## DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

| LABORATORY | | | | |
|---|---|---|---|---|
| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
| URINALYSIS | *Standard International Units are listed in italics* | | | |
| Hematuria (microscopic) | 6 – 10 RBC/HPF | > 10 RBC/HPF | Gross, with or without clots OR with RBC casts | Transfusion indicated |
| Proteinuria, random collection | 1 + | 2 – 3 + | 4 + | NA |
| Proteinuria, 24 hour collection | | | | |
| **Adult and Pediatric ≥ 10 years** | 200 – 999 mg/24 h<br>*0.200 – 0.999 g/d* | 1,000 – 1,999 mg/24 h<br>*1.000 – 1.999 g/d* | 2,000 – 3,500 mg/24 h<br>*2.000 – 3.500 g/d* | > 3,500 mg/24 h<br>*> 3.500 g/d* |
| **Pediatric > 3 mo - < 10 years** | 201 – 499 mg/$m^2$/24 h<br>*0.201 – 0.499 g/d* | 500 – 799 mg/$m^2$/24 h<br>*0.500 – 0.799 g/d* | 800 – 1,000 mg/$m^2$/24 h<br>*0.800 – 1.000 g/d* | > 1,000 mg/ $m^2$/24 h<br>*> 1.000 g/d* |

[*] Values are for term infants.

[†] *Use age and sex appropriate values (e.g., bilirubin), including preterm infants.*

付録 2)

（様式）

# 予期しない重篤な有害事象報告

平成　　年　　月　　日

厚生労働大臣　殿

以下の臨床研究に関連する予期しない重篤な有害事象について、下記の通り報告する。

1. 報告者情報

(1) 臨床研究機関名・その長の職名及び氏名：

(2) 研究責任者名：

(3) 臨床研究課題名：

(4) 臨床研究登録 ID：

（※あらかじめ登録した臨床研究計画公開データベースより付与された登録 ID 等、臨床研究を特定するための固有な番号等を記載する。当該臨床研究に係る報告は、関係する全ての研究機関において同じ番号を用いること。）

(5) 連絡先：　TEL：　FAX：

e-mail：

2. 報告内容

(1) 発生機関：　□自施設　□他の共同臨床研究機関（機関名：　）

(2) 重篤な有害事象名・経過

（発生日、重篤と判断した理由、介入の内容と因果関係、経過、転帰等を簡潔に記入）

(3) 重篤な有害事象に対する措置

（新規登録の中断、同意・説明文書の改訂、他の被験者への再同意等）

(4) 倫理審査委員会における審査日、審査内容の概要、結果、必要な措置等

(5) 共同臨床研究機関への周知等：

共同臨床研究機関　□無し　□有り（総機関数（自施設含む）　機関）

当該情報周知の有無　□無し　□有り

以上

（資　料　3）

日中韓大臣声明に基づく医薬品の民族差に関する国際共同臨床研究
健康成人男性を対象としたメロキシカムの薬物動態学的臨床試験

# 安全性に関する報告

（終了報告：2011 年 3 月 31 日）

研究統括責任者　　川合　眞一
東邦大学医学部内科学講座（大森）膠原病科　教授

## 要約

この試験の目的は、既に市販されているメロキシカムを用いて、日本人、中国人および韓国人の健康成人男性における薬物動態に関する民族差の有無を、同一の試験計画に基づいて 3 国間で検討するものである。また対照として、米国在住のヨーロッパ系コケージアンに対して同様の試験計画に基づく臨床試験を行った。

試験デザインは、非盲検、メロキシカム 7.5 mg の単回経口投与試験であった。北里大学臨床薬理研究所（日本）、北京大学第一医院（中国）、ソウル大学病院（韓国）、SNBL Clinical Pharmacology Center（米国）の 4 施設が試験に参加し、2010 年 11 月 16 日から 2010 年 12 月 21 日にかけて試験が実施された。

日本、中国、韓国および米国の 4 ヵ国で 121 例（日本、中国、韓国は各 30 例、米国 31 例）が試験に組み込まれた。日本、中国ではその全例に試験薬としてメロキシカム 7.5 mg が単回経口投与された。韓国では 1 例が投与前に除外基準に抵触することが判明し、コケージアンでは 1 例が投薬前に同意を撤回したため、メロキシカムを投与された被験者数はそれぞれ 29 例と 30 例であった。その結果、選択基準を満たし、除外基準に抵触しなかった被験者は合計 119 例であり、これら全例について背景（人口統計学的データ）および安全性の評価を行った。有害事象は 23 件（日本人 3 例 3 件、中国人 4 例 5 件、韓国人 8 例 11 件、コケージアン 3 例 4 件）発現した。最も多く発現した有害事象は、血中トリグリセリド増加とそう痒症（各 2 件）であった。重症度においては、高ビリルビン血症、C-反応性蛋白増加、総コレステロール増加、LDL コレステロール増加の各 1 件が中等度であった以外はすべて軽度であった。試験薬との因果関係が「多分関連あり」と判定されたのは 8 件であった。内訳は、中国人 2 例に 3 件（血中尿酸増加、白血球数減少、ヘモグロビン減少の各 1 件）および韓国人 3 例に 5 件（斑状丘疹状皮疹、全身性皮疹、そう痒性皮疹の各 1 件、そう痒症の 2 件）であった。有害事象の持続期間はフォローアップに応じなかった 2 例 3 件（C-反応性蛋白増加、総コレステロール増加、LDL コレステロール増加）を除いていずれも短く、治療や処置を必要とせずに回復した。また、臨床検査値、バイタルサインおよび

診察所見による安全性評価においては、メロキシカムの投与に起因する異常所見は認められなかった。

この試験で得られたデータから、メロキシカム 7.5 mg 経口投与は日本人、中国人、韓国人およびヨーロッパ系コケージアンの健康成人男性において安全で、忍容性が良好であることが示された。

添付資料

Clinical Study Safety Report

Study Title: Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health,
Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects

Author: Executive Investigator: Professor Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

## 1. TITLE PAGE

# Clinical Study Safety Report

Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health

Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects

Division of Rheumatology, Department of Internal Medicine (Omori),
Toho University School of Medicine
6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan
Professor Shinichi Kawai, MD, PhD

## EXECUTIVE INVESTIGATOR SIGNATURE

**Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health**

**Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects**

Study No ID: UMIN000004173

I, the undersigned, hereby declare that the safety part of this study was performed according to the procedures herein described and that this report represents a true and accurate record of the results obtained.

## EXECUTIVE INVESTIGATOR

Division of Rheumatology,
Department of Internal Medicine (Omori),
Toho University School of Medicine
6-11-1 Omori-nishi,
Ota-ku,
Tokyo 143-8541
Japan

_____ _____

Professor Shinichi Kawai, MD, PhD Date

# 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Executive Investigator:** Shinichi Kawai | **Individual Study Table Referring to Part of the Dossier** | |
| **Name of Study Drug:** Meloxicam | Volume: | |
| **Name of Active Ingredient:** Meloxicam | | |

**Study Title:** Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health

Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects

**Principal Investigators:** <Japan> Tomoko Hasunuma
<China> Cui Yimin
<Korea> In-Jin Jang
<US> Masaru Kaneko

**Study Sites:** <Japan> Kitasato University, Research Center for Clinical Pharmacology Bioiatric Center
<China> Peking University First Hospital
<Korea> Seoul National University Hospital
<US> SNBL Clinical Pharmacology Center, Inc.

**Publications:** Not applicable

**Study Period*:**

| | Date of first admission | Date of final follow-up |
|---|---|---|
| <Japan> | 16 November 2010 | 4 December 2010 |
| <China> | 18 November 2010 | 29 November 2010 |
| <Korea> | 24 November 2010 | 17 December 2010 |
| <US> | 13 December 2010 | 21 December 2010 |

*When the study was conducted in the divided several groups, the date of the first admission of the first group and the date of final follow-up of the last group were described.

**Clinical Phase**:
Clinical pharmacokinetic study

**Objectives:**
Presence/absence of ethnicity differences in pharmacokinetics 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.

**Methodology:**
This was an open-label, single administration study in male healthy volunteers. In Japan, China (only Han people) and Korea, persons whose paternal and maternal parents and grandparents have their own country's citizenship were eligible. In the US, European Caucasians were included.
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. Food intake was prohibited within 4 hours after administration.
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.
Safety assessments were performed at pre-determined times during the study period. Adverse events were monitored throughout the study.

**Number of subjects (planned):** 30 subjects for each country (Total 120 subjects)

**Diagnosis and main criteria for inclusion:**
Healthy adult male volunteers aged 20-35 years, with body mass index of 18.5 to <30.0 kg/m$^2$and body weight of 50.0 to 100.0 kg, having given written informed consent.

## SYNOPSIS (continued)

| | | |
|---|---|---|
| **Name of Executive Investigator:** Shinichi Kawai | **Individual Study Table Referring to Part of the Dossier** | |
| **Name of Study Drug:** Meloxicam | Volume: | |
| **Name of Active Ingredient:** Meloxicam | | |

**Study drug, dose, administration route and batch numbers:**
One 7.5-mg tablet of meloxicam (Batch No.084081) was administered with 150 mL of soft mineral water (less than 100 of hardness, Volvic® etc.).

**Duration of study:** 5 days: hospitalization (-Day 1) to discharge (Day 4)

**Reference therapy, dose, administration route and batch numbers:** None

**Criteria for evaluation:**
**Safety:**
Laboratory test values (hematology, blood biochemistry and urinalysis), vital signs (body temperature, blood pressure and pulse rate), body weight and adverse events were included in the safety evaluation.

**Statistical methods:**
**Safety parameters:**
For laboratory test values (hematology and blood biochemistry), vital signs (temperature, blood pressure and pulse rate) and body weight, basic statistics (means and standard deviations) were obtained at each test period. For the laboratory safety data out of range values were flagged in the data listings and a list of clinically significant abnormal values was presented.
Adverse events were tabulated and summarised according to MedDRA (Ver.13.0), and classified by System Organ Class and Preferred Term.

**SAFETY RESULTS:**
A total of 121 eligible subjects that consisted of 30 subjects each for Japanese, Chinese and Koreans and 31 Caucasians were enrolled in the study in order to investigate the PK profile of single oral dose of 7.5 mg of meloxicam. Of 121 subjects, two were withdrawn from the study before administrating the study drug because 1 Korean subject did not fulfil any inclusion or any exclusion criteria and 1 Caucasian subject withdrew his consent. All other subjects fulfilled all of the inclusion criteria and none of the exclusion criteria. Consequently, 119 subjects were evaluated for safety and completed the study.

Totally, 23 AEs were reported by 18 subjects. The most frequent AEs were blood triglyceride increased and pruritus (2 events each). Eight AEs were judged as "probably related" (each 1 event of blood uric acid increased, white blood cell count decreased, haemoglobin decreased, rash maculo-papular, rash generalised and rash pruritic, and 2 events of pruritus). Four events were judged moderate in severity (each 1 event of hyperbilirubinaemia, elevated C-reactive protein, elevated total cholesterol and elevated LDL cholesterol). AEs other than 3 AEs (each 1 event of elevated C-reactive protein, elevated total cholesterol and elevated LDL cholesterol) were short lasting and resolved without concomitant medication or other intervention. No serious AE were observed in these 4 ethnic groups. There were no deaths or other serious AEs.

Laboratory measurements and clinical safety assessments (vital signs and physical examinations) did not show any clinically relevant abnormalities arising from the administration of meloxicam.

**CONCLUSION:**
Most of treatment-related AEs were mild in severity, and none required concomitant medication or intervention. Laboratory and other safety assessments did not appear to show any clinically relevant abnormalities arising from the administration of meloxicam. Meloxicam showed the similar safety results in these 4 ethnic groups.
The data from this study indicate that meloxicam given in oral dose of 7.5 mg is safe and relatively well-tolerated by healthy male Japanese, Chinese, Korean and Caucasian subjects.

**Date of the final report: 31 March 2011**

# 3. TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES

## LIST OF APPENDICES

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

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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