavastatin 4 mg group and by 6.9% in the simvastatin 40 mg group. The adjusted mean difference between treatment groups was -1.3%, which was not statistically significant (P=0.330).

Non-HDL:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	198.8 (25.2)	199.6 (29.3)
Endpoint mean (SD)	118.3 (26.8)	120.4 (27.6)
Mean % change (SD)	-40.44 (11.7)	-39.24 (13.5)
Adjusted Mean Difference (95% CI)	1.35 (-1.17; 3.87)	
P-value	0.293	

Non-HDL cholesterol was similar in both treatment groups at baseline and decreased by approximately 40% to endpoint. The adjusted mean difference for the treatment group comparison was 1.4%, which was not statistically significant (P=0.293).

Non-HDL:HDL ratio:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	4.449 (1.25)	4.500 (1.090)
Endpoint mean (SD)	2.510 (0.991)	2.614 (0.823)
Mean change (SD)	-1.939 (0.905)	-1.886 (0.912)
Adjusted Mean Difference (95% CI)	0.073 (-0.071; 0.218)	
P-value	0.319	

The ratio of non-HDL:HDL was similar in both treatment groups at baseline. At endpoint, non-HDL:HDL decreased by approximately 1.9 in both treatment groups. The adjusted mean difference for the treatment group comparison was 0.07, which was not statistically significant (P=0.319).

TC:HDL Ratio:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	5.45 (1.25)	5.50 (1.09)
Endpoint mean (SD)	3.51 (0.99)	3.61 (0.823)
Mean change (SD)	-1.94 (0.905)	-1.89 (0.912)
Adjusted Mean Difference (95% CI)	0.073 (-0.071; 0.218)	
P-value	0.319	

The ratio of TC:HDL was similar in both treatment groups at baseline. At endpoint, TC:HDL decreased by approximately 1.9 in both treatment groups. The adjusted mean difference for the treatment group comparison was 0.07, which was not statistically significant (P=0.319).

Apo-B:Apo-A1 Ratio:

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	0.99 (0.239)	1.00 (0.197)
Endpoint mean (SD)	0.61 (0.215)	0.62 (0.153)
Mean change (SD)	-0.38 (0.197)	-0.38 (0.174)
Adjusted Mean Difference (95% CI)	0.00 (-0.03; 0.04)	
P-value	0.929	

The ratio of Apo-B:Apo-A1 was similar in both treatment groups at baseline. At endpoint, Apo-B:Apo-A1 decreased by 0.38 in both treatment groups. The adjusted mean difference between treatment groups was 0.00, which was not statistically significant (P=0.929).

High Sensitivity C-Reactive Protein (hsCRP):

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

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

	Pitavastatin 4 mg QD N=233	Simvastatin 40 mg QD N=118
Baseline mean (SD)	3.21 (4.89)	3.77 (7.93)
Endpoint mean (SD)	2.85 (4.54)	3.88 (11.3)
Mean change (SD)	-0.36 (6.04)	0.05 (5.46)
Adjusted Mean Difference (95% CI)	0.48 (-0.81; 1.78)	
P-value	0.0462	

Mean CRP values at baseline were similar in both treatment groups. At endpoint, CRP decreased by 0.36 mg/L in the pitavastatin 4 mg group and increased by 0.05mg/L in the simvastatin 40 mg group. The adjusted mean difference between treatment groups was 0.48 mg/L, which was not statistically significant (P=0.462).

Efficacy Conclusions:

- Pitavastatin 4 mg was non-inferior to simvastatin 40 mg for the percent change from baseline to Week 12 or endpoint in LDL in the FAS, COM and PP populations.
- NCEP LDL target attainment was achieved in a similar proportion of subjects in both treatment groups. The proportions of subjects with LDL target attainment were, for the pitavastatin 4 mg and simvastatin 40 mg groups respectively, 87.1% and 85.6% using NCEP criteria.
- There was a significantly greater decrease from baseline to endpoint in TG in the pitavastatin 4 mg group compared with the simvastatin 40 mg group (19.76% vs. 14.81%, respectively; P=0.044).
- There was a greater increase from baseline in HDL in the pitavastatin 4 mg group (6.81%) than in the simvastatin 40 mg group (4.50%). The difference was not statistically significant in the FAS (P=0.083), but the adjusted mean difference in the PP population was -3.37%, which was statistically significant (P=0.021).
- There were no significant differences in the change from baseline to endpoint between pitavastatin 4 mg and simvastatin 40 mg for the secondary lipid variables TC, Apo-B, non HDL, non-HDL:HDL, TC:HDL, Apo-A1, Apo-B:Apo-A1, and hsCRP.

3.4 Study of Pitavastatin 4 mg vs. Atorvastatin 20 mg (Following Up-Titration) in subjects with Type II Diabetes Mellitus and Combined Dyslipidemia [NK-104-305]

First subject in date: 05 December 2005

Last subject out date: 26 June 2007

3.4.1.1 General Discussion of Study Objectives, Endpoints and Methods

Primary Objective:

- To demonstrate the non-inferiority of pitavastatin 4 mg QD vs. atorvastatin 20 mg QD in reducing low-density lipoprotein cholesterol (LDL) when administered for 12 weeks using an up-titration regimen in subjects with Type II DM and combined dyslipidemia.

Secondary Objectives:

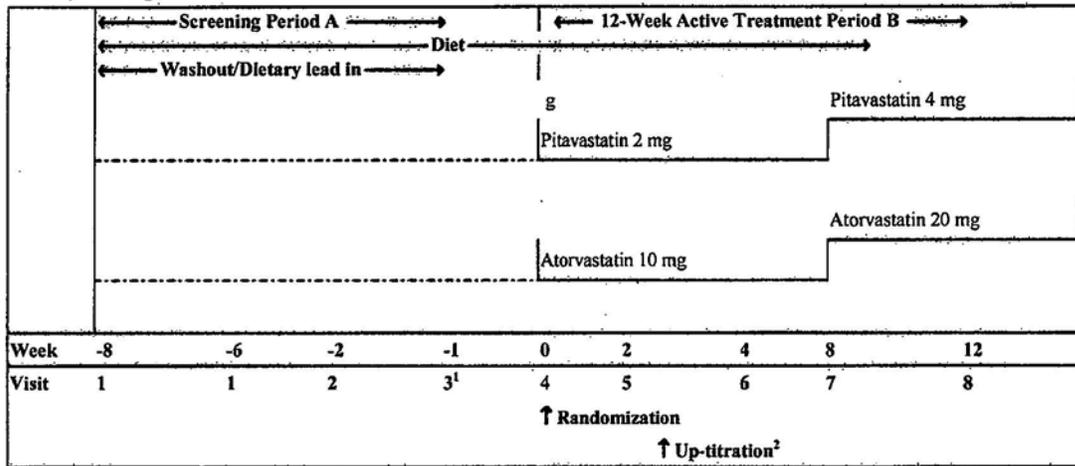
- To compare the efficacy of pitavastatin 4 mg QD vs. atorvastatin 20 mg QD with respect to changes from baseline in other lipid and lipoprotein fractions (TC, HDL], TC:HDL ratio, non-HDL, non-HDL:HDL ratio, TG, Apo-B and Apo-A1, Apo-B:Apo-A1 ratio, hsCRP, adiponectin, small-dense-LDL, RLP-C, LDL, and LDL target attainment according to NCEP criteria in subjects with Type II DM and combined dyslipidemia; and
- To assess the safety and tolerability of pitavastatin 4 mg QD when administered for 12 weeks with a forced up-titration at Week 4.

Study Design:

This was an 18 to 20 week, randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, non-inferiority study. The study planned to recruit approximately 400 subjects with Type II DM and combined dyslipidemia. Subjects who qualified entered a 6 to 8-week washout/dietary lead-in period followed by a 12-week treatment period. Subjects were randomly assigned to one of the two treatment groups: pitavastatin 4 mg QD or atorvastatin 20 mg QD in a ratio of 2:1. Subjects assigned to pitavastatin 4 mg started with pitavastatin 2 mg at Visit 4 (Week 0) and had their dose titrated to 4 mg at Visit 6 (Week 4). Similarly, subjects assigned to atorvastatin 20 mg started with atorvastatin 10 mg at Visit 4 (Week 0) and had their dose titrated to 20 mg at Visit 6 (Week 4).

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

Study Design:



Dose selection:

Atorvastatin was chosen as the comparator since it is one of the most commonly used and well-studied statins.

In the European Phase 2 dose ranging studies in subjects with primary hypercholesterolemia and combined hyperlipidemia, doses of 1, 2, 4, 8 mg of pitavastatin were well tolerated¹ and the 4 mg dose has been shown to lower LDL, TC, TG, Apo-B, as well as increase HDL. Since pitavastatin was well tolerated at these doses, a favorable risk-benefit ratio was expected in this study.

b(4)

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

Selection of Study Population:

Inclusion Criteria:

- Males and females (age 18-75 years);
- Type II DM treated with oral anti-diabetic medication (e.g., sulfonylurea, metformin or combination therapy) or insulin but excluding glitazones;
- Glycosylated HbA_{1c} ≤7.5% (at Visit 1);
- Absence of proliferative diabetic retinopathy, cataract(s) (if this precluded satisfactory ophthalmoscopic examination of the retina) or diabetic nephropathy (other than microalbuminuria - urine albumin excretion ≤300 mg/24 hours);
- Body Mass Index (BMI) ≤35 kg/m²;
- Non-pregnant, non-lactating females. Women of child bearing potential were allowed to enter the study only if they used sustained contraceptive preparations (e.g., implants or intramuscular injections) or complied with an approved mechanical contraceptive method. A woman was considered to be of childbearing potential unless she was post-hysterectomy

(b) (4)

or at least one year post-menopausal or post-tubal ligation. All women of childbearing potential had a negative pregnancy test at the beginning of the dietary lead-in period (Visit 1/Week -8/-6), and before initiating active treatment (Visit 4/Week 0);

- Subjects who were eligible and able to participate in the study and gave informed consent after the purpose and nature of the investigation had been explained to them;
- In order to qualify for randomization at Visit 4 (Week 0), subjects must have been following a fat and cholesterol restrictive diet as advised by the EAS during the dietary stabilization lead-in period (i.e., for at least 8 weeks for those subjects previously taking lipid-lowering medication and at least 6 weeks for those not previously taking lipid-lowering medication). Subjects also agreed not to eat grapefruit or to drink grapefruit juice for the duration of the study;
- In order to qualify for randomization at Visit 4 (Week 0), subjects presented with combined dyslipidemia, as defined by elevated plasma LDL (LDL ≥ 100 mg/dL and ≤ 220 mg/dL) despite dietary therapy and elevated TG levels of ≥ 150 mg/dL at two consecutive visits during the dietary lead-in period (the mean of the two consecutive visits was used). If these criteria were not satisfied at Visit 2 (Week -2) and Visit 3 (Week -1), or if the LDL concentration of the lower qualifying specimen differed by $\geq 15\%$ from the higher qualifying specimen, one additional lipid sample was permitted for both variables one week after Visit 3 (Visit 3A) to enable the subject to qualify for randomization; and
- Subjects who agreed to be available for every clinic visit, which occurred in the morning.

Exclusion Criteria:

- Homozygous familial hypercholesterolemia (heterozygous component of familial hypercholesterolemia was acceptable for inclusion);
- Any conditions that may have caused secondary dyslipidemia. This included, but was not restricted to, alcoholism, auto-immune disease, nephrotic syndrome, uremia, any viral, or non viral hepatitis clinically active within 12 months from study entry, obstructive hepatic or biliary disease, dys- or macroglobulinemia, multiple myeloma, glycogen storage disease, chronic pancreatitis, porphyria, and uncontrolled hypothyroidism or hyperthyroidism (controlled hypo- or hyperthyroidism [i.e., condition presenting with normal baseline serum TSH and treatment stable during at least the last two months prior to study entry] was permitted);
- Uncontrolled diabetes mellitus as defined by glycosylated hemoglobin (HbA_{1c}) $>7.5\%$;
- Any surgical or medical condition that might have significantly altered the absorption, distribution, metabolism, or excretion of any drug. The investigator was guided by the evidence of any of the following: history of major gastrointestinal tract surgery (e.g., gastrectomy, gastroenterostomy, or small bowel resection, gastritis, current active ulcers, gastrointestinal or rectal bleeding);
- Current active or recurrent irritable bowel syndrome (IBS) or history of inflammatory bowel syndrome. Subjects with a past history of IBS without symptoms for at least the last six months prior to the study start were allowed to enter the study;
- Any history of pancreatic injury or pancreatitis, or impaired pancreatic function/injury as indicated by abnormal lipase or amylase;

- Liver injury as indicated by serum transaminase levels ($[\text{ALAT}]/[\text{SGPT}]$; $\text{ALAT}/\text{SGPT}=\text{ALAT}, [\text{ASAT}]/[\text{SGOT}]; \text{ASAT}/\text{SGOT}=\text{ASAT}) >1.5$ x upper limit of reference range (ULRR) over the lead-in period. The ALAT/SGPT and ASAT/SGOT levels were required to be ≤ 1.5 x ULRR on at least two of the three evaluations between Visit 1 (Week -8/-6) and Visit 3 (Week -1) for the subject to have been eligible for further study participation. If ALAT/SGPT and/or ASAT/SGOT was >2 x ULRR at any time point between Visit 1 (Week -8/-6) and Visit 3 (Week -1), the subject was immediately excluded from further study participation;
- Impaired renal function as indicated by serum creatinine levels >1.5 x ULRR at Visit 1 (Week -8/-6). However, if creatinine was between 1.5 and 2 x ULRR, one retest was permitted at Visit 2 (Week -2), provided all other criteria were fulfilled. Serum creatinine had to be ≤ 1.5 x ULRR at the retest for the subject to have been eligible for further study participation. If serum creatinine was >2 x ULRR at Visit 1 (Week -8/-6), the subject was immediately excluded from further study participation;
- Current obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions that were likely to require intervention during the course of the study or were regarded as clinically meaningful by the investigator;
- Serum creatine kinase (CK) >5 x ULRR without a clinical explanation. If at Visit 1 (Week -8/-6) serum CK was >5 x ULRR with a clinical explanation (such as extreme exertion or intramuscular injections, etc.) a re-test was allowed. If the repeat CK was >5 x ULRR, the subject was immediately excluded from further study participation;
- Uncontrolled hypothyroidism defined as TSH $>$ ULRR. Subjects with TSH $>$ ULRR at Visit 1 were permitted to have a retest at Visit 2, and if TSH was also $>$ ULRR at Visit 2, the subject was excluded from the study;
- Any severe acute illness or severe trauma in the last 3 months prior to Visit 1 (Week -8/-6);
- Major surgery, during the three months prior to Visit 1 (Week -8/-6);
- Significant CVD prior to randomization, such as myocardial infarction, coronary or peripheral artery angioplasty, bypass graft surgery or severe or unstable angina pectoris within the previous three months;
- Evidence of symptomatic heart failure (as defined by NYHA, class 3 or 4), gross cardiac enlargement (cardiothoracic ratio >0.5); significant heart block or cardiac arrhythmias. History of uncontrolled complex ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardia with a ventricular response rate of >100 beats per minute at rest. Subjects whose electrophysiological instability were controlled with a pacemaker or implantable cardiac device were eligible;
- Left ventricular ejection fraction <0.25 ;
- History of symptomatic cerebrovascular disease including cerebrovascular hemorrhage, transient ischemic attack or carotid endarterectomy within one month prior to randomization;
- **Any other medical or surgical conditions, which, in the investigator's opinion, placed the subject at higher risk derived from his or her participation in the study, which could confound the result of the study, or were likely to prevent the subject from complying with the requirements of the study or completing the study period;**

- Known HIV infection;
- Poorly controlled or uncontrolled hypertension. Subjects had to have a systolic blood pressure ≤ 160 mmHg and diastolic blood pressure ≤ 90 mmHg with or without antihypertensive therapy;
- Prior or current known muscular or neuromuscular disease of any type;
- Current active neoplastic disease or subjects who might have required antineoplastic treatment during the course of the study. History of prior malignancy except those subjects who had been cancer free for >10 years prior to screening. Subjects with prior history of basal cell carcinoma or squamous cell carcinoma of the skin remained eligible if they had been cancer free for >5 of the previous years prior to screening;
- Within the last two years prior to randomization, a history of drug abuse or continuous consumption of more than 65 mL pure alcohol per day (e.g., more than 3 x 125 mL glasses of wine or 1.5 glasses of spirits per day);
- Exposure to any investigational new drug within 30 days of study entry (Visit 1/Week -8/-6) or ingestion of any drug known to have been toxic to a major organ system (such as those producing blood dyscrasias, nephrotoxicity, hepatotoxicity or neurotoxicity) within 12 weeks prior to study entry (Visit 1/Week -8/-6);
- Current or recent (within 4 weeks of Visit 1 [Week -8/-6]) use of supplements known to alter lipid metabolism, (e.g., soluble fibers [including >2 teaspoons of Metamucil or psyllium containing supplement per day]), or other dietary fiber supplements, fish oils, or other products at the discretion of the investigator;
- History of hypersensitivity reactions to other HMG-CoA reductase inhibitors;
- Concomitant medications listed below:

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

1. All agents used for or under investigation for lowering or modifying plasma lipid levels, including statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors (including ezetimibe), and nicotinic acid >500 mg per day. Subjects on these medications could participate in the study, provided treatment was interrupted at least eight weeks prior to randomization;
2. Oral contraceptives or any systemic steroid hormones (including estrogens, progestins, androgens or glucocorticoids) for any condition, except for noncyclic (continuous) administration of estrogen/progesterone replacement therapy or sustained contraceptive preparations (e.g., implants or intramuscular injections) that must have been constant for at least the three months prior to study entry (Visit 1/Week -8/-6) and were anticipated to remain unchanged for the duration of the study. Subjects on systemic steroidal treatment were permitted to enter the study if the treatment was discontinued at least 4 weeks prior to Visit 1 (Week -8/-6). Steroid hormones administered topically or as inhalers were permitted. Non-steroidal anti-inflammatory agents were allowed provided dosing was stable for at least four weeks

prior to entry into the study but were disallowed if used for immunosuppressive therapy;

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

Withdrawal, Removal, and Replacement of subjects:

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

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

1. Adverse events (AEs) including laboratory AEs. Abnormal laboratory values or test results were only classified as AEs if they induced clinical signs or symptoms, were considered clinically significant or required therapy;
2. Abnormal laboratory value(s);
3. Abnormal test procedure result(s);
4. Unsatisfactory therapeutic effect;

5. Protocol violation;
6. Subject withdrew consent;
7. Lost to follow-up;
8. Administrative problems; or
9. Death.

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

Treatment:

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

Identity of Study Drugs		
	Treatment	Dosage form
A	Active pitavastatin 2 mg	Small tablet
B	Placebo pitavastatin 2 mg	Small tablet
C	Active pitavastatin 4 mg	Large tablet
D	Placebo pitavastatin 4 mg	Large tablet
E	Active atorvastatin 10 mg	Capsule
F	Active atorvastatin 20 mg	Capsule
G	Placebo atorvastatin	Capsule

Study Populations:

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

Sample Size Justification:

A sample size of 400 randomized subjects was planned, with 266 subjects in the pitavastatin 4 mg group and 133 subjects in the atorvastatin 20 mg group. Assuming a SD of 12 (for percent reduction from baseline LDL), a non-inferiority limit of 6% for the treatment difference and a 1-tailed test at 2.5% significance level, this sample size would have provided 99% power to reject the null hypothesis that the mean percent decrease from baseline LDL was at least 6% greater in the atorvastatin group than in the pitavastatin group vs. the alternative that any advantage in the atorvastatin group was less than the non-inferiority limit.

Statistical Analysis of the Primary Efficacy Variable:

The percent change in LDL from baseline to Week 12 or endpoint for the FAS and the percent change in LDL from baseline to Week 12 (Visit 8) for the PP and COM populations were analyzed using analysis of covariance (ANCOVA) including treatment and country as factors and the baseline LDL as a covariate.

A two-sided 95% CI was constructed on the adjusted mean difference between treatment groups (i.e., atorvastatin 20 mg minus pitavastatin 4 mg). Pitavastatin was considered to be non-inferior to atorvastatin at the doses tested if the lowest bound on the 95% CI was greater than -6% for the difference between treatment groups.

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

The primary efficacy variable was also analyzed to compare the two treatment groups within the following subgroups. Assuming that a subgroup included a minimum of 5% of subjects, the treatment-by-subgroup interactions were tested by including them in the original ANCOVA model.

Summary statistics of the percent change in LDL from baseline are presented for each level of each subgroup.

Subgroups were defined as follows:

- Age (< 65 years, ≥65 years);
- Sex (Male, Female);
- Race (Caucasian, Non-Caucasian);
- BMI (<25 kg/m², 25-<30 kg/m², ≥30 kg/m²);
- Risk Category (Low, Moderate, High [as defined by NCEP Guidelines]);
- Baseline LDL (<160 mg/dL, 160-<190 mg/dL, ≥ 190 mg/dL);
- Hypertension (Yes, No);
- HbA_{1c} at screening (≤6.5%, >6.5%);
- Baseline HDL (<40, 40-<60, ≥60 mg/dL);

- Baseline TG (<150, 150-<200, ≥200 mg/dL).

In addition, the percent change from baseline in HDL and TG was summarized by the subgroups:

- HbA_{1c} at screening (≤6.5%, >6.5%);
- Baseline HDL (<40, 40-<60, ≥60 mg/dL);
- Baseline TG (<150, 150-<200, ≥200 mg/dL).

Subgroups were assessed for both the FAS and PP populations.

Statistical Analysis of the Secondary Efficacy Variables:

Change or percent change from baseline in the secondary efficacy lipid variables were also evaluated using ANCOVA and 95% CIs on the mean differences between the pitavastatin group and the atorvastatin group. Non-inferiority margins for secondary variables were not explicitly defined.

The LDL targets based on the NCEP ATP III Guidelines were calculated for each subject using cardiovascular risk factor data collected during screening, prior to randomization. However, all subjects in this study were diabetic and were, therefore, considered to be at high risk of CHD, with a target LDL of 100 mg/dL.

The LDL recorded at the endpoint (FAS) or Week 12 (PP population) for each subject was compared with the LDL target (100 mg/dL) to determine whether the subject attained their target LDL. The numbers of subjects who achieved their LDL goal were tabulated using frequency counts and percentages.

The proportion of subjects who reached their LDL goal was analyzed using a linear probability model, which assumes the identity link and binomial distribution (SAS PROC GENMOD), including treatment, country, and baseline LDL (categorized as <160 mg/dL, 160 mg/dL- <190 mg/dL, and ≥190 mg/dL) as factors.

Point estimates and two-sided 95% CIs are presented on the proportion of subjects achieving their goal, and on the adjusted proportion from the linear probability model.

NCEP ATP III LDL and Non-HDL cholesterol Targets:

Subjects who achieved their LDL target at Week 12 (or endpoint) and had a corresponding TG level >200 mg/dL, were assigned a Non-HDL cholesterol target that was 30 mg/dL higher than their LDL goal. These subjects had to achieve both their LDL target and their Non-HDL cholesterol target to be considered to have achieved their “target.”

Protocol Amendments:

There were two amendments to Protocol NK-104-305 dated 27 May 2005

Amendment 1 was generated to address the following changes:

- Synopsis, Study Design and Overall Study Design were revised to include approximately 30 sites and to include the Netherlands as one of the locations of the sites.
- Inclusion Criteria #2 was revised to include insulin but to exclude glitazones.
- Concomitant Therapy was revised to exclude glitazones from the list of allowed hypoglycemic agents.
- Visit Schedule was revised for the long laboratory evaluation to include retention of urine samples for proteinuria assessment at Visit 4 (Week 0) and Visit 8 (Week 12).
- Safety assessments were revised to include the urine samples retained for the assessment of protein excretion.
- Some administrative points were clarified: the manufacturing site for over encapsulation of atorvastatin tablets was identified as being in the UK; details of responsible ^{(b) (4)} study personnel were updated; details of the central laboratory were updated with the new company name; information from a post-marketing surveillance study in Japan was included, instructions to the investigator on correcting CRF errors were updated; and references to the most recent Investigator Brochure were updated.

Amendment 2 was generated to address the following changes:

- Overall Study Design were revised to increase the number of randomized subjects to 400 and to include approximately 47 sites in Germany, India, Poland, the Netherlands. The section was also revised to add the countries Denmark and UK.
- Sample Size Calculation was revised for the increase number of randomized subjects to 400.

Changes in the Planned Analysis:

The following changes from the analysis planned in the protocol were included in the final SAP:

The final protocol only stipulated the use of the intent-to-treat (ITT) and safety populations. The ITT population defined in the protocol was renamed and referred to as the FAS.

In addition to the safety, FAS, and PP populations, a COM population was defined at the request of regulators. The COM population was defined as all subjects irrespective of protocol violations, who had Week 12 (last week of study) measurements whether on drug or not. This population was used in the sensitivity analysis supporting the analysis of the primary variable at Week 12.

Changes in the Planned Analysis: Baseline Lipid Values

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

at Week 0 (Visit 4) was included in the calculation of baseline as it was the last measurement before study treatment commenced.

The baseline values for Apo-B, Apo-A1, Apo-B:Apo-A1 ratio, hsCRP, adiponectin, small-dense-LDL, and RLP-C were the results at Week 0 (Visit 4), as this was the only time at which these parameters were measured prior to receiving study treatment.

Changes in the Planned Analysis: Covariates for Analysis of Lipid Parameters

The primary and secondary efficacy endpoints of change in lipid parameters from baseline to Week 12 was to be analyzed using ANCOVA including treatment and centre as factors, and baseline lipid values as a covariate. However, as the number of subjects in each centre was expected to be small, centers were grouped by country, and country was used in the model in place of center.

Changes in the Planned Analysis: Secondary Lipid Parameters

The protocol stated that the TC:HDL ratio, non-HDL:HDL ratio and Apo-B:Apo-A1 ratio, hsCRP, adiponectin, small-dense-LDL, and RLP-C would be analyzed as percent change from baseline. However, a simple change from baseline was considered more appropriate.

In addition to the secondary lipid variables listed in the protocol, Non-HDL cholesterol was evaluated. It was calculated programmatically as TC minus HDL.

Changes in the Planned Analysis: Subgroup Analyses

The primary efficacy variable was also analyzed to compare treatments by age, sex, race, BMI, risk category, baseline LDL, presence of hypertension and presence of diabetes. Where the subgroup included a minimum of 5% of the subjects per level, the treatment by subgroup interactions were tested by inclusion in the original ANCOVA model, 1 sub-group at a time. Summary statistics of the percent change in LDL from baseline were presented by treatment for each level of each subgroup.

In addition, the primary efficacy variable was analyzed to compare treatments by baseline HbA_{1C} levels, baseline HDL level, and baseline TG level. Also, changes in HDL and TG were analyzed to compare treatments by baseline HbA_{1C} levels, baseline HDL level, and baseline TG level.

Protocol Violations and Deviations:

In summary, major protocol violations were defined as follows:

- Subjects who took less than 80% or more than 120% of required study drug throughout the total treatment duration (overall compliance <80% or >120%) or who took less than 70 days or more than 98 days (84 ± 14 days) of study medication;
- Subjects who failed the second inclusion criterion (i.e., subjects whose Type II DM was treated with oral anti-diabetic medication such as sulfonylurea, metformin or combination therapy, or insulin, but excluding glitazones);
- Subjects who failed the third inclusion criterion (i.e., HbA_{1C} ≤ 7.5 % at Visit 1);
- Subjects who failed the eighth inclusion criterion (i.e., subjects who did not follow a fat and cholesterol restrictive diet during the lead-in period);

- Subjects who failed the ninth inclusion criterion (i.e., subjects who did not present with both primary hypercholesterolemia and combined dyslipidemia);
- Subjects who failed any of the following exclusion criteria:
- Subjects with homozygous familial hypercholesterolemia;
- Subjects with any conditions that could cause secondary dyslipidemia;
- Subjects with any surgical or medical condition that could significantly alter absorption, distribution, metabolism or excretion of any drug;
- Subjects with uncontrolled hypothyroidism;
- Subjects with a history of drug or alcohol abuse in the previous 2 years;
- Subjects who received any investigational new drug within 30 days of study entry, or who ingested any drug known to be toxic to a major organ system within 12 weeks prior to study entry;
- Subjects who took any agent used or under investigation for lowering or modifying plasma lipid levels within 8 weeks prior to randomization or during study treatment;
- Subjects who did not have the baseline blood sample at Week 0 (Visit 4) within 14 days prior to the first dose of study treatment;
- Subjects who attended the Week 12 (Visit 8) visit outside of an 84 ± 14 -day window;
- Positive pregnancy test;
- Data from subjects whose Week 2 (Visit 5), Week 4 (Visit 6), or Week 8 (Visit 7) data fell outside of the specified time windows;
- Data from subjects who were not fasting before their blood was taken for lipid assessment at Visits 4 to 8 (Week 0 to Week 12);
- Subjects whose Week 12 (Visit 8) blood sample was taken >3 days after the date of the last dose of study medication; and
- **Subjects who received the “wrong” (i.e., non-randomized) study medication at any time during the treatment period.**

Disposition of subjects:

Investigators at 43 centers randomized a total of 418 subjects: 279 subjects were randomized to treatment with pitavastatin 4 mg, and 139 to atorvastatin 20 mg. Overall, 201 (48.1%) subjects were randomized at 16 centers in Poland, 80 (19.1%) subjects were randomized at seven centers in Germany, 67 (16.0%) subjects were randomized at 8 centers in the Netherlands, 52 (12.4%) subjects were randomized at five centers in India, 11 (2.6%) subjects were randomized at three centers in Denmark, and seven (1.7%) subjects were randomized at four centers in the UK. The greatest number of subjects randomized at a single center was 38 (9.1% of all subjects), at Center 5111 in Poland.

A summary of subject disposition by treatment group and analysis population is presented in the following table:

Subject Disposition

	Pitavastatin 4 mg QD	Atorvastatin 20 mg QD
Number of subjects Randomized	279 (100.0%)	139 (100.0%)
Safety Population	275 (98.6%)	137 (98.6%)
Full Analysis Set (FAS)	274 (98.2%)	136 (97.8%)
Per Protocol Population (PP)	214 (76.7%)	107 (77.0%)
Completers (COM)	248 (88.9%)	124 (89.2%)
Discontinued Study Drug	17 (6.1%)	9 (6.5%)
Reason for Discontinuation from Study Drug		
Adverse Event	7 (2.5%)	6 (4.3%)
Abnormal laboratory values(s)	1 (0.4%)	0 (0.0%)
Protocol violation	3 (1.1%)	1 (0.7%)
Withdrew consent	4 (1.4%)	0 (0.0%)
Lost to follow-up	1 (0.4%)	2 (1.4%)
Death	1 (0.4%)	0 (0.0%)

Demographic and Other Baseline Characteristics:

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

Demographic and Other Baseline Characteristics (Safety Population)

Demographic Characteristic	Pitavastatin 4 mg QD (N=275)	Atorvastatin 20 mg QD (N=137)
Sex (n [%])		
Male	155 (56.4%)	78 (56.9%)
Female	120 (43.6%)	59 (43.1%)
Age (years)		
Mean (SD)	59.1 (9.21)	59.8 (9.06)
Range	24-75	36-75
Race (n [%])		
Caucasian	243 (88.4%)	118 (86.1%)
Indian	32 (11.6%)	19 (13.9%)

Demographic and Other Baseline Characteristics (Safety Population)

Demographic Characteristic	Pitavastatin 4 mg QD (N=275)	Atorvastatin 20 mg QD (N=137)
Duration of combined dyslipidemia (years)		
Mean (SD)	4.24 (5.336)	4.78 (4.871)
Range	-0.13-36.62	-0.01-21.02
Duration of combined dyslipidemia by duration category (n [%])		
<1 year	85 (30.9%)	30 (21.9%)
1 - <3 years	65 (23.6%)	35 (25.5%)
3 - <5 years	43 (15.6%)	22 (16.1%)
≥5 years	82 (29.8%)	50 (36.5%)
Duration of Type II DM (years)		
Mean (SD)	6.24 (6.63)	6.12 (5.18)
Range	0.02-35.82	0.07-23.62
Duration Type II DM by duration category (n [%])		
<1 year	52 (18.9%)	21 (15.3%)
1 - <3 years	61 (22.2%)	24 (17.5%)
3 - <5 years	52 (18.9%)	24 (17.5%)
≥5 years	110 (40.0%)	68 (49.6%)
Height (m)		
Mean (SD)	1.69 (0.10)	1.69 (0.08)
Range	1.4-2.0	1.5-1.9
Weight (kg)		
Mean (SD)	84.43 (13.28)	83.21 (12.46)
Range	45.0-115.0	50.0-118.0
BMI (kg/m²)		
Mean (SD)	29.37 (3.35)	29.12 (3.50)
Range	19.0-34.9	17.9-35.4

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

Demographic Characteristic	Pitavastatin 4 mg QD (N=275)	Atorvastatin 20 mg QD (N=137)
NCEP risk category (n [%])		
High risk	275 (100.0%)	137 (100.0%)
Hypertension (n [%])		
Present	215 (78.2%)	104 (75.9%)
Baseline HbA_{1c} (%)		
Mean (SD)	6.49 (0.633)	6.47 (0.600)
Range	5.0-10.0	5.1-8.8
Subjects with any Prior Lipid Modifying Medication (n [%])		
cholesterol and triglyceride reducers	131 (47.6%)	71 (51.8%)
Atorvastatin and atorvastatin calcium	46 (16.7%)	22 (16.1%)
Bezafibrate	0 (0.0%)	1 (0.7%)
Ezetimibe	5 (1.8%)	5 (3.6%)
Fenofibrate	13 (4.7%)	3 (2.2%)
Fluvastatin and fluvastatin sodium	3 (1.1%)	2 (1.5%)
Gemfibrozil	1 (0.4%)	0 (0.0%)
Inegy (simvastatin + ezetimibe)	1 (0.4%)	0 (0.0%)
Lovastatin	2 (0.7%)	1 (0.7%)
Nicotinic acid	1 (0.4%)	0 (0.0%)
Pravastatin	9 (3.3%)	6 (4.4%)
Rosuvastatin	5 (1.8%)	3 (2.2%)
Simvastatin	57 (20.7%)	35 (25.5%)
Vitamins A and D, including combinations of both	1 (0.4%)	0 (0.0%)
Cod-liver oil	1 (0.4%)	0 (0.0%)

Approximately 57% (233/412 subjects) of subjects in the safety population were male and 43% were female. The proportion of males and females was closely matched in both treatment groups (56.4% vs. 43.6% pitavastatin 4 mg; 56.9% vs. 43.1% atorvastatin 20 mg). The mean age of the subjects was approximately 60 years in both treatment groups, with the highest proportion of subjects falling into the age category 60-64 years (90 [21.8%] subjects in total). The majority of subjects (approximately 88%) were Caucasian; all of the other subjects in the study were Indian. The proportion of Caucasians and Indians was similar in both treatment groups: 243 (88.4%) subjects in the pitavastatin 4 mg group and 118 (86.1%) subjects in the atorvastatin 20 mg group were Caucasian.

Mean duration of combined dyslipidemia was 4.24 years (range -0.13-36.62 years) in the pitavastatin 4 mg group and 4.78 years (range -0.01-21.0 years) in the atorvastatin 20 mg group. A slightly higher proportion of subjects in the atorvastatin 20 mg group had combined dyslipidemia for >5 years compared with the pitavastatin 4 mg group (36.5% and 29.8%, respectively), while a slightly higher proportion of subjects in the pitavastatin 4 mg group had combined dyslipidemia for <1 year compared with the atorvastatin 20 mg group (30.9% and 21.9% respectively).

All subjects had Type II DM. Mean duration of Type II DM was similar in the two treatment groups: 6.2 years (range 0.02-35.8 years) in the pitavastatin 4 mg group and 6.1 years (range 0.07-23.6 years) in the atorvastatin 20 mg group. The largest duration category in both treatment groups was ≥5 years, with a slightly higher proportion of subjects in the atorvastatin 20 mg group falling in this duration category compared with the pitavastatin 4 mg group (110 [40.0%] subjects in the pitavastatin 4 mg group; 68 [49.6%] subjects in the atorvastatin 20 mg group).

Since all of the subjects were diabetic, they were all at high risk of CHD, according to NCEP criteria.

Mean baseline HbA_{1c} was similar in both treatment groups: 6.49% in the pitavastatin 4 mg group and 6.5% in the atorvastatin 20 mg group. The proportion of subjects with HbA_{1c} ≤6.5% and >6.5% was close to 50% in each category in both treatment groups.

Concurrent hypertension was recorded for 215 (78.2%) subjects in the pitavastatin 4 mg group and for 104 (75.9%) subjects in the atorvastatin 20 mg group.

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

Approximately 50% of subjects in the two treatment groups had prior lipid modifying medication. The most common prior lipid modifying medications were simvastatin (57 [20.7%] subjects in the pitavastatin 4 mg group and 35 [25.5%] subjects in the atorvastatin 20 mg group) and atorvastatin (46 [16.7%] and 22 [16.1%] subjects in the pitavastatin 4 mg and atorvastatin 20 mg groups, respectively). In addition to the cholesterol and triglyceride reducing agents, one subject in the pitavastatin 4 mg group took cod-liver oil as well as simvastatin.

In summary, there were no apparent treatment group differences in the demographic summaries of either the FAS or safety populations.

Treatment Compliance:

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

Treatment Compliance (Safety Population)

	Pitavastatin 4 mg QD N=275	Atorvastatin 20 mg QD N=137
Overall % compliance		
N=	274	137
Mean (SD)	98.8 (3.53)	98.4 (3.95)
Median	100.0	100.0
Quartiles	98.8-100.0	98.8-100.0
Range	71-104	67-101

Compliance was good with mean compliance being approximately 98% in both treatment groups. There were 12 (4.3%) subjects in the pitavastatin 4 mg group and 5 (3.6%) subjects in the atorvastatin 20 mg group who were poorly compliant (<80% or >120%) and were excluded from the PP population for this reason.

Analysis of Efficacy:

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

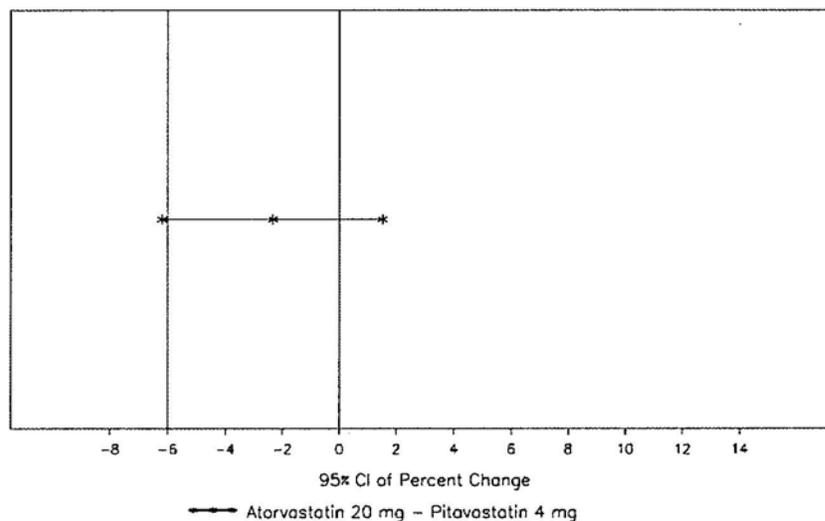
The percent changes in LDL from baseline to endpoint, (i.e., Week 12 or the last on-treatment assessment) for the FAS, and to Week 12 for the PP and COM populations, are presented the following table:

Change from Baseline to Endpoint or Week 12 in LDL (mg/dL) (FAS, Population)

	Pitavastatin 4 mg QD	Atorvastatin 20 mg QD
N	274	136
Baseline LDL		
Mean (SD)	142.8 (27.4)	146.0 (27.0)
Endpoint LDL		
Mean (SD)	84.3 (31.0)	82.4 (27.5)
% change from baseline to endpoint		
Mean (SD)	-40.78 (19.6)	-43.25 (16.4)
Adjusted Mean Difference (95% CI)	-2.33 (-6.2; 1.5)	
P-value (test for difference)	0.235	

Changes in the PP and COM populations were similar.

95% Confidence Intervals on Treatment Difference in Adjusted Mean Percent Change in LDL (FAS) are shown in the following figure:

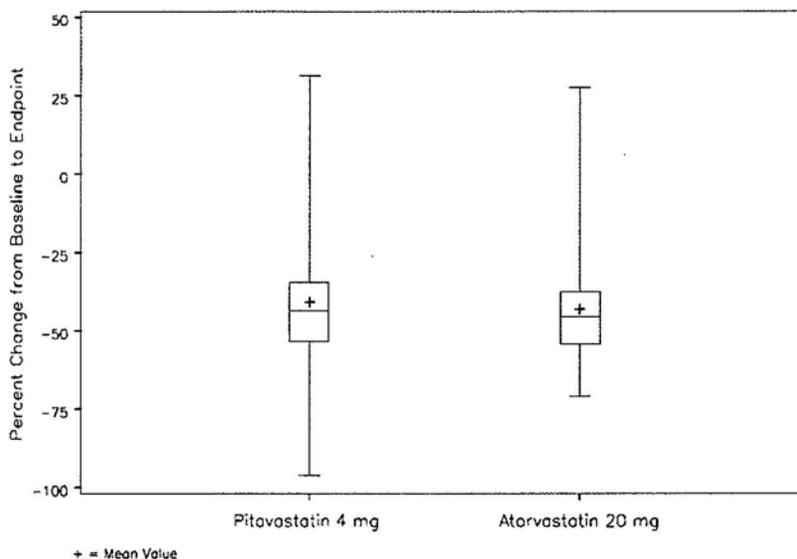


The mean baseline LDL level was slightly higher in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group for each of the efficacy populations (FAS, PP and COM).

The mean change from baseline to endpoint in LDL in the FAS was -40.8% in the pitavastatin 4 mg group and -43.3% in the atorvastatin 20 mg group. The adjusted mean difference between the treatments was -2.33%. The lower bound on the 95% CI, at -6.2%, was lower than -6%. Therefore, pitavastatin 4 mg was not non-inferior to atorvastatin 20 mg.

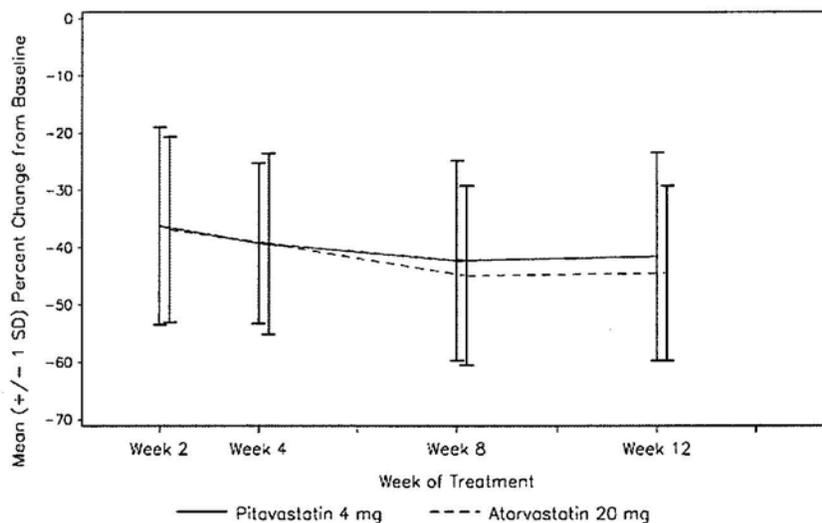
The analysis of this variable in both the PP and COM populations supported the findings in the FAS population.

The percent change from baseline to endpoint for each treatments are illustrated in the following box plot:



The box plots illustrate that the mean and median effect of the two treatments were similar.

The mean percent change from baseline of LDL over time is illustrated in the figure below.



The mean percent reduction in LDL was approximately 36% in both treatment groups after 2 weeks of dosing and approximately 39% after 4 weeks. After dose titration at Week 4, LDL levels continued to decrease until Week 8 and were maintained until the end of the study. The decrease was greater in the atorvastatin 20 mg group compared with the pitavastatin 4 mg group.

Secondary Efficacy Variables:

LDL Target Attainment:

A summary of the number (percent) of subjects who attained the LDL target, and the LDL and Non-HDL cholesterol target at endpoint is provided by treatment group in the following table:

Subjects With NCEP Target Attainment (FAS)		
	Pitavastatin 4 mg QD N=274	Atorvastatin 20 mg QD N=136
Number (%) of subjects with LDL target attained according to NCEP criteria		
Unadjusted proportion achieving target results (n [%])	212 (77.4%)	111 (82.2%)
Difference	4.8	
(95% CI)	(-3.3; 13.0)	
P-value	0.242	
Adjusted proportion achieving target results (%)		
Difference	62.8%	67.2%
(95% CI)	(-4.6; 13.3)	
P-value	0.343	
Number (%) of subjects with LDL and Non-HDL cholesterol target attained according to NCEP criteria		
Unadjusted proportion achieving target results (n [%])	181 (66.1%)	101 (74.8%)
Difference	8.8	
(95% CI)	(-0.5; 18.0)	
P-value	0.063	
Adjusted proportion achieving target results (%)		
Difference	57.9%	66.3%
(95% CI)	(-0.7; 17.4)	
P-value	0.069	

The unadjusted proportion of subjects with LDL target attainment using NCEP criteria was 77.4% in the pitavastatin 4 mg group and 82.2% of subjects in the atorvastatin 20 mg group. The difference between the groups was 4.8% and was not statistically significant (P=0.242).

The unadjusted proportion of subjects meeting the NCEP target was 66.1% in the pitavastatin 4 mg group and 74.8% in the atorvastatin 20 mg group. The difference between the groups of 8.8% was not statistically significant (P=0.063).

LDL Sub-Group Analyses

LDL by Country:

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