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 *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

*Values are for term infants.

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

付録 2) 試験薬との因果関係が否定できない、未知または重篤な有害事象発現時の製造販売元への報告すべき内容一覧

1. 報告医師名
2. 施設名
3. 試験薬 アベロックス
4. Study Number 14988
5. 被験者の識別番号
6. 被験者の性別　男性 / 女性
7. 被験者の年齢
8. 有害事象 1　※有害事象が複数ある場合は、9 以下の項目をコピーして繰り返して下さい。

9. 有害事象名
10. 重篤と判断した理由
    ※該当するもののみ記載
    ※複数選択可（死に至るもの／生命を脅かすもの／入院または入院期間の延長／先天異常を来たすもの／永続的または顕著な障害・機能不全／その他の重大な状態）
11. 試験薬（アベロックス）との因果関係　あり／なし
12 判定理由　※「判定理由」は必須
13. 発現日　2010/MM/DD
14. 転帰　※該当するもののみ記載
    （死亡／軽快／未回復／回復／回復したが後遺症あり／不明/悪化）
15. 転帰日　2010/MM/DD
16. 試験薬（アベロックス）の投与
17. 投与開始日　2010/MM/DD
18. 有害事象発現後の措置
    ※副作用に対する治療薬や処置
19. 有害事象の概要（発現状況、症状、場所、処置等の経過）
    ※可能な限り、経時的に記載

（資　料　２）

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シンバスタチ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12月24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、中国で販売されているシンバスタチンを用いて、日本人、中国人、韓国人および米国在住のヨーロッパ系コケージアン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、4国間で同一の試験計画に基づく臨床試験にて検討することである。

試験デザインは、非盲検、シンバスタチン20 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7月5日から2010年10月10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164例（日本、中国、韓国は各40例、米国44例）が試験に組み込まれた。日本、中国および韓国ではその全例に試験薬としてシンバスタチン20 mgを単回経口投与した。米国では投与前に、2例が個人的理由により同意を撤回し、さらに別の2例に逸脱（他の薬剤との併用禁止の逸脱1例、研究責任者が心電図検査の必要性を認めた者1例）が認められたため、シンバスタチンを投与された被験者数は40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160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10件（日本人6例7件、韓国人2例2件、コケージアン1例1件）発現した。そのうち試験薬との因果関係が「多分関連あり」と判定されたのは、韓国人1例に発現した下痢1件であった。最も多く発現した有害事象は、傾眠と下痢（各2件）であった。重症度においては、コケージアン1例に発現したビリルビン増加1件が中等度であった以外はすべて軽度であった。追跡調査に応じなかったコケージアン1例を除いて、有害事象はいずれも持続時間が短く、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、シンバスタチン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、シンバスタチン20 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 Simvastatin 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 Simvastatin 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 Simvastatin in Healthy Adult Male Subjects

Study No ID: UMIN000003644

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: Simvastatin	Volume:	
Name of Active Ingredient: Simvastatin		

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 Simvastatin 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>	5 July 2010	9 July 2010
<China>	9 August 2010	18 August 2010
<Korea>	10 August 2010	28 August 2010
<US>	27 August 2010	10 October 2010

*When the study is 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:
To investigate whether or not there were ethnic differences in the pharmacokinetics of simvastatin in healthy adult Japanese, Chinese, Korean and Caucasian male subjects based on the same protocol among the four countries.

Methodology: This was an open-label, single administration study in male healthy volunteers. In Japan, China (the Han race) and Korea, the nationalities of these subjects were the same as those of grandfather, grandmother, father and mother. In the US, only European Caucasian was eligible.
One 20 mg tablet of simvastatin 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 the balance of three major nutrients (PFC balance) of the dinner on the day before administration and the first lunch and dinner after administration were unified among the countries as much as possible.
Safety assessments were performed at pre-determined times during the study period. Adverse events were monitored throughout the study.

Number of subjects (planned): 40 subjects for each country (Total 160 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 20 mg tablet of simvastatin (Lot No.107093) was administered with 150 mL of soft mineral water (hardness<100, Volvic® etc.).

SYNOPSIS (continued)

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

Duration of study: 3 days: hospitalization (-Day 1) to discharge (Day 2)

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

Criteria for evaluation:
Safety:
Subjective symptoms and physical examination, 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, blood biochemistry, and urinary pH), 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 to be flagged in the data listings and a list of clinically significantly abnormal values was to be presented.
Adverse events were tabulated and summarized according to MedDRA (Ver.13.0), and classified by System Organ Class and Preferred Term.

SAFETY RESULTS:
A total of 164 eligible subjects that consisted of 40 subjects each for Japanese, Chinese and Koreans and 44 Caucasians were enrolled in the study. Two Caucasian subjects withdrew their informed consent with personal reason before administrating the study drug, and 1 Chinese subject withdrew his informed consent after administration. Other 2 Caucasian subjects were judged as deviation because of Ineligible (the use of a prohibited concomitant medication) or other deviation (the principal investigator's judgment on the necessity of ECG investigation). All other subjects satisfied with all of the inclusion criteria and none of the exclusion criteria. Consequently, 160 subjects were evaluated for safety and 159 subjects completed the study.

A total of 10 adverse events occurred in the study. Seven events in 6 Japanese subjects, 2 events in 2 Korean subjects and 1 event in 1 Caucasian subject were reported. One diarrhoea in 1 Korean subject was judged to be "probably related" to the study drug. The most frequently reported adverse events were somnolence and diarrhoea (2 events each). Only 1 event of elevated bilirubin observed in 1 Caucasian subject was moderate in severity, and all the others were mild. Adverse events other than the Caucasian subject who did not accept a follow-up test were short lasting and resolved without concomitant medication or other intervention. There were no deaths or other serious adverse events.
Laboratory measurements and clinical safety assessments (vital signs and physical examinations) did not show any clinically relevant abnormalities.

CONCLUSION:
Almost all of the reported adverse events were mild in severity, and none required concomitant medication or intervention. Laboratory and other safety assessments did not show any clinically relevant abnormalities by the administration of simvastatin.

The data from this study indicate that simvastatin 20 mg is safe and relatively well-tolerated similarly in healthy male Japanese, Chinese, Korean and Caucasian.

Date of the final report: 24 December 2010

3. TABLE OF CONTENTS

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

•List of Abbreviations

ABC	ATP-binding cassette ABC transporter: gene ABCB1, gene ABCG2
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BMI	Body Mass Index
CK	Creatine kinase
Cl	Chlorine
CRF	Case Report Form
CRP	C-reactive protein
CYP	Cytochrome P450: Collective term of hydroxylase family
CV	Curriculum Vitae
DBP	Diastolic blood pressure
ECG	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
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
OATP	Organic anion-transporting polypeptide
PFC balance	Protein-Fat-Carbohydrate balance
PK	Pharmacokinetics
SBP	Systolic blood pressure

•Definition of term

Anonymized number that is linkable to subjects:	The numbers are given to the subjects (anonymized). The record of the linkage of the numbers and the subjects is kept, if necessary to identify the subjects.

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 9 June 2010 (minor change required in the protocol and the informed consent document/form) and 14 June 2010 (quick review without holding committee), in China on 23 June 2010 (minor change required in the protocol and the informed consent document/form) and 6 July 2010 (quick review without holding committee), in Korea on 28 June 2010 (minor change required in the informed consent document/form) and 22 July (quick review without holding committee), and in the US on 29 June 2010. The study protocol and protocol amendments, the informed consent document/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 both the study protocol and the informed consent document/form to conduct gene polymorphism examination in all countries on 28 June and 28 July 2010, respectively.

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 the informed consent document and form 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 document and form for obtaining consent for the pharmacokinetic (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 investigators obtained voluntary consent of the volunteers in writing upon full understanding of the contents of both informed consent document and form 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 document and form for obtaining informed consent and keep one copy each. When the study site personnel other than the principal investigator 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, 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 and verified their will as to whether or not to remain in the study, and document such a fact with the date of confirmation. 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/form such as the case of obtaining new important information that might have been related to the subjects' consent, the principal investigator were promptly to amend the informed consent document/form and obtain approval of the Ethics (Institutional) Review Committee.

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

In Korea, back-up sample tubes for gene test were cracked while they were stored at -60°C in the deep freezer. Upon the verbal approval, 8 subjects were requested for re-blood sampling. At the time of audit, it was recommended to record subjects' consent or obtain written consent. To cope with it, the principal investigator created file note to submit the sponsor and IRB.

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 the 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

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<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, MD21201, 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
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<China>
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<US>
Jay Piliponskiy, Odunayo Obisesan
SNBL Clinical Pharmacology Center, Inc.
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TEL: +1-410-706-8763 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 investigator at each study site was 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

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Responsible person: Hideto Ushijima

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Responsible person: Li Lei

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CMIC Korea Co. Ltd

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

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Responsible person: Mira Park

<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