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APPLICATION NUMBER

21-366

**Clinical Pharmacology and Biopharmaceutics
Review**

7/21/03

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-366
Submission Date(s): February-12-2003, May-8-2003
Brand Name: Crestor™
Generic Name: Rosuvastatin calcium
Reviewer: Sang M. Chung, Ph. D.
Team Leader: Hae-Young Ahn, Ph. D.
OCPB Division: Division of Pharmaceutical Evaluation 2 (DPE-2, HFD-870)
OND division: Division of Metabolic and Endocrine (DMEDP, HFD-510)
Sponsor: AstraZeneca
Relevant IND(s): 56,385
Submission Type: 1S
Strength(s): 5 mg, 10 mg, 20 mg, and 40 mg
Indication: Cholesterol lowering

1 Executive Summary

The sponsor submitted this Amendment to the original NDA21-366 (Crestor™, rosuvastatin calcium) as a response to the Action Letter that the Agency sent on May 31, 2002 (Attachment 1).

The Amendment contained 3 major information related to Clinical Pharmacology and Biopharmaceutics (CPB) as follows:

- Correlation between creatinine clearance and steady state rosuvastatin pharmacokinetics was assessed to measure impact of mild to moderate renal impairment on rosuvastatin exposure. In addition, pharmacokinetics of rosuvastatin in the end-stage renal disease (ESRD) was provided.
- Pediatric pharmacokinetics was assessed.
- Rosuvastatin systemic exposure in the patients experienced with myopathy or acute renal failure (n=11) was summarized.

The results of the renal impairment study showed no significant association between rosuvastatin exposure and mild to moderate renal impairment. However, steady-state AUC and C_{max} in ESRD subjects with chronic hemodialysis were increased by 50% and 58%, respectively, compared to historic healthy volunteer results.

Pediatric pharmacokinetics was not significantly different from that in adults. The number of subjects reported to develop myopathy or acute renal failure were total 11 at

80-mg dosing and systemic exposure of rosuvastatin in those subjects was significantly higher than that in subjects without the serious adverse events.

Additional *in vitro* dissolution data were provided from the second manufacturing site including the 5-mg tablet, new proposed strength. The results demonstrated comparable dissolution profiles between the manufacturing sites, Carolina, PR and Canovanas, PR.

The original NDA reported approximately a 2-fold rosuvastatin exposure elevation in Japanese residing in Japan compared to Caucasian subjects. Safety of rosuvastatin has not been fully evaluated in subjects of Asian ethnicity residing in U.S.A. compared to that in Caucasian subjects. Therefore, the Agency recommends a Phase IV study as follow:

- A single dose pharmacokinetic study in subjects of Asian ethnicity residing in U.S.A. and comparing the results to those in historical Caucasian subjects.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the amendment and finds it acceptable. This recommendation and Phase IV Commitment should be sent to the sponsor as appropriate.

1.2 Phase IV Commitment

A single dose pharmacokinetic study in subjects of Asian ethnicity residing in U.S.A. and comparing the results to those in historical Caucasian subjects.

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2 Summary of CPB findings

2.1 Impact of renal function on rosuvastatin systemic exposure

In the original application, the sponsor evaluated (Study 17) the relationship between systemic exposure of rosuvastatin and degree of renal impairment after 20-mg daily dose for 22 subjects (Figure 1). OCPB/DPE-2 concluded that the results of mild to moderate renal impairment were not conclusive because of bimodal distribution and variability in the small number of subjects. Therefore, OCPB/DPE-2 recommended that the sponsor provide additional data to assess the effect of renal function on rosuvastatin and the sponsor agreed to evaluate correlation between creatinine clearance (CL_{cr}), a renal function maker, and exposure of rosuvastatin.

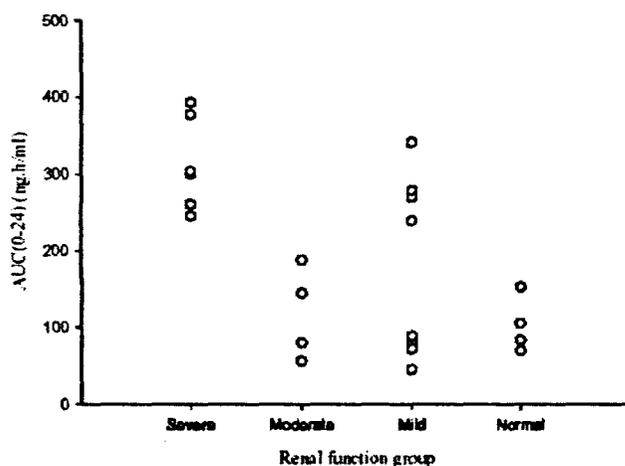
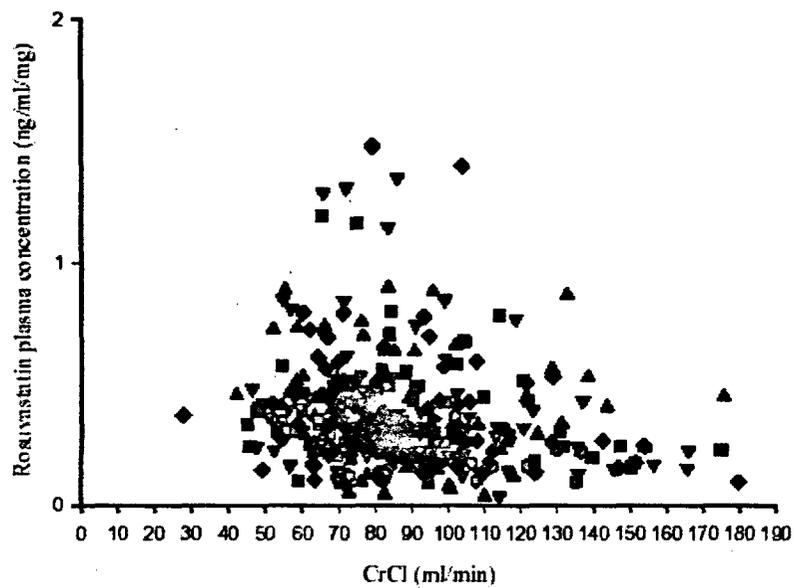


Figure 1 systemic exposure of rosuvastatin and degree of renal impairment

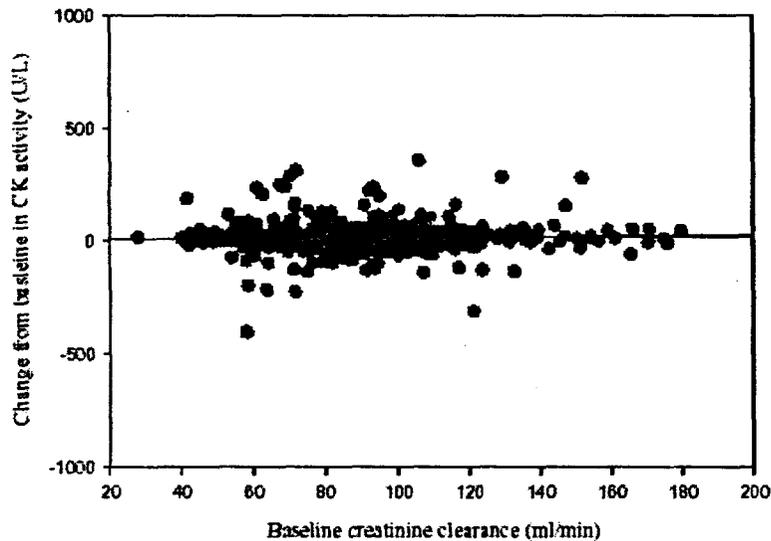
The sponsor evaluated the relationship between estimated CL_{cr} and steady-state exposure of rosuvastatin. Single steady-state plasma concentrations were obtained from 386 dyslipidemia patients among Phase II/III trials. Doses in the trials were 1 to 40 mg daily. Dose normalized plasma concentrations and estimated CL_{cr} are summarized in Figure 2. There is no significant association between CL_{cr} and the dose normalized plasma concentrations.



▲	rosuvastatin 1 mg	N=9
●	rosuvastatin 2.5 mg	N=14
■	rosuvastatin 5 mg	N=77
▼	rosuvastatin 10 mg	N=79
▲	rosuvastatin 20 mg	N=77
◆	rosuvastatin 40 mg	N=96

Figure 2 Dose normalized steady-state concentrations of rosuvastatin at week 6 and estimated creatinine clearance.

In addition, the relationship between serum creatine kinase activity (biomarker of adverse events) and estimated CLcr was evaluated and the results are summarized in Figure 3. The slope of the regression line is 0.07393 ($r^2 < 1\%$) and there is no significant correlation between the parameters.



The CK activity reference range for each of the studies is given below:
 Studies 8 and 23: men (22 to 198 U/L), women (21 to 169 U/L)
 Studies 33 and 35: men and women (0 to 120 U/L)
 Study 55: men (57 to 197 U/L), women (32 to 180 U/L)
 Subjects were stratified on creatinine clearance as follows:
 Normal renal function (> 80 ml/min)
 Mild impairment (50 to < 80 ml/min)
 Moderate impairment (30 to 50 ml/min)
 Severe impairment (≤ 30 ml/min)
 Baseline creatinine clearance was estimated using the Cockcroft-Gault equation at Week 0 (and Week -1 in Studies 33 and 35).
 Baseline for CK activity is Week 0.

Figure 3 Creatine kinase activity change from baseline and estimated creatinine clearance (based on Study 8, 23, 33, 35, and 55; dosing 1-80mg).

The sponsor also estimated rosuvastatin pharmacokinetics in the end-stage renal disease patients with chronic hemodialysis (Study 97, $n=11$). The exposure was increased 50% and 58% for AUC and C_{max} , respectively, compared to those in historic healthy subjects after 10-mg daily dose.

2.2 Rosuvastatin pharmacokinetics in pediatric subjects (Study 86)

Rosuvastatin pharmacokinetics was assessed in the pediatric subjects and results were summarized in Figure 4. There was no significant difference in pediatric pharmacokinetics for rosuvastatin compared to that in adult patients.

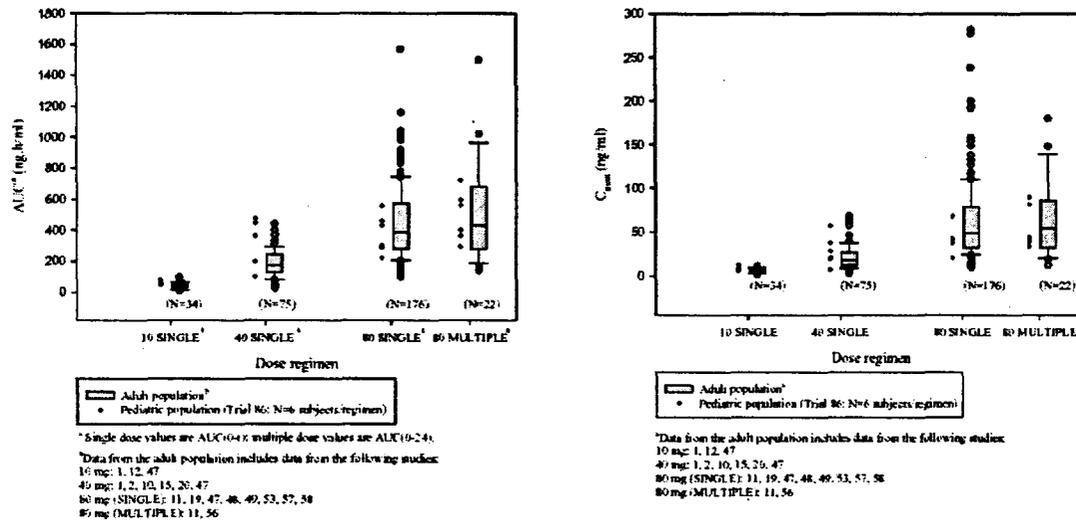
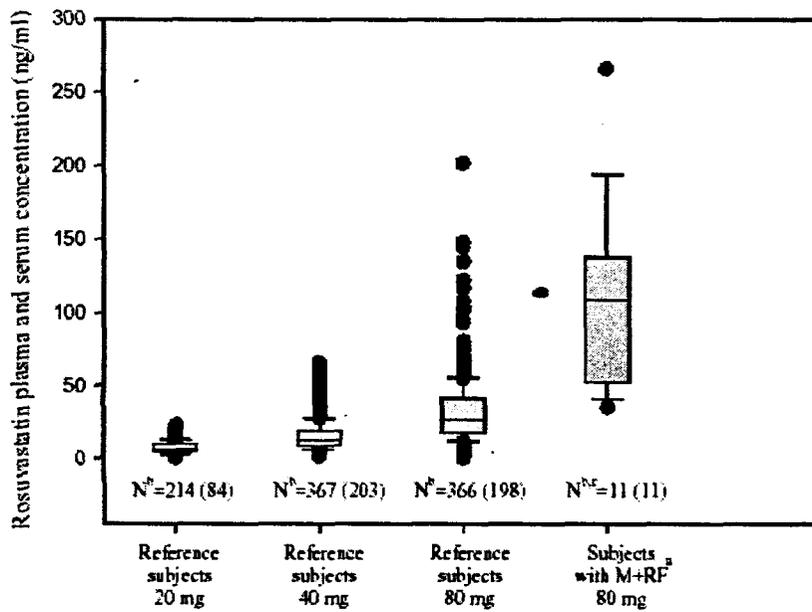


Figure 4 AUC (left panel) and C_{max} (right panel) of rosuvastatin in pediatric subjects.

2.3 Rosuvastatin exposure in patients developed myopathy or renal failure

Nine subjects were reported to experience myopathy with creatine kinase (CK) elevation greater than 10 times of the upper limit of normal range at the 80-mg dosing. Also, two subjects were reported to have renal failure with the 80-mg dosing. Total 22 steady-state plasma concentrations were obtained in the patients who experienced the serious adverse events and compared with the historical data in patients without the adverse reaction. The results were summarized in Figure 5. The rosuvastatin exposure in patients with the adverse events were significantly higher than that in patients without the adverse events.



^a M+RF includes subjects reporting myopathy or renal failure.

^b N represents Number of measurements (Number of subjects).

^c For subjects with myopathy or renal failure, each measurement is a within-subject mean concentration.

This figure presents only concentrations which were collected between 8 and 16 hours following the subject's most recent dose.

Reference subjects may provide more than one concentration.

Figure 5 Rosuvastatin steady-state concentrations in patients with (indicated as subjects with M+RF) and without (indicated as reference subjects) experienced adverse events.

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3 Question Based Review

3.1 What is the relationship between degree of renal impairment and exposure after oral administration of rosuvastatin?

In the original application, the sponsor proposed the dose adjustment for the severe renal impairment patients (creatinine clearance is less than 30 ml/min) because rosuvastatin exposure increased about 3-fold in the patients with severe renal impairment (Table I).

Table I Statistical analysis of renal function on rosuvastatin exposure after 14th dose of 20-mg.

PK parameter ^b	Severe:normal ratio (90% CI)	Moderate:normal ratio (90% CI)	Mild:normal ratio (90% CI)
AUC(0-24) (ng.h/ml)	3.16 (1.47 to 6.78)	1.07 (0.46 to 2.48)	1.42 (0.69 to 2.93)
C _{max} (ng/ml)	3.11 (1.26 to 7.69)	1.13 (0.42 to 3.04)	1.75 (0.74 to 4.12)

Data derived from Tables H4.1 and H4.2

^a Subjects were stratified based on creatinine clearance as calculated by the sponsor. The renal status categories are as follows:

Severe: CrCL <30 ml/min/1.73 m²
 Moderate: CrCL 30 to <50 ml/min/1.73 m²
 Mild: CrCL 50 to 80 ml/min/1.73 m²
 Normal: CrCL >80 ml/min/1.73 m²

^b Geometric mean of the ratio of the parameter for the specified groups.

CI Confidence interval.

CrCL Creatinine clearance.

Although mean ratio of AUC and C_{max} did not increase significantly in mild to moderate renal impairment patients compared to those in normal subjects, there seemed to be bimodal distribution with variability.

To support no significant association, the sponsor evaluated the correlation between creatinine clearance (CL_{cr}) as a renal function marker and rosuvastatin exposure in the retrospective data analyses. The CL_{cr} was estimated based on Cockcroft-Gault formula as follows:

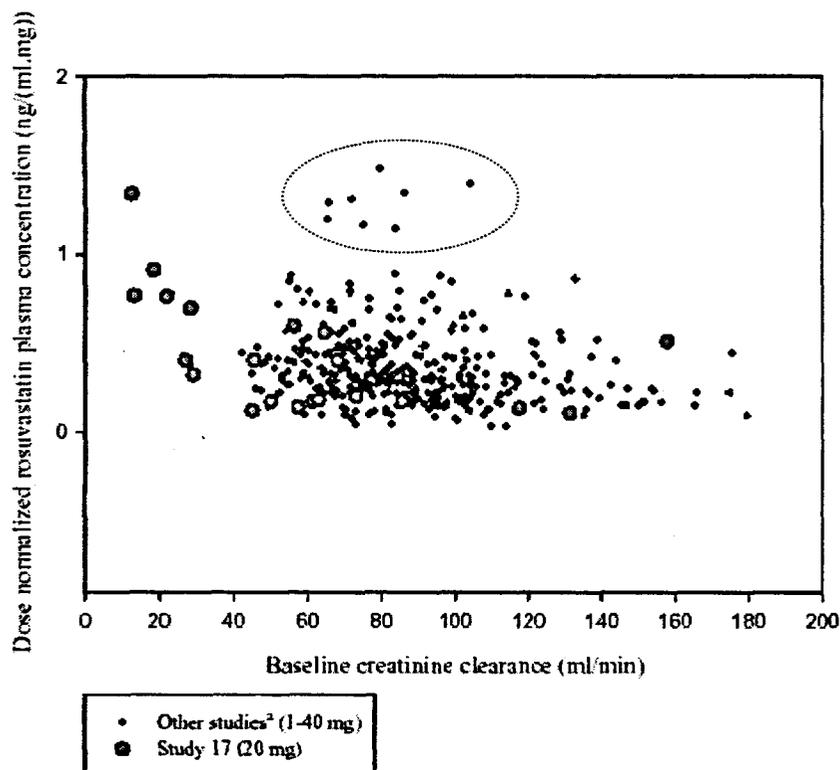
$$\text{Males: } CL_{cr} = \frac{88.4 \times WT \times (140 - AGE)}{72 \times S_{cr}} \quad \text{Equation 1}$$

$$\text{Females: } CL_{cr} = \frac{0.85 \times 88.4 \times WT \times (140 - AGE)}{72 \times S_{cr}} \quad \text{Equation 2}$$

Here, WT is the body weight in kg, and AGE is the age in years, and S_{cr} is serum creatinine level.

It should be noted that CLcr is a function of Scr, AGE, and WT by the formula. In this regard, the results of any analyses based on the CLcr should be cautiously evaluated by the confounding factors.

Steady-state plasma concentrations were collected mainly from Phase II/III trials (Study 8, 23, 33, and 35). Plasma sampling in the trials was based on sparse sampling schedules in dyslipidemia patients at week 6 approximately 8-12 hours after various dosing (1 to 40 mg). The results were summarized in Figure 5. It appeared to be no significant association between estimated CLcr and dose normalized steady-state concentrations. There were 8 dose normalized concentrations in the upper limit (circle in Figure 5): 2 out of 77 from 5mg, 4 out of 79 from 10mg, and 2 out of 96 from 40-mg dosing. In general, there was no significant dose related distribution of the results. Results from Study 17 are plotted as a reference in the same figure and steady-state concentrations were obtained 9 hours after 20-mg dosing and CLcr was measured.



* Other studies include Studies 8, 23, 33, and 35.
Baseline creatinine clearance was estimated using the Cockcroft-Gault formula, except for subjects in Study 17 in which creatinine clearance was measured correcting for body surface area.
Subjects in Study 17 received rosuvastatin for 2 weeks.

Figure 6 Estimated CLcr (except Study 17, where CLcr was measured) and dose normalized rosuvastatin steady-state concentrations in dyslipidemia patients.

For further analysis about renal function and exposure, steady-state exposure (AUC_{ss} and C_{ss}) was predicted using population pharmacokinetic analysis based on the same clinical trials data (Study 8, 23, 33, and 35) and correlation was estimated between the predicted exposure and estimated CL_{cr}. The predicted steady-state exposure with dose normalization and estimated CL_{cr} are summarized in Figure 7 (dosing range of 1-80mg). The correlation parameters are summarized in Table 3. The association between the predicted steady-state exposure and the estimated CL_{cr} appeared to be insignificant.

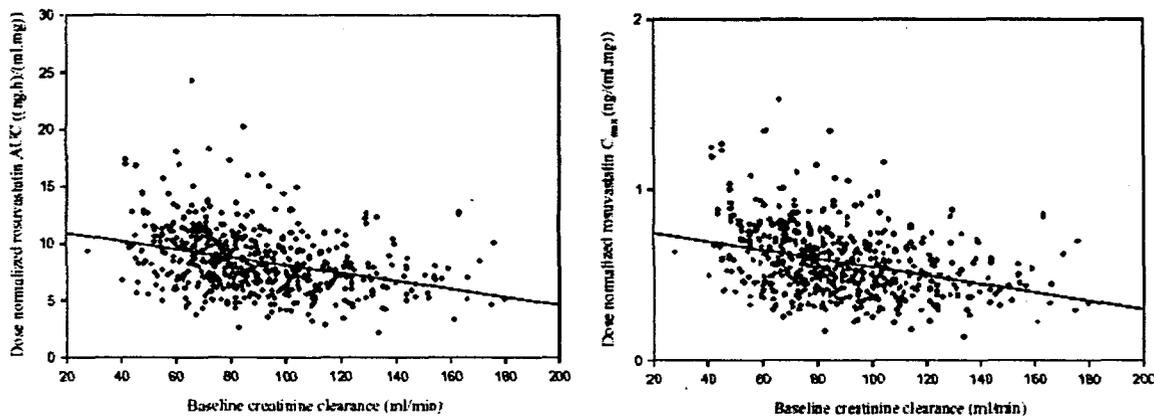


Figure 7 Estimated CL_{cr} and dose normalized rosuvastatin AUC (left) and C_{max} (right) in the dosing range of 1-80mg.

Brief summary on data collection, models, comments on the models, and NONMEM control stream can be found in Attachment 4.1-4.2.

Table 2 Correlation constants between CL_{cr} and predicted rosuvastatin exposure.

		AUC	C _{max}
1-80mg dosing	Slope (p)	-0.3517 (p<0.0001)	-0.0025 (p<0.0001)
	R ²	12%	12%
5-40mg dosing	Slope (p)	-0.03344 (p<0.0001)	-0.00233 (p<0.0001)
	R ²	10%	10%

The sponsor extended the population analyses on the relationship between CLcr and CK activity (baseline activity and change from the baseline activity). There was no significant association between the estimated parameters.

The sponsor included new pharmacokinetic information from the end-stage renal disease (ESRD) patients with chronic hemodialysis (Study 97). Pharmacokinetics after single and multiple 10-mg doses were characterized and parameters were summarized in Table 2. There was no significant change of rosuvastatin pharmacokinetics in the ESRD patients with chronic hemodialysis compared to that in healthy subjects.

Table 3 Rosuvastatin exposure in subjects with end-stage renal disease under chronic hemodialysis after single and daily administration of 10-mg dose

Parameter	Geometric mean (coefficient of variation, %) unless specified			
	Single administration		Multiple administrations	
	Study 97 N=11	Healthy volunteers ^a N=34	Study 97 N=11	Healthy volunteers ^b N=49
AUC ₍₀₋₂₄₎ (ng·h/mL)	44.0 (58.5)	38.7 (60.7)	60.1 (59.9)	40.1 (46.7)
C _{max} (ng/mL)	4.73 (67.4)	4.79 (56.7)	6.47 (65.9)	4.09 (49.3)

Data derived from Study 97, and Tables 10 and 13 in Human Pharmacokinetics and Bioavailability Summary 26 June 2001.

^a Subjects were enrolled in Studies 1, 12, and 47.

^b Subjects were enrolled in Studies 4, 5, and 18.

AUC₍₀₋₂₄₎: Area under the plasma concentration-time curve from time zero to 24 hours.

C_{max}: Maximum concentration.

3.2 Are pediatric rosuvastatin pharmacokinetics significantly different from those in adult subjects?

The study results were reported as IND56,385-N-357-IM and the review was completed to the IND study reported before (Attachment 4.3).

In brief, pediatric pharmacokinetic parameters are summarized in Table 4 and 5 and there was no significant difference in pediatric rosuvastatin pharmacokinetics from those in adult subjects.

Table 4

Pharmacokinetics of rosuvastatin in pediatric subjects (Primary parameters).

Parameter	Summary statistic	Single-dose			Multiple-dose
		10 mg N=6	40 mg N=6	80 mg N=6	80 mg N=6
Primary end points					
C _{max} , ng/mL	gmean (CV)	6.3 (58.1)	23.5 (79.6)	42.6 (46.8)	50.6 (43.4)
	range ^a				
	n	6	6	6	6
AUC ₍₀₋₂₄₎ , ng·h/mL	gmean (CV)	48.7 (48.3)	234 (62.9)	313 (37.1)	467 (35.3)
	range ^a				
	n	6	6	6	6
AUC ₍₀₋₁₆₎ ^b , ng·h/mL	gmean (CV)	52.2 (52.3)	288 (65.2)	361 (35.2)	467 (35.3)
	range ^a				
	n	6	6	6	6
AUC, ng·h/mL	gmean (CV)	47.6 (71.6)	299 (63.5)	371 (35.6)	NC
	range ^a				NC

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Table 5 Pharmacokinetics of rosuvastatin in pediatric subjects (Secondary parameters).

Parameter	Summary statistic	Single-dose			Multiple-dose
		10 mg N=6	40 mg N=6	80 mg N=6	80 mg N=6
	n	3	6	6	NA
Secondary end points					
t_{max} , h	median	2.5	3.0	4.5	5.0
	range ^a		—		
	n	6	6	6	6
$t_{1/2}$, h	mean ^b (SD ^b)	8.6 (1.4)	14.8 (4.9)	20.0 (10.7)	NC
	range ^a		—		NC
	n	3	6	6	NC
CL _f , L/h	gmean (CV)	210 (71.5)	134 (63.5)	215 (55.7)	NC
	range ^a		—		NC
	n	3	6	6	NA
CL _R , L/h	gmean (CV)	6.0 (40)	9.3 (17)	12.9 (28)	5.6 (30)
	range ^a		—		
	n	6	6	5	6
Fe, %	gmean (CV)	2.9 (45)	5.5 (53)	5.2 (41)	3.3 (24)
	range ^a		—		
	n	6	6	5	6
X_e , μ g	gmean (CV)	294 (45)	2180 (53)	4150 (41)	2630 (24)
	range ^a		—		
	n	6	6	5	6

Data derived from Table 12 of Clinical Study Report 86.

^a These statistics are calculated on untransformed data.

^b The last sampling time was 24 h for subjects in the multiple-dose group.

AUC: area under the plasma concentration-time curve from time zero to infinity; AUC₀₋₂₄: area under the plasma concentration-time curve from time zero to 24 hours; AUC_{0-∞}: area under the plasma concentration-time curve from time zero to the last quantifiable concentration; CL_f: apparent oral clearance; CL_R: renal clearance; C_{max}: maximum concentration; CV: coefficient of variation; Fe: fraction excreted in urine; gmean: geometric mean; NA: not applicable; NC: not calculated; SD: standard deviation; $t_{1/2}$: terminal elimination half-life; t_{max} : time of maximum concentration; X_e : amount excreted in urine.

3.3 Is there any significant association between rosuvastatin exposure and incidence of myopathy or renal failure?

There were 11 patients reported to experience myopathy or renal failure in the rosuvastatin clinical trials. The reported patients received the 80-mg dose and other information was summarized in Table 6.

The rosuvastatin concentrations measurements in these patients did not coincide with the timing of the adverse events because concentrations were retrospectively measured from plasma samples that were obtained for safety assessments.

Table 6 demographic and clinical summaries of selected subjects with myopathy or renal failure

Study ^a	Center/Subject ^b	Age (yr)	Sex	Event day ^c	Blood draw ^c (day)	Serum or plasma concentration on day of blood draw (ng/mL)
Subjects with myopathy						
34 (31)	0037/0006 (0037/0001)	66	M	280	39 123 207	44.8 41.4 49.8
34 (25)	0224/0003 (0224/0009)	56	M	154	11 32 116	32.2 53.0 20
34 (25)	0229/0004 (0229/0004)	73	F	118	41	266
34 (35)	0229/0024 (0229/0008)	72	M	43 ^d	17 ^d 29 ^d 43 ^d	135 202 103
34 (30)	0277/0017 (0277/0221)	59	M	463	15 380	38.5 51.0
34 (25)	0279/0008 (0279/0009)	68	M	26	4	141
34 (30)	0317/0003 (0317/0201)	64	F	191	15 43	106 140
34 (35)	0393/0012 (0393/0002)	75	F	511	405 491	69 76.1
35	0268/0002	68	F	29	15 29	148 108
Subjects with renal failure						
65	0026/0049	70	F	20	15	109
65	0044/0014	46	F	34	17 34 ^e	82 81

^a Study in which the subject reported the adverse event. Subjects enrolled into Study 34 completed previous rosuvastatin clinical studies assigned to subject numbers shown parenthetically. All subjects received rosuvastatin 80 mg in previous studies (feeder trials) except for Subject 34:0277/0017, who received placebo for 6 weeks.

^b All subjects were Caucasian except for Subject 65:0044/0014, who was Hispanic.

^c Day numbers are relative to the day of the first administration of rosuvastatin in which symptoms consistent with myopathy or renal failure were evident, ie, the study in the leftmost column, unless specified.

^d Day numbers are relative to the day of the first administration of rosuvastatin in the feeder trial.

For the reference, steady-state concentrations were obtained from several Phase II/III studies (Study 8, 23, 33, 35, and 34 sub-study). Brief information on the study was summarized in Table 7.

Table 7 Reference subjects who did not experience myopathy or renal failure

Study	Subject description (N)	Rosuvastatin dosage (mg/day)	Time of blood draws relative to start of rosuvastatin administration ^a
8	Primary hypercholesterolemia (35)	20 or 40	2, 4, and 6 weeks
23	Primary hypercholesterolemia (47)	40 or 80	2, 4, and 6 weeks
33	Hypercholesterolemia (126)	20, 40, or 80	2, 4, and 6 weeks
35	Hypertriglyceridemia (type IIb or IV) (81 ^b)	20, 40, or 80	2, 4, and 6 weeks
34 ss ^c	Completed 1 of the following rosuvastatin feeder studies: 23 through 33, 35, 36, 44, or 54 (98)	80 down titrated to 40 (for 4 weeks)	while on 80 mg prior to titration to 40 mg after 4 weeks on 40 mg

^a Protocols specified that rosuvastatin was to be administered daily in the evening. Blood was drawn on the morning following the previous evening dose, ie, between 8 and 16 hours post dose for most subjects. Data from blood draws outside this interval were not included in the comparator data pool.

^b Two subjects enrolled in Study 35 experienced myopathy and are included with the selected subjects, not with the reference subjects tabulated here.

^c The substudy (ss) investigated plasma exposure before and after reduction of the 80-mg dose of rosuvastatin to 40 mg.

Results are summarized in Figure 11 and Table 8. Median plasma concentration (109 ng/ml) of the patients with the adverse events were significantly higher than that in patients without those after 80 mg (26.6 ng/ml) dosing.

The results indicated that the risk of myopathy or renal failure be greater in subjects with the elevated systemic exposure of rosuvastatin.

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the approval package consisted of draft labeling

5 ATTACHMENT

5.1 Studies included in the analyses

Study	Clinical phase	Number of subjects included	Dosage scheme	Plasma sampling schedules
1	I	13 normal subjects	Capsules 5mg (4), 10mg (4), 4x5mg (4), and 4x 10mg (4) as single dose. Subjects 2, 6, 10, and 12 were given more than one dose.	Day 1: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48, 72, and 96 h post dosing.
2	I	12 normal subjects	Capsules 2x10mg (6), or 4x10mg (6) as single dose, 4d washout, repeated doses for 7 d (administered at 0700)	Day 1: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post dosing. Days 5, 6, 7, 8, 9, and 10: immediately before the morning intake. Days 11: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post the last intake.
6	I	34 normal subjects	Capsules 10mg (18), or 4x10mg (16) as single dose Tablet 18mg (18), or 40mg (16) as single dose	Day 1: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post dosing.
7	I	24 normal Japanese subjects (6 placebo subjects)	Capsules 10mg (6), 2x10mg (6), 4x10mg (6) as single dose, 4d washout, repeated doses for 7 d (administered fasted at 0700)	Day 1: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post dosing. Days 5, 6, 7, 8, 9, and 10: immediately before the morning intake. Days 11: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post the last intake.
8	III	106 subjects with primary hypercholesterolemia	Capsules 1mg (15), 2.5mg (15), 5mg (18), 10mg (17), 2x10mg (17), and 4x10mg (18) for 6wks	Randomized sparse sampling schedules at 0, 2, 4, and 6 weeks.
10	III	15 normal subjects	Phase I: Rosuvastatin iv infusion 4mg (3), 6 mg (3), 8 mg (3) over 2.2, 4 hr, respectively. Phase II: Exc. tablets 40mg (10) as single oral dose	For oral dose: Day 1: 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post dosing.
11	I	8 normal subjects (2 placebo subjects)	Capsules 8x10mg (6) as single dose, 4d washout, repeated doses for 7 d (administered fasted at 0700)	Day 1: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post dosing. Days 5, 6, 7, 8, 9, and 10: immediately before the morning intake. Days 11: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post the last intake.
15	I	32 normal subjects	Capsules 4x10mg (32) as single dose	Day 1: 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48, 72, and 96 h post dosing.
17	I	26 renally-impaired subjects and normal subjects	Capsules 2x10mg (4) as single dose for subjects requiring dialysis. Capsule 2x10mg (22) for 2 wks for others	Subjects requiring dialysis: Day 1: 0, 1, 2, 3, 4, 6, 8, 9, 16, 12, 18, 24, 48, and 72 h post dosing. Other subjects: Days 1, 2, 3, and 11: immediately before the morning intake. Day 15: 0, 1, 2, 3, 4, 6, 8, 9, 10, 12, 18, 24, 48, and 72 h post dosing.
23	III	47 subjects with primary hypercholesterolemia	Capsule 4x10mg (16) and 8x10mg (31) for 6wks	Randomized sparse sampling schedules at 0, 2, 4, and 6 weeks.
33	III	280 subjects with hypercholesterolemia	Exc. Tablets 5mg (78), 10mg (45), 2x10mg (39), 40mg (45), and 2x40mg (42) for 6wks	Randomized sparse sampling schedules at 0, 2, 4, and 6 weeks.
34 Substudy	III	98 subjects with hypercholesterolemia who completed one of the following rosuvastatin feeder studies: 23 through 33, 35, 36, 44, or 54 (98)	Exc. Tablets 2x40mg (98) initially for 2 weeks and then titrated to 40mg for long-term efficacy	Randomized sparse sampling schedules for one sample at 80 mg and then the other sample after 4wks at 40 mg
35	III	150 subjects with hypertriglyceridemia	Exc. Tablets 5mg (26), 10mg (23), 20mg (28), 40mg (26), and 80mg (27) for 6wks	Randomized sparse sampling schedules at 0, 2, 4, and 6 weeks.
49	I	128 normal subjects	Phase III tablets 20 mg (32), conc. tablets 20 mg (32), and Phase III tablets 80 mg (32) and exc. tablets 80 mg (32) as single dose	Day 1: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 54, 60, 72, and 96 h post dosing.
55	III	94 Japanese subjects with primary hypercholesterolemia	Exc. Tablets 1 mg (18), 2.5mg (14), 5mg (15), 10mg (19), 20mg (14), and 40mg (14) for 6wks	Randomized sparse sampling schedules at 0, 2, 4, and 6 weeks.
63	III	20 normal Japanese subjects	Phase I: Rosuvastatin iv infusion 4mg (3), or 6 mg (3) over 4 hr, respectively. Phase II: Exc. tablets 40mg (10) as single oral dose Rosuvastatin iv infusion 6 mg (10) over 4 hr.	For oral dose: Day 1: 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 54, 72, and 96 h post dosing.

5.2 Brief summary on the final pharmacokinetic model, comments on the models, and NONMEM control stream

To predict steady-state exposures in dyslipidemia patients, a total of 10078 plasma concentration measurements from 945 subjects were included as follows:

- 10 clinical trials from Phase I either in single dosing or in multiple dosing using frequent sampling
 - 9 trials in healthy volunteers; Study 1, 2, 6, 7, 10, 11, 15, 49, and 63
 - 1 trial in renal failure patients; Study 17
- 6 clinical trials from Phase II/III in patients with hypercholesterolemia or hypertriglyceridemia in a sparse schedule (Study 8, 23, 33, 35, 55, and 34 sub-study)

The data obtained from the Phase I trial were to build structural models and to analyze covariates for the final model to predict steady-state exposure in dyslipidemia patients. Detailed information about studies included in this analysis was summarized in the Attachment 4.1. The NONMEM control stream of final pharmacokinetic model was summarized in the Attachment 4.2. Two-compartment open models with simultaneous zero- and first-order absorption models were incorporated in the population analyses (Figure 9).

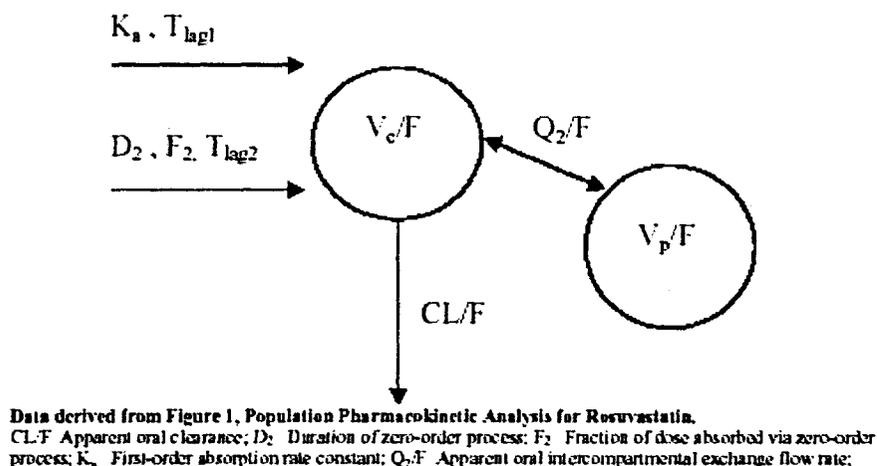


Figure 9 Population pharmacokinetic structure model.

Based on population analyses, the sponsor concluded that the contribution of zero-order process was the major pathway in the rosuvastatin absorption because 86% of the oral absorption was from the zero-order and 14% was from the first-order process.

However, data presented in the original application (DBIT1131) appeared to be different from the population analyses on absorption. By a deconvolution method on absolute bioavailability data, it was reported that on average, 20%, 55%, 80%, 88%, and 96% of the maximum bioavailability (19%) was systematically available at 3, 6, 12, 24, and 48 hours after the dose, respectively. The relationship between fraction to be absorbed and time (Figure 10) indicated that there was no significant contribution of the zero-order absorption process in the oral absorption. It appeared to be two first-order processes involved in the absorption. In this regard, the population structural model is not acceptable in terms of mechanistic interpretation of the results based on the model. However, interpretation of results based on empirical approach using the model is acceptable.

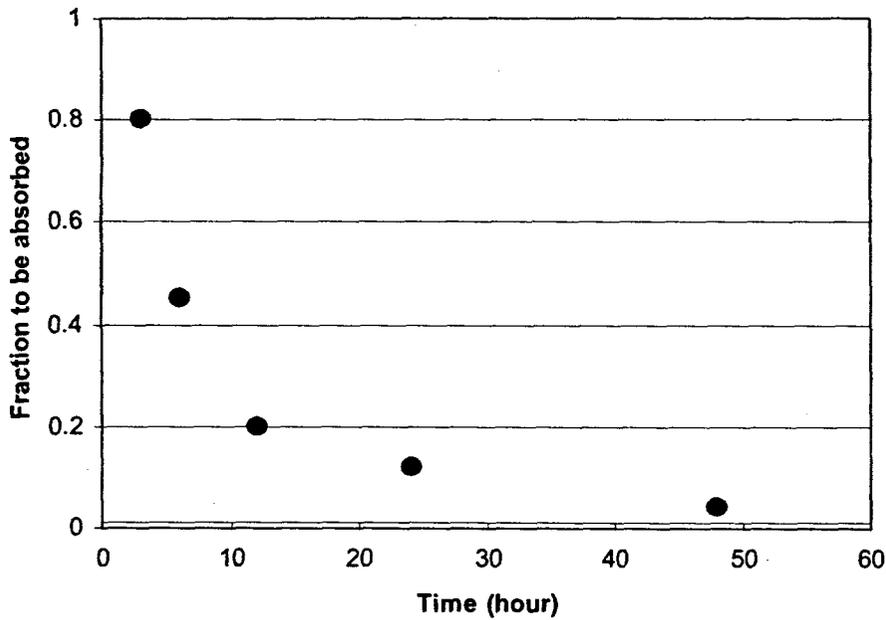


Figure 10 Relationship between fraction to be absorbed and time.

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/s/

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BIOPHARMACEUTICS

4/15/02

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-366
Submission Date(s): 26-June-2001, 21-February-2002
Brand Name: Crestor™
Generic Name: Rosuvastatin calcium
Reviewer: Sang M. Chung, Ph. D.
PM Reviewer: He Sun, Ph. D.
Team Leader: Hae-Young Ahn, Ph. D.
OCPB Division: DPE-2
OND division: Metabolic and Endocrine (HFD-510)
Sponsor: AstraZeneca
Relevant IND(s): 56,385
Submission Type: 1S
Strength(s): 10 mg, 20 mg, 40 mg, and 80 mg
Indication: Cholesterol lowering

1 Executive Summary

AstraZeneca Pharmaceuticals LP (US agent of IPR Pharmaceuticals, Inc.) is seeking approval of Crestor™ (rosuvastatin calcium) tablets for the treatment of hypercholesterolemia. Rosuvastatin calcium, a new chemical entity, is developed as a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the enzyme responsible for the rate-limiting step in cholesterol biosynthesis. Proposed strengths are 10, 20, 40 to 80 mg as tablets. It is proposed to administer orally once daily at any time of day.

Clinical pharmacology and biopharmaceutics (CPB) of Crestor™ was elucidated appropriately through 39 clinical trials in Section 6 of NDA 21-366: twelve studies for characterization of basic pharmacokinetics (PK), nine studies for PK following oral administration in special populations, thirteen studies for drug interactions, three studies for pharmacokinetic and pharmacodynamic (PK/PD) relationships, and three studies for bioequivalence (BE).

Human pharmacokinetic characteristics in brief is as follows:

Absolute bioavailability of Crestor™ was 20 % after 40 mg oral administration as referred to 8 mg intravenous infusion. About 90% of total radioactivity was found in feces after 20 mg oral dose with [¹⁴C]-rosuvastatin. Majority of the total radioactivity in feces was from rosuvastatin (77% of oral dose). Metabolism appeared to be a minor elimination pathway. Rosuvastatin seemed to be neither an inhibitor nor an inducer of P450s. There was minimal accumulation after multiple daily oral doses up to 40 mg. However, there was some degree of accumulation in 80 mg dosing (AUC₀₋₂₄ ratio of multiple dose to single dose was about 1.3). Dose proportionality in PK was demonstrated up to 80 mg. Food did not affect significantly 40 mg bioavailability of rosuvastatin. There was no significant pharmacokinetic difference of Crestor™ between healthy subjects and hypercholesterolemia patients. Exposure of rosuvastatin was higher in patients with severe renal insufficiency compared to those of patients without the condition. Absolute bioavailability was 29 % in Japanese. Crestor™ showed clinically significant pharmacodynamic interaction with warfarin and pharmacokinetic interaction with cyclosporine and

gemfibrozil. Bioequivalence was established between the to-be-marketed tablets and the formulations used in clinical trials (capsules, tablets, encapsulated tablets).

In conclusion, human pharmacokinetics of rosuvastatin calcium is properly characterized through clinical trials. However, Phase III clinical trials revealed that there were a few rhabdomyolysis cases in the 80 mg dose, and there were not enough safety data in the 20 mg and 40 mg doses. Based on the findings from pharmacometric consult, it was indicated that the 2.5 mg of rosuvastatin is as efficacious as 10 mg of atorvastatin and 20 mg of rosuvastatin is equivalent to 80 mg atorvastatin.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB/DPE-II) has reviewed NDA21-366 (Crestor™) submitted on 26-June-2001 and recommends that lower than 10 mg be considered as a starting dose. The Recommendation and Comments should be sent to the sponsor as appropriate.

1.2 Comments

1. Results of pharmacokinetic characterization on mild to moderate renal insufficient patients seem to be not conclusive. Although mean values of exposure (AUC and C_{max}) were similar between mild to moderate renal insufficient patients and healthy volunteers, there was significant variability with a bimodal distribution of exposure in the mild patients and number of data in moderate patients were relatively small to support the sponsor's conclusion. Therefore, it is recommended that the sponsor submit further supportive data such as clinical information, indicating no safety concerns for mild to moderate renal insufficient patients.
2. Based on pharmacometrics analyses on dose-efficacy relationships, and considering the potential toxicity and higher variability at higher doses, the optimal starting dose could be 10 mg or lower. At 10 mg dose, the mean LDL concentration change was -49% and about 85% of subjects would have blood LDL concentration drop by at least 39%.
3. It is recommended that the sponsor measure rosuvastatin concentration and response (LDL-C, HDL etc.) at rough time points (i.e. time just before next dose) in future clinical trials, if any, for further analyses on exposure-response relationship for efficacy and/or toxicity assessment.
4. The following dissolution method and specification are recommended:
 - Dissolution test conditions
 - Medium:
 - Apparatus:
 - Volume:
 - Temperature:
 - Sampling times:
 - Dissolution specification
 - Q = - % at 30 minutes

S

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Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

12-April-2002
Date

S

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12-April-2002
Date

Final version signed by Team Leader

S

Hae-Young Ahn, Ph.D.

12-April-2002
Date

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Accumulation was minimal as indicated by accumulation ratio of AUC_{0-24} between multiple daily doses and single dose. Relations between dose and C_{max} or AUC after multiple doses are summarized in Figure 3 based on cross study comparison.

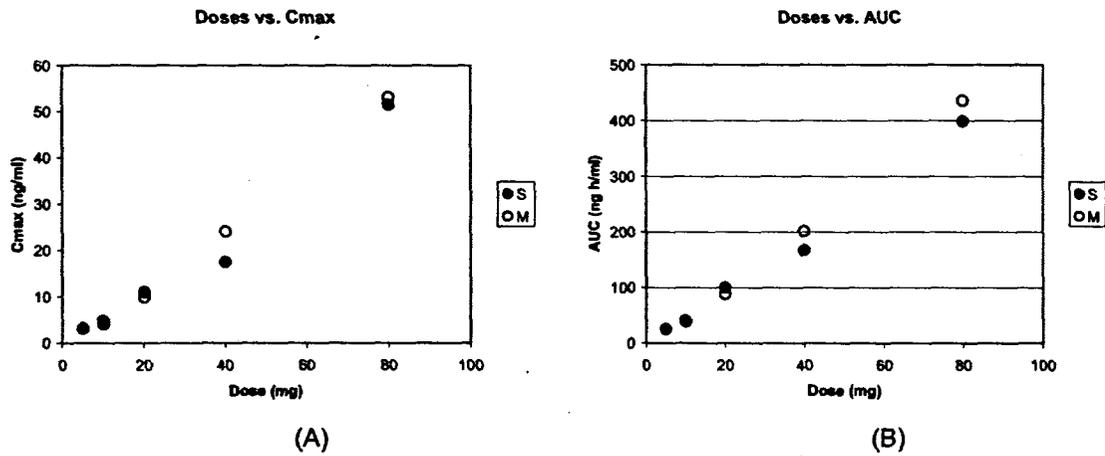


Figure 3 Relation between multiple daily doses and C_{max} (A) or AUC. Open circle is for multiple daily doses and close circle is for single dose.

There was no significant difference in time of drug administration (morning vs. evening). Plasma concentration-time profiles are shown in the following figure.

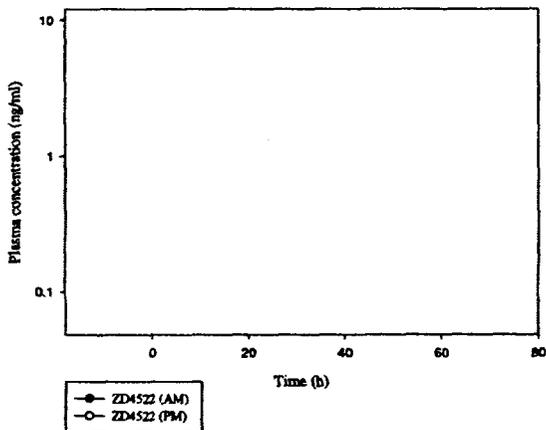


Figure 4 Plasma concentration-time profiles of rosuvastatin at Day 14 after morning (closed circle) and evening (open circle) 10 mg daily administration.

There was no significant food effect on rosuvastatin AUC but C_{max} was decreased about 20% after 15 minutes evening meal (fed) compared to that of after 3 hours evening meal (fast). Plasma concentration-time profiles are shown in the following figure.

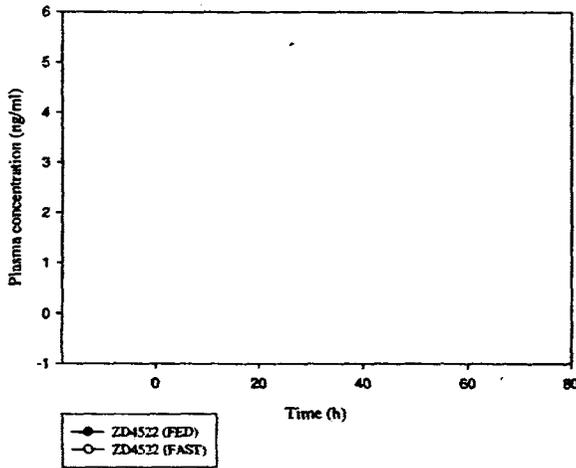


Figure 5 Plasma concentration-time profiles after 15 minutes evening meal (close circle) and after 3 hours of evening meal (open circle).

Essential dose-response relationship was characterized by 3 clinical trials with doses of 1, 2.5, 5, 10, 20, 40, and 80 mg as part of Phase-II/III trials and 2 trials (Trial 8 and 33) were active control studies with atorvastatin. Results are summarized in the following figure.

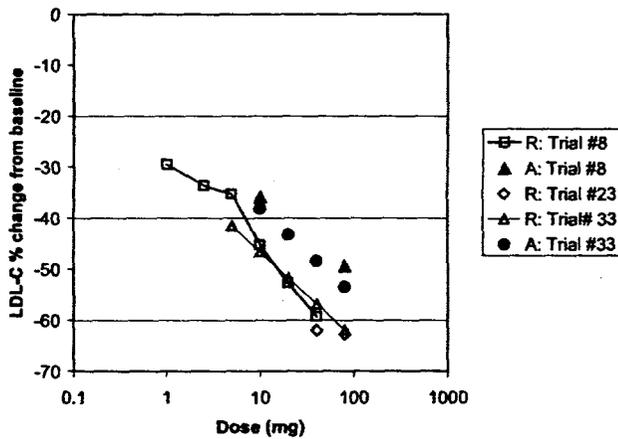


Figure 6 Dose-response (% LDL-C change from baseline) relation. R represents rosuvastatin and A represents atorvastatin.

According to a reviewer for statistics, efficacy (i.e., LDL-C % change) appeared to begin convergence at 80 mg dose.

• PHARMACOKINETICS IN SPECIAL POPULATION

Exposure in Japanese lived in Japan was significantly higher than that in Western volunteers. Body weight was not an important factor in the difference. The exposure difference is summarized in the following figures.

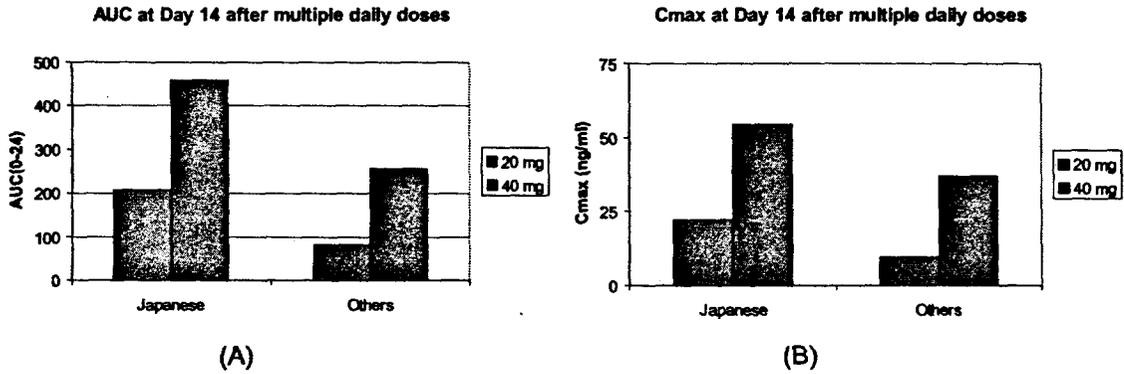


Figure 7 Mean values of AUC (A) and C_{max} in Japanese and Western volunteers after 20 mg and 40 mg multiple oral doses.

Also, absolute bioavailability in Japanese was 29% and the corresponding value was 20% in Western volunteers. The sponsor did not provide factor(s) to explain the difference.

There was no significant pharmacokinetic difference in gender or age. Results after 40 mg oral dose are summarized in the following figures (N=16 in each group).

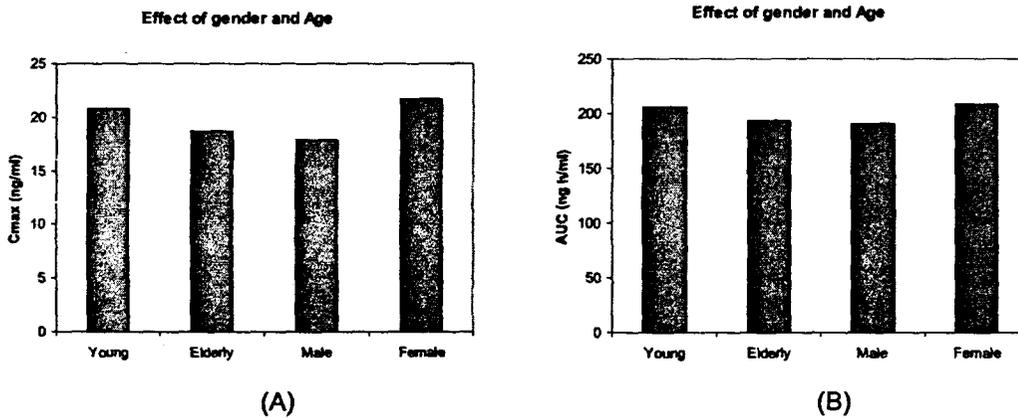


Figure 8 Exposure as C_{max} (A) and AUC (B) after 40 mg of oral administration

Exposure of rosuvastatin in mild (N=8) to moderate (N=4) renal impairment patients was similar to normal volunteers but that in severe (N=6) renal insufficient patients was about 3-fold higher than normal volunteers. Results are shown in the following figures.

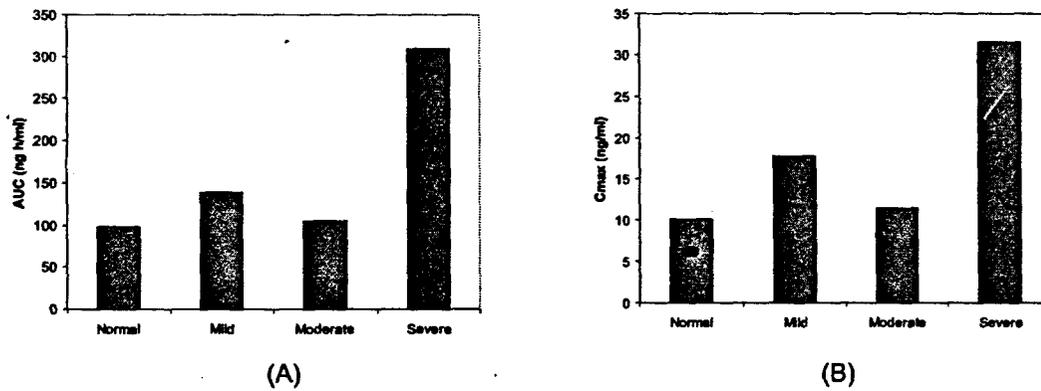


Figure 9 Exposure of rosuvastatin in renal insufficient patients: AUC (A) and C_{max} (B) at Day 14 after multiple daily dose of 20 mg

There was no statistically significant difference in exposure between normal and hepatic impairment patients. Results are summarized in the following figures.

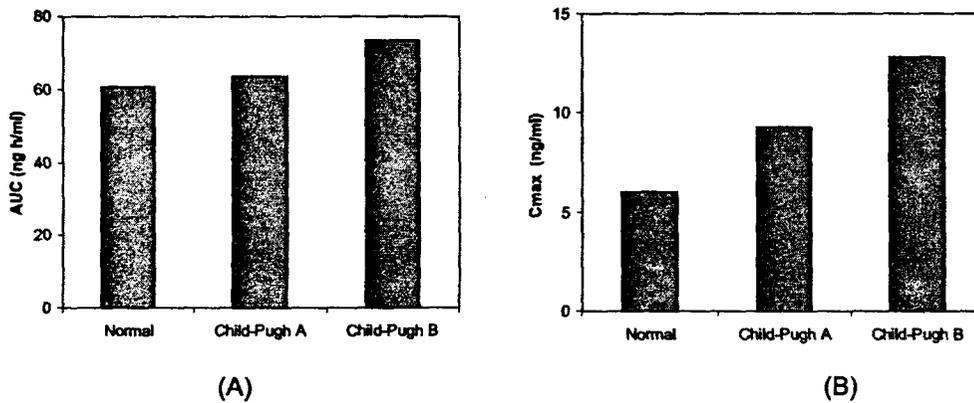


Figure 10 Exposure of rosuvastatin in hepatic insufficient patients: AUC (A) and C_{max} (B) at Day 14 after multiple daily dose of 10 mg

• **DRUG-DRUG INTERACTION**

There was no significant drug effect on rosuvastatin pharmacokinetics except cyclosporine, gemfibrozil and antacid coadministration. Cyclosporine increased rosuvastatin AUC and C_{max} of 7- and 10-fold, respectively, in stable heart transplant patients based on a cross study comparison. Also, gemfibrozil increased about 2-fold rosuvastatin exposure. Separation of 2 hours drug administration between antacid and rosuvastatin reduced magnitude of interaction significantly (54% vs. 22% in AUC). Results are summarized in the following figures.

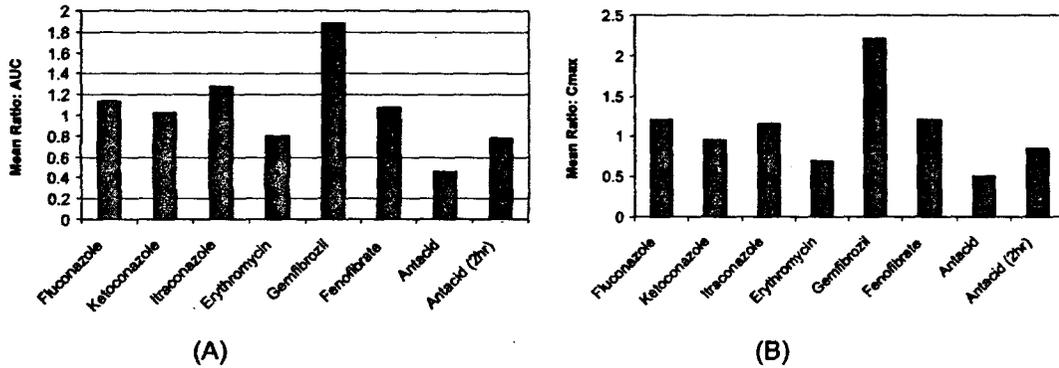


Figure 11 Geometric mean ratio of AUC (A) and C_{max} (B) of rosuvastatin in drug interaction.

There was some extent of effect of rosuvastatin on other drugs including oral contraceptives, digoxin, and warfarin. However, there were no significant safety concerns except warfarin. For warfarin, there appeared to be pharmacodynamic interaction though pharmacokinetic interaction seemed to be insignificant.

• **BIOEQUIVALENCE AMONG FORMULATIONS USED IN CLINICAL TRIALS AND COMMERCIAL TABLETS**

The to-be-marketed tablets were bioequivalent to the formulations used in clinical trials. Also, bioequivalence was demonstrated among the formulations used in clinical trials, which were capsules, tablets, and encapsulated tablets.

• **PROPOSED DISSOLUTION CONDITION AND SPECIFICATION**

Dissolution test conditions for commercial formulation were;

- Medium:
- Apparatus:
- Volume:
- Temperature:
- Sampling times:

The method of analysis is _____ with samples quantitated against external standards diluted in _____

The proposed specifications were:

- for 2.5-, 5-, and 10-mg tablets, $Q = _\%$ at $_\$ minutes
- for 40- and 80-mg tablets, $Q = _\%$ at $_\$ minutes

The recommended specification is:

- $Q = _\%$ at 30 minutes

3 Question-Based Review (QBR)

3.1 General Attributes

Rosuvastatin calcium is a selective and competitive inhibitor of HMG-CoA reductase. Therapeutic indication of Crestor is cholesterol lowering. The proposed dosage regimen is starting with 10 mg once daily in patients with primary hypercholesterolemia and 20 to 80 mg in patients with homozygous familial hypercholesterolemia. The proposed dosing range is 10 to 80 mg.

1. What are the highlights of the physicochemical properties of rosuvastatin ?

Rosuvastatin calcium is a salt of a carboxylic acid and its molecular weight is 1001.14. The carboxylic acid has a measured pK_a of 4.5. Measured partition coefficient (log P [octanol/water]) is 2.49 and it indicates relative lipophilic nature of the compound. Partition coefficient in various pH is summarized in the following table.

Table I Partition coefficient for rosuvastatin calcium in various pH range of media

pH/media	$[C]_{\text{Octanol}}$ (mg/10 ml)	$[C]_{\text{Aqueous}}$ (mg/10 ml)	$([C]_{\text{Octanol}} + [C]_{\text{Aqueous}})$ (mg/10 ml)	Partition coefficient (P) $\frac{[C]_{\text{Octanol}}}{[C]_{\text{Aqueous}}}$	Log p
pH 1 buffer	0.64	0.0026 ^a			
pH 3 buffer	1.02	0.0033	1.023	311.62	2.49
pH 5 buffer	0.89	0.01	0.90	84.89	1.93
pH 7 buffer	0.55	0.41	0.96	1.34	0.13
pH 9 buffer	0.13	0.81	0.94	0.16	-0.80
pH 11 buffer	0.18	0.89	1.07	0.21	-0.68

^a The chromatogram indicated that the ZD4522 calcium had undergone degradation to ZD4522

Equilibrium solubility measured at a range of pH values (see the following table) shows pH dependence. The compound is relatively soluble at pH values above 4.

Table II Solubility of rosuvastatin calcium (24 hours, 37C)

	Solvent solubility (mg/ml) ^a	Final pH
pH 1.2 Hydrochloric acid (0.1 N)	0.5 ±0.0	1.2
pH 1.2 Hydrochloric Acid Buffer (USP)	0.5 ±0.0	1.2
pH 3.6 Acid Phthalate Buffer (USP)	1.6 ±0.1	4.1
pH 4.0 Acid phthalate Buffer (USP)	2.2 ±0.2	4.5
pH 4.6 Neutralized Phthalate Buffer (USP)	3.7 ±0.2	5.0
pH 5.6 Neutralized Phthalate Buffer (USP)	9.2 ±0.5	5.8
pH 6.0 Phosphate Buffer (USP)	10.7 ±0.3	5.6
pH 6.6 Citrate buffer (0.05 M)	48.8 ±0.6	6.7
pH 7.0 Phosphate Buffer (USP)	17.1 ±0.0	6.8
pH 7.4 Phosphate Buffer (USP)	21.0 ±0.7	7.1
Deionized Water (USP)	7.8 ±0.1	7.0

^a mean ± standard deviation of triplicate values

2. What is the composition of Crestor ?

Qualitative and quantitative descriptions of composition are summarized in the following tables.

Table III Description of Crestor

Strength (mg)	Color	Size/shape	Compression weight (mg)	Tablet markings	
				Obverse	Reverse
2.5	Yellow	biconvex round	75	'ZD4522'	'2½'
5	Yellow	biconvex round	150	'ZD4522' and '5'	None
10	Pink	biconvex round	150	'ZD4522' and '10'	None
20	Pink	biconvex round	300	'ZD4522' and '20'	None
40	Pink	biconvex oval	300	'ZD4522'	'40'

Table IV Description of components in Crestor

Ingredient	Function	Reference to standards
Tablet core		
ZD4522 calcium	Drug substance	This document
Lactose monohydrate		USNF
Microcrystalline cellulose		USNF
Tribasic calcium phosphate		USNF
Croscopvidone		USNF
Magnesium stearate		USNF
Tablet coating		
Lactose monohydrate		USNF
Hydroxypropyl methylcellulose		USP
Triacetin		USNF
Titanium dioxide	Colorant	USP, 21 CFR 73.575, 21 CFR 73.1575
Ferric oxide, yellow (5 mg tablets only)	Colorant	USNF, 21 CFR 73.1200
Ferric oxide, red (10 mg, 20 mg, 40 mg tablets only)	Colorant	USNF, 21 CFR 73.1200

* Removed during processing.

Alternative names for the ingredients used are:

Tribasic calcium phosphate : Calcium phosphate
 Triacetin : Glycerol triacetate
 Hydroxypropyl methylcellulose : Hypromellose

Total tablet weights are proportional among 2.5, 5, 20, and 80 mg tablets. Total tablet weight of 10 mg is same as 5 mg (154.5 mg/tablet) and that of 40 mg is also same as 20 mg tablet (309.0 mg/tablet). Inactive ingredients of core tablet were adjusted accordingly as summarized in the following table.

Table V Composition of Crestor

Ingredient	Amount (mg/tablet)					
	F12846 2.5 mg tablet	F12847 5 mg tablet	F12848 10 mg tablet	F12849 20 mg tablet	F12850 40 mg tablet	F12851 80 mg tablet
Tablet core						
ZD4522 calcium ^a			—			
Lactose monohydrate			—			
Microcrystalline cellulose ^a			—			
Tribasic calcium phosphate			—			
Crospovidone			—			
Magnesium stearate ^b			—			
Nominal core tablet weight	75.0	150.0	150.0	300.0	300.0	600.0
Tablet coating ^c						
	Approximate amount (mg/tablet)					
Lactose monohydrate ^{4x}			—			
Hydroxypropyl methylcellulose ^{4x}			—			
Triacetin ^{4x}			—			
Titanium dioxide ^{4x}			—			
Ferric oxide, yellow ^d	—	—	—	—	—	—
Ferric oxide, red ^e	—	—	—	—	—	—
Nominal coated tablet weight	77.3	154.5	154.5	309.0	309.0	618.0

[

]

3.2 General Clinical Pharmacology

The sponsor appropriately measured active moieties in the plasma, urine, and feces, and thus estimated pharmacokinetic characterization. The main analytical tool was an HPLC and there were additional supportive methods including measuring radioactivity and HMG-CoA reductase inhibitory index of samples. Detailed description of the analytical procedures is summarized in the Section IV-D (Analytical Section).

1. What is the basic pharmacokinetic characteristics of Crestor ?

Basic pharmacokinetics of rosuvastatin was characterized in a randomized, single-center trial (Trial 10) with healthy volunteers (N=10). Dosing was one 40 mg of encapsulated tablet and infusion of 8 mg over 4 hours for oral and IV administration, respectively. Plasma concentration-time profiles are shown in the following figure and pharmacokinetic parameters are summarized in the following table. Absolute bioavailability was estimated as 20% based on AUC. Time to reach C_{max} of 18.8 ng/ml was about 5 hours and terminal half-life was about 20 hours after oral administration of rosuvastatin. Pharmacokinetic parameters were estimated using 3-exponential decay model after intravenous infusion of rosuvastatin and the contribution of AUC time from the last sampling to the infinity was insignificant with less than 2% difference in clearance estimation. Half-life after intravenous administration was parallel to that after oral administration. Renal clearance of rosuvastatin was about 28% of total clearance.

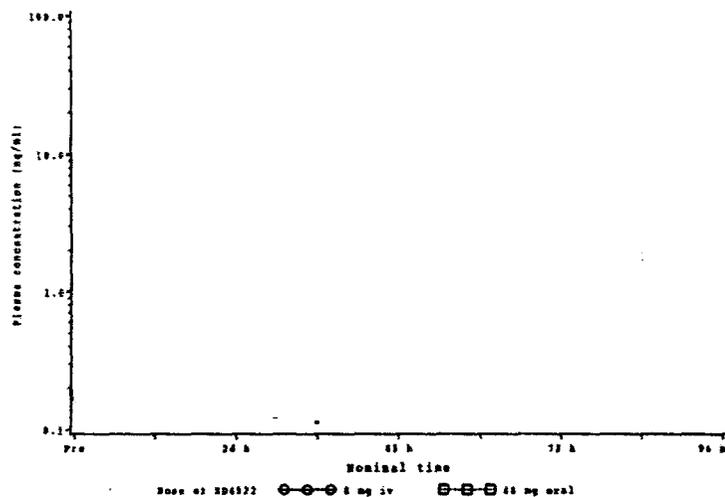


Figure 12 Plasma concentration-time profile of rosuvastatin after 8 mg intravenous and 40 mg oral administration.

Table VI Pharmacokinetic parameters after oral and IV administration of rosuvastatin.

Parameter (units)	Summary statistic	Rosuvastatin 8 mg IV N = 10	Rosuvastatin 40 mg oral N = 10
AUC (ng·h/ml)	gmean (CV%)	NC ^a	176 (32.3) ^b
AUC(0-t) (ng·h/ml)	gmean (CV%)	164 (21.7)	165 (35.9)
C _{max} (ng/ml)	gmean (CV%)	NC ^c	18.8 (33.9)
t _{max} (h)	Median (range)	NC ^c	5.0 —
t _{1/2} (h)	Mean ^d (SD)	NC ^a	20.3 (5.46) ^b
t _{1/2λ1} (h) ^e	Mean ^d (SD)	0.08 (0.02)	NC ^f
t _{1/2λ2} (h) ^e	Mean ^d (SD)	2.01 (0.46)	NC ^f
C _{inf} (ng/ml)	gmean (CV%)	37.1 (16.2)	NC ^f
CL _p (L/h) ^g	gmean (CV%)	48.9 (21.7)	NC ^f
V _{ss} (L) ^g	Mean ^d (SD)	134 (40.1)	NC ^f
E _H	Mean ^d (SD)	0.63 (0.13)	NC ^f
CL _r (L/h)	gmean (CV%)	13.6 (39.1)	11.9 (39.4)
f _e (%)	Mean ^d (SD)	29.5 (7.32)	5.09 (1.77)

Data derived from Clinical Trial Report (see Trial 10, Section 4.2).

^a N = 2; ^b N = 8; ^c N = 0; ^d Arithmetic mean; ^e Estimated using compartmental analysis; ^f These parameters were not relevant for an oral dose; ^g Estimated using non-compartmental analysis.

AUC = Area under the curve from 0 to infinity; C_{inf} = Concentration at end of infusion; CL_p = Plasma clearance; CL_r = Renal clearance; E_H = Hepatic-extraction ratio; f_e = fraction of drug excreted unchanged in the urine; NC = Not calculable (less than 50% of the data were calculable); SD = Standard deviation; t_{1/2} = terminal elimination half-life; t_{1/2λ1} = half-life associated with the 1st exponent of a polyexponential equation; t_{1/2λ2} = half-life associated with the 2nd exponent of a polyexponential equation; V_{ss} = Volume of distribution at steady state.

CVs are derived from SDs calculated on the log scale and back transformed. SDs are calculated on untransformed data.

The sponsor estimated hepatic extraction (ER) to be 0.63 based on well-stirred model:

$$ER = CL_B/Q_H$$

here, CL_B is hepatic blood clearance and Q_H is hepatic blood flow. The value appears to be a possible maximum because of the following factors:

- Hepatic blood flow (Q_H) of 1.35 L/min was used but it is within lower boundary from publications.
- Hepatic blood clearance (CL_B) can be calculated from plasma hepatic clearance (CL_p) and concentration ratio (C_p/C_B) of blood (C_B) and plasma (C_p):

$$CL_B = (C_p/C_B) \cdot CL_p$$

However, CL_B = (C_B/C_p)·CL_p was used in the calculation rather than CL_B = (C_p/C_B)·CL_p. Concentration ratio (C_B/C_p) of 1.45 was calculated in an in vitro experiment.

- Plasma hepatic clearance (CL_p) was calculated using CL_{hepatic} = CL_{nonrenal} = CL_{total} - CL_{renal} and it is based on the assumption that there is no nonrenal clearance except hepatic clearance.

The hepatic extraction was recalculated by the reviewer and it would be 0.27 by the following factors:

- Q_H = 1.5 L/min, which is an average value in the publications and
- after correction for concentration ratio of C_p/C_B = 0.6897.

In this regarding, rosuvastatin should be regarded as a drug with low hepatic extraction and the extent of absorption might be slightly higher than absolute bioavailability counting low hepatic extraction.

2. Is dose proportionality of Crestor established ?

Dose proportionality was established in a randomized, double-blind, incomplete crossover trial (Trial 47, N=18). A power model was used to evaluate dose proportionality and results are summarized in the following tables. One of each 10, 20, 40, and 80 mg encapsulated tablet was administered in the trial under overnight fasting condition.

Power model: AUC or $C_{max} = (a) \times (Dose)^b$

Table VII Summary of pharmacokinetic parameters after oral dose of 10, 20, 40, and 80 mg tablets.

Parameter (units)	Summary statistic	ZD4522 10 mg (n=18)	ZD4522 20 mg (n=9)	ZD4522 40 mg (n=9)	ZD4522 80 mg (n=18)
Primary end-points					
AUC(0-t) (ng-h/ml)	Mean ^a (CV %)	31.6 (62.7)	56.8 (58.9)	98.2 (77.1)	268 (46.1)
C _{max} (ng/ml)	Mean ^a (CV %)	3.75 (52.2)	6.79 (52.9)	10.3 (88.3)	30.1 (50.5)
Secondary end-points					
AUC (ng-h/ml)	Mean ^a (CV %)	NC	NC	NC	313 (36.6) ^c
AUC(0-24) (ng-h/ml)	Mean ^a (CV %)	30.7 (56.4)	51.5 (54.1)	84.4 (74.4)	220 (46.7)
t _{1/2} (h)	Mean ^b (SD)	NC	NC	NC	18.3 (3.77) ^c
t _{max} (h)	Median (range)	5.0 (—)	5.0 (—)	5.0 (—)	5.0 (—)

Data derived from Table T4.1.2

^a Geometric mean

^b Arithmetic mean

^c n=15

AUC(0-t) = area under the curve up to time t; C_{max} = maximum plasma concentration; AUC = area under the curve;

AUC(0-24) = area under the curve for the dosing interval; t_{1/2} = half-life, CV = coefficient of variation;

t_{max} = time to maximum plasma concentration; n = number of volunteers; SD = standard deviation;

NC = not calculated

Table VIII Results of power model analysis

	Estimate of b	Lower 90% CL	Upper 90% CL
AUC(0-t)	1.024	0.941	1.107
C _{max}	0.999	0.898	1.099

Data derived from Table T4.1.3

b = dose proportionality coefficient; AUC(0-t) = area under the curve up to time t;

C_{max} = maximum plasma concentration; CL = confidence limit

Based on the results of power model analysis, it should be concluded that dose proportionality is established from 10 mg to 80 mg.

The sponsor also included cross study comparison for dose proportionality (Table IX).

Table IX Pooled data analysis of dose proportionality across clinical trials.

Dose mg	N	C_{max} ng/ml		t_{max} h	AUC(0-t) ng.h/ml		AUC ng.h/ml		$t_{1/2}$ h
		gmean (CV%)	Median (range)		gmean (CV%)	gmean (CV%)	Mean (SD)		
5 ^a	4	3.12 (42.2)	5.0	25.0 (25.5)	NC	NC			
10 ^b	34	4.79 (56.7)	5.0	38.7 (60.7)	NC	NC			
20 ^c	121	11.0 (71.8)	4.5	99.4 (62.9)	132 (51.7) ^d	16.4 (4.15) ^d			
40 ^e	75	17.5 (69.2)	4.5	167 (56.6)	212 (40.1) ^f	20.3 (8.16) ^f			
80 ^g	176	51.5 (66.2)	3.5	399 (53.6)	421 (48.9) ^h	17.4 (5.02) ^h			

Data derived from Summary Table T2.2.

^a Trial 1; ^b Trials 1, 12, 47; ^c Trials 1, 2, 3, 19, 47, 49; ^d N = 68; ^e Trials 1, 2, 10, 15, 20, 47; ^f N = 46; ^g Trials 11, 19, 47, 48, 49, 53, 57, 58; ^h N = 147. (See Table 44 for individual trial information.)

Mean = Arithmetic mean; N = Number of volunteers; NC = Not calculable (less than 50% of the data were calculable); SD = Standard deviation.

Mean values of AUC and C_{max} in the all CPB studies are summarized in Figure 13 including single dose studies, multiple daily doses studies, studies in special population, and drug interaction studies. In general, it showed linear relationship between doses and PK parameters. Also, PK parameters appeared to be log-normal distribution with some exceptions from certain special populations, and drug interaction studies.

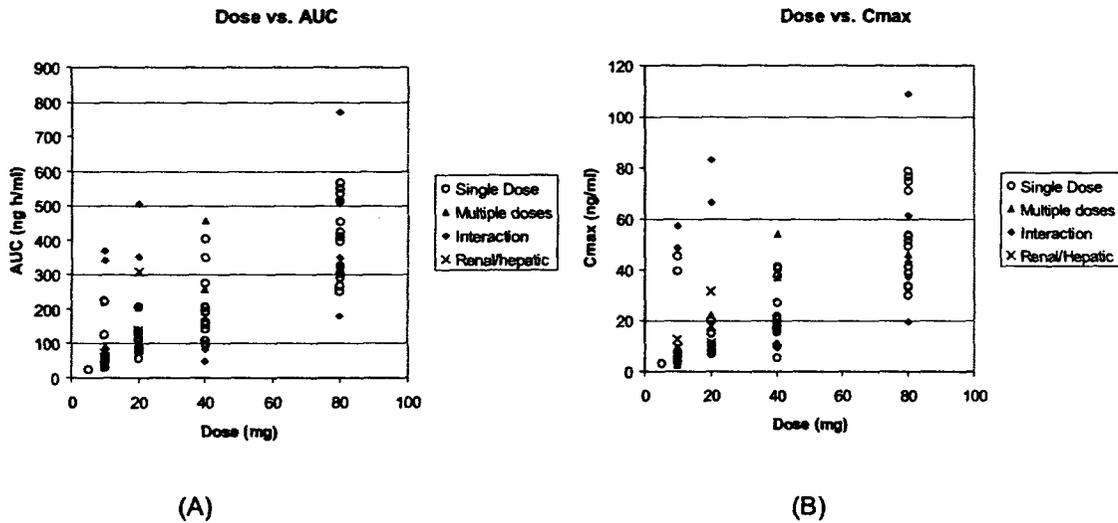


Figure 13 Relation between doses and AUC (A) or C_{max} (B) in CPB studies.

3. Do pharmacokinetic parameters change with time following chronic dosing ?

Pharmacokinetic parameters were compared on Day1 to on Day 11 after multiple daily doses of 20 mg (two 10 mg capsules) and 40 mg (four 10 mg capsule) administration under fasting conditions (Trial 2). In a separate study (Trial 11), results were obtained for 80 mg (one 80 mg capsule). Volunteers received a single oral dose of Crestor or placebo on Day 1, followed by a 4 day washout period, after which they received repeated oral doses of the same treatment for 7 days on Days 5 to 11. Results are shown in the following figures.

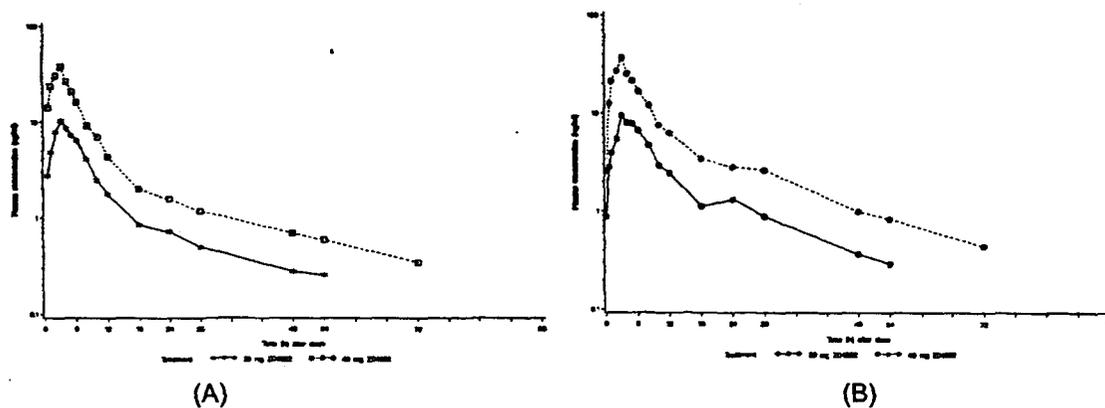


Figure 14 Geometric mean plasma concentrations of rosuvastatin on Day 1 (A) and Day 11 (B) following multiple daily doses of 20 and 40 mg Crestor

There was no significant change in pharmacokinetics after multiple daily doses for 20 and 40 mg dosing (Table X).

Table X Pharmacokinetic parameters at Day 1 and Day 11 after daily doses of 20 mg and 40 mg.

Parameter		20 mg ZD4522 (n=6)		40 mg ZD4522 (n=6)	
		Day 1	Day 11	Day 1	Day 11
C_{max} (ng/ml)	Geometric mean (CV%)	10.7 (52.6)	9.7 (69.0)	38.0 (70.0)	37.0 (38.1)
	Range				
t_{max} (h)	Median (range)	3 (3 to 4)	3 (3 to 4)	3 (3 to 3)	3 (3 to 3)
AUC(0-24 h) (ng·h/ml)	Geometric mean (CV%)	77.8 (48.8)	81.7 (61.0)	238.4 (51.5)	255.9 (24.6)
	Range				
AUC(0-t) (ng·h/ml)	Geometric mean (CV%)	89.4 (48.8)	101.3 (59.9)	277.5 (46.3)	324.8 (24.8)
	Range	52.7 to 157.9	45.9 to 210.6	151.1 to 437.9	231.2 to 434.1
$t_{1/2}$ (h)	Arithmetic mean (SD)	16.8* (6.4*)	14.9 (2.6)	22.8 (5.0)	20.8 (12.8)
	Range				

* n=5 for $t_{1/2}$ on Day 1 at 20 mg ZD4522 dose level
 CV Coefficient of variation; C_{max} Maximum plasma concentration
 t_{max} Time to maximum plasma concentration; AUC Area under the curve; $t_{1/2}$ Half-life

However, exposure was increased by 36-38% after multiple daily doses of 80 mg compared to that of single dose.

Table XI Pharmacokinetic parameters at Day 1 and Day 11 after daily doses of 80 mg.

Parameter	Statistic	80 mg ZD4522 (n=6)	
		Day 1	Day 11
C _{max} (ng/ml)	Geometric mean (CV%)	33.4 (68.1)	46.2 (53.1)
	Range	—	—
t _{max} (h)	Median (range)	4 (3 to 6)	5 (1 to 6)
AUC(0-24 h) (ng·h/ml)	Geometric mean (CV%)	241.2 (55.1)	329.0 (49.6)
	Range	—	—
AUC(0-4) (ng·h/ml)	Geometric mean (CV%)	293.4 (56.0)	402.5 (56.6)
	Range	—	—
t _{1/2} (h)	Arithmetic mean (SD)	25.7 (8.2)	13.4 (2.0)
	Range	—	—

CV Coefficient of variation; C_{max} Maximum plasma concentration
t_{max} Time to maximum plasma concentration; AUC Area under the curve; t_{1/2} Half-life

It should be noted that systemic exposure after the 40 mg dose was higher than that from other studies.

4. Is there PK difference in timing of dose during a day ?

Effect of timing of dose on PK or PD was evaluated after multiple daily doses of 10 mg capsule in the morning or evening before 2 hours of meal (Trial 4, N=24).

There was neither significant PK nor PD difference between the treatments. Pharmacokinetic parameters are summarized in the following table and pharmacodynamic results are shown in the following figure.

Table XII Parameters and statistical results after 14th dose of 10 mg in the morning or evening.

Parameter (units)	Analysis	n	AM ZD4522 treatment	PM ZD4522 treatment	Estimate of treatment effect ^a	90% CI	p-value
C _{max} (ng/ml)	Mean ^b	21	4.63	4.60	1.01	0.88, 1.15	0.941
AUC(0-4) (ng·h/ml)	Mean ^b	21	50.87	54.56	0.93	0.83, 1.05	0.325
AUC (ng·h/ml)	Mean ^b	14 ^c	71.54	74.28	0.96	0.84, 1.11	0.647
AUC(0-24) (ng·h/ml)	Mean ^b	21	40.42	43.12	0.94	0.86, 1.03	0.237
t _{1/2} (h)	Mean ^d	14 ^c	33.10	27.21	5.89	0.91, 10.88	0.057

Data derived from Table T5.3.

^a Estimate of treatment effect for t_{1/2} = AM minus PM least squares geometric mean; for all other PK parameters, ratio of AM/PM least squares geometric mean.

^b Least-squares geometric mean.

^c n=14 because some subjects' data were not calculated (see Table 14, Section 3.4).

^d Least-squares arithmetic mean.

CI = Confidence interval; C_{max} = Maximum plasma concentration.

t_{max} = Time to maximum plasma concentration; AUC = Area under the curve; t_{1/2} Half-life.

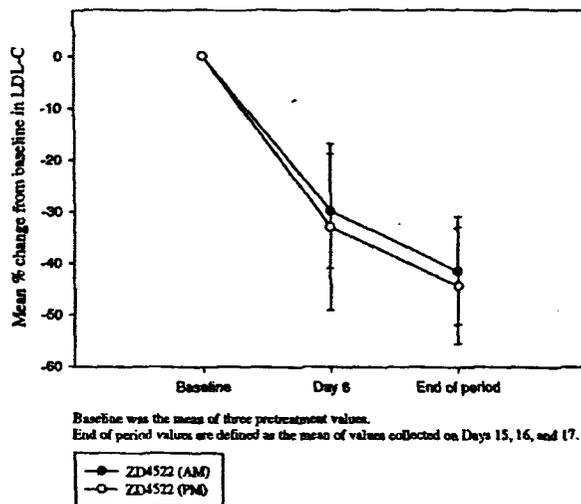


Figure 15 LDL-C lowering effect of rosuvastatin after 14th dose of 10 mg in the morning or evening before 2 hours of meal.

5. Is major route of elimination identified ?

Fecal excretion appeared to be a major route of elimination after oral doses. A mass balance study was performed with six volunteers (Trial 3). Volunteers were received a single dose of 20 mg [¹⁴C]-rosuvastatin given as an oral solution with a mean radioactivity of 45.7 μ Ci (range \sim to \sim μ Ci).

Mean total recovery of radioactivity was about 108% of dose. The fecal and urinary excretion of total radioactivity was 91% and 9%, respectively. Among the total radioactivity in excreta, 77% and 5% of dose was in feces and urine as the parent compound, respectively. At T_{max} , approximately 50% of circulating radioactivity was from parent compound indicating the presence of circulating metabolites. Profiles in plasma and excreta are shown in the following figures.

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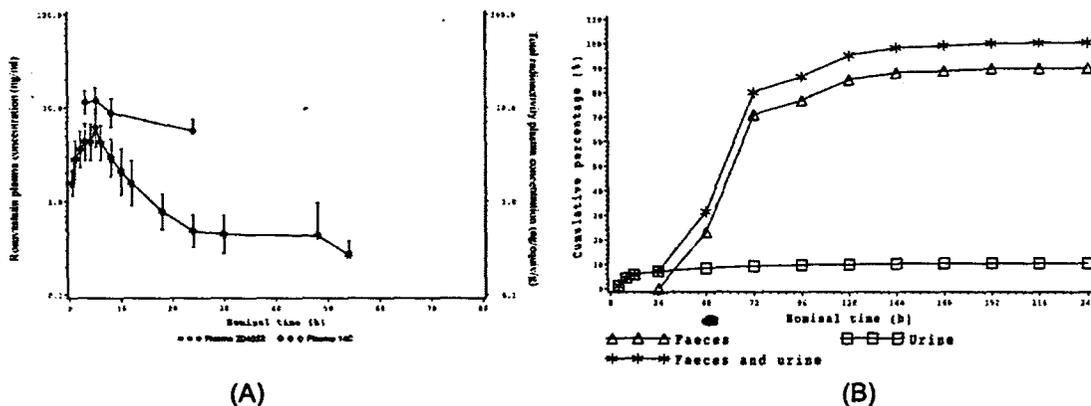


Figure 16 Mean plasma concentrations (A) and mean cumulative urinary and fecal recovery of radioactivity up to 240 hours (B) after administration of [14 C]- rosvastatin 20 mg.

Possible metabolic pathways were elucidated using in vitro studies. Metabolism was not detected in microsomal studies but there was moderate degree of metabolism in human hepatocyte system. Metabolic isozymes involved in rosvastatin metabolism were identified through known specific inhibitors for P450s. Mainly 2C9 was the principal isozyme for N-desmethyl reaction with lesser degree of involvement of 2C19, 3A4, and 2D6.

In human excreta and plasma, two rosvastatin derivatives were detected. One was N-desmethyl rosvastatin and the other one was rosvastatin lactone. Levels of both compounds were less than 10% of rosvastatin in radioactivity or area of

3.3 Intrinsic Factors

Intrinsic factors of age, gender, and organ dysfunction were evaluated.

1. Is there age or gender effect on rosvastatin pharmacokinetics ?

Effects of age and gender on rosvastatin pharmacokinetics were evaluated in an open-label, non-randomized, non-controlled, parallel-group trial conducted at a single center (Trial 15). The trial consisted of a single oral dose of Crestor 40 mg (four 10 mg capsules) under fasting condition with a 96-hour follow-up period. Thirty-two volunteers entered this trial; 16 male (8 young; 18-35 years and 8 elderly; >65) and 16 female (8 young and 8 elderly).

There was no significant pharmacokinetic difference in the covariates including comparison between young male vs. elderly women in ANOVA for test of statistical mean difference. Results are summarized in the following table.

Table XIII Pharmacokinetic parameters after 40 mg oral dose in different age and gender.

Parameter (units)	Summary statistic	Young ^a (n=16)	Elderly ^a (n=16)	Male ^a (n=16)	Female ^a (n=16)
Primary end-points					
C _{max} (ng/ml)	Mean ^b (CV %)	20.8 (65.5)	18.7 (39.8)	17.9 (42.3)	21.7 (62.1)
AUC(0-t) (ng-h/ml)	Mean ^b (CV %)	206 (41.0)	194 (27.7)	191 (31.0)	209 (38.0)
Secondary end-points					
AUC (ng-h/ml)	Mean ^b (CV %)	234 (39.0) ^c	204 (31.4) ^d	202 (30.7) ^d	238 (39.0) ^c
t _{max} (hours)	Median (range)	3.0 —	4.0 —	5.0 —	3.0 —
t _{1/2} (hours)	Mean ^c (SD)	17.5 (4.0) ^c	24.4 (12.5) ^d	19.2 (4.4) ^d	23.6 (14.0) ^c

Data derived from Tables T3.2.2 and T3.2.3

^a Volunteers are included in 2 categories, 1 age category and 1 gender category

^b Geometric mean

^c n = 11

^d n = 13

^e Arithmetic mean

CV = coefficient of variation; C_{max} = maximum plasma concentration;

t_{max} = time to maximum plasma concentration; AUC = area under the curve;

AUC(0-t) = area under the curve from zero to last quantifiable concentration; t_{1/2} = half-life;

n = number of volunteers

The C_{max} and AUC_(0-t) were variable within each group. For C_{max} values, there was an approximately 8-fold range in young volunteers and a 3-fold range in the elderly volunteers. For males, the range in C_{max} was 3-fold and for females it was 8-fold. Variability was less for AUC_{0-t}, with ranges of 3.5- (young), 3- (elderly), 3- (male) and 3.5-fold (female), respectively.

2. Does the renal function affect rosuvastatin pharmacokinetics ?

Effect of renal function on rosuvastatin pharmacokinetics was characterized in an open-label trial (Trial 17). Subjects with normal renal function (creatinine clearance >80 ml/min/1.73 m²), those with varying degrees of renal insufficiency: mild (creatinine clearance of 50 to 80 ml/min/1.73 m²), moderate (30 to <50 ml/min/1.73 m²), severe (<30 ml/min/1.73 m²), and subjects requiring dialysis were included. Oral doses of 20 mg (two 10 mg capsules) were administered for 14 days. Detailed pharmacokinetics was characterized after the 14th dose. Results are shown in the following figures.

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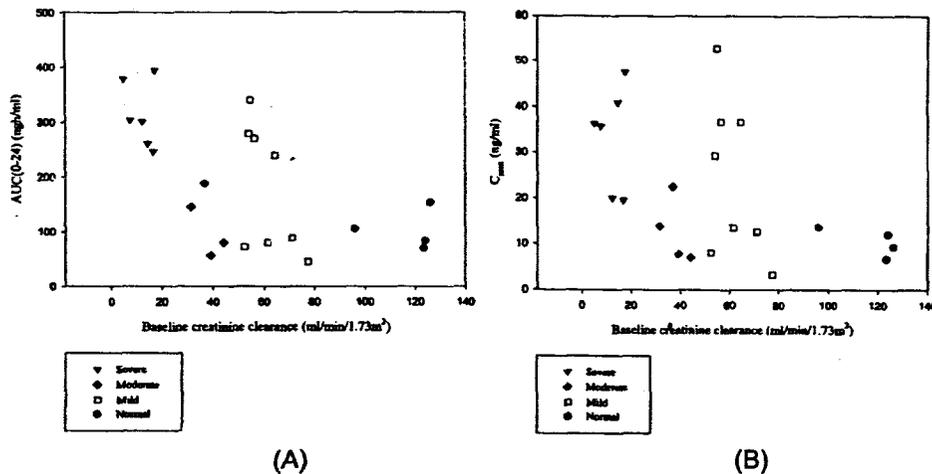


Figure 17 Rosuvastatin AUC₍₀₋₂₄₎ (ng.h/ml) (A) and C_{max} (ng/ml) (B) vs. baseline creatinine clearance (ml/min/1.73 m²) by renal function stratum

The sponsor concluded that exposure of rosuvastatin in mild to moderate renal impairment patients was equivalent to that of normal subjects. However, exposure was increased about 3-fold in severe renal impaired patients compared to normal subjects. Therefore, doses should be adjusted in severe renal impaired patients.

In addition, half of the mild impairment patients showed similar rosuvastatin exposure to that in severe impairment patients and only 4 moderate impairment patients studied. Although mean PK values of mild to moderate renal impaired patients were equivalent to those of normal subjects, the results should not be conclusive because of variability and lack of power in the study.

Pharmacokinetic parameters and statistical analysis are summarized in the following tables.

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Table XIV Pharmacokinetic parameters after 14th dose of 20 mg

PK parameter	Renal status based on creatinine clearance ^a			
	Group 1 (severe) N = 6	Group 2 (moderate) N = 4	Group 3 (mild) N = 8	Group 4 (normal) N = 4
ZD4522				
AUC(0-24) (ng.h/ml)				
geometric mean (CV)	309.27 (19.21)	105.14 (59.57)	138.82 (91.68)	97.98 (35.30)
ratio to normals ^b	3.16	1.07	1.42	—
(90% CI)	(1.47 to 6.78)	(0.46 to 2.48)	(0.69 to 2.93)	
C _{max} (ng/ml)				
geometric mean (CV)	31.51 (39.00)	11.44 (58.77)	17.69 (117.79)	10.12 (32.30)
ratio to normals ^b	3.11	1.13	1.75	—
(90% CI)	(1.26 to 7.69)	(0.42 to 3.04)	(0.74 to 4.12)	
N-des-methyl-ZD4522				
AUC(0-24) (ng.h/ml)				
geometric mean (CV)	99.27 (57.73)	15.70 (75.92)	23.22 (176.00)	10.85 (121.67)
ratio to normals ^b	9.15	1.45	2.14	—
(90% CI)	(2.61 to 32.08)	(0.37 to 5.72)	(0.65 to 7.04)	
C _{max} (ng/ml)				
geometric mean (CV)	10.33 (70.08)	2.68 (44.43)	4.44 (99.29)	2.68 (86.01)
ratio to normals ^b	3.86	1.00	1.66	—
(90% CI)	(1.48 to 10.07)	(0.35 to 2.86)	(0.67 to 4.12)	

Data derived from Tables H4.1 to H4.4

^a Subjects were stratified based on creatinine clearance as calculated by the sponsor. The renal status categories are as follows:

Severe: CrCL <30 ml/min/1.73 m²
 Moderate: CrCL 30 to <50 ml/min/1.73 m²
 Mild: CrCL 50 to 80 ml/min/1.73 m²
 Normal: CrCL >80 ml/min/1.73 m²

^b Geometric mean of the ratio of the parameter for the specified groups.

CI Confidence interval.

CrCL Creatinine clearance.

CV Coefficient of variation.

PK Pharmacokinetic.

Table XV Statistical analysis of renal function on rosuvastatin exposure.

PK parameter ^b	Severe/normal ratio (90% CI)	Moderate/normal ratio (90% CI)	Mild/normal ratio (90% CI)
AUC(0-24) (ng.h/ml)	3.16 (1.47 to 6.78)	1.07 (0.46 to 2.48)	1.42 (0.69 to 2.93)
C _{max} (ng/ml)	3.11 (1.26 to 7.69)	1.13 (0.42 to 3.04)	1.75 (0.74 to 4.12)

Data derived from Tables H4.1 and H4.2

^a Subjects were stratified based on creatinine clearance as calculated by the sponsor. The renal status categories are as follows:

Severe: CrCL <30 ml/min/1.73 m²
 Moderate: CrCL 30 to <50 ml/min/1.73 m²
 Mild: CrCL 50 to 80 ml/min/1.73 m²
 Normal: CrCL >80 ml/min/1.73 m²

^b Geometric mean of the ratio of the parameter for the specified groups.

CI Confidence interval.

CrCL Creatinine clearance.

3. Does the hepatic function affect rosuvastatin pharmacokinetics pharmacokinetics?

Effect of hepatic function on rosuvastatin exposure was evaluated in an open-label, parallel, multiple-dose trial (Trial 18). Dose was 10 mg capsule. Pharmacokinetics was evaluated after 14th dose and the results are shown in the following figure.

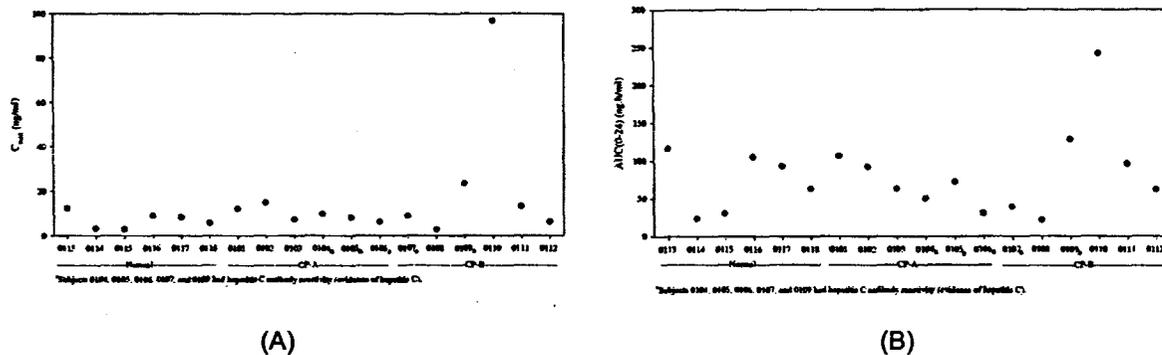


Figure 18 Rosuvastatin AUC (A) and Cmax (B) at Day 14 after 10 mg daily doses in hepatic insufficient patients.

There was no significant effect of hepatic insufficiency on rosuvastatin exposure and results are summarized in the following tables.

Table XVI Pharmacokinetic parameters of rosuvastatin in hepatic insufficient patients

Pharmacokinetic parameter	Subjects with normal hepatic function	Subjects with Child-Pugh Classification A	Subjects with Child-Pugh Classification B
AUC(0-24) (ng·h/ml)			
Geometric mean	60.7	63.7	73.3
CV (%)	76	47	105
Range			
N	6	6	6
C_{max} (ng/ml)			
Geometric mean	6.0	9.3	12.8
CV (%)	63	33	187
Range			
N	6	6	6

AUC = Area under the plasma concentration-time curve; CV (%) = Coefficient of variation expressed as a percentage of the geometric mean.

Table XVII Results of statistical analysis

Pharmacokinetic parameter	Ratios (90% CI) relative to subjects with normal liver function	
	Subjects with Child-Pugh Classification A	Subjects with Child-Pugh Classification B
AUC(0-24)	1.05 (0.58, 1.91)	1.21 (0.51, 2.84)
C _{max}	1.54 (0.94, 2.52)	2.13 (0.65, 6.95)

CI Confidence interval.

AUC(0-24) Area under the plasma concentration versus time curve from 0 to 24 hours.

C_{max} Maximum plasma concentration.

4. Is race a covariate in rosuvastatin pharmacokinetics ?

Exposure in Japanese who living in Japan was estimated in a double-blind, placebo-controlled trial (Trial 63). Oral dose of 40 mg encapsulated tablet and 6 mg IV infusion were employed to estimate absolute bioavailability. Absolute bioavailability was higher in Japanese (29%) compared to Western volunteers (20%) and systemic clearance was lower in Japanese (31.9 L/h) compared to Western volunteers (48.9 L/h). Results are summarized in the following tables.

Table XVIII Pharmacokinetic parameters after oral dose of 40 mg and 6 mg IV infusion of rosuvastatin.

Parameter (units)	Summary statistic	ZD4522 40 mg oral N=10	ZD4522 6 mg IV N=9
AUC (ng·h/mL)	Mean ^a (CV %)	395 (64.2) ^f	NC ^d
AUC(0-t) (ng·h/mL)	Mean ^a (CV %)	351 (46.3)	175 (20.4)
C _{max} (ng/mL)	Mean ^a (CV %)	40.7 (44.8)	NC
t _{max} (h)	Median (range)	4.5	NC
t _{1/2} (h)	Mean ^b (SD)	12.4 (4.33) ^f	NC ^d
t _{1/2α1} (h)	Mean ^b (SD)	NC ⁱ	0.064 (0.018) ^f
t _{1/2α2} (h)	Mean ^b (SD)	NC ⁱ	1.37 (0.469) ^e
t _{1/2α3} (h)	Mean ^b (SD)	NC ⁱ	6.44 (2.68) ^f
C _{inf} (ng/mL)	Mean ^a (CV %)	NC ⁱ	39.1 (20.0) ^f
CL _p (L/h)	Mean ^a (CV %)	NC ⁱ	31.9 (17.8)
V _{ss} (L)	Mean ^b (SD)	NC ⁱ	67.9 (21.5) ^f
E _H	Mean ^b (SD)	NC ⁱ	0.363 (0.056)
V _c (L)	Mean ^b (SD)	NC ⁱ	5.24 (1.28) ^f
K ₁₀	Mean ^b (SD)	NC ⁱ	6.71 (2.24) ^f
K ₁₂	Mean ^b (SD)	NC ⁱ	3.43 (1.33) ^f
K ₂₁	Mean ^b (SD)	NC ⁱ	1.03 (0.968)
K ₁₃	Mean ^b (SD)	NC ⁱ	1.23 (0.461) ^g
K ₂₁	Mean ^b (SD)	NC ⁱ	0.149 (0.048) ^f

Data derived from Tables T4.2.1 and T4.2.2

^a Geometric mean

^b Arithmetic mean

^c N=5; ^d N=2; ^e N=8; ^f N=7; ^g N=10; ^h N=6

ⁱ These parameters were not relevant for an oral dose and were therefore not calculated

Table XIX Absolute bioavailability of rosuvastatin in Japanese

	ZD4522 6 mg IV glsmean N=9	ZD4522 40 mg oral glsmean N=10	Estimate of F (%)	90% CI for F
Dose normalised AUC(0-t) (ng·h/mL)	30.31	8.782	29.0	24.1 to 34.9

Data derived from Table T4.3

AUC(0-t) = area under the curve to time t; F = absolute bioavailability; CI = confidence interval; glsmean = geometric least square mean; N = number of volunteers

3.4 Extrinsic Factors

1. What is the effect of food on the bioavailability of Crestor ?

Food effect on rosuvastatin was estimated in an open-label, randomized, 2-way crossover trial conducted at a single center (Trial 5). Subjects were given one rosuvastatin 10 mg capsule during the evening meal (15 minutes after beginning the meal) or 3 hours after the evening meal. Subjects were given single daily oral doses of Crestor for 14 days.

There was no statistical significant food effect on AUC₀₋₄ but C_{max} was decreased by 20%. Pharmacokinetic parameters and results of statistical analysis are summarized in the following table.

Table XX Pharmacokinetic parameters after 14th dose and results of statistical analysis.

Parameter (units)	Analysis	n	Fed ZD4522 treatment	Fasted ZD4522 treatment	Estimate of treatment effect ^a	90% CI Lower Upper	p-value
C _{max} (ng/ml)	Mean ^b	20	2.53	3.16	0.80	0.73, 0.88	<0.001
t _{max} (h)	Mean ^b	20	5.26	3.42	1.84	1.22, 2.47	<0.001 ^c
AUC(0-4) (ng.h/ml)	Mean ^b	20	39.08	37.93	1.03	0.94, 1.13	0.576
AUC (ng.h/ml)	Mean ^b	7 ^d	56.16	58.55	0.96	0.69, 1.33	0.808
AUC(0-24) (ng.h/ml)	Mean ^b	20	32.31	34.27	0.94	0.88, 1.01	0.153
t _{1/2} (h)	Mean ^e	7 ^d	20.10	22.19	-2.09	-11.38, 7.20	0.669

Data derived from Table 15.3.

^a Estimate of treatment effect for t_{1/2} = fed minus fasted least squares geometric mean; for all other PK parameters, ratio of fed/fastest least squares geometric mean.

^b Least-squares geometric mean.

^c p-value on t_{max} on rank-transformed data.

^d n=7 because some subjects' data were NC (see Table 14, Section 3.4).

^e Least-squares arithmetic mean.

CI = Confidence interval; C_{max} = Maximum plasma concentration.

t_{max} = Time to maximum plasma concentration; AUC = Area under the curve; t_{1/2} Half-life.

Mean trough concentration was reached to 0.9 ng/ml and 0.7 ng/ml for fed and 3 hours post prandial condition, respectively, after 14 days oral administration of 10 mg. Mean trough concentrations during the treatments are shown in the following figure.

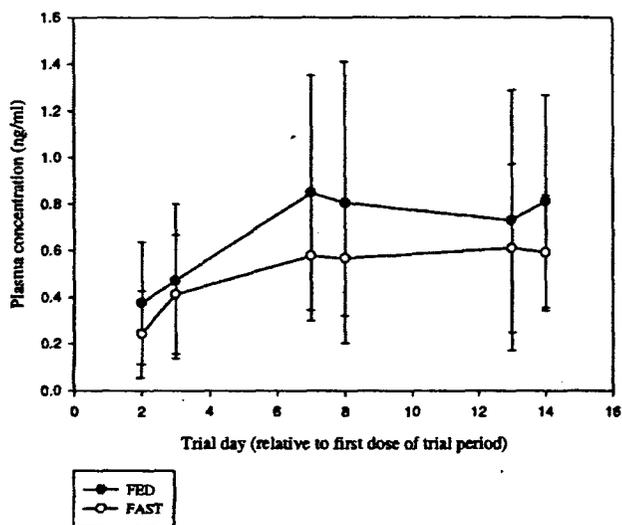


Figure 19 Mean trough concentrations during treatments.

Mean LDL-C was measured and it was concluded that there was no food effect on rosuvastatin PD because mean % changes from baseline in LDL-C were not statistically different between treatments as shown in the following figure.

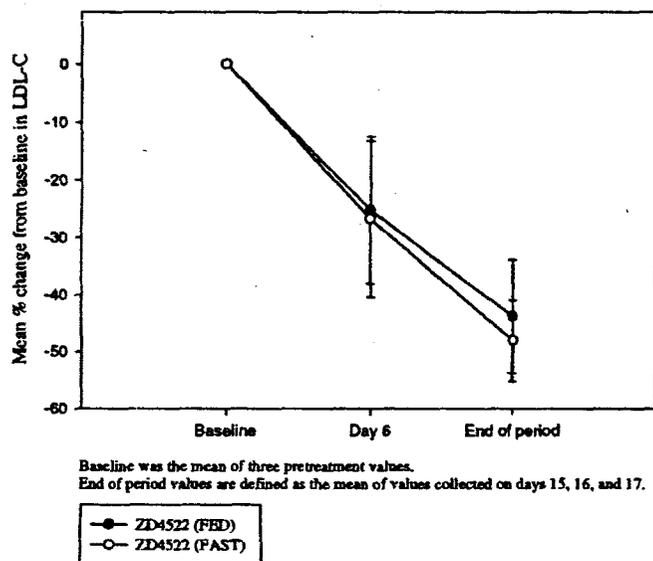


Figure 20 Mean % changes from baseline in LDL-C during treatments

Therefore, it was concluded that there was no food effect on rosuvastatin BA and PD.

2. Drug Drug Interaction

1) What are the effects of drugs on rosuvastatin pharmacokinetics ?

Itraconazole

Effect of itraconazole, a CYP3A4 inhibitor, was estimated in a randomized, double-blind, crossover study (Trial 12, N=11). During each treatment period, 6 volunteers were to receive 5 daily doses (Days 1 to 5) of 200 mg itraconazole and 6 volunteers were to receive 5 daily doses of placebo. All volunteers received a single dose of 10 mg rosuvastatin capsule on the fourth day (Day 4), 1 hour after the dose of placebo or itraconazole. Another study was performed with the same design as above except 80 mg (one encapsulated tablet) rosuvastatin (Trial 53).

Table XXI Statistical comparison of $AUC_{(0-4)}$ for 10 mg rosuvastatin in presence and absence of itraconazole

Parameter	n	10mg rosuvastatin + 200 mg itraconazole (glsmean)	10 mg rosuvastatin + placebo glsmean	Ratio of glsmean ^a	90% CI for ratio ^a
AUC_{0-t} (ng h/ml)	11	62.100	44.714	1.389	1.210-1.594

a Ratio and 90% CI are expressed as a ratio of glsmean (rosuvastatin+itraconazole) / glsmean (rosuvastatin+placebo)
glsmena geometric least square mean

Table XXII Statistical comparison of $AUC_{(0-4)}$ and C_{max} for 80 mg rosuvastatin in presence and absence of itraconazole

Parameter	n	80mg rosuvastatin + 200 mg itraconazole (glsmean)	80 mg rosuvastatin + placebo glsmean	Ratio of glsmean ^a	90% CI for ratio ^a
AUC_{0-t} (ng h/ml)	14	508	397	1.28	1.149-1.426
C_{max} (ng/ml)	14	61.3	53.5	1.145	0.949-1.381

a Ratio and 90% CI are expressed as a ratio of glsmean (rosuvastatin+itraconazole) / glsmean (rosuvastatin+placebo)
glsmena geometric least square mean

Itraconazole increased significantly exposure of rosuvastatin based on AUC by 39% and 28% after 10 mg and 80 mg Crestor, respectively. Mean values of C_{max} were also increased by 36% and 15% for 10 mg and 80 mg Crestor, respectively. However, the sponsor considered that these increases were not of clinical significance.

Based on enzyme assay, the sponsor concluded that rosuvastatin accounted for the majority (approximately 88%) of the circulating active HMG-CoA reductase inhibitors. Circulating concentrations of rosuvastatin-lactone were about 15% of rosuvastatin (at C_{max}).

Safety was carefully monitored in the study because of possible significant drug interaction. T-wave flattening and inversion were noted at the 3 hour post-dose ECG in one volunteer after receiving rosuvastatin 10 mg and itraconazole. These changes spontaneously reversed to normal by 12 hours post-dose with no associated signs or symptoms. There were no clinically significant changes observed in vital signs, laboratory biochemical or haematological parameters, or medical examination for any of the other volunteers during the trial.

Ketoconazole

Effect of ketoconazole, a strong CYP3A4 inhibitor, was evaluated in a randomized, double-blind, placebo-controlled, 2-way crossover trial conducted at a single center (Trial 57). The trial consisted of two seven-day treatment periods (Periods A and B). During Period A volunteers received either oral doses of ketoconazole 200 mg twice a day or placebo twice a day for seven days. In Period B, volunteers crossed over to the treatment they had not received in Period A. On Trial Day 4 of each period a single oral dose of rosuvastatin 80 mg (one encapsulated tablet) was taken with the morning dose of ketoconazole or placebo.

There was no significant effect of ketoconazole on rosuvastatin. Results of statistical analysis are summarized in the following table.

Table XXIII Statistical comparison of $AUC_{(0-t)}$ and C_{max} for 80 mg rosuvastatin in presence and absence of ketoconazole

Parameter (units)	ZD4522 + ketoconazole		ZD4522 + placebo		Ratio of glsmeans ^a	90% CI for ratio ^a
	glsmean	N	glsmean	N		
$AUC_{(0-t)}$ (ng·h/ml)	310	13	305	14	1.016	0.839 to 1.230
C_{max} (ng/ml)	37.2	13	39.0	14	0.954	0.722 to 1.260

Data derived from Table T4.13

^a Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + ketoconazole) / glsmean (ZD4522 + placebo)

glsmean = geometric least square mean; $AUC_{(0-t)}$ = area under the curve up to time t;

C_{max} = maximum plasma concentration; CI = confidence interval; N = number of volunteers

Erythromycin

Effect of erythromycin, a strong CYP3A4 inhibitor, was evaluated in a randomized, double-blind, placebo-controlled, 2-way crossover trial conducted at a single center (Trial 58). The trial consisted of two seven-day treatment periods (Periods A and B). Volunteers received oral doses of erythromycin 500 mg four times a day or placebo four times a day for seven days. The single dose of rosuvastatin 80 mg (one encapsulated tablet) was taken with the first morning dose of erythromycin or placebo on Trial Day 4.

Table XXIV Statistical comparison of $AUC_{(0-t)}$ for 80 mg rosuvastatin in presence and absence of erythromycin

	ZD4522 + erythromycin		ZD4522 + placebo		Ratio of glsmeans ^a	90% CI ^a
	N	glsmean	N	glsmean		
$AUC_{(0-t)}$ (ng·h/ml)	11	202	14	253	0.80	0.68 to 0.94
C_{max} (ng/ml)	11	23.2	14	33.7	0.69	0.52 to 0.91

Data derived from Table T4.13

^a = Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + erythromycin) / glsmean (ZD4522 + placebo)

$AUC_{(0-t)}$ = area under the curve from time zero to time of last quantifiable concentration; C_{max} = maximum plasma concentration; CI = confidence interval;

glsmean = geometric least square mean; N = number of volunteers

Rosuvastatin exposure was decreased in the presence of erythromycin for 20% and 31% of AUC and C_{max} , respectively, compared to those of without erythromycin. The sponsor concluded that there were no safety concerns in the interaction because the decrease may be a consequence of the profound effect that erythromycin has on gastroduodenal motor activity and would not warrant a dosage adjustment.

Cyclosporine

Effect of cyclosporine, a strong CYP3A4/transporter inhibitor, was evaluated in an open-label, single center trial in which 2 cohorts of heart transplant recipients on stable regimens of cyclosporine (plus prednisone and azathioprine) were given single- and multiple-doses of rosuvastatin (10 mg in Cohort 1 and 20 mg in Cohort 2) (Trial 21). The overview of trial design is shown in the following figures.

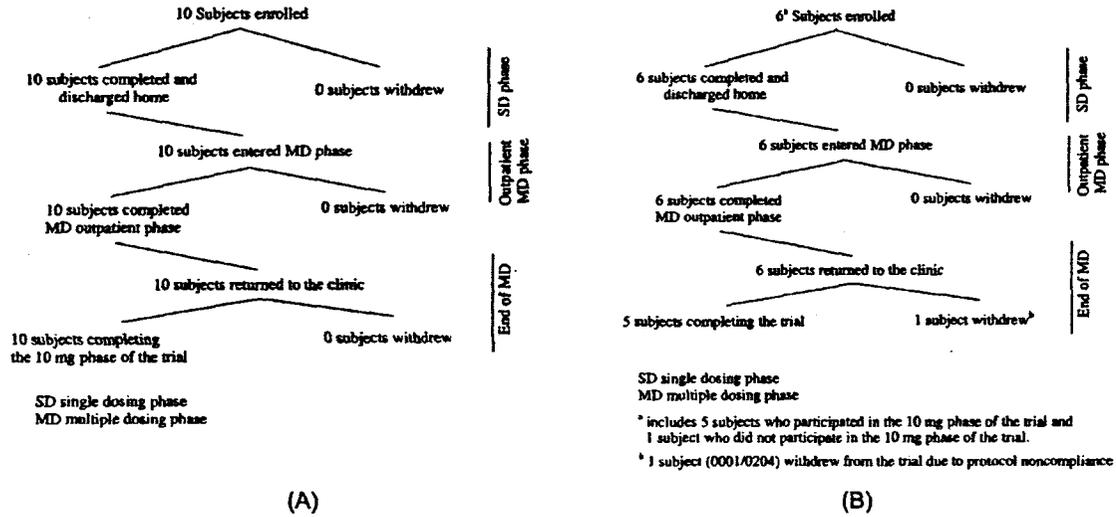


Figure 21 Overview of trial design in the 10 mg (A) and 20 mg (B) phase of rosuvastatin dosing

Results are summarized in the following figure and table.

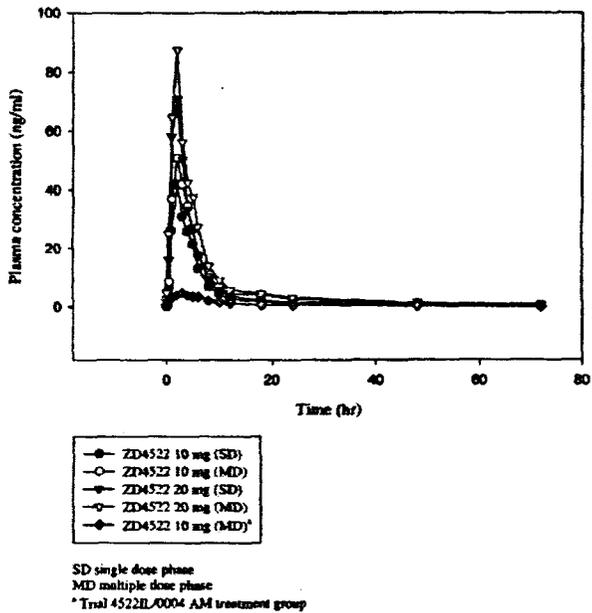


Figure 22 Mean plasma concentration of rosuvastatin. In the figure, the sponsor chose Trial 4 as a historical control study without cyclosporine for 10 mg rosuvastatin.

Table XXV Summary of multiple dose pharmacokinetics

PK parameter	ZD4522 + cyclosporine			ZD4522 only
	Cohort 1 (10 mg) (n = 10)	Cohort 1B ^a (10 mg) (n = 5)	Cohort 2 (20 mg) (n = 5)	4522IL/0004 ^b (10 mg) (n = 21)
C _{max} (ng/ml) ^c	48.67 (47.2)	57.60 (37.44)	83.40 (37.3)	4.58 (46.9)
AUC(0-24) (ng.h/ml) ^c	284.37 (31.33)	313.25 (28.33)	423.69 (21.70)	40.10 (39.39)
AUC(0-t) (ng.h/ml) ^c	341.46 (27.68)	369.73 (23.48)	506.82 (20.94)	50.35 (46.98)
AUC (ng.h/ml) ^c	360.54 (16.89) ^f	337.33 (19.30) ^g	463.08 (4.08) ^g	71.81 (30.93) ^h
t _{max} (h) ^d	2.0 (—)	2.0 (—)	2.0 (—)	3.0 (—)
t _{1/2} (h) ^e	14.76 (4.05) ^f	15.20 (5.27) ^g	20.20 (5.37) ^g	31.28 (12.02) ^h
Cohort 2 (20 mg) / Cohort 1B (10 mg) ratioⁱ				
C _{max} (ng/ml) ^c	—	1.485 (0.367)	—	—
AUC(0-24) (ng.h/ml) ^c	—	1.379 (0.295)	—	—

Data derived from Table T5.2.1 and Trial 4522IL/0004

^a Cohort 1B consists of subjects in Cohort 1 who also participated in Cohort 2.

^b Data for ZD4522 only are from the morning dosing treatment group of Trial 4522IL/0004.

^c Geometric mean (coefficient of variation).

^d Median (range).

^e Arithmetic mean (standard deviation).

^f n = 5; some subjects' values were not calculated because no reliable estimate of the terminal elimination could be obtained due to concentrations below the sensitivity of the assay.

^g n = 3; as above. Mean values less than those for AUC(0-t) are a result of the different number of included subjects.

^h n = 16; as above.

ⁱ Produced for the ratio of log transformed paired data for Day B11/Day 15 values (standard deviation) and includes only those subjects who participated in both cohorts (n = 5).

PK Pharmacokinetic.

Cyclosporine (and other anti-rejection medications including azathioprine and prednisone) increased rosuvastatin C_{max} and AUC₍₀₋₂₄₎ by approximately 10- and 7-fold, respectively, compared to historical controls (Trial 4). There was no serious adverse events reported.

Fluconazole

Effect of fluconazole, a CYP2C9/2C19 inhibitor, was evaluated in a randomized, double blind, 2-way crossover, placebo-controlled trial conducted at a single center (Trial 48, N=14). Volunteers received once-daily doses of either fluconazole 200 mg or placebo for 11 days. On the eighth day of dosing (Trial Day 8) in each treatment period, volunteers also received a single oral dose of rosuvastatin 80 mg (one 80 mg encapsulated tablet) at the same time as dosing with fluconazole or placebo.

Pharmacokinetic parameters and results of statistical analysis are summarized in the following table. There was no statistically significant interaction between fluconazole and rosuvastatin.

Table XXVI Summary of trial results

Parameter (units)	ZD4522 + fluconazole		ZD4522 + placebo		Ratio of glsmeans ^a	90% CI for ratio ^a
	glsmean	N	glsmean	N		
AUC(0-t) (ng.h/ml)	370	13	325	14	1.139	0.967 to 1.341
C _{max} (ng/ml)	45.1	13	41.4	14	1.089	0.874 to 1.355

Data derived from Table T4.2.3

^a Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + fluconazole) / glsmean (ZD4522 + placebo)

glsmean = geometric least square mean; AUC(0-t) = area under the curve up to time t;

C_{max} = maximum plasma concentration; CI = confidence interval; N = number of volunteers

Fenofibrate

Interaction between fenofibrate and rosuvastatin was evaluated in a randomized, non-controlled, open-label, 3-way crossover trial conducted at a single center (Trial 22). Volunteers received in randomized order, single daily oral doses of rosuvastatin 10 mg (one 10 mg capsule), 3 daily oral doses of fenofibrate 67 mg (morning, afternoon and evening), or rosuvastatin 10 mg (morning) + fenofibrate (3 x 67 mg; morning, afternoon and evening) in combination.

Results are summarized in the following table. There was no significant pharmacokinetic interaction between fenofibrate and rosuvastatin.

Table XXVII Summary of key pharmacokinetic findings

Comparison	ZD4522 + fenofibrate		ZD4522		Ratio of glsmeans ^a	90% CI ^a
	glsmean	n	glsmean	n		
ZD4522						
AUC(0-24) (ng·h/ml)	40.7	14	38.0	14	1.07	1.00 to 1.15
C _{max} (ng/ml)	5.29	14	4.36	14	1.21	1.14 to 1.28
Parameter	ZD4522 + fenofibrate		Fenofibrate		Ratio of glsmeans ^b	90% CI ^b
	glsmean	n	glsmean	n		
Fenofibric acid						
AUC(0-8) (µg·h/ml)	54.3	14	56.5	13	0.96	0.90 to 1.02
C _{max} (µg/ml)	8.23	14	9.00	13	0.91	0.84 to 1.00

Data derived from Tables T4.3 and T5.3

^a Ratio and 90% CI are expressed as a ratio of the glsmean (ZD4522 + fenofibrate) / glsmean (ZD4522)

^b Ratio and 90% CI are expressed as a ratio of the glsmean (ZD4522 + fenofibrate) / glsmean (fenofibrate)

AUC(0-24) = area under the curve from 0 to 24 hours; n = number of volunteers;

AUC(0-8) = area under the curve from 0 to 8 hours; C_{max} = maximum plasma concentration;

glsmean = geometric least squares mean; CI = confidence interval

Gemfibrozil

The effect of gemfibrozil on rosuvastatin was evaluated in a phase I, single center, randomized, double-blind, placebo-controlled, 2-way crossover trial (Trial 95). Either current highest approved dose of gemfibrozil (1200 mg daily, 600 mg BID) or placebo was administered for 7 days and a single dose of 80 mg rosuvastatin (1x80 mg) was administered on trial Day 4 (N=20). Plasma AUC and C_{max} were estimated to examine magnitude of drug interaction.

Plasma concentration-time profiles are shown in the following figures and table.

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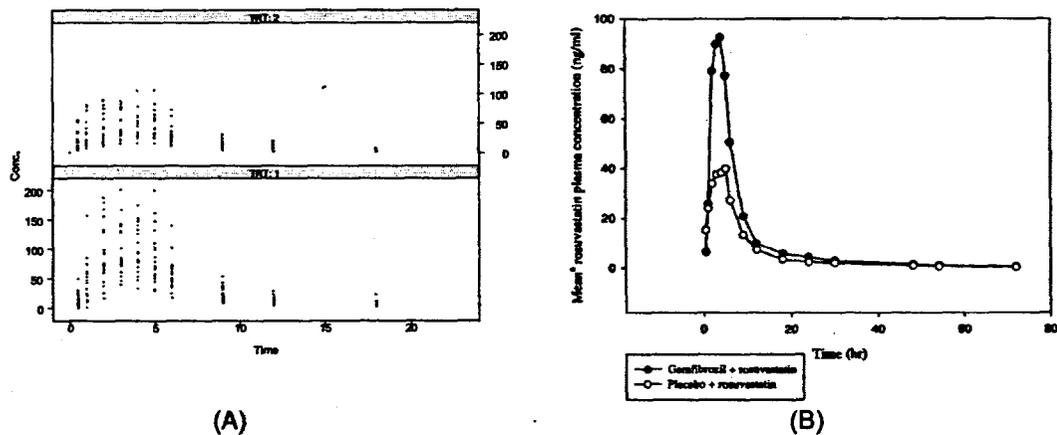


Figure 23 Rosuvastatin plasma concentration-time profile of all (A) and geometric mean (B) data. In figure (A), treatment for coadministration of rosuvastatin and gemfibrozil is indicated by TRT 1, and rosuvastatin alone is indicated by TRT 2.

Rosuvastatin exposure was increased about 2-fold by gemfibrozil compared to that in placebo. In 2 subjects out of 20, values of C_{max} increased to 520% and 560% by gemfibrozil. The interaction was concluded as clinically significant. However, the mechanism of drug interaction is unknown but may be through phase II metabolism (transferases) or transporter(s).

Pharmacokinetic parameters and results of statistical analysis are summarized in the following tables.

Table XXVIII Pharmacokinetic parameters of rosuvastatin in the drug interaction with gemfibrozil

Parameter (units)	Summary statistic	Gemfibrozil+rosuvastatin	Placebo+rosuvastatin
AUC_{0-4} (ng h/ml)	Geometric mean (CV %)	771 (48.8)	410 (47.7)
	Arithmetic mean (SD)	853 (404.6)	457 (211.8)
	(range)		
	N	20	20
C_{max} (ng/ml)	Geometric mean (CV %)	109 (42.9)	446 (42.9)
	Arithmetic mean (SD)	118(43.7)	486 (225.5)
	(range)		
	N	20	20
t_{max} (h)	Median (range)	3.0	4.0
	N	20	20
$t_{1/2}$ (hr)	Arithmetic mean (SD)	23.3 (17.7)	17.1 (6.3)
	N	16	14

Table XXIX Statistical analysis of drug interaction between rosuvastatin and gemfibrozil

Primary endpoints	Gemfibrozil+Rosuvastatin		Placebo+Rosuvastatin		Ratio of glsmean	90% CO for ratio
	glsmean	N	glsmean	N		
AUC _{0-t} (ng h/ml)	771	20	410	20	1.88	1.60-2.21
C _{max} (ng/ml)	109	20	49.5	20	2.21	1.81-2.69

Co-magaldrox (Antacid)

Effect of co-magaldrox was evaluated in a randomized, non-controlled, open-label, 3-way crossover trial conducted at a single center (Trial 20). Volunteers received either a single oral dose of rosuvastatin 40 mg alone (four 10 mg capsules), rosuvastatin plus co-magaldrox 20 ml simultaneously or rosuvastatin plus co-magaldrox 20 ml taken 2 hours later, in randomized order.

Results are summarized in the following table. Simultaneous administration of co-magaldrox decreased significantly rosuvastatin exposure by 54% and 50% for AUC and C_{max}, respectively, compared to those of rosuvastatin alone. Co-magaldrox taken after 2 hours rosuvastatin decreased rosuvastatin exposure by 22% and 16% for AUC and C_{max}, respectively, compared to those of rosuvastatin alone. Therefore, it would be recommended that rosuvastatin should be given at least 2 hours before the antacid.

Table XXX Summary of interaction between co-magaldrox and rosuvastatin

Comparison Parameter	ZD4522 + co-magaldrox (simultaneously)		ZD4522		Ratio of glsmeans ^a	90% CI ^a
	glsmean	n	glsmean	n		
AUC(0-t) (ng·h/ml)	50.1	14	110	14	0.46	0.40 to 0.53
C _{max} (ng/ml)	5.56	14	11.2	14	0.50	0.41 to 0.60
Comparison Parameter	ZD4522 + co-magaldrox (taken 2 hours later)		ZD4522		Ratio of glsmeans ^b	90% CI ^b
	glsmean	n	glsmean	n		
AUC(0-t) (ng·h/ml)	85.6	14	110	14	0.78	0.68 to 0.98
C _{max} (ng/ml)	9.40	14	11.2	14	0.84	0.70 to 1.01

Data derived from Table T4.3

^a Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + co-magaldrox simultaneously) / glsmean (ZD4522)

^b Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + co-magaldrox taken 2 hours later) / glsmean (ZD4522)

glsmean = geometric least squares mean; AUC(0-t) = area under the curve up to time t;

C_{max} = maximum plasma concentration; CI = confidence interval; n = number of volunteers

2) What is the effect of rosuvastatin on other drugs ?

Digoxin

Rosuvastatin effect on digoxin was evaluated in a double-blind, randomized, 2-way crossover trial conducted at a single center (Trial 13). Volunteers were given single daily oral doses of either rosuvastatin 40 mg (four 10 mg capsules) or placebo. Volunteers were given a single oral dose of 0.5 mg digoxin on Trial Day 8 of each trial period.

Results are summarized in the following tables. There was no significant pharmacokinetic effect of rosuvastatin on digoxin indicated by 4% exposure increase of digoxin in the presence of rosuvastatin. Also, urinary excretion of digoxin remained unchanged in the presence of rosuvastatin.

Table XXXI Summary of the trial

Parameter (units)	ZD4522 + digoxin		Placebo + digoxin		Ratio of glsmeans ^a	90% CI for ratio ^a
	glsmean	n	glsmean	n		
AUC _(0-t) (ng·h/ml)	8.14	18	7.80	16	1.04	0.88 to 1.24
C _{max} (ng/ml)	2.22	18	2.12	16	1.04	0.89 to 1.22

Data derived from Table 14.3

^a ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + digoxin) / glsmean (placebo + digoxin)

glsmean = geometric least squares mean; AUC_(0-t) = area under the curve up to time t;

C_{max} = maximum plasma concentration; CI = confidence interval; n = number of volunteers

Table XXXII Urinary excretion of digoxin up to 96 hours after dosing

Parameter	Summary statistic	ZD4522 + digoxin (n=18)	Placebo + digoxin (n=16)
Ae ₀₋₉₆ (µg)	Mean ^a (CV %)	196.4 (28.3)	195.3 (26.9)
Renal Clearance (l/h)	Mean ^a (CV %)	9.63 (25.3)	9.19 (27.2)

Data derived from Table 14.5

^a geometric mean

Ae₀₋₉₆ = amount excreted in urine between 0 and 96 hours after dose; n = number of volunteers

Oral Contraceptives (OCS)

Rosuvastatin effect on OCS was evaluated in an open-label, multiple-dose, nonrandomized trial conducted at a single center (Trial 9). Subjects were given Ortho Tri-Cyclen (3 weeks of EE 0.035 mg and NGM 0.180 mg during week 1, 0.215 mg week 2, and 0.250 mg week 3; and 1 week of OCS placebo) for two 28-day cycles (Cycles A and B). Each subject was also given concomitant rosuvastatin 40 mg (four 10 mg capsules, formulation F12420, lot 983167E) once daily for the first 21 days in Cycle B. All trial treatments were to be taken at approximately 0800.

Pharmacokinetics of ethinyl estradiol (EE), norgestimate (NGM), 17-desacetyl norgestimate (DesAc-NGM), and norgestrel (NG) was estimated at Day 21 of each treatment. Results are summarized in the following tables. Coadministration of OCS and ZD4522 resulted in increases in AUC₍₀₋₂₄₎ for EE (26%), DesAc-NGM (15%) and NG (34%) and in C_{max} for EE (25%) and NG (23%). It was concluded that there were no clinical concerns for increased exposure of OCS.

Table XXXIII Effect of rosuvastatin on pharmacokinetic parameters of ethinyl estradiol (Day 21)

PK parameter	n	Cycle A (OCS)	Cycle B (OCS+ZD4522)	Geometric mean ratio or arithmetic mean difference ^a	Lower 90% CL ^b	Upper 90% CL ^b
AUC(0-24) (pg.h/ml) ^c	18	1338.8 (35)	1690.0 (31)	1.262	1.187	1.343
C _{max} (pg/ml) ^c	18	159.36 (41)	198.43 (36)	1.245	1.165	1.331
t _{1/2} (h) ^d	17 ^f	13.844 (3.310)	16.629 (3.682)	2.369	0.892	3.847
T _{max} (h) ^e	18	1.0 (1, 4)	1.0 (1, 4)	NA	NA	NA

Data derived from Tables 15.4 and 5.7

^a Geometric mean of the ratio (OCS+ZD4522)/OCS for AUC(0-24) and C_{max}; arithmetic mean of the difference (OCS+ZD4522)-OCS for t_{1/2}.

^b Confidence intervals that include one indicate that the geometric mean ratio is not statistically different from one; CIs that include zero indicate that the arithmetic mean difference is not statistically different from zero.

^c Geometric mean (coefficient of variation, %).

^d Arithmetic mean (standard deviation).

^e Median (minimum, maximum).

^f t_{1/2} data in both Cycles A and B were available for 16 subjects.

CL = Confidence limit.

NA = Not applicable.

OCS = Oral contraceptive steroids.

PK = Pharmacokinetic.

Table XXXIV Effect of rosuvastatin on pharmacokinetic parameters of 17-desacetyl norgestimate

PK parameter	n	Cycle A (OCS)	Cycle B (OCS+ZD4522)	Geometric mean ratio or arithmetic mean difference ^a	Lower 90% CL ^b	Upper 90% CL ^b
AUC(0-24) (ng.h/ml) ^c	18	19.13 (16)	21.99 (16)	1.150	1.103	1.198
C _{max} (ng/ml) ^c	18	2.465 (33.9)	2.526 (19.3)	1.025	0.906	1.159
t _{1/2} (h) ^d	18 ^f	23.74 (4.22)	24.02 (4.71)	0.707	-0.500	1.914
T _{max} (h) ^e	18	1.00 (0.5, 4.0)	1.00 (1.0, 3.0)	NA	NA	NA

Data derived from Tables 15.5 and 5.7

^a Geometric mean of the ratio (OCS+ZD4522)/OCS for AUC(0-24) and C_{max}; arithmetic mean of the difference (OCS+ZD4522)-OCS for t_{1/2}.

^b Confidence intervals that include one indicate that the geometric mean ratio is not statistically different from one; CIs that include zero indicate that the arithmetic mean difference is not statistically different from zero.

^c Geometric mean (coefficient of variation, %).

^d Arithmetic mean (standard deviation).

^e Median (minimum, maximum).

^f t_{1/2} data were available for 15 subjects in Cycle B (OCS + ZD4522).

CL = Confidence limit.

NA = Not applicable.

OCS = Oral contraceptive steroids.

PK = Pharmacokinetic.

Table XXXV Effect of rosuvastatin on pharmacokinetic parameters of norgestrel

PK parameter	n	Cycle A (OCS)	Cycle B (OCS+ZD4522)	Geometric mean ratio or arithmetic mean difference ^a	Lower 90% CL ^b	Upper 90% CL ^b
AUC(0-24) (ng.h/ml) ^c	18	61.96 (44)	82.81 (48)	1.337	1.246	1.434
C _{max} (ng/ml) ^c	18	3.461 (41.0)	4.272 (44.8)	1.234	1.143	1.333
t _{1/2} (h) ^d	3 ^f	31.20 (3.31)	29.50 (NC)	1.200	NC	NC
T _{max} (h) ^e	18	2.00 (0.5, 8.0)	3.00 (0.5, 10.0)	NA	NA	NA

Data derived from Tables T5.6 and 5.7

^a Geometric mean of the ratio (OCS+ZD4522)/OCS for AUC(0-24) and C_{max}; arithmetic mean of the difference (OCS+ZD4522)-OCS for t_{1/2}.

^b Confidence intervals that include one indicate that the geometric mean ratio is not statistically different from one.

^c Geometric mean (coefficient of variation, %).

^d Arithmetic mean (standard deviation).

^e Median (minimum, maximum).

^f t_{1/2} data were available for 1 subject in Cycle B (OCS + ZD4522).

CL = Confidence limit.

NA = Not applicable.

NC = Not calculable.

OCS = Oral contraceptive steroids.

PK = Pharmacokinetic.

Warfarin

Rosuvastatin effect on warfarin was evaluated in a double-blind, placebo-controlled, 2-period crossover trial conducted at a single center (Trial 14). Subjects were given single daily oral doses of either rosuvastatin 40 mg (four 10 mg capsules) or placebo for 10 days. One 25-mg oral dose of warfarin was coadministered with either rosuvastatin or placebo on the 7th day of rosuvastatin or placebo exposure during each treatment period.

Pharmacodynamics was evaluated in addition to PK: The warfarin pharmacodynamic (PD) endpoints were the area under the prothrombin time (PT reported as INR) - time curve (AU-INR), the maximum INR following coadministration of warfarin (max INR), and the time following coadministration of warfarin at which max INR occurs (t_{max} INR).

Results are summarized in the following tables. There was no significant PK interaction between rosuvastatin and warfarin. The coadministration of daily rosuvastatin 40 mg (10 days) and warfarin 25 mg (single dose) produced a higher mean max INR (p<0.001) and AU-INR (p<0.001) than achieved with warfarin alone. However, the mechanism of the dynamic interaction is unknown.

Table XXXVI Rosuvastatin effect on pharmacokinetic parameters of R- and S-warfarin

Parameter (units)	Analysis	N	R-warfarin		S-warfarin	
			ZD4522 period	Placebo period	ZD4522 period	Placebo period
C _{max} (ng/ml)	Geometric mean	18	1769.91	1784.43	1705.28	1710.58
	CV (%)		16.16	18.75	17.02	21.04
t _{max} (h)	Median	18	0.50	1.00	0.50	0.99
	Minimum					
	Maximum					
AUC(0-t) (ng.h/ml)	Geometric mean	18	75234.75	73290.04	47624.71	45246.37
	CV (%)		27.51	25.49	27.29	30.73
AUC (ng.h/ml)	Geometric mean	18	82937.25	79885.21	49710.80	46895.88
	CV (%)		31.81	29.28	29.77	33.69
t _{1/2} (h)	Arithmetic mean ^a	18	47.64	45.24	33.60	31.90
	Minimum					
	Maximum					

Data derived from Tables T5.3 and T5.4.

^a These statistics are calculated on untransformed data.

Table XXXVII ANOVA results for AU-INR and max INR

Parameter	N	GLS mean (ZD4522) period	GLS mean (Placebo) period	Estimate of treatment effect	Lower 90% confidence limit	Upper 90% confidence limit	p-value
AU-INR(0-t)	18	248.69	225.77	1.10	1.08	1.13	<0.001
max INR	18	2.36	1.99	1.19	1.14	1.23	<0.001

Data derived from Table T4.1.3.

max INR = Maximum INR following coadministration of warfarin; AU-INR(0-t) = Area under the INR-time curve.

Additional effect of 80 mg dose on warfarin was assessed based on PD measures in the combination (Trial 60). This was an open-label, multiple-dose, nonrandomized trial conducted at a single center. The trial consisted of 3 clinic visits during a screening period of no more than 30 days to obtain baseline INR values, two sequential 14-day treatment periods (rosuvastatin 10 mg and 80 mg encapsulated tablet once daily), and a 14-day follow-up period. All subjects were on a stable warfarin regimen throughout the trial. The administration of rosuvastatin to subjects receiving warfarin and with stable baseline INR values resulted in clinically meaningful increases in INR (values >4.0) in 2 of 7 subjects at the 10 mg dose and in 4 of 5 subjects at the 80 mg dose of rosuvastatin. These results demonstrate that concomitant administration of ZD4522 can significantly increase the anticoagulant activity of warfarin. No major bleeding events were associated with the increase in INR, and no other safety concerns were identified. The mechanism of interaction is unknown.

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3.5 General Biopharmaceutics

1. Is bioequivalence established between the to be marketed formulation and the Phase 3 trial formulation ?

This trial was performed to investigate the bioequivalence of formulation between the to be marketed (TBM) and the clinical trial tablets used in pivotal efficacy trials (Trial 49). To facilitate blinding during the pivotal Phase III trials, rosuvastatin tablets (and placebo) were encapsulated, with a lactose backfill.

BE of TBM and tablets used in clinical trials were assessed in a randomized, open-label, non-controlled, single center trial. The trial consisted of four study cohorts, with each cohort receiving two single doses of rosuvastatin, separated by at least a one-week washout period. In three of the cohorts the "to be marketed" tablets were compared with the non-encapsulated clinical trial tablets, at doses of 4 x 5 mg, 1 x 20 mg and 1 x 80 mg. In the fourth cohort, rosuvastatin 80 mg encapsulated clinical trial tablets were compared with 80 mg non-encapsulated trial tablets. Composition of Phase III tablet is summarized in the Appendix I

Results are summarized in the following table. Bioequivalence was concluded between the "to be marketed" tablets and non-encapsulated clinical trial tablets at strengths of 5 mg, 20 mg and 80 mg. Bioequivalence was also concluded between encapsulated and non-encapsulated 80 mg clinical trial tablets.

Table XXXVIII Summary of pharmacokinetic parameters and results of statistical analysis

Cohort (dose) Parameter (units)	glsmean	N	glsmean	N	Ratio of glsmeans ^a	90% CI ^b
	"To be marketed"		Non-encapsulated clinical trial			
Cohort 1 (4 x 5 mg)						
AUC(0-t) (ng·h/ml)	130	32	129	31	1.010	0.930 to 1.096
C _{max} (ng/ml)	15.1	32	14.8	31	1.015	0.891 to 1.156
Cohort 2 (1 x 20 mg)						
AUC(0-t) (ng·h/ml)	137	32	127	32	1.084	1.004 to 1.170
C _{max} (ng/ml)	14.9	32	14.8	32	1.005	0.911 to 1.108
Cohort 3 (1 x 80 mg)						
AUC(0-t) (ng·h/ml)	545	31	513	32	1.062	0.968 to 1.164
C _{max} (ng/ml)	73.9	31	71.2	32	1.038	0.885 to 1.217
	Non-encapsulated clinical trial		Encapsulated clinical trial			
Cohort 4 (1 x 80 mg)						
AUC(0-t) (ng·h/ml)	546	30	535	32	1.020	0.945 to 1.101
C _{max} (ng/ml)	76.4	30	76.6	32	0.997	0.881 to 1.130

Data derived from Tables 14.1.3, 14.2.3, 14.3.3 and 14.4.3

^a Ratio and 90% CIs are expressed as a ratio of glsmean (ZD4522 "to be marketed" tablets) / glsmean (ZD4522 non-encapsulated clinical trial tablets) or glsmean (ZD4522 non-encapsulated clinical trial tablets) / glsmean (ZD4522 encapsulated clinical trial tablets) for Cohort 4

AUC = area under the curve; CI = confidence interval; glsmean = geometric least square mean; N = number of volunteers
C_{max} = maximum plasma concentration

Although direct bioequivalence has not been established between TBM and the clinical tablets (encapsulated), it is safe to consider the two formulations are bioequivalent based on a bridge study between encapsulated and non-encapsulated tablets in Cohort 4.

2. Is BE established formulations between Phase 2 (capsules) and Phase 3 (encapsulated tablets) ?

Phase II dose-ranging trials and some of phase I trials used capsules and pivotal Phase 3 trials used encapsulated tablets.

BE of the capsules and encapsulated formulations were assessed in a randomized, open-label, non-controlled, 2-period cross-over trial conducted at a single center (Trial 19). The trial consisted of two independent study cohorts (Cohorts 1 and 2). Each cohort participated in two treatment periods (Periods A and B). During Period A, volunteers in Cohort 1 received a single dose of either 2 x 10 mg Phase II clinical trial capsules or 2 x 10 mg Phase III encapsulated clinical trial tablets. Volunteers in Cohort 2 received either 8 x 10 mg of Phase II clinical trial capsules or 1 x 80 mg Phase III encapsulated clinical trial tablet. Results are summarized in the following table.

Table XXXIX Summary of pharmacokinetic parameters and results of statistical analysis

Cohort (dose) Parameter (units)	glsmean	N	glsmean	N	Ratio of glsmeans ^a	90% CI ^a
	Phase II capsules	Phase III encapsulated tablets	Phase III encapsulated tablets			
Cohort 1 (2 x 10 mg ZD4522)						
AUC(0-t) (ng·h/ml)	77.6	31	77.1	32	0.993	0.944 to 1.046
C _{max} (ng/mL)	7.53	31	8.41	32	1.118	1.012 to 1.234
Cohort 2 (80 mg ZD4522)						
AUC(0-t) (ng·h/ml)	464	31	424	32	0.915	0.838 to 0.999
C _{max} (ng/mL)	55.0	31	51.5	32	0.936	0.811 to 1.081

Data derived from Tables T4.1.3 and T4.2.3

^a Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 Phase III encapsulated clinical trial tablet) / glsmean (ZD4522 Phase II clinical trial capsule)

glsmean = geometric least squares mean; C_{max} = maximum plasma concentration; CI = confidence interval;

AUC(0-t) = area under the curve from zero to the time of the last quantifiable concentration; N = number of volunteers

The Phase 2 trials formulation and the Phase 3 trials formulation are bioequivalent.

3. Has dosage form equivalence been established among the tablet strengths ?

Although the sponsor has not done a study of which the objective was to establish dosage form equivalence between strengths, results of the dose proportionality study (Trial 47) indicated dosage form equivalence because one of each strength (10, 20, 40, and 80 mg) was used in the study and linearity was demonstrated in relation of doses and PK parameters.

In addition, it is reasonable to assume dosage form equivalence for commercial formulations with the following factors:

- Bioequivalence was established between clinical formulations and commercial formulations for the 5, 20, and 80mg strength.
- Commercial formulations were quantitatively proportional within the same blends (i.e., 2.5 vs. 5 mg, 10 vs. 20 mg, and 40 vs. 80mg). For example, 40 and 80 mg formulations were from the same blend and both strengths were quantitatively proportional each other.

4. What is the appropriate dissolution test condition and specification ?

The proposed dissolution test condition is as follows:

Parameter
Medium
Apparatus
Volume
Temperature
Sampling times

Among several tested dissolution media, _____ was chosen with the Agency's concurrence because it showed no tablet swelling, linear intrinsic dissolution, and a non-inverted relationship between intrinsic dissolution and solubility.

Dissolution profiles of the to be marketed formulation were obtained in the proposed dissolution methods and those are summarized in Table XL.

Table XL Dissolution results for commercial formulation: the highest strength tablet for each of the 3 formulation blends used in the manufacture of the to be marketed tablets.

Strength (mg)	Collection time (min)	Mean % claim	Range % claim
5		94.2	/
		97.0	
		97.8	
20		87.8	/
		91.2	
		92.7	
80		79.8	/
		85.8	
		88.9	

Table XLI Dissolution results for commercial formulation: the lowest strength tablet for each of the 3 formulation blends used in the manufacture of the to be marketed tablets.

Strength (mg)	Collection time (min)	Mean % claim	% RSD
2.5		89.2	4.9
		95.2	2.8
		97.0	1.9
10		92.6	6.8
		96.5	3.6
		97.7	2.7
40		81.8	4.6
		88.2	4.1
		90.7	3.9

The proposed specifications are:

- for 2.5-, 5-, and 10-mg tablets, Q = _____ % at _____ minutes
- for 40- and 80-mg tablets, Q = _____ % at _____ minutes

Based on the provided dissolution data, it is recommended to have one specification as follows:

Q = _____ % at 30 minutes

5. Can we consider that different manufacturing sites and scale-up will produce equivalent tablets ?

In vitro dissolution studies were conducted for commercial tablets manufactured at different sites and/or scale-up. Types of changes are as follows:

- Site and scale change
 - from _____ to Carolina, PR
 - _____ scale change
- Scale change
 - _____ kg

Similarity factor (f_2) were performed to assess equivalence of dissolution profiles and three media were selected based on recommendation by the Agency as follows:

-
-
-

Similarity factors were higher than 50 in all media for 5, 10, 20, and 80 mg and the results were acceptable to show equivalence during the changes via in vitro dissolution profiles.

3.6 Analytical

1. Is the analytical methods appropriately validated ?

Rosuvastatin, N-desmethyl metabolites, rosuvastatin lactone, and the deuterated internal standard (IS) were analyzed using an _____ method.

Samples were extracted by _____ analyzed by an _____ and detected by a _____ respectively. Rosuvastatin concentration was quantified by peak area ratio of rosuvastatin to IS. No significant interference was observed in the chromatogram of samples.

Intra-batch inaccuracy was found to be between - _____ and the imprecision to be between _____ in the dose-proportionality study as an example (see the following table). The effective limit of quantification was _____ $\mu\text{g/ml}$. About _____ % of rosuvastatin was recovered from human plasma at 25 ng/ml with a _____ % recovery for the internal standard.

Table XLII Intra-batch inaccuracy and imprecision for the validation of rosuvastatin in human plasma

Concentration n (ng/ml)	QC 1	QC 2	QC 3	QC 4	QC 5	QC 6	n	Mean	SD	Inaccuracy	Imprecision
										(%)	(%)
0.100			—				6	0.102	0.0150		
0.300			—				6	0.279	0.0198		
15.0			—				6	15.2	0.416		
25.0			—				6	24.5	0.713		

The inter-batch inaccuracy was to range between — and imprecision — as determined over 3 batches prepared on 3 separate days (see the following table).

Table XLIII Inter-batch inaccuracy and imprecision for the validation of rosuvastatin in human plasma

Concentration (ng/ml)	Batch Reference			n	Mean	SD	Inaccuracy	Imprecision
	1	2	3				(%)	(%)
0.100		— —		5	0.107	0.0127		
0.300		— —		6	0.301	0.0181		
15.0		— —		6	15.0	0.528		
25.0		— —		6	24.9	1.19		

* Denotes a point dropped from calculations

Calibration line for rosuvastatin in human plasma is shown in the following figure from dose-proportionality study.

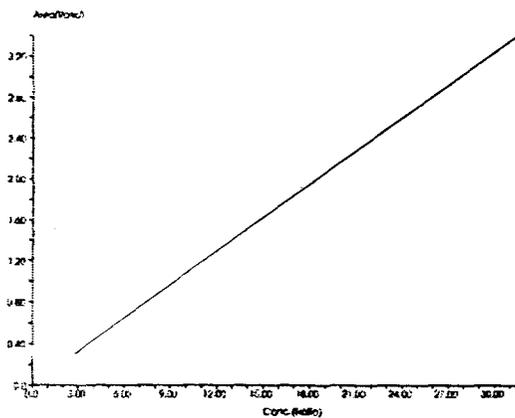


Figure 24 Calibration curve of rosuvastatin in human plasma

4 Appendix

4.1. Composition of Phase III tablets.

Ingredient	Amount per tablet (mg)						
	1.0	2.5	5	10	20	40	80
Formulation number	F12633	F12496	F12554	F12497	F12511	F12507	F12555
Tablet core							
ZD4522 calcium *							
Microcrystalline Cellulose USNF							
Tribasic Calcium Phosphate USNF							
Magnesium Stearate USNF							
Nominal tablet core weight	49.42	123.55	247.10	494.20	200.56	401.12	802.24
Tablet coating							
Hydroxypropyl Methylcellulose USP,							
Titanium Dioxide USP ^{b,c}							
Ferric Oxide, Red USNF ^{b,c}							
Ferric Oxide, Yellow USNF ^c							
Nominal coated tablet weight	50.66	126.64	253.28	506.55	205.58	411.15	822.29

4.2. Pharmacometrics Review - He Sun, Ph.D.

NDA:	21-366
Product Trade Name:	Crestor™
Active Ingredient/s:	Rosuvastatin (ZD4522)
Indication:	Cholesterol lowering
Submission Date:	June 26, 2001
Sponsor:	AstraZeneca
Type of Submission:	Original
Primary NDA Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.

Summary

Using Δ LDL-C% as a clinical surrogate endpoint, exposure-response (E-R) analyses for both studies 008 and 033 indicated that plasma LDL-C gradually drops and essentially reaches plateau over the 6-week treatment time. After approximately 4 weeks of treatment time, percent change of low-density lipoprotein concentration (Δ LDL-C%) reaches 86-90% of its maximum effect of a given dose. This is observed within the entire dose levels studied (1 to 80 mg).

In both studies 008 and 033, the maximum LDL-C lowering effect approaches at 10-mg dose. An Inhibitory Effect Emax model describes the response-time relationship at a given dose, and response-dose relationship at a given time point very well. Concentration-response data does not offer advantage over dose-response data in this analysis.

Parametric analysis and χ^2 statistics (conducted using Nonlinear Mixed Effect Modeling approach) confirmed that there were significant treatment effect, dose effect, and time effect on % LDL-C lowering profiles for rosuvastatin and its comparator, atorvastatin. The model excellently predicts individual Δ LDL-C% over time. Based on the model, it is concluded that (1) rosuvastatin offers superior potency to atorvastatin. For example, 10-mg rosuvastatin produces approximately equal degree of LDL-C lowering effect as 40-mg atorvastatin. (2) at the same dose level (e.g. 10 mg), rosuvastatin will produce 20% more LDL lowering effect than atorvastatin (e.g. 49.95% drop in LDL-C for rosuvastatin versus 37.87% drop in LDL-C for atorvastatin), and (3) 4-6 weeks of treatment time are needed regardless of doses.

Data visualization and Loess local fit shows that rosuvastatin produces up to about 4-times LDL-C lowering effect compared to atorvastatin, in both studies 008 and 033. Statistical analyses (t-test and 90% CI analyses) on raw observation of study 033 provided further support to these observations.

Age, sex, body mass index, and baseline LDL-C appear not to affect these observations.

In conclusion, doses of 1 to 10-mg rosuvastatin will provide clinically significant LDL-C lowering effects.

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Recommendation

1. Based on the pharmacometrics analyses, the review team recommends a daily dose of 10-mg to be considered for approval. The resulted % ΔLDL-C with this dose range are as follows:

Rosuvastatin Dose mg/day	Mean %ΔLDL-C at Week 4	Mean %ΔLDL-C at Week 6	Study 008 Observed %ΔLDL-C at wk 6 (mean and SD)	Study 033 Observed %ΔLDL-C at wk 6 (mean and SD)	The approximate minimum % ΔLDL-C at wk 6 in about 85% of patients
0*	-1.38	-1.99	-0.598 7.18	-1.318 6.58	-
1	-36.67	-38.32	-35.23 8.81	-	-26
2.5	-39.16	-40.93	-41.57 9.27	-	-28
5	-42.55	-44.47	-44.63 7.16	-41.6 9.94	-32
10	-47.39	-49.53	-49.43 17.0	-49.95 10.67	-39
20*	-53.09	-55.9	-54.26 11.9	-52.21 9.86	-43
40*	-58.43	-61.08	-63.15 8.715	-58.11 12.05	-49
80*	-62.47	-65.29	-	-61.99 14.07	-53

* for comparison purpose only.

2. Dose adjustment based on baseline LDL-C, BMI, age, and sex for efficacy control is not suggested.
3. 2.5-mg tends to be the optimal starting dose considering potential toxicity and variabilities at lower and higher doses.
4. The sponsor is encouraged to determine rosuvastatin concentration and response measures (LDL-C, HDL etc.) at trough time points (i.e. time just before next dose) in future clinical trials, if any, for future analyses on exposure-response relationship for efficacy and/or toxicity assessment.

/s/

Dated _____

He Sun, Ph.D., Pharmacometrics, DPE2/OCPB

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Weighted Residual (P) vs Predicted (P)

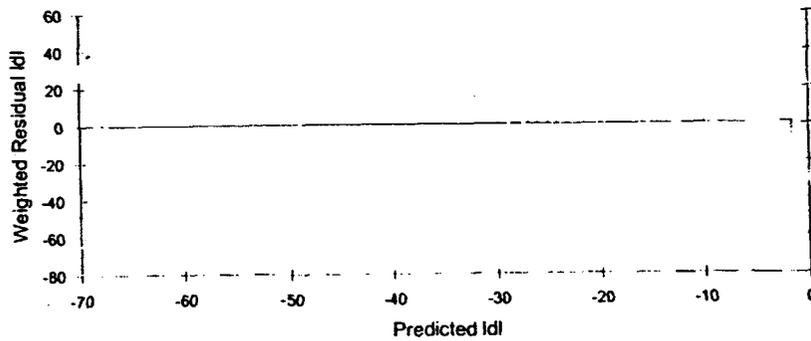
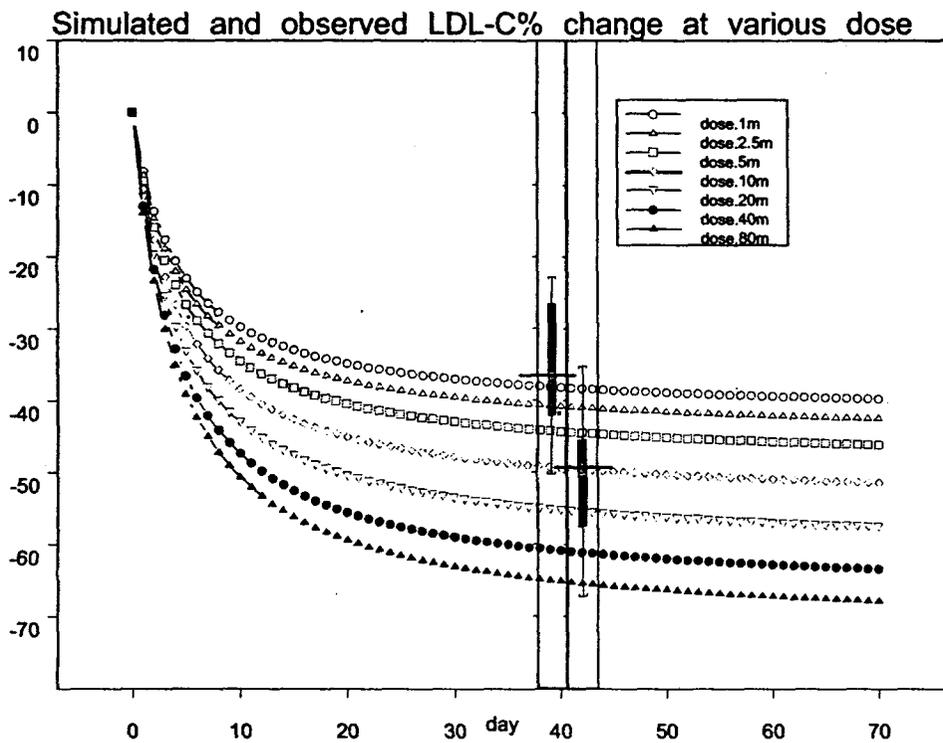


Table 4. Model predicted and actual observed mean Δ LDL-C% at various rosuvastatin doses.

Rosuvastatin dose	Δ LDL-C% at Week 4	Δ LDL-C% at Week 6	Minimum Δ LDL-C% in about 85% subj.	Observed Δ LDL-C% Study 008	Observed Δ LDL-C% Study 033
0	-1.99	-1.99		-1.38	-1.687
1	-36.6667	-38.32		-35.23 8.81	-
2.5	-39.1622	-40.93		-41.57 9.27	-
5	-42.545	-44.47		-44.63 7.16	-41.6 9.94
10	-47.3908	-49.53		-49.43 17.0	-49.95 10.67
20	-53.0919	-55.9		-54.26 11.9	-52.21 9.86
40	-58.4323	-61.08		-63.15 8.715	-58.11 12.05
80	-62.4674	-65.29		-	-61.99 14.07

Figure 6. Simulated LDL-C% change over time profile for 1 to 80 mg rosuvastatin doses. The two insert boxplots are observed LDL-C% change from study 008 for 1 and 10 mg doses.



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/s/

Sang Chung
4/12/02 02:37:24 PM
PHARMACOLOGIST

Hae-Young Ahn
4/15/02 10:21:38 AM
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**Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form**

General Information About the Submission

	Information		Information	
NDA Number	21-366	Brand Name	Crestor	
OCPB Division (I, II, III)	DPE-II	Generic Name	Rosuvastatin	
Medical Division	DMEDP	Drug Class	Lipid altering agents II	
OCPB Reviewer	Sang M. Chung, Ph.D.	Indication(s)	Treatment of Cholesterol	
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	Tablet	
		Dosing Regimen	q.d.	
Date of Submission	26-JUN-2001	Route of Administration	Oral	
Estimated Due Date of OCPB Review	23-DEC-2001	Sponsor	IPR Pharm., Inc.	
PDUFA Due Date	26-APR-2002	Priority Classification	S	
Division Due Date	23-MAR-2001			

Clin. Pharm. and Biopharm. Information

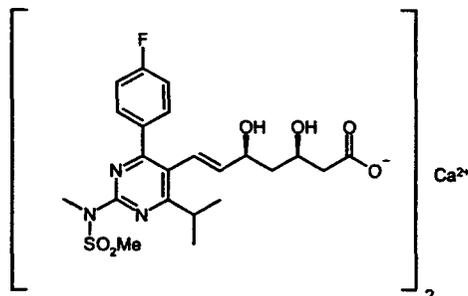
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	X			
Mass balance:	X	1		
Isozyme characterization:	X	3		In vitro (2) and animal (1)
Blood/plasma ratio:	X			
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-	X			
single dose:	X	6		
multiple dose:	X	3		
Patients-	X			
single dose:				
multiple dose:	X	3		
Dose proportionality -	X			
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	X			
In-vivo effects on primary drug:	X	11		
In-vivo effects of primary drug:	X	10		
In-vitro:	X	3		
Subpopulation studies -	X			
ethnicity:	X	6		Studies in Japanese*
gender:	X	1		
pediatrics:				
geriatrics:				
renal impairment:	X	1		
hepatic impairment:	X	1		

PD:				
Phase 2:				
Phase 3:				
PK/PD:	X			2 active control with atorvastatin
Phase 1 and/or 2, proof of concept:				Studies in Japanese
Phase 3 clinical trial:	X	4		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics	X			
Absolute bioavailability:	X	2		1 study in Japanese
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X			
traditional design; single / multi dose:	X	3		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		1 study in Japanese
Dissolution:	X			
(IVVC):				
Bio-wavier request based on BCS	X	2		Site change, Scale-up
BCS class				
III. Other CPB Studies	X	1		
Genotype/phenotype studies:				
Chronopharmacokinetics	X	1		
Pediatric development plan				
Literature References				
Total Number of Studies		44		
Fiability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • What is pharmacokinetic characteristics of rosuvastatin ? • What are the characteristics of the exposure-response relationships for efficacy and safety? • How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients? • What intrinsic and extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? 			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

*: Single/Multiple dose(s) (2), absolute BA (1), dose tolerance (1), D-R (2)

Submission in Brief

AstraZeneca Pharmaceuticals LP (US agent of IPR Pharmaceuticals, Inc.) has submitted NDA 21-366 (Crestor™) for the indication of lowering cholesterol. It is the NME of statin. Proposed strengths are from 10 to 80 mg as a tablet. It is proposed to administer orally once daily at any time of day.



Human pharmacokinetic characteristics are elucidated through 39 studies including 12 drug interaction, 9 special population, and 3 BE studies. Among 9 special population studies, 6 studies are from Japanese subpopulation. In addition, 4 *in vitro* studies are submitted to clarify further metabolism and absorption of the drug.

Pharmacokinetic characteristics in brief is as follows:

Absolute bioavailability, plasma protein binding of rosuvastatin are reported to be 20.1% (29% in Japanese) and 88% (blood cell binding 35%), respectively. CYP2C9 appears to be the major metabolic isozyme for the compound but metabolism seems to be minor elimination pathway. Also it is reported that the compound is neither an inducer of P450s in animals nor inhibitor of P450s in human hepatic microsomes. Therefore, it is expected no major drug-drug interaction. Accumulation will be minor with accumulation index of about 1 after multiple doses. Its extent appears to be unchanged but C_{max} and t_{max} altered after fed compared to those of fasting condition. Dose proportionality is claimed to be established between 1 and 80 mg. The special populations with mild to moderate renal or hepatic impaired patients show to be similar pharmacokinetic characteristics to those of healthy volunteers but systemic exposure appears to increase with severe renal or hepatic disease conditions.

CC: NDA 21-249, HFD-850(Lee), HFD-510(Koch), HFD-870(Chung, Ahn, Malinowski), CDR (B. Murphy)

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/s/

Sang Chung
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PHARMACOLOGIST

Hae-Young Ahn
8/29/01 01:01:44 PM
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