1. Title Page

Study title	A study to evaluate the efficacy and safety of rosuvastatin in the long-term treatment of hypercholesterolaemic subjects with coronary heart disease as measured by intravascular ultrasonography
Drug substance	Rosuvastatin
Target indication	Hypercholesterolaemia
Study design, Comparison, Study period, Dosage, Study population	[Study Design] Multicentre postmarketing clinical study [Comparison] Not applicable [Study Period] Run-in Period: 0-8 weeks Treatment period: 76 weeks [Dosage] 2.5-20 mg, once daily [Study population] Hypercholesterolaemic patients from 20 to 75 years old
Study sponsor	AstraZeneca K.K. Shionogi & Co., Ltd.
SH Protocol No	0407E1841
Development phase	Postmarketing clinical study
Study start date	18 November 2005 (the first dose of the first patient)
Premature discontinuation date	Not applicable
Study end date	31 October 2008 (the last visit of the last patient)
Medical expert	
Sponsor's personnel responsible for Clinical Trial Report Contact information	
Statement of GCP compliance	This study was conducted in compliance with "Good Clinical Practice (GCP)", and all study-related documents are being properly retained at each responsible department. Responsible persons for the postmarketing clinical study: Manager, Clinical Research Department, Shionogi & Co., Ltd
Date of the report:	25 May 2009

2. SYNOPSIS

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Name of Active Ingredient: Rosuvastatin calcium		

Title of Study:	A study to evaluate the efficacy and safety of rosuvastatin in the long-term treatment of hypercholesterolaemic subjects with coronary heart disease as measured by intravascular ultrasonography
Investigators:	
Study centres:	Department of Cardiovascular Medicine, Hokkaido University Hospital and 39 medical institutions
Publication:	Tadateru T. E*t al*. Rationale and Design for a Study Using Intravascular Ultrasound to Evaluate Effects of Rosuvastatin on Coronary Artery Atheroma in Japanese Subjects —COSMOS Study (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects)— Circulation Journal 2007 ; 71 (2) : 271-275

Study period: 3 years 18 November 2005 (the first dose of the first patient) 31 October 2008 (the last visit of the last patient)	Phase of development: Postmarketing clinical study

Objectives:

To evaluate that 76 weeks of treatment with rosuvastatin 2.5-20 mg inhibits progression of plaque volume (PV) as measured by Intra-vascular ultrasound-graphy (IVUS) imaging in hypercholesterolaemic patients with coronary heart disease (CHD).

Study method:

The efficacy and safety of oral once daily doses of rosuvastatin 2.5-20 mg were assessed in an open-label study in hypercholesterolaemic patients with CHD who need percutaneous coronary intervention (PCI)

[Dosage and mode of administration]

Treatment with rosuvastatin was started from 2.5 mg once daily. If low density lipoprotein cholesterol (LDL-C) level is still 80 mg/dL or above after 4 weeks or more treatment at the starting dose or an increased dose, the dose is escalated stepwise to a maximum of 20 mg/day. If the principal investigators judge it necessary to reduce the dose for some reason, such as an excessive decrease in LDL-C (LDL-C <50 mg/dL) and occurrence of an adverse event, the dose is reduced up to 2.5 mg once

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daily. The treatment period is 76 weeks.

[Efficacy variables]

1. IVUS
2. Coronary angiography (CAG) findings
3. Fasting serum lipids, lipoproteins and apolipoproteins
4. Inflammatory marker (hs-CRP)

[Safety variables]

1. Subjective symptoms and objective findings (adverse events)
2. Vital signs
3. Physical tests (body weight, resting 12-lead electrocardiogram (ECG) and chest X-ray)
4. Clinical laboratory parameters (haematology, clinical chemistry, glucose metabolism test, urinalysis)

Sample size:

Target number of patients: 200 (to be enrolled into the treatment period)

Number of patients enrolled into the run-in period: 314

Number of patients enrolled into the treatment period: 214

Efficacy Analysis Set:

Full Analysis Set (hereinafter referred to as 'FAS'): 213

Per-Protocol Set (hereinafter referred to as 'PPS'): 126

Safety Analysis Set: 213

Diagnosis and main inclusion criteria:

Inclusion criteria (for the run-in period)

1. Signed written informed consent to participate in the study after the details of the study is explained to the patient
2. Men or women from 20 to 75 years old
3. Plan to undergo coronary angiography (CAG) or percutaneous coronary intervention (PCI)
4. Inpatient or outpatient
5. Serum cholesterol levels
   1) Untreated patients: serum LDL-C ≥140 mg/dL [calculated with Friedewald equation (triglyceride (TG) <400 mg/dL) or directly measured] or total cholesterol (TC) ≥220 mg/dL

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measured within a month prior to the ruin-in period

2) Patients already treated with lipid-lowering agents: serum LDL-C ≥100 mg/dL [calculated with Friedewald equation (TG <400 mg/dL) or directly measured] or TC ≥180 mg/dL measured within a month prior to the ruin-in period

Exclusion criteria (for the run-in period)

1. Pregnant or possibly pregnant women, lactating mothers, or women willing to become pregnant during the study
2. Acute myocardial infarction within 72 hours after the onset
3. Heart failure of NYHA Class III or above
4. Serious arrhythmia
5. Familial hypercholesterolaemics who cannot obtain lipid control with HMG-CoA reductase inhibitor alone
6. Secondary hyperlipidemia associated with diseases such as abnormal thyroid function, Cushing syndrome, nephrotic syndrome, and systemic lupus erythematosus
7. Being treated with LDL-apheresis
8. Taking cyclosporin
9. Being treated with haemodialysis
10. History of serious reaction or hypersensitivity to other HMG-CoA reductase inhibitors
11. Malignancy, suspected malignancy, or history of malignancy
12. Participating in another clinical study or possible participation in another clinical study during the period of this study
13. Judged by the principal investigator or subinvestigator (hereafter the principal investigators) that the patient is inappropriate for the study

Inclusion criteria (for the treatment period)

1. CAG and PCI

1) Before PCI

(1) At least one significant stenosis of 75% or more, as defined by American Heart Association (AHA) classification, being a candidate for PCI

(2) In addition to the candidate lesion for PCI, at least one lesion of 50% or less stenosis, as

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defined by AHA classification, meeting the following criteria:

- IVUS is applicable with auto-pullback system
- No history of PCI
- Not involving any lesion responsible for myocardial infarction

2) After PCI

Undergone PCI for at least one lesion and complete IVUS measurement by the specified procedure in the lesion that has not undergone PCI, with recording of measurement.

2. Serum cholesterol levels

1) Untreated patients: LDL-C ≥140 mg/dL centrally measured once or more during the run-in period (excluding immediately after PCI and the first day to administer rosuvastatin) or TC ≥220 mg/dL measured at hospital (only under unavoidable circumstances such as patient's personal reason)

2) Patients already treated with lipid-lowering agents: LDL-C ≥100 mg/dL centrally measured once or more during the run-in period (excluding immediately after PCI and the first day of rosuvastatin dosing) or TC ≥180 mg/dL measured at hospital (only under unavoidable circumstances such as patient's personal reason)

Exclusion criteria (for the treatment period)

1. Lesion requiring active intervention (eg >50% stenosis of AHA classification in the left main coronary artery) on CAG
2. Uncontrolled hypertension (diastolic blood pressure ≥110 mmHg or systolic blood pressure ≥200 mmHg at all measurements during the run-in period)
3. Uncontrolled diabetes (hemoglobin A1c (HbA1c) ≥9.5%)
4. Active hepatic disease or hepatic dysfunction that is evidenced by ≥2.5 × ULN (upper limit of the normal) of either L-alanine aminotransferase (ALT), L-asparatate aminotransferase (AST) or alkaline phosphatase (ALP), or ≥3.0 mg/dL of total bilirubin
5. Creatinine clearance <30 mL/min/1.73 m^2 or serum creatinine >2.0 mg/dL
6. Serum creatinine kinase (CK) >3 × ULN
7. Obvious involvement of thrombosis in the lesion on CAG
8. Judged by the principal investigators that IVUS image of the patient is inappropriate for evaluation of this study
9. Judged by the principal investigators that the patient is inappropriate for the study

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Test product, dosage and mode of administration, batch number:

1. Investigational product (rosuvastatin)

   rosuvastatin 2.5 mg tablet, 5 mg tablet and 10 mg tablet

2. Dosage

   Treatment period: 1 x rosuvastatin 2.5 mg tablet, 1 x 5 mg tablet, 1 or 2 x 10 mg tablet

3. Mode of administration

   Once daily, administered orally

4. Batch Nos (manufacturing Nos)

   Rosuvastatin 2.5 mg tablet: 20145 (shelf life: October 2007), 21665 (shelf life: September 2009)

   Rosuvastatin 5 mg tablet: 40145 (shelf life: September 2007), 40665 (shelf life: August 2009)

   Rosuvastatin 10 mg tablet: 00140 (shelf life: September 2007), 105301 (shelf life: March 2010)

Treatment period:

Duration of treatment: 76 weeks

Reference therapy, dosage and mode of administration, batch number:

Not applicable

Criteria for evaluation:

1. Efficacy outcome variables

   1) Primary outcome variable: Assessment of PV by IVUS

   Percentage change in PV from baseline (before the start of rosuvastatin treatment) to Week 76 was measured/calculated using IVUS.

   2) Secondary outcome variables

   (1) The following variables were measured/calculated and assessed using IVUS.

   - Change in PV in the target lesion from baseline to Week 76
   - Absolute change and percentage change in plaque area (PA) from baseline to Week 76 at the same coronary artery cross-section where the maximum PA was found at baseline within the target lesion of PV
   - Absolute changes and percentage changes in the vascular cross-sectional lumen area and total vascular area from baseline to Week 76 at the same coronary artery cross-section where the maximum PA was found at baseline within the target lesion of PV

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- Absolute changes and percentage changes in the vascular lumen volume and total vascular volume from baseline to Week 76 in the target lesion

(2) The effect on serum lipids was assessed by measuring/calculating the following variables.

- Percentage changes from baseline to specified measurement time points in TC, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), nonHDL-C (TC－HDL-C), TG and Remnant like particles (RLP-C)
- Percentage changes from baseline to specified measurement time points in Apolipoprotein (Apo) A-I, ApoA-II, ApoB, Lipoprotein(a) (Lp(a)), small dense LDL, HDL-2 and HDL-3

(3) Changes in hs-CRP from baseline to specified measurement time points were measured/calculated to investigate inflammatory marker

2. Safety assessment

The presence and incidence of adverse events were assessed by the following methods: Monitoring of subjective symptoms/objective findings during the treatment period and up to 4 weeks after the last dose of rosuvastatin, vital sign measurement (blood pressure and pulse), physical tests (body weight, resting 12-lead electrocardiogram and chest X-ray), safety clinical laboratory tests (haematology, biochemical examination of blood, glucose metabolism and urinalysis) and plasma drug concentration measurement, and investigation on the effect of rosuvastatin use on pregnancy.

An adverse drug reaction (ADR) is defined as an adverse event (AE) for which a causal relationship to rosuvastatin could not be ruled out (other than those assessed as “unrelated”). According to the definition, the incidence of ADRs was calculated.

For the assessment of AEs and ADRs, type, severity, causality and duration of the event were summarised.

The severity of AEs and ADRs was assessed using the following 3-grade scale*.

1. mild; 2. moderate; 3. severe

The causal relationship between AEs and rosuvastatin was assessed using the following 4-grade scale*. The AEs for which the causality was assessed as 1-3 were handled as adverse reactions.

1. Definitely related; 2. Probably related; 3. Possibly related; 4. Not related

In this study, AEs also include any serious undesirable medical event occurred during the run-in period

Change in serum lipids associated with the target diseases (hypercholesterolaemia and familial

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hypercholesterolaemia) was not reported as an AE, but excessive increase and decrease in serum lipids requiring discontinuation of the study were reported as an AE.

*: This is direct translation of common regulatory reporting form in Japan. The draft was obtained from Shionogi.

Statistical method:

All statistical tests were two-sided with a significance level of 0.05. Clopper-Pearson method was used to calculate 95% confidence interval of percentages. Basic statistics were mean, standard deviation, minimum, median and maximum.

[Disposition of patients enrolled in the study]

The number of these patients in individual analysis populations was calculated, considering the patients in FAS, PPS and safety analysis population as evaluable patients. Unevaluable patients were classified by reason as violators of GCP, etc., patients with no observed post-dose data, ineligibles, untreated patients, treatment violators, treatment non-compliers, withdrawals and dropouts/patients lost to follow-up. The number of patients was calculated according to the reason.

[Distributions of demographic characteristics and other baseline characteristics]

Using PPS and safety analysis population, the distributions of demographic characteristics (sex, age at the start of treatment, body weight during the run-in period, inpatient/outpatient status at the start of run-in period) and other baseline characteristics (presence or absence of complications, medical history, presence or absence of prior drug therapy and/or prior therapy; and length of lesion at the time of measurement of PV) was evaluated. For categorical variables, the number of patients was summarised by each category. For continuous variables, basic statistics were calculated.

[Distribution according to the last dose level and the duration of treatment]

Using PPS, the number of patients was calculated according to the last dose level (2.5 mg, 5 mg, 10 mg, 20 mg) and the duration of treatment (≤4 weeks, 5-12 weeks, 13-24 weeks, 25-48 weeks, 49-60 weeks, 61-71 weeks, ≥72 weeks).

1. Efficacy analysis

The primary analysis population of efficacy comprised patients who comply with the protocol and have evaluable IVUS data both at baseline and Week 76. The per-protocol set (PPS) was defined as this analysis population. A full analysis set (FAS) separately defined was used as the secondary

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analysis population.

[FAS (Full Analysis Set)]

FAS comprised all registered patients, excluding the following patients:

1. Violators of GCP, etc.: Patients who commit serious GCP or GPSP violations, eg, patients who do not give the written informed consent, or patients enrolled at a medical institution where the study is not reviewed by the IRB or the contract of study consignment is not concluded with the sponsor
2. Untreated patients: Patients who move to the treatment period but do not take rosuvastatin at all
3. Patients with no observed post-dose data: Patients with no observed post-dose data after moving to the treatment period

[PPS (Per Protocol Set)]

PPS comprised all patients in FAS, excluding the following patients:

4. Ineligibles: Patients who do not satisfy all inclusion criteria or who meet any exclusion criterion
5. Treatment violators: Patients who violate the concomitant medication/therapy rules, the dosage and administration rules, the method and time of observation or evaluation and such.
6. Treatment non-compliers: Patients who do not take rosuvastatin as instructed by the investigators
7. Patients missing some IVUS data: Patients who do not undergo IVUS either at baseline or at Week 76, or those whose observed values of outcome variables related to plaque are unevaluable due to poor images although IVUS was carried out
8. Withdrawals: Patients withdrawn from the rosuvastatin treatment due to aggravation of symptoms, cure of the disease under study, occurrence of AEs, etc. in medical judgment of the study doctor and whose evaluation is discontinued prematurely

[Analysis of primary outcome variables]

Basic statistics (mean, standard deviation, minimum, median, maximum) and 95% confidence interval of percentage changes (%) in PV were calculated. Next, the null hypothesis that the mean percentage change in PV is equal to 0 was tested by 1-sample t-test. Basic statistics of PV at baseline and Week 76 were calculated.

[Secondary outcome variables]

The change is defined as the value at a specific observation time minus the baseline value. The percentage change (%) is defined as the change divided by the baseline value, multiplied by 100.

1. Changes from baseline to Week 76 in PV

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2. Changes and percentage changes from baseline to Week 76 in vascular luminal volume
3. Changes and percentage changes from baseline to Week 76 in total vascular volume
4. Changes and percentage changes from baseline to Week 76 in PA, total vascular area and vascular luminal area
5. Percentage changes from baseline to Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60 and 76 in lipid parameters (TC, LDL-C, VLDL-C, HDL-C, nonHDL-C, TG, RLP-C)
6. Percentage changes from baseline to Week 76 in apoproteins and lipoproteins (ApoA-I, ApoA-II, ApoB, Lp(a), small dense LDL, HDL-2, HDL-3). Similarly, changes from baseline to each observation time until Week 36.
7. Changes from baseline to Week 76 in hs-CRP. Similarly, changes from baseline to each observation time until Week 36.

[Analysis of secondary outcome variables]]

The change was defined as the value at a specific observation time minus the baseline value. The percentage change (%) was defined as the change divided by the baseline value, multiplied by 100.

1. For changes and percentage changes, basic statistics and 95% confidence intervals of their mean values were calculated. The null hypothesis that the mean change and percentage change are equal to 0 is tested by 1-sample t-test.
2. Basic statistics of secondary outcome variables listed above were calculated by each observation time.
3. The changes over time in mean values and 95% confidence intervals of lipid parameters and hs-CRP were presented graphically. The changes between observation time points were evaluated by fitting the mixed effect model with observation time points as fixed effects and patients as random effects.

2. Safety analysis

The safety analysis population comprised patients who take at least one dose of rosuvastatin and have some safety information, excluding violators of GCP, etc. (patients who do not give the written informed consent, or patients enrolled at a medical institution where the study is not reviewed by the IRB or the contract of study consignment is not concluded with the sponsor).

The following analysis was performed using the safety analysis population.

The number of patients with AE, the percentage of these patients in the analysis population and its 95%

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confidence interval were calculated. Also the number of patients with AE was obtained separately for subjective symptoms/objective findings and abnormal changes in laboratory values, and then the percentages of these patients in the analysis population and their 95% confidence intervals were calculated. Similarly, the percentages of patients with ADR under the above three categories and their 95% confidence intervals were calculated.

1. According to the type of AE and ADR, the number of patients and the percentage in the analysis population were calculated.
2. According to the type of subjective symptoms/objective findings and abnormal changes in laboratory values, the numbers of events were obtained by each of severity, outcome of AE or ADR, and measures taken.
3. According to the type of AE and ADR, the number of events was obtained by category of time to the onset of AE or ADR after the start of treatment, separately for subjective symptoms/objective findings and abnormal changes in laboratory values.
4. For quantitative (continuous) variables of clinical laboratory tests and physical tests, mean values and standard deviations were calculated at each observation time. The changes in mean value and standard deviation over time were plotted against each test parameter. For qualitative (categorical) variables, two-way layout was prepared at baseline and at each observation time after the start of treatment.
5. For vital signs (systolic and diastolic blood pressures, pulse rate), basic statistics were calculated by each parameter at each observation time. The changes in mean value and standard deviation over time were plotted.

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