9.5 Pharmacokinetic and Safety Evaluations

9.5.1 Procedure for Study Implementation

9.5.1.1 Screening

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

Table 9-1 Observation and tests at screening

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

[Rationales for selection of observation and tests]

General items, which are found to be necessary for verification of the health condition of subjects to be enrolled in the study, were adopted.

The infectious disease test was specified for the purpose of the prevention of infection to personnel handling blood.

9.5.1.2 Study

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

Table 9-2 Observation and tests during the study

Clinical observation		Physical examination by the investigator
PK		Plasma drug concentrations
Laboratory tests	Hematology	WBC, differential WBC, RBC, hemoglobin concentration, hematocrit value, platelet count, and reticulocyte count
	Blood biochemistry	Blood sugar, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, total protein, albumin, uric acid, creatinine, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, LDH, ALP, CK, Na, K, Cl, and CRP
	Urinalysis	Glucose, bilirubin, ketone bodies, occult blood, pH, protein, urobilinogen, and sediment (to be conducted if protein or occult blood is positive)
Vital signs, body weight measurement		Blood pressure/pulse rate (sitting), body temperature, and body weight
Gene polymorphism examination		Collected blood specimens (e.g., EDTA-2K added) was refrigerated at -20°C or less, and sent to the institute for gene polymorphism analysis using dry ice within 2 weeks after sampling, if possible.

Table 9-3 Study Schedule

		Screening	Primary Study														
Days of the study		Within 30 days	Day -1	Day 1									Day 2		Day 3		Day 4
Time			Admitted by 16:30	8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	17:00	21:00	9:00	21:00	9:00	21:00	9:00
Time after oral administration (h)					0	1	2	3	4	5	6	8	12	24	36	48	60	72
Admission/visit		Visit	Admission	←														→
Consent obtainment		○																
Subject backgrounds		○																
Administration of Study drug					○													
Physician's examination		○		○								○		○		○		○
Body weight		○		○														○
Body height		○																
Vital sign		○		○										○		○		○
12-lead ECG		○																
Adverse events			←															→
Blood sampling	Detection of gene polymorphism[a)]																	○
	PK[b)]			○		○	○	○	○	○	○	○	○	○	○	○	○	○
	Laboratory test	○		○														○
	Infectious disease test	○																
Urinalysis	Laboratory test	○		○														○

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

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

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

9.5.2 Evaluation Items for the Safety Endpoints

9.5.2.1 Subjective Symptoms and Their Confirmation

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

9.5.2.2 Physical Examination Findings (Inquiry, Auscultation Percussion)

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

9.5.2.3 Clinical Laboratory Evaluation

9.5.2.3.1 Hematology

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

9.5.2.3.2 Blood Biochemistry

1) Test items: Blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, total protein, albumin, uric acid, creatinine, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, LDH, ALP, CK, Na, K, Cl, CRP
2) Test period: Prior to and 72 hours after administration (Time allowance: ±1 hour)
3) Evaluation method: "H" was added to values deviated from the upper limit of baseline, and "L" was added to those deviated from the lower limit of baseline. In addition, for deviations, grade and abnormal changes were determined.

9.5.2.3.3 Urinalysis

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

9.5.2.4 Vital Signs

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

9.5.2.5 Body Weight

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

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

[Rationales for setting test items, 9.5.2.1 to 9.5.2.5]

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

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

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

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

9.5.2.6 Number and Amount of Blood Sampling in the Entire Study

Total number of blood collection per subject: 15 times

<Frequency and amount of blood collection>

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

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

9.5.2.7 Adverse Events

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

9.5.2.7.1 Definitions

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

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

A serious AE referred to any unfavorable medical occurrence in the subjects during the study period that

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

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

9.5.2.7.2 Assessment of AEs

• Physical examination

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

• Vital signs

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

• Laboratory values

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

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

When laboratory values were not listed in the scale of DAIDS AE grading table, the following grade was used. It was documented in the CRF. If the grading became 2 or more after administration, it was to be regarded as an AE. However, the grading did not become worse; it was not to be regarded as an AE.

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

Moderate: (Grade 2) An event that interferes with the subject's daily activities because of discomfort, or affects the clinical condition and requires treatment.

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

The grade of abnormal value was written in the CRF.

9.5.2.7.3 Evaluation of AEs

If an 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 the 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 the AE.

Moderate: Treatment or action was required for the AE.

Severe: Therapy or treatment was required for the 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 subjects 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 not a temporal correlation with study drug administration, or there is enough 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) Reporting at onset of serious AE

When a serious AE occurred, the principal investigator was immediately to report to the head of the study site, executive investigator, and principal investigators in other study sites (by e-mail or Fax). And the principal investigator was to inform manufacturer, Boehringer Ingelheim and its affiliated companies in Japan, China and the US. Only in Korea, a serous AE was to be reported to KFDA. (by e-mail or Fax in Japan, China, and Korea; by telephone in the US). What was informed by e-mail or Fax is shown in "Protocol 22 Appendix 2".

【Contact address for serious AEs 】

- Executive investigator

  Professor Shinichi Kawai

  Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

  e-mail : skawai@med.toho-u.ac.jp

  Fax : +81-3-5753-8513

- Manufacturer

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Drug Information Unit
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9.5.2.8 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, 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 Assurance Department, Quality Management Division, CMIC Co., Ltd. conducted a procedural audit at Pharmacokinetics and Bioanalysis Center, Shin Nippon Biomedical Laboratories, Ltd in Japan and Seoul National University Hospital in Korea 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 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) Acceptable range of blood collection time (plasma concentration)

- 1 to 8 hours after administration: ± 5 minutes
- 12 and 24 hours after administration: ± 10 minutes
- 36 to 72 hours after administration: ± 30 minutes

(2) Acceptable range of laboratory testing time

- 72 hours after administration: ± 1 hour

(3) Acceptable range of vital sign measuring time

- 24 hours after administration: ± 30 minutes
- 48 and 72 hours after administration: ± 1 hour

How to deal with missing and outlying (abnormal) 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 of the container, back-up samples were to be measured and used to compensate the data as references. The outlying (abnormal) 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, pulse 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 those 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 significant abnormal values was to be presented.

AEs were to be tabulated and summarised 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 for the study examining PK differences between the ethnic groups was calculated. The number of subjects of each ethnic group required for detecting 20% differences of $AUC_{0-\infty}$ between the ethnic groups at 5% of significance level and 80% or more of detective power was calculated. For multiplicity of the test, the significant level of each test can be set to be 5%, assuming that the equivalence of 4 countries can be indicated only if the equivalence between Japanese/Koreans, Japanese/Chinese, and Japanese/Caucasians is statistically verified. In addition, calculation is made with 0.928... ($\sqrt[3]{0.8}$) of detective power of each study so that the detective power of the whole study may be 80% or more. The number of subjects of each ethnic group was estimated, using the existing Japanese data as basic mean and variance, to be 29, but considering discontinued cases and withdrawals, the target number of subjects of this study was defined to be 30.

9.8 Changes to the Conduct of the Study and Planned Analyses

<Japan, China, Korea and the US>
Two protocol amendments were issued for this study.
Amendment 1 (Version 1.1) was issued on 28 September 2010, and called for the following change:

- Two drug-concentration-measuring sites in Japan became integrated according to SNBL's convenience.

Amendment 2 (Version 1.2) was issued on 4 October 2010, and called for the following change:

- Since the space for seal or signature is not set for CRF of this study, the last sentence of item 1 in Chapter 14 was deleted.

<Korea>
One more protocol amendment was issued in Korea.

Amendment of the protocol attachment (Version 1.3K) was issued on 7 January 2011, and called for the following change:

- The monitor has been changed.

The same version number, 1.3K, has assigned to both main part and attachment according to the IRB's request although there was no change in main part.

The pre and post amendment points 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 16 November 2010 to 21 December 2010 (Table 10-2).

Total 121 subjects (30 in Japan, 30 in China, 30 in Korea and 31 in the US) were enrolled into the study after confirmation of the eligibility, and 119 subjects (30 in Japan, 30 in China, 29 in Korea and 30 in the US) except 2 (1 in Korea and 1 in the US) were completed the study. The incomplete 2 subjects were withdrawn from the study because 1 Korean subject did not fulfill inclusion or exclusion criteria and 1 Caucasian subject withdrew his consent before administration of the study drug. Information about the 2 subjects with withdrawal and the 10 subjects with ineligible/action violation/other deviations is shown in Appendix 8.3 and Appendix 8.4, respectively. The 119 subjects were regarded as the safety population (Table 10-1).

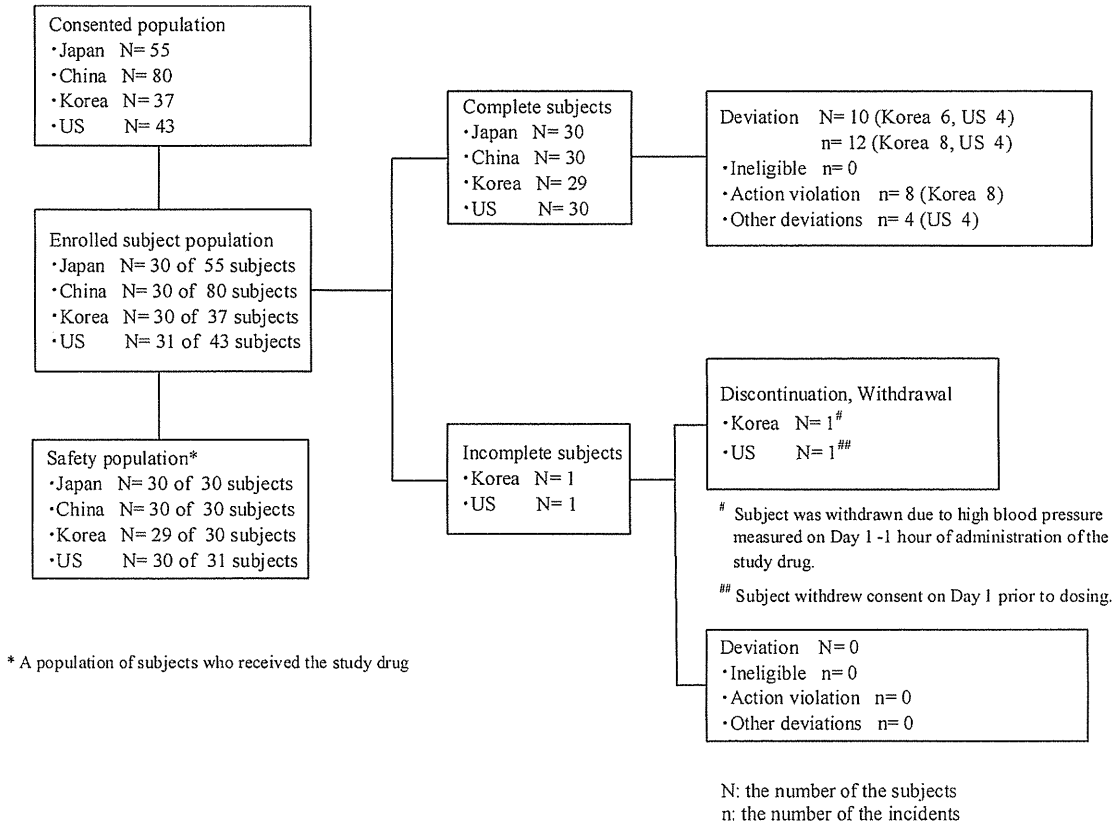

Figure 10- 1 Disposition of Subjects

Table 10-1 Analysis Population

Population	Japanese (Japan)	Chinese (China)	Korean (Korea)	Caucasian (US)	Total
Consented population	55	80	37	43	215
Enrolled subject population	30	30	30	31	121
Safety population	30	30	29*	30**	119

* After enrolling the subject into the study, it was confirmed that this subject deviated from the study protocol. The subject dropped out before study drug administration.

** The subject withdrew the consent on Day 1 prior to dosing.

Table 10-2 Study period in each ethnic group

Group No.	Japanese (Japan)	Chinese (China)	Korean (Korea)	Caucasian (US)
Group 1	16-20 Nov 2010 (15)	18-22 Nov 2010 (19)	24-28 Nov 2010 (6)	13-17 Dec 2010 (11)
Group 2	30 Nov-4 Dec 2010 (15)	25-29 Nov 2010 (11)	1-5 Dec 2010 (7)	17-21 Dec 2010 (19)
Group 3			6-10 Dec 2010 (7)	
Group 4			8-12 Dec 2010 (3)	
Group 5			13-17 Dec 2010 (6)	

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 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)>

No deviation.

<Korean (Korea)>

The PK sampling at 6 hours was conducted 8 minutes later than the scheduled time in 1 subject (Subject No. 000030001). It was deviated 3 minutes from time allowance (acceptable range: ± 5 minutes).

Four subjects* drank water from water purifier instead of soft mineral water.

* Subject Nos. 000030007, 000030011, 000030013, 000030014

The assessments of 3 incidents (body temperature, blood pressure and pulse rate) at 24 hours after administration of the study drug were conducted 34 minutes earlier than the scheduled time in 1 subject (Subject No. 000030024). These were deviated 4 minutes from the time allowance (acceptable range: ± 30 minutes).

<Caucasian (US)>

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

* Subject Nos. 000040003, 000040009, 000040032, 000040039

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 fulfilled 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		30	30	29	30
Sex	Male	30 (100.0)	30 (100.0)	29 (100.0)	30 (100.0)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race	Chinese	0 (0.0)	30 (100.0)	0 (0.0)	0 (0.0)
	Japanese	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Korean	0 (0.0)	0 (0.0)	29 (100.0)	0 (0.0)
	White	0 (0.0)	0 (0.0)	0 (0.0)	30 (100.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age [years]	Mean	24.6	31.3	24.2	26.5
	SD	2.99	2.52	2.05	4.08
	Minimum	21.0	23.0	21.0	21.0
	Median	24.00	31.00	24.00	25.50
	Maximum	30.0	34.0	29.0	35.0
Height [cm]	Mean	171.2	168.7	176.7	176.5
	SD	4.85	5.17	5.21	7.88
	Minimum	160.5	160.0	168.1	162.0
	Median	172.00	168.00	176.50	176.75
	Maximum	179.6	180.0	186.3	195.0
Body Weight [kg]	Mean	64.7	67.0	69.7	77.8
	SD	9.59	9.25	7.56	12.96
	Minimum	52.1	51.0	56.3	55.9
	Median	63.50	67.00	69.10	74.45
	Maximum	84.5	91.0	84.4	100.0
BMI [kg/m^2]	Mean	22.1	23.5	22.3	24.9
	SD	3.01	2.57	1.93	3.10
	Minimum	18.6	19.2	19.2	19.9
	Median	21.65	23.45	22.60	24.55
	Maximum	29.1	29.0	26.3	29.8
Medical History	No	15 (50.0)	30 (100.0)	23 (79.3)	16 (53.3)
	Yes	15 (50.0)	0 (0.0)	6 (20.7)	14 (46.7)
Smoking History	No	21 (70.0)	29 (96.7)	27 (93.1)	24 (80.0)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Previously	9 (30.0)	1 (3.3)	2 (6.9)	6 (20.0)
Alcohol History	No	5 (16.7)	30 (100.0)	17 (58.6)	9 (30.0)
	Yes	10 (33.3)	0 (0.0)	12 (41.4)	21 (70.0)
	Previously	15 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
SBP [mmHg]	Mean	109.7	118.0	119.1	121.3
	SD	11.59	10.60	9.83	11.38
	Minimum	93.0	90.0	98.0	100.0
	Median	109.00	120.00	120.00	120.00
	Maximum	136.0	136.0	137.0	152.0
DBP [mmHg]	Mean	64.5	76.5	71.0	67.2
	SD	9.36	6.21	10.81	7.55
	Minimum	50.0	64.0	46.0	54.0
	Median	64.00	80.00	72.00	66.00
	Maximum	86.0	90.0	89.0	84.0
Pulse Rate [bpm]	Mean	66.4	65.3	71.2	64.2
	SD	9.59	6.65	9.68	11.50
	Minimum	46.0	58.0	50.0	50.0
	Median	66.50	63.00	70.00	61.50
	Maximum	89.0	90.0	90.0	90.0
Body Temperature [°C]	Mean	36.3	36.2	36.4	36.1
	SD	0.38	0.28	0.42	0.32
	Minimum	35.6	35.8	35.7	35.5
	Median	36.40	36.20	36.40	36.10
	Maximum	36.9	36.8	37.2	36.7
12 Lead ECG	Normal	25 (83.3)	27 (90.0)	12 (41.4)	14 (46.7)
	Abnormal-NCS[1)]	5 (16.7)	3 (10.0)	17 (58.6)	16 (53.3)
	Abnormal-CS[2)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1) Abnormal - not clinically significant
2) Abnormal - clinically significant

Allergy to drugs, food, etc.

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

Medical History

Of 119 subjects, 35 subjects (15 in Japan; 6 in Korea; 14 in the US) had medical history at screening. None of these were significant for inclusion of the subjects into the study. All subjects were well at the screening visit.

Smoking History

None of the patients smoked just before the study. Although 18 patients (9 in Japan; 1 in China; 2 in Korea; 6 in the US) smoked previously, they refrained from smoking more than 6 months before the study.

Alcohol History

About 40 percent or more subjects in each study site except China drank alcohol less than 50 g per day just before the study or previously, did not comply with the exclusion criteria. In China, none of subjects drank alcohol.

Vital Signs and 12-Lead ECG

All values of vital sign measurements (SBP, DBP, pulse rate and body temperature) were judged as normal. Several abnormalities were observed in ECG measurements, but were not clinically significant.

10.4 Measurement of Treatment Compliance

A hand-and-mouth check was performed following study drug administration, and all drug administration times were recorded in the appropriate CRF.

10.5 Concomitant Medication or Intervention

No concomitant medications or intervention was necessary in any country during the course of this study.

11. PHARMACOKINETIC EVALUATION

PK evaluation of meloxicam and gene polymorphism test of the CYP2C9 were conducted in healthy adult male subjects in each ethnic group. See the report written by Dr. Masahiro Tohkin.