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[Duties of the investigator]
- To give explanation to volunteers using the informed consent document and form and obtain voluntary consent from them.
- To conduct a clinical study in healthy adult subjects in their countries in accordance with the protocol.
- To adjust the entire study.

Study drug storage manager:
<Japan>
Mariko Kawashima
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[Duties]
・ To be in charge of control and storage of the study drug during the study.

Document control manager:
<Japan, China, Korea and US>
The principal investigators at the study sites were in charge of document management.
[Duties]
・ To be in charge of retention and control of essential documents to be kept at the sites.

Monitoring:
<Japan>
CMIC, Co., Ltd., CRO Company, Clinical Research Dept. CRO East Japan Head Office
Address: Gotanda First Bldg. 2-8-1 Nishigotanda, Shinagawa-ku, Tokyo 141-0031, Japan
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Responsible person: Kunimitsu Yamazaki

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Responsible person: YunJeong Choi

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A Scientific Consulting, LLC
Address: 6871 Daly Road, Dexter, MI 48130, USA
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Responsible person: Emily Huston
[Duties]
・ To perform monitoring activities.

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<US>
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LABCORP Clinical Trials

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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, Director

<China>
Biomedical Research (GZ), Ltd.
Jiaxing Pharmacokinetics and Bioanalysis Center
Address: No2, Lig Gong Tang Road. Jiaxing, Zhe Jiang Province, China
TEL: +86-573-8258-6381 FAX: +86-573-8258-6058
Responsible person: Zheng Guodong
[Duties]
・ To perform the gene polymorphism examination and keep the specimens for 3 years at -20°C or less.
・ Data analysis of gene polymorphism are performed at Division of Medicinal Safety Science of National Institute of Health Sciences

Laboratory center for measurement of drug concentrations
Bayer HealthCare AG / Bayer Schering Pharma AG
Address: Wuppertal, Elberfeld, 0468, Germany
TEL: +49-202-36-5223 FAX: +49-202-36-4224
Responsible person: Dr. Uwe Thuß
[Duties]
・ To measure plasma and urine drug concentrations.

Summary of the safety data
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Responsible person: Tomoka Inoue Davidsen
[Duties]
・ To check the safety data, and making tables and figures.

Statistical analysis
<Pharmacokinetics and polymorphism>
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Responsible person: Masahiro Tohkin, Director
[Duties]
・ To draw up the statistical analysis plan, implement the PK analysis and other tabulation analyses, prepare reports.

Audit
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TEL: +81-3-5745-7045 FAX: +81-3-5745-7095
Responsible person: Noriaki Suzuki
[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 pharmacokinetic (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 was planned with a study drug which had been selected based on evaluation results using existing data to collect supplemental data on ethnic difference or to improve data reliability.

Moxifloxacin which was used as a study drug in this study is quinolone antimicrobial which has been already marketed in all the countries and its usual dosage and administration was 400 mg once daily. The PK characteristics of moxifloxacin are as follows: high absolute bioavailability (approximately 90%) at the time of oral administration, identified sulfate conjugate (catalyzed by SULT2A1) and glucuronide conjugate (catalyzed by UGT1A1) as its plasma and urinary metabolites and approximately 35% and 61% excrement of the dose in urine and feces, respectively. In the evaluation by the Tohkin Group based on the unified statistical procedure among ethnic groups, this drug showed the difference between Japanese and Western populations and also among Asian (Japanese, Chinese and Korean) populations. However, the protocols of the conducted studies differed in each country and clear conclusion has not been made on the ethnic difference.

As the first investigator-initiated study by our research group, "Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects, 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" was planned and a PK study based on the same protocol with moxifloxacin[1,2] in healthy adult male subjects in each ethnic group, namely Japanese, Chinese and Korean populations (Mongoloid), was conducted. In addition, a clinical study based on the same protocol in European Caucasian subjects was performed in the US as a reference.

8. STUDY OBJECTIVES

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

9. INVESTIGATIONAL PLAN

9.1 Overall Design and Plan Description

This was conducted as an open-label, single administration study in which 20 healthy adult male subjects for each country (80 subjects in total in Japan, China, Korea and the US) aged 20-35 were to receive a single oral dose of 400 mg of moxifloxacin.

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

One 400-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 and the subjects were to drink 300 mL of soft mineral water (hardness <100, Volvic® etc.) during a period from 2 to 4 hours after administration. Soft mineral water (hardness <100, Volvic® etc.) was given during the study period.

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

The calories and 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. Intake of milk, cheese and yoghurt was not allowed.

Blood and urine sampling for assay of moxifloxacin and metabolites, and safety assessments including vital sign measurements, 12-lead ECG recording, and clinical laboratory tests (hematology, blood biochemistry and urinalysis) were to be performed at

pre-determined times during the study period. Adverse events 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.

UGT1A1 and the enzymes related to the pharmacokinetics of moxifloxacin were to be obtained for each subject 48 hours after moxifloxacin administration in order to exclude the subjects with UGT1A1 and other enzyme-gene polymorphism.

Confinements and Restrictions

In order to avoid a wide variation in absorption of study drug from the digestive track, the intake of water after administration of study drug, and calories and PFC balance at the dinner on the day before and the first lunch and dinner after administration were to be unified among all the countries as much as possible. Absorption and effects of study drug may be prohibited since study drug makes chelate with calcium or magnesium in drinking water. Therefore, soft mineral water like Volvic® etc. having a hardness (index of amount of calcium and magnesium contained) <100 was selected. Intake of milk, yoghurt and chesses that contain a lot of calcium was not allowed, based on the same reason at the dinner on the day before administration and the first lunch and dinner after 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 pharmacokinetic profile of an oral dose of moxifloxacin, 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 principal 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 variations.
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 (QTc prolongation* etc.), lung, liver and/or kidney, etc. and hypokalemia. (* See "Definition of term" in Chapter 4)
2) A history of diseases involving the heart, lung, kidney, blood (such as coagulation system disorder), central nervous system, metabolic system and skeletal muscle system, etc. that may interfere with the study.
3) Hypersensitivity or allergies to drugs, food, etc. (Particularly, a history of allergy or adverse reactions associated with quinolone antibacterials)
4) Oral administration of drugs such as over-the-counter drugs, supplements or healthy foods within 1 week prior to the study drug administration, and the necessity for using other medications before study completion.
5) Smokers and a smoking history within the last 6 months. (The cotinine test is performed, if necessary.)

6) Drug abuse or suspicion of drug abuse. (The drug screening test is performed, if necessary.)

7) 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)]

Reference) Alcohol content of each beverage

Beer 5.5%, sake 15% (14 to 16), wine 15% (12 to 15), shochu 25% (25 to 40), awamori 40% (20 to 60), Chinese rice wine 17% (16 to 18), makgoli 7% (6 to 8), whisky 40% (40 to 50), brandy 40%, gin 40% (40 to 50), rum 40% (40 to 75), tequila 40%, vodka 40% (35 to 50), cocktail 35% (15 to 35)

Example: When drinking 1000 mL of beer (alcohol content: 5.5%),

alcohol intake $= 0.055 \times 1000 \times 0.8 = 44$ g

8) Total bilirubin or direct bilirubin is 1.5 times higher, or other liver function tests items are 1.25 times higher than the upper limits of normal at the sites.

9) Transfusion of 200 mL or more within 1 month prior to study drug administration, blood component donation (plasma donation or platelet donation) within 2 weeks, or blood collection of 400 mL or more within 3 months.

10) 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.

11) Those who are determined by the principal investigator to be not suitable as subjects of the study.

[Rationales for selection]

1) to 3) The criteria were specified for subject safety assurance.

4) to 8) The criteria were selected for safety assurance and for the reason why they might interfere with PK analysis and safety evaluation.

9) 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).

10) 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.
11) 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 requested to withdraw from study participation after providing informed consent.
2) When the principal 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 principal 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, the measurement of plasma concentrations after administration was to be carried out only if possible.

3) In the presence of adverse events, 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 tablet containing 400 mg of moxifloxacin as follows:

- 400 mg moxifloxacin (A film-coated light reddish gray tablet containing moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin)

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

9.4.2 Identity of Investigational Products

The product of moxifloxacin (single lot) that was manufactured by Bayer AG in Germany and marketed in China was used in every study site.

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

The lot number and expiry date were as follows:

	Lot number	Expiry date
400 mg tablets	117268	18 January 2012

All unused supplies of moxifloxacin were to be discarded at the end of the study under the direction of the principal investigator.

9.4.3 Methods of Assigning Subjects to Treatment Groups

Subject Identifier (9 digits) was consisted of the study site code (Japan: 00001, Korea: 00002, China: 00003 and the US: 00004) and the number that was anonymized and linkable to the subject. Following confirmation of eligibility on admission, subjects were assigned numbers from 0001 – 0020 in Japan, Korea and China, and from 0001 – 0031 in the US.

There was no randomisation in this study.

9.4.4 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 400 mg, with which the plasma concentrations of the unchanged drug and each metabolite could be measured for a sufficient period of time, was selected.

9.4.5 Selection and Timing of Dose for Each Subject

Each subject was to receive 400 mg of moxifloxacine, following an overnight fast from after having a dinner. On the day of administration, after performing tests such as the physical examination by the principal investigator, laboratory test, vital signs (blood pressure, pulse rate and body temperature) and electrocardiography, and blood sampling for measurements of drug concentrations before administration, study drug administration was started sequentially at 9:00 am.

9.4.6 Blinding

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

9.4.7 Prior and Concomitant Therapy

Co-administration 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 adverse events, the principal investigator were to enter information such as the name, dosage/administration, duration and purpose of use of the drug in the CRF.

9.4.8 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 characteristics and clinical observation	Sex, height, body weight/ BMI, background characteristics (birth date, current health condition, history of drug allergy, past history, and smoking/ drinking habits) and physical examination by the investigators
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, urea nitrogen, 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
Vital signs, electrocardiography	Blood pressure/ pulse rate (sitting), body temperature and 12-lead electrocardiography
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 investigators
PK	Plasma drug concentrations and urine 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, urea nitrogen, uric acid, creatinine, creatinine clearance, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, LDH, ALP, CK, Na, K, Cl and CRP
Renal function	Creatinine clearance
Urinalysis	Glucose, bilirubin, ketone bodies, occult blood, pH, protein, urobilinogen and sediment
Vital signs, electro-cardiography, body weight measurement	Blood pressure/ pulse rate (sitting), body temperature, 12-lead electrocardiography and body weight
Gene polymorphism examination	Collected blood specimens (EDTA-2Na or EDTA-2K added) were to be refrigerated at -20°C or less and sent to the institute for gene polymorphism analysis using dry ice within 2 weeks after sampling.

Table 9-3 Study Schedule

		Screening	Study												
Date of study		Within 30 days	- Day 1	Day 1									Day 2		Day 3
Time			Admission by 16:30	8:00	9:00	9:30	10:00	10:30	11:00	12:00	13:00	15:00	21:00	9:00	21:00	9:00
Time after oral administration (h)				-1	0	0.5	1	1.5	2	3	4	6	12	24	36	48
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]
	PK			○		○	○	○	○	○	○	○	○	○	○	○
	Laboratory test	○		○												○
	Infectious disease test	○														
Urine sampling	PK			Urine pooling	←							→	→	→	→	→
	Laboratory test	○		○[b]												○[c]

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

1 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)
Day 2 and 3 (Having a breakfast after completion of blood sampling and tests at 24 hours (Day 2) and 48 hours (Day 3) after administration each)

a): Collected specimens (EDTA-2Na or EATD-2K added) were to be refrigerated at -20°C or less, and sent to the institute for gene polymorphism analysis using dry ices within 2 weeks after sampling.
b): The remaining urine collected for urinalysis was to be used as a specimen for measurement of blank of urine drug concentrations.
c): The remaining urine collected for urinalysis was to be added in the container for urine pooling from 24 to 48 hours after administration.

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, investigators and others 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, 3, 24 and 48 hours after administration
3) Test method: The principal investigator, investigators and others 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 48 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 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, urea nitrogen, 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 48 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 was to be performed.

9.5.2.3.3 Urinalysis

1) Tests: Glucose, bilirubin, ketone bodies, occult blood, pH, protein, urobilinogen and sediment
2) Test timing: Before administration (baseline) and 48 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 and grading were to be performed.

9.5.2.4 Renal Function

1) Tests: creatinine clearance (CCr)
2) Test timing: Before administration
3) Evaluation method: CCr was to be calculated using the following Cockcroft-Gault Formula (Male):
   CCr [mL/min] = (140 - age) x body weight [kg] / (72 x serum creatinine)

9.5.2.5 Vital Signs

1) Tests: Blood pressure, pulse rate and body temperature
2) Test timing: Before administration (baseline), 3, 24 and 48 hours after administration
3) Test method: Body temperature was to be measured in the same way at the site (axillary, ear or oral (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 adverse event.

9.5.2.6 Electrocardiography

1) Test: 12-lead electrocardiography
2) Test timing: Before administration (baseline), 3, 24 and 48 hours after administration
3) Test method: 12-lead electrocardiography was to be performed at rest.
4) Evaluation method: The judgment of abnormality and grading were to be performed as compared with baseline.

9.5.2.7 Body Weight

1) Test: Body weight measurement
2) Test timing: Before administration and 48 hours after administration
3) Test method: Body weight (net) was to be measured and recorded in the CRF.

9.5.2.8 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)	72 mL (6 mL×12)	115 mL
China	3 mL (3 mL×1)	21 mL (7 mL×3)	12 mL (12 mL×1)	72 mL (6 mL×12)	108 mL
Korea	0 mL[c)]	21 mL (7 mL×3)	14 mL (14 mL×1)	72 mL (6 mL×12)	107 mL
US	8.5 mL (8.5 mL×1)	36 mL (12 mL[d)]×3)	14 mL (14 mL×1)	72 mL (6 mL×12)	130.5 mL

a): Including back-up samples
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 9.5.2.7]

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

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