KOWA

RESEARCH INSTITUTE, INC.

July 27, 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
Pitavastatin (NK-104)
Amendment #0038 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.

A July 13, 2009 e-mail from Dr. Eric Colman requested the following:

> We have a request related to diabetes. For Group 1, please provide the CRFs for the subjects from all treatment groups who are coded as having any of the following AEs [Table 1.6 (ISS)]: diabetes mellitus, diabetes mellitus inadequate control, diabetes mellitus non-insulin dependent, glucose tolerance impaired, or hyperglycemia.
>
> Let me know if you have any questions.

A response to this question was provided to Dr. Colman in several e-mails on July 14, July 15 and July 23, 2009. The formal NDA response to this request is now presented in the Appendix to this cover letter.

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

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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 OfficeScan
Version 8.0
Virus Definitions: 6.307.00, created July 23, 2009

Sincerely yours,

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

Appendix

FDA Request:

We have a request related to diabetes. For Group 1, please provide the CRFs for the subjects from all treatment groups who are coded as having any of the following AEs [Table 1.6 (ISS)]: diabetes mellitus, diabetes mellitus inadequate control, diabetes mellitus non-insulin dependent, glucose tolerance impaired, or hyperglycemia.

Kowa Response:

We have identified 15 patients (listed in the table below) in response to your inquiry. Thirteen (13) are from Phase 3 studies, 1 is from a Negma Phase 2 study and one is from a (b) (4) Phase 2 study. The CRFs from the Negma and (b) (4) studies are not readily available and, as agreed with Dr. Colman, using the ISS database we are submitting program listings of Demography, Patient Disposition, AEs, and Labs (chemistry and hematolog). ECG listings for these two patients were not produced as they were normal for both patients.

The CRFs from the 13 Phase 3 patients and the listings for the 2 Negma (b) (4) patients described above are included in this amendment. As agreed with Dr. Colman, we have not provided comprehensive links between the DCFs and CRFs.

Study/Patient	Drug/Dose	Adverse Event
KOW301_113_121	Pitavastatin 2 mg	Diabetes Mellitus
KOW306_102_015	Pitavastatin 2 mg	Diabetes Mellitus Non-Insulin-Dependent
KOW306_105_002	Pitavastatin 2 mg	Diabetes Mellitus Non-Insulin-Dependent
KOW301_208_045	Pitavastatin 4 mg	Glucose Tolerance Impaired
KOW302_116_053	Pitavastatin 4 mg	Diabetes Mellitus
KOW305_102_079	Pitavastatin 4 mg	Diabetes Mellitus
KOW305_102_084	Pitavastatin 4 mg	Diabetes Mellitus
KOW305_104_012	Pitavastatin 4 mg	Diabetes Mellitus Inadequate Control

Study/Patient	Drug/Dose	Adverse Event
KOW305_113_002	Pitavastatin 4 mg	Diabetes Mellitus
KOW305_210_054	Pitavastatin 4 mg	Diabetes Mellitus Non-Insulin-Dependent
KOW306_205_028	Pitavastatin 4 mg	Diabetes Mellitus Non-Insulin-Dependent
NEG203_086_011	Pitavastatin 4 mg	Hyperglycaemia
NOV204_001_004	Pitavastatin 4 mg	Hyperglycaemia
KOW301_309_046	Atorvastatin 10 mg	Diabetes Mellitus Non-Insulin-Dependent
KOW306_503_007	Pravastatin 10 mg	Hyperglycaemia

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July 13, 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

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JUL 13 2009
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N000-8M
ORIG AMENDMENT

RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0037 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.

A June 17, 2009 e-mail from Kati Johnson transmitted the following request from Johnny Lau:

> Per our brief discussion, I need to locate ezetimibe and ezetimibe glucuronide's bioanalytical validation reports for Study JPC-04-335-18. This study's report hyperlinked the following 2 validation reports but I cannot locate them in EDR so as to complete my review:
>
> - [redacted] (b) (4): NB02125: Validation of the method for the measurement of the unconjugated form of SCH 58235 in human plasma. In-house document of (b) (4) [redacted]
>
> [redacted] (b) (4): NB02126: Validation of the method for the measurement of the unconjugated form and total conjugated form of SCH 58235 in human plasma. In-house document of (b) (4) [redacted]
>
> Would you kindly inform the sponsor to retrieve these 2 validation reports in English for us at their earliest convenience please?

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

The requested translated bioanalytical reports were provided to Ms. Johnson in an e-mail on July 8, 2009. The formal NDA response to this request is now presented in this amendment. The two bioanalytical reports are included and have been linked to the titles cited in the request above. The reports have been placed in Module 5.3.3.4 in the folder for clinical study report JPC-04-335-18.

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 OfficeScan
Version 8.0
Virus Definitions: 6.259.00, created July 8, 2009

Sincerely yours,

Ross S. Laderman

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

7/9/09

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 8, 2009

TO: Kati Johnson, Regulatory Project Manager
Iffat Chowdhury, M.D., Medical Officer
Division of Metabolic and Endocrine Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-363

APPLICANT: Kowa Research Institute

DRUG: Livalo (Pitavastatin)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: For use in patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total cholesterol, LDL-C, Apo B, non-HDL-C, TG, and increase HDL-C

CONSULTATION REQUEST DATE: December 11, 2008

DIVISION ACTION GOAL DATE: August 3, 2009
PDUFA DATE: August 3, 2009

I. BACKGROUND:

Kowa Research Institute has submitted NDA 22-363, an application for pitavastatin, a new molecular entity (NME) for the indication of cholesterol reduction in patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total cholesterol, LDL-C, Apo B, non-HDL-C, triglycerides (TG), and increase HDL-C.

Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The primary efficacy endpoint is Percent change from baseline LDL-C to Visit 8 (Week 12). Baseline LDL-C is the mean of LDL-C measurements obtained at Visits 2 and 3 (Weeks -2 and -3).

Sites were chosen by high enrollment, geographic location, and inspectional history. Inspection of (b) (4) the contract research organization (CRO), was conducted because this application is for an NME. The inspection of the clinical laboratory, (b) (4) , was conducted because the clinical sites were blinded to the primary endpoint, LDL-C, after Visit 3.

The protocols inspected include:

A. Protocol NK-104-301 entitled "Study of Pitavastatin 2 mg vs. Atorvastatin 10 mg and Pitavastatin 4 mg vs. Atorvastatin 20 mg (following up-titration) in Patients with Primary Hypercholesterolemia or Combined Dyslipidemia"

B. Protocol NK-104-302 entitled "Study of Pitavastatin 2 mg vs. Simvastatin 20 mg and Pitavastatin 4 mg vs. Simvastatin 40 mg (Following Up-Titration) in Patients with Primary Hypercholesterolemia or Combined Dyslipidemia"

II. RESULTS (by Site):

Name of Clinical Investigator (CI), Clinical Laboratory (CL), or Contract Research Organization (CRO) and Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI #1 Dr. A. Blokhin Federal State Institution "Out-patient Clinic # 3 of Russian Federation President's Management Department" 31, Grokholsky Lane, Moscow, 129010, Russia	Protocol NK-104-301 100 screened/ 76 randomized	May 18 to 22, 2009	Pending (Preliminary classification NAI)
CI #2 Prof. Svetlana Tchurina State Medical Institution "St.Petersburg Pokrovskaya Hospital" Cardiology Department #2 85, Bolshoy Prospect Vasilievsky Island St.Petersburg, 199106, Russia	Protocol NK-104-301 85 screened/ 68 randomized	May 25 to 29, 2009	Pending (Preliminary classification NAI)
CI#3 Dr. Leiv Ose Director of Lipid Clinic Forkingsvein 2B NO-0027 Oslo, Norway	Protocol NK-104-302 111 screened/ 68 randomized	March 23 to 27, 2009	NAI
CI#4 Dr. Mark Blagden Avondale Surgery 3-5 Avondale Road, Chesterfield, S40 4TP, UK	Protocol NK-104-302 52 screened/ 33 randomized	March 30 to April 3, 2009	VAI

(b) (4)

[redacted]

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

1. Dr. A. Blokhin
   Federal State Institution
   "Out-patient Clinic # 3 of Russian Federation President's Management Department"
   31, Grokholsky Lane, Moscow, 129010, Russia

   Note: Observations noted for this site are based on communications with the FDA investigator and review of the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

   a. **What was inspected**: For Protocol NK-104-301 at this site, 100 subjects were screened, 76 subjects were randomized. The inspection compared 35 completed subjects' records.

   b. **General observations/commentary:** There was no under-reporting of adverse events. There were some test article supply problems during the study, with some visits having to be delayed because drug supplies were not available. The most lengthy of the delays was in late March / early April 2006, with some study subjects actually running out of study drug for a few days. The problem was apparently due to a late shipment to the depot, with an additional delay when the shipment was held up in Russian customs. There were protocol violations due to the drug supply problem, as visit schedules were disrupted. Because the clinical sites were blinded to the primary endpoint, LDL-C, after Visit 3, the primary endpoint data were verified by audit of the clinical laboratory in (b) (4). No regulatory violations were noted.

   c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Prof. Svetlana Tchurina
   State Medical Institution "St.Petersburg Pokrovskaya Hospital"
   Cardiology Department #2, 85, Bolshoy Prospect, Vasilievsky Island
   St. Petersburg, 199106, Russia

   Note: Observations noted for this site are based on communications with the FDA investigator and review of the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

   a. **What was inspected:** For Protocol NK-104-301 at this site, 85 subjects were screened, 68 subjects were randomized. The inspection compared 33 completed subjects' records.

   b. **General observations/commentary**: There was no under-reporting of adverse events. There were some test article supply problems during the study, with some visits having to be delayed because drug supplies were not available. The most lengthy of the delays

was in late March / early April 2006, with some study subjects actually running out of study drug for a few days. The problem was apparently due to a late shipment to the depot, with an additional delay when the shipment was held up in Russian customs. There were protocol violations due to the drug supply problem, as visit schedules were disrupted. Because the clinical sites were blinded to the primary endpoint, LDL-C, after Visit 3, the primary endpoint data were verified by audit of the clinical laboratory in (b) (4) No regulatory violations were noted.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Dr. Leiv Ose
Director of Lipid Clinic
Forkingsvein 2B
NO-0027
Oslo, Norway

a. **What was inspected**: For Protocol NK-104-302 at this site, 111 subjects were screened, 56 subjects were randomized, and 50 subjects completed the study. An audit of all 56 subjects' consent forms, LDL cholesterol value at baseline, and adverse drug experiences was conducted. A complete review of 30 subjects' records was conducted.

b. **General observations/commentary**: There were no deaths or SAEs reported. Two subjects experienced adverse events and discontinued from the study, one subject began a prohibited medication and was withdrawn, and 3 subjects withdrew consent. There was no evidence of under-reporting of adverse events. The site was blinded to LDL cholesterol after visit 3. The primary endpoint, percent change from baseline LDL-C to Visit 8 (Week 12), was verified by audit of the clinical laboratory in (b) (4) . At this site, there was no under-reporting of adverse events. No regulatory violations were noted.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Dr. Mark Blagden
Avondale Surgery
3-5 Avondale Road,
Chesterfield, S40 4TP, UK

a. **What was inspected:** For Protocol NK-104-302 at this site, 52 subjects were screened, 33 subjects were randomized, and 28 subjects completed the study. An audit of 17 subjects' records was conducted.

b. **General observations/commentary**: The primary endpoint, percent change from baseline LDL-C to Visit 8 (Week 12), was verified by audit of the clinical laboratory in (b) (4). The following regulatory violations were noted:
   i. A single adverse event of chronic obstructive pulmonary disease and use of concomitant medication of prednisolone and amoxicillin for subject 2501037 was found to not have been reported as an adverse event.
   ii. Subject 2501044 was enrolled with an elevated TSH in violation of the exclusion criterion.
   iii. The clinical investigator had not retained a complete set of case report forms for three subjects.
   iv. Drug disposition records were not adequate so that shipped, received, used and returned amounts of test article could not be reconciled.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. (b) (4)

a. **What was inspected:** For both Protocol NK-104-301 and Protocol NK-104-302 subjects' LDL-C for the above four clinical sites were reviewed.

b. **General observations/commentary**: The primary endpoint, percent change from baseline LDL-C to Visit 8 (Week 12), was verified by comparing the records at the clinical laboratory with the data submitted in the NDA.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

6. (b) (4)

a. **What was inspected:** The inspection reviewed the following: quality assurance and clinical operations, selection of clinical investigators, monitoring procedures and activities, data collection and handling, auditing procedures, adverse experience reporting and test article labeling and shipping. The FDA investigator also compared selected subject CRFs and were compared with the firm's data listings.

An audit of four subjects' records from each of the four clinical sites was conducted. No significant observations of noncompliance were noted.

b. **General observations/commentary**: No regulatory violations were noted for the CRO, PharmaNet.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections (b) (4) [redacted], and Drs. Blokhin, Tchurina, and Ose did not find regulatory violations. The inspection of Dr. Blagden found violations as noted above. The final classifications for the inspections of Drs. Blokhin and Tchurina are pending. The data from all sites appear acceptable in support of the proposed indication. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for Drs. Blokhin and Tchurina.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Susan Leibenhaut
7/9/2009 01:43:35 PM
MEDICAL OFFICER

Constance Lewin
7/9/2009 01:56:50 PM
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