Study drug	A film-coated light reddish gray tablet containing moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin. The same product lot will be used in all the countries.
Dosage and administration	One 400-mg tablet of the study drug is orally administered with 150 mL of soft mineral water (hardness <100, Volvic® etc.) after fasting for at least 10 hours. Water drinking is prohibited up to 2 hours after taking the study drug. The subjects should 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.) is given during the study period. Food intake is not allowed up to 4 hours after administration. The calories and the balance of three major nutrients (PFC balance) of the dinner on the day before administration and the first lunch and dinner after administration are unified among the countries as much as possible. Intake of milk, cheese and yoghurt is not allowed.
Endpoints	**PK endpoints** 1) Plasma concentrations of moxifloxacin and metabolites (glucuronide conjugate and sulfate conjugate of moxifloxacin) [Blood sampling points] Before administration (baseline), 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 36 and 48 hours after administration (12 points in total) [PK parameters to be calculated] PK parameters of moxifloxacin and metabolites are calculated using model-independent analysis and compartmental model. The following parameters should be calculated using model-independent analysis: Peak plasma concentration (C_{max}), time to peak plasma concentration (t_{max}), elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve (AUC_{0-t}, $AUC_{0-\infty}$), mean residence time(MRT), apparent total clearance (CL/f) and volume of distribution (Vd/f) C_{max} normalized to dose per body weight ($C_{max,\ norm}$) and AUC normalized to dose per body weight ($AUC_{0-t,\ norm}$,$AUC_{0-\infty,\ norm}$) of moxifloxacin and metabolites 2) Urinary concentrations and excretion of moxifloxacin and metabolites (glucuronide conjugate and sulfate conjugate of moxifloxacin) [Urine pooling period] 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours after administration (4 intervals in total) [PK parameters to be calculated] Urinary excretion and urinary excretion rate are calculated each for moxifloxacin and metabolites, and the total of them (mole equivalent: for each pooling interval and cumulative 4 pooling intervals). **Gene analysis for polymorphism** ・Gene analysis for polymorphism of the UGT1A1 and the enzymes related to the pharmacokinetics of moxifloxacin. **Safety endpoints** ・Types, severity, duration, number of subjects, number of cases and incidence of adverse events that occurred after study drug administration will be examined. ・For laboratory values, vital signs (body temperature, blood pressure and pulse rate), 12-lead electrocardiography and body weight, basic statistics (mean and standard deviation) should be calculated by each test point.
Observation and tests	1) Observation period: From the day of study drug administration (Day 1) to discharge from the hospital (Day 3). 2) Tests: Physical examination findings (history taking etc.), pharmacokinetics, hematology, blood biochemistry, renal function, urinalysis, vital signs (blood pressure, pulse rate and body temperature), 12-lead electrocardiography, body weight measurement and gene polymorphism examination.
Target sample size	20 subjects for each country (80 subjects in total in Japan, China, Korea and the US)
Planned study period	November 2009 to July 2010

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	Admissio◄													►
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	Pharmacokinetics			Urine pooli	◄							►	◄►	◄►	◄	►
	Labo tests	○		○[b)]												○[c)]

Meal time during hospitalization: Morning of Day 1 is fasting. Meal time is 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 Added) will be refrigerated at -20℃ or less, and sent to the institute for gene polymorphism analysis using dry ices within 2 weeks after sampling, if possible.
b): The remaining urine collected for urinalysis should be used as a specimen for measurement of blank of urine drug concentrations.
c): The remaining urine collected for urinalysis should be added in the container for urine pooling from 24 to 48 hours after administration.

List of abbreviations

Abbreviation	Full expression
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve AUC_{0-t}: Area under the plasma concentration-time curve from time zero to the last blood sampling $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time zero to infinity
BMI	body mass index
CCr	creatinine clearance
CK	creatine kinase
CL/f	apparent total clearance
C_{max}	peak concentration
CRP	C-reactive protein
f	bioavailability
γ-GTP	gamma glutamyl transpeptidase
HBs antigen	hepatitis B surface antigen
HCV antibody	anti-hepatitis C virus antibody
HDL	high density lipoprotein
HIV antibody	human immunodeficiency virus antibody
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
PFC	Protein- Fat- Carbohydrate balance
SULT	Sulfotransferase. SULT2A1: One of the enzymes among the subfamily of hydroxysteroid sulfotransferase (SULT2A)
$t_{1/2}$	half-life
t_{max}	time of peak concentration
UGT	uridine diphosphate glucuronosyltransferase UGT1A1: one of the UGT molecular species, and there are gene polymorphisms (UGT1A1*1, *6, *28, *36, *37 and *60).
Vd/f	volume of distribution

List of definitions of terms

Terms	Definition
QTc prolngation	450 msec or more prolongation in QTc in this study
Creatinine clearance (CCr)	To be calculated using Cockcroft-Gault formula, based on serum creatinine, age and body weight
Anonymized number that is linkable to subjects	The numbers are given to the subjects (anonymized). The record of the linkage of the numbers and the subjects is kept, if necessary to identify the subjects

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1. 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 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 pharmacokinetic 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.

This time, 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" is planned and a pharmacokinetic 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), is to be conducted. In addition, a clinical study based on the same protocol in European Caucasian subjects will be performed in the U.S as a reference.

Meanwhile, moxifloxacin which is used as a study drug in this study is quinolone antimicrobial which has already been marketed in all the countries and its usual dosage and administration is 400 mg once daily. The pharmacokinetic characteristics of moxifloxacin are as follows: high absolute bioavailability (approximately 90%) at the time of oral administration, identified sulfate conjugate and glucuronide conjugate (SULT2A1 and 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.

Starting with this study, our research group will continue to secure reliable data on ethnic difference and examine how to implement global clinical studies including East Asian populations for promoting clinical development.

2. STUDY OBJECTIVE

To investigate whether or not there are ethnic differences in the pharmacokinetics 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 conducted on the same protocol.

2.1 Endpoints

2.1.1 PK Endpoints

1) Plasma concentrations of moxifloxacin and metabolites (glucuronide conjugate and sulfate conjugate of moxifloxacin)

[Blood sampling points]

Before administration (baseline), 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 36 and 48 hours after administration (12 points in total)

[PK parameters to be calculated]

PK parameters of moxifloxacin and metabolites are calculated using model-independent analysis and compartmental model.

The following parameters should be calculated using model-independent analysis:

Peak plasma concentration (C_{max}), time to peak plasma concentration (t_{max}), elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve (AUC_{0-t}, $AUC_{0-\infty}$), mean residence time (MRT), apparent total clearance (CL/f) and volume of distribution (Vd/f)、C_{max} normalized to dose per body weight ($C_{max,\ norm}$) and AUC normalized to dose per body weight ($AUC_{0-t,\ norm}$,$AUC_{0-\infty,\ norm}$) of moxifloxacin and metabolites

2) Urinary concentrations and excretion of moxifloxacin and metabolites (glucuronide conjugate and sulfate conjugate of moxifloxacin)

[Urine pooling period]

0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours after administration (4 intervals in total)

[PK parameters to be calculated]

Urinary excretion and urinary excretion rate are calculated each for moxifloxacin and metabolites, and the total of them (mole equivalent: for each pooling interval and cumulative 4 pooling intervals).

2.1.2 Gene polymorphism examination

・Gene analysis for polymorphism of the UGT1A1 and the enzymes related to the pharmacokinetics of moxifloxacin.

2.1.3 Safety endpoints

- Types, severity, duration, number of subjects, number of cases and incidence of adverse events that occurred after study drug administration should be examined.
- For laboratory values, vital signs (blood pressure, pulse rate and body temperature), 12-lead electrocardiography and body weight, basic statistics (mean and standard deviation) should be calculated by each test point.

3 STUDY TYPE AND DESIGN

3.1 Study Type

This is conducted as an open-label, single administration study.

3.2 Study design

The study design is described in **Table 3-1**.

Table 3-1 Study design

Method	Open-label, single administration study
Study drug	Moxifloxacin. The same product lot is used in all the countries.
Target sample size	20 subjects for each country (80 subjects in total in Japan, China, Korea and the US)
Dosage and administration	One 400-mg tablet of the study drug is orally administered with 150 mL of soft mineral water (hardness<100, Volvic® etc.) after fasting for at least 10 hours. Water drinking is prohibited up to 2 hours after taking the study drug and the subjects should 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.) is given during the study period. Food intake is not allowed up to 4 hours after administration. The calories and three major nutrients (PFC balance) of the dinner on the day before administration and the first lunch and dinner after administration are unified among the countries as much as possible. Intake of milk, cheese and yoghurt is not allowed.

[Rationales for selection]

Target sample size: The number of subjects required to investigate ethic differences in the pharmacokinetics was caluculated.[3] As a result, the number of subjects was calculated to be at least 6 subjects from each population for detecting a 20 % difference in $AUC_{0-\infty}$ with a power of 80 % among the ethnic populations. When taking account of a multiplicity problem, the number of subjects was at least 8 subjects. This number excluded the subjects with UGT1A1 gene polymorphism. Analysis of gene polymorphism is performed after PK analysis. Based on these, the target sample size of this study was determined to be 20 subjects from each ethnic population, considering the subjects excluded from the results of analysis of UGT1A1 gene polymorphism, dropouts by discontinuation or withdrawals.

The reason why the target sample size was approximately doubled from the number of subjects necessary for statistical analysis was based on information on ethnic differences of UGT1A1 polymorphism. According to the investigation[4], the frequencies of UGT1A1*6, *28, *36, *37 polymorphism in Japanese, Korean, Asian people (mostly, East Asian people including Japanese and Korean) were 0.244-0.282, 0.247 and 0.24, respectively. On the other hand, the frequency in Caucasian was about 0.34-0.413.

Dosage and administration: 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 can be measured for a sufficient period of time, was selected.

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 and 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.

4 SUBJECTS

In Japan, China and Korea, the nationalities of the subjects should be the same as those of grandfathers, grandmothers, father and mother. In China, only the Han race is eligible. In the U.S., only European Caucasian is eligible.
In this study, subjects are healthy adult male volunteers who satisfy all of the following "**4.1 Inclusion criteria**" and none of the following "**4.2 Exclusion criteria**".

4.1 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) 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.

4.2 Exclusion criteria

1) Organopathy involving the heart (QTc prolongation* etc.), lung, liver and/or kidney, etc. and hypokalemia. (*See the definition of the terms, page vi)
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 to 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 or 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 and 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 or platelet) 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 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 because 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 principle investigator to be able to make determination in consideration of overall factors.

4.3 Discontinuation/ withdrawal criteria

Subjects, who meet any of the following criteria, will 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 principle 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 criteria were 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.

4.4 Procedures for discontinuation/ withdrawal

1) When discontinuing the study, the principle investigator should promptly explain such a fact to the

subject (When the subject requested to terminate the study, the principle investigator should check the detailed reason whenever possible). The principle investigator should also enter information such as the timing of discontinuation/ withdrawal and reason in the case report form (CRF).

2) When discontinuing the study or withdrawing the subject from the study after study drug administration, the principle investigator should perform observation in accordance with the Section "**8.2.4 Evaluation items for the safety endpoints**." However, the measurement of plasma concentrations after administration should be carried out only if possible.
3) In the event of adverse events, the principle investigator should investigate until the symptoms resolve or become stable (1 month at the longest).
4) When the drop outs take place by discontinuation or withdrawal, additional subjects will not be recruited.

5 STUDY DRUG

5.1 Supply of the Study Drug

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

5.2 Name of the Study Drug and Other Explanations

The brand name, manufacturer and indications are as follows;

Brand name: 拜复乐

Distributor: Bayer China Co Ltd. (Beijing)

Indications:

- Adult patients (greater than or equal to 18) with upper respiratory infection, lower respiratory infection, e.g acute sinusitis
- acute episode chronic bronchitis
- community acquired pneumonia, skin, Soft tissue infection

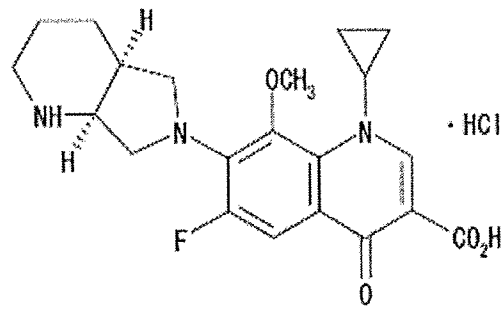
Moxifoloxacin is a new quinolone antibacterial agent that was developed by Bayer AG in Germany. Marketing approval of oral moxifloxacin was obtained first in Germany in June, 1999 and totally 109 countries approved as of May 2008. Japanese brand name is Avelox® 400 mg tablet. It is distributed by Shionogi & Co., Ltd (marketing approval: Bayer Yakuhin, Ltd, Japan)

Active ingredient:

[Nonproprietary name] Moxifloxacin hydrochloride

[Chemical name] 1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS, 7aS)-octahydropyrrolo[3,4-b]pyridine-6-yl] -4-oxo-1,4-dihydroquinoline-3-carboxylic acid monohydrochloride

[Chemical structure]



[Molecular formula] $C_{21}H_{24}FN_3O_4 \cdot HCl$

[Molecular weight] 437.89

Contents and dosage form:

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

Storage condition:

Store at room temperature.

5.3 Control/ Storage of the Study Drug

The executive investigator should provide the study drug and entrust the control and storage of the study drug to the storage personnel at the study site. The study drug should be delivered, controlled and collected in accordance with the "Procedure for Control of the Study Drug" provided by the executive investigator. When the study is completed, the study drug storage personnel should take a count of the remaining study drug and discard them under the direction of the principle investigator .

6 PROHIBITED CONCOMITANT MEDICATIONS

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

When they are used due to inevitable reasons such as treatment of adverse events, the principle investigator should enter information such as the name, dosage/administration, duration of use and purpose of use of the drug in the CRF.

7 MANAGEMENT OF SUBJECTS

7.1 Management of Subjects in Each Period

1) Screening

The principle investigator should perform the screening test within 30 days before study drug administration after acquisition of informed consent

2) Day before study drug administration (-Day 1, hospitalization) to 3 days after administration (Day 3, discharge)

The principle investigator should hospitalize the subjects by 16:30 on the day before study drug administration. The subjects should be kept fasted from after having a dinner on the day of hospitalization to 4 hours after study drug administration. On the day of administration, after performing tests such as the physical examination by the principle 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 should be started sequentially at 9:00 am. Thereafter, blood sampling and urine pooling for tests and measurements of drug concentrations should be implemented in accordance with the study schedule.

On Day 3, the investigators should conduct physical examination, blood sampling and urine pooling for measurements of drug concentrations, and blood sampling for gene analysis for polymorphism of the UGT1A1 and the enzymes related to the pharmacokinetics of moxifloxacin. After confirming

that there is no safety (health condition) problem, the investigator should discharge the subjects from the hospital. However, when safety assurance is determined to be necessary, the principle investigator should prolong the hospitalization period and carry out a reexamination or additional examination to implement a follow-up investigation. In such a case, the details of the actions taken should be recorded in the CRF.

7.2 Intake of supplements or health foods

The use of supplements or health foods will be prohibited, as a rule, from 1 week before study drug administration to 3 days after administration (Day 3, discharge).

[Rationales for selection]

Intake of all the supplements or health foods was prohibited. Not only the supplements or health foods including iron, magnesium, aluminum and calcium, but also the supplements or health foods not including these minerals may affect absorption of the study drug.

7.3 Drinking and Eating

During the hospitalization period, intake of meals and water (soft mineral water, hardness < 100, Volvic® etc.) other than those supplied by the site will be prohibited.

Water drinking will be prohibited for 2 hours after drug administration, and the subjects should drink 300 mL of soft mineral water during a period from 2 to 4 hours after administration. Soft mineral water (hardness < 100, Volvic® etc.) is given during study period.

Timing of hospitalization and meal time will be as follows. Morning of Day 1 is fasting. Meal time is free except for the following:

-Day 1 (day of hospitalization): 19:00

Day 1 (day of administration) : 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.

7.4 Smoking

Smoking will be prohibited during the hospitalization period (after hospitalization on the day before administration).

[Rationales for selection]

It was specified because nicotine contained in cigarette may affect test values such as blood pressure and pulse rate.

7.5 Physical exercise

Strenuous exercise and work giving a heavy physical burden will be prohibited during the hospitalization period (after hospitalization on the day before administration).

[Rationales for selection]

It was stipulated because physical exercise may increase enzyme levels such as AST, ALT and CK.

7.6 Posture

It will be prohibited to be in the supine or prone position from study drug administration to the completion of the tests at 3 hours after administration except during the tests such as blood pressure.

[Rationales for selection]

It was specified for avoiding changes in absorption caused by the physical position.

8 OBSERVATIONS AND ENDPOINTS

8.1 Procedure for Study Implementation

8.1.1 Screening

The investigator should perform the screening test in subjects who provided written informed consent. Observation and tests listed in **Table 8-1** should be implemented as the screening test to verify whether the subjects are eligible for the study. The investigator should also record the details in the CRF.

Table 8-1 Observation and tests at screening

Subject background characteristics and clinical observation	Sex, height, body weight/ BMI, background characteristics (birth day/month/year), current health condition, history of drug allergy, past history, and smoking/ drinking habits) and 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, 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.

8.1.2 Study

The investigator should perform the observation and tests listed in **Table 8-2** in the subjects, who provided consent for study participation, in accordance with the study schedule in **Table 8-3**.

Table 8-2 Observation and tests during the study

Clinical observation	Physical examination by the investigator
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, 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, electrocardiography, body weight measurement	Blood pressure/ pulse rate (sitting), body temperature, 12-lead electrocardiography and body weight
Gene polymorphism examination	Collected blood specimens (EDTA-2Na Added) will be refrigerated at -20℃ or less and sent to the institute for gene polymorphism analysis using dry ice within 2 weeks after sampling, if possible.

Table 8-3 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]
	Pharmacokinetics			○		○	○	○	○	○	○	○	○	○	○	○
	Laboratory test	○		○												○
	Infectious disease test	○														
Urine sampling	Pharmacokinetics			Urine pooling	←							→	→	→	→	→
	Labo tsets	○		○[b]												○[c]

Meal time during hospitalization: Morning of Day 1 is the fast. Meal time is 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 Added) will be refrigerated at -20℃ or less, and sent to the institute for gene polymorphism analysis using dry ice within 2 weeks after sampling, if possible.
b): The remaining urine collected for urinalysis should be used as a specimen for measurement of blank for urine drug concentrations.
c): The remaining urine collected for urinalysis should be added in the container for urine pooling from 24 to 48 hours after administration.

8.2 Investigations/ evaluations

8.2.1 Evaluation items for the PK endpoints

(1) Plasma drug concentrations

1) Test substance: Moxifloxacin and metabolites (glucuronide conjugate and sulfate conjugate of moxifloxacin)

2) Blood sampling point: Before administration, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 36 and 48 hours after administration (12 points in total)

3) Processing method: At the specified blood sampling points, 6 mL of blood should be taken from an antecubital vein using Heparin-Lithium vacutainer tubes. Blood sample should be centrifuged at 1500 -2770 x g for 10 minutes (Cooling of the centrifuge is desirable but not mandatory). 1.0 – 1.5 mL of the obtained plasma should be transferred into the labeled polypropylene tube to transfer it to the measurement site and stored at -20°C or less until measurement. The remaining plasma should be stored at the study site as back-up samples at the said condition. Don't expose the blood samples to direct sunlight.

4) Labeling and transport method of a storage container for plasma specimens:

The example of the label is as follows. The label describing the analyte, trial number (14988) that is made by Bayer HealthCare AG, the number (9 digits) that consists of the study site code (Japan:00001, Korea: 00002, China: 00003 and the US:00004) and the number that is anonymized and linkable to the subjects, date of administration, time of blood sampling, specimen type.

The label should be attached to the storage container for specimens.

Analyte	MOXIFLOXACIN
Trial No.	14988
Subject No.	000010001
Visit No.	Day1
Planned Time	5 MIN
Matrix	PLASMA

If possible, within 2 weeks after sampling, the frozen plasma specimens should be packed in dry ice and sent to the laboratory center for measurement of drug concentration (Bayer HealthCare AG in Germany) from the study site. The procedure for sending should be given separately.

5) Back-up samples:

Back-up samples are stored to compensate the missing specimens, for example, the specimens might be broken during the transportation to the center for measurement of drug concentration. The back-up samples are stored at the study site at -20°C or less until measurement is completed. After that, the back-up samples should be sent to the National Institute of Health Sciences. The procedure for transportation, storage and discard of the back-up samples should be given separately.

[Rationales for selection of the blood sampling points]

When Avelox Tablets 400 mg was orally administered to 6 healthy Japanese adult male subjects, the t_{max} and $t_{1/2}$ of plasma moxifloxacin concentrations were 1.75 and 13.9 hours, respectively[2]. Based on these findings, a total of at least 7 blood sampling points were selected