

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-363**

**STATISTICAL REVIEW(S)**

5/26/09



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

**Statistical Review and Evaluation**  
CARCINOGENICITY STUDIES

**IND/NDA Number:** NDA 22-363

**Drug Name:** Pitavastatin (NK-104)

**Applicant:** Sponsor: Kowa Company Ltd. Fuji Research Laboratories  
Pharmaceutical Division 332-1 Ohnoshinden Fuji, Shizuoka 417-8650,  
Japan  
Test Facility (b) (4) [REDACTED]

**Documents Reviewed:** Electronic data submitted on March 11, 2009.

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics -6

**Statistical Reviewer:** Min Min, Ph.D.

**Concurring Reviewer:** Karl Lin, Ph.D.

**Medical Division:** Division of Metabolism and Endocrinology Products

**Reviewing Pharmacologist:** Calvin (Lee) Elmore Ph.D.

**Project Manager:** Kati Johnson

**Keywords:** Carcinogenicity, Dose response

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## 1. Background

In this submission the sponsor included reports of an animal carcinogenicity study in transgenic mice. These studies were intended to further assess the carcinogenic potential of Pitavastatin in CB6F1-Tg rasH2 transgenic mice when administered by oral gavage at appropriate drug levels for a period of 26 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Elmore.

## 2. Study design

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one positive control and one vehicle control group. One hundred and twenty five CB6F1-Tg rasH2 transgenic mice of each sex were randomly allocated to treated and control groups in equal size of 25 animals. The dose levels of treated groups were 30, 75 and 150 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The test article, NK-104, was formulated in the vehicle/control article, 0.5% CMC-Nasolution (0.5% w/v sodium carboxymethylcellulose in Sterile Water for Injection, USP). The positive control article, MNU (N-Methyl-N-nitrosourea), was formulated in 0.9% Saline for Injection, USP.

### Study design

Group	Test/Control Article	Dose Level (mg/kg)	Number of Animals (Male/Female)		Necropsy (Male/Female)
			Tox Group	TK Group	
1	Vehicle	0	25/25	3/3 <sup>a</sup> +3/3 <sup>b</sup>	25/25
2	Positive Control (MNU)	75	25/25	N/A	25/25
3	NK-104	30	25/25	18/18+5/5 <sup>c</sup>	25/25
4	NK-104	75	25/25	18/18+5/5 <sup>c</sup>	25/25
5	NK-104	150	25/25	18/18+5/5 <sup>c</sup>	25/25

<sup>a</sup>: Used as controls for TK groups at estimated Tmax after first dose administration of control article on nominal D1

<sup>b</sup>: Used as controls for TK groups at estimated Tmax after last dose administration of control article on D182

<sup>c</sup>: Additional animals were dosed at the respective dose levels and used for either Toxicity or TK groups as necessary (as spares).

N/A: Not applicable

Clinical observations, food consumption, and body weights were recorded throughout the study. Hematology was assessed at necropsy. At the time of necropsy, gross observations and organ weights were recorded. Histopathology evaluation was conducted on tissues collected at necropsy.

### 2.1. Sponsor's analyses

#### 2.1.1. Survival analysis

The sponsor presented some descriptive summaries of the survival data.

**Sponsor's findings:**

There were no deaths attributed to NK-104. Spontaneous mortalities occurred sporadically in the NK-104 treatment groups, but because a comparable number of deaths occurred in the vehicle control group the deaths in the NK-104 treatment cohort were considered not to be test article-related. A high incidence of unscheduled mortality occurred in the positive control group and most deaths and moribund euthanizations in this cohort appeared to be tumor-related. The table below summarizes the numbers of animals found dead or sacrificed on an unscheduled basis throughout the study. The table includes all animals from the toxicity and toxicokinetics groups.

Sex	Vehicle control	Positive Control	Low dose	Medium dose	High dose
Male	5/31	20/25	2/48	0/48	3/48
Female	2/31	15/25	0/48	5/48	2/48

**2.1.2. Tumor data analysis**

Examination of the positive control group animals revealed many tumors, primarily lymphosarcomas of thymus and spleen and papilloma/squamous cell carcinomas of the stomach. The high abundance and diversity of tumors observed in the positive control group animals indicates that this group served as a satisfactory positive control and confirmed that the transgenic model was capable of expressing appropriate neoplastic responses in various tissues. For incidence of neoplastic lesions, the test article group and positive control group were compared to the vehicle control group using Fisher's exact tests adjusted for multiple comparisons. For pair-wise comparisons, caution is advised in the interpretation of p-values as the recommended minimum sample size is 5 per group for nonparametric tests. P-values <0.05 were considered statistically significant.

The sponsor performed the pairwise comparisons of vehicle control and positive control, and vehicle control and each of the treated groups for the incidence of observed tumor types using Fisher Exact test.

**Sponsor's findings:**

For the incidence of any neoplastic lesion, Fisher's exact test indicated a statistically significant difference between positive control group and the control ( $p < .0001$ ) in both male and female mice.

**2.2. Reviewer's analyses**

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

**2.2.1. Survival analysis**

The survival distributions of animals in all four treatment groups (three treated groups and one vehicle control group) were estimated by the Kaplan-Meier product limit method. Here the positive control group is excluded.

The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The intercurrent mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

**Reviewer's findings:** The test results showed no statistically significant dose-response relationship and statistically significant difference in mortality in either sex when compared with the vehicle control group.

### 2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. For short term study of 26 weeks no such suggestion is available. In this analysis the first analysis was performed using k=3. If needed, for borderline cases, the analysis was repeated with other value of k (e.g. k=2 and k=4). For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

As suggested by the reviewing pharmacologist Dr. Elmore, this reviewer did the analysis of the combinations of hemangiosarcomas from all sites and adenomas/carcinomas for lung/bronchi.

**Reviewer's findings:** Tests did not show statistically significant positive dose response relationship or increased tumor incidence in the treated groups compared to the vehicle control in any tumor type.

## 3. Evaluation of validity of the design of the mouse study

As seen, the tumor data showed no statistically significant dose-response relationship in any of the tested tumor types. However, before drawing any conclusion regarding the non-carcinogenic potential of the study drug in CB6F1-Tg rasH2 transgenic mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

- (i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
- (ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

For long term 104 weeks regular rat and mouse studies there are some published statistical criteria to deal with the above mentioned issues. These statistical criteria along with the histopathological findings are generally applied to evaluate negative long term rat and mouse carcinogenicity studies. However, for CB6F1-Tg rasH2 transgenic mouse studies there are no such published statistical criteria. A determination regarding the above issues in this short term CB6F1-Tg rasH2 transgenic mice might be made using the clinical signs and histopathological toxic effects alone.

#### 4. Summary

In this submission the sponsor included a report of an animal carcinogenicity study in transgenic mice. These studies were intended to assess the carcinogenic potential of Pitavastatin in CB6F1-Tg rasH2 transgenic mice when administered orally by gavage at appropriate drug levels for 26 weeks.

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one positive control and one vehicle control group. One hundred and twenty five CB6F1-Tg rasH2 transgenic mice of each sex were randomly allocated to treated and control groups in equal size of 25 animals. The dose levels of treated groups were 30, 75 and 150 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively.

The test article, NK-104, was formulated in the vehicle/control article, 0.5% CMC-Nasolution (0.5% w/v sodium carboxymethylcellulose in Sterile Water for Injection, USP). The positive control article, MNU (N-Methyl-N-nitrosourea), was formulated in 0.9% Saline for Injection, USP.

The tests showed no statistically significant dose response relationship or difference between the vehicle control and any of the treated groups in survivals across treatment groups in either sex. Tests did not show statistically significant positive dose response relationship or increased tumor incidence in the treated groups compared to the vehicle control in any tumor type.

Min Min, Ph.D.  
Mathematical Statistician

Concur: Karl Lin, Ph.D.  
Team Leader, Biometrics-6

cc:  
Archival NDA 22-117  
Dr. Elmore  
Dr. Tiwari  
Dr. Nevius

Dr. Machado  
Dr. Lin  
Dr. Min

5. Appendix

**Table 1A: Intercurrent Mortality Rate  
Male Mice**

Week	Vehicle_CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-10	.	.	.	.	.	.	.	.
11-15	1	4.0%	.	.	.	.	.	.
16-20	.	.	1	4.0%	.	.	1	4.0%
21-26	2	12.0%	.	.	.	.	.	.
Term. Sac.	22	100.0%	24	100.0%	25	100.0%	24	100.0%

**Table 1B: Intercurrent Mortality Rate  
Female Mice**

Week	Vehicle_CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-10	1	4.0%	.	.	1	4.0%	.	.
11-15	.	.	.	.	2	12.0%	.	.
16-20	.	.	.	.	.	.	.	.
21-26	.	.	.	.	.	.	1	16.0%
Term. Sac.	24	100.0%	25	100.0%	21	100.0%	25	100.0%

**Table 2A: Intercurrent Mortality Comparison  
Male Mice**

Test	P-Value (across four groups)	P-Value (vehicle_contr ol vs low)	P-Value (vehicle_con trol vs medium)	P-Value (vehicle_contro l vs high)
Dose Response	0.8011	0.7727	0.6647	0.7727
Homogeneity	0.2637	0.3073	0.0770	0.3073

**Table 2B: Intercurrent Mortality Comparison  
Female Mice**

Test	P-Value (across four groups)	P-Value (vehicle_contr ol vs low)	P-Value (vehicle_con trol vs medium)	P-Value (vehicle_contro l vs high)
Dose Response	0.9713	0.8875	0.6665	0.8875
Homogeneity	0.0293	0.3173	0.1732	0.3173

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Mice (vehicle control, low, medium and high dose groups)**

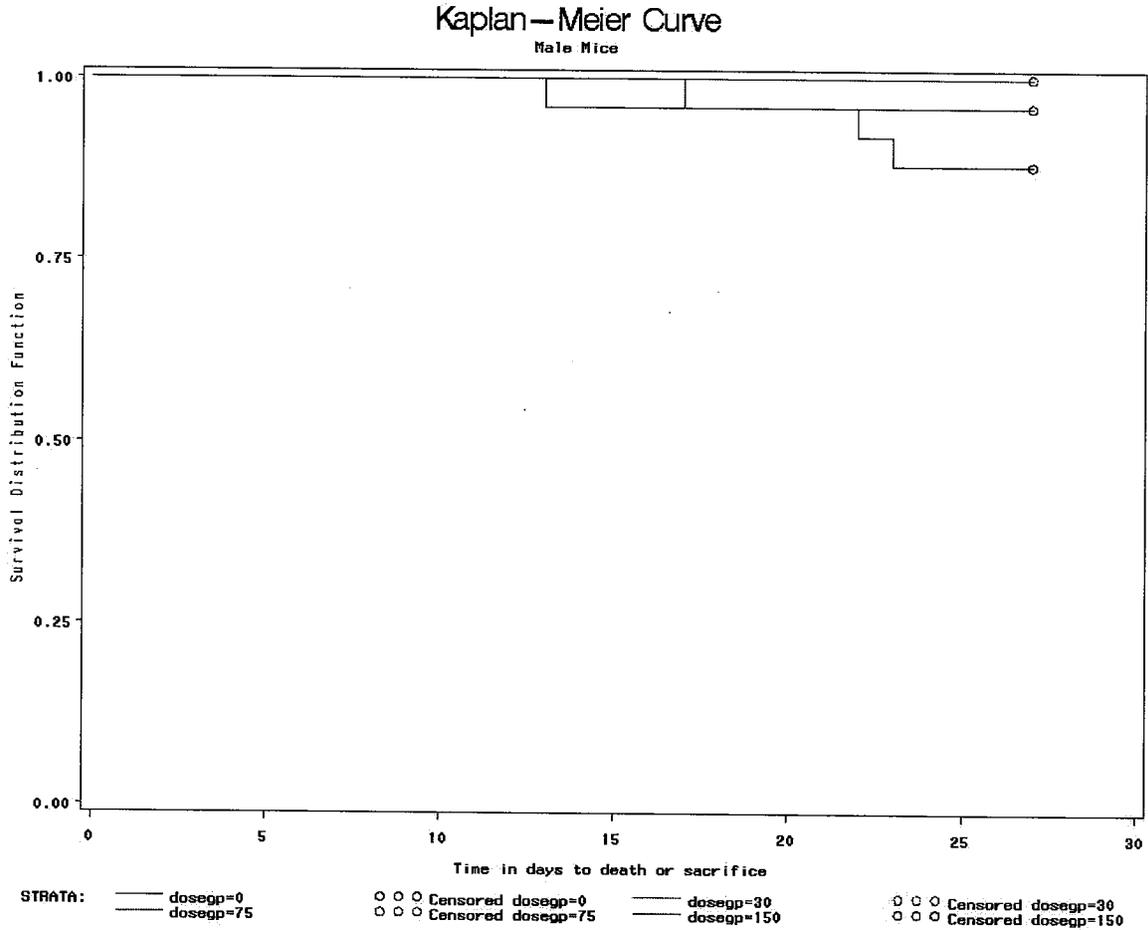
Organ Name	Tumor Name	Vehicle	30 mg	75 mg	150 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		e_Cont N=25	Low N=25	Med N=25	High N=25				
ALL	HEMANGIOSARCOMA	3	2	0	3	0.474	0.522	0.899	0.354
Lungs/Bronchi	B-A/B adenoma	0	0	0	2	0.060	.	.	0.256
Mesentery	M-Hemangiosarcoma	1	0	0	0	0.761	0.511	0.522	0.511
Spleen	M-Hemangiosarcoma	2	1	0	2	0.511	0.517	0.777	0.321
Stomach	M-Forestomach SCC	0	0	0	1	0.250	.	.	0.511
	M-Hemangiosarcoma	0	1	0	0	0.511	0.511	.	.

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	Vehicle	30 mg	75 mg	150 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		e_Cont N=25	Low N=25	Med N=25	High N=25				
ALL	HEMANGIOSARCOMA	1	1	2	1	0.504	0.255	0.483	0.255
Duodenum	M-Hemangiosarcoma	0	0	0	1	0.261	.	.	0.511
Lung+Bronchi	ADENOMA+CARCONOMA	1	1	2	0	0.686	0.255	0.465	0.511
Lungs/Bronchi	B-A/B adenoma	1	0	2	0	0.603	0.511	0.465	0.511
	M-A/B carcinoma	0	1	0	0	0.489	0.511	.	.
Reticuloendothe	C-Lymphosarcoma	0	0	1	0	0.495	.	0.489	.
Spleen	M-Hemangiosarcoma	1	1	2	0	0.689	0.255	0.483	0.511

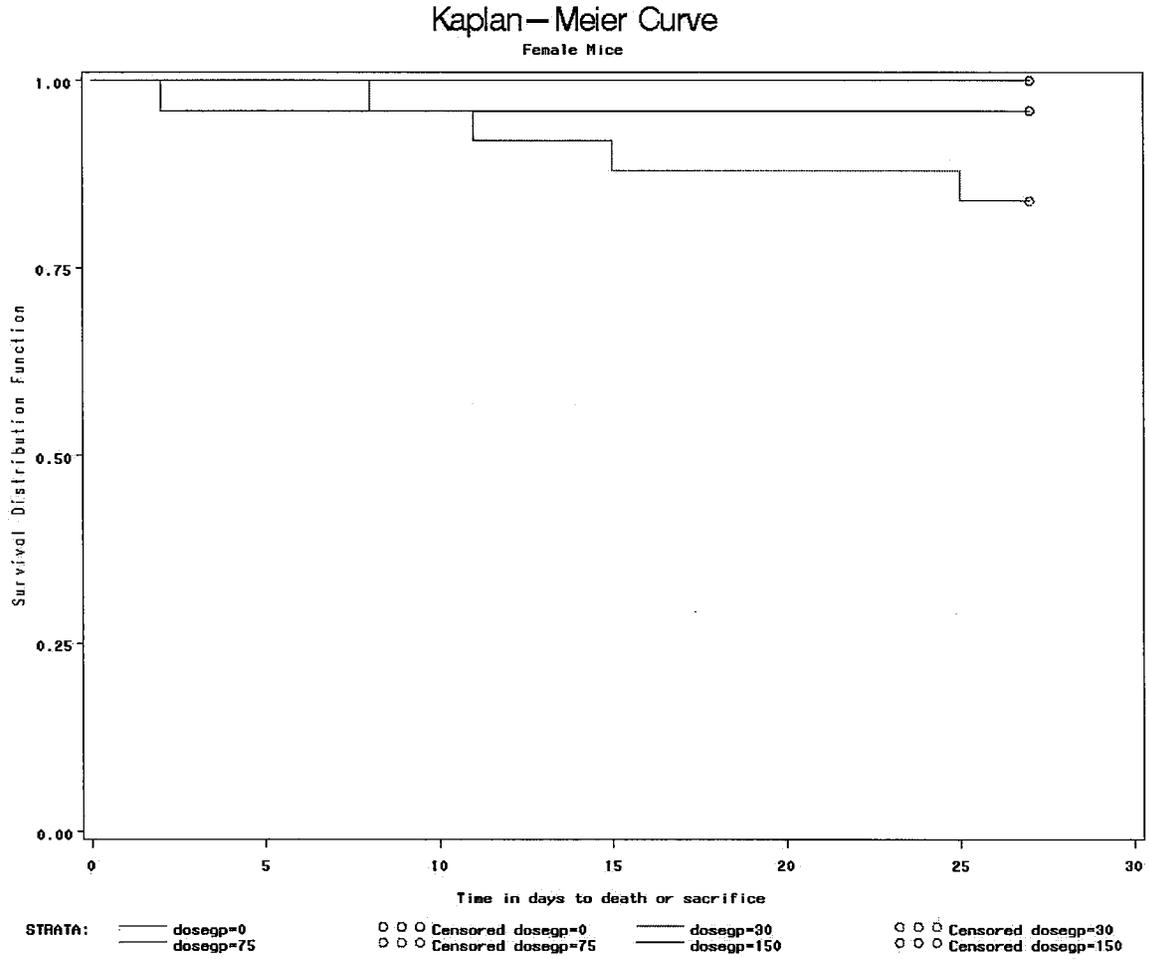
**Figure 1A: Kaplan-Meier Survival Functions for Male Mice**

Male Mice (vehicle control, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

**Figure 1B: Kaplan-Meier Survival Functions for Female Rats**  
Female Mice (Vehicle control, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

## 6. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
3. Cox D. R. (1972) "Regression models and life tables", *Journal of the Royal Statistical Society*, B, 34, 187-220.
4. Gehan (1965) "A generalized Wilcoxon test for comparing arbitrarily singly censored samples", *Biometrika*, 52, 203-223.
5. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.
6. Lin, K.K. and Rahman, M.A. (1998), "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15.
7. Rahman, M.A. and Lin, K.K. (2008), "A comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
8. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J. Wahrendorf (1980), "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426.
9. Tarone RE (1975), "Test for trend in life table analysis", *Biometrika*, 62: 679-82.
10. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, 2001.

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/s/

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Min Min  
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Karl Lin  
5/26/2009 04:12:28 PM  
BIOMETRICS  
concur with review

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

12/17/08

**NDA Number: 022363**

**Applicant: KOWA**

**Stamp Date: 10/01/2008**

**Drug Name: pitavastatin**

**NDA/BLA Type: New Protocol**

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			For each of NK-104-301, NK-104-302, NK-104-304, NK-104-305, NK-104-306
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes**

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			Use the LOCF procedure

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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Reviewing Statistician

Date

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Supervisor/Team Leader

Date

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/s/  
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Wei Liu  
12/17/2008 11:45:55 AM  
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Todd Sahlroot  
12/17/2008 11:59:59 AM  
BIOMETRICS



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoeconomics and Statistical Science  
Office of Biostatistics

6/19/09

## Statistical Review and Evaluation

### CLINICAL STUDIES

**NDA/Serial Number:** 022363/0000  
**Drug Name:** Livalo<sup>®</sup> (pitavastatin)  
**Indication(s):** Treatment of Subjects with Primary Hypercholesterolemia or Combined Dyslipidemia  
**Applicant:** KOWA  
**Date(s):** Received 10/1/2008  
**Review Priority:** Standard (10-month)

**Biometrics Division:** Division of Biometrics 2  
**Statistical Reviewer:** Wei Liu, Ph.D.  
**Concurring Reviewers:** J. Todd Sahlroot, Ph.D. (Deputy Director and Team Leader)  
Thomas Permutt, Ph.D. Division Director

**Medical Division:** Metabolism and Endocrinological Products (HFD-510, DMEP)  
**Clinical Team:** Iffat Chowdhury, M.D.  
Eric Colman, M.D., (Deputy Director and Team Leader)  
Mary Parks, M.D. (Division Director)

**Project Manager:** Kati Johnson

**Keywords:** NDA review, active control/non-inferiority, clinical studies

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

### Efficacy Conclusions:

Based on an evaluation of the five Phase 2 studies, this reviewer conclude that all pitavastatin doses (1, 2, and 4 mg) were statistically superior to placebo on lowering LDL-C in all Phase 2 studies.

Based on an evaluation of the five Phase 3 core studies, this reviewer conclude that using a non-inferiority margin of -6% the mean percent decrease from baseline to endpoint in LDL-C for pitavastatin was non-inferior to atorvastatin (Study NK-104-301), simvastatin (Studies NK-104-302 and NK-104-304), and pravastatin (Study NK-104-306) for all the pair-wise comparisons of the core studies with the exception of Study NK-104-305 of which all subjects were Type 2 diabetic..

In study NK-104-306, all 3 pitavastatin doses (1 mg, 2 mg, and 4 mg) showed statistically significantly greater mean percent reductions in LDL-C from baseline to endpoint when compared with the 3 corresponding doses of pravastatin (10 mg, 20 mg, and 40 mg;  $p < 0.001$ ). No significant differences between pitavastatin and active comparators were observed from the subgroup efficacy analyses (age, sex, and race) across the Phase 3 core studies.

In my opinion, the statistical results from the five Phase 2 studies and five Phase 3 studies support the recommended dosages (1, 2, and 4 mg) for lowering LDL-C level. However, it is interesting to note that in the Phase 2 studies for dose finding, the levels of HDL-C and Apo-A1 (as secondary efficacy endpoints) decreased with increasing Livalo dosage.

### Safety Conclusion:

The FDA medical officer identified myalgia incidence, acute renal failure, possible treatment induced hepatic disorder, and new proteinuria as important safety endpoints. To evaluate the safety of pitavastatin as compared with active control statins, this reviewer performed stratified analyses of the safety data, including subgroup comparisons (gender, race, and age), across the core studies as well as the core plus extended studies. Overall, Livalo was associated with a numerical increase in the incidence of myalgia compared to active controls. The difference was not statistically significant ( $p$ -value=0.21). The treatment difference was significant ( $p$ -value=0.053) for Caucasians. Livalo 4 mg was associated with a significant increase in myalgia in the atorvastatin 20 mg–controlled studies ( $p$ -value = 0.018). This reviewer found no significant differences in patients with possible treatment induced hepatic disorder or new proteinuria between Livalo and active control treatments, both in the overall and the subgroup comparisons. Acute renal failures were rare in patients treated with either pitavastatin (2 out of 2376) or active control statins (3 out of 972) in the five core studies.

Recommendations for Labeling.

ref. Sponsor's Proposed Labeling section 14.1 (submitted on 01/23/2009)

(b) (4)

(b) (4)

(3) The sponsor should include a table describing the design and results for the diabetes trial NK-104-305 following the format of Table 4; and a similar table for NK-104-304 following the format of Table 5.

(b) (4)

## 1.2 Brief Overview of Clinical Studies

Kowa Company Limited (KCL) submitted this New Drug Application, NDA 22-363, for pitavastatin tablets (NK-104) with the proposed trade name, Livalo®. Pitavastatin is a member of the statin class of compounds and has been developed as an adjunct to diet to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia. The objective of the clinical studies is to evaluate the clinical efficacy and safety of pitavastatin compared with other statins and placebo in male and females patients with primary hypercholesterolemia or combined dyslipidemia and certain diagnosis criteria at the end of the run-in period. There are 5 Phase II studies, 5 Phase III core studies, and 4 Phase III extension studies.

The primary efficacy criterion in all studies was the percentage decrease from baseline to study endpoint in LDL-C. The Phase III core studies looked at the 1 mg, 2 mg and 4 mg doses of pitavastatin compared to other statins. These studies were 12-week, randomized, multicenter, multinational, double-blind, active (NK-104-301 and NK-104-305: atorvastatin; NK-104-302 and NK-104-304: simvastatin; and NK-104-306: pravastatin) controlled, parallel, fixed dose or forced titration, conducted in male and females patients.

There were 3365 subjects randomized and treated in the core Phase 3 studies. The randomized patients who received at least 1 dose of study drug and who had at least 1 on-treatment lipid assessment are the main focus for efficacy analysis. The randomized patients who received at least 1 dose of study drug are for safety analysis.

## 1.3 Statistical Issues and Findings

The goal of this review is to examine the statistical significance of clinical efficacy and safety of pitavastatin compared with placebo and the active comparators.

In Phase 2 studies all Livalo doses (1, 2, and 4 mg) were statistically superior to placebo in lowering LDL-C. While the levels of LDL-C, TC, TG, and Apo-B decreased with increasing Livalo doses as expected, levels of HDL-C and Apo-A1 did not increase but actually decreased with increasing Livalo doses in the dose response studies.

Statistical analyses of non-inferiority of pitavastatin to active comparators were conducted in Phase 3 core studies using a non-inferiority margin of -6%. The 6% non-inferiority margin has been used historically in the medical division for evaluating active-control studies with LDL-C as the primary endpoint. The basis for using 6% as the non-inferiority margin is primarily clinical. LDL-C for a given dose of a statin is usually expected to decrease by approximately 6% when the dose is doubled. Any LDL lowering that is less than what could be expected from doubling a statin dose has been considered to be clinically unimportant. One can of course compute a statistical non-inferiority margin using the usual methods. These margins are much greater in magnitude than 6% and therefore considered less relevant than the clinical margin.

The mean percent decrease from baseline to endpoint in LDL-C for pitavastatin was non-inferior to atorvastatin (Study NK-104-301), simvastatin (Studies NK-104-302 and NK-104-304), and pravastatin (Study NK-104-306) for all the pair-wise comparisons of the core studies with the exception of Study NK-104-305. The subjects in study NK-104-305 (pitavastatin 4 mg vs. atorvastatin 20 mg) were Type 2 diabetics and had lower mean baseline LDL-C levels compared to the other core studies. In study NK-104-306, all 3 pitavastatin doses (1 mg, 2 mg, and 4 mg) showed statistically significantly greater mean percent reductions in LDL-C from baseline to endpoint when compared with the 3 corresponding doses of pravastatin (10 mg, 20 mg, and 40 mg;  $p < 0.001$ ).

This reviewer also performed subgroup analyses of LDL-C based on sex, age and race. The results showed no consistent significant subgroup differences between Livalo and active controls. Study NK-104-304 had nominally a significant treatment-by-age interaction in which younger patients experienced greater LDL-C lowering on Livalo compared to elderly patients. In study NK-104-305 females experienced greater LDL-C lowering than did males on Livalo compared to controls.

The sponsor did not perform statistical analyses of safety endpoints. Instead, the sponsor provided descriptive summaries of AEs within each pitavastatin dose (1 mg, 2 mg, and 4 mg). This reviewer performed subgroup analyses that incorporated information from the control groups. The safety analyses were applied to integrated data from Phase 3 studies, stratified by study and comparing pitavastatin and active controls. The primary safety endpoints identified by the FDA medical officer in this NDA included myalgia, possible treatment induced hepatic disorder, new proteinuria, and acute renal failure. No significant differences were identified between Livalo and the active comparators for these safety endpoints from the overall and subgroup safety analyses.

## 2. INTRODUCTION

### 2.1 Overview

Pitavastatin is a synthetic chemical as a competitive inhibitor of HMG-CoA reductase with preferential effects on the liver. It is a member of the statin class of compounds and has been developed as an adjunct to diet to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia. Pitavastatin has been approved in Japan since September 2003 under the tradename Livalo<sup>®</sup>, in Korea since January 2005 and Thailand since November 2007. The sponsor, Kowa Company Limited (KCL), submitted a New Drug Application, NDA 22-363 with data, for pitavastatin tablets (NK-104) with the proposed trade name, Livalo<sup>®</sup>. In this submission, there are 5 Phase II studies, 5 Phase III core studies, and 4 Phase III extension studies.

The objective of the clinical studies was to evaluate the clinical efficacy and safety of pitavastatin compared with other statins and placebo in male and females patients with primary hypercholesterolemia or combined dyslipidemia and certain diagnosis criteria at the end of the run-in period. The Phase II core studies, with 1417 randomized and treated subjects, were dose finding studies compared to placebo or an active control. There were 3365 subjects randomized and treated in the core Phase 3 studies. The phase III studies looked at the 1 mg, 2 mg and 4 mg doses of pitavastatin compared to other statins. These studies were 12-week, randomized, multicenter, multinational, double-blind, active (atorvastatin, simvastatin, and pravastatin ) controlled, parallel, fixed dose or forced titration. The selections of specific pairwise comparisons of pitavastatin against the various doses of the comparators were based on comparable responses of the primary efficacy endpoint from the Phase 2 studies. The Phase III extension studies were intended to collect additional long-term safety information on pitavastatin.

The studies were performed and the data were submitted to FDA in compliance with Good Clinical Practice.

### 2.2 Data Sources

The sponsor submitted study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. Individual study reports were submitted for each study. The data were submitted in SAS Xport transport format.

<b>Application:</b>	<b>N022363</b>
<b>Document:</b>	<b>3932298</b>
<b>Location:</b>	<b>\\CDSESUB1\EVSPROD\NDA022363\0000</b>

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study Design

#### Phase II Studies

The designs for the phase II studies are summarized in Table 1.

**Table 1:** Summary of Phase II Study Designs.

Study	Design	Treatment groups	n
NK-104.2.02 (N=251)	multinational, multicentre, randomized, double-blind, placebo-controlled, dose-ranging study with five parallel groups in patients with primary hypercholesterolaemia for 12 weeks of active double-blind treatment	Pitavastatin 1 mg Pitavastatin 2 mg Pitavastatin 4 mg Pitavastatin 8 mg Placebo	52 49 50 49 51
NK-104.2.03 (N=252)	multinational, multicentre, randomized, double-blind, placebo-controlled, dose-ranging study with five parallel groups in patients with primary mixed or combined hyperlipidaemia for 12 weeks of active double-blind treatment	Pitavastatin 1 mg Pitavastatin 2 mg Pitavastatin 4 mg Pitavastatin 8 mg Placebo	49 50 51 52 50
NKS104A2204	multi-centre, randomized, double-blind (observer-blind-to-lipid-values) parallel-group study in patients with primary hypercholesterolemia or mixed hyperlipidemia (Fredrickson types IIa or IIb) for 12 weeks of active double-blind treatment	Pitavastatin 4 mg Pitavastatin 8 mg Placebo Atorvastatin 10→20→40 mg~	70 209 35 36
NK-104-209	randomized, multi-center trial in patients with primary hypercholesterolemia [Fredrickson Type IIa and IIb hyperlipidemia] for 16 weeks of active treatment	Pitavastatin 8 mg# Pitavastatin 16 mg# Pitavastatin 32 mg# Pitavastatin 64 mg# Placebo#* Atorvastatin 80 mg^	103 103 34 33 53 96
NK-104-210/211	randomized, multicenter study in patients with primary hypercholesterolemia [Fredrickson Type IIa and IIb hyperlipidemia] for 12 weeks of treatment	Pitavastatin 4 mg# Pitavastatin 8 mg# Placebo# Atorvastatin 10 mg^ Atorvastatin 40 mg^	28 58 16 16 15

~ Atorvastatin 10mg QPM for 4 weeks forced titrated to 20mg QPM for an additional 4 weeks and then to 40mg QPM (once daily at bedtime) for the remaining 4 weeks.

# double-blind treatment

\* Switched to NK-104 64 mg QD after 8 weeks.

^ open-label treatment

### **Phase III Core Studies**

The five phase III core studies were 12-week, randomized, multicenter, multination, double-blind, active (atorvastatin, simvastatin, and pravastatin ) controlled, parallel, fixed dose or forced titration, conducted in patients with primary hypercholesterolemia or combined dyslipidemia. In each of the 5 core studies patients were randomized to 1 of 3 doses of pitavastatin (1 mg, 2 mg or 4 mg) or to a comparator (atorvastatin, simvastatin or pravastatin). Randomization to these groups was performed at Visit 4 (Week 0) in ratios as specified in each study and was stratified by center.

The primary objective of the studies was to demonstrate the non-inferiority of pitavastatin to the active comparators using a non-inferiority margin of -6%. The primary endpoint is the percent reduction in LDL-C levels from baseline to the end of 12 weeks of treatment. The specific designs of the clinical trials are summarized in Table 2.

The secondary efficacy variables include the proportion of patients with LDL-C target attainment (NCEP and EAS) at the end of 12 weeks of treatment; and the percent change from baseline to endpoint in other lipid parameters TC, HDL C, non-HDL-C, TG, Apo-B, Apo-A1, hs-CRP, Lp(a); and the change from baseline in TC:HDL-C ratio, non-HDL-C:HDL-C ratio, and Apo-B:Apo-1 ratio, hs-CRP, oxidized LDL, adiponectin, small-dense LDL, and remnant like particle cholesterol [RLP-C]) at the end of 12 weeks of treatment.

**Table 2: Key Design Features of Phase III Core Clinical Studies of Pitavastatin in the Treatment of Patients with Primary Hypercholesterolemia or Combined Dyslipidemia**

Protocol #	Number and Location of Centers	Patient Population	pitavastatin : comparator <sup>a</sup> (n1: n2) <sup>b</sup>	Patients no. by Arm	Sex (M/F) Mean Age (Range)
NK-104-301	40 centers India, Denmark, Russia, and Spain	Male and female patients with primary hypercholesterolemia or combined dyslipidemia who at the end of the run-in period had an average LDL-C $\geq 4.2$ mmol/L and $\leq 5.7$ mmol/L, and a TG level of $\leq 4.6$ mmol/L	2mg : 10mg <sup>1</sup> (316:102)  4mg : 20mg <sup>1</sup> (300:103)	800 (300 per pitavastatin group and 100 per atorvastatin group)	378/443 58.38 years (18, 75)
NK-104-302	45 centers Finland, Italy, Norway, Russia and UK		2mg : 20mg <sup>2</sup> (311:107)  4mg : 40mg <sup>2</sup> (320:110)	800 (300 per pitavastatin group and 100 per simvastatin group)	332/516 58.35 years (25, 75)
NK-104-304	40 centers Denmark, Netherlands, Spain, Sweden and UK	Male and female patients with primary hypercholesterolemia with 2 or more cardiovascular risk factors as defined by elevated plasma LDL-C ( $\geq 3.4$ mmol/L and $\leq 5.7$ mmol/L) despite dietary therapy and elevated TG levels of $\leq 4.6$ mmol/L	4mg : 40mg <sup>2</sup> (233:119)	300 (200 pitavastatin and 100 simvastatin)	240/112 60.50 years (35, 75)
NK-104-305	44 centers Denmark, Germany, India, The Netherlands, Poland, UK	Male and female patients with primary hypercholesterolemia and with Type II DM ([HbA1c] $\leq 7.5\%$ ) and combined dyslipidemia as defined by elevated plasma LDL-C ( $\geq 2.6$ mmol/L and $\leq 5.7$ mmol/L) despite dietary therapy, and elevated TG of $\geq 1.7$ mmol/L	4mg : 20mg <sup>1</sup> (275:137)	400 (2:1 ratio, pitavastatin: atorvastatin)	233/179 59.45 years (24, 75)
NK-104-306	57 centers Denmark, Germany, Israel, The Netherlands and UK	male and female patients ( $\geq 65$ years) with primary hypercholesterolemia as defined by elevated plasma LDL-C ( $\geq 3.4$ mmol/L and $\leq 5.7$ mmol/L) despite dietary therapy, and elevated TG of $\leq 4.6$ mmol/L	1mg : 10mg <sup>3</sup> (206:103)  2mg : 20mg <sup>3</sup> (224:96)  4mg : 40mg <sup>3</sup> (210:102)	900 (200 per pitavastatin group and 100 per pravastatin group)	417/525 70.22 years (65, 89)

<sup>a</sup> Study & Control Dose, Route & Administration:

Pitavastatin 2 mg QD or 2 mg QD (first 4 weeks) → 4 mg QD (remaining 8 weeks)

atorvastatin 10 mg QD or 10 mg QD (first 4 weeks) → 20 mg QD (remaining 8 weeks) simvastatin 20 mg QD or

20 mg QD (first 4 weeks) → 40 mg QD (remaining 8 weeks)

For NK-104-306 only

pitavastatin 1mg, 2 mg or 2 mg (first 4 weeks) → 4 mg QD (remaining 8 weeks)

Pravastatin 10 mg, 20 mg or 20 mg QD (first 4 weeks) → 40 mg QD (remaining 8 weeks)

<sup>b</sup> Number of patients treated in the pitavastatin arm: that in the comparator arm.

<sup>1</sup> atorvastatin

<sup>2</sup> simvastatin

<sup>3</sup> pravastatin

### Phase III Extension Studies

The designs of the phase 3 extension studies are summarized in Table 3.

**Table 3. Summary of Phase III Extension Study Designs**

Extended Study	Core Phase 3	Design
NK-104-307	NK-104-301 or NK-104-302	52 weeks open-label treatment with pitavastatin 4 mg QD; no control treatments. It was expected that approximately 1400 patients would enter the study.
NK-104-308	NK-104-306	60 weeks open-label treatment with pitavastatin 2 mg QD
NK-104-309	NK-104-304	Treatment was administered according to a 44 weeks double-blind, double-dummy design up to Week 16, and then to a single-blind, double-dummy design for the remainder of the study.
NK-104-310	NK-104-305	44-week double-dummy active-controlled. The first 16 weeks were double-blind and were followed by a 28 week single-blind phase in patients. Those patients who received atorvastatin 20 mg and did not achieve NCEP LDL-C target at Visit 7 (Week 8) of the core study, were up-titrated to atorvastatin 40 mg for the extension study while pitavastatin-treated patients who did not achieve NCEP LDL-C target at Visit 7 (Week 8) of the core study continued to receive pitavastatin 4 mg in the extension study. An interim report of safety and efficacy up to Visit 4 (Week 16 of study NK-104-310) was planned. This will be followed by a final updated report of safety and efficacy after completion of the study.

### 3.1.2 Baseline/ Demographic Characteristics of the Core Studies

Demographic characteristics of the core studies including country, sex, age, and race are summarized for each treatment group in each study as shown in Table 4. The age of patients ranged from 18-89 years old. Mean age ranged from 50 to 60 years, with the exception of Study NK-104-306 (carried out in elderly patients) where the mean age was approximately 70 years. The distribution of males to females was generally similar across all treatment groups and doses in most of the core studies. The exception was Study NK-104-304 where the proportion of males was a higher than that of females (68-69% vs. 31-32%, respectively).

The majority of patients in the core studies, as well as in each treatment and dose group, were Caucasians (>75%); non-Caucasians present mainly in studies NK-104-301 and NK-104-305. Although the non-Caucasians in these two studies were classified by the sponsor as Asians/Indians in the Table 4, there were 192 Indians from India and one Asian from Russia in study NK-104-301 and 50 Indians from India and one Asian from Netherlands in study NK-104-

305, respectively (APPENDIX I: Appendix Table 1). Hence, the subsequent subgroup analyses of race were broken down by Caucasians and Indians.

The baseline lipid values of the primary efficacy endpoint LDL-C and some important secondary efficacy endpoints (HDL-C, TC, and TG) are listed in Appendix Table 2 of this review. Note that the baseline values of LDL-C for patients with type 2 diabetes mellitus (study NK-401-305) were much lower than for patients in other studies while TG values were much higher in diabetic patients.

### **3.1.3 patient disposition**

The following analysis populations were defined for the Phase III core studies (Table 5):

- The Safety population was defined as all randomized patients who received at least 1 dose of the study drug.
- The FAS was defined as all randomized patients who received at least 1 dose of study drug and who had at least 1 on-treatment lipid assessment.
- The PP population was defined as all patients in the FAS, who had no major protocol violations, and who had an on-treatment lipid assessment at Week 12 (Visit 8).
- The Completers (COM) population was defined as all patients, irrespective of protocol violations, who had a Week 12 (last week of measurement) measurement whether or not on drug.

A total of 261 patients discontinued from these core studies.

The patient disposition in analysis populations was shown in Table 5.

**Table 4: Demographic Characteristics in Core Studies. (Part I) (sponsor's Table 8 in ise.pdf).**

Study Treatment	N	Age		Sex n (%)		Race n (%)			
		Mean (SD)	Range	Male	Female	Caucasian	Black	A/I	H/O
<b>NK-104-301 (Safety population)</b>									
Pitavastatin									
2 mg	316	58.4 (9.5)	23, 75	142 (45)	174 (55)	238 (75)	0	78 (25)	0
4 mg	300	57.9 (10.1)	18, 74	136 (45)	164 (55)	232 (77)	0	68 (23)	0
Atorvastatin									
10 mg	102	59.2 (8.6)	28, 74	52 (51)	50 (49)	79 (78)	0	23 (22)	0
20 mg	103	58.0 (9.1)	35, 73	48 (47)	55 (53)	79 (77)	0	24 (23)	0
<b>NK-104-302 (Safety population)</b>									
Pitavastatin									
2 mg	311	58.7 (8.8)	30, 75	115 (37)	196 (63)	310 (100)	1 (0)	0	0
4 mg	320	57.7 (9.0)	29, 75	125 (39)	195 (61)	318 (100)	0	1 (0)	1 (0)
Simvastatin									
20 mg	107	58.6 (9.6)	34, 74	44 (41)	63 (59)	106 (99)	0	0	1 (1)
40 mg	110	58.4 (9.5)	25, 74	48 (44)	62 (56)	110 (100)	0	0	0
<b>NK-104-304 (Safety population)</b>									
Pitavastatin 4 mg	233	60.1 (6.8)	35, 75	158 (68)	75 (32)	233 (100)	0	0	0
Simvastatin 40 mg	119	60.9 (6.8)	40, 74	82 (69)	37 (31)	118 (99)	1 (1)	0	0
<b>NK-104-305 (Safety population)</b>									
Pitavastatin 4 mg	275	59.1 (9.2)	24, 75	155 (56)	120 (44)	243 (88)	0	32 (12)	0
Atorvastatin 20 mg	137	59.8 (9.1)	36, 75	78 (57)	59 (43)	118 (86)	0	19 (14)	0
<b>NK-104-306 (Safety population)</b>									
Pitavastatin									
1 mg	207	70.0 (4.6)	65, 89	89 (43)	118 (57)	207 (100)	0	0	0
2 mg	224	70.5 (4.5)	65, 87	100 (45)	124 (55)	222 (100)	1 (0)	0	1 (0)
4 mg	210	70.2 (4.1)	65, 82	89 (42)	121 (58)	207 (99)	0	0	3 (1)
Pravastatin									
10 mg	103	70.5 (4.6)	65, 82	49 (48)	54 (52)	103 (100)	0	0	0
20 mg	96	69.9 (4.5)	65, 86	48 (50)	48 (50)	94 (98)	0	2 (2)	0
40 mg	102	70.2 (4.9)	65, 89	42 (41)	60 (59)	102 (100)	0	0	0

A/I: Asian/ Indian  
H/O: Hispanic/ Other

**Table 5: Patient Populations by Study and Dose – Core Studies (ref sponsor’s Table 6 in ise.pdf)**

Study Treatment	N	Safety n (%)	FAS/ITT n (%)	Completer n (%)	Per Protocol n (%)
<b>NK-104-301</b>					
Pitavastatin					
2 mg	321	316 (98.4)	315 (98.1)	301 (93.8)	236 (73.5)
4 mg	303	300 (99.0)	298 (98.3)	288 (95.0)	250 (82.5)
Atorvastatin					
10 mg	103	102 (99.0)	102 (99.0)	98 (95.1)	82 (79.6)
20 mg	103	103 (100)	102 (99.0)	100 (97.1)	82 (79.6)
<b>NK-104-302</b>					
Pitavastatin					
2 mg	315	311 (98.7)	307 (97.5)	295 (93.7)	266 (84.4)
4 mg	323	320 (99.1)	319 (98.8)	304 (94.1)	282 (97.3)
Simvastatin					
20 mg	108	107 (99.1)	107 (99.1)	99 (91.7)	87 (80.6)
40 mg	111	110 (99.1)	110 (99.1)	107 (96.4)	95 (85.6)
<b>NK-104-304</b>					
Pitavastatin 4 mg	236	233 (98.7)	233 (98.7)	223 (94.5)	182 (77.1)
Simvastatin 40 mg	119	119 (100)	118 (99.2)	107 (89.9)	84 (70.6)
<b>NK-104-305</b>					
Pitavastatin 4 mg	279	275 (98.6)	274 (98.2)	248 (88.9)	214 (76.7)
Atorvastatin 20 mg	139	137 (98.6)	136 (97.8)	124 (89.2)	107 (77.0)
<b>NK-104-306</b>					
Pitavastatin					
1 mg	209	207 (99.0)	207 (99.0)	188 (90.0)	171 (81.8)
2 mg	226	224 (99.1)	224 (99.1)	208 (92.0)	179 (79.2)
4 mg	216	210 (97.2)	210 (97.2)	194 (89.8)	170 (78.7)
Pravastatin					
10 mg	108	103 (95.4)	103 (95.4)	89 (82.4)	82 (75.9)
20 mg	99	96 (97.0)	96 (97.0)	88 (88.9)	76 (76.8)
40 mg	104	102 (98.1)	102 (98.1)	95 (91.3)	82 (78.8)

FAS = Full analysis set; ITT=intent-to-treat.

Patients randomized to 4 mg Pitavastatin, 20 mg Atorvastatin, 40 mg Simvastatin or 40 mg Pravastatin in Studies 301, 302, 304, 305 or 306 received lower doses [2 mg Pitavastatin, 10 mg Atorvastatin, 20 mg Simvastatin or 20 mg Pravastatin] for the first 4 weeks of treatment.

### 3.1.4 Statistical methodology used

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

The active-controlled studies all used analysis of covariance (ANCOVA) with treatment and country as factors and baseline LDL-C as a covariate. Adjusted means for the treatment differences and the corresponding 95% confidence intervals (CIs) on the differences were constructed. For each pair-wise comparison, non-inferiority of pitavastatin was claimed if the lower bound of the 95% CI was greater than -6%.

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

Subgroups in Secondary Efficacy Analysis include:

- Sex
- Age: <65,  $\geq$  65
- Age and Sex: Male < 65, Male  $\geq$  65, Female < 65, Female  $\geq$  65
- Risk Category: Low, Moderate, High (NCEP guidelines)
- LDL-C at baseline: < 160, 160- < 190, 190- < 220,  $\geq$  220 mg/dL
- HDL-C at baseline: < 40, 40- < 60,  $\geq$  60 mg/dL
- TG at baseline: < 150, 150- < 200,  $\geq$  200 mg/dL
- Primary Diagnosis: hypercholesterolemia, combined dyslipidemia, heterozygous familial hypercholesterolemia
- Diabetes: Yes, No
- Hypertension: Yes, No
- BMI: < 19, 19- < 30,  $\geq$  30
- Race: Caucasian, Black, Asian + Indian, Hispanic + other

In addition, the change from baseline HDL-C was summarized by Diabetes (Yes/No) and HDL-C at baseline (Y<40, Y 40-<60, Y  $\geq$ 60 mg/dL; N <40, N 40-<60, N  $\geq$ 60 mg/dL).

### **3.1.5 Applicant's results**

In Phase 2 studies all Livalo doses (1, 2, and 4 mg) were statistically superior to placebo in lowering LDL-C. A summary of dose-response in patients with primary hypercholesterolaemia in study NK-104-202 was shown in Table 6 (see Appendix II. Table 3 in the Sponsor's proposed Labeling (submitted on 01/23/2009)). Note that the levels of LDL-C, TC, TG, and Apo-B decreased with increasing Livalo dosage. However, the dose responses of HDL-C and Apo-A1 were odd that their levels decreased also with increasing Livalo dosage.

**Table 6.** Dose-Response in Patients with Primary Hyperlipidemia (Adjusted Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	HDL-C	TG	TC	Apo-A1	Apo-B
Placebo	51	-4.0	2.5	-2.1	-1.3	3.2	0.3
Pitavastatin 1 mg	52	-33.3	9.4	-14.8	-22.8	8.5	-24.1
Pitavastatin 2 mg	49	-38.2	9.0	-17.4	-26.1	5.6	-30.4
Pitavastatin 4 mg	50	-46.5	8.3	-21.2	-32.5	4.7	-36.1

(b) (4)

LDL-C=low density lipoprotein cholesterol; TC=total cholesterol; HDL-C=high density lipoprotein cholesterol; TG=triglycerides; Apo-A1=apolipoprotein A1; Apo-B=apolipoprotein B

The results of the Phase III core studies (Table 7) showed that, with the exception of Study NK-104-305, the mean percent decrease from baseline to endpoint in LDL-C for pitavastatin was non-inferior to atorvastatin (Study NK-104-301), simvastatin (Studies NK-104-302 and NK-104-304), and pravastatin (Study NK-104-306) for both the low dose (pitavastatin 1 mg vs. pravastatin 10 mg [NK-104-306], pitavastatin 2 mg vs. atorvastatin 10 mg [NK-104-301], simvastatin 20 mg [NK-104-302], or pravastatin 20 mg [NK-104-306]) and high dose (pitavastatin 4 mg vs. atorvastatin 20 mg [NK-104-301], simvastatin 40 mg [NK-104-302 and NK-104-304], or pravastatin 40 mg [NK-104-306]) comparisons. In Study NK-104-305 pitavastatin 4 mg did not achieve non-inferiority to atorvastatin 20 mg.

In addition, in Study NK-104-306, all 3 pitavastatin doses (1 mg, 2 mg, and 4 mg) showed statistically significantly greater mean percent reductions in LDL-C from baseline to endpoint when compared with the 3 corresponding doses of pravastatin (10 mg, 20 mg, and 40 mg;  $p < 0.001$ ). For the other comparators, a statistically significantly greater reduction in LDL-C was achieved only for pitavastatin 2 mg compared with simvastatin 20 mg in Study NK-104-302. These efficacy results were confirmed using the PP and completer's populations as shown in Appendix Table 3 of this review.

The efficacy results of some important secondary endpoints are summarized in Table 8.

**Table 7. Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) (FAS Populations).**

Treatment	N	Baseline LDL-C Mean (SD)	Endpoint LDL-C Mean (SD)	Percent Change from Baseline to endpoint Mean (SD)	Adjusted Mean Difference (95% CI) *	P-value
NK-104- 301						
Pitavastatin 2 mg	315	183.6 (16.8)	113.9 (28.0)	-37.9 (14.0)	-0.15 (-3.42; 3.11)	0.93
Atorvastatin 10 mg	102	179.8 (16.8)	111.5 (28.2)	-37.8 (15.6)		
Pitavastatin 4 mg	298	182.0 (16.7)	100.3 (26.9)	-44.6 (15.0)	0.96 (-2.32; 4.24)	0.56
Atorvastatin 20 mg	102	181.9 (16.7)	102.5 (31.0)	-43.5 (16.2)		
NK-104- 302						
Pitavastatin 2 mg	307	183.6 (17.0)	111.9 (28.4)	-39.0 (14.6)	4.08 (0.82; 7.34)	0.01
Simvastatin 20 mg	107	184.1 (17.2)	119.1 (27.7)	-35.0 (15.5)		
Pitavastatin 4 mg	319	184.1 (16.5)	103.0 (27.6)	-44.0 (14.5)	1.08 (-2.13; 4.29)	0.51
Simvastatin 40 mg	110	184.0 (15.7)	104.6 (27.5)	-42.8 (15.8)		
NK-104- 304						
Pitavastatin 4 mg	233	166.1 (20.3)	92.9 (23.5)	-44.0 (12.8)	0.31 (-2.47; 3.09)	0.83
Simv 40 mg	118	166.9 (23.5)	93.3 (24.7)	-43.8 (14.4)		
NK-104- 305						
Pitavastatin 4 mg	274	142.8 (27.4)	84.3 (31.0)	-40.8 (19.6)	-2.33 (-6.18; 1.52)	0.24
Atorvastatin 20 mg	136	146.0 (27.0)	82.4 (27.4)	-43.2 (16.4)		
NK-104- 306						
Pitavastatin 1 mg	207	164.4 (22.9)	112.2 (22.4)	-31.4 (11.8)	8.79 (5.76; 11.81)	<0.001
Pravastatin 10 mg	103	163.6 (22.3)	126.7 (28.6)	-22.4 (14.0)		
Pitavastatin 2 mg	224	162.8 (20.5)	99.2 (24.0)	-39.0 (13.1)	10.23 (7.17; 13.29)	<0.001
Pravastatin 20 mg	96	163.7 (19.3)	116.2 (20.8)	-28.8 (11.1)		
Pitavastatin 4 mg	210	163.5 (21.9)	90.7 (23.6)	-44.3 (13.7)	10.46 (7.43; 13.49)	<0.001
Pravastatin 40 mg	102	166.6 (21.9)	109.5 (25.3)	-34.0 (14.3)		

\* Positive differences favor pitavastatin treatment.

**Table 8. Mean Percent Change in some important secondary endpoints from Baseline to Endpoint by Study and Dose – Core Studies (FAS Population)**

Treatment*	Mean difference (95% CI) p-value					
	HDL-C <sup>1</sup>	TC <sup>2</sup>	TG <sup>2</sup>	Apo-B <sup>2</sup>	Non- HDL-C <sup>2</sup>	Apo-A1 <sup>1</sup>
<b>NK-104-301</b>	<b>Source: Tables 14-17, 20</b>					
Pit 2 mg	-0.36	-0.52	-3.6	0.18	-0.63	0.20
At 10mg	(-3.9, 3.1)	(-3.0, 2.0)	(-9.5, 2.3)	(-3.0, 3.3)	(-3.7, 2.5)	(-2.7, 3.1)
	0.84	0.68	0.24	0.91	0.69	0.89
Pit 4 mg	-3.0	-0.37	-2.8	-0.08	0.47	-2.0
At 20mg	(-6.5, 0.54)	(-2.9, 2.1)	(-8.8, 3.1)	(-3.3, 3.1)	(-2.6, 3.6)	(-4.9, 0.96)
	0.10	0.77	0.35	0.96	0.77	0.19
<b>NK-104-302</b>	<b>Source: Tables 14-17, 20, 21</b>					
Pit 2 mg	-0.46	2.6	0.66	3.0	3.6	0.76
Si 20mg	(-3.7, 2.8)	(0.10, 5.1)	(-5.1, 6.4)	(-0.1, 6.0)	(0.54, 6.7)	(-2.1, 3.6)
	0.78	0.04	0.82	0.06	0.02	0.598
Pit 4 mg	0.44	0.88	0.48	0.52	1.04	0.29
Si 40mg	(-2.8, 3.7)	(-1.6, 3.3)	(-5.2, 6.1)	(-2.5, 3.5)	(-2.0, 4.0)	(-2.5, 3.1)
	0.79	0.48	0.87	0.73	0.50	0.84
<b>NK-104-304</b>	<b>Source: Tables 21- 26</b>					
Pit 4 mg	-2.3	0.28	5.2	0.46	1.4	-1.3
Si 40mg	(-4.9, 0.3)	(-1.8, 2.3)	(0.15, 10.3)	(-2.1, 3.1)	(-1.2, 3.9)	(-3.9, 1.3)
	0.08	0.79	0.04	0.73	0.29	0.33
<b>NK-104-305</b>	<b>Source: Tables 22,23, 28, 32, 33, 34</b>					
Pit 4 mg	0.22	-3.1	-6.7	-1.6	-3.7	-1.92
At 20mg	(-2.9, 3.4)	(-5.8, -0.49)	(-12.8, -0.71)	(-5.2, 2.0)	(-7.1, -0.32)	(-4.5, 0.69)
	0.89	0.02	0.03	0.38	0.03	0.15
<b>NK-104-306</b>	<b>Source: Tables 20-24, 27</b>					
Pit 1 mg	1.1	6.5	8.7	8.1	9.0	0.32
Pr 10mg	(-3.7, 1.6)	(4.3, 8.8)	(3.7, 13.7)	(5.4, 10.8)	(6.2, 11.8)	(-2.3, 2.9)
	0.42	<0.001	0.001	<0.001	<0.001	0.81
Pit 2 mg	-3.4	6.2	4.8	9.0	9.4	-2.0
Pr 20mg	(-6.0, -0.7)	(3.9, 8.5)	(-0.27, 9.9)	(6.2, 11.8)	(6.6, 12.3)	(-4.7, 0.61)
	0.01	<0.001	0.06	<0.001	<0.001	0.13
Pit 4 mg	-3.1	6.8	6.2	9.1	9.6	-2.5
Pr 40mg	(-5.7, -0.42)	(4.6, 9.2)	(1.2, 11.2)	(6.4, 11.8)	(6.8, 12.4)	(-5.1, 0.11)
	0.02	<0.001	0.02	<0.001	<0.001	0.06

\* Pit - Pitavastatin; At - Atorvastatin; Si - Simvastatin; Pr - Prravastatin

<sup>1</sup> Positive differences favor active control

<sup>2</sup> Positive differences favor pitavastatin

### 3.1.6 reviewer's findings

This reviewer verified the sponsor's dose-response results Table 6 which was proposed for labeling using the dataset LIPIDS.XLS for study NK-104-202. The results of this reviewer are shown in Table 9.

**Table 9.** Dose-Response in Patients with Primary Hypercholesterolaemia (Adjusted Mean % Change from Baseline at Week 12) (data: LIPIDS.XLS for study NK-104-202)

Treatment	N	LDL-C	HDL-C	TG	TC	Apo-A1	Apo-B
Placebo	53*	-3.1	0.1	1.2	-2.0	1.6	-2.1
Livalo 1mg	52	-32.1	8.4	-15.0	-22.7	8.2	-24.9
Livalo 2mg	49	-35.7	7.2	-18.8	-25.6	5.8 <sup>a</sup>	-29.6
Livalo 4mg	51 <sup>#</sup>	-42.8	5.4	-18.1	-31.1	3.0 <sup>b</sup>	-35.0

The numbers of subjects for Apo-A1 and Apo-B were N=51 (\*) and N=49 (#), respectively

(b) (4) this reviewer identified two results \* were not significant (Livalo vs. placebo) at level 0.05 (two-sided), <sup>a</sup> p-value=0.069 and <sup>b</sup> p-value=0.54. (b) (4)

The changes of the primary efficacy endpoint LDL-C from the baseline to the endpoint or 12 weeks treatment of Livalo and active controls for the core studies are shown in Figure 1 using the FAS population. The non-inferiority margin (M in the Figure) is 6% (not -6% because of using Livalo minus comparator instead of the sponsor's comparator minus Livalo). The reviewer's efficacy analyses of the core studies for the PP and completers populations are in Appendix Table 5. Key secondary efficacy endpoints are shown in Appendix Table 6 that are consistent with sponsor's results.

### 3.2 Evaluation of Safety

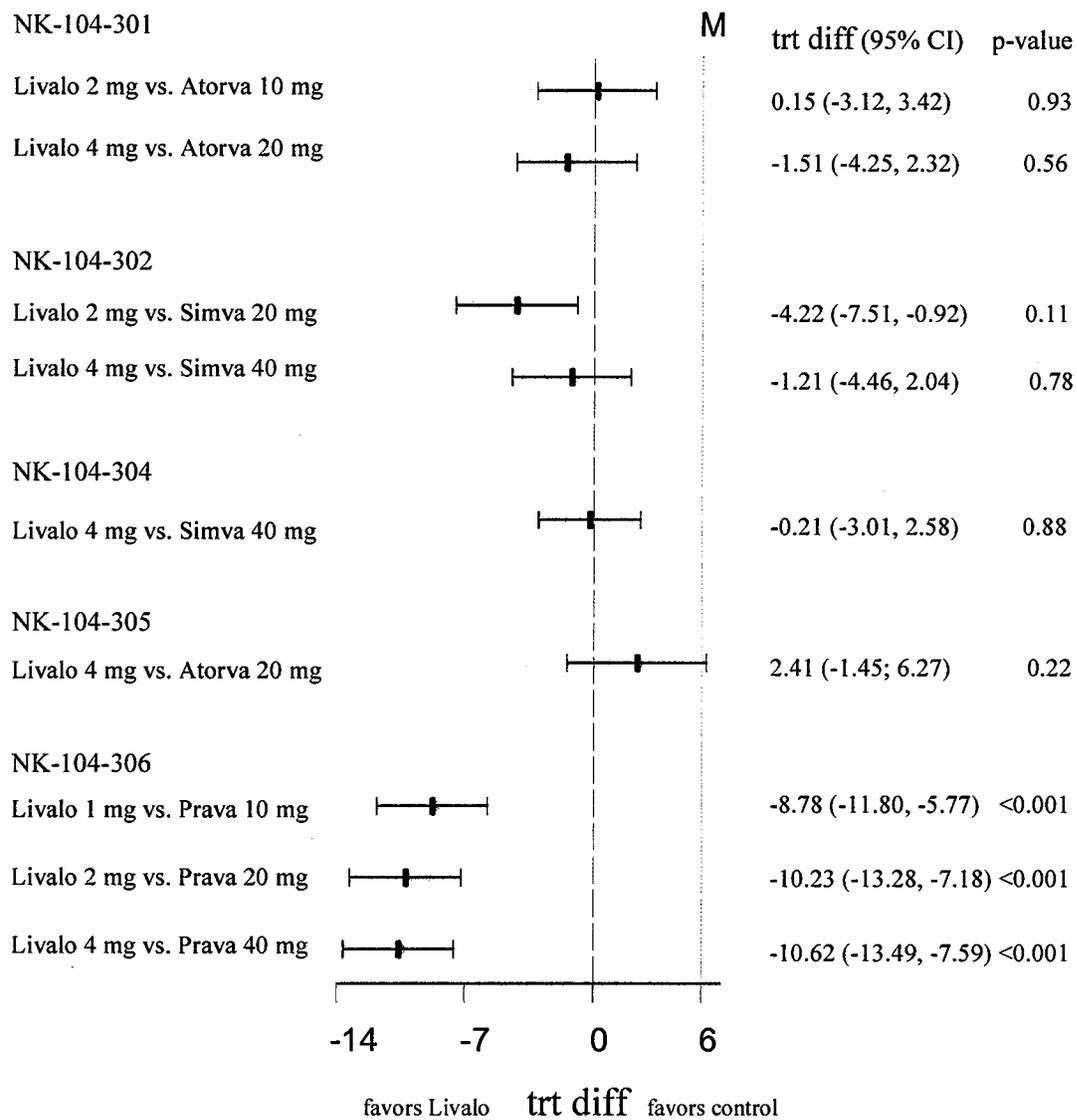
The sponsor did not perform statistical analyses of safety endpoints. Instead, the sponsor provided descriptive summaries of AEs by each pitavastatin dose (1 mg, 2 mg, and 4 mg).

This reviewer conducted analyses of the overall safety population and subgroups based on gender, race, and age. The analyses were applied to integrated data from Phase 3 studies, stratified by study and comparing pitavastatin and active controls. The primary safety endpoints identified by the FDA medical officer in this NDA included myalgia, possible treatment induced hepatic disorder, new proteinuria, and acute renal failure.

#### 3.2.1 Myalgia

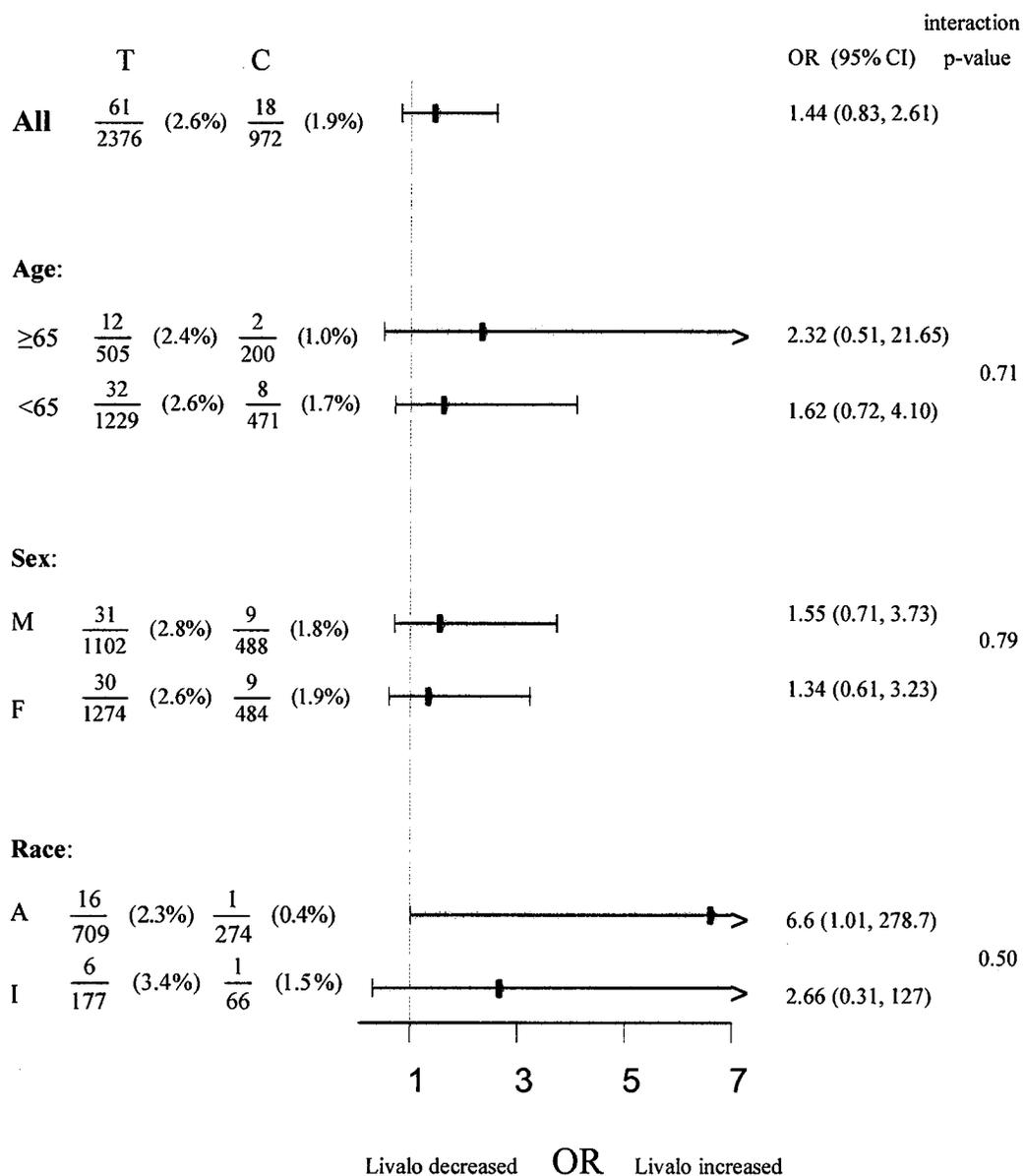
The incidence rates, odds ratios (OR), and 95% confidence intervals for myalgia are shown in Figure 2. Livalo was associated with a numerical increase in myalgia compared to the active controls.

**Figure 1. Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL)**  
(FAS population).



**Figure 2.** Odds ratio (OR) of myalgia incidence between Livalo (T) and active controls (C) in the core studies (safety population).

A: Caucasian; I: Indian



### 3.2.2 Hepatic Disorder

Results for possible treatment induced hepatic disorder are shown in Figure 3. There were no significant differences between Livalo and active control treatments for the overall safety database.

### 3.2.3 Urine Protein/Creatinine ratio

The applicant analyzed a spot urine protein/ creatinine ratio in subpopulations of studies NK-104-301 (~43%), NK-104-302 (~34%), NK-104-304 (~93%), and NK-104-305 (~91%) from both Livalo and active comparator arms. A value of <0.2 mg/mg for protein/ creatinine ratio was determined to be normal. The lower limit of 0.26 mg/mg was determined to be the clinical threshold for new proteinuria by the FDA medical officer (also used by the sponsor). This reviewer conducted statistical analyses across the integrated data stratified. Table 10 summarizes the results which suggest no significant difference between Livalo and the active comparators.

**Table 10.** Summary of Statistical Analyses in Difference of Spot Urine Protein/ Creatinine Ratios between Livalo (T) and active controls (C) Changes from Baseline to Endpoint or Week 12. Analyses were conducted across integrated data stratified by study from a subpopulation of the core studies NK-104-301, NK-104-302, NK-104-304, and NK-104-305 using Proc GLM of SAS 9.1.

subgroup	N <sub>T</sub>	N <sub>C</sub>	Mean, T	Mean, C	Diff. (C-T)	95% CI	p-value	Interaction p-value
All	232	104	0.143	0.004	-0.14	(-0.44, 0.16)	0.37	
Age, years								
>=65	73	36	0.143	-0.080	-0.22	(-0.59, 0.15)	0.24	
<65	159	68	0.140	0.027	-0.11	(-0.38, 0.16)	0.41	0.80
Gender								
male	132	70	0.202	-0.018	-0.22	(-0.47, 0.03)	0.09	
female	100	34	0.067	0.064	-0.004	(-0.42, 0.41)	0.99	0.43
Race*								
Caucasian	50	16	0.098	-0.156	-0.25	(-1.02, 0.51)	0.51	
Indian	21	7	-0.025	0.457	0.48	(0.09, 0.87)	0.017	0.23

\* Studies 302, 304, and 305 not included due to inadequate representation of non-Caucasians.

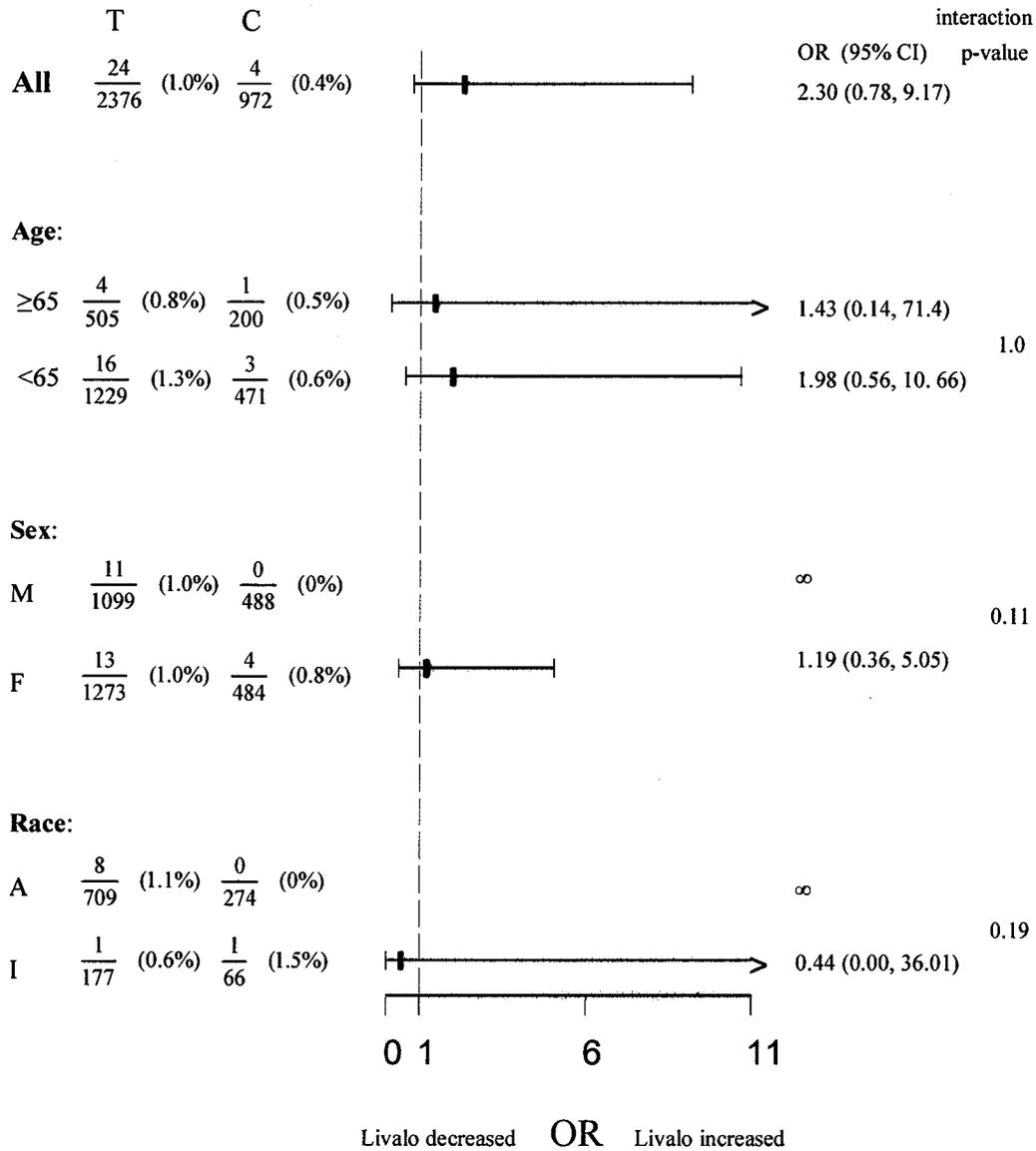
In addition, categorical analyses for new proteinuria (Y/N) were performed and the results are shown in Figure 4. The 95% confidence intervals do not exclude the odds ratio 1, suggesting no significant differences in the new proteinuria incidence between Livalo and active controls.

### 3.2.4 Renal Failure

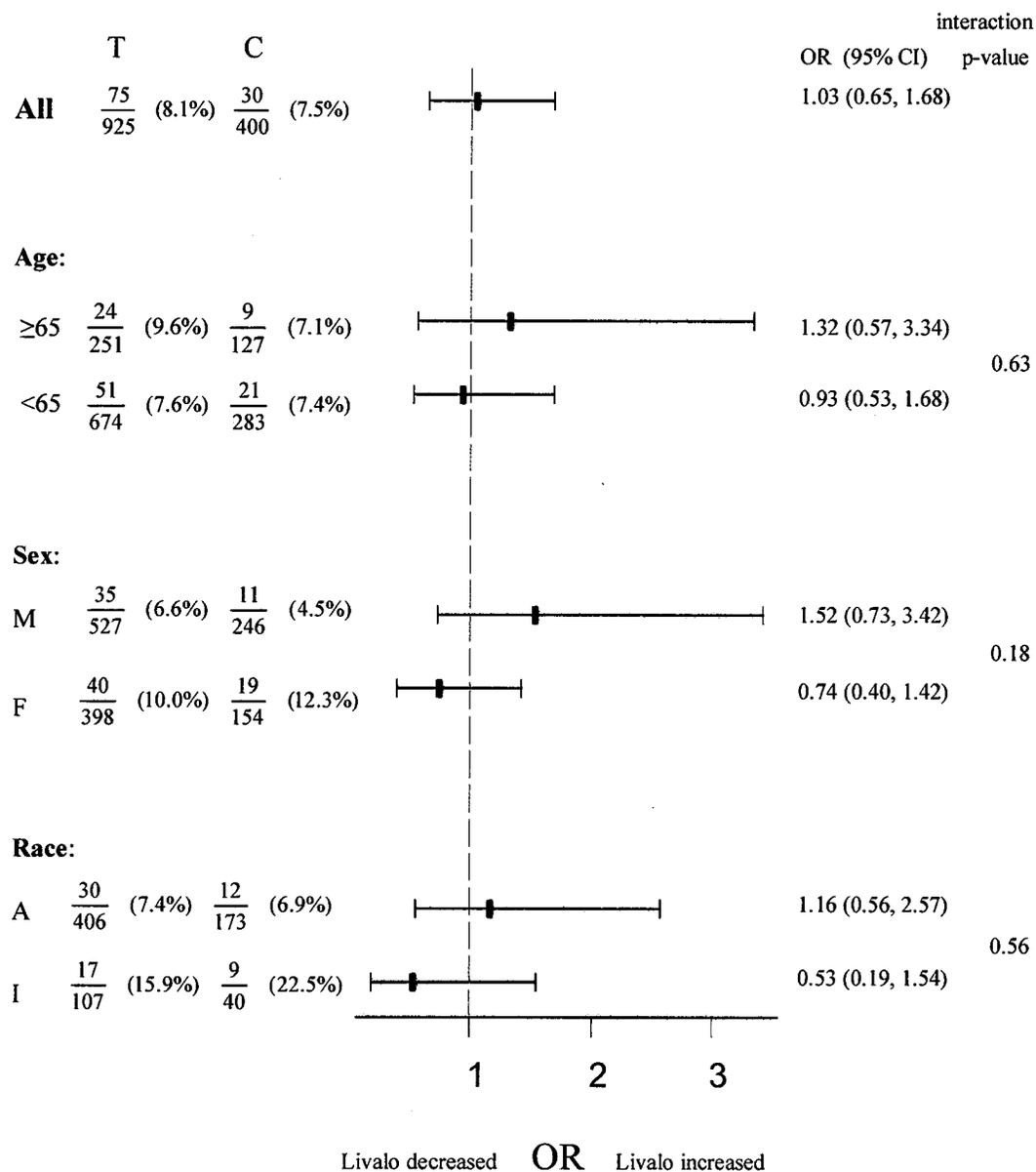
Acute renal failures were rare both in patients treated with pitavastatin (2 out of 2376) or active control statins (3 out of 972) in the five core studies (Appendix Table 6). No statistical analyses were conducted for these endpoints.

As shown in the Phase 3 extension study designs (Table 3), there were only two active-controlled studies (NK-104-309 extension from NK-104-304; and NK-104-310 from NK-104-305). This reviewer performed an integrated safety analysis using the integrated data from the core and extension studies. The (core + extension) safety datasets consist of the combined safety data from extensions NK-104-309 and NK-104-310, and the five core studies NK-104-301, NK-104-302, NK-104-304, NK-104-305, and NK-104-306. The results using the (core+extension) safety datasets are shown in Appendix Figures 1-5, and are similar to the core studies.

**Figure 3.** Odds ratio (OR) of possible hepatic disorder between Livalo (T) and active controls (C) in the core studies (safety population). A: Caucasian; I: Indian



**Figure 4.** Odds ratio (OR) of new proteinuria between Livalo (T) and active controls (C) in a subpopulation of the core studies NK-104-301, NK-104-302, NK-104-304, and NK-104-305. A: Caucasian; I: Indian



## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

#### 4.1.1 Efficacy

The sponsor's subgroup analyses (such as age <65 years vs. age ≥65 years; males vs. females; and Caucasians vs. non-Caucasians as shown in Appendix Table 4) for the core studies compared, say, males and females taking pitavastatin at different doses and ignored all control data.

For the primary endpoint, this reviewer analyzed subgroups differently than the sponsor's approach which ignored control data. The overall approach was to compare treatment differences (Livalo minus comparator) between levels of the subgroup variable. P-values were generated by tests of interaction. A confidence interval approach, similar to the interaction test, was also used. All the comparators were active controls and therefore the confidence interval approach provides information on the range of subgroup differences consistent with the observed treatment differences. To illustrate the approach, let

$L_1$  = mean LDL-C % change from baseline for subgroup 1 treated with Livalo at a given dose

$C_1$  = mean LDL-C % change from baseline for subgroup 1 treated with an active control at a given dose

$L_2$  = mean LDL-C % change from baseline for subgroup 2 treated with Livalo at a given dose

$C_2$  = mean LDL-C % change from baseline for subgroup 2 treated with an active control at a given dose

and

$$m_1 = (C_1 - L_1)$$

$$m_2 = (C_2 - L_2)$$

$$d = m_1 - m_2$$

This reviewer tested the hypothesis  $H_0: d=0$  versus  $H_a: d \neq 0$

$d$  follows a normal distribution. The 95% CI of  $d$  is estimated using  $\hat{d} \pm 1.96 \times se(\hat{d})$

$$\text{where } se^2(\hat{d}) = \frac{s^2(\hat{C}_1)}{n_{C_1}} + \frac{s^2(\hat{L}_1)}{n_{L_1}} + \frac{s^2(\hat{C}_2)}{n_{C_2}} + \frac{s^2(\hat{L}_2)}{n_{L_2}}.$$

The 95% CIs for each of subgroup analyses are listed in Tables 11 (age), 12 (gender) and 13 (race). Results are depicted graphically in Figures 5-7.

**Table 11.** Difference in Changes from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) between elderly (m1, age  $\geq$  65 years) and young (m2, age < 65 years) in each treatment pair (FAS population).

Treatment	N, $\geq$ 65	N, <65	m1-m2	s.e.(m1-m2)	95% CI	Interaction p-value
<b>NK-104-301</b>						
Pitavastatin 2 mg	96	219	1.06	1.88	[-5.87, 7.99]	0.57
Atorvastatin 10 mg	27	75				
Pitavastatin 4 mg	93	205	3.05	3.45	[-3.71, 9.81]	0.38
Atorvastatin 20 mg	30	72				
<b>NK-104-302</b>						
Pitavastatin 2 mg	96	206	-3.70	3.60	[-10.76, 3.36]	0.30
Simvastatin 20 mg	35	70				
Pitavastatin 4 mg	87	226	-2.12	3.65	[-9.28, 5.04]	0.56
Simvastatin 40 mg	33	75				
<b>NK-104-304</b>						
Pitavastatin 4 mg	49	184	-6.87	3.66	[-14.05, 0.31]	0.06
Simvastatin 40 mg	31	87				
<b>NK-104-305</b>						
Pitavastatin 4 mg	84	190	-2.82	4.26	[-11.18, 5.53]	0.51
Atorvastatin 20 mg	44	92				

**Table 12.** Difference in Changes from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) between male (M, m1) and female (F, m2) in each treatment pair (FAS population).

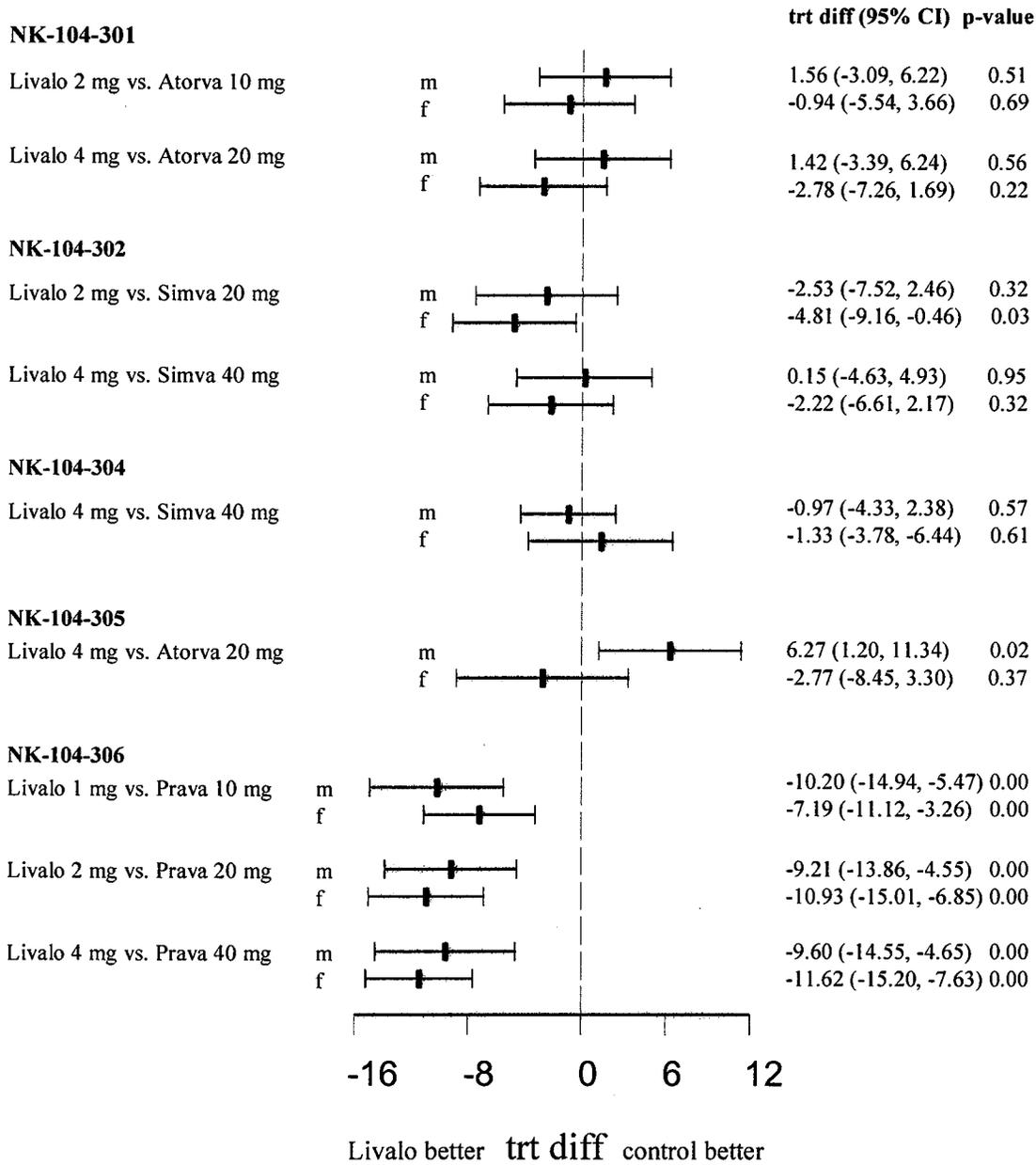
Treatment	N, M	N, F	m1-m2	s.e.(m1-m2)	95% CI	Interaction p-value
<b>NK-104-301</b>						
Pitavastatin 2 mg	142	173	-2.51	3.33	[-9.03, 4.02]	0.45
Atorvastatin 10 mg	52	50				
Pitavastatin 4 mg	136	162	-4.21	3.34	[-10.76, 2.35]	0.21
Atorvastatin 20 mg	48	54				
<b>NK-104-302</b>						
Pitavastatin 2 mg	111	191	-2.28	3.36	[-8.87, 4.31]	0.50
Simvastatin 20 mg	43	62				
Pitavastatin 4 mg	122	191	-2.37	3.30	[-8.84, 4.10]	0.47
Simvastatin 40 mg	47	61				
<b>NK-104-304</b>						
Pitavastatin 4 mg	158	75	2.30	3.09	[-3.75 8.36]	0.46
Simvastatin 40 mg	81	37				
<b>NK-104-305</b>						
Pitavastatin 4 mg	155	119	-9.05	4.01	[-16.90, -1.19]	0.02
Atorvastatin 20 mg	78	58				
<b>NK-104-306</b>						
Pitavastatin 1 mg	89	118	3.02	3.13	[-3.12, 9.15]	0.33
Pravastatin 10 mg	49	54				
Pitavastatin 2 mg	100	124	-1.72	3.15	[-7.90, 4.45]	0.56
Pravastatin 20 mg	48	48				
Pitavastatin 4 mg	89	121	-1.82	3.17	[-8.03, 4.39]	0.57
Pravastatin 40 mg	42	60				

**Table 13.** Difference in Changes from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) between Caucasian (C, m1) and Indian (I, m2) in each treatment pair (FAS population).

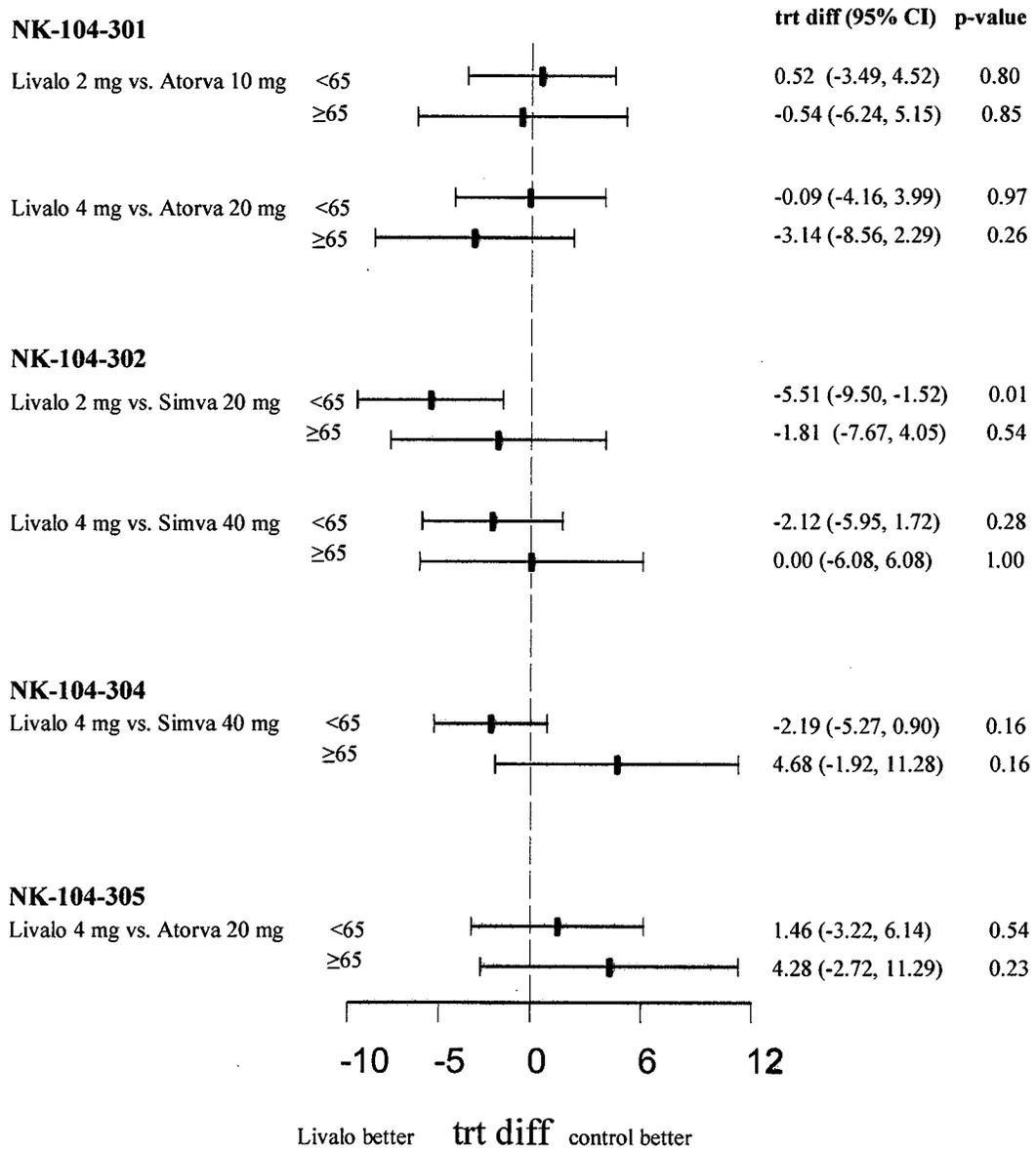
Treatment	N, C	N, I	m1-m2	s.e.(m1-m2)	95% CI	Interaction p-value
<b>NK-104-301</b>						
Pitavastatin 2 mg	237	77	-3.70	4.48	[-12.47, 5.08]	0.41
Atorvastatin 10 mg	79	23				
Pitavastatin 4 mg	230	68	-2.89	4.47	[-11.66, 5.87]	0.52
Atorvastatin 20 mg	78	24				
<b>NK-104-305</b>						
Pitavastatin 4 mg	242	32	1.31	5.83	[-10.12, 12.74]	0.82
Atorvastatin 20 mg	117	18				

Note: Studies 302, 304, and 306 not included due to inadequate representation of non-Caucasians.

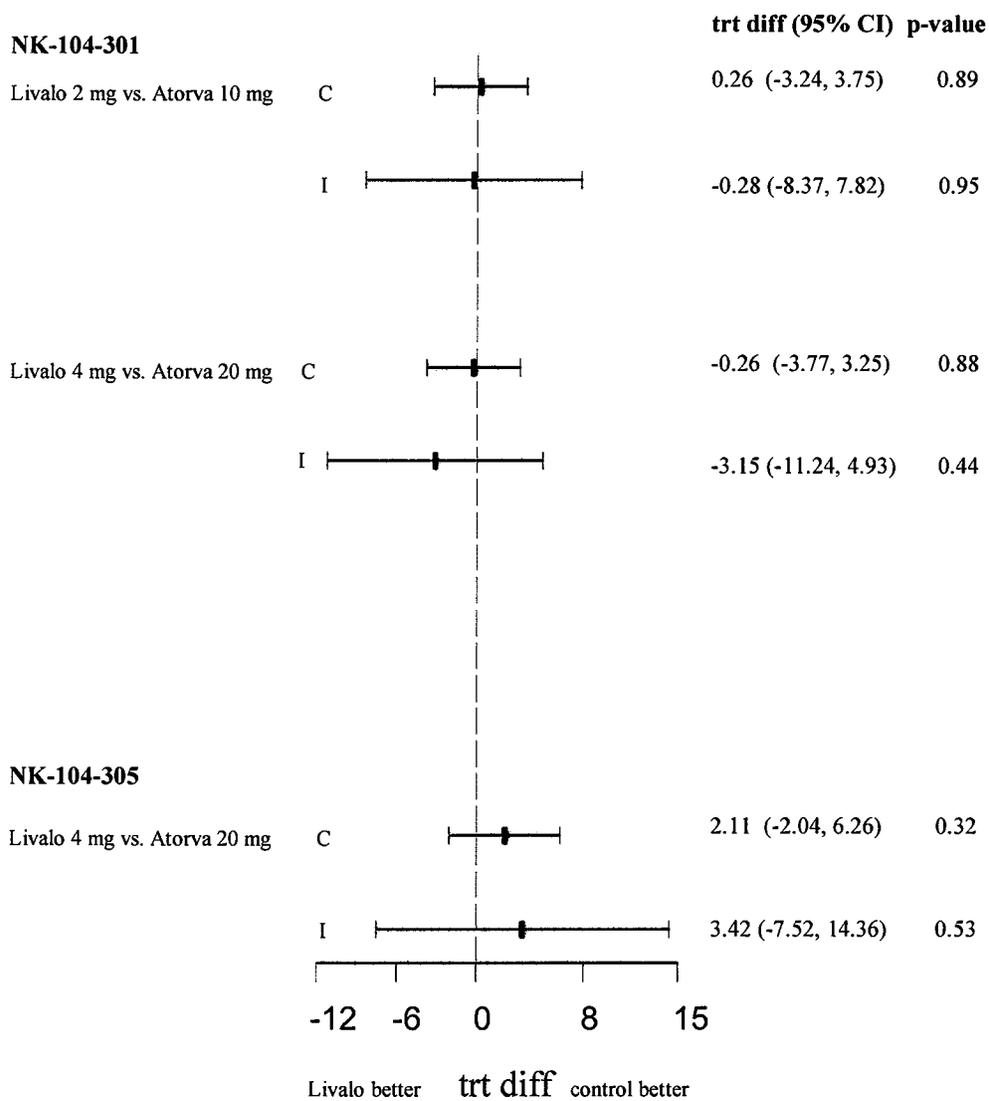
**Figure 5.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) between males (m) and females (f) (FAS population)



**Figure 6.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) between young (age < 65 years) and elderly (age ≥ 65 years) (FAS population)



**Figure 7.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) between Caucasians (C) and Indians (I) (FAS population)



#### **4.1.2 Safety Subgroup Analysis**

This reviewer conducted subgroup analyses of the safety endpoints across the integrated data stratified by study. The results were described by each of the safety endpoints.

##### **Myalgia**

The incidence rates, odds ratios (OR), and 95% confidence intervals for myalgia are shown in Figure 2. The overall results were replicated with subgroups.

##### **Hepatic Disorder**

The incidence rates, odds ratios (OR), and 95% confidence intervals for possible treatment induced hepatic disorder are shown in Figure 3. There were no significant differences between Livalo and active control treatments in subgroup analyses. Subgroups showed consistent effects with the overall results.

##### **Urine Protein/Creatinine ratio**

This reviewer conducted statistical analyses across the integrated data of the subpopulations, stratified by study. Table 10 summarizes the results which suggest no significant difference between Livalo and the active comparators in the mean spot urine protein/ creatinine ratio. In addition, the incidence rates, odds ratios (OR), and 95% confidence intervals for new proteinuria in subgroups are shown in Figure 3. The 95% confidence intervals do not exclude the odds ratio 1, suggesting no significant differences in the new proteinuria incidence between Livalo and active controls in the subgroups. Subgroups showed consistent effects with the overall results.

#### **4.2 Other Special/Subgroup Populations**

Note that the sponsor's safety Summary Table 2.7.4.152 (in iss.pdf), listed that Asians+Indian reported more myalgia with pitavastatin 4 mg than Caucasians at that dose level. However, the results of this reviewer's analyses suggest no significant difference between Caucasians and Indians at this dosage (Table 14). Overall, however, Livalo 4 mg was associated with more myalgia than atorvastatin 20 mg (p-value=0.018).

**Table 14.** Livalo 4 mg vs. atorvastatin 20 mg in NK-104-301 and NK-104-305. The Homogeneity of Odds-ratio test was Zelen's test and was conducted using StatXact 8 to establish that there is indeed a common odds-ratio across all the strata. The exact p-values were computed using Zelen's formulation.

subgroup	n <sub>AE</sub> /n, (%), T	n <sub>AE</sub> /n, (%), C	OR	95% CI	Interaction p-value
All	17/572 (3.0%)	1/238 (0.4%)	7.60	(1.17, 320)	overall p=0.018
<b>Age, years</b>					
>=65	4/177 (2.3%)	0/74 (0%)	inf	(0.45, inf)	1
<65	13/395 (3.3%)	1/164 (0.6%)	5.83	(0.86, 250)	
<b>Gender</b>					
male	13/291 (4.5%)	1/126 (0.8%)	5.88	(0.86, 253)	1
female	4/281 (1.4%)	0/112 (0.0%)	inf	(0.29, inf)	
<b>Race</b>					
Caucasian	13/472 (2.8%)	0/195 (0.0%)	5.08	(0.74, 219)	0.37
Indian	4/100 (4.00%)	1/43 (2.30%)	4.51	(0.37, 250)	

No other subgroups were analyzed.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

#### Efficacy

This reviewer confirmed the sponsor's efficacy results (the primary and key secondary endpoints) for the 1 mg, 2 mg, and 4 mg doses of pitavastatin using a non-inferiority margin of -6%. The mean percent decrease from baseline to endpoint in LDL-C for pitavastatin was non-inferior to atorvastatin (Study NK-104-301), simvastatin (Studies NK-104-302 and NK-104-304), and pravastatin (Study NK-104-306) for all the pair-wise comparisons of the core studies with the exception of Study NK-104-305. The subjects in study NK-104-305 (pitavastatin 4 mg vs. atorvastatin 20 mg) were Type 2 diabetics with lower mean baseline LDL-C levels compared to the other core studies which enrolled patients with high LDL-C values (not necessary to be diabetics) which may have played a role in the difference in results. In study NK-104-306, all 3 pitavastatin doses (1 mg, 2 mg, and 4 mg) showed statistically significantly greater mean percent reductions in LDL-C from baseline to endpoint when compared with the 3 corresponding doses of pravastatin (10 mg, 20 mg, and 40 mg; p<0.001).

This reviewer also performed subgroup analyses of LDL-C based on sex, age and race. The results showed no consistent significant subgroup differences between Livalo and active controls. Study NK-104-304 had nominally a significant treatment-by-age interaction in which younger patients experienced greater LDL-C lowering on Livalo compared to elder

patients. In study NK-104-305 females experienced greater LDL-C lowering than did males on Livalo.

### **Safety**

In summary, the FDA medical officer identified myalgia, possible treatment induced hepatic disorder, new proteinuria, and acute renal failure as important safety endpoints. To evaluate the safety of pitavastatin as compared with active control statins, this reviewer performed analyses of the safety data, including subgroup comparisons (gender, race, and age), stratified by study across the core studies as well as the core plus extended studies. Safety subgroup analyses were conducted for the young (age < 65 years) and elderly (age ≥65 years) patients, males and females, and Caucasians and Indians in the pitavastatin and active control treatment groups. Livalo was associated with a numerical increase in the incidence of myalgia compared to active controls. The difference was not statistically significant (p-value=0.21). The overall results were replicated with subgroups. The treatment difference was significance (p-value=0.053) for Caucasians. Livalo 4 mg was associated with a significant increase in myalgia in the atorvastatin 20 mg–controlled studies (p-value = 0.018). Indians did not have significantly more myalgia than Caucasians did (interaction p-value=0.37) for this specific dose comparison. This reviewer found no significant differences in patients with possible treatment induced hepatic disorder or new proteinuria between Livalo and active control treatments, both in the overall and the subgroup comparisons. Acute renal failures were rare in patients treated with either pitavastatin (2 out of 2376) or active control statins (3 out of 972) in the five core studies. The results in the (core+extension) safety datasets are similar to that in the core studies. The p-values reported for safety endpoints are nominal p-values taken from a number of analyses and are not adjusted for the total number of analyses. Therefore, they should be interpreted cautiously.

## **5.2 Conclusions and Recommendations**

### **Efficacy**

This reviewer conclude that all pitavastatin doses (1, 2, and 4 mg) were statistically superior to placebo on lowering LDL-C in all Phase 2 studies.

This reviewer conclude that based on the evaluation of the five Phase 3 core studies using a non-inferiority margin of -6% the mean percent decrease from baseline to endpoint in LDL-C for pitavastatin was non-inferior to atorvastatin (Study NK-104-301), simvastatin (Studies NK-104-302 and NK-104-304), and pravastatin (Study NK-104-306) for all the pair-wise comparisons of the core studies with the exception of Study NK-104-305.

The subjects in the study NK-104-305 (pitavastatin 4 mg vs. atorvastatin 20 mg) were all Type 2 diabetic with lower mean baseline LDL-C as compared to that in other core studies. The upper limit of the 95% CI for the treatment difference was -6.3%. In study NK-104-306, all 3 pitavastatin doses (1 mg, 2 mg, and 4 mg) showed statistically significantly greater mean percent reductions in LDL-C from baseline to endpoint when compared with the 3 corresponding doses of pravastatin (10 mg, 20 mg, and 40 mg; p<0.001). No significant

differences between pitavastatin and active comparators were observed from the subgroup efficacy analyses (age, sex, and race) across the Phase 3 core studies.

The statistical results from the five Phase 2 studies and five Phase 3 studies support the recommended dosages (1, 2, and 4 mg) for lowering LDL-C level. However, not that in the Phase 2 studies for dose finding, the levels of HDL-C and Apo-A1 (as secondary efficacy endpoints) decreased with increasing Livalo dosage.

**Safety Conclusion:**

The FDA medical officer identified myalgia incidence, acute renal failure, possible treatment induced hepatic disorder, and new proteinuria as important safety endpoints. To evaluate the safety of pitavastatin as compared with active control statins, this reviewer performed stratified analyses of the safety data, including subgroup comparisons (gender, race, and age), across the core studies as well as the core plus extended studies. Overall, Livalo was associated with a numerical increase in the incidence of myalgia compared to active controls. The difference was not statistically significant (p-value=0.21). The treatment difference was significant (p-value=0.053) for Caucasians. Livalo 4 mg was associated with a significant increase in myalgia in the atorvastatin 20 mg–controlled studies (p-value = 0.018). This reviewer found no significant differences in patients with possible treatment induced hepatic disorder or new proteinuria between Livalo and active control treatments, both in the overall and the subgroup comparisons. Acute renal failures were rare in patients treated with either pitavastatin (2 out of 2376) or active control statins (3 out of 972) in the five core studies.

Recommendations for Labeling.

ref. Sponsor's Proposed Labeling section 14.1 (submitted on 01/23/2009)

(b) (4)

(b) (4)

(3) The sponsor should include a table describing the design and results for the diabetes trial NK-104-305 following the format of Table 4; and a similar table for NK-104-304 following the format of Table 5.

(b) (4)

(5) There are too many significant digits in tables and text.

Other information in the sponsor's labeling of the core studies appears acceptable.

## APPENDIX I

**Appendix Table 1.** Demographic Characteristics in Core Studies (Part II).

Study	Caucasian	Black	Asian	Hispanic	Indian	Other
<b>NK-104-301 (SAF n=821)</b>						
country	1, 10, 11		Russia		India	
N	628		1		192	
Age (years)	<65	406	1		167	
	≥ 65	222			25	
Sex	Male	274	1		103	
	Female	354			89	
<b>NK-104-302 (SAF n=848)</b>						
country	2,6,9,10,13	United Kingdom	Norway	Norway		United Kingdom
N	844	1	1	1		1
Age (years)	<65	589	1	1	1	1
	≥ 65	255				
Sex	Male	329		1	1	1
	Female	515	1			
<b>NK-104-304 (SAF n=352)</b>						
country	1,7,11,12,13	United Kingdom				
N	351	1				
Age (years)	<65	271	1			
	≥ 65	80				
Sex	Male	239	1			
	Female	112				
<b>NK-104-305 (SAF n=412)</b>						
country	1,3,7,8,13		Netherlands		India	
N	361		1		50	
Age (years)	<65	240	1		43	
	≥ 65	121			7	
Sex	Male	203	1		29	
	Female	158			21	
<b>NK-104-306 (SAF n=942)</b>						
country	1,3,5,7,13	Netherlands	United Kingdom	Israel		7, 13
N	935	1	2	1		3
Age (years)	65-69	491	1			1
	70-74	281	1	1		1
	≥ 75	163			1	1
Sex	Male	412	1	2		2
	Female	523			1	1

Country code: 1='Denmark', 2='Finland', 3='Germany', 4='India', 5='Israel', 6='Italy', 7='Netherlands', 8='Poland', 9='Norway', 10='Russia', 11='Spain', 12='Sweden', 13='United Kingdom'

**Appendix Table 2.** The baseline lipid values of some important secondary efficacy endpoints in the core studies.

Study Treatment	N <sup>1</sup>	Mean values (SD) , mg/dL			
		LDL-C	HDL-C	TC	TG
<b>NK-104-301</b>					
Pitavastatin					
2 mg	316	183.49 (16.782)	48.50 (11.352)	263.50 (22.705)	157.70 (56.034)
4 mg	300	181.81 (16.819)	49.92 (12.229)	263.26 (22.121)	157.36 (57.982)
Atorvastatin					
10 mg	102	179.76 (16.846)	50.16 (11.689)	261.30 (22.624)	156.84 (60.670)
20 mg	103	181.81 (16.686)	48.65 (12.932)	262.63 (22.463)	161.03 (66.352)
<b>NK-104-302</b>					
Pitavastatin					
2 mg	311	183.59 (16.999)	51.28 (12.762)	267.64 (22.188)	163.66 (60.907)
4 mg	320	183.99 (16.447)	52.78 (12.911)	268.03 (20.759)	156.40 (61.864)
Atorvastatin					
10 mg	107	184.07 (17.152)	50.99 (11.830)	268.38 (22.668)	166.70 (56.831)
20 mg	110	184.00 (15.657)	52.26 (10.687)	267.03 (20.307)	153.86 (55.389)
<b>NK-104-304</b>					
Pitavastatin 4 mg	233	166.09 (20.312)	47.52 (11.386)	246.35 (25.468)	164.01 (67.866)
Simvastatin 40 mg	119	166.68 (23.459)	46.04 (8.179)	245.43 (30.261)	163.71 (66.093)
<b>NK-104-305</b>					
Pitavastatin 4 mg	275	143.00 (27.488)	41.79 (9.235)	233.23 (32.616)	244.15 (77.999)
Atorvastatin 20 mg	137	145.87 (26.945)	40.88 (7.484)	235.57 (31.364)	244.75 (88.815)
<b>NK-104-306</b>					
Pitavastatin					
1 mg	209	164.36 (22.909)	60.80 (15.272)	253.41 (29.163)	141.21 (53.910)
2 mg	226	162.83 (20.495)	60.24 (15.454)	250.48 (25.351)	137.20 (48.702)
4 mg	216	163.48 (21.861)	58.08 (14.621)	250.65 (25.532)	145.42 (55.835)
Pravastatin					
10 mg	108	163.57 (22.285)	57.70 (15.347)	249.66 (28.150)	142.03 (54.039)
20 mg	99	163.71 (19.321)	59.68 (14.193)	252.89 (25.760)	147.91 (61.449)
40 mg	104	166.58 (21.893)	59.39 (15.189)	253.77 (24.511)	139.07 (53.657)

**Appendix Table 3-1.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM, and PP Populations) of NK-104- 301 (ref. sponsor's NK-104- 301 Table 8).

	<b>Pitavastatin 2 mg QD</b>	<b>Atorvastatin 10 mg QD</b>	<b>Pitavastatin 4 mg QD</b>	<b>Atorvastatin 20 mg QD</b>
<b>FAS Population</b>				
N	315	102	298	102
Baseline LDL-C Mean (SD)	183.6 (16.76)	179.8 (16.85)	182.0 (16.72)	181.9 (16.73)
Endpoint LDL-C Mean (SD)	113.9 (27.96)	111.5 (28.21)	100.3 (26.86)	102.5 (31.00)
Percent Change from Baseline to endpoint Mean (SD)	-37.91 (13.969)	-37.81 (15.604)	-44.61 (14.983)	-43.53 (16.153)
Adjusted Mean Difference		-0.15		0.96
Difference (95% CI)		(-3.42; 3.11)		(-2.32; 4.24)
P-value		0.926		0.565
<b>COM Population</b>				
N	301	98	288	100
Baseline LDL-C Mean (SD)	183.3 (16.93)	179.6 (17.00)	181.9 (16.70)	181.7 (16.27)
Week 12 LDL-C Mean (SD)	114.1 (27.99)	109.8 (26.68)	98.7 (25.31)	101.6 (29.31)
Percent Change from Baseline to endpoint Mean (SD)	-37.89 (13.841)	-38.76 (14.582)	-45.50 (14.005)	-43.90 (15.853)
Adjusted Mean Difference		-1.13		1.51
(95% CI)		(-4.34; 2.07)		(-1.68; 4.70)
P-value		0.488		0.352
<b>PP Population</b>				
N	236	82	250	82
Baseline LDL-C Mean (SD)	183.8 <sup>1</sup> (16.11)	179.8 (16.08)	182.5 (16.01)	181.8 (15.79)
Week 12 LDL-C Mean (SD)	112.0 (24.68)	109.4 (26.89)	99.1 (25.30)	99.6 (29.42)
Percent Change from Baseline to endpoint Mean (SD)	-38.95 (12.596)	-39.01 (14.895)	-45.52 (13.753)	-45.07 (15.320)
Adjusted Mean Difference		-0.50		0.23
(95% CI)		(-3.91; 2.91)		(-3.14; 3.60)
P-value		0.773		0.895

<sup>1</sup> Baseline N=236

**Appendix Table 3-2.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM, and PP Populations) of NK-104- 302 (ref. sponsor's NK-104- 302 Table 8).

	<b>Pitavastatin 2 mg QD</b>	<b>Simvastatin 20 mg QD</b>	<b>Pitavastatin 4 mg QD</b>	<b>Simvastatin 40 mg QD</b>
<b>FAS Population</b>				
N	307	107	319	110
Baseline LDL-C Mean (SD)	183.6 (16.98)	184.1 (17.15)	184.1 (16.45)	184.0 (15.66)
Endpoint LDL-C Mean (SD)	111.9 (28.44)	119.1 (27.65)	103.0 (27.58)	104.6 (27.49)
Percent Change from Baseline to endpoint Mean (SD)	-38.99 (14.573)	-34.97 (15.528)	-43.97 (14.494)	-42.84 (15.769)
Adjusted Mean Difference	4.08		1.08	
Difference (95% CI)	(0.82; 7.34)		(-2.13; 4.29)	
P-value	0.014		0.509	
<b>COM Population</b>				
N	295	99	304	107
Baseline LDL-C Mean (SD)	183.3 (16.90)	184.1 (17.03)	184.4 (16.35)	184.2 (15.69)
Week 12 LDL-C Mean (SD)	111.2 (27.97)	118.0 (27.02)	101.6 (26.49)	103.9 (27.42)
Percent Change from Baseline to endpoint Mean (SD)	-39.32 (14.367)	-35.63 (14.969)	-44.85 (13.603)	-43.28 (15.536)
Adjusted Mean Difference	3.73		1.54	
(95% CI)	(0.47; 6.99)		(-1.62; 4.70)	
P-value	0.025		0.338	
<b>PP Population</b>				
N	266	87	282	95
Baseline LDL-C Mean (SD)	183.4 (16.63)	184.4 (16.37)	184.3 (16.46)	184.2 (15.78)
Week 12 LDL-C Mean (SD)	109.7 (25.99)	117.6 (26.84)	101.1 (26.91)	101.7 (25.38)
Percent Change from Baseline to endpoint Mean (SD)	-40.09 (13.764)	-36.09 (14.360)	-45.10 (13.860)	-44.40 (15.047)
Adjusted Mean Difference	4.08		0.74	
(95% CI)	(0.69; 7.48)		(-2.52; 4.00)	
P-value	0.019		0.655	

**Appendix Table 3-3.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM, and PP Populations) of NK-104- 304 (ref. sponsor's NK-104- 304 Table 10).

	<b>Pitavastatin 4 mg QD</b>	<b>Simvastatin 40 mg QD</b>
<b>FAS Population</b>		
N	233	118
Baseline LDL-C Mean (SD)	166.1 (20.31)	166.9 (23.47)
Endpoint LDL-C Mean (SD)	92.9 (23.51)	93.3 (24.67)
Percent Change from Baseline to Endpoint Mean (SD)	-43.96 (12.770)	-43.77 (14.416)
Adjusted Mean Difference		0.31
Difference (95% CI)		(-2.47; 3.09)
P-value		0.829
<b>COM Population</b>		
N	223	107
Baseline LDL-C Mean (SD)	166.0 (20.37)	167.3 (22.75)
Week 12 LDL-C Mean (SD)	90.8 (19.87)	91.1 (23.69)
Percent Change from Baseline to Endpoint Mean (SD)	-45.21 (10.606)	-45.39 (13.065)
Adjusted Mean Difference		0.03
(95% CI)		(-2.41; 2.47)
P-value		0.979
<b>PP Population</b>		
N	182	84
Baseline LDL-C Mean (SD)	167.0 (20.58)	166.0 (21.56)
Week 12 LDL-C Mean (SD)	90.8 (19.77)	87.5 (22.06)
Percent Change from Baseline Mean (SD)	-45.64 (9.913)	-47.13 (12.454)
Adjusted Mean Difference		-0.61
(95% CI)		(-3.17; 1.94)
P-value		0.637

**Appendix Table 3-4.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM, and PP Populations) of NK-104- 305 (**ref. sponsor's NK-104- 305 Table 10**).

	<b>Pitavastatin 4 mg QD</b>	<b>Atorvastatin 20 mg QD</b>
<b>FAS Population</b>		
N	274	136
Baseline LDL-C Mean (SD)	142.8 (27.41)	146.0 (26.98)
Endpoint LDL-C Mean (SD)	84.3 (31.01)	82.4 (27.45)
Percent Change from Baseline to Endpoint Mean (SD)	-40.78 (19.599)	-43.25 (16.378)
Adjusted Mean Difference		-2.33
Difference (95% CI)		(-6.18; 1.52)
P-value		0.235
<b>COM Population</b>		
N	248	124
Baseline LDL-C Mean (SD)	142.4 (27.23)	144.3 (25.66)
Week 12 LDL-C Mean (SD)	83.0 (28.47)	79.5 (23.80)
Percent Change from Baseline to Endpoint Mean (SD)	-41.36 (18.058)	-44.59 (15.331)
Adjusted Mean Difference		-2.76
(95% CI)		(-6.43; 0.90)
P-value		0.139
<b>PP Population</b>		
N	214	107
Baseline LDL-C Mean (SD)	143.6 (27.71)	144.3 (25.70)
Week 12 LDL-C Mean (SD)	84.0 (29.63)	78.4 (21.32)
Percent Change from Baseline Mean (SD)	-41.14 (18.852)	-45.01 (13.981)
Adjusted Mean Difference		-3.72
(95% CI)		(-7.77; 0.32)
P-value		0.071

**Appendix Table 3-5.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM, and PP Populations) of NK-104- 306 (ref. sponsor's NK-104- 306 Table 9).

	Pitavastatin 1 mg QD	Pravastatin 10 mg QD	Pitavastatin 2 mg QD	Pravastatin 20 mg QD	Pitavastatin 4 mg QD	Pravastatin 40 mg QD
<b>FAS Population</b>						
N	207	103	224	96	210	102
Baseline LDL-C Mean (SD)	164.4 (22.91)	163.6 (22.29)	162.8 (20.50)	163.7 (19.32)	163.5 (21.86)	166.6 (21.89)
Endpoint LDL-C Mean (SD)	112.2 (22.35)	126.7 (28.59)	99.2 (24.03)	116.2 (20.85)	90.7 (23.58)	109.5 (25.34)
Percent Change from Baseline to endpoint Mean (SD)	-31.43 (11.833)	-22.41 (14.051)	-38.99 (13.069)	-28.83 (11.054)	-44.31 (13.695)	-33.98 (14.299)
Adjusted Mean Difference	8.79		10.23		10.46	
Difference (95% CI)	(5.76; 11.81)		(7.17; 13.29)		(7.43; 13.49)	
P-value	<0.001		<0.001		<0.001	
<b>COM Population</b>						
N	188	89	208	88	194	95
Baseline LDL-C Mean (SD)	164.6 (21.97)	163.3 (22.28)	162.6 (20.24)	164.6 (19.43)	163.4 (21.80)	167.4 (21.98)
Week 12 LDL-C Mean (SD)	110.5 (21.20)	123.5 (22.99)	97.4 (22.56)	114.5 (19.17)	87.8 (20.66)	106.7 (23.22)
Percent Change from Baseline to endpoint Mean (SD)	-32.57 (10.972)	-23.99 (12.186)	-40.02 (12.196)	-30.28 (9.460)	-46.11 (11.409)	-36.10 (12.186)
Adjusted Mean Difference	8.12		9.82		10.05	
Difference (95% CI)	(5.28; 10.96)		(7.02; 12.62)		(7.28; 12.81)	
P-value	<0.001		<0.001		<0.001	
<b>PP Population</b>						
N	171	82	179	76	170	82
Baseline LDL-C Mean (SD)	165.5 (22.09)	163.2 (22.05)	162.3 (19.71)	164.6 (19.99)	162.3 (21.06)	167.9 (22.53)
Week 12 LDL-C Mean (SD)	110.4 (20.87)	122.7 (22.60)	96.1 (22.22)	114.5 (19.44)	85.3 (17.83) <sup>1</sup>	105.1 (22.16)
Percent Change from Baseline to endpoint Mean (SD)	-33.04 (10.529)	-24.47 (11.846)	-40.84 (11.112)	-30.30 (9.338)	-47.35 (9.528) <sup>1</sup>	-37.31 (10.438)
Adjusted Mean Difference	8.13		10.73		9.99	
Difference (95% CI)	(5.42; 10.83)		(7.97; 13.48)		(7.27; 12.70)	
P-value	<0.001		<0.001		<0.001	

**Appendix Table 4-1: Mean Percent Change in LDL-C (mg/dL) from Baseline to Endpoint by Age, Sex, and race (Full Analysis Set, ref. sponsor's Tables NK-104-301: 11; NK-104-302: 11, 8.1.6; NK-104-304: 13, 14, 8.1.6; NK-104-305: 13, 14, 15)**

Treatment	age <65 Years		age ≥65 Years		male		female		Caucasian		Other <sup>a</sup>	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>NK-104-301</b>												
Pitavastatin												
2 mg	219	-36.55 (14.11)	96	-41.00 (13.19)	14	-37.08 (13.06)	173	-38.58 (14.67)	237	-39.11 (12.98)	78	-34.24 (16.15)
4 mg	205	-42.90 (15.62)	93	-48.40 (12.74)	13	-41.13 (14.64)	162	-47.54 (14.68)	230	-45.28 (14.99)	68	-42.35 (14.85)
Atorvastatin												
10 mg	75	-37.04 (16.85)	27	-39.96 (11.45)	52	-38.64 (15.90)	50	-36.96 (15.41)	79	-38.85 (13.56)	23	-34.24 (21.19)
20 mg	72	-42.87 (16.33)	30	-45.09 (15.88)	48	-42.81 (18.74)	54	-44.17 (13.60)	78	-44.87 (13.70)	24	-39.17 (22.17)
<b>p-value*</b>			0.867				0.106				0.883	
<b>NK-104-302</b>												
Pitavastatin												
2 mg	210	-38.89 (13.35)	97	-39.21 (17.00)	11	-35.49 (14.24)	194	-41.04 (14.41)	306	-38.97 (14.59)	1	-47.77 (-)
4 mg	230	-42.45 (15.20)	88	-47.94 (11.63)	12	-40.99 (14.12)	194	-45.87 (14.44)	316	-43.88 (14.50)	2	-57.35 (4.10)
Simvastatin												
20 mg	72	-33.45 (13.95)	35	-38.10 (18.17)	44	-33.40 (12.62)	63	-36.07 (17.29)	106	-34.91 (15.59)	1	-41.29 (-)
40 mg	76	-40.48 (17.06)	34	-48.12 (10.89)	48	-41.60 (13.82)	62	-43.81 (17.17)	110	-42.84 (15.77)	0	NA
<b>p-value*</b>			0.101				0.679				0.952	
<b>NK-104-304</b>												
Pitavastatin 4 mg	184	-44.24 (11.53)	49	-42.90 (16.74)	15	-43.71 (12.06)	75	-44.48 (14.23)	233	-43.96 (12.77)	0	NA
Simvastatin 40 mg	87	-42.30 (15.49)	31	-47.91 (9.92)	81	-42.79 (14.86)	37	-45.91 (13.32)	117	-43.61 (14.38)	1	-62.23 (-)
<b>p-value*</b>			0.024				0.511				NA	
<b>NK-104-305</b>												
Pitavastatin 4 mg	190	-40.28 (19.41)	84	-41.90 (20.09)	15	-38.39 (20.21)	119	-43.89 (18.39)	242	-40.74 (19.49)	32	-41.04 (20.71)
Atorvastatin 20 mg	91	-41.71 (16.75)	44	-46.43 (15.25)	78	-44.85 (12.99)	57	-41.05 (20.03)	116	-42.90 (16.76)	19	-45.39 (14.00)
<b>p-value*</b>			0.477				0.017				0.894	

**Appendix Table 4-2 A: Mean Percent Change in LDL-C (mg/dL) from Baseline to Endpoint by Age (Full Analysis Set, ref. sponsor's NK-104-306 Tables: 12, 8.1.4).**

Treatment	age 65 -69 Years		age 70 - 74 Years		age ≥ 75 Years	
	N	Baseline (mg/dL)	N	Baseline (mg/dL)	N	Baseline (mg/dL)
		Mean (SD)		Mean (SD)		Mean (SD)
<b>NK-104-306</b>						
Pitavastatin 1 mg	118	165.85 -31.20 (11.808)	56	162.81 -31.69(11.817)	33	161.67 -31.80(12.293)
Pitavastatin 2 mg	108	162.57 -37.55(14.155)	73	163.41 -39.16(11.244)	43	162.51 -42.31(12.766)
Pitavastatin 4 mg	108	165.70 -45.77(12.193)	67	159.05 -42.58(14.803)	35	165.09 -43.10(15.666)
Pravastatin 10 mg	51	163.35 -21.79(13.027)	33	168.22 -23.05(16.099)	19	156.05 -22.98(13.581)
Pravastatin 20 mg	52	163.74 -29.09(11.063)	27	161.23 -27.47(12.302)	17	167.53 -30.17(9.174)
Pravastatin 40 mg	56	169.46 -36.03(12.335)	28	165.30 -26.58(17.063)	18	159.63 -39.15(11.298)
<b>p-value*</b>	0.059					

\* Interaction between treatment and age group

**Appendix Table 4-2 B: Mean Percent Change in LDL-C (mg/dL) from Baseline to Endpoint by Sex, and race (Full Analysis Set, ref. NK-104-306 Table 13, 8.1.5, 8.1.6).**

Treatment	male		female		Caucasian		Other <sup>a</sup>	
	N	Baseline(mg/dL)	N	Baseline(mg/dL)	N	Baseline(mg/dL)	N	Baseline(mg/dL)
		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)
<b>NK-104-306</b>								
Pitavastatin 1 mg	89	158.81 -31.09(12.20)	118	168.54 -31.68(11.595)	207	164.36 -31.43(11.83)	0	NA NA
Pitavastatin 2 mg	100	160.39 -37.92(12.899)	124	164.81 -39.85(13.193)	222	162.80 -38.96(13.12)	2	166.83 -41.57(5.26)
Pitavastatin 4 mg	89	163.62 -42.51(15.762)	121	163.37 -45.62(11.846)	207	163.76 -44.12(13.70)	3	143.67 -56.88 (5.49)
Pravastatin 10 mg	49	156.76 -20.54(13.130)	54	169.75 -24.11(14.754)	103	163.57 -22.41(14.05)	0	NA NA
Pravastatin 20 mg	48	161.57 -28.98(11.964)	48	165.8 -28.68(10.187)	94	164.04 -29.17(10.79)	2	148.00 -12.83(15.68)
Pravastatin 40 mg	42	167.73 -33.17(14.207)	60	165.78 -34.55(14.454)	102	166.58 -33.98(14.30)	0	NA NA
<b>p-value</b>	0.771*				NA <sup>^</sup>			

\* Interaction between treatment and sex group

<sup>^</sup> Interaction between treatment and race group

**Appendix Table 5-1.** Table 8 Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) of study NK-104-301 (FAS, COM, and PP Populations)

	<b>Pitavastatin 2 mg QD</b>	<b>Atorvastatin 10 mg QD</b>	<b>Pitavastatin 4 mg QD</b>	<b>Atorvastatin 20 mg QD</b>
<b>FAS (815)</b>				
N	315	102	298	102
Percent Change from Baseline to endpoint	-37.80	-37.95	-44.53	-43.57
LSMean (95% CI)	(-39.63, -35.97)	(-40.94, -34.96)	(-46.42, -42.64)	(-46.54, -40.59)
LS Mean Difference (95% CI)	0.15	(-3.12, 3.42)	-1.51	(-4.25, 2.32)
P-value		0.929		0.565
<b>COM Population (787)</b>				
N	301	98	288	100
Percent Change from Baseline to endpoint	-37.65	-38.76	-45.91	-46.041
LSMean (95% CI)	(-39.74, -35.55)	(-42.54, -34.98)	(-48.14, -43.67)	(-49.79, -42.29)
LS Mean Difference (95% CI)	1.11	(-4.56, 6.78)	0.14	(-5.58, 5.86)
P-value		0.6139		0.9505
<b>PP Population (650)</b>				
N	236	82	250	82
Percent Change from Baseline to endpoint	-38.34	-39.21	-45.85	-46.67
LSMean (95% CI)	(-40.77, -35.91)	(-43.14, -35.27)	(-48.17, -43.54)	(-50.63, -42.72)
LS Mean Difference (95% CI)	0.87	(-5.19, 6.93)	0.83	(-5.18, 6.83)
P-value		0.7128		0.7230

**Appendix Table 5-2.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) of study NK-104-302 (FAS, COM, and PP Populations)

	<b>Pitavastatin 2 mg QD</b>	<b>Simvastatin 20 mg QD</b>	<b>Pitavastatin 4 mg QD</b>	<b>Simvastatin 40 mg QD</b>
<b>FAS</b>				
N	302	105	313	108
Percent Change from Baseline to endpoint	-38.78	-34.56	-43.61	-42.40
LSMean (95% CI)	(-40.86, -36.69)	(-37.68, -31.44)	(-45.68, -41.55)	(-45.45, -39.36)
LS Mean Difference (95% CI)	-4.22	(-7.51, -0.92)	-1.21	(-4.46, 2.04)
P-value	0.1091		0.7761	
<b>COM Population</b>				
N	291	97	298	105
Percent Change from Baseline to endpoint	-39.65	-35.81	-45.05	-43.37
LSMean (95% CI)	(-41.74, -37.56)	(-38.96, -32.67)	(-47.12, -42.99)	(-46.37, -40.38)
LS Mean Difference (95% CI)	-3.84	(-7.13, -0.54)	-1.68	(-4.87, 1.51)
P-value	0.0227		0.3017	
<b>PP Population</b>				
N	262	85	276	93
Percent Change from Baseline to endpoint	-41.03	-36.95	-45.99	-45.11
LSMean (95% CI)	(-43.25, -38.80)	(-40.25, -33.65)	(-48.14, -43.85)	(-48.24, -41.97)
LS Mean Difference (95% CI)	-4.08	(-7.53, -0.63)	-0.89	(-4.20, 2.42)
P-value	0.0205		0.5986	

**Appendix Table 5-3.** Table 8 Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) of study NK-104-304 (FAS, COM, and PP Populations).

	Pitavastatin 4 mg QD	Simvastatin 40 mg QD
<b>FAS</b>		
N	233	117
Baseline LDL-C Mean (SD)	166.1 (20.31)	166.9 (23.47)
Endpoint LDL-C Mean (SD)	92.9 (23.51)	93.3 (24.67)
Percent Change from Baseline to Endpoint Mean (SD)	-43.33 (-45.06, -41.59)	-43.12 (-45.49, -40.74)
Adjusted Mean Difference	-0.21	
Difference (95% CI)	(-3.01, 2.58)	
P-value	0.8819	
<b>COM</b>		
N	223	107
Baseline LDL-C Mean (SD)	166.0 (20.37)	167.3 (22.75)
Week 12 LDL-C Mean (SD)	90.8 (19.87)	91.1 (23.69)
Percent Change from Baseline to Endpoint Mean (SD)	-44.42 (-45.91, -42.92)	-44.38 (-46.47, -42.30)
Adjusted Mean Difference	-0.03	
(95% CI)	(-2.47, 2.41)	
P-value	0.979	
<b>PP</b>		
N	182	84
Baseline LDL-C Mean (SD)	167.0 (20.58)	166.0 (21.56)
Week 12 LDL-C Mean (SD)	90.8 (19.77)	87.5 (22.06)
Percent Change from Baseline Mean (SD)	-44.97 (-46.53, -43.41)	-45.58 (-47.80, -43.36)
Adjusted Mean Difference	0.61	
(95% CI)	(-1.94, 3.17)	
P-value	0.637	

**Appendix Table 5-4.** Table 8 Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) of study NK-104-305 (FAS, COM, and PP Populations)

	<b>Pitavastatin 4 mg QD</b>	<b>Atorvastatin 20 mg QD</b>
<b>FAS</b>		
N	274	136
Baseline LDL-C Mean (SD)	<b>142.8 (27.41)</b>	<b>146.0 (26.98)</b>
Endpoint LDL-C Mean (SD)	<b>84.3 (31.01)</b>	<b>82.4 (27.45)</b>
Percent Change from Baseline to Endpoint Mean (SD)	-42.50 (-46.01, -38.99)	-44.91 (-49.03, -40.80)
Adjusted Mean Difference	<b>2.41</b>	
Difference (95% CI)	<b>(-1.45; 6.27)</b>	
P-value	<b>0.2202</b>	
<b>COM</b>		
N	248	124
Baseline LDL-C Mean (SD)	<b>142.4 (27.23)</b>	<b>144.3 (25.66)</b>
Week 12 LDL-C Mean (SD)	<b>83.0 (28.47)</b>	<b>79.5 (23.80)</b>
Percent Change from Baseline to Endpoint Mean (SD)	-43.81 (-47.13, -40.50)	-46.58 (-50.42, -42.73)
Adjusted Mean Difference	<b>2.76</b>	
(95% CI)	<b>(-0.90, 6.43)</b>	
P-value	<b>0.139</b>	
<b>PP</b>		
N	214	107
Baseline LDL-C Mean (SD)	<b>143.6 (27.71)</b>	<b>144.3 (25.70)</b>
Week 12 LDL-C Mean (SD)	<b>84.0 (29.63)</b>	<b>78.4 (21.32)</b>
Percent Change from Baseline Mean (SD)	-43.00 (-46.73, -39.27)	-46.73 (-51.13, -42.32)
Adjusted Mean Difference	<b>3.72</b>	
(95% CI)	<b>(-0.32, 7.77)</b>	
P-value	<b>0.071</b>	

**Appendix Table 5-5.** Change from Baseline to Endpoint or Week 12 in LDL-C (mg/dL) of study NK-104-306 (FAS, COM, and PP Populations)

	Pitavastatin 1 mg QD	Pravastatin 10 mg QD	Pitavastatin 2 mg QD	Pravastatin 20 mg QD	Pitavastati n 4 mg QD	Pravastatin 40 mg QD
<b>FAS Population</b>						
N	206	103	223	95	210	102
Baseline LDL-C Mean (SD)	164.4 (22.91)	163.6 (22.29)	162.8 (20.50)	163.7 (19.32)	163.5 (21.86)	166.6 (21.89)
Endpoint LDL-C Mean (SD)	112.2 (22.35)	126.7 (28.59)	99.2 (24.03)	116.2 (20.85)	90.7 (23.58)	109.5 (25.34)
Percent Change from Baseline to endpoint Mean (SD)	-30.19 (-32.02, -28.36)	-21.41 (-23.92, -18.90)	-37.87 (-39.64, -36.10)	-27.64 (-30.26, -25.02)	-43.33 (-45.14, -41.51)	-32.71 (-35.23, -30.18)
Adjusted Mean Difference	-8.78		-10.23		-10.62	
Difference (95% CI)		(-11.80, -5.77)		(-13.28, -7.18)		(-13.49, -7.59)
P-value	<0.001		<0.001		<0.001	
<b>COM Population</b>						
N	187	89	207	87	194	95
Baseline LDL-C Mean (SD)	164.6 (21.97)	163.3 (22.28)	162.6 (20.24)	164.6 (19.43)	163.4 (21.80)	167.4 (21.98)
Week 12 LDL-C Mean (SD)	110.5 (21.20)	123.5 (22.99)	97.4 (22.56)	114.5 (19.17)	87.8 (20.66)	106.7 (23.22)
Percent Change from Baseline to endpoint Mean (SD)	-32.57 (10.972)	-23.99 (12.186)	-40.02 (12.196)	-30.28 (9.460)	-46.11 (11.409)	-36.10 (12.186)
Adjusted Mean Difference	-8.12		-9.82		-10.05	
Difference (95% CI)		(-10.96, -5.28)		(-12.62, -7.02)		(-12.81, -7.28)
P-value	<0.001		<0.001		<0.001	
<b>PP Population</b>						
N	171	82	179	76	170	82
Baseline LDL-C Mean (SD)	165.5 (22.09)	163.2 (22.05)	162.3 (19.71)	164.6 (19.99)	162.3 (21.06)	167.9 (22.53)
Week 12 LDL-C Mean (SD)	110.4 (20.87)	122.7 (22.60)	96.1 (22.22)	114.5 (19.44)	85.3 (17.83) <sup>1</sup>	105.1 (22.16)
Percent Change from Baseline to endpoint Mean (SD)	-33.04 (10.529)	-24.47 (11.846)	-40.84 (11.112)	-30.30 (9.338)	-47.35 (9.528) <sup>1</sup>	-37.31 (10.438)
Adjusted Mean Difference	-8.13		-10.73		-9.99	
Difference (95% CI)		(-10.83, -5.42)		(-13.48, -7.97)		(-12.70, -7.27)
P-value	<0.001		<0.001		<0.001	

**Appendix Table 6. Mean Percent Change in some important secondary endpoints from Baseline to Endpoint by Study and Dose – Core Studies (Difference=C-T, FAS Population, LOCF)**

Treatment	Mean difference (95% CI) p-value					
	HDL-C <sup>1</sup>	TC <sup>2</sup>	TG <sup>2</sup>	Non- HDL-C <sup>2</sup>	Apo-A1 <sup>1</sup>	Apo-B <sup>2</sup>
<b>NK-104-301</b>						
Pitav 2 mg	-0.41	-0.542	-3.60	-0.63	0.29	0.22
Ator 10mg	(-3.92, 3.09)	(-3.04, 1.97)	(-9.51, 2.30)	(-3.71, 2.45)	(-3.55, 4.13)	(-3.92, 4.36)
Pitav 4 mg	0.817	0.675	0.231	0.686	0.84	0.89
Ator 20mg	(-6.51, 0.54)	(-2.88, 2.14)	(-8.77, 3.12)	(-2.62, 3.56)	(-5.75, 1.99)	(-4.46, 3.89)
Pitav 2 mg	2.98	-0.37	-2.82	0.47	-1.88	-0.29
Ator 20mg	(-6.51, 0.54)	(-2.88, 2.14)	(-8.77, 3.12)	(-2.62, 3.56)	(-5.75, 1.99)	(-4.46, 3.89)
Pitav 4 mg	0.097	0.774	0.351	0.766	0.21	0.86
Ator 20mg	(-6.51, 0.54)	(-2.88, 2.14)	(-8.77, 3.12)	(-2.62, 3.56)	(-5.75, 1.99)	(-4.46, 3.89)
<b>NK-104-302</b>						
Pitav 2 mg	-0.51	2.62	0.51	3.71	1.00	3.23
Simv 20mg	(-3.84, 2.81)	(0.10, 5.15)	(-5.30, 6.32)	(0.61, 6.81)	(-2.79, 4.78)	(-0.82, 7.28)
Pitav 4 mg	0.761	0.042	0.863	0.019	0.50	0.04
Simv 40mg	(-2.91, 3.64)	(-1.47, 3.50)	(-4.95, 6.51)	(-1.86, 4.25)	(-3.36, 4.04)	(-3.25, 4.69)
Pitav 2 mg	0.37	1.01	0.78	1.19	0.34	0.72
Simv 40mg	(-2.91, 3.64)	(-1.47, 3.50)	(-4.95, 6.51)	(-1.86, 4.25)	(-3.36, 4.04)	(-3.25, 4.69)
Pitav 4 mg	0.826	0.423	0.789	0.443	0.81	0.64
Simv 40mg	(-2.91, 3.64)	(-1.47, 3.50)	(-4.95, 6.51)	(-1.86, 4.25)	(-3.36, 4.04)	(-3.25, 4.69)
<b>NK-104-304</b>						
Pitav 4 mg	-2.32	0.20	4.94	1.24	-1.23	0.26
Simv 40mg	(-4.84, 0.40)	(-1.88, 2.27)	(0.16, 10.04)	(-1.29, 3.77)	(-3.82, 1.36)	(-2.34, 2.87)
Pitav 4 mg	0.096	0.852	0.057	0.337	0.35	0.84
Simv 40mg	(-4.84, 0.40)	(-1.88, 2.27)	(0.16, 10.04)	(-1.29, 3.77)	(-3.82, 1.36)	(-2.34, 2.87)
<b>NK-104-305</b>						
Pitav 4 mg	-0.10	-3.14	-6.75	-3.57	-2.35	-1.16
Ator 20mg	(-3.25, 3.05)	(-5.79, -0.49)	(-12.79, -0.71)	(-7.02, -0.12)	(-5.06, 0.35)	(-4.94, 2.62)
Pitav 4 mg	0.950	0.020	0.029	0.042	0.09	0.55
Ator 20mg	(-3.25, 3.05)	(-5.79, -0.49)	(-12.79, -0.71)	(-7.02, -0.12)	(-5.06, 0.35)	(-4.94, 2.62)
<b>NK-104-306</b>						
Pitav 1 mg	1.08	6.52	8.72	9.01	0.32	8.00
Prav 10mg	(-3.72, 1.57)	(4.25, 8.79)	(3.70, 13.75)	(6.20, 11.81)	(-3.44, 4.09)	(4.08, 11.9)
Pitav 2 mg	0.424	<0.001	0.001	<0.001	0.81	<.0001
Prav 20mg	(-6.04, -0.70)	(3.93, 8.52)	(-0.27, 9.90)	(6.57, 12.25)	(-5.81, 1.96)	(4.95, 13.06)
Pitav 2 mg	-3.37	6.23	4.81	9.41	-1.93	9.00
Prav 20mg	(-6.04, -0.70)	(3.93, 8.52)	(-0.27, 9.90)	(6.57, 12.25)	(-5.81, 1.96)	(4.95, 13.06)
Pitav 4 mg	0.014	<0.001	0.063	<0.001	0.16	<.0001
Prav 40mg	(-5.67, -0.38)	(4.56, 9.11)	(1.17, 11.23)	(6.95, 12.58)	(-6.28, 1.31)	(5.31, 13.2)
Pitav 4 mg	-3.02	6.84	6.20	9.77	-2.49	9.26
Prav 40mg	(-5.67, -0.38)	(4.56, 9.11)	(1.17, 11.23)	(6.95, 12.58)	(-6.28, 1.31)	(5.31, 13.2)
Pitav 4 mg	0.025	<0.001	0.016	<0.001	0.06	<.0001
Prav 40mg	(-5.67, -0.38)	(4.56, 9.11)	(1.17, 11.23)	(6.95, 12.58)	(-6.28, 1.31)	(5.31, 13.2)

\* Pitav - Pitavastatin; Ator - Atorvastatin; Simv - Simvastatin; Prav - Pravastatin

<sup>1</sup> Positive differences favor active control

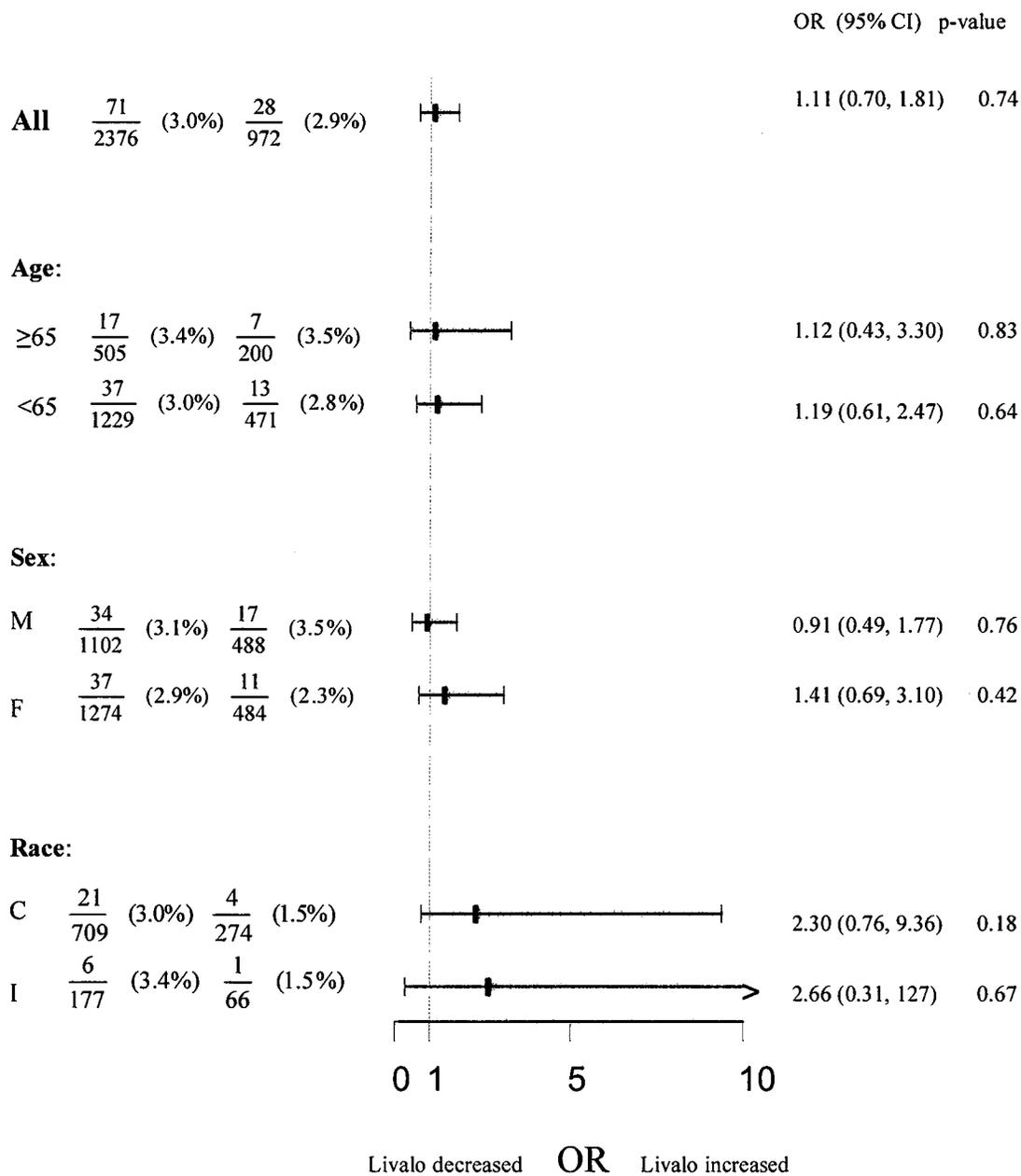
<sup>2</sup> Positive differences favor pitavastatin

**Appendix Table 7. ACUTE RENAL FAILURE in core and extension studies**

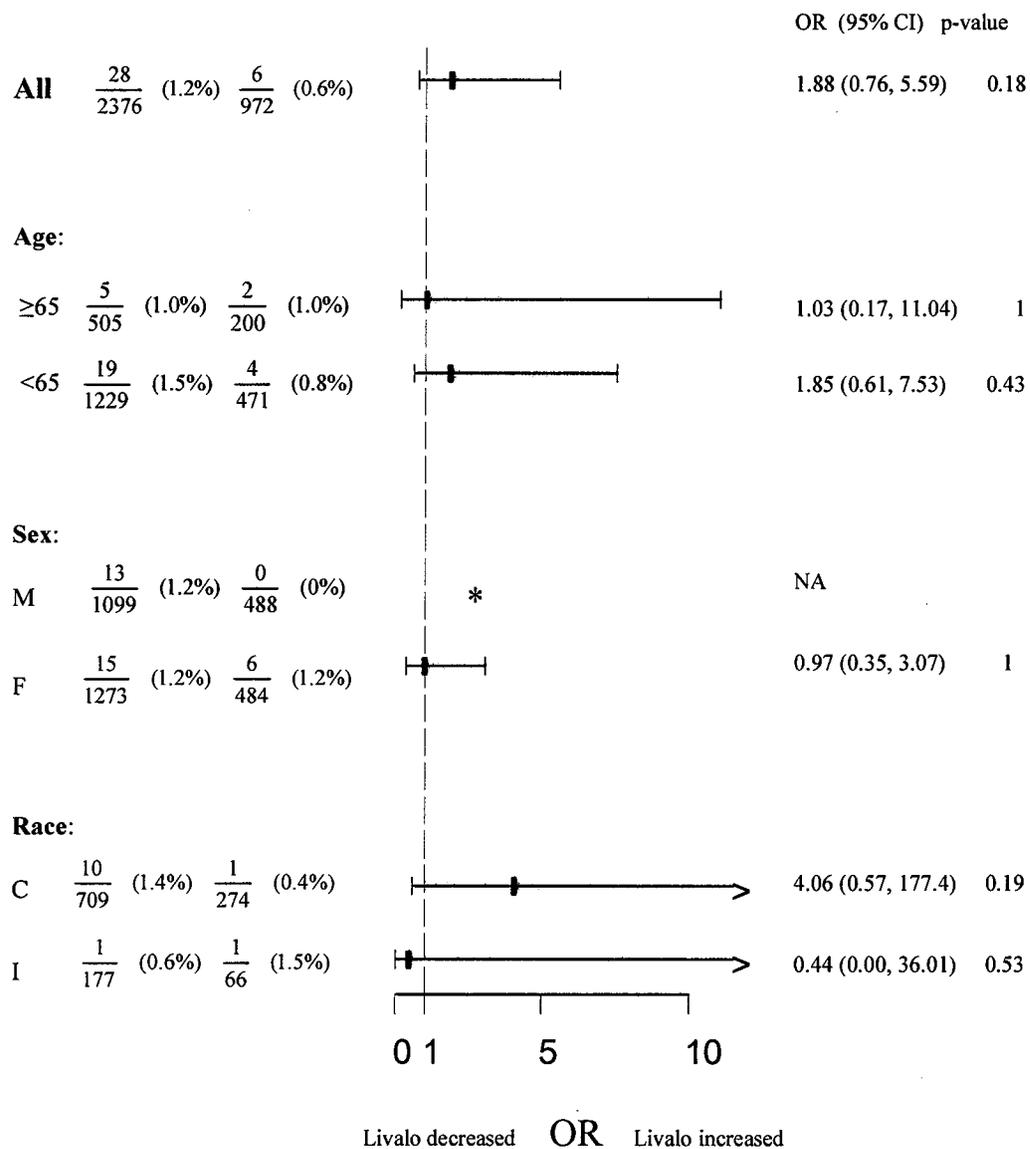
Treatment	n <sub>AE</sub> /n	AE %	Odds ratio	95% CI	p-value
<b>NK-104-301</b>					
Pitavastatin 2 mg	0/315	0%	NA		
Atorvastatin 10 mg	0/102	0%			
Pitavastatin 4 mg	0/298	0%	NA		
Atorvastatin 20 mg	0/102	0%			
<b>NK-104-302</b>					
Pitavastatin 2 mg	1/302	0.3%	0.347	[0.00439, 27.38]	0.4499
Simvastatin 20 mg	1/105	1.0%			
Pitavastatin 4 mg	0/312	0%	NA		
Simvastatin 40 mg	0/108	0%			
<b>NK-104-304-309</b>					
Pitavastatin 4 mg	0/233	0%	0	[0, 19.75]	0.3362
Simvastatin 40 mg	1/118	0.8%			
<b>NK-104-305-310</b>					
Pitavastatin 4 mg	1/274	0.4%	0.495	[0.006, 39.1]	0.5539
Atorvastatin 20 mg	1/136	0.7%			
<b>NK-104-306</b>					
Pitavastatin 1 mg	0/207	0%	NA		
Pravastatin 10 mg	0/103	0%			
Pitavastatin 2 mg	0/224	0%	NA		
Pravastatin 20 mg	0/96	0%			
Pitavastatin 4 mg	0/207	0%	NA		
Pravastatin 40 mg	0/102	0%			

**Appendix Figure 1.** Odds ratio (OR) of myalgia incidence between Livalo (I) and active controls (C) in the core and extension studies (safety population).

C: Caucasian; I: Indian

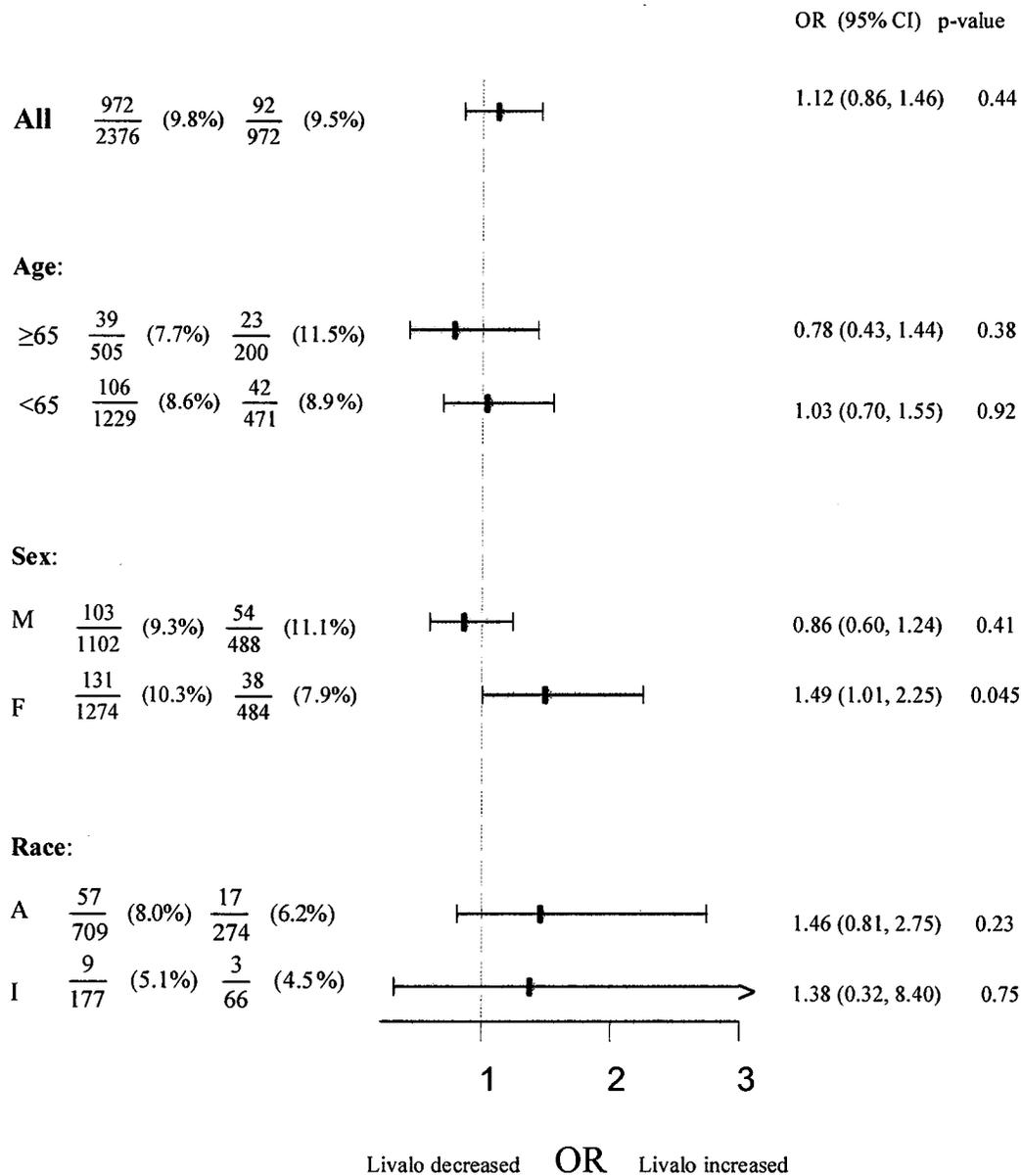


**Appendix Figure2.** Odds ratio (OR) of possible hepatic disorder between Livalo (T) and active controls (C) in the core and extension studies (safety population). C: Caucasian; I: Indian



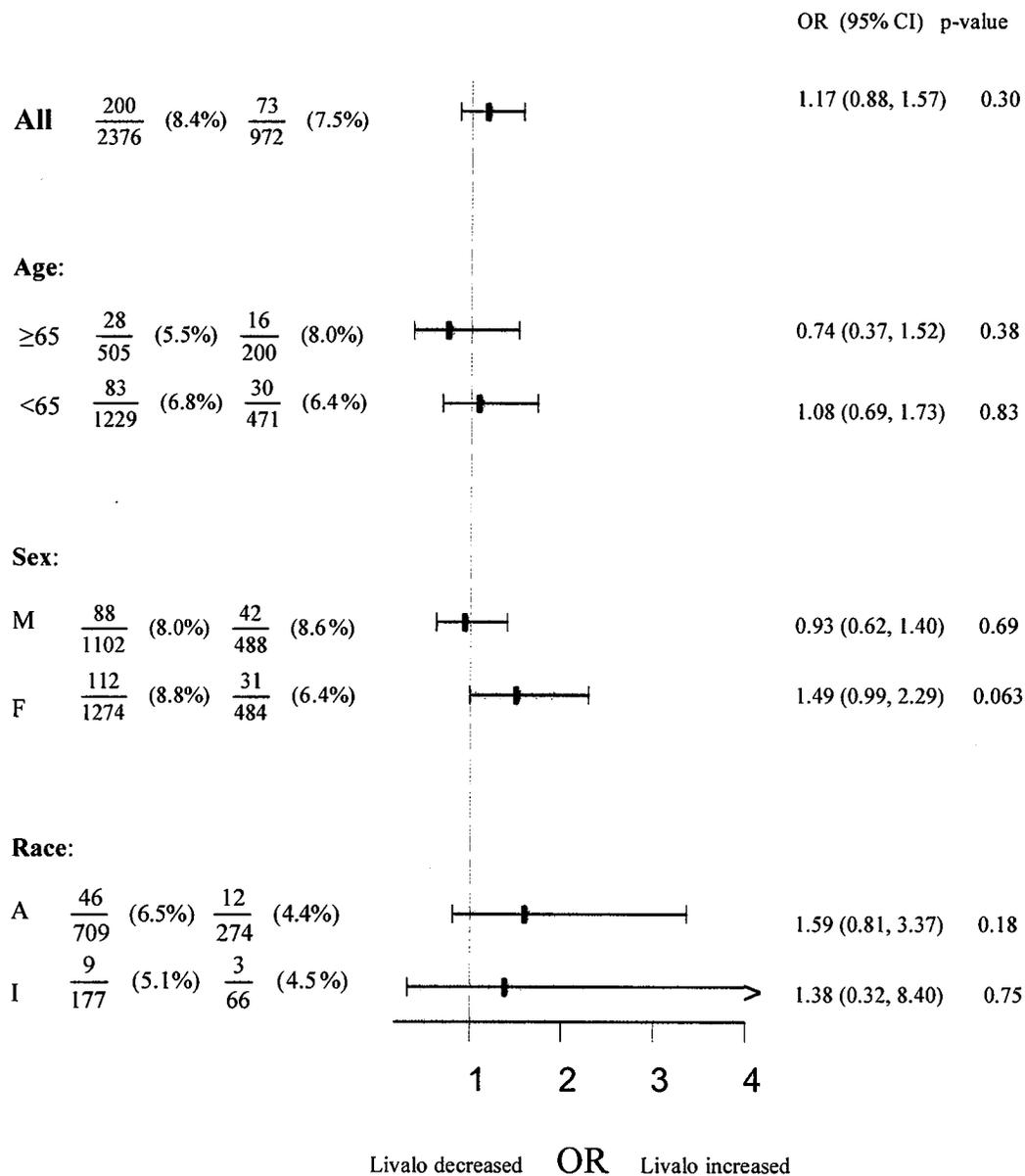
**Appendix Figure 3.** Odds ratio (OR) of AE between Livalo (T) and active controls (C) in the core and extension studies (safety population).

A: Caucasian; I: Indian

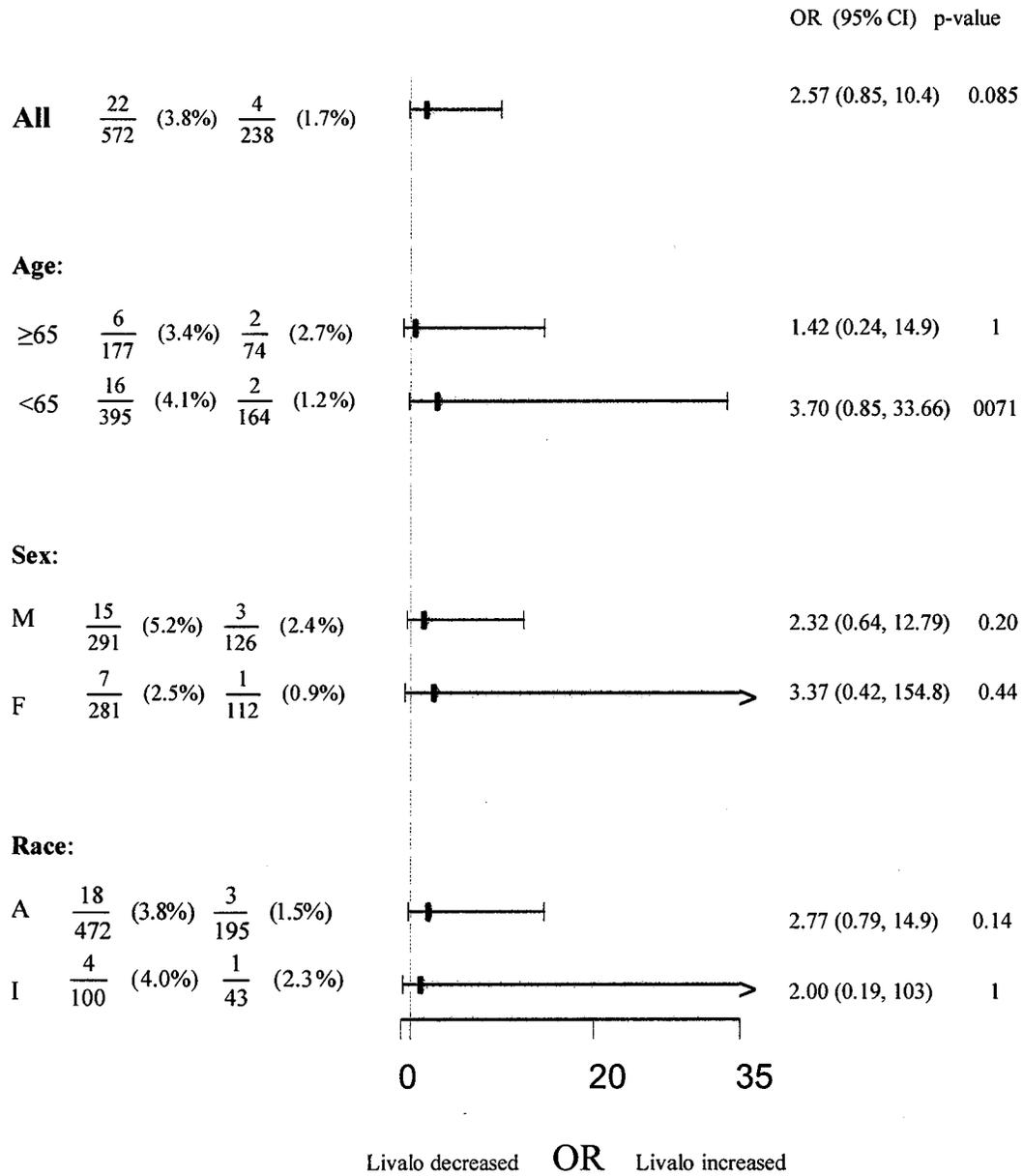


**Appendix Figure 4.** Odds ratio (OR) of AE between Livalo (T) and active controls (C) in the core studies (safety population).

A: Caucasian; I: Indian



**Appendix Figure 5.** Odds ratio (OR) of myalgia incidence between Livalo (T) and active controls (C) in the core and extension studies (Nk-104-301 and NK-104-305, Livalo 4 mg and Atorvastatin 20 mg, safety population). A: Caucasian; I: Indian



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