4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

•List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CK	Creatine kinase
CRF	Case Report Form
CRP	C-reactive protein
CYP	Cytochrome P450: Collective term of hydroxylase family
CV	Curriculum Vitae
DBP	Diastolic blood pressure
ECG	Electrocardiogram, Electrocardiography
γ-GTP	Gamma glutamyl transpeptidase
HBs antigen	Hepatitis B surface antigen
HCV antibody	anti-hepatitis C virus antibody
HDL	high density lipoprotein
HIV	Human immunodeficiency virus
IEC	Independent Ethics Committee
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
PFC balance	Protein-Fat Carbohydrate balance
PK	Pharmacokinetics
SBP	Systolic blood pressure

•Definition of term

Anonymized number that is linkable to subjects:	The record of the linkage of the given numbers and the subjects is kept, if necessary to identify the subjects.
Researchers:	Persons involved with the clinical study other than the executive investigator, principal investigator and head of the study site [Quoted from "Researchers, etc." of the "Ethics Guidelines for Clinical Research" (all revised on 31 July 2008)]

5. ETHICS

5.1 Independent Ethics Committee (IEC)

The study in each country was implemented after reviewed and approved by the Ethics (Institutional) Review Committee held in Japan on 13 October 2010, in China on 20 October 2010, in Korea on 1 October 2010 (minor change required in the protocol synopsis), and 27 October 2010, and in the US on 9 November 2010. The study protocol and protocol amendments, the informed consent document/form, and a completed application for approval for an investigation on teaching or research involving male subjects were submitted for review.

Moreover, Ethics Review Committee at the National Institute of Health Sciences in Japan reviewed and approved the study protocol and the informed consent documents/forms for both the pharmacokinetic (PK) study and gene polymorphism examination in Japan on 25 October 2010, and the informed consent documents/forms for both the PK study and gene polymorphism examination in other three countries on 29 November 2010.

Copies of the study protocol and protocol amendments, Japanese versions and English versions, are provided in Appendix 1. Each IEC approval letter, a list of IEC members, and background information and specimen consent forms are provided in Appendix 3.

5.2 Ethical Conduct of the Study

This study was conducted in compliance with the protocol and procedures and while giving full consideration to protection of participants in accordance with the ethical principles of the Declaration of Helsinki, the standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Pharmaceutical Affairs Law (PAL), "Ministerial Ordinance on Partial Revision of the Ordinance on Good Clinical Practice" (dated 29 February 2008, Ordinance No. 24 of the Ministry of Health, Labour and Welfare (MHLW)) (Revised GCP), "Ethical Guidance on Clinical Studies" (entirely amended on 31 July 2008, MHLW), "Guideline for Gene Tests" (August 2003, genetic medicine-related societies), "Ethical Guidance on Human Genome/Genetic Analysis

Researches" (partially revised on 1 December 2008, Ministry of Education, Culture, Sports, Science and Technology/Ministry of Economy, Trade and Industry).

5.3 Subject Information and Consent

5.3.1 At Enrollment

The principal investigator issued and obtained approval of the Ethics (Institutional) Review Committee for both informed consent documents and forms used for obtaining consent for study participation from the subjects and for the conduct of gene polymorphism examination based on the "Ethical Guidance on Human Genome/Genetic Analysis Researches" (partially revised on 1 December 2008, Ministry of Education, Culture, Sports, Science and Technology/Ministry of Economy, Trade and Industry).

Prior to the screening, the principal investigator, investigators and others handed the informed consent documents/forms for obtaining consent for the PK study and gene polymorphism examination to volunteers and gave explanations on them for the volunteers to be able to correctly understand the matters. The investigator obtained voluntary consent of the volunteers in writing upon full understanding of the contents of both informed consent documents by them.

The principal investigator, who provided the explanation, and the subject affixed their names/seals or signatures and the date in these two kinds of informed consent documents and forms for obtaining informed consent and kept one copy each. When the study site personnel other than the principal investigator such as an investigator provided a supplemental explanation, the investigator also affixed his/her name/seal or signature and the date to the said documents and forms. The dates of informed consent obtained for each matter were recorded in the case report form (CRF, see Appendix 2).

5.3.2 In the Event of Obtaining Information Possibly Affecting the Subject's Will

In the case where information (such as safety information) possibly affecting the subject's will for continuing study participation was obtained, the principal investigator was requested to notify the information to the subjects, verified their will as to whether or not to remain in the study, and documented such a fact with the date of confirmation; however, such information was not obtained during the study.

5.3.3 Revision of the Informed Consent Document and Form

When it was found necessary to revise the informed consent document and form such as the case of obtaining new important information that might have been related to the subjects' consent, the principal investigator was promptly to amend the informed consent document and form and obtain approval of the Ethics (Institutional) Review Committee.

When the informed consent document and form were revised, the principal investigator was to obtain consent from the subjects.

Executive Investigator's letter of 19 October 2010 recommended every principal investigator that he/she should obtain written informed consent in case of re-blood sampling for PK (see Appendix 3).

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Executive Investigator:

Professor Shinichi Kawai, MD, PhD

Division of Rheumatology Department of Internal Medicine (Omori) Toho University School of Medicine

Address: 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan

TEL: + 81-3-3762-4151 (ext. 6591) FAX: + 81-3-5753-8513

[Duties]

- Supervising study-related activities, and analyzing ethnic differences using PK data.

Study Site and Principal Investigator:

<Japan>

Study site code: 00001

Tomoko Hasunuma

Kitasato University, Research Center for Clinical Pharmacology Bioiatric Center

Address: 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan

TEL: +81-3-5791-6178 FAX: +81-3- 3440-5469

<China>

Study site code: 00002

Cui Yimin

Peking University First Hospital

Address: No.8, Xishiku Street, Western District, Beijing, China

TEL: +86-10-6611-0802 FAX: +86-10-6655-1289

<Korea>

Study site code: 00003

In-Jin Jang

Seoul National University Hospital

Address: 28 Yeongeon-dong Jongno-gu Seoul, 110-744, Korea

TEL: +82-2-2720-8290 FAX: +82-2-2745-7996

<US>
Study site code: 00004
Masaru Kaneko
SNBL Clinical Pharmacology Center, Inc.
Address: 800 W. Baltimore St., 6th FL, Baltimore, MD 21201, USA
TEL: +1-410-706-8926 FAX: +1-410-706-8964
[Duties]
・ Obtaining voluntary consent from subjects, conducting clinical study, and adjusting entire study.

Study Drug Storage Manager:
<Japan>
Mariko Kawashima
Kitasato University, Research Center for Clinical Pharmacology Bioiatric Center
Address: 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan
TEL: +81-3-5791-6350

<China>
Zhao Dongfang
Peking University First Hospital
Address: No.8, Xishiku Street, Western District, Beijing, China
TEL: +86-10-6611-0802 FAX: +86-10-6655-1289

<Korea>
Min-Jung Kim
Seoul National University Hospital
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TEL: +82-2-2072-1688 FAX: +82-2-2072-1970

<US>
Jay Piliponskiy, Odunayo Obisesan
SNBL Clinical Pharmacology Center, Inc.
Address: 800 W. Baltimore St., 6th FL, Baltimore, MD 21201, USA
TEL: +1-410-706-8876 FAX: +1-410-706-8964
[Duties]
・ To be in charge of control and storage of the study drug.

Document Control Manager:

<Japan, China, Korea and US>

The principal investigators at the study sites were in charge of document management.

[Duties]

・ Retention and control of essential documents.

Monitoring:

<Japan>

CMIC, Co., Ltd., CRO Company, Clinical Research Dept. CRO East Japan Head Office

Address: Gotanda First Bldg. 2-8-1 Nishigotanda, Shinagawa-ku, Tokyo 141-0031, Japan

TEL: +81-3-5719-6325 FAX: +81-3-5496-9805

Responsible person: Hideto Ushijima

<China>

CMIC, Beijing Co. Ltd.

Address: B610-612, COFCO Plaza No.8 Jianguomennei Avenue, Beijing 100005, China

TEL: +86-10-6513-9211 FAX: +86-10-6513-9213

Responsible person: Li Lei

<Korea>

CMIC Korea Co. Ltd

Address: #702 Hansan Bldg. 47-2 Seosomun-dong, Jung-gu, Seoul 100-110, Korea

TEL: +82-2-3708-3674 FAX: +82-2-3789-6900

Responsible person: Eun-Jae Maeng

<US>

Scientific Consulting, LLC

Address: 6871 Daly Road, Dexter, MI 48130, USA

TEL: +1-734-424-9227 FAX: +1-734-424-0105

Responsible person: Emily Huston, Wendy Eggleston

[Duties]

・ Performing monitoring activities.

Clinical Laboratory Center

<Japan>

Hosen Clinic, Kitasato University Center for Clinical Pharmacology

Address: 1-28-16 Komagome, Toshima-ku, Tokyo 170-0003, Japan

TEL: +81-3-5976-7611
Responsible person: Sayoko Morita

<China>
Peking University First Hospital
Address: No. 8, Xishiku Street, Western District, Beijing, China
TEL: +86-10-6655-1122 (ext. 2043, 3456)
Responsible person: Feng Zhenru

<Korea>
Clinical Trials Center Core Lab Clinical Research Institute, Seoul National University Hospital
Address: 28 Yeongeon-dong, Jongno-gu, Seoul 110-744, Korea
TEL: +82-2-2072-1679 FAX: +82-2-3675-8334
Responsible person: Sung-Hee Han

<US>
Esoterix-LABCORP
Address: 13900 Park Center RD, Herndon, VA 20171, USA
LABCORP Clinical Trials
Address: 69 First Ave., Raritan, NJ 08869, USA
TEL: +1-908-526-2400 (ext. 2505) FAX: +1-908-707-9049
Responsible person: Angela Murphy
[Duties]
・ To measure samples for hematology, blood biochemistry and urinalysis.

Gene Polymorphism Test Facility

<Japan, Korea and US>:

Division of Medicinal Safety Science, National Institute of Health Sciences

Address: 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan

TEL: +81-3-3700-1141 FAX: +81-3-3700-9788

Responsible person: Masahiro Tohkin

<China>

Biomedical Research (GZ), Ltd.

Address: Tong You Village, Gao Yao City, Guang Dong Province, 526100, China

TEL: +86-758-816-6660 FAX: +86-758-816-6633

Responsible person: Setsuo Nagata

[Duties]

- To perform the gene polymorphism examination
- Data analysis of gene polymorphism

Laboratory Center for Measurement of Drug Concentrations

<Japan, Korea, China and US>

Shin Nippon Biomedical Laboratories, Ltd. Pharmacokinetics and Bioanalysis Center

Address: 16-1, Minamiakasaka, Kainan, Wakayama, 642-0017, Japan

TEL: +81-73-483-8881 FAX: +81-73-483-7377

Responsible person: Masayuki Mogi

[Duties]

- To measure plasma drug concentrations.

Summary of the Safety Data

<Japan, Korea and China>

CMIC Korea Co., Ltd.

Address: #702 Hansan Bldg. 47-2 Seosomun-dong, Jung-gu, Seoul 100-110, Korea

TEL: +82-2-3708-3600 FAX: +82-2-3789-6900

Responsible person: Dong Ryeol Lee, Jeong Sook Bang

<US>

SNBL Clinical Pharmacology Center

Address: 800 W. Baltimore St., 6th FL, Baltimore, MD 21201, USA

TEL: +1-410-706-8707 FAX: +1-410-706-8964

Responsible person: Tomoka Inoue Davidsen

[Duties]

- To check the safety data, and making tables and figures.

Statistical Analysis

<PK and polymorphism>

Division of Medicinal Safety Science, National Institute of Health Sciences

Address: 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan

TEL: +81-3-3700-1141 FAX: +81-3-3700-9788

Responsible person: Masahiro Tohkin

[Duties]

- To draw up the statistical analysis plan, implement the PK analysis, and prepare reports (draft).

Audit

CMIC, Co., Ltd., Quality Management dept

Address: Kongo Bldg. 7-10-4 Nishigotanda, Shinagawa-ku, Tokyo 141-0031, Japan

TEL: +81-3-5745-7045 FAX: +81-3-5745-7095

Responsible person: Seiichi Hata

[Duties]

- To perform the audit of the study sites.

Curriculum vitae (CV) of the executive investigator and the principal investigators are presented in Appendix 4.

7. INTRODUCTION

Lately, global clinical studies have been promoted from the perspectives of effective and prompt development of new drug and of solving drug lag issue. At the "First Meeting of the Japanese, Chinese and Korean Health Ministers" held in April 2007 in Seoul, the 3 countries worked on the clarification of racial and ethnic differences in clinical study data and ultimately agreed to aim at the mutual acceptance of clinical research data.

In consideration of this circumstance, Japan has analyzed ethnic difference by using existing clinical PK study data in the "Study Group for Evaluation of Ethnic Factors in Clinical Data in Japanese, Chinese and Korean Populations (Tohkin Group)". In response to the result of this research, in the "Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare (Kawai Group)," a 2009 Health Labour Sciences Research Grants (Global-Scale Health Topic Promotion Research), implementation of a global PK study is planned with a study drug which has been selected based on evaluation results using existing data to collect supplemental data on ethnic difference or to improve data reliability.

Meloxicam, the study drug in this study, is an oxicam non-steroidal anti-inflammatory drug (NSAID) that has been already commercialized in each country. The routine dose is 7.5 mg/day in Korea, China, and the US, while 10 mg/day in Japan, but the maximum dose is 15 mg/day in each country. For PK characteristics, the absolute bioavailability is high in oral administration, 89% to 97%, mainly metabolized by metabolic enzyme (CYP2C9) to inactivated drug, and unchanged drug is rarely eliminated in urine or feces. The elimination rate is 42.8% and 47% in urine and feces, respectively. Tokin group compared ethnicity differences by the uniform statistical process, showing similar results in Japanese, Koreans, and Europeans, but those in Chinese were different from others in drug disposition. However, there were differences in the protocol conducted in the countries (for example, the dosage form used in the study was different), and therefore, no obvious conclusions have been obtained yet. With these backgrounds, we decided to conduct a clinical PK study, conforming to the same protocol, with Caucasians, as a control, to examine ethnicity differences between East Asian ethnic groups.

8. STUDY OBJECTIVES

Presence/absence of ethnicity differences in PK in Japanese, Chinese, and Korean healthy adult males was examined between three countries, using meloxicam that had been already commercialized, based on the same protocol. As a control, a clinical study based on the similar protocol was conducted in European Caucasians residing in the US.

9. INVESTIGATIONAL PLAN

9.1 Overall Design and Plan Description

This was conducted as an open-label, single administration study in which 30 healthy adult male subjects for each country (120 subjects in total in Japan, China, Korea and the US) aged 20-35 were to receive a single oral dose of 7.5 mg of meloxicam.

Potential subjects were to be screened for eligibility within 30 days of admission to the study period.

Single dose of one 7.5-mg tablet of meloxicam was administered with 150 mL of soft mineral water (less than 100 of hardness, Volvic® etc.) after 10 hours or more fasting. Water intake was prohibited within 2 hours after administration of the study drug, and 500 mL or less soft mineral water (less than 100 of hardness, Volvic® etc.) was taken from 2 hours after administration to within 4 hours after administration.

Food intake was prohibited within 4 hours after administration of the study drug. Since then, water to be taken in the study was soft mineral water in any cases (less than 100 of hardness, Volvic® etc.).

Calories and balance of three main nutrients (protein-fat-carbohydrate [PFC] balance) of the supper on the previous day and lunch/supper on the day of administration of the study drug were equalized wherever possible between the countries.

Blood sampling for assay of meloxicam, and safety assessments including both vital sign measurements and clinical laboratory tests (hematology, blood biochemistry and urinalysis) were to be performed at pre-determined times during the study period.

Adverse events (AEs) were to be monitored throughout the study. Following the study period subjects were to undergo a final follow up assessment. A detailed account of the study evaluations is given in Section 9.5.

Gene polymorphism of the metabolic enzyme (CYP2C9) involved with PK of meloxicam was to be analysed for each subject 72 hours after meloxicam administration.

9.2 Discussion of Study Design and Choice of Control Groups

Since the aim of the study was to investigate whether or not there were ethnic differences in the PK profile of an oral dose of meloxicam, it was carried out as an open-label study with no control group.

9.3 Selection of Study Population

In Japan, China and Korea, persons whose paternal and grandparents had their own country's citizenship were eligible. For Chinese, only Han people were included. In the US, European Caucasians were included.

In the study, among the above candidates, healthy adult male candidates who met all of the following "9.3.1 Inclusion Criteria" and did not meet any of "9.3.2 Exclusion Criteria" were to be targeted.

9.3.1 Inclusion Criteria

1) Those who are capable of providing written informed consent.
2) Men aged 20 to 35 years at the time of signing informed consent.
3) Body Mass Index (BMI) of 18.5 to < 30.0 and body weight of 50.0 to 100.0 kg at screening.
4) Those who are determined by the principal investigator to be healthy in the screening test and eligible for the study.

[Rationales for setting]

1) It is defined, considering the ethnic of this study.
2) Based on the premise that subjects participate voluntarily in the study, persons of 20 years or above from whom first-person consent can be legally obtained were

included, and the upper limit of age was set to be 35 years of age so that variability of test values and PK variations can be minimized.

Females were not included in the study for the following reasons;

- Ethically, women who can be pregnant should not be exposed to risks.
- If females are included in the study, it will become more difficult to recruit participants because the inclusion and exclusion criteria become more rigid.
- It will become difficult to compare PK profiles between the ethnic groups if male / female ratio is difficult between them.

3) It is defined to reduce variations between individuals.
4) Since healthy adults are targeted, it is defined to exclude persons who are inappropriate for the study from the viewpoint of health.

9.3.2 Exclusion Criteria

1) Organopathy involving the heart, lung, liver and/or kidney etc.
2) Persons with diseases of heart, lung, kidney, blood (such as coagulation system disorder), central nervous system, metabolic system, peptic ulcer, inflammatory enteropathy, hypertension, asthma, and diseases of skeletal muscles etc. and those with a history of any of the above diseases.
3) Persons with hypersensitivity or allergy to drugs, foods, etc. [Particularly, persons with allergy to or adverse effects related to NSAIDs and salicylic acid (aspirin, etc.) or those with a history of any of the above allergy or adverse effects]
4) Persons who have received any of other drugs, such as OTC drugs, health food or supplements from 1 week prior to the study drug administration to the completion of the study (Day 4).
5) Persons who are smoking or those have stopped smoking in 6 months (the cotinine test is conducted if necessary).
6) Persons who are drug-dependent or those suspected to be drug-dependent (drug screening is conducted if necessary).
7) Habitual alcohol drinkers (persons with 50 g or more of alcohol intake* per day)

* Alcohol intake (g) = [alcohol content] × [amount of alcohol intake (mL)] × [0.8 (ratio: weight per 1 mL of alcohol)]

Example: when drinking 1000 mL of beer (Alcohol content: 5.5%)

Alcohol intake = 0.055 × 1000 × 0.8 = 44 g

8) Total bilirubin or direct bilirubin, AST, ALT and ALP is 1.5 times higher, or other liver and renal function tests items are 1.25 times higher than the upper limits of normal at the sites.
9) Persons who underwent 200 mL or more of blood collection within one month, blood component donation (plasma or platelet) within two weeks or those who underwent more than 400 mL of blood collection within 3 months before administration of the study drug.
10) Persons who participated in a phase I study on drugs containing new active ingredient within 4 months, or those who participated in other studies and received administration within 3 months, before administration of the study drug (For patch test, those who received within one month before administration of the study drug). And persons who participated in any of the above studies and received administration outside the defined period shall also be excluded, if determined to be inappropriate for participation in the study, considering the characteristics of the previous investigational product.
11) Other persons determined by the principal investigator to be inappropriate for the study

[Rationales for selection]

1) to 3) It is defined to secure subjects' safety.
4) to 8) It is defined to secure safety and prevent possibility of effects on PK analysis and safety evaluation.
9) It is defined, considering safety and ethics for subjects, so that blood donation criteria, summarized by the blood donation study group, might be met (healthy adult males; 400 mL per collection, 3 months or more of an interval between collections, 1200 mL or less of annual total amount of blood collection, 3 times or less of blood collection).
10) It is defined, considering safety and ethics for subjects, to exclude effects of drugs having interactions with the study drug or long-acting drugs.
11) It is defined so that the principal investigators for the study can determine the results, considering general factors.

9.3.3 Removal of Subjects from Therapy or Assessment

Discontinuation/withdrawal criteria

Subjects who met any of the followings were to be discontinued or withdrawn from the study;

1) When the subject requests himself/herself withdrawal from participation in the study after consent obtainment.
2) When the principal investigator determines that the subject cannot observe the protocol.
3) Others (when the principal investigator determines that the study should be discontinued)

   [Obvious fever (37.5°C or more), onset of serious acute diseases, etc.]

[Rationales for setting]

1) It is defined, respecting for subjects' own free will.
2) It is defined to secure safety of subjects.
3) It is defined so that the principal investigators could determine discontinuation of administration of the study drug, considering general factors.

Procedures for discontinuation/withdrawal

1) When the study was discontinued, the principal investigator immediately informed the subject accordingly (When the subject requested discontinuation of the study, detailed reasons were to be confirmed wherever possible). The time of discontinuation/withdrawal, reasons, etc. were to be entered to the CRF.
2) When the study was discontinued or withdrawn after administration of the study drug, the principal investigator was to perform observation, conforming to Section "9.5.2. Evaluation items for the safety endpoints" (however, "9.5.2.5 Body weight" was excluded)." For subjects who were discontinued or withdrawn from the study, blood collection for plasma concentration measurement after administration was to be performed only if possible.
3) In the presence of AEs, the principal investigator was to investigate until the symptoms resolve or become stable (1 month at the longest).
4) For discontinued cases or withdrawals, the relevant subjects were not to be replaced.

9.4 Treatments

9.4.1 Treatments Administered

Subjects received a single oral dose of a tablet containing 7.5 mg of meloxicam. The tablet was administered with 150 mL of soft mineral water (less than 100 of hardness, Volvic® etc.). Administration of meloxicam tablet was only performed by authorized members of each study site staff.

9.4.2 Identity of Investigational Products

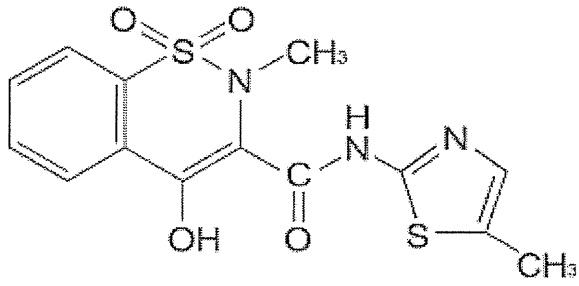
Meloxicam is a NSAID, developed by Boehringer Ingelheim GmbH, with chemical formula of oxicam, which selectively inhibits cyclooxygenase-2. Meloxicam was launched in Europe in 1996, and currently sold in 100 or more countries in the world.[1)]

In this study, meloxicam (single batch) that was manufactured by Boehringer Ingelheim Shanghai Pharmaceuticals Co., Ltd. and sold in China was used.

A copy of the certificate of analysis is provided in Appendix 5.

Brand name	Mobic®
Indications	Anti-inflammation and pain relief for the following diseases and symptoms: Osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis
Active ingredient	
[Nonproprietary name]	Meloxicam
[Chemical name]	4-Hydroxy-2-methyl- N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

[Chemical structure]



[Molecular formula] $C_{14}H_{13}N_3O_4S_2$

[Molecular weight] 351.40

[Content and dosage form]

A slight yellow tablet containing 7.5 mg of meloxicam

[Storage condition] Meloxicam was stored at 30°C or less in a light-resistant airtight container, and prevented moisture absorption after opening.

The batch number and expiry date were as follows:

	Batch number	Expiry date
7.5 mg tablets	084081	January 2015

Source: Appendix 5 (Certificate of Analysis)

9.4.3 Management and storage of the study drug

The executive investigator delegated management and storage of the drug sold in China, as the study drug, to the storage manager of each study site. Delivery and management of the study drug were performed, according to the "The study drug shipping and handling procedure", provided by the executive investigator. For residual study drug after completion of the study, after indicated by the principal investigator, the storage manager confirmed the quantity of the residual drug and discarded or disposed them after destruction, according to the procedures of the study site.

9.4.4 Methods of Assigning Subjects to Treatment Groups

Subject Identifier (9 digits) was consisted of 5-digit study site code (Japan: 00001, China: 00002, Korea: 00003 and the US: 00004) linked with anonymous 4-digit subject identification code. Following confirmation of eligibility on admission, subjects were assigned numbers from 0001 – 0030 in each study site.

There was no randomisation in this study.

9.4.5 Selection of Doses in the Study

The dosage and administration was chosen to be within the range of those approved, and single oral administration of 7.5 mg, with which the plasma concentrations of the unchanged meloxicam could be measured for a sufficient period of time, was adopted.

9.4.6 Blinding

This was an open-label PK study. Neither the subjects nor the investigators were blinded.

9.4.7 Prohibited Concomitant Medications

Concomitant use of meloxicam with any other drugs was prohibited from one week before administration of the study drug to completion of the study (Day 4: discharge).

When any of other drugs was concomitantly used for any compelling reasons, such as treatment of AEs, the principal investigator was to enter the name, dosage/ administration, duration of use, objective of use, etc. of the relevant drug to the CRF.

9.4.8 Management of subjects

9.4.8.1 Screening

The principal investigator performed screening within 30 days before administration of the study drug after acquisition of the consent.

9.4.8.2 Previous day of administration of the study drug (Day -1: admission) to the 4th day after administration (Day 4: discharge)

The principal investigator admitted the subject to the hospital before about 16:30 on the previous day of administration of the study drug. The subject was fasted after having supper on the day of admission to 4 hours after administration of the study drug. On the day of administration, after completion of physical examination by the physician, laboratory test, tests including vital signs (blood pressure, pulse rate, temperature) and blood collection for drug concentration measurement prior to administration, administration of the study drug were started subsequently from 9:00 am. After that, the defined tests and blood collection for drug concentration measurement were performed, according the study schedule.

On Day 4 of administration, the researcher discharged all subjects from the hospital after completing the defined tests, blood collection for drug concentration measurement and blood collection for detection of gene polymorphism for CYP2C9 involved with PK of meloxicam and confirming absence of safety problems (health condition). However, when safety securing was determined to be necessary, hospitalization of the relevant subject was to be prolonged, and re-test or additional test was to be performed as a follow-up investigation. In this case, measures taken were to be entered to the CRF.

9.4.9 Treatment Compliance

Administration of study drug to the volunteers was performed in each study site by qualified and accredited members of the study site staff. Administration of oral tablet was followed by a hand and mouth check.