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

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, 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
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, MD21201, USA
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

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: +82-2-3708-3692 FAX: +82-2-3789-6900

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

<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, 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: Masahiro Utoh

[Duties]

· To measure plasma and urine drug concentrations.

Summary of the safety data

<Japan, Korea and China>

CMIC Korea Co., Ltd.

Address: #702 Hanseong Bldg. 47-2 Seosomun-dog, 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.

Simvastatin, used as a study drug in this study, is a statin-type antihyperlipidemia drug which has been already marketed in all the countries. Its dosage is different, depending on countries, and the initial dose is 5 mg/day and maximum dose is 20 mg/day in Japan, while the initial dose range is 20-40 mg/day in Korea, China and US. The initial doses in those countries are four times higher than that in Japan. The PK characteristics of simvastatin are as follows; Simvastatin is a prodrug, showing its pharmacological activity by changing to an open acid form in liver in humans. Simvastatin is metabolized mainly by CYP3A4/5 in the intestinal tract/liver, and its metabolites show their pharmacological activity, too. The PK parameters of unchanged simvastatin can be affected by functional change of CYP3A4/5 or OATP1B1 etc., drug transporters involved in hepatic uptake. Oral bioavailability is low, less than 5% as an open acid form. The elimination rate is about 60% in the feces and about 13% in urine, considered that simvastatin is mainly eliminated in bile. Comparison of existing PK data by the statistic process combining the results in Japanese and Western populations showed a large difference in the PK of simvastatin between Japanese and Western populations, but information on PK of simvastatin in East Asian populations is insufficient due to the lack of the data on Chinese and Korean. Considering these

backgrounds, we decided to obtain the data on East Asian populations and conduct a clinical PK study, according to the same protocol, in East Asian populations and Caucasian population (as a reference), to examine the difference in PK of simvastatin among these populations.

8. STUDY OBJECTIVES

To investigate whether or not there are ethnic differences in the PK of simvastatin in healthy adult Japanese, Chinese, Korean and Caucasian male subjects based on the same protocol among the four countries.

9. INVESTIGATIONAL PLAN

9.1 Overall Design and Plan Description

This was conducted as an open-label, single administration study in which 40 healthy adult male subjects for each country (160 subjects in total in Japan, China, Korea and the US) aged 20-35 were to receive a single oral dose of 20 mg of simvastatin.

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

One 20-mg tablet of the study drug 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. The subjects were to drink of soft mineral water (hardness <100, Volvic® etc.) up to 500 mL during a period from 2 to 4 hours after administration. The soft mineral water was given during the study period.

Food intake was not allowed up to 4 hours after administration.

The calories and the balance of three major nutrients (protein, fat, carbohydrate balance: 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.

Blood sampling for assay of simvastatin and its open acid form (major active metabolite), and safety assessments including vital sign measurements, and clinical laboratory tests (hematology, blood biochemistry and urinalysis) were to be performed at pre-determined times during the study period. AEs were to be monitored throughout the study. Following the study period subjects were to undergo a final follow up assessment. Detailed items of the study evaluations are given in Section 9.5.

Gene analysis for polymorphism of CYP3A4, CYP3A5, ABCB1, OATP1B1 and ABCG2 related to the PK of simvastatin were to be obtained for each subject 24 hours after simvastatin 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 simvastatin, it was carried out as an open-label study with no control group.

9.3 Selection of Study Population

In Japan, China and Korea, the nationalities of the subjects were to be the same as those of grandfathers, grandmothers, father and mother. In China, only the Han race was eligible. In the US, only European Caucasian was eligible.

In this study, subjects were healthy adult male volunteers who satisfied all of the following "9.3.1 Inclusion Criteria" and none of the following "9.3.2 Exclusion Criteria".

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 investigator to be healthy in the screening test and eligible for the study.

[Rationales for selection]

1) The criterion was selected by giving ethical consideration to the study.
2) For voluntary participation in the study, the age was set at 20 years or older at which individual consent is legally established, and the upper limit of age was specified at 35 years for minimizing variations in laboratory values and changes in PK.
3) The criterion was chosen for further reducing interindividual changes.

4) Because the subjects are healthy adults, the criterion was specified for excluding people who are unsuitable for study enrollment in terms of health.

9.3.2 Exclusion Criteria

1) Organopathy involving the heart, lung, liver and/or kidney etc.
2) A history of diseases involving the heart, lung, kidney, blood (such as coagulation system disorder), central nervous system and metabolic system that may interfere with the study.
3) Hypothyroidism, genetic myopathy or family history of it, history of drug-induced myopathy.
4) Hypersensitivity or allergies to drugs and food etc. (Particularly, a history of allergy to or adverse reactions associated with statin-type antihyperlipidemia drugs.)
5) Oral administration of drugs such as over-the-counter drugs within 1 week prior to the study drug administration, or taking any kind of health food/supplement, grapefruit, drink/food containing grapefruit from 2 week prior to the study drug administration to the day 2, or taking any kind of fruit juice, drink containing caffeine or green tea from 1day before the study drug administration to the day 2, or the necessity for using other medications before study completion.
6) Smokers or a smoking history within the last 6 months. (The cotinine test is performed, if necessary.)
7) Drug abuse or suspicion of drug abuse. (The drug screening test is performed, if necessary.)
8) Alcohol drinkers (daily alcohol intake* of 50 g or more).

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

   Example: When drinking 1000 mL of beer (alcohol content: 5.5%), alcohol intake = 0.055 × 1000 × 0.8 = 44 g
9) 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.
10) Blood sampling of 200 mL or more within 1 month prior to study drug administration, blood component donation (plasma or platelet) within 2 weeks, or blood collection of 400 mL or more within 3 months.

11) Participation in a Phase I study of a drug containing a new active ingredient within 4 months prior to study drug administration or another clinical study within 3 months, and being administered the investigational drug (within 1 month prior to study drug administration for a patch test). However, even if the period is longer than these, those who are determined to be not eligible for enrollment in the study in consideration of the characteristics of the previous investigational drug.
12) Those who are determined by the investigator to be not suitable as subjects of the study.

[Rationales for selection]

1) to 4) The criteria were specified for subject safety assurance.
5) to 9) The criteria were selected for safety assurance and because they might interfere with PK analysis and safety evaluation.
10) The criterion was specified for taking subjects' safety and ethics into consideration and satisfying the criteria for blood donation organized by the Study Group on Blood Donation (healthy adult men: 400 mL per donation, blood sampling interval: 3 months or more, total annual amount of blood sampling: 1200 mL or less, number of donations: 3 or less).
11) The criterion was set to exclude the influence of drugs having interactions with the study drug and long-acting drugs and take subjects' safety and ethics into consideration.
12) The criterion was chosen for the principal investigator to be able to make determination in consideration of overall factors.

9.3.3 Removal of Subjects from Therapy or Assessment

Discontinuation/withdrawal criteria

Subjects, who met any of the following criteria, were to be withdrawn or dropped out from the study:

1) When the subject requests to withdraw from study participation after providing informed consent.
2) When the investigator determined that the subject is incapable of respecting the protocol.
3) When the principal investigator judged that the study should be discontinued.

(When the subject clearly developed a fever (37.5°C or higher), when the subject is affected by serious acute disease, etc.)

[Rationales for selection]

1) The criterion was set from the perspective of respecting the subject's free will.
2) The criterion was specified for giving consideration to subjects' safety.
3) The criterion was selected for the investigator to be able to determine the discontinuation of study drug administration in consideration of overall factors.

Procedures for discontinuation/withdrawal

1) When discontinuing the study, the principal investigator was promptly to explain such a fact to the subject (when the subject requested to terminate the study, the principal investigator was to check the detailed reason whenever possible). The principal investigator was also to enter information such as the timing of discontinuation/withdrawal and reason in the CRF.
2) When discontinuing the study or withdrawing the subject from the study after study drug administration, the principal investigator was to perform observation in accordance with the Section "9.5.2 Evaluation items for the safety endpoints" (however, "9.5.2.5 Body weight" was excluded). Blood sampling for measurements of plasma drug concentrations of the subjects with discontinuation/withdrawn after administration was to be carried out 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) When the drop outs took place by discontinuation or withdrawal, additional subjects were not to be recruited.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were to receive a single oral dose, administered as a film-coated tablet containing 20 mg of simvastatin.

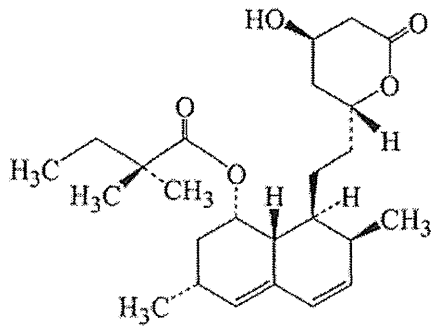
The tablet was administered with 150 mL of soft mineral water (hardness<100, Volvic® etc.). Administration of simvastatin tablet was only performed by authorized members of each study site staff.

9.4.2 Identity of Study drug

Simvastatin is a compound inhibiting 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, developed by Merck USA, in 1979. Simvastatin, since approval in Sweden in 1988, is approved as an oral drug in 117 or more countries in March, 2010. Simvastatin is a prodrug (inactive form) and its active form is an open acid form.

The product of simvastatin (single lot) that was manufactured by Merck China and marketed in China was used in every study site.

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

Brand name	ZOCOR®
Indications	Hyperlipidemia, Coronary heart disease, Pediatric patients with heterozygous familial hypercholesterolemia
Active ingredient:	
[Nonproprietary name]	Simvastatin
[Chemical name]	(+)-(1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl 2,2-dimethylbutanoate
[Chemical structure]	
[Molecular formula]	$C_{25}H_{38}O_5$
[Molecular weight]	418.57
[Storage condition]	store at room temperature

The lot number and expiry date were as follows:

	Lot number	Expiry date
20 mg tablets	107093	05 February 2013

9.4.3 Control/Storage of the study drug

The executive investigator provided the study drug that is sold in China and entrusted the control and storage of the study drug to the storage personnel at the study site. The study drug was delivered, controlled and collected in accordance with the "Procedure for Control of the Study Drug" provided by the executive investigator. When the study was completed, the study drug storage personnel took a count of the remaining study drug. The study drug storage personnel discarded or disposed study drug after destruction under the direction of the principal investigator following the standard procedure at the study site.

9.4.4 Methods of Assigning Subjects to Treatment Groups

Subject Identifier (9 digits) was consisted of the study site code (Japan: 00001, China: 00002, Korea: 00003 and the US: 00004) and the number that was anonymized and linkable to the subject.

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 20 mg, with which the plasma concentrations of the unchanged simvastatin (inactive form) and its open acid form (active form) can be measured for a sufficient period of time, was selected.

9.4.6 Blinding

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

9.4.7 Prior and Concomitant Therapy

Coadministration of any drugs was prohibited during a period from 1 week before study drug administration to study completion.

When they were used due to inevitable reasons such as treatment of AEs, the principal investigator were to enter information such as the name, dosage/administration, duration of use and purpose of use of the drug in the CRF.

9.4.8 Management of subjects

9.4.8.1 Screening

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

9.4.8.2 Day before the study drug administration to 2 days after administration

The principal investigator hospitalized the subjects by 16:30 on the day before the study drug administration. The subjects were kept fasted from after having a dinner on the day of hospitalization to 4 hours after the study drug administration. On the day of administration, after performing tests such as the physical examination, laboratory test, vital signs (blood pressure, pulse rate and body temperature), and blood sampling for measurements of drug concentrations before administration, the study drug administration was started sequentially at 9:00 am. Thereafter, blood sampling for tests and measurements of drug concentrations was implemented in accordance with the study schedule.

On Day 2, the investigators conducted physical examination, blood sampling for measurements of drug concentrations, and blood sampling for gene analysis for polymorphism of the CYP3A4, CYP3A5, ABCB1, OATP1B1 and ABCG2 related to the PK of simvastatin. After confirming that there was no safety (health condition) problem, the investigator discharged the subjects from the hospital. However, when safety assurance was determined to be necessary, the principal investigator was to prolong the hospitalization period and carry out a re-examination or additional examination to