



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

2/27/08

IND 60,492

Kowa Research Institute, Inc.
Attention: Ross Laderman
Senior Director, Regulatory Affairs
430 Davis Drive, Suite 200
Morrisville, NC 27560

Dear Mr. Laderman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NK-104 (pitavastatin) Tablets.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on January 28, 2008. The purpose of the meeting was to discuss clinical and nonclinical matters relating to the submission of an NDA in 4Q 2008.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Monday, January 28, 2008
TIME: 11 am to noon
LOCATION: FDA White Oak Campus
Building 22, Conference Room 1311
APPLICATION: IND 60,492
DRUG NAME: NK-104 (pitavastatin) Tablets
TYPE OF MEETING: Pre-NDA

MEETING CHAIR: Eric Colman, MD

MEETING RECORDER: Kati Johnson, Project Manager

FDA ATTENDEES:

Office of Drug Evaluation II

Curt Rosebraugh, MD-Acting Director

Division of Metabolism & Endocrinology Products

Mary Parks, MD-Director

Eric Colman, MD-Deputy Director, Lipid Clinical Team Leader

Iffat Chowdhury, MD-Clinical Reviewer

Karen Davis Bruno, PhD-Pharmacology/Toxicology Supervisor

Kati Johnson-Project Manager

Office of New Drug Quality Assessment

Suong Tran, PhD-Product Assessment Lead, Division of Pre-Marketing Assessment II

Office of Translational Sciences, Office of Clinical Pharmacology

Sang Chung, PhD-Biopharmaceutics Reviewer

Office of Translational Sciences, Office of Biostatistics

Japo Choudhury, PhD-Statistical Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Kowa Research Institute, Inc.

Claus Kuhl, MD, PhD-President

Ross Laderman-Senior Director, Regulatory Affairs

Roger Morgan, MD-Medical Director

Vasudev Anand, PhD-Director, Preclinical Development

Yoichi Inagaki-Director, Project Management

Kowa Company, Ltd. (Japan)

Mutsumi Moribe-Director, Global Project Strategy & Planning Department

Futoshi Imura-Manager, Global Project Strategy & Planning Department

For the February 4, 2008 teleconference to discuss statistical issues, the following were in attendance:

FDA: Dr. Japobatra Choudhury, Ms. Kati Johnson

Kowa Research Institute: Mr. Ross Laderman

Pharmanet UK (Kowa Statistical Consultants):

James Mann, Director, Statistical Programming

Valerie Arneson, Sr. Director, Biostatistics

Andy Cross, Lead Statistical Programmer

BACKGROUND:

Pitavastatin is a statin being developed as an adjunct to diet to reduce total cholesterol, LDL-C, Apo-B, and triglycerides and to increase HDL-C in adult patients with primary hypercholesterolemia and mixed dyslipidemia. The compound has been approved in Japan since September 2003 under the tradename, Livalo[®]. An End-of-Phase 2 meeting was held on September 20, 2005. The firm is anticipating submitting the NDA in October 2008. The firm requested the meeting on October 4, 2007, and the background package was submitted December 6, 2007.

There are 2 pivotal studies (301 and 302) and 3 special population studies (304, 305 and 306) that will form the basis for the clinical portion of the NDA.

-Study 301- “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”.

This 42-site study was conducted in Europe. Eight hundred thirty patients entered, and 794 completed. According to the background package, for the percent change from baseline to endpoint in LDL-C, pitavastatin was non-inferior to atorvastatin for both the low dose (pitavastatin 2 mg vs. atorvastatin 10 mg) and high dose (pitavastatin 4 mg vs. atorvastatin 20 mg) comparisons in the full analysis set population.

-Study 302- “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”.

This study was also conducted in Europe. Eight hundred patients completed the 12-week study. According to the background package, for the percent change from baseline to endpoint in LDL-C, pitavastatin was non-inferior to simvastatin for both the low dose (pitavastatin 2 mg vs. simvastatin 20 mg) and high dose (pitavastatin 4 mg vs. simvastatin 40 mg) comparisons in the full analysis set population.

The title of the other studies conducted are:

-Study 304-“Study of Pitavastatin 4 mg vs. Simvastatin 40 mg (Following Up-titration) in Patients with Primary Hypercholesterolemia or combined Dyslipidemia and 2 or More Risk Factors for Coronary Heart Disease”

-Study 305-“Study of Pitavastatin 4 mg vs. Atorvastatin 20 mg (Following Up-titration) in Patients with Type II Diabetes Mellitus and Combined Dyslipidemia”

-Study 306-“Study of Pitavastatin 1 mg vs. Pravastatin 10 mg, Pitavastatin 2 mg vs. Pravastatin 20 mg and Pitavastatin 4 mg vs. Pravastatin 40 mg (Following Up-titration) in elderly Patients with Primary Hypercholesterolemia or Combined Dyslipidemia”

MEETING OBJECTIVES:

1. To obtain responses to the specific questions posed and identify any other FDA concerns or comments about the planned NDA.
2. To identify any specific FDA concerns or comments about the proposed NDA that may be related to prior experience with other products having a similar structure of profile.

DISCUSSION POINTS:

Preliminary responses were forwarded to the firm on Friday, January 25, 2008. The firm's questions are followed by our **bolded** responses. Discussions at the January 28, 2008 meeting are underlined. A follow-up teleconference was held on Monday, February 4, 2008 to discuss statistical issues (Questions 10 and 12). For the teleconference, their questions are in ***bold italics***, and the agreements are in ***underlined bold italics***.

CLINICAL

- 1) The projected human exposure from clinical trials is outlined in the background document and updates the numbers discussed at the EOP2 Meeting. Does the FDA agree that the extent and duration of exposure are sufficient to support the filing of the NDA?

Preliminary Response: Yes, the extent and duration of the clinical trials appears sufficient. According to the Lipid Guidance, for an approval of an orally absorbable drug, a minimum of 1500 patients with one year and 500 patients with 2 years is desirable. The ICH guidance directs 300-600 patients over 6 months. The number of patients exposed to 1, 2, or 4 mg will be ~ 1725 patients for greater than 1 year.

Meeting Discussion: None

(b) (4)



Preliminary Response: (b) (4)

(b) (4)

Meeting Discussion: The firm recognized that the number of patients is small. However, according to the firm, duration of treatment was approximately twice that for Lipitor (2 yrs. vs. 1 yr.). The Agency said that extended duration would have some effect on the number of patients required for this indication, but a specific number was not agreed to.

3) Is a pharmacovigilance plan required in the NDA?

Preliminary Response: Yes, a risk-management plan is required in the submitted NDA. Refer to the following guidance document:

-Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:

<http://www.fda.gov/cder/guidance/6359OCC.htm>

Meeting Discussion: In response to a question from the firm, they were told that the risk management plan should be placed in Module 1 as an OTHER item.

4) A full summary of safety from the Japanese post-marketing registration studies, that will include a description of the adverse events from the Japanese market, will be included in the NDA (in publication form). However, KRI does not intend to integrate these data into the clinical trial database or provide narratives for the SAEs that occurred in the PM studies. Does the FDA agree that this is acceptable?

Preliminary Response: The Agency would like additional information, including the protocol, on the post-marketing registry (LIVS-01) that included approximately 20,000 patients in Japan.

Any safety report/post-market study update report (quarterly, semi-annually, or yearly) that is submitted to the Japanese drug authorities would be appropriate for submission to the Agency. Please also submit patient narratives on all deaths and SAEs that occurred in the post-market studies. These reports do not need to be integrated with the clinical trial database.

Meeting Discussion: Regarding the post-marketing registry, the firm stated that it involves approximately 20,000 patients registered at physician offices and followed for 2 years. There was no comparator. Information was collected on adverse events such as liver transaminase elevations, cataracts, myalgia/myopathy and rhabdomyolysis. An English report for the

completed study will be completed approximately 2 months prior to the planned NDA submission. The Agency requested that the NDA include the serious adverse events judged "related to the drug" by the investigator. Additional information may be requested during the NDA review.

- 5) A translated summary of the clinical portion of the Japanese NDA (356 pages submitted to the IND as SN 106) was proposed for inclusion in the NDA by KRI at the EOP 2 Meeting as a suitable alternative to individual translations of early clinical trial reports and data that formed the basis of the Japanese NDA. The Division seemed supportive of this proposal if all relevant safety information is included. Does the Division agree that this is acceptable?

Preliminary Response: Yes

Meeting Discussion: None

- 6) Study NK-104-310 (extension to core study NK-104-305 in diabetic patients) will not be completed at the time of planned NDA submission. An interim report will be submitted in the European CTD by agreement with the European authorities. Since the NDA will be based on the content of the European submission, KRI proposes to leave interim data from the NK-104-310 study intact in the databases and tables. The interim study report would also be included in the NDA as a measure of completeness in the submission. No efficacy data from this study will be considered in the proposed labeling and KRI does not view the data as integral to evaluation of the NDA. Is this acceptable to the FDA?

Preliminary Response: The Agency would like to know the timeline for completion of Study NK-104-310 and the number of patients in the extension study.

Meeting Discussion: The firm stated that the study enrolled 71 patients on atorvastatin and 143 patients on pitavastatin. The final report will be available in 4Q 2008, but after the NDA is planned for submission. After additional discussion, the firm's initial proposal was found acceptable.

- 7) KRI plans to follow the format for Structured Product Labeling (SPL) for the package insert (PI); however, we propose that coding for the PI remain MedDRA (version 8.1), rather than SNOMED. Does the FDA concur?

Preliminary Response: We would expect the labeling to conform to the Physician Labeling Rule (PLR). We have requested clarification internally regarding the use of MedDRA coding rather than SNOMED.

Meeting Discussion: MedDRA coding is acceptable.

- 8) Does the FDA agree that the clinical development program summarized in the background document is sufficient to support the NDA filing?

Preliminary Response: It appears acceptable.

Meeting Discussion: None

- 9) Does the FDA agree that the Phase 1 clinical pharmacology program is sufficient to support the NDA filing and includes studies that address potential concerns in this class of drug products?

Preliminary Response: It appears acceptable.

Meeting Discussion: None

STATISTICAL

- 10) As it is currently not a requirement and Kowa's data and data integration do not follow the Study Data Tabulation Model (SDTM) developed by the Clinical Data Interchange Standards Consortium (CDISC), KRI proposes that these standards will not be followed in the NDA. Does the FDA agree with this approach?

Preliminary Response: The sponsor is encouraged to follow SDTM if possible, even if it is not mandatory.

In any case, the statistical reviewer would like to have the following dataset for his analyses:

An "Analysis Data Set" in SAS transport format to our Electronic Document Room (EDR). Whatever other files are submitted following guidelines, there should be this reviewer-friendly file without the necessity to merge files: on demographics, baseline status, and other prognostic variables, and efficacy (original as well as "derived" or "transformed" like "percent change from baseline", "log of percent change from baseline"), along with site or investigator and patient identifications. A separate SAS variable corresponding to each efficacy variable (derived or original), instead of the need to identify it through one SAS variable EFPARM, is preferable. Kindly provide in the define.pdf file the descriptions (how coded, which value stands for what) of variable names on SAS data sets. LOCF data also for each visit should be provided without the necessity for the reviewer to create them from OC data sets. Please provide a flag (or four separate data sets, if that is more convenient) to identify the four patient-sets: (ITT, LOCF), (ITT, OC), (PP, LOCF), and (PP, OC).

For the February 4, 2008 telecon, the firm requested the following clarification:

- 1. We would like clarification on the request for "Analysis Data Set". We will provide what the Division wants, but some of the specifications are not clear to us.***
- 2. Should this analysis data set be prepared for each study? Or does the Division want pooled studies?***

3. *Should we include both Phase 2 and Phase 3 study data? Or can we limit it to Phase 3 data (which is of a more uniform structure)?*
4. *We did not do LOCF at each visit. We defined an Endpoint Visit for the ITT population, but not for the PP population. Will an Endpoint flag suffice?*
5. *We would like to know if the format and content of our current Data Definition Tables will be adequate for the “define.pdf file” that the Division is asking for. (We’ll be happy to provide an example)*

Dr. Choudhury requested an “Analysis Data Set” with defined characteristics. After some discussion there was agreement on the following points:

- 1. An “Analysis Data Set” will be constructed for each of the 5 core Phase 3 studies.*
- 2. An additional analysis data set will be prepared for the 4 extension studies*
- 3. Demographic, baseline, and subgroup variables will be included, along with the primary and secondary efficacy variables.*
- 4. The analysis data set will have one row per visit per patient.*
- 5. For each lipid (e.g., LDL-C) there will be variables for a) the original value, b) change from baseline, c) percent change from baseline, d) baseline value and e) endpoint flag.*
- 6. Both coded (numeric) and decoded (character) variables will be provided.*
- 7. A Data Definition Table (DDT), defining all of the variables in the proposed Analysis Data Set will be submitted to Dr. Choudhury for his review in March 2008.*

- 11) Kowa’s current plan is to include the Phase 1 data in a pooled database with the Phase 2-3 data to provide a full database. However we do not intend to examine the Phase 1 data in the ISS. The ISS will include only Phase 2 and 3 data. Is this acceptable?

Preliminary Response:. This is acceptable. However, we request that you include in the NDA an assessment of liver safety per the appropriate sections of the FDA document: “Premarketing Evaluation of Drug-Induced Liver Injury”.

Meeting Discussion: None

- 12) The ISS and ISE statistical analysis plans for the NDA are based upon those to be submitted in the European CTD which are contained in this background document. Does the FDA agree with the ISS and ISE statistical analysis plans? Does the FDA have any further comment?

Preliminary Response: Please provide p-values along with the summaries for:

- (1) efficacy results (2) subgroup results (3) interaction p-values (4) baseline comparison p-values.

For the February 4, 2008 telecon, the firm requested the following clarification:

The FDA is asking for p-values for 1) efficacy results, 2) subgroup results, 3) interactions and 4) baseline comparisons. We have these p-values available for all individual studies,

but not for the integrated efficacy data. For the ISE integrated tables we have prepared only summary statistics. If the Division wants statistical testing in the ISE tables, we have a number of questions/concerns. For example:

- 1. Not all studies had the same comparators or doses of comparators. We would like to discuss appropriate treatment group comparisons.*
- 2. Entrance criteria also differ across studies. Should we group studies by population characteristics?*
- 3. In the ISE we only included "target doses" of pitavastatin (1mg, 2mg and 4mg). We also limited the doses of comparators.*

Ms. Arneson expressed concern regarding the difficulty of doing pooled statistical analyses considering how much the study designs differ among the 5 core studies. Three different comparators were used and the studies were carried out in several different populations, i.e., one in diabetics, one in patients at high risk of cardiovascular events and one in the elderly. It will be difficult to develop valid pooling rationale for statistical analyses of these studies.

Dr. Choudhury acknowledged the difficulties, but said that he would still like to see p-values on combined results. He said that some of the p-values are used in a descriptive way and help to have a bird's eye view of the whole submission quickly. He suggested combining studies to the extent that it "makes sense" to combine them. It was agreed that Kowa would consider this request and submit a proposal to Dr. Choudhury for pooling of some studies as appropriate. This proposal will be submitted at the same time as the DDT mentioned above.

NONCLINICAL

- 13) The TK data from some nonclinical studies were measured using validated methods that preceded the existing FDA guidance. We believe that the results of these studies are valid. Does the FDA agree that this is acceptable for filing in the NDA?

Preliminary Response: It appears acceptable.

Meeting Discussion: None

- 14) The PK profile of NK-104 has been extensively characterized in both nonclinical and clinical studies. The PK data from some early studies may also have been generated using methods that may not conform to the FDA guidance. KRI believes that these studies are not essential to the complete evaluation of the PK properties of NK-104 but nonetheless Kowa plans to include the reports of these studies in the NDA for completeness. Is this acceptable to the FDA?

Preliminary Response: It appears acceptable.

Meeting Discussion: None

- 15) There are some earlier study reports and cited references in reports written in Japanese for which only summary translations in English exist. While KRI plans to submit those

summary translations, all study reports of a pivotal nature will be fully translated. Is this acceptable to the FDA?

Preliminary Response: If the studies (pivotal) indicated in the TOC draft module 4 of the CTD (page 139 of the meeting package) will be fully translated, then submission of the earlier Japanese studies as summary translations will be acceptable.

Meeting Discussion: None

- 16) Does the FDA agree that the nonclinical development program summarized in the background document is sufficient to support NDA filing?

Preliminary Response: It appears acceptable.

Meeting Discussion: None

CHEMISTRY, MANUFACTURING AND CONTROLS

- 17) Are the proposed release specifications for the (b) (4) API adequate to support the NDA filing?

Preliminary Response: The proposed release specification for the drug substance is adequate for the NDA filing. Its acceptability for the NDA approval will be determined as part of FDA's review of the NDA. We remind to include a justification for your proposed specification as per ICH guidelines.

Meeting Discussion: The firm recognizes the need for a justification to be included in the NDA.

- 18) Are the proposed release and stability specifications, including the dissolution test, for the drug product manufactured by Patheon adequate to support the NDA filing?

Preliminary Response: The proposed release and stability specifications for the drug product are adequate for the NDA filing. Their acceptability for the NDA approval will be determined as part of FDA's review of the NDA. We remind to include a justification for your proposed specifications as per ICH guidelines. Provide an explanation for the lack of Water Content testing.

(b) (4)

- 19) The proposed stability program and stability data to be submitted in the NDA are outlined in the background document. Does the FDA agree that this is sufficient to support filing of the NDA?

Preliminary Response: Because the dissolution acceptance criteria will be finalized as part of FDA's review of the NDA, we strongly recommend that you obtain multi-point dissolution profiles, instead of sampling only at 30 minutes, during your stability studies and include the profiles in the NDA.

Meeting Discussion: FDA clarified that the proposed 9 months of data from the bottle-packaged commercial product and 6 months of data from the blister-packaged commercial product will be acceptable for the NDA filing. Because the stability studies have been initiated and up to now the dissolution sampling has only been at the 30-minute time point, FDA will accept all available multi-point dissolution profiles from the later portion of the stability studies. The profiles should have adequate time points to show the change in the dissolution curve and the relevance of the proposed 30-minute time point.

- 20) Comparability data on the drug product from clinical trials (manufactured at (b) (4) and commercial registration batches (b) (4)) will be generated from dissolution studies currently underway. Does the FDA agree that this data, if positive, will form a sufficient basis to request a waiver of bioequivalence studies? If so, when should a request for the waiver be submitted?
If the Division does not grant a waiver of the bioequivalence study, what dose(s) does the Division recommend for the study?

Preliminary Response: This will be addressed at the meeting.

Meeting discussion: The biowaiver request for the change in manufacturers of the drug product (commercial vs. clinical) should be included in the NDA submission and accompanied by supporting information as discussed in FDA's guidances such as "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" and "Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" (refer to applicable principles in the latter). In addition, comparative impurity profiles of product batches manufactured at the different sites should be included in the NDA. FDA clarified that the sponsor should provide adequate information in support of a biowaiver request and justify why such a request should be granted. FDA's published guidelines are clear on situations that do or do not require a bioequivalence study. For example, in the SUPAC-IR (Scale-Up and Postapproval Changes-Immediate Release) guidance, there are only 2 situations where a bioequivalence study would be required: if the formulation is very different or if the manufacturing process is very different. The sponsor will have to show to FDA that neither applies, in support of the biowaiver request. In addition, if there are differences in the dissolution profiles or in the impurity profiles, a bioequivalence study or a non-clinical study may be required, respectively.

The sponsor's follow-up question is on the requirements for a bioequivalence study with regard to the 3 dosage strengths.

Clinical Pharmacology Response: In general, a bioequivalence (BE) study should be conducted comparing the clinical trial formulation to the to-be-marketed (commercial)