

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 20, 2005
TIME: 3:00 to 4:30 pm
LOCATION: Parklawn Building, Conference Room C
APPLICATION: IND 60,492
DRUG NAME: NK-104 (pitavastatin) Tablets
TYPE OF MEETING: End-of-Phase 2

MEETING CHAIR: David Orloff, MD

MEETING RECORDER: Kati Johnson

FDA ATTENDEES: (Title and Office/Division)

Robert J. Meyer, M.D.	Director, Office of Drug Evaluation II
David Orloff, M.D.	Division Director
Mary Parks, M.D.	Deputy Director
William Lubas, M.D.	Medical Officer
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Supervisor
Kati Johnson	Chief Project Management Staff
Hae Young Ahn, Ph.D.	Biopharmaceutics Team Leader
Todd Sahlroot, Ph.D.	Pharmacoepidemiology/Statistical Sciences Team Leader
Japobrata Choudhury, Ph.D.	Statistical Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Ross S. Laderman, M.P.H. KRI	Senior Director, Regulatory Affairs
Roger Morgan, M.D., F.A.C.S KRI	Medical Director
Yoichiro Inagaki, M.S, R.Ph. KRI	NK-104 Project Manager

Stephen B. Montgomery, Ph.D. Hugh Black and Associates, Inc.	Preclinical Consultant to KRI
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Kowa Company Ltd. (KCL):

Masahiro Tanaka, Ph.D. Fuji Laboratories	Deputy Director, Research Planning and Administration Department
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BACKGROUND:

NK-104 is a competitive inhibitor of HMG-CoA reductase (Statin). The compound has been marketed in Japan under the brand name Livalo, in strengths of 1 to 4 mg, since 2003. The compound is currently in Phase 3 development in Europe, and the firm is planning to use the data generated outside the US as the sole basis for approval in the US.

The IND was submitted in June 2000 by Sankyo Pharmaceuticals, with sponsorship being transferred to Kowa Research Institute in April 2005. The firm requested a clinical EOP2 meeting on July 18, 2005. A separate chemistry EOP2 meeting is scheduled for November 28, 2005.

The indication being pursued is 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 2 primary efficacy studies proposed are similar except for the comparator. The first proposed study (3.01EU), 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, proposes to randomize a total of 800 patients. Prior to randomization, there will be a screening period (8 weeks for patients withdrawing from lipid-lowering medicine; 6 weeks for those not on medications) where patients will be instructed to consume a diet conforming to EAS guidelines. Blood samples will be taken during the screening period to determine eligibility for randomization. Patients will be randomized to 1 of the following 4 treatment groups, for a total of 12 weeks of treatment:

- Pitavastatin 2 mg QD
- Pitavastatin 4 mg QD (2 mg QD titrated to 4 mg QD after 4 weeks of treatment)
- Atorvastatin 10 mg QD
- Atoravastatin 20 mg QD (10 mg QD titrated to 20 mg QD after 4 weeks of treatment)

Patients randomized to any treatment who complete the study can enter a 52-week, open-label extension protocol (Study NK-104-307)

The primary endpoint is the non-inferiority of pitavastatin 2 mg QD vs. atorvastatin 10 mg QD and pitavastatin 4 mg QD vs. atorvastatin 20 mg QD with respect to the reduction of LDL-C when administered for 12 weeks using an up-titration regimen for the higher doses.

The second study (3.02EU) is similar except that simvastatin 20 mg and 40 mg QD are the comparators.

MEETING OBJECTIVES:

DISCUSSION POINTS:

The firm's questions are followed by the Agency's **bolded** response.

General

1. Please identify nonclinical or clinical concerns (if any) and provide any additional comments concerning NK-104 (and the proposed Phase III program) that we should consider in completing the development program to support US marketing approval for the proposed indication.

In response to a question from the Agency, the firm stated that the frequency of CK evaluation for potential muscle toxicity had not yet been finalized. The Agency stated their preference for evaluation every 3 to 4 months in the long term open label extensions.

Since all pivotal studies will be conducted in Europe, all study sites must be available for inspection.

2. Please advise us of any specific FDA concerns or advice about this program that may be related to prior experience with other products having similar structure, pharmacological activity, or intended clinical use.

Since potent statins can lead to proteinuria, the Agency would like this monitored in the clinical trials. It was recommended that urinalysis be evaluated at the same interval as CK and LFTs in the short labs (SL) evaluations. Dr. Orloff mentioned that we would have comments about renal monitoring after the meeting.

Following internal discussion after the meeting, Dr. Orloff recommends that urine protein be measured in a subset of patients at baseline and 12 weeks, using 3 consecutive 8 hour overnight urine collection.

Chemistry, Manufacturing, and Controls – To be covered under a separate meeting request

Pharmacology/Toxicology

3. Does the Division concur that given:
 - the Japanese post-marketing experience and
 - the results of the rat and mouse carcinogenicity study peer review (submitted as SN 014) and statistical analysis in mice (Appendix 6) which was suggested to the Sponsor by the ECAC and subsequent teleconference with FDA on 11 October 2000, that there is a sufficient context to adequately complete the carcinogenicity evaluation of NK-104 for the proposed indication and a marketing application?

Response: ECAC has reviewed the rat and mouse carcinogenicity studies and indicated concern for the adequacy of these evaluations. In the rat bioassay the doses were

considered adequate, however the early termination (at week 92) in females because of liver and forstomach findings was concerning. The mouse bioassay was also terminated early at 92 weeks, dose selection for the females appeared adequate but not so for the males. ECAC recommended survival adjusted analysis for tumor and non-neoplastic lesions to correct for the excess mortality in the high dose group. A survival adjusted analysis for mice was included in the EOP2 meeting package, but this has not been re-evaluated by ECAC because of time constraints. A peer review of the rat data was previously submitted to the IND according to the sponsor. In a follow-up Tcon, ECAC indicated that reinterpretation of the pathology would not be sufficient to determine the progression of preneoplastic findings to tumors which was possibly confounded by the studies early termination. Therefore ECAC had suggested performing a 6 month transgenic mouse study to address this concern. Kowa plans to submit a "white paper" outlining their rationale for not performing this study.

4. Does the FDA concur that the toxicology program is adequate to support a potentially approvable NDA submission?

Response: Complete study reports of the genotoxicity and reproductive test batteries need to be submitted for review since the Division has only seen summaries of these studies so far. Kowa indicated that they will provide the reports or a listing of when and in which volumes these studies were submitted to the IND. The Division referred to the response to question 3 for the carcinogenicity evaluation concern.

Biopharmaceutics

5. Are the clinical pharmacology studies completed to date and proposed for the Phase III program sufficient to support a potentially approvable NDA for the proposed indication?

The information appears complete for the filing of an NDA. Approvability can only be determined following a comprehensive review of the data.

Clinical

6. Based on the information provided in the briefing document, does the Division agree that the number of patients and duration of exposure are sufficient to support a potentially approvable NDA for the proposed indication?

Patient exposure will be approximately 1600 patients for 1 year, and 4500 patients total. This appears to be sufficient for exposure and duration to support filing of the application. Approvability can only be determined following a comprehensive review of the data.

The firm voiced concern with the need to translate Japanese study reports, and inquired whether an application could be approved without the 886 patients included in these studies. The division stated that while full translations may not be necessary, information on the safety and efficacy would need to be included in the application. The firm was asked to propose a way that this could be done and the division would consider it. However, any case report forms required under the regulations (for deaths

or dropouts due to adverse events) would have to be translated and included in the NDA to be submitted.

The firm was asked if any safety data on black patients is planned for inclusion in the NDA. The firm stated that no differences in either blacks or Hispanics have been seen with other statins, and added that blacks will be enrolled into studies in Western Europe. It was suggested that the firm consider conducting a pharmacokinetic study in blacks compared to Caucasians to assure the agency that no differences exist.

7. Does the FDA concur that the design of the two primary adequate and well-controlled studies (Studies 3.01EU and 3.02EU – documents included as Appendices 1 and 2, respectively) will support a potentially approvable NDA for the proposed indication?

Response: In both proposed studies, subjects are started at the 2 mg daily dose. then the dose is later increased to 4 mg. ^{(b) (4)}

According to the firm, the active control doses chosen are the most commonly used doses. They were informed that their compound could not be promoted as comparing to atorvastatin and simvastatin unless they study the full dose range of those drugs. In addition, there can be no implied claim of superiority if numerically superior to the comparator. The firm was asked to consider using the full range of doses of the chosen comparators; the higher dose(s) of the comparator do not have to be evaluated as part of the structured statistical comparisons. Instead of a forced titration, the sponsor could consider conducting the standard dose response study; 1, 2, and 4 mg NK-104 compared to 10, 20, and 40 mg Lipitor. With this design, an 8-week duration should be sufficient. In addition, in lieu of 2 separate studies, and given the similarity between atorvastatin and simvastatin, the firm could do a single, larger study, representative of the population being treated, and using either one of the statins proposed.

When the protocol(s) are submitted, the firm was asked to also include the statistical analysis plans. Type 1 error control should also be implemented for all secondary endpoints the sponsor intends to label.

8. At the present time, Kowa is not proposing to seek an indication for use of NK-104 in pediatric populations. The clinical plan does not include completion of pediatric studies for submission as part of a New Drug Application. Does the Division agree that pediatric studies for NK-104 are not necessary for approval of a NDA and may be exempt or deferred?

Response: Pediatric studies can be deferred. When the NDA is submitted, the firm should cite these minutes as documentation of this decision.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

The firm will provide the location (date of submission, serial number) in the IND where the genotoxicity and reproductive test batteries preclinical reports are located. The firm will also submit a position paper as to why the 6-month transgenic mouse study will not be conducted.

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this page is the manifestation of the electronic signature.**

/s/

Kati Johnson
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