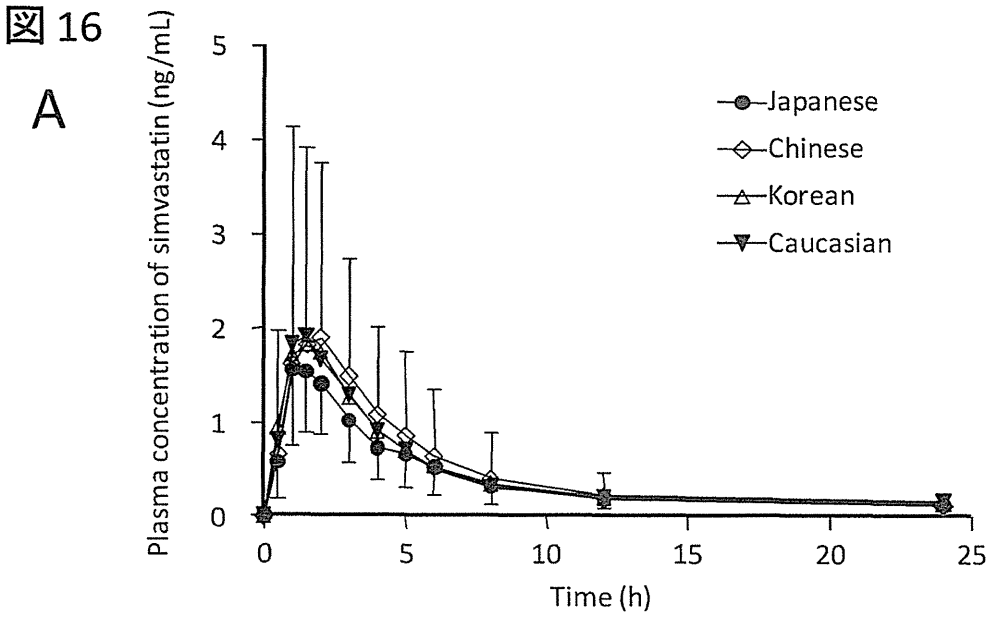
図16



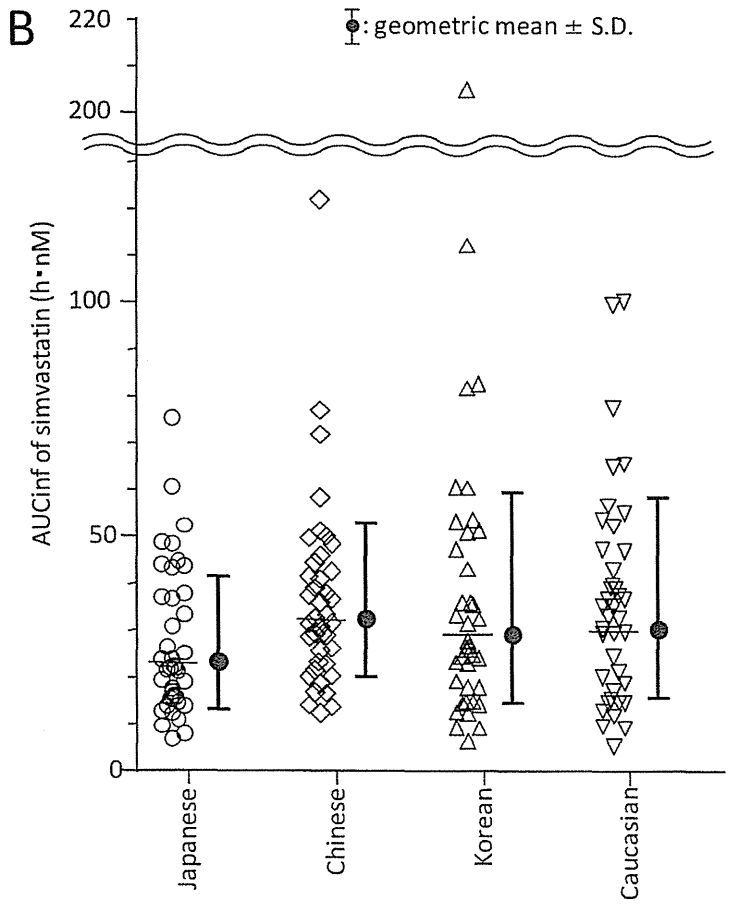
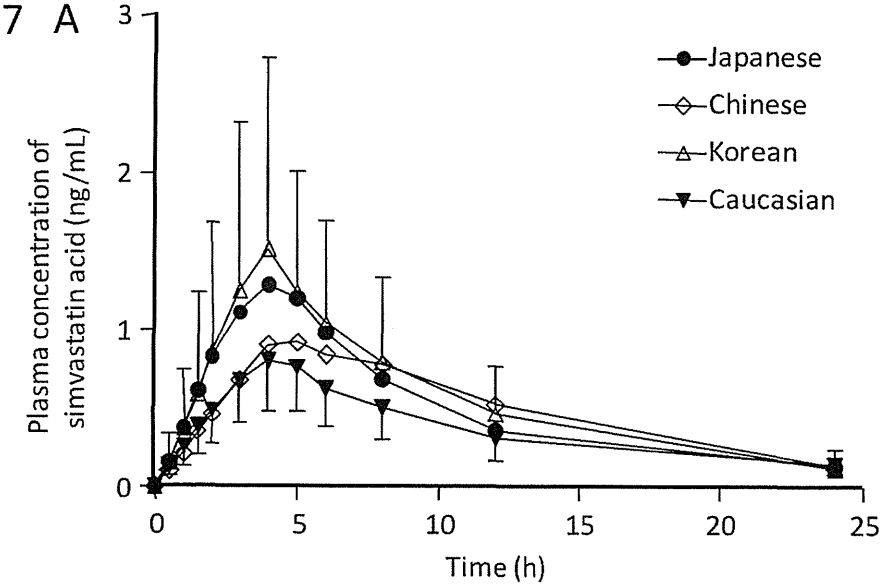


Fig 16. (A) Plasma concentration-time curve of simvastatin after administration of a single 20-mg dose of simvastatin in 4 ethnic population (geometric mean and SD). (B) Individual data and geometric mean with SD of the AUCinf of simvastatin in 4 ethnic populations.

図17 A



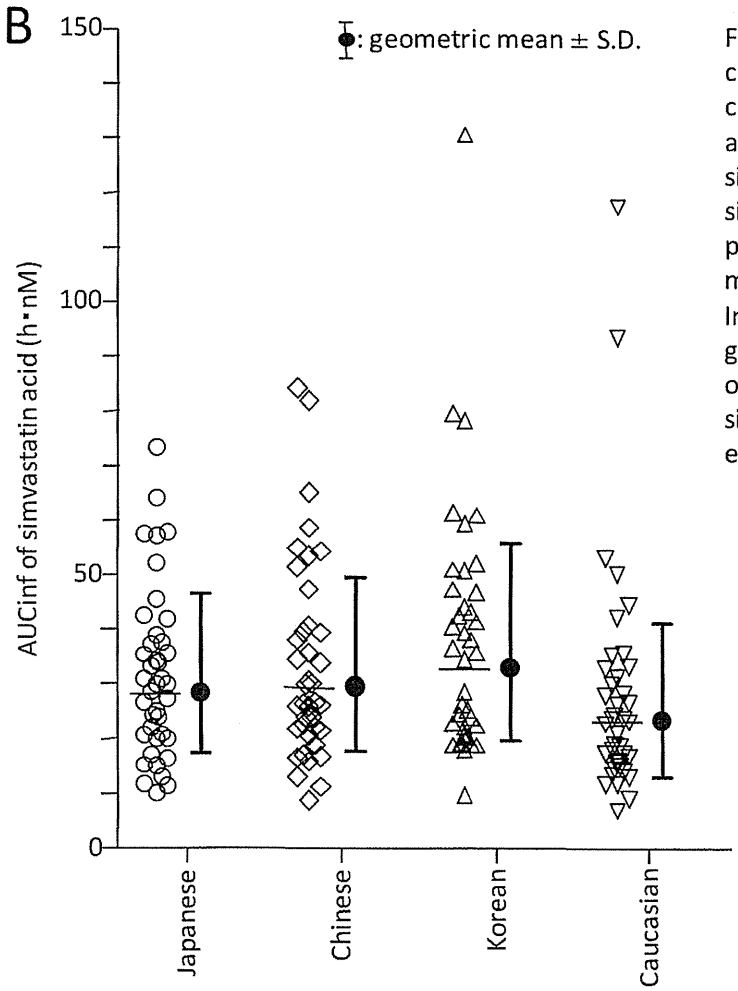


Fig 17. (A) Plasma concentration-time curve of simvastatin acid after administration of a single 20-mg dose of simvastatin in 4 ethnic population (geometric mean and SD). (B) Individual data and geometric mean with SD of the AUCinf of simvastatin acid in 4 ethnic populations.

図 18

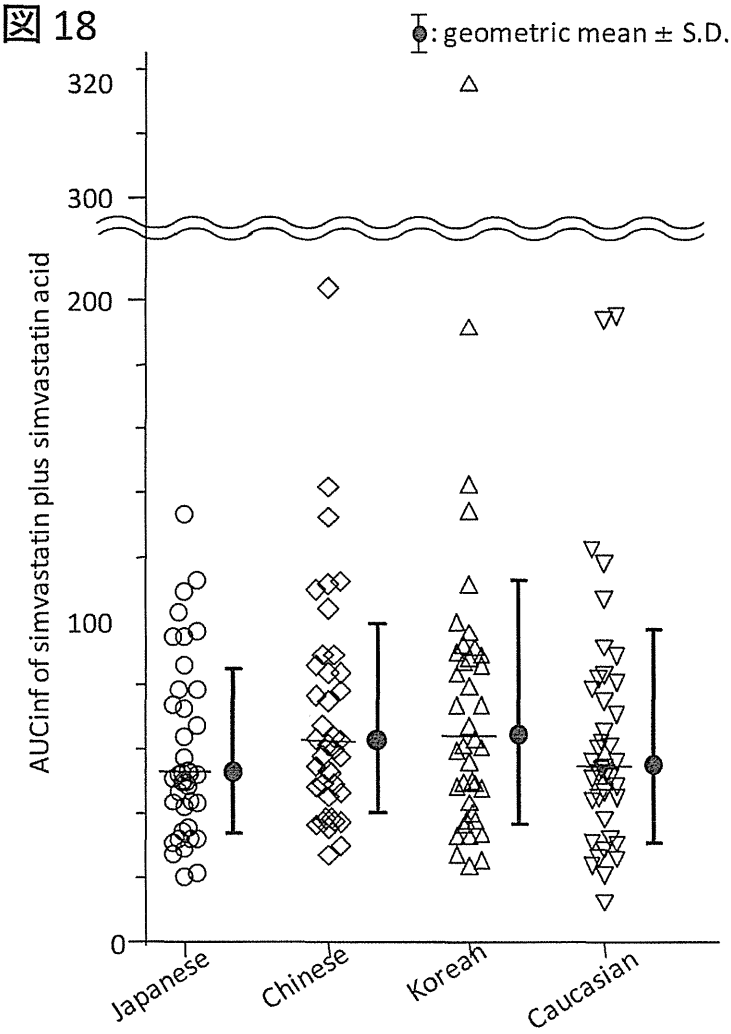


Fig. 18 Individual data and geometric mean with SD of the AUCinf of simvastatin plus simvastatin acid in 4 ethnic populations.

図 19

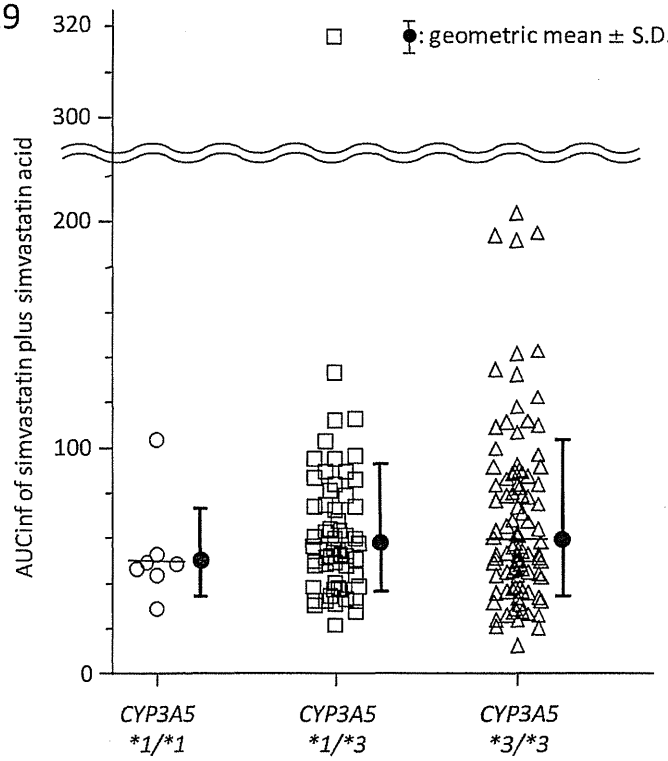


Fig. 19 Individual data and geometric mean with SD of the AUCinf of the simvastatin plus simvastatin acid in the three genotype of *CYP3A5*3*.

図 20

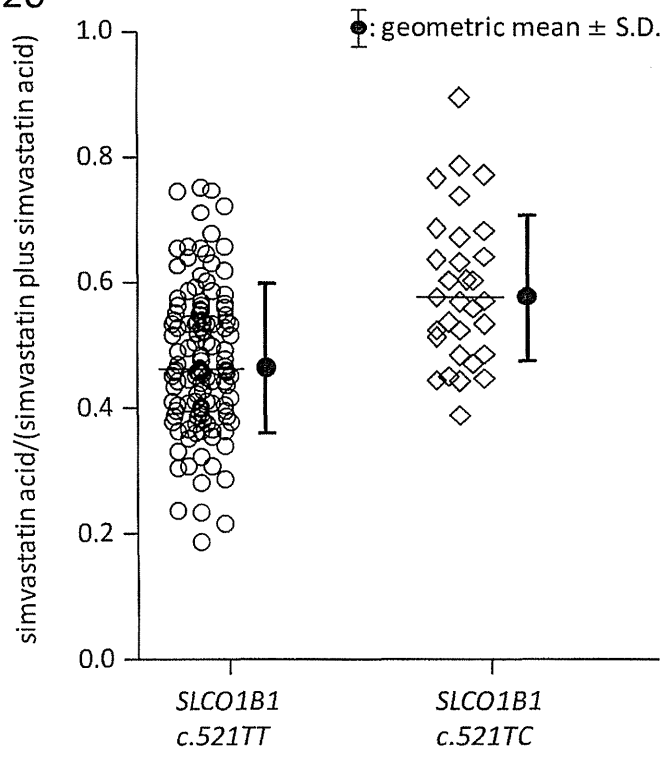


Fig.20 Individual data and geometric mean with SD of the AUCinf ratio of simvastatin acid to that of simvastatin and simvastatin acid in the two genotype of *SLCO1B1c.521T>C*.

（資　料　１）

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モキシフロキサシンの薬物動態学的臨床試験

安全性に関する報告

（終了報告：2010年7月31日現在）

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モキシフロキサシンを用いて、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、モキシフロキサシン400 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）、ソウル国立大学病院（韓国）、SNBL Clinical Pharmacology Center（米国）の4施設が試験に参加し、2010年2月23日から2010年4月12日にかけて試験が実施された。

日中韓および米国の4ヵ国で80例（各国20例ずつ）が試験に組み込まれた。日本、中国、米国ではその全例に試験薬としてモキシフロキサシン400 mgを単回経口投与した。韓国では、1例が投薬前日の入院後に個人的理由により同意を撤回したため、モキシフロキサシンを投与された被験者数は19例であった。 その結果、選択基準を満たし、除外基準に該当しない被験者は合計79例であった。これらの被験者について背景（人口統計学的データ）および安全性について評価を行った。有害事象は合計で14件(日本人5例6件、中国人1例1件、韓国人3例4件、コケージアン3例3件)が観察された。そのうち試験薬と因果関係があると思われるものは4件であった。内訳は、日本人1例にじんましん、韓国人2例にめまい、頭痛、コケージアン1例に頭痛であった。最も多く見られた有害事象は不快感(日本人2例3件)と頭痛(コケージアン2例2件、韓国人1例1件)であった。有害事象は概して持続時間が短く、治療や処置を必要とせずに回復し、重症度においては、頭痛(1件)を除き軽度であった。また臨床検査値やバイタルサイン、診察所見、心電図による安全性の評価においてはモキシフロキサシンの投与に起因する異常所見は見られなかった。4つの人種のグループの安全性評価において同じような傾向が観察された。

この試験から得られたデータより、日本人、中国人、韓国人、ヨーロッパ系コケージアンの健康成人男性におけるモキシフロキサシン400 mg経口投与は安全で忍容性が良好であるのが示された。

添付資料：Clinical Study Safety Report, 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, Clinical Pharmacokinetic Study of Moxifloxacin 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 Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare

Clinical Pharmacokinetic Study of Moxifloxacin 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 Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare

Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

Study No ID: UMIN000002968

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** Volume:	
Name of Study Drug: Moxifloxacin		
Name of Active Ingredient: Moxifloxacin hydrochloride		

Study Title: 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
Clinical Pharmacokinetic Study of Moxifloxacin 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

Publications: Not applicable

Study Period:

	Date of first admission	Date of final follow-up
<Japan>	23 February 2010	26 February 2010
<China>	8 March 2010	11 March 2010
<Korea>	4 March 2010	15 March 2010
<US>	26 March 2010	12 April 2010

Clinical Phase:
Clinical pharmacokinetic study

Objectives:
To investigate whether or not there were ethnic differences in the pharmacokinetics of the marketed moxifloxacin in healthy adult Japanese, Chinese and Korean male subjects based on the same protocol among the three countries. For comparison, a US clinical study in European Caucasians was to be conducted on the same protocol.

Methodology: This was an open-label, single administration study. In Japan, China (the Han race) and Korea, the nationalities of these subjects were the same as those of grandfather, grand-mother, father and mother. In the US, only European Caucasian was eligible.
One 400-mg tablet of moxifloxacine was orally administered with 150 mL of soft mineral water (hardness<100, Volvic® etc.) after fasting for at least 10 hours. Water drinking was prohibited up to 2 hours after taking the study drug. Food intake was not allowed up to 4 hours after administration. The calories and three major nutrients (PFC balance) of the dinner after administration were unified among the countries as much as possible. Intake of milk, cheese and yoghurt was not allowed.
Safety assessments were performed at pre-determined times during the study period. Adverse events were monitored throughout the study.

Number of subjects (planned): 20 subjects for each country (Total 80 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.

Study drug, dose, administration route and batch numbers:
One 400-mg tablet of moxifloxacin (Lot No.117268) was administered with 150 mL of soft mineral water (hardness<100, Volvic® etc.).

Duration of study: 4 days: hospitalization (-Day 1) to discharge (Day 3)

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

SYNOPSIS (continued)

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

Criteria for evaluation:
Safety:
Laboratory values, vital signs (body temperature, blood pressure and pulse rate), 12-lead ECG and adverse events were included in the safety evaluation.

Statistical methods:
Safety parameters:
Laboratory values, vital signs (body temperature, blood pressure and pulse rate), ECG and body weight were presented in tabular form with mean, standard deviation, median, minimum and maximum. For the laboratory safety data out of range values were flagged in the data listings and a list of clinically significantly abnormal values was presented.
Adverse events were tabulated and summarised according to MedDRA (Ver.12.1 or more), and classified by SOC and PT.

SAFETY RESULTS:
Eighty eligible subjects were enrolled for this clinical pharmacokinetic study in order to investigate the pharmacokinetic profile of single oral dose of 400 mg of moxifloxacin in healthy adult male subjects among four ethnics. Of 80 subjects, one was withdrew his consent with personal reason and dropped out before administrating the study drug. All other subjects satisfied with all of the inclusion criteria and none of the exclusion criteria. Seventy-nine subjects completed the study and were evaluated for safety in each study site.

A total of 14 adverse events (6 in 5 Japanese subjects, 1 in a Chinese subject, 4 in 3 Korean subjects and 3 in 3 Caucasian subjects) were observed during the study, of which it was considered that 4 events (urticaria in a Japanese subject, dizziness and headache in 2 Korean subjects, headache in a Caucasian subject) were considered to be probably related to the study drug. The most frequently reported adverse events were malaise (3 incidents in 2 Japanese subjects) and headache (2 incidents in 2 Caucasian subjects and 1 incident in a Korean subject). All adverse events except one incident of headache were mild in severity. Adverse events were generally short lasting and resolved without concomitant medication or other intervention. There were no deaths or serious adverse events.

Laboratory measurements and clinical safety assessments (vital signs, physical examinations and 12-lead ECG) did not appear to show any clinically relevant abnormalities arising from the administration of moxifloxacin.

CONCLUSION:
All treatment-related adverse events except one 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 moxifloxacin. Moxifloxacin showed the similar safety results in these four ethnic groups.

The data from this study indicate that moxifloxacin given in oral dose of 400 mg is safe and relatively well-tolerated by healthy male Japanese, Chinese, Korean and Caucasian subjects.

Date of the final report: 31 May 2010

3. TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

•List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine amino transferase
AST	Aspartate amino transferase
AUC	Area under the plasma concentration-time curve
BMI	Body Mass Index
CCr	Creatinine clearance
CK	Creatine kinase
CPK	Creatine phosphokinase
CRF	Case Report Form
CRP	C-reactive protein
CV	Curriculum Vitae
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EM	Extensive Metabolizer
GCP	Good Clinical Practice
γ-GTP	Gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
Hbs antigen	Hepatitis B surface antigen
HIV	Human immunodeficiency viruses
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PFC balance	Protein-Fat Carbohydrate balance
PK	Pharmacokinetics
SBP	Systolic blood pressure
SD	Standard Deviation
SOP	Standard Operating Procedure
SULT	Sulfotransferase
UGT	Uridine diphosphate glucuronosyltransferase

•Definition of term

QTc prolongation	450 msec or more prolongation in QTc in this study

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 January 2010, China on 20 January, Korea on 27 January (conditional approval) and 4 February, and the US on 26 January. The study protocol and protocol amendments, the informed consent document and form, and a completed application for approval for an investigation for 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, the informed consent document and the form to conduct gene polymorphism examination on 25 December 2009.

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

The principal investigators, who provided the explanation, and the subject affixed their names / seals or signatures and the date in these two informed consent documents and forms for obtaining informed consent and keep one copy each. When the study site personnel other than the principal investigators such as an investigator or collaborator provided a supplemental explanation, he / she 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).

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 investigators notified the information to the subjects, verified their will as to whether or not to remain in the study, and document such a fact with the date of confirmation.

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 investigators were 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 investigators were to obtain consent from the subjects.

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 Ohmori-nishi, Ohta-ku, Tokyo 143-8541, Japan

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

[Duties]

- To supervise study-related activities.
- To analyze ethnic differences using PK data collected from study sites in the four countries.

Study Sites and principal investigators:

<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