

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

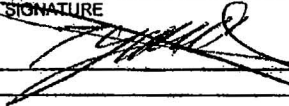
Please mark the applicable checkbox.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached listings	

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Torao Yamamoto	TITLE Representative Director Executive Vice President
FIRM / ORGANIZATION Kowa Company Limited, 4-14 Nihonbashi-honcho 3-chome, Chuō-ku, Tokyo 103-8433, Japan	
SIGNATURE 	DATE 07/29/2009

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Kowa Company Limited
NDA 22-363, Pitavastatin
Section 1.3 Administrative Information

CTD Module 1 Administrative Information

1.3.3 Debarment Certification Statement

Kowa Company Limited, hereby certifies that it has not used and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Attested to by:

Name: Torao Yamamoto	Title: Representative Director Executive Vice President
Company: Kowa Company Limited 4-14 Nihonbashi-honcho 3-chome, Chuo-ku, Tokyo 103-8433 Japan	
Signature 	Date: 07/29/2009

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22363	ORIG 1		LIVALO TABLETS

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

/s/

KATI JOHNSON
08/04/2009

Fax-301-796-9718
Kati.Johnson@fda.hhs.gov

From: Ross Laderman [mailto:rladerman@kowaus.com]
Sent: Monday, July 27, 2009 12:12 PM
To: Johnson, Kati
Subject: Pitavastatin Phase 4 requirements -- timeline

Kati,

As a follow-up to our telephone conversation on Friday, our timeline for the 2 Phase 4 studies (same timeline for both studies) to be required by the FDA for the Livalo NDA approval is as follows:

- 1) Date of protocol submission ---October 30, 2009
- 2) Date of study completion ----October 30, 2010
- 3) Submission of final CSR---December 31, 2010

For the renal impairment study the timelines are based on performance of a single dose pitavastatin study utilizing 4 mg dose in severe renal insufficiency patients (eGFR <30 , MDRD) not on hemodialysis. 8 patients will be recruited to the study, with 8 matching (based on age and sex) healthy volunteer controls. Hepatitis C patients with normal LFTs would be permitted in the renal insufficiency group if no clinical or laboratory evidence of liver dysfunction. Smokers will not be excluded. The timeline also provides for a 30-60 day protocol review/comment period if required by the FDA or if requested by Kowa.

Ross

Ross S. Laderman, MPH
Senior Director, Regulatory Affairs
Kowa Research Institute
430 Davis Drive, Suite 200
Morrisville, NC 27560
Ph: (919) 433-1603

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7/28/2009

Johnson, Kati

From: Ross Laderman [rladerman@kowaus.com]
Sent: Monday, August 03, 2009 3:09 PM
To: Johnson, Kati
Subject: RE: NDA 22-362 AP letter
Attachments: emfalert.txt 3

Kati,

Thank you very much. Confirming receipt of the approval letter for NDA 22-363. Best news we ever got.

Ross S. Laderman, MPH
Senior Director, Regulatory Affairs
Kowa Research Institute
430 Davis Drive, Suite 200
Morrisville, NC 27560
Ph: (919) 433-1603

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From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Monday, August 03, 2009 1:47 PM
To: Ross Laderman; rladerman@nc.rr.com
Subject: NDA 22-362 AP letter

<<22363finalAP.pdf>>

Hi Ross,
please confirm receipt.
Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone-301-796-1234
Fax-301-796-9718
Kati.Johnson@fda.hhs.gov

8/4/2009

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 #0039 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 17, 2009 e-mail from Dr. Iffat Chowdhury requested the following:

Please submit the laboratory values for Subject #KOW305-108-047 after 4/24/2007. The datasets have only laboratory values up to 4/24/07 for this patient. Please clarify the discrepancy in the NDA on her status in the study; she is listed as having discontinued the study in Table 2 (DILI assessment, ISS); however, the narrative indicates that she continued on pitavastatin. Does Kowa have fractionated bilirubin values for this subject?

A response to this question was provided to Dr. Chowdhury in an e-mail of July 17, 2009. The formal response (to the NDA) to this request is now presented in the Appendix to this cover letter (following the repeated request above) since, as stand-alone data, it has no other location in the prescribed CTD hierarchy.

KOWA



RESEARCH INSTITUTE, INC.

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,

A handwritten signature in black ink, appearing to read "Ross S. Laderman".

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

KOWA



RESEARCH INSTITUTE, INC.

Appendix

FDA Request:

Please submit the laboratory values for Subject #KOW305-108-047 after 4/24/2007. The datasets have only laboratory values up to 4/24/07 for this patient. Please clarify the discrepancy in the NDA on her status in the study; she is listed as having discontinued the study in Table 2 (DILI assessment, ISS); however, the narrative indicates that she continued on pitavastatin. Does Kowa have fractionated bilirubin values for this subject?

Kowa Response:

As indicated on the CRF, the patient temporarily discontinued the 305 study, then resumed it and completed that trial.

As you know study NK-104-310 was the extension study to the 305 study. This subject was in both studies 305 and 310. In the initial NDA, for study 310, we submitted only the interim clinical report (up to 16W) as the study was still on-going at the time. We explained this both in the NDA and our plan to do so at the pre-NDA meeting because we did not intend to use the 310 data in the NDA. Therefore, the ISS included only safety data up from study 310 only up to 16 weeks. In this subject's case, the visit at 16 weeks was April 25, 2007. That is why there is no data after 4/24/2007 in the database. In our 4-month safety update to the NDA (Amendment # 0012) the final CSR for study 310 was submitted (the dataset was not submitted). Below is the subject's lab data listed in page 3369 of the 310 final CSR. Her narrative is in page 552 of the 310 final CSR. The cause of the elevations was food poisoning. Bilirubin was 2.07mg/dl at onset (recorded in the narrative). Fractionated bilirubin values were not obtained.

(b) (4)

