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Responsible person: Angela Murphy
[Duties]
・ To measure samples for hematology, blood biochemistry and urinalysis.

Gene polymorphism test facility
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Address: 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
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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>

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Responsible person: Tomoka Inoue Davidsen

[Duties]

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

Statistical analysis

<PK and polymorphism>

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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.

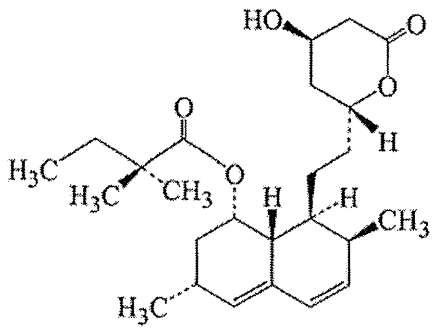
The tablet was administered with 150 mL of soft mineral water (hardness<100, Volvic® etc.). Administration of simvastatin tablet was only performed by authorized members of each study site staff.

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

implement a follow-up investigation. In such a case, the details of the actions taken were to be recorded in 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.

9.5 Pharmacokinetic and Safety Evaluations

9.5.1 Procedure for Study Implementation

9.5.1.1 Screening

Subjects were screened within 30 days of admission. The investigators performed the screening test in subjects who provided written informed consent. Observation and tests listed in Table 9-1 were implemented as the screening test to verify whether the subjects were eligible for the study. The investigators also recorded the details in the CRF.

Table 9-1 Observation and tests at screening

Subject background and characteristics	Sex, height, body weight/BMI, birth day/month/year, current health condition, history of drug allergy, medical history, and smoking/drinking habits
Clinical observation	Physical examination by the investigator
Hematology	White blood cell count (WBC), differential WBC, red blood cell count (RBC), hemoglobin concentration, hematocrit value, platelet count and reticulocyte count
Blood biochemistry	Blood sugar, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, total protein, albumin, uric acid, creatinine, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, LDH, ALP, CK, Na, K, Cl and CRP
Urinalysis	Glucose, bilirubin, ketone bodies, occult blood, pH, protein, urobilinogen and sediment (to be conducted if protein or occult blood is positive)
Vital signs, electro-cardiography	Blood pressure/pulse rate (sitting), body temperature and 12-lead electrocardiography (ECG)
Infectious disease test	HBs antigen, HCV antibody, serologic tests for syphilis and HIV antibody

[Rationales for selection of observation and tests]

General items, which are found to be necessary for verification of the health condition of subjects to be enrolled in the study, were adopted. The infectious disease test was specified for the purpose of the prevention of infection to personnel handling blood.

9.5.1.2 Study

The investigators performed the observation and tests listed in Table 9-2 in the subjects, who provided consent for study participation, in accordance with the study schedule in Table 9-3.

Table 9-2 Observation and tests during the study

Clinical observation	Physical examination by the investigator
PK	Plasma drug concentrations
Hematology	WBC, differential WBC, RBC, hemoglobin concentration, hematocrit value, platelet count and reticulocyte count
Blood biochemistry	Blood sugar, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, total protein, albumin, uric acid, creatinine, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, LDH, ALP, CK, Na, K, Cl and CRP
Urinalysis	Glucose, bilirubin, ketone bodies, occult blood, pH, protein, urobilinogen and sediment (to be conducted if protein or occult blood is positive)
Vital signs, body weight measurement	Blood pressure/pulse rate (sitting), body temperature and body weight
Gene polymorphism examination	Collected blood specimens (e.g., EDTA-2Na Added) was refrigerated at -60°C or less, and sent to the institute for gene polymorphism analysis using dry ice within 2 weeks after sampling, if possible.

Table 9-3 Study Schedule

		Screening	Study												
Date of study		Within 30 days	Day -1	Day 1											Day 2
Time			Admission by 16:30	8:00	9:00	9:30	10:00	10:30	11:00	12:00	13:00	14:00	15:00	17:00	21:00	9:00
Time after oral administration (h)				-1	0	0.5	1	1.5	2	3	4	5	6	8	12	24
Admission/visit		Visit	Admission	←												→
Informed consent		○														
Subject background characteristics		○														
Study drug administration					○											
Physical examination by the investigator		○		○												○
Body weight		○		○												○
Height		○														
Vital sign		○		○												○
12-lead electrocardiography		○														
Adverse event			←													→
Blood sampling	Gene polymorphism examination															○[a)]
	Pharmacokinetics			○		○	○	○	○	○	○	○	○	○	○	○
	Laboratory test	○		○												○
	Infectious disease test	○														
Urine sampling	Laboratory tests	○		○												○

Meal time during hospitalization: Morning of Day 1 was the fast. Meal time was to be free except for the following:

One day before administration (at 19:00 on Day -1)

Day of administration (Day 1: Having a lunch after completion of blood sampling and tests at 4 hours after administration)

One day after administration (Day 2: Having a breakfast after completion of blood sampling and tests at 24 hours after administration)

a): Collected specimens (e.g., EDTA-2Na Added) was refrigerated at -60°C or less, and sent to the institute for gene polymorphism analysis using dry ice within 2 weeks after sampling, if possible.

9.5.2 Evaluation Items for the Safety Endpoints

9.5.2.1 Subjective Symptoms and Their Verification

1) Tests: Subjective symptoms occurred during the hospitalization period and their verification
2) Test timing: Hospitalization period
3) Test method: For subjective symptoms during the hospitalization period, the subject documented the presence or absence of symptoms, type, onset time and resolution time in the specified recording form accordingly. The principal investigator or investigator performed history taking based on this record and filled out the CRF.

9.5.2.2 Physical Examination Findings (History Taking and Phonacoscopy)

1) Tests: History taking and phonacoscopy
2) Test timing: Before administration, and 24 hours after administration
3) Test method: The principal investigator or investigator verified the presence or absence of abnormal physical findings based on history taking and recorded physical examination findings in the CRF.

9.5.2.3 Clinical Laboratory Evaluation

9.5.2.3.1 Hematology

1) Tests: WBC, differential WBC (neutrophil ratio, lymphocyte ratio, monocyte ratio, eosinophil ratio and basophil ratio), RBC, hemoglobin concentration, hematocrit value, platelet count and reticulocyte count
2) Blood sampling points: Before administration and 24 hours after administration
3) Evaluation method: "H" was to be entered in the CRF when a value deviated from the upper limit of normal, and "L" was to be entered when a value deviated from the lower limit. In addition, the judgment of abnormality change and grading were to be performed.

9.5.2.3.2 Blood Biochemistry

1) Tests: Blood sugar, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, total protein, albumin, uric acid, creatinine, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, LDH, ALP, CK, Na, K, Cl, and CRP
2) Test timing: Before administration and 24 hours after administration
3) Evaluation method: "H" was to be entered in the CRF when a value deviated from the upper limit of normal, and "L" was to be entered when a value deviated from the lower limit. In addition, the judgment of abnormality change and grading was to be performed.

9.5.2.3.3 Urinalysis

1) Tests: Glucose, bilirubin, ketone bodies, occult blood, pH, protein, urobilinogen and sediment (To be performed when protein or occult blood is positive)
2) Test timing: Before administration and 24 hours after administration
3) Evaluation method: "H" was to be entered in the CRF when a value deviated from the upper limit of normal or the result is positive, and "L" was to be entered when a value deviated from the lower limit. In addition, the judgment of abnormality change and grading were to be performed.

9.5.2.4 Vital Signs

1) Tests: Blood pressure, pulse rate and body temperature
2) Test timing: Before administration and 24 hours after administration
3) Test method: Body temperature was to be measured in the same way at the site (axillary, ear, oral or sublingual). Blood pressure and pulse rate were to be measured in the sitting position.
4) Evaluation method: When a clinically significant change was confirmed as compared with baseline, it was to be written in the CRF as AE.

9.5.2.5 Body Weight

1) Test: Body weight measurement
2) Test timing: Before administration and 24 hours after administration
3) Test method: Body weight (net) was to be measured and recorded in the CRF.

9.5.2.6 Number and Amount of Blood Sampling in the Entire Study

Total number of blood sampling per subject: 13

<Details of the number and amount of blood sampling>

	Infectious disease test	Laboratory test	Polymorphism examination[a)]	PK[b)]	Total
Japan	2 mL (2 mL×1)	27 mL (9 mL×3)	14 mL (14 mL×1)	84 mL (7 mL×12)	127 mL
China	3 mL (3 mL×1)	21 mL (7 mL×3)	14 mL (14 mL×1)	96 mL (8 mL×12)	134 mL
Korea	0 mL[c)]	21 mL (7 mL×3)	14 mL (14 mL×1)	84 mL (7 mL×12)	119 mL
US	8.5 mL (8.5 mL×1)	36 mL (12 mL[d)]×3)	14 mL (14 mL×1)	84 mL (7 mL×12)	142.5 mL

a): Including back-up samples (12 mL when a 6 mL syringe for specimens)
b): Including back-up samples
c): Not necessary since the specimen for the screening was used (Korea)
d): Details: Hematology 3.5 mL per test, Blood biochemistry 8.5 mL per test (US)

[Rationales for selection of the tests 9.5.2.1 to 9.5.2.5]

9.5.2.1: They were selected to verify a subjective symptom as AE and a symptom objectively observed by a doctor.

9.5.2.2: They were selected to verify AEs in a medical examination by a doctor.

9.5.2.5: They were selected to calculate the PK parameters normalized to dose per body weight.

9.5.2.1 to 9.5.2.5: They were adopted as general items found to be necessary for verification of the subjects' health condition in a clinical study in healthy adults.

9.5.2.7 Adverse Events

All clinical AEs were to be monitored throughout the entire study period.

9.5.2.7.1 Definitions

An AE was defined as any unfavorable and unintended sign, symptom or disease newly occurred after administration of the study drug, regardless of the causal relationship with the study drug.

However, signs or symptoms, which had been present before study drug administration and did not significantly worsen, were not considered to be AEs.

A serious AE was defined as any unfavorable medical occurrence in the subjects during the study period that

1) resulted in death,
2) was life-threatening,
3) required inpatient hospitalization or prolongation of existing hospitalization,

4) resulted in persistent or significant disability / incapacity,
5) was a congenital anomaly / birth defect, or
6) was any other significant medically

Adverse reactions were defined as AEs occurred for which the causal relationship with the study drug could not be ruled out.

9.5.2.7.2 Assessment of AEs

• Physical examination

At each physical examination during the hospitalization period, the investigators were to determine the presence or absence of abnormality. When it was assessed as "with abnormality," the investigators were to document its details as an AE in the CRF.

• Vital signs

The investigators were to review the contents of vital signs during the hospitalization period and assess AEs based on medical judgment of each country.

• Laboratory values

In the study, laboratory values referred to hematology, blood biochemistry and urinalysis.

When determining whether or not laboratory values were abnormal, it was to be made based on whether or not they were values deviated (abnormal values) from the normal specified at the study site or the laboratory center. The grade of the abnormal value were to be rated in accordance with the scale of Division of AIDS (DAIDS) AE grading table (see "Protocol 22 Appendix 1") issued by National Institute of Allergy and Infectious Disease (NIAID).

When laboratory values were not listed in the scale of DAIDS AE grading table, the following grade was used.

Mild: (Grade 0); The value was deviated from the normal ranges at the site, but the value did not satisfy the Grade 1 of DAIDS grading. (Grade 1); A sign or symptom was present, but did not interfere with the subject's daily activities and did not require treatment.

Moderate: (Grade 2); An event that interfered with the subject's daily activities because of discomfort, or affected the clinical condition and required treatment.

Severe: (Grade 3, Grade 4); An event by which the subject was unable to conduct daily activities or significant clinical effects were observed.

The grade of abnormal value was written in the CRF.