KOWA

RESEARCH INSTITUTE, INC.

January 26, 2009

Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266
ATTN: Central Document Room

RE: NDA 22-363
NK-104 (pitavastatin)
Amendment #0008 to New Drug Application

Dear Dr. Parks:

Kowa Company Limited (KCL) submitted its initial New Drug Application, NDA 22-363, for pitavastatin tablets (NK-104) dated October 1, 2008.

This amendment is to respond to a December 15, 2008 request received by Kowa via e-mail from the Division (Dr. Iffat Chowdhury) as identified below:

> Would it be possible for you to submit narratives of patients who had CPK values ≥ 10XULN with 1mg to 64 mg dose range of pitavastatin? It would be helpful if those narratives contained the baseline relevant laboratory values (including SCr) and the changes in those laboratories values with the elevations in CPK. If this information is already contained in the NDA submission, please indicate the location.

In response to Dr. Chowdhury's request we have presented a new discussion and table in the attached Module 5.3.5. Note the reference to two additional tables, "FDA Patient Data Listing 1.1" and "FDA Patient Data Listing 1.3" for BUN and serum creatinine, presented specifically for this inquiry.

430 Davis Drive, Suite 200, Morrisville, North Carolina 27560 Telephone: 919.433.1600 Fax: 919.433.1620

This amendment to NDA 22-363 consists of 1 CD, totaling less than 0.5 gigabytes. The submission is virus free. The following was used to check the files for viruses:

Trend Micro Office Scan
Version 7.3
Virus Definitions: 5.789.00, created January 23, 2009

Sincerely yours,

Ross S. Laderman, MPH
Senior Director, Regulatory Affairs
Kowa Research Institute, Inc.
(U.S. Agent for Kowa Company Limited)

5.3.5 Reports of Efficacy and Safety Studies

This section in this amendment is presented **specifically to respond to Dr. Chowdhury's** December 15, 2008 e-mail inquiry.

To identify patients with > 10x CPK in any dose of pitavastatin, the database of the integrated summary of safety (ISS database) for Group 1 and Group 3, narratives of SAEs and discontinuation due to AE and other additional narratives were searched.

The ISS database Group 1 includes Phase 2 and Phase 3 studies but no extension studies. The ISS database Group 3 includes Phase 2, Phase 3 and the extension studies but no higher doses than pitavastatin 4 mg. Therefore, we searched Group 1 for the higher doses and Group 3 for extension studies and identified patients with >10x CPK together with their BUN and serum creatinine values. As expected, some patients appeared in both searches.

The ISS database does not include unscheduled lab values of Phase 2 studies and also a local lab, which were only recorded in narratives. We searched narratives of SAE, discontinuation due to AE, and important abnormal creatine kinase values for patients with > 10x CPK. Narratives for important abnormal creatine kinase values are available for one Phase 2 study and all Phase 3 and extension studies. Table 2.7.4.122 in Module 2.7.4 in the CTD provides links to narratives of SAE and discontinuation due to AE. Narratives for important abnormal creatine kinase values are in the CSR of Study HEC/NK98402N/NK-104.2.02 (Page 82 Section 8.4.2.1), Study HEC/NK98403N/NK-104.2.03 (Page 83, Section 8.4.2.1), Study 210/211 (page 21 as pdf file in Section 5.3.2 in the CSR), Study 301 (Page 116, Section 12.4.1.3.2 in the CSR), Study 302 (Page 118, Section 12.4.1.3.2 in the CSR), Study 304 (Page 126, Section 12.4.1.3.2 in the CSR), Study 305 (Page 151, Section 12.4.1.3.2 in the CSR), Study 306 (Page 140, Section 12.4.1.3.2 in the CSR), Study 307 (Page 132, Section 12.4.1.3.2 in the CSR), Study 308 (Page 139, Section 12.4.1.3.2 in the CSR), Study 309 (Page 116, Section 12.4.1.3.2 in the CSR) and Study 310 interim (Page 132, Section 12.4.1.3.2 in the CSR). Of note, during **the review of "other narratives", one error** was identified in page 114 of the CSR of Study 301. It says that myoglobin was measured for 5 patients who had CK ≥ 10 x ULRR but it **incorrect. It should say "5 patients who had** at least one myoglobin value recorded on Listing 17.3.c". **Among them, only one** patient (Patient 301-208-014) had ≥ 10 x ULRR who was identified in the ISS database Group 1 search.

- ***Results of Search in ISS Database***

  (Please see table "FDA Patient Data Listing 1.1" and table "FDA Patient Data Listing 1.3" for BUN and serum creatinine)

In the pitavastatin 2 mg group, only Patient 301-208-014 in Study 301 (recorded as 1208014 in CSR) had >10x CPK at Week 2. Due to this abnormal value, the patient discontinued the trial. The patient was recorded as discontinuation due to abnormal lab value, which should have been recorded as discontinuation due to an AE; therefore this patient is not in the list of discontinuation due to AE. Nevertheless, the narrative is available.

In the pitavastatin 4 mg group, 1 patient had >10x CPK which was considered not drug-related. Patient 305-111-022 in Study 305 (recorded as 5111022 in CSR) had >10x CK at Week 4 but the patient completed the trial. The investigator considered that this elevated CK had been due to the patient's restricted diet and improbably related to the study drug.

In the pitavastatin 8 mg group, 2 patients had >10x CPK. These were Patients 0002/00013 and 0070/00013 in Study NKS104/A2204 and reported as SAE leading to discontinuation of study treatment. While these two SAEs were reported as rhabdomyolysis by the investigators, only patient 002/00013 met the criteria of the rhabdomyolysis definition used in the study and both of them did not meet the definition of rhabdomyolysis by ACC/AHA & NLA. Their BUN and serum creatinine were within normal range. Details are discussed in Module 2.7.4.2.1.5.1.2.6 in the CTD.

All other patients who had >10x CPK were taking pitavastatin 16 mg or higher.

Only one additional patient was picked up in the Group 3 search. Patient 301-207-025 (recorded as 1207025 in the CSR) had >10x CPK on Day 57 in the extension study 307 when he was taking pitavastatin 4 mg and discontinued the study-treatment.

Patient 1103043 was identified in the list for >10xCPK but it occurred when the patient was taking atorvastatin 20 mg.

All other patients were overlapped in the results of the ISS database Group 1 search.

Location of narratives

Search Group	Study Number	Patient Number	Dose (mg)	SAE?	Discontinued study treatment?	Location of narrative in CSR
Group 1	301	310-208-014	2	No	**Yes** (Due to abnormal lab value)	Page 115 ,Section 12.4.1.3.1 Page 117, Section 12.4.1.3.2
Group 1	305	305-111-022	4	No	No	Page 150, Section 12.4.1.2 Page 152, Section 12.4.1.3.2
Group 3	307	301-207-205	4	No	**Yes**	Page 392 Section 14.3.3
Group 1	NKS104 /A2204	0002/00013	8	**Yes**	**Yes**	Page 72 (page 73 as pdf. file),Section 2.5
Group 1	NKS104 /A2204	0070/00013	8	**Yes**	**Yes**	page 73 (page 74 as pdf. file), Section 2.5
Group 1	209	002-025	16	No	**Yes**	Page 75 (page 78 as pdf file)
Group 1	209	012-008	16	No	**Yes**	Page 80 (page 83 as pdf file)
Group 1	209	013-007	16	No	**Yes**	Page 81 (page 84 as pdf file)
Group 1	209	024-005	16	No	**Yes**	Page 84 (page 87 as pdf file)
Group 1	209	026-019	16	No	**Yes**	Page 86 (page 89 as pdf file)
Group 1	209	035-001	16	No	**Yes**	Page 90 (page 93 as pdf file)
Group 1	209	048-020	16	No	No	Not available
Group 1	209	002-009	32	No	No	Not available
Group 1	209	023-004	32	**Yes**	**Yes**	Page 97 (page 100 as pdf file)
Group 1	209	023-010	32	No	No	Not available
Group 1	209	026-002	32	**Yes**	**Yes**	Page 99 (page 102 as pdf file)
Group 1	209	027-002	32	No	**Yes**	Page 109
Group 1	209	033-001	32	No	No	Not available

Location of narratives

Search Group	Study Number	Patient Number	Dose (mg)	SAE?	Discontinued study treatment?	Location of narrative in CSR
Group 1	209	037-001	32	**Yes**	No	Page 101 (page 104 as pdf file)
Group 1	209	049-007	32	No	No	Not available
Group 1	209	002-011	64	No	No	Not available
Group 1	209	026-021	64	No	**Yes**	Page 115
Group 1	209	045-008	64	**Yes**	**Yes**	Page 105 (page 108 as pdf file)

13 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 2