AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Rosuvastatin calcium
Study Code	D3560C00059
Date	16 September 2009

A Phase I, Open Label, Parallel Group, Single and Multiple Dose Study in Taiwanese Subjects Identified as CYP2C19 Poor Metabolisers or Extensive Metabolisers Receiving 20 Milligrams of Rosuvastatin Calcium

Study dates: First healthy subject enrolled: 26 September 2008
Last healthy subject completed: 24 February 2009

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This was a single-site study conducted at the Division of Cardiology, National Taiwan University Hospital, Taiwan. The first healthy subject was enrolled on 26 September 2008.

Publications

None at the time of writing this report.

Objectives

Rosuvastatin is not extensively metabolised. Rosuvastatin lactone is formed from rosuvastatin by a metabolic pathway not mediated by cytochrome P450. The major metabolite, N-desmethyl rosuvastatin, results from conversion of rosuvastatin lactone, principally by cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9).

The primary objectives of this study were

- To explore the exposure of rosuvastatin calcium in Taiwanese subjects who have been identified as cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19) poor metabolisers (PMs) to exposure in Taiwanese subjects who have been identified as CYP2C19 extensive metabolisers (EMs) by examining the pharmacokinetic (PK) profile of rosuvastatin and its metabolites after single and multiple dosing of 20 mg rosuvastatin calcium

- To measure the effect of rosuvastatin calcium on lipid parameters of Taiwanese subjects after 2 weeks of daily dosing of 20 mg rosuvastatin calcium

The secondary objective of the study was to assess safety and tolerability.

Study design

This was an open-label, parallel-group, single and multiple dose study. Subjects received rosuvastatin 20 mg as a single dose on Day 1, and then, on Days 4 through 17 (14 days), they received a single dose of rosuvastatin 20 mg daily.

Target subject population and sample size

The target population included healthy Taiwanese subjects genotyped as EMs and PMs of either sex, between 20 and 65 years old (inclusive), and a body mass index (BMI) between 18 and 29 kg/m^2 (inclusive). Approximately 50 subjects (25 per EM and PM groups, respectively) were to receive treatment with investigational product to obtain at least 40 evaluable subjects (20 per EM and PM groups, respectively). An evaluable subject was defined as a subject satisfying the inclusion and exclusion criteria, completing all study procedures from the screening period to the final blood sampling for plasma levels of rosuvastatin, and having had no major protocol deviation or violation.

Inclusion criteria

The inclusion criteria healthy subjects had to fulfil to enrol in the study included provision of signed written informed consent; age between 20 and 65 years (inclusive); a BMI between 18 and 29 kg/m^2 (inclusive); use of an adequate method of contraception (for women of childbearing potential) to avoid pregnancy throughout the study period; and genotyping for the determination of EM or PM of CYP2C19, organic anion transporter polypeptide solute carrier family, member 1B1 (OATPC1B1), breast cancer resistance protein (BCRP) 421C>A, and CYP2C9.

Exclusion criteria

Some major exclusion criteria from the study included use of prescription medication for a chronic medical condition; subjects with deoxyribonucleic acid that codes for OATPC1B1 *5 and *15, BCRP 421C>A, and/or non wild-type CYP2C9; acute illness or use of prescription medication for an acute medical condition within 2 weeks of Day –1; a contraindication determined by review of a detailed medical and drug history, complete physical examination, vital signs, blood chemistry, haematology, and electrocardiogram (ECG); a history of adverse drug reaction or hypersensitivity to statins; history or presence of gastrointestinal, hepatic, or renal disease; positive test for human immunodeficiency virus antibody, hepatitis B surface antigen, or hepatitis C antibody; history of alcohol abuse or positive urine drug screen; any involvement in the planning and conduct of the study; or participation in a clinical study in the previous 30 days.

Criteria for discontinuation

Subjects could be discontinued at any time. Specific reasons for discontinuing a subject from this study included voluntary discontinuation by the subject, safety reasons, severe non-compliance to protocol, incorrect enrolment, and lost to follow-up.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Rosuvastatin was provided in 20-mg oral tablets (batch number: 6003F08). Rosuvastatin administration included a single, 20-mg dose on Day 1, and on Days 4 through 17 (14 days), a single dose of rosuvastatin 20 mg daily.

Duration of treatment

The duration of each subject's participation was up to approximately 2 weeks, including a single dose of rosuvastatin 20 mg on Day 1, followed by a single daily dose of rosuvastatin 20 mg on Days 4 through 17. Blood samples were collected during the 72 hours between the single dose on Day 1 and the administration of rosuvastatin on Day 4 to assess the subject's PK profile.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (primary variables)

Samples were analysed to examine the PK profile of rosuvastatin and its metabolites. For single-dose rosuvastatin exposure, maximum concentration (C_{max}) and area under the

concentration curve from zero to infinity (AUC) were the primary variables. The secondary variables for rosuvastatin were area under the curve of plasma concentration against time from zero to time of last quantifiable concentration ($AUC_{[0-t]}$); area under the first moment curve; time to maximum concentration (t_{max}); terminal elimination rate constant (λ_z); half-life associated with the terminal slope of a semi logarithmic plasma concentration-time curve ($t_{1/2\lambda z}$); mean residence time; apparent oral clearance; and apparent volume of distribution.

Secondary variables for the metabolites (N-desmethyl rosuvastatin and rosuvastatin lactone) included C_{max}; AUC; area under the plasma concentration curve from zero to 24 hours post-dose ($AUC_{[0-24]}$); $AUC_{(0-t)}$; t_{max}; λ_z; and $t_{1/2\lambda z}$.

For multiple-dose rosuvastatin exposure, the primary variables for rosuvastatin were maximum plasma concentration at steady state ($C_{ss,max}$) and area under the concentration-time curve at steady state (AUC_{ss}). Secondary variables for rosuvastatin were minimum plasma concentration at steady state ($C_{ss,min}$); average plasma concentration at steady state ($C_{ss,av}$); time to maximum concentration at steady state ($t_{ss,max}$); degree of fluctuation (at steady state) (DF); accumulation ratio (at steady state) (AR); and temporal change parameter (TCP).

Secondary variables for the metabolites included $C_{ss,max}$; $C_{ss,min}$; $C_{ss,av}$; $t_{ss,max}$; AUC_{ss}; $AUC_{(0-24)}$; AR; DF; and TCP.

To measure the effect of rosuvastatin on lipid parameters, the variables were total cholesterol (tChol), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG).

Criteria for evaluation - safety (secondary variables)

Safety and tolerability assessments were based on medical review of adverse event (AE) reports, clinical laboratory results (ie, clinical chemistry, haematology, and urinalysis), vital sign measurements, ECGs, and physical examination results.

Statistical methods

This study was exploratory and not powered to obtain a formal statistical comparison between PMs and EMs and exposure to rosuvastatin. Therefore, no formal statistical hypothesis testing was performed.

All summary data were presented separately for each group. Unless otherwise stated, descriptive statistics for continuous data included the number of subjects, arithmetic mean, standard deviation (SD), median, minimum, and maximum. Descriptive statistics for categorical data included the frequency and proportion. Demographics and baseline endpoints were analysed using descriptive statistics (number, mean, SD, median, minimum, and maximum) for continuous variables and frequency counts and percentages for categorical variables. Graphical methods were used in exploring the characteristics of PK and pharmacodynamics (PD).

AEs were listed and summarised by system organ class and preferred term. Vital signs, clinical laboratory measures, and ECG assessments were summarised, and clinically significant results were flagged.

Subject population

The study population consisted of 49 healthy subjects between the ages of 20 and 59 years. All subjects were Asian (100%), and 69.4% were female. The PM and the EM groups were similar in terms of demographic and baseline characteristics. The lipid profile data obtained at baseline for the 2 groups were also similar.

No subjects discontinued the study. All 25 subjects who were EMs and all 24 subjects who were PMs completed the study and were included in the PK, PD, and safety analysis sets.

Based on accountability information (Appendix 12.2, see Listing 12.2.5.2), Subject 1206 (E0001096) in the PM group missed a dose sometime between Day 10 and Day 16, and Subject 1216 (E0001084) in the PM group took a double dose on Day 14. These dosing discrepancies were considered as not affecting PK assessments during PK monitoring days and at Day 17, PD assessments at Day 18, or the safety profile; therefore, all subjects were included in the PK, PD, and safety analysis sets.

Summary of pharmacokinetic results

Table S1 summarises the PK parameters for single and multiple dosing for rosuvastatin, N-desmethyl rosuvastatin, and rosuvastatin lactone.

Table S1 Summary of PK parameters (PK evaluable volunteers)

			Day 1 (single dose)		Day 17 (steady state)	
PK parameter	**Statistic**	**Group**	**n**	**Results**	**n**	**Results**
Rosuvastatin						
C_{max} (ng/mL)	Geometric mean (CV%)[a]	EM	25	19.69 (35.091)	25	22.65 (48.229)
		PM	24	17.17 (53.936)	24	21.85 (42.888)
AUC (ng h/mL)	Geometric mean (CV%)[a]	EM	25	171.78 (30.428)		NC
		PM	24	167.25 (45.428)		NC
$AUC_{(0-t)}$ (ng h/mL)	Geometric mean (CV%)[a]	EM	25	168.23 (30.369)		NC
		PM	24	163.77 (45.076)		NC
t_{max} (h)	Median (range)	EM	25	3.00 (1.00 to 6.00)	25	4.00 (1.00 to 6.00)
		PM	24	3.00 (2.00 to 5.00)	24	4.00 (2.00 to 6.00)
$t_{1/2\lambda z}$ (h)	Geometric mean (CV%)[a]	EM	25	14.76 (28.045)		NC
		PM	24	14.72 (31.367)		NC
CL/F (L/h)	Geometric mean (CV%)[a]	EM	25	116.37 (30.390)		NC
		PM	24	119.52 (45.439)		NC
$AUC_{(0-24)}$ (ng h/mL)	Geometric mean (CV%)[a]	EM	25	147.35 (31.41)	25	188.19 (39.415)

Table S1 Summary of PK parameters (PK evaluable volunteers)

			Day 1 (single dose)		Day 17 (steady state)	
PK parameter	**Statistic**	**Group**	**n**	**Results**	**n**	**Results**
		PM	24	143.03 (46.62)	24	190.17 (44.243)
$C_{ss, av}$ (ng/mL)	Geometric mean (CV%)[a]	EM		NC	25	7.84 (39.412)
		PM		NC	24	7.92 (44.253)
TCP	Geometric mean (CV%)[a]	EM		NC	25	1.10 (24.118)
		PM		NC	24	1.14 (72.752)
N-desmethyl rosuvastatin						
C_{max} (ng/mL)	Geometric mean (CV%)[a]	EM	25	3.21 (39.644)	25	3.19 (42.520)
		PM	24	3.42 (70.182)	24	3.48 (58.408)
AUC (ng h/mL)	Geometric mean (CV%)[a]	EM	25	28.85 (36.992)		NC
		PM	24	35.03 (71.882)		NC
$AUC_{(0-t)}$ (ng h/mL)	Geometric mean (CV%)[a]	EM	25	25.58 (40.006)		NC
		PM	24	30.02 (72.981)		NC
t_{max} (h)	Median (range)	EM	25	3.00 (1.00 to 5.00)	25	4.00 (1.00 to 6.00)
		PM	24	3.03 (2.00 to 5.00)	24	4.00 (2.00 to 6.00)
$t_{1/2\lambda z}$ (h)	Geometric mean (CV%)[a]	EM	25	7.25 (62.663)		NC
		PM	22[b]	7.65 (54.226)		NC
$AUC_{(0-24)}$ (ng h/mL)	Geometric mean (CV%)[a]	EM	25	25.57 (35.162)	25	28.31 (38.606)
		PM	24	29.59 (61.483)	24	32.35 (56.059)
$C_{ss, av}$ (ng/mL)	Geometric mean (CV%)[a]	EM		NC	25	1.18 (38.744)
		PM		NC	24	1.35 (56.050)
TCP	Geometric mean (CV%)[a]	EM		NC	25	0.98 (32.189)
		PM		NC	24	0.92 (29.271)
Rosuvastatin lactone						
C_{max} (ng/mL)	Geometric mean (CV%)[a]	EM	25	2.31 (59.933)	25	3.58 (62.464)
		PM	24	2.26 (60.295)	24	3.93 (47.272)
AUC (ng h/mL)	Geometric mean (CV%)[a]	EM	25	44.22 (43.121)		NC
		PM	24	45.66 (38.259)		NC
$AUC_{(0-t)}$ (ng h/mL)	Geometric mean (CV%)[a]	EM	25	40.55 (47.524)		NC
		PM	24	42.03 (43.433)		NC
t_{max} (h)	Median (range)	EM	25	4.00 (2.00 to 18.00)	25	4.00 (0.50 to 10.00)
		PM	24	4.00 (2.42 to 18.00)	24	4.00 (2.00 to 12.00)
$t_{1/2\lambda z}$ (h)	Geometric mean (CV%)[a]	EM	25	16.07 (24.214)		NC
		PM	24	15.95 (27.877)		NC
$AUC_{(0-24)}$ (ng h/mL)	Geometric mean (CV%)[a]	EM	25	29.42 (45.922)	25	43.67 (43.170)
		PM	24	30.32 (44.117)	24	46.25 (32.776)

Table S1 Summary of PK parameters (PK evaluable volunteers)

			Day 1 (single dose)		Day 17 (steady state)	
PK parameter	**Statistic**	**Group**	**n**	**Results**	**n**	**Results**
$C_{ss, av}$ (ng/mL)	Geometric mean (CV%)[a]	EM		NC	25	1.82 (43.106)
		PM		NC	24	1.93 (32.765)
TCP	Geometric mean (CV%)[a]	EM		NC	25	0.99 (30.180)
		PM		NC	24	1.01 (20.799)

[a] CV%=sqrt (exp [SD^2] - 1)*100, where SD denotes standard deviation of the log-transformed data.
[b] The N-desmethyl rosuvastatin half-lives for Subject 1207 (E0001144) and Subject 1223 (E0001129) were not reported and not included in the descriptive summaries, because the available data did not support an accurate estimate of half-life in either subject.

$AR_{(AUC24)}$ Accumulation ratio (at steady state) based on $AUC_{(0-24)}$; $AUC_{(0-24)}$ Area under the plasma concentration curve from zero to 24 hours post-dose; $AUC_{(0-t)}$ Area under the curve of plasma concentration against time from zero to time of last quantifiable concentration; AUC Area under the concentration curve from zero to infinity; CL/F Apparent oral clearance; C_{max} Maximum concentration; $C_{ss,av}$ Average plasma concentration at steady state; CV% Coefficient of variation in percent; CYP2C19 Cytochrome P450, family 2, subfamily C, polypeptide 19; EM CYP2C19 extensive metaboliser; n Number of evaluable subjects; NC Not calculated; PK Pharmacokinetic; PM CYP2C19 poor metaboliser; $t_{1/2\lambda z}$ Half-life associated with the terminal slope of a semi logarithmic plasma concentration-time curve; TCP Temporal change parameter; t_{max} Time to maximum concentration.

Overall, the PK properties of rosuvastatin for both EM and PM groups were well characterised after single and multiple dose administrations of rosuvastatin 20 mg. Following multiple dose administrations, a steady state for rosuvastatin was achieved within 5 days of multiple dose administrations. Time effect on PK properties of rosuvastatin in both groups was not observed. Accumulation of rosuvastatin was minimal. The PK properties of rosuvastatin, as evaluated by ratios of geometric mean AUC or $AUC_{(0-24)}$ and C_{max} on Day 1 and Day 17 between the 2 groups, were highly comparable. Terminal elimination half-life of rosuvastatin between the 2 groups was approximately equal. Thus, these observations suggest that CYP2C19 polymorphism does not affect PK of rosuvastatin.

The PK properties of metabolites N-desmethyl rosuvastatin and rosuvastatin lactone for both EM and PM groups were well characterised after single and multiple dose administrations of 20 mg rosuvastatin. A steady state for both metabolites was achieved within 5 days of multiple dose administrations. Time effect on PK properties of both metabolites in both groups was not observed. The PK properties of N-desmethyl rosuvastatin and rosuvastatin lactone, as evaluated by ratios of geometric mean AUC or $AUC_{(0-24)}$ and C_{max} on Day 1 and Day 17 between the 2 groups, were comparable except for changes noted between PM and EM in the ratio N-desmethyl rosuvastatin/rosuvastatin at Day 1, but not at Day 17. Terminal elimination half-lives of rosuvastatin lactone and N-desmethyl rosuvastatin for the 2 groups were approximately equal. As expected, some accumulations in rosuvastatin lactone were demonstrated in both groups. Based on a comparison of geometric mean AUC values, exposure to N-desmethyl rosuvastatin on Day 1 is approximately 17% that of rosuvastatin for EM and approximately 21% for PM, and exposure to rosuvastatin lactone on Day 1 is approximately 26% that of rosuvastatin for EM and approximately 27% for PM. Thus, these

observations suggest that CYP2C19 polymorphism does not affect PK of N-desmethyl rosuvastatin or of rosuvastatin lactone in any clinically meaningful way.

Summary of pharmacodynamic results

Table S2 summarises data comparing the effect of rosuvastatin on the lipid profiles for subjects in the EM and PM groups.

Table S2 Summary for lipid variables, fasting (PD analysis set)

		Baseline (Day -1)		Day 18		Percent change from baseline	
PD variable	**Group**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
HDL-C (mmol/L)	EM	25	12.84 (3.164)	25	12.16 (2.739)	25	-4.54 (8.614)
	PM	24	12.66 (2.804)	24	12.38 (2.926)	24	-1.58 (12.388)
LDL-C (mmol/L)	EM	25	2.32 (0.665)	24	1.05 (0.304)	24	-53.33 (9.727)
	PM	24	2.85 (0.724)	24	1.34 (0.463)	24	-52.42 (14.866)
tChol (mmol/L)	EM	25	4.41 (0.882)	25	3.05 (0.481)	25	-30.00 (8.482)
	PM	24	5.02 (0.962)	24	3.25 (0.622)	24	-34.23 (11.211)
TG (mmol/L)	EM	25	0.88 (0.564)	25	0.92 (0.574)	25	11.84 (45.612)
	PM	24	1.26 (1.133)	24	0.97 (0.361)	24	-5.72 (31.587)

Volunteers received a single dose on Day 1, no doses on Day 2 and 3, and once-daily doses on Days 4 to 17.
CYP2C19 Cytochrome P450, family 2, subfamily C, polypeptide 19; EM CYP2C19 extensive metaboliser; HDL-C High density lipoprotein cholesterol; LDL-C Low density lipoprotein cholesterol; n Number of evaluable subjects; PD Pharmacodynamic; PM CYP2C19 poor metaboliser; SD Standard deviation; tChol Total cholesterol; TG Triglycerides.

In general, although no formal statistical analysis was performed, rosuvastatin 20 mg treatment appeared to result in similar effects on lipid profiles in EM and PM groups.

On Day 18 (after 14 days of continuous once daily therapy; 15 doses total) evaluating changes from baseline for EM and PM treatment arms, respectively, HDL-C decreased 4.54% and 1.58%, LDL-C decreased 53.33% and 52.42%, tChol decreased 30.00% and 34.23%. TG increased 11.84% for EMs and decreased 5.72% for PMs. The percent changes from baseline were generally similar for all lipid parameters between EM and PM groups with the exception of TG. The inter-subject variability, however, was high for HDL-C and TG but generally under 33% for LDL-C and tChol. Thus, these data suggest that CYP2C19 polymorphism does not affect the PD lipid response to rosuvastatin treatment.

Summary of safety results

- Rosuvastatin 20 mg was generally well-tolerated in Taiwanese subjects (both EM and PM).

- There were no deaths, serious AEs, discontinuations due to AE, or other significant AEs during this study.

- In the study, 1 (2.0%) of the 49 subjects experienced at least 1 AE. This subject (Subject 1203; E0001045) was in the PM group and experienced 2 AEs with preferred terms of Myalgia and Constipation on Day 11 of the study. Both were of mild intensity, were considered related to the study treatment, and resolved by the end of the study while still receiving drug.

- There were no treatment-related changes in any clinical laboratory variables that were clinically relevant during the study. Specifically, there were no elevations greater than or equal to 3 times the upper limit of normal for alanine aminotransferase or for creatine kinase.

- No changes assessed as clinically relevant were observed in haematology, clinical chemistry, urinalysis, vital sign, ECG, or physical examination results.