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, 526100, 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: Masayuki Mogi

[Duties]

- To measure plasma drug concentrations.

Summary of the Safety Data

<Japan, Korea and China>

CMIC Korea Co., Ltd.

Address: #702 Hansan Bldg. 47-2 Seosomun-dong, 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.

Meloxicam, the study drug in this study, is an oxicam non-steroidal anti-inflammatory drug (NSAID) that has been already commercialized in each country. The routine dose is 7.5 mg/day in Korea, China, and the US, while 10 mg/day in Japan, but the maximum dose is 15 mg/day in each country. For PK characteristics, the absolute bioavailability is high in oral administration, 89% to 97%, mainly metabolized by metabolic enzyme (CYP2C9) to inactivated drug, and unchanged drug is rarely eliminated in urine or feces. The elimination rate is 42.8% and 47% in urine and feces, respectively. Tokin group compared ethnicity differences by the uniform statistical process, showing similar results in Japanese, Koreans, and Europeans, but those in Chinese were different from others in drug disposition. However, there were differences in the protocol conducted in the countries (for example, the dosage form used in the study was different), and therefore, no obvious conclusions have been obtained yet. With these backgrounds, we decided to conduct a clinical PK study, conforming to the same protocol, with Caucasians, as a control, to examine ethnicity differences between East Asian ethnic groups.

8. STUDY OBJECTIVES

Presence/absence of ethnicity differences in PK in Japanese, Chinese, and Korean healthy adult males was examined between three countries, using meloxicam that had been already commercialized, based on the same protocol. As a control, a clinical study based on the similar protocol was conducted in European Caucasians residing in the US.

9. INVESTIGATIONAL PLAN

9.1 Overall Design and Plan Description

This was conducted as an open-label, single administration study in which 30 healthy adult male subjects for each country (120 subjects in total in Japan, China, Korea and the US) aged 20-35 were to receive a single oral dose of 7.5 mg of meloxicam.

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

Single dose of one 7.5-mg tablet of meloxicam was administered with 150 mL of soft mineral water (less than 100 of hardness, Volvic® etc.) after 10 hours or more fasting. Water intake was prohibited within 2 hours after administration of the study drug, and 500 mL or less soft mineral water (less than 100 of hardness, Volvic® etc.) was taken from 2 hours after administration to within 4 hours after administration.

Food intake was prohibited within 4 hours after administration of the study drug. Since then, water to be taken in the study was soft mineral water in any cases (less than 100 of hardness, Volvic® etc.).

Calories and balance of three main nutrients (protein-fat-carbohydrate [PFC] balance) of the supper on the previous day and lunch/supper on the day of administration of the study drug were equalized wherever possible between the countries.

Blood sampling for assay of meloxicam, and safety assessments including both vital sign measurements and clinical laboratory tests (hematology, blood biochemistry and urinalysis) were to be performed at pre-determined times during the study period.

Adverse events (AEs) were to be monitored throughout the study. Following the study period subjects were to undergo a final follow up assessment. A detailed account of the study evaluations is given in Section 9.5.

Gene polymorphism of the metabolic enzyme (CYP2C9) involved with PK of meloxicam was to be analysed for each subject 72 hours after meloxicam 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 meloxicam, it was carried out as an open-label study with no control group.

9.3 Selection of Study Population

In Japan, China and Korea, persons whose paternal and grandparents had their own country's citizenship were eligible. For Chinese, only Han people were included. In the US, European Caucasians were included.

In the study, among the above candidates, healthy adult male candidates who met all of the following "9.3.1 Inclusion Criteria" and did not meet any of "9.3.2 Exclusion Criteria" were to be targeted.

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

[Rationales for setting]

1) It is defined, considering the ethnic of this study.
2) Based on the premise that subjects participate voluntarily in the study, persons of 20 years or above from whom first-person consent can be legally obtained were

included, and the upper limit of age was set to be 35 years of age so that variability of test values and PK variations can be minimized.

Females were not included in the study for the following reasons;

- Ethically, women who can be pregnant should not be exposed to risks.
- If females are included in the study, it will become more difficult to recruit participants because the inclusion and exclusion criteria become more rigid.
- It will become difficult to compare PK profiles between the ethnic groups if male / female ratio is difficult between them.

3) It is defined to reduce variations between individuals.
4) Since healthy adults are targeted, it is defined to exclude persons who are inappropriate for the study from the viewpoint of health.

9.3.2 Exclusion Criteria

1) Organopathy involving the heart, lung, liver and/or kidney etc.
2) Persons with diseases of heart, lung, kidney, blood (such as coagulation system disorder), central nervous system, metabolic system, peptic ulcer, inflammatory enteropathy, hypertension, asthma, and diseases of skeletal muscles etc. and those with a history of any of the above diseases.
3) Persons with hypersensitivity or allergy to drugs, foods, etc. [Particularly, persons with allergy to or adverse effects related to NSAIDs and salicylic acid (aspirin, etc.) or those with a history of any of the above allergy or adverse effects]
4) Persons who have received any of other drugs, such as OTC drugs, health food or supplements from 1 week prior to the study drug administration to the completion of the study (Day 4).
5) Persons who are smoking or those have stopped smoking in 6 months (the cotinine test is conducted if necessary).
6) Persons who are drug-dependent or those suspected to be drug-dependent (drug screening is conducted if necessary).
7) Habitual alcohol drinkers (persons with 50 g or more of alcohol intake* per day)

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

Example: when drinking 1000 mL of beer (Alcohol content: 5.5%)

Alcohol intake = 0.055 × 1000 × 0.8 = 44 g

8) 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.
9) Persons who underwent 200 mL or more of blood collection within one month, blood component donation (plasma or platelet) within two weeks or those who underwent more than 400 mL of blood collection within 3 months before administration of the study drug.
10) Persons who participated in a phase I study on drugs containing new active ingredient within 4 months, or those who participated in other studies and received administration within 3 months, before administration of the study drug (For patch test, those who received within one month before administration of the study drug). And persons who participated in any of the above studies and received administration outside the defined period shall also be excluded, if determined to be inappropriate for participation in the study, considering the characteristics of the previous investigational product.
11) Other persons determined by the principal investigator to be inappropriate for the study

[Rationales for selection]

1) to 3) It is defined to secure subjects' safety.
4) to 8) It is defined to secure safety and prevent possibility of effects on PK analysis and safety evaluation.
9) It is defined, considering safety and ethics for subjects, so that blood donation criteria, summarized by the blood donation study group, might be met (healthy adult males; 400 mL per collection, 3 months or more of an interval between collections, 1200 mL or less of annual total amount of blood collection, 3 times or less of blood collection).
10) It is defined, considering safety and ethics for subjects, to exclude effects of drugs having interactions with the study drug or long-acting drugs.
11) It is defined so that the principal investigators for the study can determine the results, considering general factors.

9.3.3 Removal of Subjects from Therapy or Assessment

Discontinuation/withdrawal criteria

Subjects who met any of the followings were to be discontinued or withdrawn from the study;

1) When the subject requests himself/herself withdrawal from participation in the study after consent obtainment.
2) When the principal investigator determines that the subject cannot observe the protocol.
3) Others (when the principal investigator determines that the study should be discontinued)

[Obvious fever (37.5°C or more), onset of serious acute diseases, etc.]

[Rationales for setting]

1) It is defined, respecting for subjects' own free will.
2) It is defined to secure safety of subjects.
3) It is defined so that the principal investigators could determine discontinuation of administration of the study drug, considering general factors.

Procedures for discontinuation/withdrawal

1) When the study was discontinued, the principal investigator immediately informed the subject accordingly (When the subject requested discontinuation of the study, detailed reasons were to be confirmed wherever possible). The time of discontinuation/withdrawal, reasons, etc. were to be entered to the CRF.
2) When the study was discontinued or withdrawn after administration of the study drug, the principal investigator was to perform observation, conforming to Section "9.5.2. Evaluation items for the safety endpoints" (however, "9.5.2.5 Body weight" was excluded)." For subjects who were discontinued or withdrawn from the study, blood collection for plasma concentration measurement after administration was to be performed 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) For discontinued cases or withdrawals, the relevant subjects were not to be replaced.

9.4 Treatments

9.4.1 Treatments Administered

Subjects received a single oral dose of a tablet containing 7.5 mg of meloxicam. The tablet was administered with 150 mL of soft mineral water (less than 100 of hardness, Volvic® etc.). Administration of meloxicam tablet was only performed by authorized members of each study site staff.

9.4.2 Identity of Investigational Products

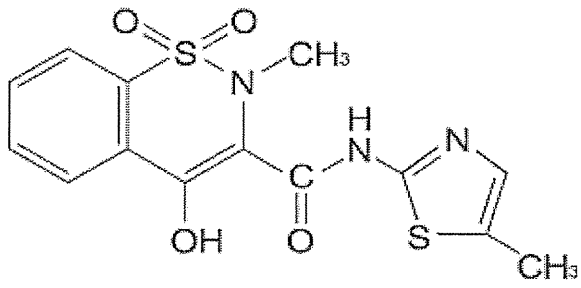
Meloxicam is a NSAID, developed by Boehringer Ingelheim GmbH, with chemical formula of oxicam, which selectively inhibits cyclooxygenase-2. Meloxicam was launched in Europe in 1996, and currently sold in 100 or more countries in the world.[1)]

In this study, meloxicam (single batch) that was manufactured by Boehringer Ingelheim Shanghai Pharmaceuticals Co., Ltd. and sold in China was used.

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

Brand name	Mobic®
Indications	Anti-inflammation and pain relief for the following diseases and symptoms: Osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis
Active ingredient	
[Nonproprietary name]	Meloxicam
[Chemical name]	4-Hydroxy-2-methyl- N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

[Chemical structure]



[Molecular formula] $C_{14}H_{13}N_3O_4S_2$

[Molecular weight] 351.40

[Content and dosage form]

A slight yellow tablet containing 7.5 mg of meloxicam

[Storage condition] Meloxicam was stored at 30°C or less in a light-resistant airtight container, and prevented moisture absorption after opening.

The batch number and expiry date were as follows:

	Batch number	Expiry date
7.5 mg tablets	084081	January 2015

Source: Appendix 5 (Certificate of Analysis)

9.4.3 Management and storage of the study drug

The executive investigator delegated management and storage of the drug sold in China, as the study drug, to the storage manager of each study site. Delivery and management of the study drug were performed, according to the "The study drug shipping and handling procedure", provided by the executive investigator. For residual study drug after completion of the study, after indicated by the principal investigator, the storage manager confirmed the quantity of the residual drug and discarded or disposed them after destruction, according to the procedures of the study site.

9.4.4 Methods of Assigning Subjects to Treatment Groups

Subject Identifier (9 digits) was consisted of 5-digit study site code (Japan: 00001, China: 00002, Korea: 00003 and the US: 00004) linked with anonymous 4-digit subject identification code. Following confirmation of eligibility on admission, subjects were assigned numbers from 0001 – 0030 in each study site.

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 7.5 mg, with which the plasma concentrations of the unchanged meloxicam could be measured for a sufficient period of time, was adopted.

9.4.6 Blinding

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

9.4.7 Prohibited Concomitant Medications

Concomitant use of meloxicam with any other drugs was prohibited from one week before administration of the study drug to completion of the study (Day 4: discharge).

When any of other drugs was concomitantly used for any compelling reasons, such as treatment of AEs, the principal investigator was to enter the name, dosage/ administration, duration of use, objective of use, etc. of the relevant drug to the CRF.

9.4.8 Management of subjects

9.4.8.1 Screening

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

9.4.8.2 Previous day of administration of the study drug (Day -1: admission) to the 4th day after administration (Day 4: discharge)

The principal investigator admitted the subject to the hospital before about 16:30 on the previous day of administration of the study drug. The subject was fasted after having supper on the day of admission to 4 hours after administration of the study drug. On the day of administration, after completion of physical examination by the physician, laboratory test, tests including vital signs (blood pressure, pulse rate, temperature) and blood collection for drug concentration measurement prior to administration, administration of the study drug were started subsequently from 9:00 am. After that, the defined tests and blood collection for drug concentration measurement were performed, according the study schedule.

On Day 4 of administration, the researcher discharged all subjects from the hospital after completing the defined tests, blood collection for drug concentration measurement and blood collection for detection of gene polymorphism for CYP2C9 involved with PK of meloxicam and confirming absence of safety problems (health condition). However, when safety securing was determined to be necessary, hospitalization of the relevant subject was to be prolonged, and re-test or additional test was to be performed as a follow-up investigation. In this case, measures taken were to be entered to 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		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
Laboratory tests	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, electrocardio-graphy (ECG)		Blood pressure/pulse rate (sitting), body temperature, and 12-lead 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
Laboratory tests	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-2K added) was refrigerated at -20°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	Primary Study														
Days of the study		Within 30 days	Day -1	Day 1									Day 2		Day 3		Day 4
Time			Admitted by 16:30	8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	17:00	21:00	9:00	21:00	9:00	21:00	9:00
Time after oral administration (h)					0	1	2	3	4	5	6	8	12	24	36	48	60	72
Admission/visit		Visit	Admission	←														→
Consent obtainment		O																
Subject backgrounds		O																
Administration of Study drug					O													
Physician's examination		O		O								O		O		O		O
Body weight		O		O														O
Body height		O																
Vital sign		O		O										O		O		O
12-lead ECG		O																
Adverse events			←															→
Blood sampling	Detection of gene polymorphism[a)]																	O
	PK[b)]			O		O	O	O	O	O	O	O	O	O	O	O	O	O
	Laboratory test	O		O														O
	Infectious disease test	O																
Urinalysis	Laboratory test	O		O														O

Mealtime during hospitalization: Breakfast was not taken on the day of administration and mealtimes other than the followings were defined, according to the rules of each site.
One day before administration (Day -1: Approx. 19:00)
Dosing day (Day 1: Lunch was taken after completion of the defined tests and blood collection performed 4 hours after administration)
The 2nd day of dosing (Day 2: Breakfast was taken after completion of the defined tests and blood collection performed 24 hours after administration.)
The 3rd day of dosing (Day 3: Breakfast was taken after completion of the defined tests and blood collection performed 48 hours after administration)
The 4th day of dosing (Day 4: Breakfast was taken after completion of the defined tests and blood collection performed 72 hours after administration.)

a): Collected blood samples (EDTA-2K added) were stored under -20°C or less in a frozen state. The samples were transported in dry ice to the testing site detecting gene polymorphism within 2 weeks after collection wherever possible.

b): Plasma samples for PK were stored under -20°C in a frozen state. The samples were transported in dry ice to the measuring site as rapidly as possible.

9.5.2 Evaluation Items for the Safety Endpoints

9.5.2.1 Subjective Symptoms and Their Confirmation

1) Test items: Subjective symptoms that appeared during hospitalization and their confirmation
2) Test period: During hospitalization
3) Test method: For subjective symptoms during hospitalization, the subject recorded as needed, presence/absence, type, onset time and elimination time of symptoms in the defined sheet. Based on the record, the principal investigator and researcher performed inquiry and recorded the results in the CRF.

9.5.2.2 Physical Examination Findings (Inquiry, Auscultation Percussion)

1) Test items: Inquiry, auscultation, and percussion
2) Test period: Prior to, 8, 24, 48, and 72 hours after administration
3) Test method: The principal investigator and researcher confirmed presence/ absence of abnormal physical findings, by inquiry, auscultation, and percussion, and recorded physical examination findings in the CRF.

9.5.2.3 Clinical Laboratory Evaluation

9.5.2.3.1 Hematology

1) Test items: WBC, differential count of leukocytes (neutrophil ratio, lymphocyte ratio, monocyte ratio, eosinophil ratio, basophil ratio), RBC, hemoglobin, hematocrit, platelet count, and reticulocyte count
2) Blood collection time: Prior to and 72 hours after administration (Time allowance: ±1 hour)
3) Evaluation method: "H" was added to values deviated from the upper limit of baseline, and "L" was added to those deviated from the lower limit of baseline. In addition, for deviations, grade and abnormal changes were determined.

9.5.2.3.2 Blood Biochemistry

1) Test items: Blood glucose, 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, CRP
2) Test period: Prior to and 72 hours after administration (Time allowance: ±1 hour)
3) Evaluation method: "H" was added to values deviated from the upper limit of baseline, and "L" was added to those deviated from the lower limit of baseline. In addition, for deviations, grade and abnormal changes were determined.

9.5.2.3.3 Urinalysis

1) Test items: Glucose, bilirubin, ketone body, occult blood, pH, protein, urobilinogen, sediment (Test was to be performed if protein or occult blood was positive.)
2) Test period: Prior to and 72 hours after administration (Time allowance: ±1 hour)
3) Evaluation method: "H" was added to values deviated from the upper limit of baseline or positive in qualitative testing, and "L" was added to those deviated from the lower limit of baseline. In addition, for deviations, grade and abnormal changes were determined.

9.5.2.4 Vital Signs

1) Test items: Blood pressure, pulse rate, and temperature
2) Test period: For each parameter, prior to, 24, 48, and 72 hours after administration (Time allowance: ±30 minutes for 24 hours after administration, ±1 hour for 48 and 72 hours after administration)
3) Test method: Temperature was measured at the same site for all subjects at each study site (measured under armpit, in ear or mouth [sublingually]). Blood pressure and pulse rate were measured at sitting position.
4) Evaluation method: When clinically significant changes from those before administration were recognized, the changes were recorded as AEs in the CRF.

9.5.2.5 Body Weight

1) Test items: Body weight
2) Test period: Prior to and 72 hours after administration (No time allowance was set. Difference in test timing was not regarded as deviation.)

3) Test method: Body weight (after extracting tare weight) was measured and the value was recorded in the CRF.

[Rationales for setting test items, 9.5.2.1 to 9.5.2.5]

9.5.2.1: It was defined to understand subjective symptoms as AEs and confirm objectively by physician.

9.5.2.2: It was defined to confirm AEs by physicians at general physical examination.

9.5.2.5: It was defined to use for calculation of PK parameters standardized by dose per body weight.

9.5.2.1 to 9.5.2.4: These were adopted as general items that might be required for confirmation of health condition of the subjects in clinical studies in healthy adults.

9.5.2.6 Number and Amount of Blood Sampling in the Entire Study

Total number of blood collection per subject: 15 times

<Frequency and amount of blood collection>

	Infectious disease test	Laboratory test	Gene polymorphism test [a)]	PK [b)]	Total
Japan	2 mL (2 mL × 1 time)	27 mL (9 mL × 3 times)	12 mL (12 mL × 1 time)	84 mL (6 mL × 14 times)	125 mL
China	3 mL (3 mL × 1 time)	21 mL (7 mL × 3 times)	12 mL (12 mL × 1 time)	84 mL (6 mL × 14 times)	120 mL
Korea	0 mL[c)]	21 mL (7 mL × 3 times)	12 mL (12 mL × 1 time)	84 mL (6 mL × 14 times)	117 mL
US	8.5 mL (8.5 mL × 1 time)	36 mL (12 mL[d)] × 3 times)	12 mL (12 mL × 1 time)	84 mL (6 mL × 14 times)	140.5 mL

a): Samples for backup were included.
b): Samples for backup were included.
c): Not required because samples for the laboratory test (for screening) were used (Korea).
d): Disposition [3.5 mL/time for hematology, 8.5 mL/time for blood biochemistry] (US)

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 referred to 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 the study drug administration and did not significantly worsen, were not considered to be AEs.

A serious AE referred to 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. It was documented in the CRF. If the grading became 2 or more after administration, it was to be regarded as an AE. However, the grading did not become worse; it was not to be regarded as an AE.