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.

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

9.5.2.1 to 9.5.2.7: They were adopted as general items found to be necessary for verification of the subjects' health condition in a clinical study in healthy adults.

9.5.2.9 Adverse Events

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

9.5.2.9.1 Definitions

An adverse event (AE) was defined as any unfavorable and unintended sign (laboratory values, vital signs and 12-lead electrocardiography), symptom or disease newly occurred after administration of the study drug, regardless of the causal relationship with the study drug.

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

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

1) resulted in death,
2) was life-threatening,
3) required inpatient hospitalization or prolongation of existing hospitalization,
4) resulted in persistent or significant disability / incapacity, or
5) was a congenital anomaly / birth defect.
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.

9.5.2.9.2 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 / electrocardiography

The investigators were to review the contents of vital signs and

electrocardiography during the hospitalization period and assess AEs based on medical judgment.

• 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 and clinical sample 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 (NAID).

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

Mild: (Grade 1); A sign or symptom was present, but did not interfere with the subject's daily activities and did not require treatment.

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

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

The grade of abnormal value was written in the CRF.

9.5.2.9.3 Evaluation of AEs

The principal investigator was to enter the following information in the CRF: the presence or absence of AE, if present, the details, onset date, severity and seriousness (serious or non-serious) of AE, action for the study drug (discontinuation, and the details of the action when AE occurred after the date of the completion of administration or in other cases), other actions, outcome (not resolved, resolved with sequelae, resolved, unknown or; for other cases, their details), and the causal relationship with the study drug. The severity and causal relationship with the study drug were to be assessed using the following criteria as a reference.

• Criteria for severity

Mild: Treatment or action was not necessary for the adverse event.

Moderate: Treatment or action was required for the adverse event.

Severe: Study treatment was discontinued due to the adverse event.

• Criteria for assessment of the causal relationship with the study drug

Changes over time in symptoms, laboratory values, etc. before/ after administration and at follow-up observation were to be fully compared, and while taking account of changes, diurnal variation, measurement errors, etc. in related symptoms or tests, the causal relationship with the study drug was to be evaluated. For events assessed as "not related" with the study drug, the reasons were to be recorded in the CRF.

(1) Related:

There is a clear temporal correlation with study drug administration, and the known response of the study drug is shown, and there are hardly other possible reasons.

(2) Probably related:

There is a clear temporal correlation with study drug administration. The expected response based on pharmacological effect of the study drug is shown. The relationship with medical history of patients and factors other than study drug are denied, and the relationship with the study drug cannot be denied.

(3) Unknown:

There is a clear temporal correlation with study drug administration. The relationship with medical history of patients and factors other than study drug are supposed, but the relationship with the study drug cannot be denied.

(4) Probably not related:

There is unlikely to be a temporal correlation with study drug administration, or there is some information denying the relationship with the study drug.

(5) Not related:

There is unlikely to be a temporal correlation with study drug administration, or there is information that the event is not related to the study drug.

9.5.2.9.4 Handling at Onset of AE and Follow-up Action

(1) Handling at onset of AE (clinical symptom)

1) In the event of AEs, the principal investigator was to consider medical actions, etc. as necessary for assurance of subjects' safety.
2) When medical actions were required, the principal investigator was to take the best action and, in principle, continue a follow-up until the symptoms resolved

after informing such a fact to the subject.

3) When AE was judged as unknown and the causal relationship with study drug could not be denied [Protocol: 9.3.2 (1)-(3)], be to follow the below section (4).
4) The principal investigator was to confirm that the developed AE resolved or became stable.
5) When the continuation of the study was judged to be difficult due to AEs, the principal investigator was to discontinue the study and follow up the subsequent course.

Predictability was defined as follows: Unknown was when the onset trend, such as onset, number of cases, incidence and onset condition, of the case could not be predicted based on information in the package insert of the study drug, and known was when the case could be predicted.

(2) Actions at the onset of abnormal laboratory values

1) When abnormal laboratory values were noted after study drug administration, the principal investigator was to, in principle, perform a follow-up investigation until they returned to reference or baseline levels and as necessary give treatment.
2) When the continuation of the study was judged to be difficult due to AEs, the principal investigator was to discontinue the study and follow up the subsequent course.
3) When AE was judged as unknown and the causal relationship with study drug could not be denied [Protocol: 9.3.2 (1)-(3)], follow the below section (4).

(3) Handling at onset of serious AE

1) In the event of serious AEs, the principal investigator was to consider medical actions, etc. as necessary for assurance of subjects' safety.
2) When medical actions were required, the principal investigator was to inform such a fact to the subject.
3) The principal investigator was to confirm that the developed AE resolved or became stable.
4) When the causal relationship between serious AE and the study drug could not be denied [Protocol: 9.3.2 (1)-(3)], follow the below section (4).

(4) Reporting of unknown or serious AEs that the causal relationship with study drug cannot be denied

When AE was judged unknown or serious, and the causal relationship with study drug could not be denied, the principal investigator was to report its information to

the head of the study site, the executive investigator, and marketing approval holder by e-mail immediately.

If the reporting was not done at the same time, the principal investigator was to report its information to the marketing approval holder within 24 hours by e-mail from the occurrence of the event. The contents that should have been informed to the marketing holder were described in "Protocol 22 Appendix 2". The principal investigator was to report to Ethics Review Committee and the executive investigator in the form of "Report of serious AEs in a clinical study" through the head of the study site as quickly as possible.

[Contact information when AE was judged unknown or serious, and the causal relationship with study drug could not be denied]

・ Executive investigator

Professor Shinichi Kawai, MD, PhD
Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine
e-mail: skawai@med.toho-u.ac.jp
(TEL: +81-3-5762-4151, FAX: +81-3-5753-8513)

・ Marketing approval holder

<Japan> Bayer Yakuhin Co. Ltd. Umeda 2-4-9, Kita-ku, Osaka 530-0001
e-mail:BYL_AE_REPORT_POST@BAYER.co.jp

<China> Bayer Healthcare Company, 16th Floor, Fortune Plaza, No. 7, Dong San Huan Zhong Road, Chaoyang District, Beijing 100020
e-mail:drugsafety.china@bayerhealthcare.com

<Korea> Bayer Korea Ltd. Samsung Boramae Omni, Tower 395-62, Shindaebang-dong, Dongjak-ku, Seoul 156-712
e-mail:pvkorea@bayerhealthcare.com

<US> Bayer HealthCare Pharmaceuticals Inc. P.O. Box 1000, Montville 07045-1000
e-mail:DrugSafety.GPV.US@bayer.com

9.5.2.10 Appropriateness of Measurements

All clinical and laboratory procedures that were used in this study were standard and generally accepted. Details of all methodology and reference ranges are provided in Appendix 7.

9.6 Data Quality Assurance

Throughout the study, close interaction was maintained between the principal investigator, his/her staff, the Executive investigator and the study monitor. Periodic visits were made to the study site to carry out trial monitoring and source document review.

The Quality Assurance Department at CMIC Co., Ltd. conducted a procedural audit at Kitasato University, Research Center for Clinical Pharmacology Bioatric Center in Japan, SNBL Clinical Pharmacology Center in the U.S, and Peking University First Hosipital in China after the study, which included review of the trial master file and the obtaining of informed consent. The audit certificate is included in Appendix 6.

A quality control check of the database against the source data was performed. Further quality control checks were performed on the data listings and summary tables presented in this report.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Handling of Data in Analyses

After study completion, the executive investigator was to fix the CRFs and decide the handling of incomplete subjects falling into the following items, as necessary, based on the specialist's advice:

1) Ineligible: Those who did not fulfill the inclusion criteria or met the exclusion criteria
2) Discontinuation: Those who satisfied the discontinuation criteria for subjects
3) Action violation: Those who deviated from the protocol in terms of administration, observation methods, implementation timing, etc.
4) Other deviations

Of the above Items 1) to 4), "1) Ineligible," "3) Action violation" and "4) Other deviations" were considered to be deviations.

The following time allowance of blood sampling and laboratory tests was not to be regarded as deviations. As to collecting urine (drug concentration in urine), it was to be regarded as deviation if the urine was discarded without collecting in the 2L-urine bottle.

(1) Time allowance of blood sampling (drug concentration in plasma)

- 0.5 to 6 hours from administration: less than 5 minutes
- 12 to 24 hours from administration: less than 10 minutes
- 36 to 48 hours from administration: less than 30 minutes

(2) Time allowance of laboratory tests

- 48 hours from administration: less than 1 hour

How to deal with missing and outlying values:

When the subject discontinued the study at early stage, the data were to be treated as missed and not compensated. Missing data due to the leakage of specimens by the breakage, back-up samples were to be measured and used to compensate the data. The outlying value was not to be disregarded and handling of these data was to be written in the study report, if necessary.

9.7.2 Statistical and Analytical Plan for Clinical Safety Data

9.7.2.1 Criteria for Evaluation

Individual and summary blood pressure, heart rate, body temperature, ECG ,clinical laboratory tests (haematology, plasma biochemistry, urinalysis and microscopy), and AEs were to be included in the evaluation of safety.

9.7.2.2 Analytical Plan

All subjects who received treatment, including any who did not complete the study were to be included in the safety data analysis.

Individual and summary blood pressures, heart rate, body temperature, ECG parameters and clinical laboratory data, were to be presented in tabular form with mean, median, SD and range (minimum and maximum) as appropriate.

For the laboratory safety data out of range values were to be flagged in the data listings and a list of clinically significantly abnormal values was to be presented.

AEs were to be tabulated and summarised according to MedDRA (Ver. 12.1 or more), and classified by preferred term and system organ class.

9.7.3 Determination of Sample Size

The number of subjects required to investigate ethic differences in the PK 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 sum of UGT1A1*6, *28, *36 and *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.

9.8 Changes to the Conduct of the Study and Planned Analyses

<Japan>

Two protocol amendments were issued for this study in Japan:

Amendment 1 was issued on 13 January 2010, and called for the following changes:

- Amount of blood sampling was changed for laboratory test and infectious disease test at the Chinese study site.
- Study No. ID (UMIN000002968) was created for this study.

Amendment 2 was issued on 18 January 2010, and called for the following change:

- US study site decided members of monitoring activities.

<China>

Two protocol amendments were issued for this study in China:

Amendment 1 was issued on 4 February 2010, and called for the following changes:

- Storage place for back-up samples of plasma and urine was changed in Chinese.
- The study site code was mistranslated as Korean study site code.

Amendment 2 was issued on 1 March 2010, and called for the following change:

- Amount of blood sampling for gene polymorphism has been changed since the 7 ml tube was not available at the study site.

<Korea>
Two protocol amendments were issued for this study in Korea:
Amendment 1 was issued on 15 February 2010, and called for the following change:

- The study site code was mistranslated as Chinese study site code.

Amendment 2 was issued on 26 February 2010, and called for the following change:

- EDTA-2K became acceptable since EDTA-2Na was not available at the study site.

<US>
No protocol amendment was issued for this study in the US.

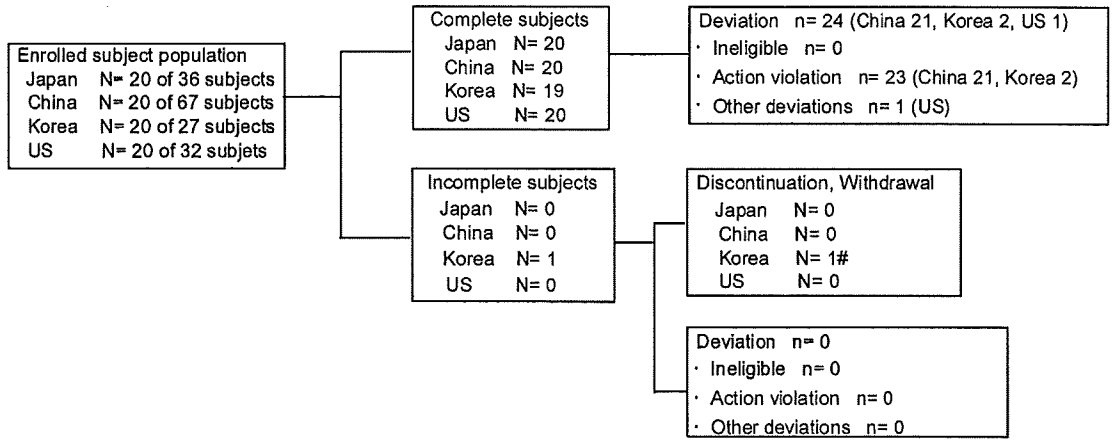
Several additional modifications were conducted in these above amendments. These copies of the amendments are included in Appendix 1.

10. STUDY SUBJECTS

10.1 Disposition of Subjects

The disposition of the subjects is shown in Figure 10-1.

In the study, 80 subjects (20 in each country) were included after reconfirmation of the eligibility. Of these, the study was discontinued in one subject (Korean) because the subject withdrew the consent with personal reason. The information about the withdrawal of the subject is shown in Appendix 8.4. The other 79 subjects (20 in Japan, 20 in China, 19 in Korea and 20 in the US) completed the study.



After the admission to study ward on time(16:30), the subject withdrew the consent with personal reason(18:00). This subject dropped out before administration of the study drug.

N: The number of the subjects
n: The number of the incidents

Figure 10-1 Disposition of Subjects

<Japanese (Japan)>

Of the total of 36 subjects who provided informed consents for both the study participation and the conduct of gene polymorphism examination, 20 subjects were enrolled in the study and received the study drug.

<Chinese (China)>

Of the total of 67 subjects who provided informed consents for both the study participation and the conduct of gene polymorphism examination, 20 subjects were enrolled in the study and received the study drug.

<Korean (Korea)>

Of the total of 27 subjects who provided informed consents for both the study participation and the conduct of gene polymorphism examination, 20 subjects were enrolled in the study and 19 subjects received the study drug. One subject withdrew his consent with personal reason before administrating the study drug.

<Caucasian (US)>

Of the total of 32 subjects who provided informed consents for both the study participation and the conduct of gene polymorphism examination, 20 subjects were enrolled in the study and received the study drug.

10.2 Data Sets Analyzed

Analysis population in each ethnic group is shown in Table 10-1.

In total, 162 male volunteers were screened. After screening, 80 volunteers (20 in each country) were included after reconfirmation of the eligibility. Out of these, all 20 volunteers except one Korean subject received 400 mg of moxifloxacin. The subject withdrew his consent with personal reason before administering the study drug.

Table 10-1 Analysis Population

	Japanese	Chinese	Korean	Caucasian	Total
Consented population	36	67	27	32	162
Enrolled subject population	20	20	20	20	80
Safety population	20	20	19*	20	79

*: After entering the study ward on time (16:30), one subject withdrew his consent with personal reason (18:00). This subject dropped out before administrating the study drug.

10.3 Protocol Deviations

The subjects with ineligible, action violation or other deviation are listed in Appendix 8.5. There were no major protocol deviations. A number of minor deviations were noted for various study assessments, and a small number of assessments were not performed in error. These were not considered to have a significant effect on the validity of the study.

No subjects were excluded from the safety population due to the protocol deviation.

<Japanese (Japan)>

No deviation.

<Chinese (China)>

All 20 subjects showed minor deviations at a parameter, blood urea nitrogen (BUN), in the blood biochemistry; BUN was not measured at screening, and the blood urea concentration was measured instead of BUN before and 48 hours after administration of the study drug.

Hematocrit was not measured before administration (Subject No. 000020002).

<Korean (Korea)>

The blood sampling for plasma drug concentration at 1.5 hours after administration of the study drug was obtained at a delay of 6 min (Subject Nos. 000030009, 000030011).

<Caucasian (US)>

The urine during 12-24 hours was discarded without collecting in a 2L-urine bottle (Subject No. 000040004).

10.4 Demographic and Other Baseline Characteristics

Table 10-2 shows summary statistics of demographic and other baseline characteristic data for the safety population. All subjects in each study site were healthy male volunteers who satisfied all of the inclusion criteria and none of the exclusion criteria. Demographic and other baseline characteristics by subject are listed in Appendix 8.7.

Table 10-2 Summary of demographic and other baseline characteristics

Parameter		Japan	China	Korea	US
Number of subjects		20	20	19	20
Sex	Male	20 (100.0)	20 (100.0)	19 (100.0)	20 (100.0)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race	Japanese	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Chinese	0 (0.0)	20 (100.0)	0 (0.0)	0 (0.0)
	Korean	0 (0.0)	0 (0.0)	19 (100.0)	0 (0.0)
	Caucasian	0 (0.0)	0 (0.0)	0 (0.0)	20 (100.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age [years]	Mean	23.0	29.2	25.7	28.0
	SD	3.91	4.20	3.58	4.76
	Minimum	20.0	22.0	20.0	21.0
	Median	22.00	30.00	26.00	27.50
	Maximum	34.0	34.0	33.0	35.0
Height [cm]	Mean	171.7	167.5	176.7	178.2
	SD	5.53	5.57	6.98	7.67
	Minimum	163.8	158.0	162.9	161.4
	Median	171.60	167.00	177.30	179.55
	Maximum	180.7	178.0	188.6	190.0
Body Weight [kg]	Mean	63.8	68.9	72.9	77.0
	SD	6.75	5.90	9.89	12.45
	Minimum	54.6	60.0	60.6	54.2
	Median	63.80	69.50	73.60	73.50
	Maximum	76.2	80.0	91.5	100.0
BMI [kg/m^2]	Mean	21.6	24.6	23.3	24.2
	SD	1.88	1.50	2.41	3.01
	Minimum	18.8	22.3	19.1	18.8
	Median	21.15	24.59	23.40	23.80
	Maximum	25.5	26.9	27.4	29.9
Allergies to drugs, food, etc.	No	20 (100.0)	20 (100.0)	19 (100.0)	20 (100.0)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Medical hystory[1)]	No	20 (100.0)	20 (100.0)	19 (100.0)	15 (75.0)
	Yes	0 (10.0)	0 (0.0)	0 (0.0)	5 (25.0)
Smoking History	No	16 (80.0)	16 (80.0)	14 (73.7)	20 (100.0)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Previously	4 (20.0)	4 (20.0)	5 (26.3)	0 (0.0)
Alcohol History	No	1 (5.0)	19 (95.0)	13 (68.4)	3 (15.0)
	Yes	14 (70.0)	0 (0.0)	6 (31.6)	14 (70.0)
	Previously	5 (25.0)	1 (5.0)	0 (0.0)	3 (15.0)
SBP [mmHg]	Mean	107.3	119.0	122.8	115.7
	SD	10.46	10.93	10.30	10.32
	Minimum	88.0	96.0	108.0	98.0
	Median	107.00	120.00	121.00	117.00
	Maximum	125.0	140.0	146.0	133.0
DBP [mmHg]	Mean	64.6	78.4	74.1	75.3
	SD	7.55	7.80	7.40	8.45
	Minimum	48.0	62.0	61.0	60.0
	Median	63.50	80.00	76.00	74.00
	Maximum	78.0	88.0	85.0	89.0
Pulse rate [bpm]	Mean	64.7	63.5	71.8	64.5
	SD	7.04	6.05	11.31	7.88
	Minimum	54.0	56.0	49.0	50.0
	Median	64.00	62.00	73.00	64.00
	Maximum	83.0	80.0	90.0	85.0
Body temperature [°C]	Mean	36.2	36.1	36.2	36.5
	SD	0.40	0.30	0.38	0.46
	Minimum	35.3	35.8	35.7	35.1
	Median	36.25	36.00	36.20	36.70
	Maximum	36.8	36.8	36.8	37.0
12 Lead ECG	Normal	18 (90.0)	20 (100.0)	11 (57.9)	4 (20.0)
	Abnormal-NCS[2)]	2 (10.0)	0 (0.0)	8 (42.1)	16 (80.0)
	Abnormal-CS[3)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1) A history of diseases involving the heart, lung, kidney, blood, central nervous system, metabolic system and skeletal muscle system
2) Abnormal - not clinically significant
3) Abnormal - clinically significant

Source: Appendix. 8.7

Demographic characteristics

<Japanese (Japan)>

Mean age, height, weight and BMI of all the 20 healthy Japanese adult male subjects were 23.0 years (median: 22.00, min: 20.0, max: 34.0), 171.7 cm (median: 171.60, min: 163.8, max: 180.7), 63.8 kg (median: 63.80, min: 54.6, max: 76.2) and 21.6 kg/m^2 (median: 21.15, min: 18.8, max: 25.5), respectively.

<Chinese (China)>

Mean age, height, weight and BMI of all the 20 healthy Chinese adult male subjects were 29.2 years (median: 30.00, min: 22.0, max: 34.0), 167.5 cm (median: 167.00, min: 158.0, max: 178.0), 68.9 kg (median: 69.50, min: 60.0, max: 80.0) and 24.6 kg/m^2 (median: 24.59, min: 22.3, max: 26.9), respectively.

<Korean (Korea)>

Mean age, height, weight and BMI of all the 19 healthy Korean adult male subjects were 25.7 years (median: 26.00, min: 20.0, max: 33.0), 176.7 cm (median: 177.30, min: 162.9, max: 188.6), 72.9 kg (median: 73.60, min: 60.6, max: 91.5) and 23.3 kg/m^2 (median: 23.40, min: 19.1, max: 27.4), respectively.

<Caucasian (US)>

Mean age, height, weight and BMI of all the 20 healthy Caucasian adult male subjects were 28.0 years (median: 27.50, min: 21.0, max: 35.0), 178.2 cm (median: 179.55, min: 161.4, max: 190.0), 77.0 kg (median: 73.50, min: 54.2, max: 100.0) and 24.2 kg/m^2 (median: 23.80, min: 18.8, max: 29.9), respectively.

Allergies to drugs, food, etc.

None of the subjects allergic to drugs, food, etc. were enrolled in any study site.

Medical History

Five subjects (all Caucasian) had medical history abnormalities at screening, although none of these abnormalities precluded inclusion into the study. All subjects were well at the screening visit.

Smoking History

None of the subjects were current smokers; 13 subjects (4 in Japan; 4 in China; 5 in Korea) were ex-smokers, but had given up more than 6 months before the study, as required by the protocol.

Alcohol History

Several subjects in each study site except China consumed alcohol, but no more than 50 g per day, complying with the exclusion criteria. In China, only one subject was ex-drunker.

Vital Signs and 12-Lead ECG

All vital sign measurements (SBP, DBP, Pulse rate and Body temperature) were considered normal. Several abnormalities were observed in ECG measurements, but were not considered to be clinically significant.

Gene Polymorphism examination

Gene polymorphism of the UGT1A1 and the enzymes related to the pharmaco-kinetics of moxifloxacin was analyzed in healthy adult male subjects in each ethnic group. The results were summarized by Dr Masahiro Tohkin in the separate report.

10.5 Measurement of Treatment Compliance

Administration of a study drug (tablet) was followed by a hand and mouth check, and all drug administration times were recorded in the appropriate CRF.

10.6 Concomitant Medication

No concomitant medications were taken in any country during the course of this study.

11. PHARMACOKINETIC EVALUATION

See the PK report written by Dr. Masahiro Tohkin.

12. SAFETY EVALUATIONS

12.1 Extent of Exposure

Every subject received 400 mg of moxifloxacin in these four ethnic groups.

12.2 Adverse Events (AEs)

An AE referred to any unfavourable and unintended sign (laboratory values, vital signs and 12-lead ECG), symptom or disease newly occurred after administration of the study drug, regardless of the causal relationship with the study drug.

12.2.1 Brief Summary of Adverse Events

Although 14 AEs were observed during the study, no serious AE was occurred in these four ethnic groups.
These 14 adverse events were reported by 12 subjects:

<Japanese (Japan)>	5 subjects reported 6 AEs
<Chinese (China)>	1 subject reported 1 AE
<Korean (Korea)>	3 subjects reported 4 AEs
<Caucasian (US)>	3 subjects reported 3 AEs

The most frequently reported AEs were malaise (3 incidents in 2 Japanese subjects) and headache (2 incidents in 2 Caucasian subjects and 1 incident in a Korean subject).

Only 4 AEs (urticaria in a Japanese subject, dizziness and headache in 2 Korean subjects, headache in a Caucasian subject) were considered to be probably related to the study drug, and the other AEs were considered to be unknown, probably not related or definitely not related.

All AEs except one were mild in severity. Only an incident of headache (Caucasian) was moderate in severity and was considered probably related to the study drug.

There were no deaths or other serious adverse events.

12.2.2 Display of Adverse Events

Complete listings of all AEs by subject reported during the course of the study are presented in Appendix 8.1. The reported term (original), MedDRA preferred term and system organ class, severity, seriousness, onset and outcome, relationship to study drug and treatment required taken are listed.

Table 12-1 summarises the numbers and incidence of subjects and the numbers of events of reporting each AE after administration of the study drug, and also present summaries of AEs by severity.

<Japanese (Japan)>

All 6 AEs were mild in severity. Five of them were considered by the investigator to be probably not related to the study drug or unknown, and an incident of urticaria was considered to be probably related to the study drug.

<Chinese (China)>

One AE occurred was mild in severity and considered by the investigator to be definitely not related to the study drug.

<Korean (Korea)>

All 4 AEs were mild in severity. Two of them were considered by the investigator to be probably not related to the study drug or unknown, and other 2 AEs (dizziness and headache) were considered to be probably related to the study drug.

<Caucasian (US)>

Two of 3 AEs were mild in severity and considered by the investigator to be probably not related to the study drug. An incident of headache was moderate in severity and considered to be probably related to the study drug.

Table 12-1 Incidence of AEs – Evaluation for severity

<Japanese>

N=20

Severity	Mild		Moderate		Severe		Total	
Adverse Event SOC PT	Number of subjects (events)	Incidence (%)	Number of subjects	Incidence (%)	Number of subjects	Incidence (%)	Number of subjects	Incidence (%)
	5 (6)	25					5 (6)	25
Skin and subcutaneous tissue disorders	1(1)	5					1(1)	5
Urticaria	1(1)	5					1(1)	5
Investigations	1(1)	5					1(1)	5
Electrocardiogram PR prolongation	1(1)	5					1(1)	5
Respiratory, thoracic and mediastinal disorders	1(1)	5					1(1)	5
Epistaxis	1(1)	5					1(1)	5
General disorders and administration site conditions	2(3)	10					2(3)	10
Malaise	2(3)	10					2(3)	10

Incidence = the percentage of subjects

<Chinese>

N=20

Severity	Mild		Moderate		Severe		Total	
Adverse Event SOC PT	Number of subjects (events)	Incidence (%)	Number of subjects	Incidence (%)	Number of subjects	Incidence (%)	Number of subjects	Incidence (%)
	1 (1)	5					1 (1)	5
Investigations	1 (1)	5					1 (1)	5
C-reactive protein increased	1 (1)	5					1 (1)	5

Incidence = the percentage of subjects

Source: Appendix. 8.1

* Coded using MedDRA (Ver. 12.1 or more)