is decided to conduct re-measurement, each study site should send only the relevant back-up sample to the measurement site. Each study site should discard or dispose the other remaining back-up samples. The procedure for transportation, storage and discard of the back-up samples should be given separately.

[Rationales for selection of the blood sampling points]

When Lipovas®, tablets 20 mg were orally administered to 6 healthy Japanese adult male subjects, the t_{max} was 2.6 hours and $t_{1/2}$ of plasma simvastatin concentration were 3.1 hour (n = 4, 2-12 hours after administration) and 15.6 hours (n = 4, 12-24 hours after administration) respectively[7]. Based on these findings, a total of at least 7 blood sampling points were selected for the study in accordance with the Guideline for Bioequivalence Studies of Generic Products [8] as follows: 1 point just before administration, 1 point before reaching the C_{max}, 2 points around the C_{max} and 3 points during the elimination phase. Moreover, it was decided that AUC_{0-t} until the final blood sampling point should become 80 % or more of $AUC_{0-\infty}$.

[Rationales for selection of labeling]

It was specified for prevention of mistaking of specimens and assurance of stability.

8.2.2 Investigation items for gene polymorphism examination

1) Analyzed gene: polymorphism of the CYP3A4, CYP3A5, ABCB1, OATP1B1 and ABCG2 related to pharmacokinetics of simvastatin
2) Blood sampling point: 24 hours after the study drug administration
3) Processing method:

   The venous blood should be taken, using two of 7 mL plastic syringes (EDTA-2Na added) for the sample and the back-up sample. If 7ml plastic syringe is not available, two of 6 mL plastic syringes (EDTA-2K added) for specimens can be used for collection of venous blood. Use the plastic syringe for collecting blood. If the glass syringes are used, blood samples should be transferred to the plastic tubes. In order to avoid the breakage of tubes, blood samples should be refrigerated at -20 °C tentatively and within 24 hours, these specimens should be refrigerated at -60°C or less. One of specimens is to be sent to the institute for gene analysis and the other is stored as a back-up at the study site.
4) Labeling and transport method of tubes for specimens:

   The example of the label is as follows. The label can be designed freely. The label should describe for gene polymorphism analysis, name of the study drug, the subject number (9 digits) that consists of the study site code (Japan: 00001, China: 00002, Korea: 00003, and the U.S.: 00004, 5 digits) and the number that is anonymized and linkable to the subjects (4 digits), date/time of blood sampling and specimen type.

The label should be attached to each tube for specimens.

Study Drug	SIMVASTATIN

Subject No.	000010001
Time	24 h
Date	DD/MM/YY
Matrix.	Whole blood <Gene>

If possible, within 2 weeks after sampling, the specimens should be sent in a refrigerated state using dry ice to the institute for gene analysis from the study site. The procedure for sending should be given, separately.

5) Back-up samples:

Back-up samples are stored to compensate the missing specimens, for example, the specimens might be broken during the transportation to the institute for gene analysis. Each study site should store the back-up samples at -60°C or less until the extraction of DNA is completed. After that, the back-up samples should be sent to Division of Medicinal Safety Science, National Institute of Health Sciences for Japan, Korea and the U.S., and to Biomedical Research (GZ), Ltd., Jiaxing Pharmacokinetics and Bioanalysis Center for China. The procedure for transportation, storage and discard of the back-up samples should be given separately.

6) Timing of Analysis:

Analysis for polymorphism of the CYP3A4, CYP3A5, ABCB1, OATP1B1 and ABCG2 related to pharmacokinetics of simvastatin will be performed after PK parameters are calculated based on plasma concentrations of simvastatin and its open acid form.

7) Method of Analysis:

Real time PCR method (PCR: Polymerase Chain Reaction)

8.2.3 Storage place/period and method of discard of specimens

The remaining specimens for measurements of plasma should be frozen at -60°C or less and stored at Pharmacokinetics and Bioanalysis Center, Shin Nippon Biomedical Laboratories, Ltd. listed in **Table 8-4** until the executive investigator gives an instruction. When it is instructed to discard the specimens or the study period is terminated, the above laboratory center should promptly discard them using autoclave, etc.

As shown in Table 8-4, the remaining blood specimens for Chinese should be frozen at -60°C or less and stored at Biomedical Research (GZ), Ltd. Jiaxing Pharmacokinetics and Bioanalysis Center for 3 years after study completion. Those of Japanese, Korean and American (European Caucasian) subjects should be frozen at -60°C or less and stored at the National Institute of Health Sciences for 3 years after study completion. All the specimens passed 3 years after study completion should be discarded using autoclave, etc. When it is necessary to measure gene polymorphisms other than that of the CYP3A4, CYP3A5, ABCB1, OATP1B1 and ABCG2 related to pharmacokinetics of simvastatin, the measurement should be performed after obtaining permission of the study ethics committee at the related study site.

Specimens will not be provided to human cell, gene or tissue banks.

Table 8-4 Addressee for specimens (storage place)

[Japan, Korea, the U.S.]

Specimen	Addressee
Measurement of drug concentrations (plasma)	Pharmacokinetics and Bioanalysis Center, Shin Nippon Biomedical Laboratories, Ltd.
Gene polymorphism examination (whole blood)	Division of Medical Safety Science, National Institute of Health Sciences

[China]

Specimen	Addressee
Measurement of drug concentrations (plasma)	Pharmacokinetics and Bioanalysis Center, Shin Nippon Biomedical Laboratories, Ltd.
Gene polymorphism examination (whole blood)	Biomedical Research (GZ), Ltd. Jiaxing Pharmacokinetics and Bioanalysis Center

8.2.4 Evaluation items for the safety endpoints

(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 should document the presence or absence of symptoms, type, onset time and resolution time in the specified recording form accordingly. The principal investigator or investigator should perform history taking based on this record and fill out the CRF.

(2) Physical examination findings (history taking, auscultation, percussion)

1) Tests : History taking, auscultation, percussion

2) Test timing : Before administration and 24 hours after administration

3) Test method : The principal investigator or investigator should verify the presence or absence of abnormal physical findings based on history taking, auscultation, percussion, and record physical examination findings in the CRF.

(3) 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 (Time allowance ±1 hr)

3) Evaluation method : "H" should be entered in the CRF when a value deviated from the upper limit of normal, and "L" should be entered when a value deviated from the lower limit. In addition, the judgment of grading and abnormal change should be performed when an abnormal value.

(4) 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 (Time allowance ±1 hr)

3) Evaluation method : "H" should be entered in the CRF when a value deviated from the upper limit of normal, and "L" should be entered when a value deviated from the lower limit. In addition, the judgment of grading and abnormal change should be performed when an abnormal value.

(5) 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 (Time allowance ± 1 hr)

3) Evaluation method : "H" should be entered in the CRF when a value deviated from the upper limit of normal, and "L" should be entered when a value deviated from the lower limit. In addition, the judgment of grading and abnormal change should be performed when an abnormal value.

(6) Vital signs

1) Tests : Blood pressure, pulse rate and body temperature

2) Test timing : Before administration and 24 hours after administration (Time allowance: ±30 minutes)

3) Test method : Body temperature should be measured in the same way at the site (axillary, ear, oral or sublingual). Blood pressure and pulse rate should be measured in the sitting position.

4) Evaluation method : When a clinically significant change is confirmed as compared with baseline, it should be written in CRF as adverse event.

(7) Body weight

1) Tests : Body weight measurement

2) Test timing : Before administration and 24 hours after administration

3) Test method : Body weight (net) should be measured and recorded in the CRF.

[Rationales for selection of the tests (1) to (7)]

(1) They were selected to verify a subjective symptom as adverse event and a symptom objectively observed by a doctor.

(2) They were selected to verify adverse events in a medical examination by a doctor.

(7) They were selected to calculate the pharmacokinetic parameters normalized to dose per body weight.

(1) to (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.

8.2.5 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)]	Pharmacokinetics [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)	84 mL (7 mL × 12)	122 mL
Korea	0 mL [c)]	21 mL (7 mL × 3)	14 mL (14 mL × 1)	84 mL (7 mL × 12)	119 mL
the U.S.	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 is used.)

[b)]: Including back-up samples

[c)]: Not necessary since the specimen for the screening is used (Korea)

[d)]: Details: Hematology 3.5 mL per test, Blood biochemistry 8.5 mL per test (the U.S.)

9. ADVERSE EVENTS

9.1 Definition of Adverse Event

9.1.1 Adverse event

An adverse event refers 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 have been present before the study drug administration and do not significantly worsen, are not considered to be adverse events.

9.1.2 Serious adverse event

A serious adverse event refers to any unfavorable medical occurrence in the subjects during the study period that

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

9.1.3 Adverse reaction

Adverse reactions are adverse events occurred for which the causal relationship with the study drug cannot be ruled out.

9.2 Assessment of Adverse Events

9.2.1 Assessment of adverse events in physical examination

At each physical examination during the hospitalization period, the investigator should determine the presence or absence of abnormality. When it is assessed as "with abnormality," the investigator should document its details as an adverse event in the CRF.

9.2.2 Assessment of adverse events based on vital signs

The investigator should review the contents of vital signs during the hospitalization period and assess adverse events based on medical judgment of each country.

9.2.3 Assessment of laboratory values

In the study, laboratory values refer to hematology, blood biochemistry and urinalysis.
When determining whether or not laboratory values are abnormal, it should be made based on whether or not they are values deviated (abnormal values) from the normal specified at the study site or the laboratory center. The grade of the abnormal value will be rated in accordance with the scale of Division of AIDS (DAIDS) AE grading table (See **22. Appendix 1**) issued by National Institute of Allergy and Infectious Disease (NIAID). When laboratory values are not listed in the scale of DAIDS AE grading table, the following grade is used. The grade of abnormal value should be written in the CRF.

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 interfere 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.

9.3 Evaluation of Adverse Events

If an adverse event occurs, the principal investigator should enter the following information in the CRF: the details, onset date/time, severity and seriousness (serious or non-serious) of the adverse event, 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 should be assessed using the following criteria as a reference.

9.3.1 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 : Therapy or treatment is required for the adverse event and the study was discontinued.

9.3.2 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 should 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 should be evaluated. For events assessed as "Unknown", "Probably not related" or "Not related" with the study drug, the reasons should be recorded in the CRF.

(1) Related : There is a clear temporal correlation with the 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 the 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 the 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 the 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 the study drug administration, or there is enough information that the event is not related to the study drug.

9.4 Handling at Onset of Adverse Event and Follow-up Action

9.4.1 Handling at onset of adverse event (clinical symptom)

1) In the event of adverse events, the investigator should consider medical actions, etc. as necessary for assurance of subjects' safety.
2) When medical actions are required, the investigator should take the best action and, in principle, continue a follow-up until the symptoms resolve after informing such a fact to the subject.
3) When the unknown serious adverse event is shown, follow 9.4.4 below.
4) The investigator should confirm that the developed adverse event resolved or became stable.
5) When the continuation of the study is judged to be difficult due to adverse events, the investigator should discontinue the study and follow up the subsequent course.

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

9.4.2 Actions at the onset of abnormal laboratory values

1) When abnormal laboratory values are noted after study drug administration, the investigator should, in principle, perform a follow-up investigation until they return to reference or baseline levels and as necessary give treatment.
2) When the continuation of the study is judged to be difficult due to adverse events, the investigator should discontinue the study and follow up the subsequent course.
3) When the unknown serious adverse event is shown, follow 9.4.4 below.

9.4.3 Handling at onset of serious adverse event

1) In the event of serious adverse events, the investigator should consider medical actions, etc. as necessary for assurance of subjects' safety.
2) When medical actions are required, the investigator should inform such a fact to the subject.
3) The investigator should confirm that the developed adverse event resolved or became stable.
4) When the unknown serious adverse event is shown, follow 9.4.4 below.

9.4.4 Reports for unknown serious adverse events

1) When the unknown serious adverse event occurs, the principal investigator should 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) should take actions required during the relevant study period after reporting to the study ethics committee.
2) When unknown serious adverse event related to the study occurs, the head of the study site (or the principal investigator) should publish the conditions and results of actions taken for the relevant adverse event, and report its information to the Minister of Health, Labor and Welfare in Japan (the MHLW). In general, unknown serious adverse events like deaths or life-threatening ones, should be reported within seven days, and other serious adverse events should be reported within 15 days after onset. Use the format shown in "22. Appendix 2" when reporting to the MHLW. The information submitted to the MHLW should be shared with the other study sites.
3) When the unknown serious adverse events occur outside Japan, the executive investigator should report it to the MHLW.

10. STATISTICAL ANALYSIS

10.1 Handling of data in analyses

After study completion, the executive investigator should 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 do not fulfill the inclusion criteria or meet the exclusion criteria
2) Discontinuation : Those who satisfy 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" are considered to be deviations.

The following time allowance of blood sampling and laboratory tests should not 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 discontinues the study at early stage, the data should be treated as missed and not compensated. Missing data due to the leakage of specimens by the breakage, back-up samples should be measured and used to compensate the data as references. The outlying value should not be disregarded and handling of these data should be written in the study report, if necessary.

10.2. Analysis Population

1) Consented population

A population of all subjects who provided informed consent.

2) Enrolled subject population

A population of subjects determined to be eligible for study enrollment and to whom subject numbers are given.

3) PK population

A population of subjects who received the study drug and from whom analyzable PK parameters are obtained

4) Safety population

A population of subjects who received the study drug

10.3 Analysis Items

1) Subject background characteristics

A list of subject background characteristics of safety population at baseline (screening) should be prepared, and frequency or basic statistics (mean, median, etc.) should be calculated.

2) PK

(1) PK parameters calculated, based on changes of plasma concentrations of simvastatin and its open acid form.

Independent PK parameters and compartmental model parameters should be calculated for each substance, and total inhibitory substance concentration. The following parameters should be calculated as independent PK parameters:

C_{max}, t_{max}, $t_{1/2}$, * AUC_{0-t}, * $AUC_{0-\infty}$, MRT, CL/f, Vd/f, and $C_{max,\ norm}$, * $AUC_{0-t,\ norm}$, * $AUC_{0-\infty,\ norm}$ normalized to dose per body weight should be calculated.

*: The AUC_{0-t} is a value from time 0 to the last blood sampling time (t_{last}) calculated using the trapezoidal integration method. $AUC_{0-\infty}$ is calculated from addition of $AUC_{t-\infty}$, which is an extrapolated t_{last} to infinity, and AUC_{0-t}.

(2) Tabulation method

Arithmetic mean should be calculated for plasma drug concentrations of each substance per blood sampling point, and a figure of changes over time should be generated. PK parameters should be summarized for each substance with basic statistics, and as necessary, geometric mean, arithmetic coefficient of variation, etc.

3) Gene analysis of polymorphism

Analysis for polymorphism of the CYP3A4, CYP3A5, ABCB1, OATP1B1 and ABCG2 related to the pharmacokinetics of simvastatin should be performed. Details of the analyzed polymorphism and statistical procedures will be described in the separate report of the results.

4) Tabulation of the safety endpoints

(1) Adverse events

Adverse events should be encoded using the MedDRA (Ver. 13.0 or more). Adverse events should be listed by subject. The type of the adverse events, severity, onset date/time, duration, the number of the subjects, the number of the cases, and the occurrence should be tabulated.

(2) Laboratory values

The incidence of normal or abnormal laboratory values should be tabulated by measurement point. Continuous data should be summarized with basic statistics, and qualitative data should be summarized using a shift table, etc.

(3) Vital signs

Basic statistics (mean, standard deviation) should be calculated by measurement point.

(4) Missing, not utilized and outlying data

The principal investigators and statistician should discuss and decide how to deal with outlying data which was unexpected prior to the study, the values deviated from the protocol, and handling of these data should be written in the study report, if necessary.

11. ETHICAL AND SCIENTIFIC CONDUCT OF THE STUDY

11.1 Subject Safety Assurance

This study will be conducted in compliance with the protocol and procedures and while giving full consideration to protection of participants in accordance with the ethical principles of the Declaration of Helsinki, the standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Pharmaceutical Affairs Law (PAL), "Ministerial Ordinance on Partial Revision of the Ordinance on Good Clinical Practice" (dated February 29, 2008, Ordinance No. 24 of the Ministry of Health, Labour and Welfare (MHLW)) (Revised GCP), "Ethical Guidance on Clinical Studies" (entirely amended on July 31, 2008, MHLW), "Guideline for Gene Tests" (August 2003, genetic medicine-related societies), "Ethical Guidance on Human Genome/Genetic Analysis Researches" (partially revised on December 1, 2008, Ministry of Education, Culture, Sports, Science and Technology/Ministry of Economy, Trade and Industry).

11.2 Ethics (Institutional) Review Committee

11.2.1 Review

This study will be implemented after reviewed and approved by the Ethics (Institutional) Review Committee prior to its conduct at the study site.

11.2.2 Provision of new information

When obtaining information that may adversely affect the subjects' safety, influence the conduct of the study or change the approval of the Ethics (Institutional) Review Committee for study continuation, the principal investigator should promptly notify it to the heads of the study sites and the executive investigator. The executive investigator should notify the information to the marketing approval holder.

11.3 Timing and Method of Acquisition of Informed Consent

11.3.1 At enrollment

The principal investigator should issue and obtain approval of the Ethics (Institutional) Review Committee for both informed consent documents and forms used for obtaining consent for study participation from the subjects and for the conduct of gene polymorphism examination based on the "Ethical Guidance on Human Genome/Genetic Analysis Researches" (partially revised on December 1, 2008, Ministry of Education, Culture, Sports, Science and Technology/Ministry of Economy, Trade and Industry).

Prior to the screening, the principal investigator or investigators and others should hand the informed consent documents and forms for obtaining consent for the study and gene polymorphism examination to volunteers and give explanations on them for the volunteers to be able to correctly understand the matters. The investigator should obtain voluntary consent of the volunteers in writing upon full understanding of the contents of both informed consent documents by them.

The principal investigator, who provided the explanation, and the subject should affix their names/seals or signatures and the date in these two informed consent documents and forms for obtaining informed consent and keep one copy each. When the study site personnel other than the principal investigator such as an investigator provided a supplemental explanation, the investigator should also affix his/her name/seal or signature and the date to the said documents and forms. The dates of informed consent obtained for each matter should be recorded in the CRF.

11.3.2 In the event of obtaining information that may affect the subject's will

In the case where information (such as safety information) possibly affecting the subject's will for continuing study participation is obtained, the principal investigator should notify the information to the subjects, verify their will as to whether or not to remain in the study, and document such a fact with the date of confirmation.

11.4 Revision of the Informed Consent Document and Form

When it is found necessary to revise the informed consent document and form such as the case of obtaining new important information that may be related to the subjects' consent, the principal investigator should promptly amend the informed consent document and form and obtain approval of the Ethics (Institutional) Review Committee.

When the informed consent document and form were revised, the principal investigator should obtain consent from the subjects.

11.5 Protection of Human Rights of Subjects

In the conduct of the study, the following items should be respected for protecting the human rights of the subjects:

1) Persons involving in the study shall give full consideration to protection of human rights of the subjects in handling of the informed consent document/form, CRF, source documents and publication of study results.
2) Linkable anonymized subject ID codes shall be used for identification of individual subjects.
3) Persons involving in the study shall give consideration to protection of privacy and secrets of the subjects for records that may reveal identify of the subjects in monitoring, auditing and other activities.

12. APPROVAL, OBSERVANCE AND REVISION OF THE PROTOCOL

12.1 Approval of the protocol

Prior to the study initiation, the principal investigator should obtain approval of the head of the study site for the contents of the protocol. The head of the study site should have the Ethics (Institutional) Review Committee to perform a prior review as to whether or not the protocol meets the "Ethical Guidance on Clinical Studies" (entirely amended on July 31, 2008, MHLW) for requirements for proper conduct of clinical studies.

12.2 Adherence to the Protocol

The principal investigator should not deviate from or modify the protocol without written approval of the Ethics (Institutional) Review Committee based on its prior review.

12.3 Modifications in the protocol

The principal investigator should promptly inform in writing the head of the study site, the executive investigator, and the Ethics (Institutional) Review Committee of any modifications in the study that may have major influence on the conduct of the study or increase risks to the subjects.

13. STUDY COMPLETION, DISCONTINUATION OR INTERRUPTION

13.1 Study Completion

When the study is completed, the principal investigator should report such a fact to the head of the study site in writing. The head of the study site should notify in writing the study completion to the executive investigator and Ethics (Institutional) Review Committee.

13.2 Discontinuation or Interruption of the Entire Study

13.2.1 Criteria for discontinuation or interruption of the entire study

The executive investigator should discontinue or interrupt the entire study when falling into any of the following cases:

1) Where ethically or medically inevitable events occurred for subject safety assurance; or
2) Where the scientific validity to conduct the study is lost.

13.2.2 Discontinuation or interruption at the study site

The principal investigator or the head of the study site should discontinue or interrupt the study at the site concerned when falling into any of the following cases:

1) Where major or continuous incompliance by the principal investigator, investigators, etc, or study site is found;
2) Where the Ethics (Institutional) Review Committee at the study site determined to discontinue or interrupt the ongoing study at the review of study continuation;

3) Where the study cannot be continued due to transfer of the principal investigator, investigators, etc;
4) Where it cannot be expected to recruit subjects meeting the inclusion criteria;
5) Where the study site failed to meet requirements for proper conduct of the study; or
6) Where the principal investigator discontinued or interrupted the study.

14. PREPARATION OF THE CRF

The principal investigator should prepare the CRFs and submit them to the executive investigator. Recording, reporting and making modifications or corrections in the CRF shall be made as follows:

1) The principal investigator should prepare the CRFs with a means that entries are not erasable such as a black ball-point pen and computer output, as necessary in collaboration with personnel predesignated with a list of collaborators. When test results, etc. are attached to the CRF, a seal should be affixed to the edges of adjacent sheets.
2) When modifying or correcting information entered, the principal investigator should correct or add the information in a manner that the information before the change can be identified. For changes made after the date of issue of the CRF, the principal investigator should also enter the date of change and seal or sign the CRF. For major modifications or corrections, their reasons should be presented.
3) The principal investigator shall ensure that data in the CRF and all other reports are accurate, complete and legible and the submission timing is appropriate.
4) The principal investigator should affix his/her name/seal or signature to the CRF after checking its contents to confirm that there is no problem, and submit it to the executive investigator.
5) The principal investigator should retain copies of the CRFs and records on modifications/corrections.
6) In the event of any inconsistencies between data presented in the CRF and source documents, the principal investigator should explain the reasons to the executive investigator.

15. RETENTIONS OF RECORDS

15.1 Executive Investigator

The executive investigator should retain documents and records, such as the protocol, CRF, clinical study report, contract and quality records of the study drug, until 3 years after study discontinuation or completion.

15.2 Study Sites

The head of the study site should retain documents and records, which should be kept at the study site such as records on acquisition of informed consent from the subjects, data (medical records, test data, etc.) based on which the CRF was prepared, records of the Ethics (Institutional) Review Committee, contract and study drug control chart, by appointing archive managers for each record. The assigned archive manager should retain these documents and records for 3 years after study discontinuation or completion. However, when the executive investigator needs to keep them for a period longer than this, it may be

extended upon discussion on the archiving period and method between the study site and executive investigator.

16. PAYMENT AND ACTIONS FOR HEALTH DAMAGE

16.1 Payment

The study collaboration fee to be paid to the subjects in the study should be as specified by the study site.

16.2 Actions for Health Damage

For health damages associated with the study to the subjects, liability insurance is available.

17. AGREEMENT ON PUBLICATION

When publishing the study results, prior approval of the executive investigator should be obtained. The publication method should be decided upon discussion.

18. IMPLEMENTATION STRUCTURE

See the attachment

19. STUDY PERIOD

June, 2010 to November, 2010

20. STUDY FINANCIAL SOURCES AND POSSIBLE CONFLICT OF INTEREST

This study will be conducted as part of the "Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare (H21-Global-Designation-01)," a Health Labour Sciences Research Grant (Global-Scale Health Topic Promotion Research), and the Grant will be used for research costs necessary for the study conduct.

Investigators, who participate as the study representative and subinvestigators in the "Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers (H21-Global-Designation-01)," a Health Labour Sciences Research Grant (Global-Scale Health Topic Promotion Research), have been determined to have no possible conflict of interest by the Committee for Conflicts of Interest at Toho university.

21. REFERENCES

1) Fujino H, Saito T, Tsunenari Y, Kojima J, Sakaeda T.; Metabolic properties of the acid and lactone forms of HMG-CoA reductase inhibitors. Xenobiotica. 34(11-12): 961-71, 2004
2) Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M.; SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics. 16(12): 873-9, 2006
3) Keskitalo JE, Kurkinen KJ, Neuvoneni PJ, Niemi M.; ABCB1 haplotypes differentially affect the pharmacokinetics of the acid and lactone forms of simvastatin and atorvastatin. Clin Pharmacol Ther. 84(4): 457-61, 2008
4) Keskitalo JE, Pasanen MK, Neuvonen PJ, Niemi M.; Different effects of the ABCG2 c.421C>A SNP on the pharmacokinetics of fluvastatin, pravastatin and simvastatin. Pharmacogenomics. 10(10): 1617-24, 2009
5) Section of Genetic Data Analysis, StaGen; Report, "Estimation of statistical power and number of subjects for testing ethnic differences in drug pharmacokinetics, No.2" (August 7, 2009)
6) Saito Y, Maekawa K, Ozawa S, Sawada J; Genetic Polymorphism and Haplotypes of Major Drug Metabolizing Enzymes in East Asiana and Their Comparison with Other Ethnic Populations. Current Pharmacogenomics 5: 49-78, 2007
7) Masakatsu Ohtawa et al.: Journal of Clinical Therapeutics and Medicine 5 (6): 1123-1140, 1989
8) "Clinical pharmacokinetic studies of drugs" (June 1, 2001, Pharmaceutical Affairs Bureau Notification No.796)

22. APPENDIX

1) DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS (PUBLISH DATE: DECEMBER, 2004) - Only laboratory tests
2) Format for reporting of unknown serious adverse event

Appendix 1)

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY	*Standard International Units are listed in italics*			
Absolute CD4+ count – **Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count – **Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.49 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 136 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.