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

9.4.9 Treatment Compliance

Administration of study drug to the volunteers was performed in each study site by qualified and accredited members of the study site staff. Administration of oral tablet was followed by a hand and mouth check.

9.5 Pharmacokinetic and Safety Evaluations

9.5.1 Procedure for Study Implementation

9.5.1.1 Screening

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

Table 9-1 Observation and tests at screening

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

[Rationales for selection of observation and tests]

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

9.5.1.2 Study

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

Table 9-2 Observation and tests during the study

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

Table 9-3 Study Schedule

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

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

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

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

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

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

9.5.2 Evaluation Items for the Safety Endpoints

9.5.2.1 Subjective Symptoms and Their Verification

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

9.5.2.2 Physical Examination Findings (History Taking and Phonacoscopy)

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

9.5.2.3 Clinical Laboratory Evaluation

9.5.2.3.1 Hematology

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

9.5.2.3.2 Blood Biochemistry

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

9.5.2.3.3 Urinalysis

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

9.5.2.4 Vital Signs

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

9.5.2.5 Body Weight

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

9.5.2.6 Number and Amount of Blood Sampling in the Entire Study

Total number of blood sampling per subject: 13

<Details of the number and amount of blood sampling>

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

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

[Rationales for selection of the tests 9.5.2.1 to 9.5.2.5]

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

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

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

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

9.5.2.7 Adverse Events

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

9.5.2.7.1 Definitions

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

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

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

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

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

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

9.5.2.7.2 Assessment of AEs

• Physical examination

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

• Vital signs

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

• Laboratory values

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

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

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

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

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

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

The grade of abnormal value was written in the CRF.

9.5.2.7.3 Evaluation of AEs

If AE occurred, the principal investigator was to enter the following information in the CRF: the details, onset date/time, severity and seriousness (serious or non-serious) of AE, 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 AE.
Moderate: Treatment or action was required for AE.
Severe: Therapy or treatment was required for AE and the study was discontinued.

• 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 "Unknown", "Probably not related" or "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.

9.5.2.7.4 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 the unknown serious AE was shown, followed 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 the unknown serious AE was shown, 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 unknown serious AE was shown, follow the below section (4).

(4) Reports for unknown serious AEs

1) When the unknown serious AE occurred, the principal investigator was to report its information to the head of the study site, the executive investigator and the principal investigators of the other study sites. The head of the study site (or the principal investigator) was to take actions required during the relevant study period after reporting to the study ethics committee.
2) When unknown serious AE related to the study occurred, the head of the study site (or the principal investigator) was to publish the conditions and results of actions taken for the relevant AE, and reported its information to the Minister of Health, Labor and Welfare in Japan (MHLW). In general, unknown serious AEs like deaths or life-threatening ones, were to be reported within seven days, and other serious AEs were reported within 15 days after onset. The format shown in "Protocol 22 Appendix 2" was used when reporting to the MHLW.
3) When the unknown serious AEs occurred outside Japan, the executive investigator was to report to the MHLW.

9.5.2.8 Appropriateness of Measurements

All clinical and laboratory procedures that were used in this study were standard and generally accepted. Reference ranges are provided in Appendix 7.

9.6 Data Quality Assurance

Throughout the study, close interaction was maintained between the principal investigator, the researchers, the executive investigator and the study monitors. Periodic visits were made to the study site to carry out trial monitoring and source document review.

The Quality Management Department at CMIC Co., Ltd. conducted a procedural audit at Seoul National University Hospital and CMIC Korea Co., Ltd on 16 and 17 September 2010 followed by at National Institute of Health Science in Japan on 24 November 2010 and at Kitasato University, Research Center for Clinical Pharmacology Bioiatric Center on 29 and 30 November 2010. It was conducted after the study, which included review of the trial master file and the obtaining of informed consent.

No findings were found except for the one in Seoul National University Hospital. It was about obtaining subjects' written consent for re-blood sampling and obligation of report to IRB and the sponsor. Afterward, the site dealt with the finding appropriately.

The audit certificates are 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 method, 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.

(1) Time allowance of blood sampling (drug concentration in plasma)
- 0.5 to 8 hours after administration: ± 5 minutes
- 12 to 24 hours after administration: ± 10 minutes

(2) Time allowance of laboratory tests
- 24 hours after administration: ± 1 hour

(3) Time allowance of testing vital sign
- 24 hours after administration: ± 30 minutes

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 as references. 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, clinical laboratory tests (hematology, blood biochemistry and urinalysis), and AEs were to be included in the evaluation of safety.

9.7.2.2 Analytical Plan

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

The list of baseline backgrounds of the safety analysis set (at screening) was prepared and frequency tabulation or basic statistics (mean, median, minimum and maximum) was calculated.

Individual and summary blood pressures, pulse rate, body temperature, body weight and clinical laboratory data, were to be presented in tabular form with mean, median, standard deviation (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 summarized according to MedDRA (Ver. 13.0 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[1]. Based on the integration of the data, the difference in $AUC_{0-\infty}$ revealed about 60% between Japanese and Western populations, and the difference in $AUC_{0-\infty}$ was not expected among East Asian population from the data of rosuvastatin. Considering this information, the number of the patients was calculated to detect 40% difference in $AUC_{0-\infty}$ at least between East Asian and Western populations with a power of 80%. As a result, under the null hypothesis "There is no difference in PK among Japanese, Chinese, Korean and Caucasian" and the alternative hypothesis that at least one ethnic group shows the difference in the mean of PK, the number of subjects was calculated to be at least 25 subjects based on information of a 40% and 20% difference in $AUC_{0-\infty}$ with a power of 80% between Japanese and Western populations, and between Japanese and Chinese/Koreans, respectively. Since the analysis of gene polymorphism is performed after PK analysis. Based on this, the target sample size of this study was determined to be 40 subjects from each ethnic population, considering the subjects excluded from the results of analysis of CYP3A5 to be CYP3A5*3 homo, dropouts by discontinuation or withdrawals.

The reason why the target sample size was approximately 1.5 times the number of subjects necessary for statistical analysis was based on information on ethnic differences of CYP3A5 polymorphism. According to the investigation[2], the frequency of CYP3A5*3 polymorphism was 0.7 to 0.77 in East Asian population and 0.85 to 0.95 in Caucasian population.

9.8 Changes to the Conduct of the Study and Planned Analyses

<Japan>
Three protocol amendments were issued for this study in Japan:

Amendment 1 (Version 1.1J) was issued on 10 June 2010, and called for the following change:

- A few expressions were not appropriate as the Japanese sentence.

Amendment 2 (Version 2.0) was issued on 18 June 2010, and called for the following change:

- Processing methods for blood sampling were not suitable.
- Telephone numbers and/or fax numbers were revised in Chinese study site (at the protocol attachment).

Amendment 3 (Version 3.0, only for attachment) was issued on 31 August 2010, and called for the following change:

- Storage location of blood sample for gene polymorphism examination has been changed in China.
- Auditor has been changed.

<China>
Four protocol amendments were issued for this study in China:

Amendment 1 (Version 1.0C) was issued on 11 June 2010, and called for the following changes:

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

Amendment 2 (Version 2.0C) was issued on 18 June 2010, and called for the following change:

- To avoid degradation of study drug, the processing time and "should be handled on ice" were given.

Amendment 3 (Version 2.1C) was issued on 25 August 2010, and called for the following change:

- Storage location of blood sample for gene polymorphism test has been changed.

Amendment 4 (Version 3.0 for attachment) was issued on 31 August 2010, and called for the following change:

- Gene polymorphism test facility (the responsible person, address and TEL/FAX numbers) have been changed.
- Auditor has been changed.

<Korea>
One protocol amendment was issued for this study in Korea:

Amendment 1 (Version 3.0K only for attachment) was issued on 31 August 2010, and called for the following change:

- Monitor and auditor have been changed.

Attachment (Version 2.0K) is not issued since Version 2.0 is exclusive to Japan.

<US>
One protocol amendment was issued for this study in the US:

Amendment 1 (Version 3.0U only for attachment) was issued on 31 August 2010, and called for the following change:

- Another person has been added to the study drug storage manager(s).
- Auditor has been changed.

Attachment (Version 2.0U) is not issued since Version 2.0 is exclusive to Japan.

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.

The study was conducted from 5 July 2010 to 10 October 2010 (Table 10-2).

Total 164 subjects (40 in Japan, 40 in China, 40 in Korea and 44 in the US) were enrolled into the study after confirmation of the eligibility, and 159 subjects (40 in Japan, 39 in China, 40 in Korea and 40 in the US) except 5 (1 in China and 4 in the US) were completed the study. Of the incomplete 5 subjects, 3 subjects were withdrawn from the study because they withdrew their informed consent with personal reason before administration of the study drug (2 in the US) and after administration (1 in China) The remaining 2 subjects (both in the US) deviated because of ineligible (the use of a prohibited concomitant medication) or other deviation (the principal investigator's judgment on the necessity of ECG investigation). Information about the former 3 subjects with withdrawal and the subjects with ineligible/action violation/other deviations including the latter 2 subjects is shown in Appendix 8.3 and Appendix 8.4, respectively. 160 subjects were regarded as safety analysis population (Table 10-1).

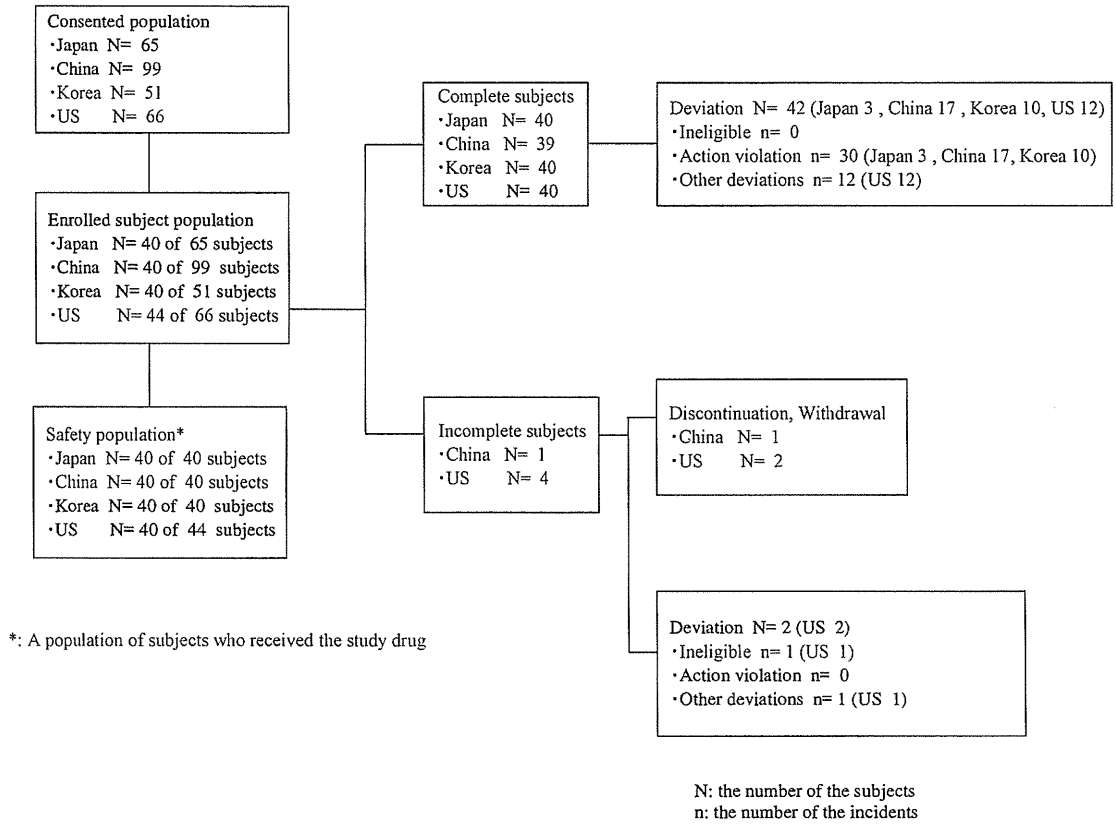

Figure 10-1 Disposition of Subjects

Table 10-1 Analysis Population

Population	Japanese (Japan)	Chinese (China)	Korean (Korea)	Caucasian (US)	Total
Consented population	65	99	51	66	281
Enrolled subject population	40	40	40	44*	164
Safety population	40	40	40	40	160

* After enrolling the study, 2 subjects withdrew their consent with personal reason, and other 2 subjects deviated from the study protocol. These 4 subjects dropped out before study drug administration.

Table 10-2 Study period in each ethnic group

Group No.	Japanese (Japan)	Chinese (China)	Korean (Korea)	Caucasian (US)
Group 1	5-7 July 2010 (20)	9-11 August 2010 (20)	10-12 August 2010 (8)	27-29 August 2010 (10)
Group 2	7-9 July 2010 (20)	16-18 August 2010 (20)	12-14 August 2010 (8)	10-12 September 2010 (9)
Group 3			16-18 August 2010 (9)	24-26 September 2010 (6)
Group 4			19-21 August 2010 (1)	8-10 October 2010 (15)
Group 5			26-28 August 2010 (14)	

The dates of the admission and follow-up of each group were described.
The figures in parentheses are the number of subjects who received the study drug.

10.2 Protocol Deviations

The subjects with ineligible, action violation or other deviation are listed in Appendix 8.4. There were 2 major deviations and 42 minor deviations as shown below.

- Major deviations

  The following two subjects with major deviation were withdrawn from the study before study drug administration.

<Caucasian (US)>

One subject (Subject No. 000040008) was judged as ineligible after enrollment due to the use of the concomitant medication at screening.

The principal investigator performed ECG investigation for 1 subject (Subject No. 000040011) after enrollment into the study. This subject was judged as deviation.

- Minor deviations

  All the minor deviations described below were not considered to have a significant effect on the evaluation of the safety data. No subjects were excluded from the safety population due to the protocol deviation.

<Japanese (Japan)>

The blood samplings for plasma drug concentration from 1-3 hours were performed in the supine position to prevent feeling sickness and keep safety by re-drawing blood due to the thinness of the blood vessel (Subject Nos. 000010012, 000010015).

Blood sampling at 1 hour after administration was conducted 7 minutes later than the scheduled time in Subject No. 000010015. It was deviated from 2 minutes from the time allowance (± 5 minutes).

<Chinese (China)>

The vital signs at 24 hours after administration were conducted 31-42 minutes earlier than the scheduled time in 17 subjects (Subject Nos. 000020003 - 000020019). They were deviated 1-12 minutes from the time allowance (± 30 minutes).

<Korean (Korea)>

The syphilis TP (Treponema pallidum) antibody test was not conducted at screening (Subject No. 0000300006).

The blood sampling for plasma drug concentration at 5 hours after administration was conducted 10-16 minutes later than the scheduled time in 4 subjects (Subject Nos. 000030013 - 000030016). They were deviated 5-11 minutes from the time allowance (± 5 minutes).

The urine sampling at 24 hours after administration was conducted 87 minutes earlier than the scheduled time in 1 subject (Subject No. 000030028). It was deviated 27 minutes from the time allowance (± 1 hour).

The assessment of vital signs was conducted 33-42 minutes earlier than the scheduled time in 3 subjects (Subject Nos. 000030032 - 000030034). They were deviated 3-12 minutes from the time allowance (± 30 minutes).

Although the evaluation of urinary protein at screening was positive, urinary sediment wasn't conducted in 1 subject (Subject No. 000030034).

<Caucasian (US)>

Nine subjects* checked in to the study site after the scheduled time (16:30) on the day before study drug administration.

* Subject Nos. 00040002, 00040005, 00040006, 00040010, 000040012, 00040016, 00040024, 00040045, 00040058

Although intake of food and drinking water other than those provided from the study site was prohibited during hospitalization, a kind of soda pop was consumed on Day -1 in 3 subjects (Subject Nos. 000040031, 000040032, 000040034).

10.3 Demographic and Other Baseline Characteristics

Table 10-3 shows summary statistics of demographic and other baseline characteristic data for the safety population. All subjects who received the study drug in each study site were healthy male volunteers who satisfied all of the inclusion criteria and none of the exclusion criteria.

Table 10-3 Summary of demographic and other baseline characteristics

Parameter		Japanese	Chinese	Korean	Caucasian
Number of subjects		40	40	40	40
Sex	Male	40 (100.0)	40 (100.0)	40 (100.0)	40 (100.0)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race	Chinese	0 (0.0)	40 (100.0)	0 (0.0)	0 (0.0)
	Japanese	40 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Korean	0 (0.0)	0 (0.0)	40 (100.0)	0 (0.0)
	White	0 (0.0)	0 (0.0)	0 (0.0)	40 (100.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age [years]	Mean	25.0	31.5	23.5	25.7
	SD	3.95	2.91	2.66	4.03
	Minimum	20.0	23.0	20.0	20.0
	Median	24.00	32.50	24.00	25.00
	Maximum	34.0	34.0	32.0	35.0
Height [cm]	Mean	171.6	167.3	173.6	176.4
	SD	6.34	4.93	5.52	6.85
	Minimum	161.3	157.0	162.8	165.0
	Median	171.40	167.00	174.00	176.40
	Maximum	184.6	177.0	185.9	198.4
Body Weight [kg]	Mean	63.6	65.9	67.9	77.5
	SD	7.46	8.37	9.36	10.30
	Minimum	51.5	50.5	52.7	54.3
	Median	62.15	65.00	66.50	77.65
	Maximum	84.0	84.0	94.2	99.1
BMI [kg/m^2]	Mean	21.6	23.5	22.5	24.9
	SD	2.44	2.43	2.58	2.77
	Minimum	18.6	19.2	18.9	19.3
	Median	20.80	23.45	21.55	24.80
	Maximum	26.7	28.4	29.5	29.9
Medical History	No	29 (72.5)	40 (100.0)	34 (85.0)	15 (37.5)
	Yes	11 (27.5)	0 (0.0)	6 (15.0)	25 (62.5)
Smoking History	No	27 (67.5)	40 (100.0)	38 (95.0)	36 (90.0)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Previously	13 (32.5)	0 (0.0)	2 (5.0)	4 (10.0)
Alcohol History	No	5 (12.5)	40 (100.0)	20 (50.0)	10 (25.0)
	Yes	12 (30.0)	0 (0.0)	20 (50.0)	28 (70.0)
	Previously	23 (57.5)	0 (0.0)	0 (0.0)	2 (5.0)
SBP [mmHg]	Mean	106.7	118.5	118.0	116.9
	SD	10.00	10.13	10.03	9.48
	Minimum	85.0	94.0	100.0	98.0
	Median	106.50	120.00	118.50	116.50
	Maximum	129.0	136.0	138.0	140.0
DBP [mmHg]	Mean	65.4	80.5	72.4	65.0
	SD	7.77	5.97	7.55	7.17
	Minimum	54.0	64.0	56.0	54.0
	Median	64.50	80.00	71.50	64.50
	Maximum	79.0	88.0	89.0	81.0
Pulse Rate [bpm]	Mean	60.5	61.6	68.7	61.0
	SD	8.38	7.52	8.20	9.49
	Minimum	47.0	52.0	55.0	43.0
	Median	60.50	60.00	67.00	61.00
	Maximum	84.0	92.0	87.0	83.0
Body Temperature [°C]	Mean	36.0	36.2	36.2	36.2
	SD	0.42	0.31	0.39	0.36
	Minimum	35.3	35.8	35.5	35.2
	Median	36.10	36.10	36.20	36.15
	Maximum	36.9	37.0	37.0	37.0
12 Lead ECG	Normal	34 (85.0)	40 (100.0)	20 (50.0)	10 (25.0)
	Abnormal-NCS[1)]	6 (15.0)	0 (0.0)	20 (50.0)	30 (75.0)
	Abnormal-CS[2)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1) Abnormal - not clinically significant

2) Abnormal - clinically significant