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July 6, 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 #0035 to New Drug Application**

K000-82
ORIG AMENDMENT

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 23, 2009 e-mail from Kati Johnson requested the following:

Based on the dissolution data provided on the clinical, stability and registration batches for each strength, a single-point dissolution test specification of NLT ^{(b) (4)} (C^{(b) (4)}) in 30 minutes is recommended.

Please submit a Phase 4 agreement to revise the dissolution test method within one year of NDA approval to have a single point specification of NLT ^{(b) (4)} (Q^{(b) (4)}) in 30 minutes.

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Module 1.11.1 in this NDA amendment contains a statement of Kowa Company Ltd agreeing to post-approval development of the requested dissolution specification change.

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: 6.233.00, created June 28, 2009

Sincerely yours,



Ross S. Laderman, MPH

Senior Director, Regulatory Affairs

Kowa Research Institute, Inc.

(U.S. Agent for Kowa Company Limited)

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June 22, 2009

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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 #0034 to New Drug Application

11-800-BM
ORIG AMENDMENT

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 9, 2009 e-mail from Dr. Iffat Chowdhury requested the following:

I'm interested in examining the subjects in Group 1 and Group 3 with outlier creatinine values. Would Kowa be able to analyze the percentage of subjects per group who had an increase of >0.5 mg/dl from baseline or from normal to > 1.5 mg/dl on drug?

An e-mail response containing tables was sent by Kowa to Dr. Chowdhury on June 12, 2009 followed by a request of the same date from Dr. Colman for narratives of the 3 patients cited in the tables. An additional e-mail below from Dr. Colman was received on June 13, 2009:

At a minimum we need to know what were these subjects' baseline serum creatinine values, the study day on which the abnormal serum creatinine values were obtained, and the values (if obtained) for any subsequent serum creatinine values in these subjects. It would be in Kowa's best interest to provide enough information about these individuals so that we can make a judgment as to whether treatment with pitavastatin caused, in whole or part, the increases in serum creatinine.

I will be out of the office next week, but you can follow-up with Dr. Chowdhury.

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An e-mail response with tables and CRFs attached was provided to Drs. Colman and Chowdhury on June 17, 2009. The formal NDA response to this request is now presented in the Appendix to this cover letter since, as stand-alone data, it has no other location in the prescribed CTD hierarchy.

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: 6.201.00, created June 16, 2009

Sincerely yours,



Ross S. Laderman, MPH

Senior Director, Regulatory Affairs

Kowa Research Institute, Inc.

(U.S. Agent for Kowa Company Limited)

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ORIG AMENDMENT

June 8, 2009

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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 #0032 to New Drug Application**

ORIGINAL

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.

An initial e-mail from Kati Johnson on May 27, 2009 requested Kowa to identify the location of ApoB data in the NDA. Follow-up e-mails resulted in further clarification and a May 29, 2009 e-mail from Kati Johnson transmitted the following request from the statistical reviewers:

Wei and I have ironed this out. The raw ApoA1 and ApoB lipid values are indeed located in the ISE analysis dataset lipids.xpt in the EDR. So we have the raw electronic data. However, we don't have the DERIVED endpt data, namely the % change from baseline for these variables. In other words, we need something more user-friendly and Wei simply doesn't have the time to re-format. Please kindly tell the sponsor we would like datasets, one for each of the 5 core Phase 3 studies (301, 302, 304, 305 and 306) and 4 phase 2 studies (203, neg204, nov2-4 and 210) that replicates the format of (say) analy301.xpt which Wei has used to analyze other lipid variables, e.g., LDL-C. Just so we're on the same page, analy301.xpt is found using the path

datasets/nk-104-301/analysis/reviewer/analy301.xpt.

Hope this clears things up.

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A response to this request was provided to Ms. Johnson in an e-mail of June 2, 2009. The formal response (to the NDA) to this request is now presented in this amendment. The enclosed Module 5.3.5.3 contains the 9 SAS export datasets requested by the statistical reviewer. There is one file for each of the 4 Phase 2 and 5 Phase 3 core studies. As requested, the Apo A1 and Apo B data have been derived in the same format as the other lipids in the AnalyNNN datasets.

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: 6.159.00, created May 31, 2009

Sincerely yours,



Ross S. Laderman, MPH

Senior Director, Regulatory Affairs

Kowa Research Institute, Inc.

(U.S. Agent for Kowa Company Limited)

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June 8, 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

N-000-B40
ORIG AMENDMENT

RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0031 to New Drug Application

ORIGINAL

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 May 22, 2009 e-mail from Dr. Iffat Chowdhury requested the following:

A list of a few requests and clarifications as we near the end of the review.

1. Please submit the mean change in creatinine levels in the subgroup that had the protein/ creatinine ratios as well as the overall Group 1 and Group 3 patients from baseline to end of treatment. In addition please submit the narratives on the patients who had $< .2$ mg/mg to $\geq .5$ mg/mg change in protein/creatinine ratios (pitavastatin as well as the other statins).
2. What was the rationale for not pooling the dipstick urinalysis data for hematuria and proteinuria? Would you be able to pool this data for Group 1 and 3?
3. Were testosterone levels monitored during the Phase III trials?
4. Please submit the mean change in glucose values for Group 1 and Group 3, from baseline to end of treatment.
5. Please submit the mean change in potassium levels for Group 1 and Group 3, from baseline to end of treatment.

I would prioritize these requests as I have numbered them. Please submit request #1 within a week if possible.

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Responses to these questions were provided to Dr. Chowdhury in e-mails of May 26, May 29 and June 1, 2009. The formal responses (to the NDA) to these requests are now presented in the Appendix to this cover letter (following each of the repeated requests above) since, as stand-alone data, they have no other location in the prescribed CTD hierarchy.

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: 6.159.00, created May 31, 2009

Sincerely yours,



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

May 7, 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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MAY 06 2009

CDR

ORIGINAL ORIG AMENDMENT

RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0030 to New Drug Application

N000-BM

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.

An April 29, 2009 e-mail from Dr. David Gortler requested the following:

Please clarify the following statements in 104-301 final clinical study report:

ITEM 1:

Page 24 states: *A dietary lead-in period of 6 weeks for statin naïve patients and 8 weeks for patients on previous statin therapy was included to ensure adequate washout of prior therapy where applicable and stable baseline lipid values.*

Please explain the above sentence. Why was 6 weeks used for statin naïve subjects versus 8 weeks in non-naïve subjects?

ITEM 2:

Protocol Amendment 2, items number two and three state the following:

2. Excluded glitazones as an allowed concomitant medication for diabetes.

3. Allowed glitazones/thiazolidinediones (pioglitazone, rosiglitazone) as prohibited

Please explain the difference in these two criteria in greater detail. It doesn't make sense to us as it is written.

Please clarify the following statements in 104-301 final clinical study report:

Inclusion criteria:

- To qualify for randomization at Visit 4 (Week 0), subjects were required to follow a fat and cholesterol restrictive diet in accordance with EAS guidelines during the dietary stabilization lead-in period (ie, for at least 8 weeks for those subjects previously taking lipid lowering medication and at least 6 weeks for those not previously taking lipid lowering medication). Subjects also agreed not to eat grapefruit or drink grapefruit juice for the duration of the study;

Please explain why there is a 6 versus 8 week difference in dietary stabilization in subjects in the two different groups.

Treatment:

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

Our understanding was that subjects would be given either simvastatin or pitavastatin. Is this paragraph an error?

Please clarify the following statements in 104-302 final clinical study report:

Page 89: Non-HDL-C values decreased 35.81% from baseline in the pitavastatin 2 mg group and 32.26% in the simvastatin 20 mg group. The adjusted mean differences were statistically significant (P=0.021). In the pitavastatin 4 mg and simvastatin 40 mg groups the decreases were 40.53% and 39.44%, respectively. The adjusted mean differences were not statistically significantly different (P=0.499).

Does the p-value of 0.021 represent a difference between or within groups?

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New Data Request:

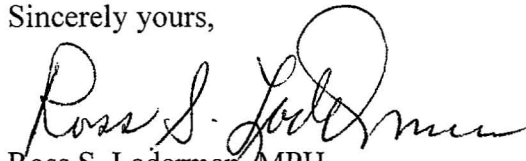
For studies NK-104-301, 02, 04, 05 and 06, please submit p-value calculations between various groups for The Demographic and Other Baseline Characteristics.

The responses to these requests are presented in the Appendix to this cover letter (following each of the repeated requests above) since, as stand-alone data, they have no other location in the prescribed CTD hierarchy. Please be reminded that the studies cited were conducted in Europe by Kowa's unit in the U.K. Therefore you may find that the English language used in the protocols and CSRs has a somewhat regional character.

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: 6.105.00, created May 3, 2009

Sincerely yours,



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