CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-366

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

IND/NDA number: NDA 21-366
Review Number: 2
Serial number/date/type of submission: SN000/February 12, 2003
Information to sponsor: Yes () No (X)
Sponsor and/or agent: AstraZeneca Pharmaceuticals, LP. 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355

Reviewer name: John Zhaolong Gong, Ph.D.
Division name: Division of Metabolic and Endocrine Drug Products
HFD #: 510
Review completion date: July 15, 2003

Drug:

Trade name: **CRESTOR**™ (rosuvastatin calcium) tablets
Generic name: rosuvastatin calcium
Code name: ZD4522, S4522
Chemical name: bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.
Molecular formula/molecular weight: $(C_{22}H_{27}FN_3O_6S)_2Ca$ /1001.14

Drug class: HMG CoA reductase inhibitor

Indication: primary hypercholesterolemia and mixed dyspipidemias

Route of administration: Oral

Proposed use: daily doses of 5, 10, 20, and 40 mg.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Studies reviewed within this submission:

Study Title: Rosuvastatin: Effect of Rosuvastatin on Protein Uptake and Cholesterol Biosynthesis in Kidney Proximal Tubule Cells

Key study findings: rosuvastatin and other statins were shown to inhibit HMG-CoA reductase in proximal tubular cells with the opossum kidney (OK) cell model. The IC_{50} values for decreases of protein uptake were generally 100 times higher than the IC_{50} values for the inhibition of HMG-CoA reductase for all four statins tested, indicating significant higher concentration is required to inhibit protein uptake. Compared to other statins, rosuvastatin was a less potent inhibitor of albumin uptake and cholesterol synthesis than fluvastatin and simvastatin, but had similar potent as pravastatin in cholesterol synthesis and more potent in albumin uptake than pravastatin.

Study No.: 022VN
Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: AstraZeneca UK Limited, Safety Assessment UK Alderley Park, Macclesfield, Cheshire SK10 4TG, England
Date of study initiation: July 2002
GLP Compliance: No
QA report: No
Drug: lot No. 62
Formulation/vehicle: 0.1% dimethylsulphoxide (DMSO)

Methods
The opossum kidney cell line (OK) was used as a model system to investigate the consequence of inhibition of HMG-CoA reductase on protein absorption. OK cell line retains characteristics of proximal tubular epithelial cells, particularly a high rate of uptake of albumin by endocytosis. OK cells have been used for studies of the mechanisms of protein endocytosis and also to study the regulation of this process. The uptake of fluorescent-labelled albumin was used to detect protein absorption by OK cells. ATP levels were concurrently assayed to assess cellular cytotoxicity. The incorporation of ^{14}C into cholesterol (cholesterol biosynthesis) was measured as an indication of HMG-CoA reductase activity.

Three types of experiments were carried out in this study.

Dose Response Experiment: Albumin uptake
Four experiments were carried out with either three or six replicate wells for each experiment. In experiment 1 the cells were treated with 0.001 μM to 10 μM simvastatin, 0.001 μM to 10 μM fluvastatin, and 0.1 μM to 1000 μM pravastatin. In experiment 2, the same dose ranges of simvastatin, fluvastatin and pravastatin were used as in experiment 1, with 0.01 μM to 100 μM ZD4522. In experiments 3 and 4, 0.001 μM to 100 μM simvastatin and ZD4522 were tested. A vehicle control (0.1 % v/v DMSO) was included in all experiments.

Dose Response Experiment: Cholesterol Biosynthesis
Three experiments were carried out with three replicate wells for each experiment. In experiments 1 and 2 the cells were treated with 0.001 μM to 10 μM simvastatin, 0.001 μM to 10 μM fluvastatin, 0.1 μM to 1000 μM pravastatin and 0.01 μM to 100 μM ZD4522. In experiment 3, 0.001 μM to 100

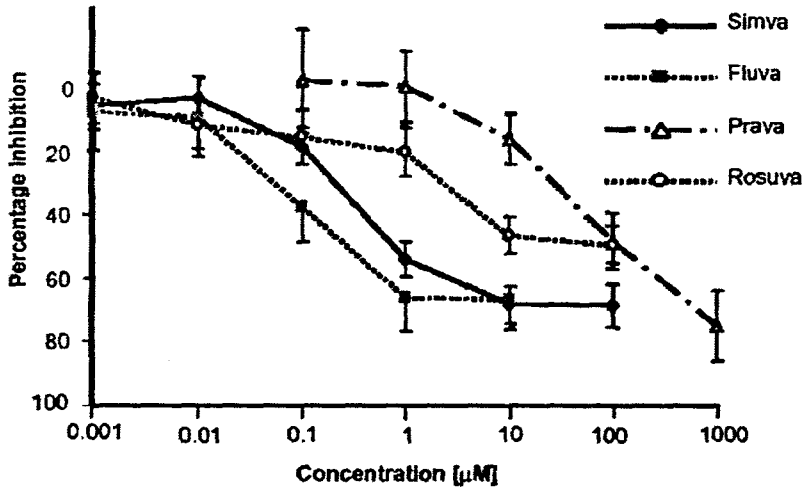
µM simvastatin and ZD4522 were tested. A vehicle control (0.1 % v/v DMSO) was included in all experiments.

Time Course Experiment
One experiment was carried out with three replicate wells for each time point. 10 µM Simvastatin and ZD4522 were tested. A vehicle control (0.1 % v/v DMSO) was included for all time points.

Mevalonate Experiment
Two experiments were carried out with 3 or 6 replicate wells. The cells were treated with 10 µM or 100 µM Simvastatin or ZD4522, with or without 100 µM Mevalonate. A vehicle control (0.1 % v/v DMSO) and 100 µM Mevalonate were included in each experiment.

Results:
Albumin Uptake and ATP cytotoxicity
Dose Response Experiment
After exposure of the cells for 22 to 24 hours, simvastatin, fluvastatin, rosuvastatin and pravastatin all produced concentration-dependant reductions of albumin uptake. Rosuvastatin and pravastatin were less effective inhibitors of albumin uptake than simvastatin and fluvastatin. The approximate concentrations which resulted in 50% inhibition of albumin uptake after 24 h were as follows: fluvastatin, 0.3 µM, simvastatin, 1 µM, rosuvastatin, 10 µM and pravastatin 100 µM. ATP levels, as marker for cytotoxicity, were not statistically significant decreased, indicating that at the concentrations used in the experiments, the statins did not cause cytotoxicity.

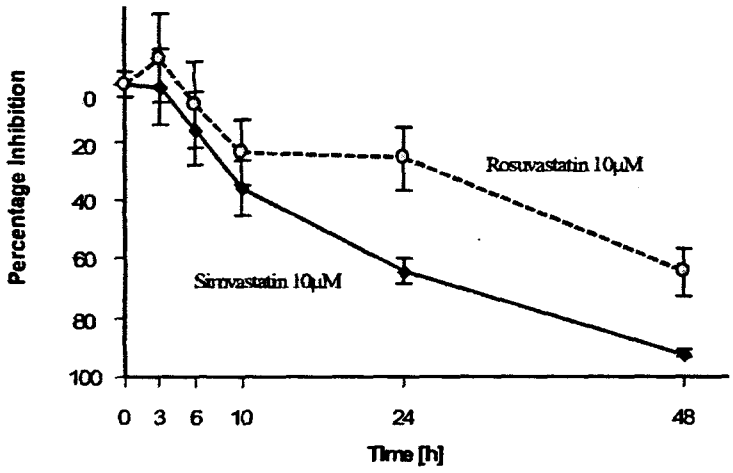
Study number 022VN. Effects of Statins on Albumin Uptake by OK Cells



Time Course Experiment

The onset of inhibition by both 10 µM simvastatin and 10 µM ZD4522 was gradual over time. The inhibition was not complete at 24 h and the degree of inhibition increased at least up to 48 h. Again no significant decrease in ATP levels was observed during the same experiment.

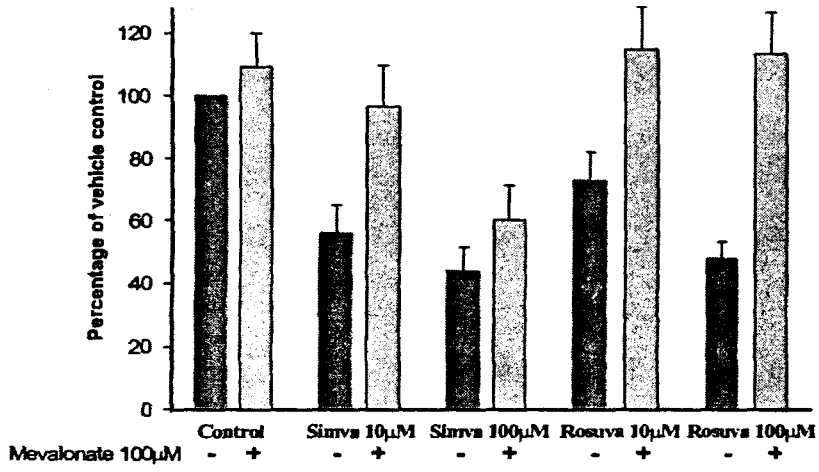
Study number 022VN. Time course of Effect of Statins on Albumin Uptake by OK Cells



Mevalonate Experiment

The inhibitory effect of 10 µM simvastatin and 10 to 100 µM ZD4522 on albumin uptake by OK cells for 24 hours was ameliorated by co-addition of 100 µM mevalonate. In contrast mevalonate did not ameliorate inhibition of albumin uptake by 100 µM simvastatin. No significant decrease in ATP levels was observed for any of the agent combinations tested.

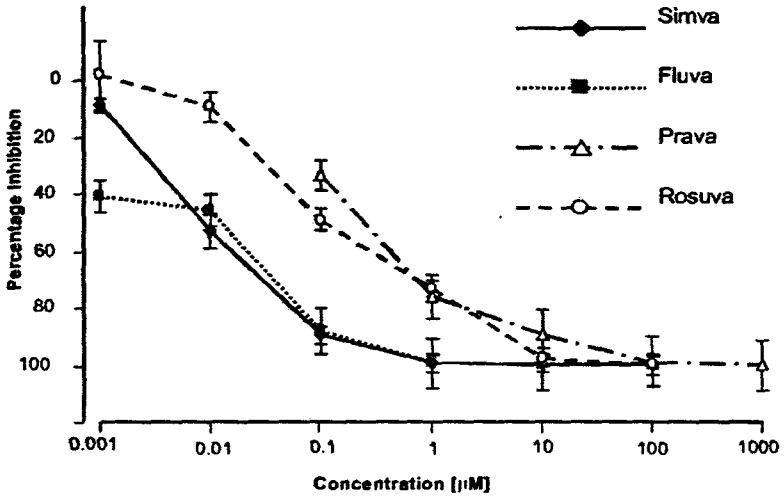
Study number 022VN. Amelioration of Statin Inhibition of Albumin Uptake by Mevalonate.



Cholesterol Biosynthesis

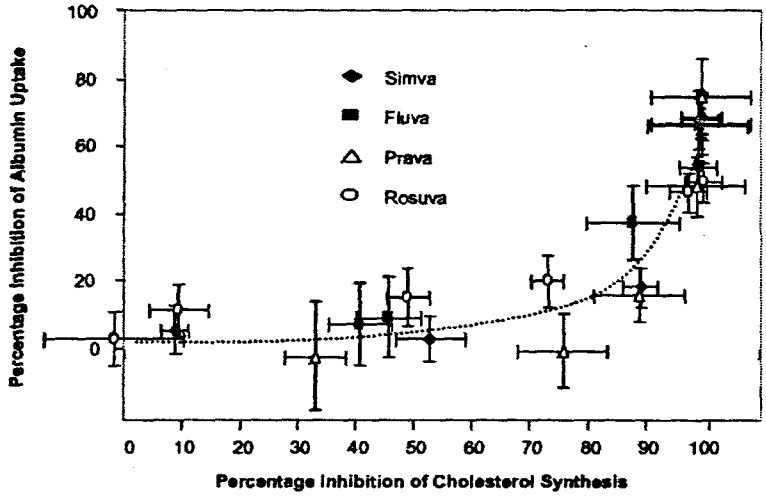
Simvastatin and fluvastatin were more potent inhibitors than rosuvastatin and pravastatin. The approximate concentrations of statins that caused 50% inhibition of cholesterol synthesis in the OK cells were as follows: simvastatin and fluvastatin, 10 nM, rosuvastatin, 100 nM and pravastatin 300 nM.

Study number 022VN. Effects of Statins on Cholesterol Synthesis in OK Cells.



When the inhibition of albumin was compared to the inhibition of cholesterol synthesis, it is apparent that the concentrations of statins that result in inhibition of albumin uptake of 20% or more are those which also cause a relatively high degree of inhibition of sterol synthesis, > 80%. The concentrations required to inhibit albumin uptake were generally 100 times higher than that inhibited cholesterol synthesis as indicated by IC_{50}. However, those statins that were more potent in inhibition of sterol synthesis were generally more potent in inhibiting albumin uptake.

Study number 022VN. Relationship between Inhibition of Albumin Uptake and the Inhibition of Cholesterol Synthesis.



Conclusion

The results show that the four statins inhibit albumin uptake by OK cells in a way that is related to the effects of the compound on cholesterol synthesis and, by implication, on HMG-CoA reductase. The statins did not cause overt cell damage as shown by the lack of effect on ATP levels. The observation that the effect on albumin uptake caused by the simvastatin and rosuvastatin could be overcome by the addition of the product of the enzyme, mevalonate, suggested a linkage to inhibition of HMG-CoA reductase. Those statins that were more potent in inhibition of sterol synthesis were also more potent in inhibiting albumin uptake.

Proteinuria - indicated by shifts in protein dipstick categories – was observed in the phase III studies of rosuvastatin, in some subjects who received 80 mg rosuvastatin. Assays of b2 microglobulin and N-acetyl-b-D-glucosaminidase (NAG) in the urine of some subjects treated with rosuvastatin and who had at least a 2 category shift in urine protein dipstick categories, suggested a tubular-type pattern of proteinuria. Compared to other statins, rosuvastatin caused significantly increases of proteinuria at the dose level of 80 mg/day.

Proportion of subjects who developed dipstick-positive proteinuria: Combined All Controlled and RTLD Pool

Treatment	N*	% (95% CI) with urine disptick protein shifts	
		"none or trace" to 1+ or greater	"none or trace" to 2+ or greater
Placebo	283	4.2 (2.21 to 7.29)	0.4 (0 to 1.95)
Rosuvastatin			
5 mg	586	3.8 (2.37 to 5.63)	0.2 (0 to 0.95)
10 mg	982	4.0 (2.84 to 5.39)	0.6 (0.22 to 1.33)
20 mg	858	4.4 (3.15 to 6.03)	0.7 (0.26 to 1.52)
40 mg	1833	6.8 (5.66 to 8.01)	1.4 (0.88 to 2.01)
80 mg	728	26.1 (22.94 to 29.45)	10.3 (8.19 to 12.74)
Pravastatin			
20 mg	163	3.1 (1.00 to 7.01)	0.6 (0.02 to 3.37)
40 mg	63	1.6 (0.04 to 8.53)	0 (0 to 5.69)
Atorvastatin			
10 mg	506	4.0 (2.43 to 6.04)	0.6 (0.12 to 1.72)
20 mg	306	4.2 (2.28 to 7.16)	0.3 (0.01 to 1.81)
40 mg	62	1.6 (0.04 to 8.66)	0 (0 to 5.78)
80 mg	322	2.8 (1.29 to 5.24)	0.3 (0.01 to 1.72)
Simvastatin			
20 mg	325	2.8 (1.27 to 5.19)	0.9 (0.19 to 2.67)
40 mg	178	5.1 (2.34 to 9.38)	0 (0 to 2.05)
80 mg	320	1.3 (0.34 to 3.17)	0 (0 to 1.15)

* Number of subjects with available urinalysis results.

Based on these *in vitro* results, the Sponsor suggested that the proteinuria observed in the clinic may be due to the inhibition of HMG-CoA reductase in proximal tubular cells. In general, the results of the *in vitro* studies with OK cells support the action consistent with other non-clinical studies. These studies are valuable to investigate the mechanism of potential toxicity seen in humans, but causal relationship can not be established solely based on these *in vitro* results, because of the general limitations with *in vitro* data, such as the difference between cell lines and living tissue, concentration in cell culture and exposure in humans.

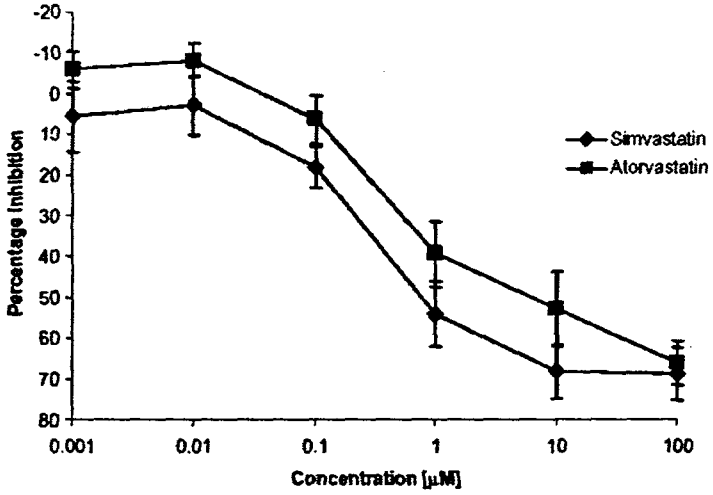
Study Title: Effect of Atorvastatin on Protein Uptake and Cholesterol Biosynthesis in Possum Kidney Cells

Study No.: 0014VU
Volume # and Page #: SN000, Electronic submission, May. 2003
GLP Compliance: No

Atorvastatin at concentrations of 0.001, 0.01, 0.1, 1, 10, and 100 μM were tested at the same conditions as the previous study with OK cell line. Simvastatin was used as a reference compound.

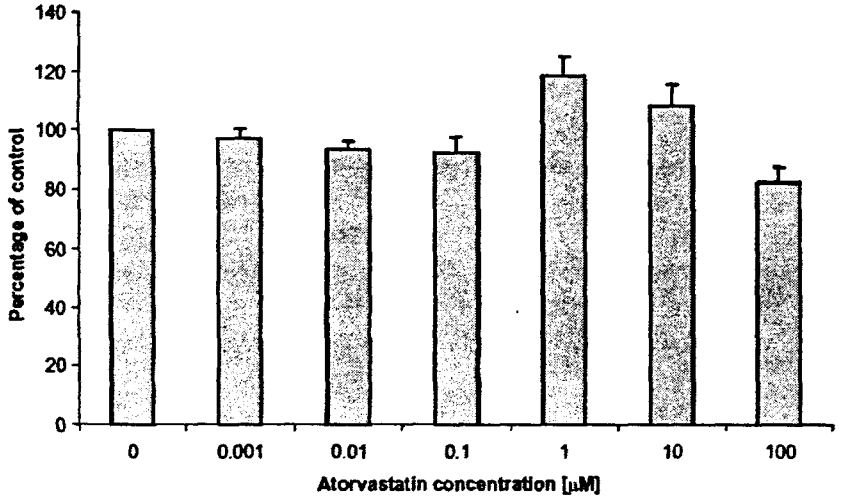
Dose Response Experiment
After exposure to the cells for 24 h, both atorvastatin and simvastatin exhibited concentration-dependant inhibition of albumin uptake. The approximate IC_{50} was 6 μM for atorvastatin or 0.3 μM for simvastatin.

Figure 1 Effect of atorvastatin and simvastatin on albumin uptake in OK cells



ATP levels were measured in cell extracts to check for cytotoxicity. At the highest concentration tested (100 µM), atorvastatin caused a moderate depletion in ATP levels.

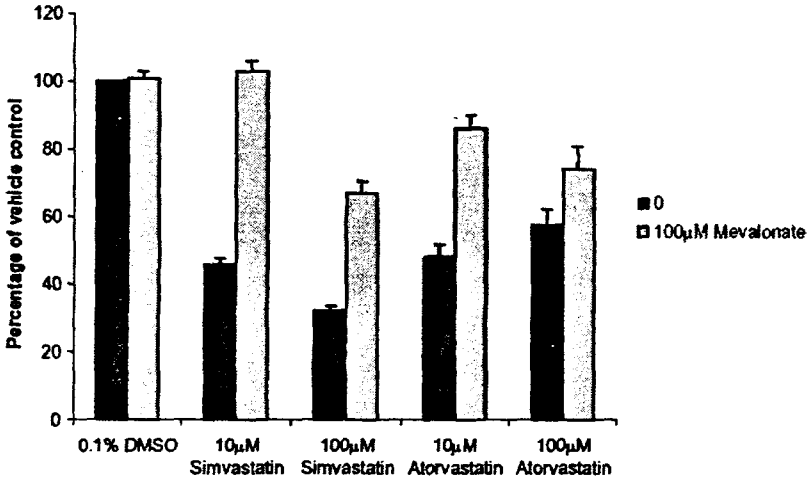
Figure 2 Effect of atorvastatin on ATP levels in OK cells during dose response experiment



Mevalonate Experiment

Atorvastatin and simvastatin were co-incubated with 100 µM mevalonate for 24 hours. Both 10 and 100 µM atorvastatin or simvastatin alone, significantly inhibited albumin uptake. In the presence of 100 µM mevalonate, albumin uptake the inhibitory effect of 10 µM simvastatin was completely prevented, and partially prevented with 10 µM or 100 µM atorvastatin, or 100 µM simvastatin.

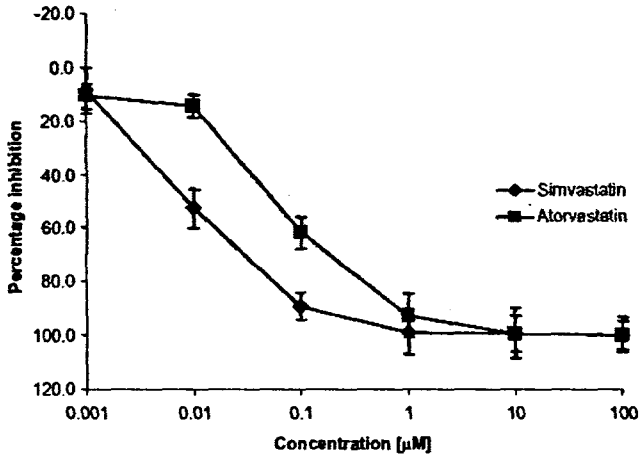
Figure 3 Effect of mevalonate on inhibition of albumin uptake by simvastatin and atorvastatin



Cholesterol Biosynthesis

After exposure to the cells for 24 h, both atorvastatin and simvastatin exhibited concentration-dependant inhibition of cholesterol biosynthesis. The approximate IC_{50} was 60 nM for atorvastatin or 10 nM for simvastatin, that is much lower that the IC_{50} for protein uptake inhibition.

Figure 4 Effect of atorvastatin and simvastatin on cholesterol biosynthesis in OK cells



Conclusion

After 24 hours exposure, atorvastatin inhibited albumin uptake and HMG-CoA reductase in OK cells in a dose-dependent manner. A high degree of inhibition of HMG-CoA reductase was required in order to observe an effect on albumin uptake. The inhibitory effect of atorvastatin on albumin uptake could be partially ameliorated by mevalonate.

These results suggested that atorvastatin can inhibit HMG-CoA reductase and renal protein uptake in OK cells in a similar manner as other statins. The potency of atorvastatin is similar to rosuvastatin.

Study Title: Effects of Statins on Albumin Uptake by Human Proximal Tubular Cells

Study No.: 0014VU
Volume # and Page #: SN000, Electronic submission, May. 2003
GLP Compliance: No

The Sponsor provided a summary of an in vitro study with human proximal tubular cells conducted

Tubular epithelial cells were isolated from normal human kidney tissue. Confluent cultures of proximal tubular (PT), distal tubular and collecting duct cells were incubated with simvastatin (0, 0.1, 1, 10, 50 µM), pravastatin (0, 1, 10, 100, 500 µM), or rosuvastatin (1, 10, 100 and 500 µM) for 6 or 16 h. Mevalonate was used to investigate the mechanism of these effects.

The results revealed that albumin uptake took place selectively in PT cells. A significant (*$p<0.05$) inhibition of albumin uptake was noted for the 3 statins and each had a similar degree of effect on the uptake. In the presence of simvastatin (0.1, 1, 10, 50 μM) the albumin uptake was reduced to respectively 74*±32, 70*±28, 64*±28 and 57*±24 % (mean±SD) of control values. For pravastatin (1, 10, 100 and 500 μM), albumin uptake was reduced to 74*±28, 73*±30, 56*±25 and 46*±27 % of control values, and for rosuvastatin (1, 10, 100 and 500 μM), the reductions were to 78±27 60±30 70±52 and 55*±23 % of the control values. Mevalonate (100μM) completely prevented the effect of the statins.

The results in this study are generally consistent with the results observed with other statins in the previous study with OK cells.

Study Title: Rosuvastatin: Effect Of Rosuvastatin on Cholesterol Synthesis in Human Skeletal Muscle Cells

Key study findings: rosuvastatin and other statins inhibited cholesterol synthesis in a dose-dependent fashion, in the absence of cytotoxicity. With the exception of pravastatin, rosuvastatin was a significantly less potent inhibitor of cholesterol synthesis in human skeletal cells than cerivastatin, fluvastatin, simvastatin and atorvastatin.

Study No.: TVN363
Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: AstraZeneca UK Limited, Safety Assessment UK Alderley Park, Macclesfield, Cheshire SK10 4TG, England
Date of study initiation: May 2002
GLP Compliance: No
QA report: No
Drug: lot No. 62
Formulation/vehicle: 0.1% dimethylsulphoxide (DMSO)

Methods
The human skeletal muscle cells were used as a model system to investigate the inhibition of cholesterol synthesis. ATP levels were concurrently assayed to assess cellular cytotoxicity. HMG-CoA reductase activity and cholesterol synthesis were assessed by measuring the incorporation of ^{14}C into cholesterol.

Results:
ATP cytotoxicity
No decrease in ATP level was observed under any of the conditions used in these experiments. These data indicate that at the maximal concentrations used in the cholesterol synthesis experiments, the statins did not cause cytotoxicity.

Study number TVN363. Effects of statins on cytotoxicity in human skeletal muscle cells during the dose response experiment after 3½ hours exposure

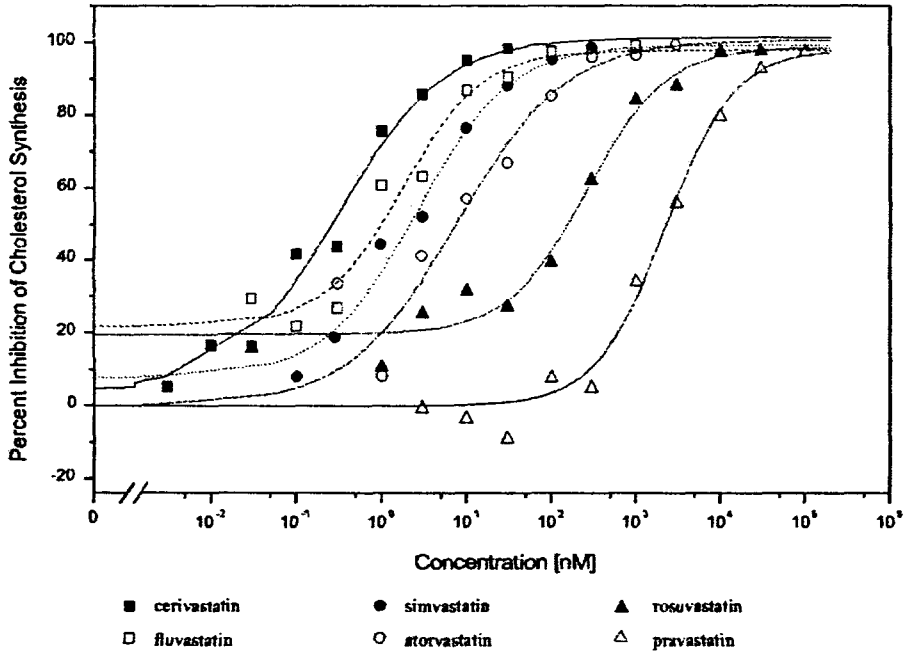
Compound	Concentration (μM)	ATP level† (+/- SD)
Control (0.1% v/v DMSO)	-	100.00 (+/- 6.84)
Rosuvastatin (calcium salt)	10	101.40 (+/- 5.93)
Atorvastatin (calcium salt)	3	102.72 (+/- 3.07)
Cerivastatin (sodium salt)	0.1	95.52 (+/- 7.55)
Fluvastatin (sodium salt)	1	99.68 (+/- 10.14)
Pravastatin (sodium salt)	100	96.87 (+/- 6.75)
Simvastatin (sodium salt)	1	101.82 (+/- 9.56)

† % of control, mean of 3 experiments

Cholesterol synthesis

The dose response of inhibition of cholesterol synthesis showed that cerivastatin, fluvastatin, simvastatin and atorvastatin were all more potent than rosuvastatin at inhibiting cholesterol synthesis, whereas pravastatin was significantly less potent. Statistically significantly lower IC_{50} values for inhibition of cholesterol synthesis were obtained for cerivastatin, fluvastatin, simvastatin and atorvastatin compared to rosuvastatin, whereas the value for pravastatin was significantly higher.

Study number TVN363. Effect of statin on cholesterol biosynthesis in human skeletal muscle cells



Study number TVN363. Human myocytes cholesterol synthesis: IC_{50} values for rosuvastatin and reference compounds after 3½ hours exposure

Compound	IC_{50} (nM)† (95% Confidence Limits)
Rosuvastatin (calcium salt)	91 (18 – 455)
Atorvastatin (calcium salt)	3.9 (0.8 – 19.6)*
Cerivastatin (sodium salt)	0.15 (0.03 – 0.76)***
Fluvastatin (sodium salt)	0.6 (0.1 – 2.8)***
Pravastatin (sodium salt)	1658 (333 – 8266)*
Simvastatin (sodium salt)	1.5 (0.3 – 7.5)**

† Mean of 3 experiments
Significance of difference from rosuvastatin, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

Conclusion

All four statins tested inhibited cholesterol synthesis in a dose-dependent fashion, in the absence of cytotoxicity. With the exception of pravastatin, rosuvastatin was a significantly less potent inhibitor of cholesterol synthesis after 3½ hour exposure in human skeletal myoblasts than cerivastatin, fluvastatin, simvastatin and atorvastatin. Compared to the current widely used atorvastatin, the IC_{50} value for rosuvastatin was 23 times higher than that for atorvastatin, suggesting rosuvastatin is a much weaker inhibitor for cholesterol synthesis in human skeletal muscle cells, and therefore it would be expected to induce less incidence of myopathy in the clinic than atorvastatin. However, in clinical studies, rosuvastatin induced higher incidence of myopathy as indicated by increased CK than atorvastatin. Therefore, the inhibition of HMG-CoA reductase inhibition could not fully explain the marked increase of myopathy in rosuvastatin treated patients, especially at dose level of 80 mg/day.

CK elevations in subjects in the Combined All Controlled and Controlled RTLD Pool

	Treatment				
	Rosuva (N=5657)	Atorva (N=2899)	Simva (N=1439)	Prava (N=1260)	Placebo (N=380)
>5 x ULN, %	0.7	0.5	0.3	0.3	0
>10 x ULN, %	0.4	0.1	0.2	0	0

Frequency of CK elevations >10 x ULN by dose: Combined All Controlled/Uncontrolled and RTLD Pool, including cases recorded at a local laboratory

Rosuvastatin dose[a]	Number of patients	>10 x ULN (%)
N (%) >10 x ULN	12,457[b,c]	0.6
5 mg	1317	0.4[d]
10 mg	7727	0.2[d]
20 mg	3883	0.3[d]
40 mg	3957	0.4[d]
Not down-titrated from 80 mg	3700	0.3
Down-titrated from 80 mg	825	0.2
80 mg	1574	1.9[b]

[a] Rosuvastatin dose at onset and number of subjects exposed to that dose (subjects are counted in each dose group to which they were exposed: therefore, subjects may be counted in more than 1 dose group).
[b] Total number of subjects who received rosuvastatin and who had at least one postbaseline value.
[c] Number of patients Includes 8 subjects with CK elevations > 10 x ULN recorded at a local laboratory.
[d] Rosuvastatin dose at onset and number of subjects with follow-up laboratory assessments at that dose (subjects are counted in each dose group to which they were exposed: therefore, subjects may be counted in more than 1 dose group).

Study title: ZD4522 containing —— impurity: Bacterial Mutation Assay in *S. typhimurium* and *E. coli.*

Key findings: ZD4522 containing —— impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate. It was concluded that, under the conditions of the assay, ZD4522 containing —— impurity gave a negative, i.e. non-mutagenic response.

Study no.: YV4572 (Sponsor Study Reference TMV 899)

Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: ——

Date of study initiation: 22 February 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Zeneca ZD4522 containing —— impurity, —— (subjected to additional degradation), Purity: 94.7 (% w/w)

Methods:
Strains/species/cell line: four *Salmonella typhimurium* tester strains (TA1535, TA1537, TA98 and TA100) and the two *Escherichia coli* strains (WP2P [WP2 (pKM101)] and WP2P *uvrA* [WP2 *uvrA* (pKM101)]

Doses used in definitive study: 100 to 5000 µg/plate

Basis of dose selection: maximum recommended for Ames test

Negative controls: Solvent Control: DMSO

Positive controls:

S9	Strains	Positive control	Solvent
-	TA100	NaN3	DMSO
	TA1535		
	TA1537	ICR 191	
	TA98	DR	
	WP2uvrA	ENNG	
	WP2P	MMC	
+	TA1535	2AA	
	TA1537		
	TA98		
	TA100		
	WP2P		
	WP2 uvrA	BP	

Acridine Mutagen ICR191, 2-Aminoanthracene (2AA), Benzo(a)pyrene (BP), Daunomycin HCl (DR), N-Ethyl-N'-nitro-Nnitrosoguanidine (ENNG), Mitomycin C (MMC), Sodium Azide (NaZ)

Incubation and sampling times: The incubation period for each experiment was 3 days (at 37°C).

Results
Study validity: negative control and positive control produced expected results.

Study outcome: ZD4522 containing [redacted] impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate.

Study title: ZD4522 containing [redacted] impurity: Bacterial Mutation Assay in *S. typhimurium* and *E. coli.*

Key findings: ZD4522 containing [redacted] impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate. It was concluded that, under the conditions of the assay, ZD4522 containing [redacted] impurity gave a negative, i.e. non-mutagenic response.

Study no.: YV4509 (Sponsor Study Reference TMV 900)

Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: [redacted]

Date of study initiation: 22 February 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Zeneca ZD4522 containing [redacted] impurity, batch reference 70799C00, Purity: 96.0 (% w/w)

Methods:
Strains/species/cell line: four *Salmonella typhimurium* tester strains (TA1535, TA1537, TA98 and TA100) and the two *Escherichia coli* strains (WP2P [WP2 (pKM101)] and WP2P *uvrA* [WP2 *uvrA* (pKM101)]

Doses used in definitive study: 100 to 5000 µg/plate

Basis of dose selection: maximum recommended for Ames test

Negative controls: Solvent Control: DMSO

Positive controls:

S9	Strains	Positive control	Solvent
-	TA100	NaN3	DMSO
	TA1535		
	TA1537	ICR 191	
	TA98	DR	
	WP2uvrA	ENNG	
	WP2P	MMC	
+	TA1535	2AA	
	TA1537		
	TA98		
	TA100		
	WP2P		
	WP2 uvrA	BP	

Acridine Mutagen ICR191, 2-Aminoanthracene (2AA), Benzo(a)pyrene (BP), Daunomycin HCl (DR), N-Ethyl-N'-nitro-Nnitrosoguanidine (ENNG), Mitomycin C (MMC), Sodium Azide (NaZ)

Incubation and sampling times: The incubation period for each experiment was 3 days (at 37°C).

Results

Study validity: negative control and positive control produced expected results.

Study outcome: ZD4522 containing —— impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate.

Study title: ZD4522 containing —— impurity: Bacterial Mutation Assay in *S. typhimurium* and *E. coli.*

Key findings: ZD4522 containing —— impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate. It was concluded that, under the conditions of the assay, ZD4522 containing —— impurity gave a negative, i.e. non-mutagenic response.

Study no.: YV6049 (Sponsor Study Reference TMV 999)

Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: ——

Date of study initiation: 22 February 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Zeneca ZD4522 containing —— impurity, batch reference C240/1, Purity: 95.1 (% w/w)

Methods:

Strains/species/cell line: four *Salmonella typhimurium* tester strains (TA1535, TA1537, TA98 and TA100) and the two *Escherichia coli* strains (WP2P [WP2 (pKM101)] and WP2P *uvrA* [WP2 *uvrA* (pKM101)]

Doses used in definitive study: 100 to 5000 µg/plate

Basis of dose selection: maximum recommended for Ames test

Negative controls: Solvent Control: DMSO

Positive controls:

S9	Strains	Positive control	Solvent
-	TA100	NaN3	DMSO
	TA1535		
	TA1537	ICR 191	
	TA98	DR	
	WP2uvrA	ENNG	
	WP2P	MMC	
+	TA1535	2AA	
	TA1537		
	TA98		
	TA100		
	WP2P		
	WP2 uvrA	BP	

Acridine Mutagen ICR191, 2-Aminoanthracene (2AA), Benzo(a)pyrene (BP), Daunomycin HCl (DR), N-Ethyl-N'-nitro-Nnitrosoguanidine (ENNG), Mitomycin C (MMC), Sodium Azide (NaZ)

Incubation and sampling times: The incubation period for each experiment was 3 days (at 37°C).

Results

Study validity: negative control and positive control produced expected results.

Study outcome: ZD4522 containing — impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate.

Study title: ZD4522 containing — impurity: Bacterial Mutation Assay in *S. typhimurium* and *E. coli.*

Key findings: ZD4522 containing — impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate. It was concluded that, under the conditions of the assay, ZD4522 containing —— impurity gave a negative, i.e. non-mutagenic response.

Study no.: YV7076 (Sponsor Study Reference TMV 1011)

Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: [redacted]

Date of study initiation: 22 February 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Zeneca ZD4522 containing [redacted] impurity, batch reference AMD82919D01, Purity: 93.5 (% w/w)

Methods:
Strains/species/cell line: four *Salmonella typhimurium* tester strains (TA1535, TA1537, TA98 and TA100) and the two *Escherichia coli* strains (WP2P [WP2 (pKM101)] and WP2P *uvrA* [WP2 *uvrA* (pKM101)]

Doses used in definitive study: 100 to 5000 µg/plate

Basis of dose selection: maximum recommended for Ames test

Negative controls: Solvent Control: DMSO

Positive controls:

S9	Strains	Positive control	Solvent
-	TA100	NaN3	DMSO
	TA1535		
	TA1537	ICR 191	
	TA98	DR	
	WP2uvrA	ENNG	
	WP2P	MMC	
+	TA1535	2AA	
	TA1537		
	TA98		
	TA100		
	WP2P		
	WP2 uvrA	BP	

Acridine Mutagen ICR191, 2-Aminoanthracene (2AA), Benzo(a)pyrene (BP), Daunomycin HCl (DR), N-Ethyl-N'-nitro-Nnitrosoguanidine (ENNG), Mitomycin C (MMC), Sodium Azide (NaZ)

Incubation and sampling times: The incubation period for each experiment was 3 days (at 37°C).

Results
Study validity: negative control and positive control produced expected results.

Study outcome: ZD4522 containing [redacted] impurity did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix, at concentrations up to 5000 µg/plate.

Study title: ZD4522 + [redacted] Impurity: in vitro cytogenetic assay for human lymphocytes

Key findings: ZD4522 containing [redacted] impurity did not induce chromosome aberration in human lymphocytes.

Study type: In vitro cytogenesis
Study no: SV1093 (Sponsor reference number TYX/122)
Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: [redacted]

Date of study initiation: June 5, 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Zeneca ZD4522 containing [redacted] impurity, batch reference C2401/1 and ADM 81865H01, Purity: 95.1(% w/w)
Formulation/vehicle: DMSO

Methods:

Strains/species/cell line: human lymphocytes
Dose selection criteria:
Basis of dose selection: 40% to 60% suppression of cell growth.
Range finding studies: up to 2000 µg/ml was used. Precipitation was noted at 1500 µg/ml.

Metabolizing system: liver metabolizing enzyme S9 from livers of phenobarbital and β-naphthoflavone-treated rats.

Controls:
Vehicle: DMSO
Negative controls: DMSO
Positive controls: mitomycin C and cyclophosphamide.

Exposure conditions:
Incubation and sampling times: 37°C, 3 or 24 hours.

Doses used in definitive study: Experiment 1: 50, 250, and 500 µg/ml with or without S9 for 3 hour treatment, Experiment 2: 50, 250, and 500 µg/ml with S9 for 3 hour treatment, 3.6, 90, and 450 µg/ml without S9 for 20 hour treatment.

Study design:

No. of replicates: 2

Counting method: 100 metaphase spreads were scored per treatment.

Analysis:

Criteria for positive results: a test is considered as positive if there are statistically significant increases over concurrent negative control in the percentages of cells with chromosomal aberrations and there is a dose-dependency.

Summary of individual study findings:

Study validity: negative control and positive control produced expected results. The test doses appeared to be appropriate, with higher doses produced > 50% reduction in mitotic index.

Study outcome: no significant increase in chromosome aberration frequency was noted. The result was judged as negative.

Study title: ZD4522 —— in vitro cytogenetic assay for human lymphocytes

Key findings: ZD4522 —— did not induce chromosome aberration in human lymphocytes.

Study type: In vitro cytogenesis
Study no: SV1098 (Sponsor reference number TYX/125)
Volume #, and Page #: SN000, Electronic submission, Feb. 2003
Conducting laboratory and location: (——
——
Date of study initiation: September 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Zeneca ZD4522 containing (—— batch reference ADM 82919D01, Purity: 93.5(% w/w)
Formulation/vehicle: DMSO

Methods:

Strains/species/cell line: human lymphocytes

Dose selection criteria:

Basis of dose selection: 40% to 60% suppression of cell growth.

Range finding studies: up to 4910 µg/ml was used. Precipitation was noted at 1500 µg/ml.

Metabolizing system: liver metabolizing enzyme S9 from livers of phenobarbital and β-naphthoflavone-treated rats.

Controls:

Vehicle: DMSO

Negative controls: DMSO

Positive controls: mitomycin C and cyclophosphamide.

Exposure conditions:

Incubation and sampling times: 37°C, 3 or 24 hours.

Doses used in definitive study: Experiment 1: 50, 250 and 500 µg/ml with S9 and 10, 100, and 250 µg/ml without S9 for 3 hour treatment, Experiment 2: 10, 100, and 250 µg/ml with S9 for 3 hour treatment, 5, 100, and 250 µg/ml without S9 for 20 hour treatment.

Study design:

No. of replicates: 2

Counting method: 100 metaphase spreads were scored per treatment.

Analysis:

Criteria for positive results: a test is considered as positive if there are statistically significant increases over concurrent negative control in the percentages of cells with chromosomal aberrations and there is a dose-dependency.

Summary of individual study findings:

Study validity: negative control and positive control produced expected results. The test doses appeared to be appropriate, with higher doses produced > 50% reduction in mitotic index.

Study outcome: no significant increase in chromosome aberration frequency was noted. The result was judged as negative.

OVERALL SUMMARY AND EVALUATION

Summary of New Preclinical Studies

The three *in vitro* studies in the opossum kidney (OK) cell line and human renal tubular cells investigated the relationship of HMG-CoA reductase inhibition and renal tubular protein re-absorption. The result indicated that five statins, including rosuvastatin, inhibited albumin uptake in a dose-dependent fashion in a way that was related to degree of inhibition of HMG-CoA reductase in the cells. However, the IC_{50} values for decreases of protein uptake were generally 100 times higher than the IC_{50} values for the inhibition of HMG-CoA reductase for all five statins tested; indicating significant higher concentration was required to inhibit protein re-absorption. Rosuvastatin was a less potent inhibitor of albumin uptake and cholesterol synthesis than fluvastatin, simvastatin and atorvastatin.

In an *in vitro* study with human skeletal cells, rosuvastatin and other statins were shown to inhibit cholesterol synthesis in a dose-dependent fashion in the absence of cytotoxicity. Rosuvastatin was a significantly less potent inhibitor *in vitro* than cerivastatin, fluvastatin, simvastatin and atorvastatin.

The effect of rosuvastatin on HMG-CoA reductase inhibition has been studied *in vitro* in rat and human hepatic microsomes, rat hepatocytes, rat and human fibroblasts, human umbilical vein endothelial cells (HUVECs), and human skeletal muscle cells (HSMC). Generally, when compared to atorvastatin, rosuvastatin appeared to be more selective on hepatocytes and less effective on other non-liver tissues. The selectivity for effect in hepatocytes compared to muscle cells was approximately 500-fold for rosuvastatin. The Sponsor suggested that this selectivity be due to the hydrophilic property of rosuvastatin. In comparison, lipophilic statins such as cerivastatin and simvastatin were non-selective.

Inhibition of cholesterol synthesis[a] by rosuvastatin and other statins in rat fibroblasts, human fibroblasts and human umbilical vein endothelial cells

	IC_{50} (nM)[b] with 95% confidence limits[c]		
Compound	**rat fibroblasts**	**human fibroblasts**	**HUVECs**
rosuvastatin	331 (153 - 726)	361	41.1 (22.3 - 75.9)
simvastatin (sodium salt)	7.07 (3.55 - 14.1)***	NT[d]	1.03 (0.56 - 1.89)***
pravastatin (sodium salt)	21500 (6500 - 39300)*	21600	1920 (1040 - 3540)***
atorvastatin (calcium salt)	193 (79.4 - 480)***	61	5.49 (2.97 - 10.1)***
cerivastatin (sodium salt)	2.54 (1.27 - 5.06)***	NT	0.36 (0.17 - 0.75)***
fluvastatin (sodium salt)	3.43 (1.72 - 6.84)***	NT	0.6 (0.28 - 1.26)***

a cell monolayers in serum-free medium were pre-incubated with statins for 30 min before addition of [2-^{14}C] acetate for 3 h and assay of cholesterol synthesis
b mean results of 3 or 4 experiments except human fibroblasts where n = 1
c statistical calculations were by analysis of variance
d not tested
significance of differences from rosuvastatin, * $p<0.05$, *** $p<0.001$
(Study: PS13; PS14)

Inhibition of cholesterol synthesis by rosuvastatin and other statins in primary rat hepatocytes[a]

Compound	IC_{50} (nM) Mean[b] and (95% confidence limits)[c]
rosuvastatin	0.16 (0.09 - 0.29)
atorvastatin (calcium salt)	1.15 (0.59 - 2.26)***
simvastatin (sodium salt)	2.74 (1.34 - 5.63)***
cerivastatin (sodium salt)	3.54 (1.37 - 9.16)***
fluvastatin (sodium salt)	3.78 (1.62 - 8.87)***
pravastatin (sodium salt)	6.93 (3.38 - 14.24)***

a monolayers of hepatocytes in serum-free medium were pre-incubated with statins for 30 min before addition of [2-^{14}C] acetate for 3 h and assay of cholesterol synthesis
b mean results of at least 4 experiments
c statistical calculations were by analysis of variance
*** significance of difference from rosuvastatin, $p<0.001$
(Study: PS12)

Inhibition of cholesterol synthesis by rosuvastatin and other statins in human non-hepatic cells

	IC_{50} (nM) mean ± SE of 3 determinations		
Compound	HUVECs	Myoblasts	HSMCs
rosuvastatin	39 ± 17	81 ± 49	28 ± 4
simvastatin (sodium salt)	0.5 ± 0.2	1.9 ± 0.8	4.0 ± 2.9
pravastatin (sodium salt)	3803 ± 1256	2786 ± 319	6971 ± 2682
atorvastatin (calcium salt)	8.9 ± 4.7	7.0[†]	4.5 ± 1.7

[†], The mean result of two divergent estimates, 0.09 and 14 nM. However, the mean result is close to previous results from the same lab in which IC_{50} = 11 ± 0.8 nM.
(Study: PS15)

APPEARS THIS WAY
ON ORIGINAL

Conclusions

The new submitted studies provided some useful information regarding the mechanisms of proteinuria and myopathy observed clinically. Stains, including rosuvastatin, were shown to induce dose-dependent inhibition of albumin uptake and cholesterol synthesis in proximal renal tubular cell line and human renal tubular cells, and inhibition of cholesterol synthesis in human skeletal muscle cells. Comparing with atorvastatin, rosuvastatin appeared to be more selective to liver and has less effect on non-liver tissues in terms of HMG-CoA reductase inhibition presumably due to its high hydrophilic property. Therefore, it would be expected to cause less renal and skeletal muscle adverse effects with clinic use. However, higher incidences of renal and skeletal muscle adverse effects have been observed with rosuvastatin at doses of 80 mg/day. Therefore, these *in vitro* results of cholesterol synthesis inhibition in tubular cell line and human skeletal muscle cells did not appear to predict clinical outcome.

In conclusion, the results of the *in vitro* studies with OK cells, human renal tubular cells and human skeletal muscle cells support the action consistent with other non-clinical studies. However, these results from these *in vitro* studies should not be over-interpreted. These studies are valuable to investigate the mechanism of potential toxicity seen in humans, but causal relationship can not be established solely based on these *in vitro* results, because of the general limitations with *in vitro* data, such as the difference between cell lines and living tissue, concentration in cell culture and exposure in humans.

Reviewer signature: /S/

John Zhaolong Gong, Ph.D. Date
Pharmacology/Toxicology Reviewer

Team leader signature [Concurrence/Non-concurrence]

/S/

Karen Davis-Bruno, Ph.D. Date
Pharmacology Team Leader

cc: IND Arch
HFD510
HFD510/Jimenez/Gong/Davis-Bruno
Review code: ND
Filename: n21366.rw2.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Gong
7/16/03 10:11:47 AM
PHARMACOLOGIST

Karen Davis-Bruno
7/16/03 01:25:08 PM
PHARMACOLOGIST
concurrence with recommendation

Memo

To: NDA 21-366
Drug: Crestor (rosuvastatin calcium)
Sponsor: AstraZeneca Pharmaceuticals
Date: May 28, 2002
From: Karen Davis-Bruno; Ph.D.; Supervisory Pharmacologist/HFD-510

The nonclinical studies in support of NDA 21-366 are adequate in establishing target organ toxicity and a NOAEL level in multiple species. The Pharmacology/Toxicology review concludes that nonclinical studies are adequate to support clinical doses of ≤ 20 mg based on establishment of exposure multiples (>5X). Rhabdomyolysis and acute renal failure have been observed in clinical trials at 40 mg and 80 mg. The concern for clinically meaningful adverse events with similar exposure, forms the basis for the reviewer's recommendation. As a consequence of the variability in AUC, the exposure multiples of the animal NOAEL compared to the human dose of 20 mg or 40 mg are similar. This similarity in exposure combined with the large variability in measurement suggests the absence of a meaningful biological difference between these doses. There is still concern for clinically relevant adverse events particularly since there is limited clinical safety data on 20 mg or 40 mg dose in humans. Additional nonclinical studies would not address this concern although further clinical safety information may.

ECAC reviewed the final mouse and rat two-year bioassays on January 29, 2001. They concluded that treatment of rats with rosuvastatin at ≥ 60 mg/kg/day was associated with an increased incidence of uterine stromal polyps, including a single stromal sarcoma in a female given 80 mg/kg/day. Based on the similar target tissue derivation, these findings were considered biologically relevant by the committee.

Three 13-Week range finding studies were performed in rat and reviewed by ECAC to support dose selection for the two year bioassay. Pancreatic acinar cell degeneration was observed. In the two-year bioassay, pancreatic acinar hypertrophy and lobular atrophy are observed at incidences, which exceed controls in males suggesting that the pancreas was a target organ. Other statins have demonstrated pancreatic tumors in carcinogenicity studies. ECAC did not consider the incidence of combined pancreatic islet cell tumors (adenoma + carcinoma) in females given rosuvastatin at ≥60 mg/kg/day biologically relevant since the finding was within the historical control reference range and was statistically significant by a trend test, but not a pairwise comparison.

Reference to the 400 mg/kg/day dose in the mouse two-year bioassay should be removed from the label since this group was terminated after only short-term exposure.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Davis-Bruno
5/30/02 12:58:38 PM
PHARMACOLOGIST

Bill, Please add to action package

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: **NDA 21,366**
Review number: 1
Sequence number/date/type of submission: SN000/June 26, 2001
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: AstraZeneca Pharmaceuticals, LP. 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355
Manufacturer for drug substance: AstraZeneca Avlon Works, UK

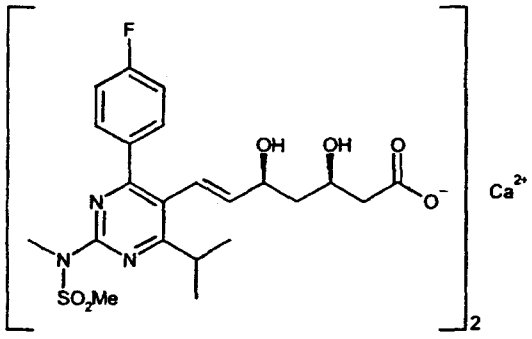
Reviewer name: John Zhaolong Gong, Ph.D.
Division name: Division of Metabolic and Endocrine Drug Products
HFD #: 510
Review completion date: March 8, 2002

Drug:

Trade name: **CRESTOR™** (rosuvastatin calcium) tablets
Generic name: rosuvastatin calcium
Code name: ZD4522, S4522

Chemical name: bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

CAS registry number: 147098-20-2
Mole file number:
Molecular formula/molecular weight: $(C_{22}H_{27}FN_3O_6S)_2Ca$ /1001.14
Structure:



Relevant INDs/NDAs/DMFs: Lovastatin (NDA 19,643), Simvastatin (NDA 19,766), Pravastatin (NDA 19,898), Fluvastatin (NDA 20,261), Atorvastatin (NDA 20,702), Cerivastatin (NDA 20, 740)

Drug class: HMG CoA reductase inhibitor

Indication: primary hypercholesterolemia and mixed dyspipidemias

Clinical formulation:

Core: ZD4522 (Calcium salt), Lactose, [redacted] Microcrystaline cellulose, [redacted] Magnesium stearate.

Capsule: Ferric oxide yellow, Ferric oxide red, Titanium dioxide [redacted]

Route of administration: Oral

Proposed use: daily doses of 10, 20, 40, or 80 mg.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability
Pharmacology recommends approval of this drug for the proposed indications.

B. Recommendation for Nonclinical Studies
The preclinical studies are adequate to support safety for 10 and 20 mg/day and no further studies are recommended.

C. Recommendations on Labeling

CNS Toxicity

[redacted]

Carcinogenesis, Mutagenesis, Impairment of Fertility

[redacted]

1 pages redacted from this section of the approval package consisted of draft labeling

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Preclinical studies include toxicology studies in rats, dogs, mice and monkeys with duration of single dose to 12 months, 2-year carcinogenicity studies in mice and rats, genotoxic studies, reproductive toxicity studies in rats and rabbits, and special toxicology studies. Generally, the toxicology findings are similar to other approved statins. The major target organs were liver, gallbladder (dog, mouse), forestomach (rodents), cornea, lens and retina (dog), kidney, and muscle.

Liver is the major target of rosuvastatin in rats, mice, and dogs. The changes in liver include increases in plasma transaminases, hepatocyte hypertrophy, and cell necrosis. These findings are consistent with the selective distribution of rosuvastatin in liver. The Sponsor suggested that the liver toxicity to the structural/functional components be due to the depletion of cholesterol by prolonged and extensive inhibition of HMG-CoA reductase. Rats were the most sensitive species to the liver toxicity, probably due to its high rate of hepatic synthesis of cholesterol. Generally, liver toxicity was observed at exposure levels about 2, 1, and 7X the human exposure for mice, rats and dogs, respectively, based on the Sponsor proposed high dose of 80 mg/day; about 4, 2, and 16X the human exposure for mice, rats and dogs, respectively, based on the human dose of 40 mg/day; about 11, 5, and 35X the human exposure for mice, rats and dogs, respectively, based on the human dose of 20 mg/day; and about 24, 11, and 78X the human exposure for mice, rats and dogs, respectively, based on the human dose of 10 mg/day. Since liver toxicity was a known class effect for statins, it was closely monitored in clinical studies.

Toxicity on gallbladder and biliary duct, including lamina propia mucosa edema, hemorrhage and inflammatory infiltration, were observed in dogs. That was consistent with the excretion route of rosuvastatin. This toxicity was observed in dogs at 6 mg/kg with exposure levels 7, 16, 35, and 78X the human exposure at human doses of 80, 40, 20, and 10 mg/kg, respectively. Gallbladder toxicity was also observed in mice at 250 mg/kg (>10X human exposure at human dose of 80 mg/day), but less severe than dogs. Gallbladder effects have also been observed with other drugs of this class.

Edema, hemorrhage and partial necrosis in the interstitium of the choroid plexus was observed in one female dog at 90 mg/kg (46X human exposure at human dose of 80 mg/day) that was sacrificed *in extremis* on day 24 of dosing. CNS lesions characterized by perivascular hemorrhage, edema, mononuclear cell infiltration, fibrinoid degeneration of vessel walls in the choroid plexus of the brain stem, and ciliary body of the eye have been observed with several drugs in this class. Toxicity on eyes including opacity of cornea and lens, and retina dysplasia was only observed in dogs at exposure levels 1/2, 1, 3 and 6X the human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively. Lenticular effects have been observed with other drugs of this class.

Forestomach toxicity (mucosal hyperkeratosis) was observed in rats at exposure levels 6, 12, 27, and 60X the human exposure at human doses of 80, 40, 20, and 10 mg/kg, respectively. This anatomical feature is unique to rodents and is therefore not considered clinically relevant.

Toxicity on endocrine organs were noted in testis (decrease in spermatogenic epithelium, giant cells and vacuolation in seminiferous tubular epithelium), pancreas (vacuolation of acinar cell), adrenal (necrosis of parenchyma) and thyroid (ectopic thymus) in monkeys at exposure levels 2, 4, 8, and 18X the human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively. Giant cells and/or mild tubular seminiferous degeneration were also observed in a one-month dog study at dose of 90 mg/kg. The effects on testis in dogs and monkeys have been seen with several drugs in this class.

Renal and muscle toxicity was seen in rats, dogs, rabbits, and monkeys. The toxicity was characterized by blood chemistry changes including increases in creatinine, CPK, urea nitrogen, and histopathologic changes including renal tubular cell degeneration /necrosis, and cardiac or intercostal muscle necrosis. Generally, renal and muscle toxicity was observed in animals dead or moribund killed after high level exposure to rosuvastatin with high multiples of human exposure (about 39 to 46X human exposure for rats and dogs, respectively, based on the human dose of 80 mg/day). The severity and low frequency nature of renal/muscle toxicity of rosuvastatin suggests that some individuals are more susceptible to rosuvastatin, presumably due to the great variations in individual exposure level in both humans and animals. Humans experiencing these type of adverse events had elevated drug plasma levels according to the medical reviewer. In addition, pre-existing condition of renal impairment will significantly enhance the risk of renal toxicity due to increased rosuvastatin plasma levels at such condition. Therefore, the potential risk of renal/muscle toxicity to human can not be excluded. Marked muscle toxicity was reported in humans when Lovastatin was combined with cyclosporin A, an immunosuppressant.

Rosuvastatin tested negative in Ames test, mouse lymphoma assay, chromosome aberration assay and mouse micronucleus test, suggesting it does not have mutagenic potential.

In the 2-year oncogenic studies, non-neoplastic alterations included changes in the forestomach (hyperkeratosis and/or hyperplasia and minor erosion and inflammation of the squamous epithelium) and liver (increased foci of alteration) were observed in both species. Neoplastic alterations were limited to hepatocellular adenomas /carcinomas in the mouse at 200 mg/kg/day (10, 21, 48, and 107X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively), and in the rat, there were an increased number of uterine stromal polyps n females at 80 mg/kg/day (11, 23, 53, and 116X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively).

Rosuvastatin induced fetal toxicity in rats at 25 mg/kg and rabbits at 3 mg/kg. In rats, both maternal toxicity (reduced body weight and food consumption, liver and renal toxicity) and fetal toxicity (lower number of pups live born, slight low fetal body weight, low incidence of pups with eyes open, and increase in startle amplitude, increases in visceral malformation and skeletal variations, and slightly retarded ossification) were observed at ≥ 25 mg/kg with NOAEL for dams and fetus of 15 mg/kg. In rabbits, severe maternal toxicity (mortality, body weight loss, hypoactivity and debility, and marked histopathologic changes in liver, gallbladder, kidney, heart, and muscle) and fetal toxicity (increase in dead fetuses, decrease in fetal viability index) were observed at 3 mg/kg with NOAEL for dams and fetus of 1 mg/kg. The corresponding exposure levels for rats at 25 mg/kg were 3, 6, 13, and 28X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively. The AUC for pregnant rabbits at 3 mg/kg were not provided. Estimates based on the exposure (C_{max}) in male rabbits at dose of 5 mg/kg, the exposure for female rabbits at 3 mg/kg might be about ½, 1, 3, and 5X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively.

There was a low distribution of rosuvastatin to fetus in rats (3% or 20% of maternal plasma concentration in fetal tissue or amniotic fluid, respectively) following a single oral dose of 25 mg/kg. Relatively higher distribution in fetal tissue (25% maternal plasma concentration) was observed in 1/4 fetus in rabbits following a single oral dose of 1 mg/kg. However, in the lactating rat, rosuvastatin was found in milk at concentrations up to 3 times those in plasma. Theses data suggested that rosuvastatin have risk to pregnant women and nursing mothers.

B. Pharmacologic Activity

Like other statins, rosuvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Rosuvastatin inhibited HMG-CoA reductase *in vitro*, and inhibit cholesterol synthesis *in vivo* with ED_{50} less than 1 mg/kg in rats and dogs (below NOAEL in toxicology studies).

C. Nonclinical Safety Issues Relevant to Clinical Use

Liver toxicity of rosuvastatin was observed across species in animal studies at exposure levels 1 to 7X the human exposure based on the Sponsor proposed high dose of 80 mg/day; about 2 to 16X the human exposure based on the human dose of 40 mg/day; about 5 to 35X the human exposure based on the human dose of 20 mg/day, and about 11 to 78X the human exposure based on the human dose of 10 mg/day. Liver toxicity appeared to be reversible and was also observed in other approved statins. It can be readily monitored during clinical use.

Opacity of cornea and lens were seen in dogs treated for 3 months at 30 mg/kg/day and 1 year at 1 and 6 mg/kg/day. The exposure levels at 1 mg/kg in the 1 year study were comparable to human exposure at 80 mg/day. Cataract was also observed in animals in other approved statins. Simvastatin induced cataracts in a 2-year rat study at 25X human exposure, in a 3-month dog study at 14 X human exposure, and 2-year dog study at 5X human exposure. The clinical association between statin treatment and cataract has not been clearly identified. Current clinical studies have not found direct association between statin treatment and cataracts.

Drug related testicular giant cell formation was seen in dogs at 90 mg/kg/day (46X human exposure at human dose of 80 mg/day) after one month treatment. This was also observed in monkeys after six months treatment at 30 mg/kg/day (about 2, 4, 8, and 18X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively), in addition to vacuolation of seminiferous tubular epithelium.

Myopathy/rhabdomyolysis has been demonstrated with rosuvastatin in clinical studies at doses of 40 and 80 mg/day. Since rhabdomyolysis is a very rare medical condition, any finding in clinical trials should be treated very seriously and considered significant. The same effect was also observed in other approved statins, leading to the withdrawal of cerivastatin. Muscle toxicity was observed in pregnant rabbits at dose of $\geq$ 3 mg/kg (lethal dose). The exposure level data were not provided. Estimates based on the exposure (C_{max}) in male rabbits at dose of 5 mg/kg, the exposure for female rabbits at 3 mg/kg might be about ½, 1, 3, and 5X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively.

A few cases of acute renal failure have been seen with rosuvastatin in clinical studies at doses of 40 and 80 mg/day. Similar effect has not been reported in other approved statins. In preclinical studies, renal toxicity was observed in rats and dogs at exposure levels 39 to 46X human exposure at 80 mg/day, and in monkeys at exposure levels comparable to human exposure at 80 mg/day, and in pregnant rabbits at lethal dose.

The incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day (11, 23, 53, and 116X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively) in a oral 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day. An increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day (10, 21, 48, and 107X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively), in a 107-week carcinogenicity study in mice given 10, 60, 200 or 400 mg/kg/day.

III. Administrative

A. Reviewer signature: /S/

B. Supervisor signature: Concurrence - /S/

Non-Concurrence - /S/
(see memo attached)

C. cc: NDA Arch
HFD 510
HFD 510/Koch/Gong/Davis-Bruno

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Primary pharmacodynamics:

Mechanism of action:

Rosuvastatin is a selective, potent, and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl glutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic low-density lipoprotein cholesterol (LDL-C) receptors on the cell surface to enhance uptake and catabolism of LDL-C. Second, rosuvastatin inhibits hepatic synthesis of very low-density lipoprotein cholesterol (VLDL-C), which reduces the total number of VLDL-C and LDL-C particles.

Cholesterol is produced in a multi-stepped pathway that begins with the catalytic reduction of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) and the formation of mevalonate by HMG-CoA reductase. The calcium salt of rosuvastatin is in the active ester form which competes with HMG-CoA for the HMG-CoA reductase enzyme binding site. As the conversion of HMG-CoA to mevalonate is the rate-limiting step in the synthesis of endogenous cholesterol in the liver, less cholesterol is secreted into the circulation as a component of VLDL particles.

Drug activity related to proposed indication:

***In vitro* studies**

Using primary preparations of hepatocytes, rosuvastatin was found to be a potent inhibitor of cholesterol synthesis from acetate. Rosuvastatin did not inhibit synthesis of cholesterol from mevalonate, indicating no effect on the enzymes downstream from this metabolite. Compared to a variety of non-hepatic cells, it was found to be highly selective for action in hepatocytes. Studies of the initial uptake rates of rosuvastatin into rat hepatocytes defined a high affinity component of uptake with a K_m of 9 mM. Rosuvastatin exhibits low rates of metabolism in animals. The high potency of effect of rosuvastatin in hepatocytes may be a combination of high affinity for the enzyme active site, active transport, and low rates of metabolism.

IC_{50} values for inhibition of HMG-CoA reductase in rat and human hepatic microsomes, rosuvastatin compared with five reference inhibitors[a]

Compound	Mean IC_{50} nM[b] (95% confidence limits) rat microsomes	human microsomes
rosuvastatin	12 (10 - 14)	18 (14 - 23)
cerivastatin (sodium salt)	13 (11 - 16)	26 (20 - 36)
atorvastatin (calcium salt)	15 (12 - 19)	26 (19 - 35)
fluvastatin (sodium salt)	18 (15 - 22)**	76 (56 - 103)***
simvastatin (sodium salt)	18 (15 - 22)**	38 (28 - 52)**
pravastatin (sodium salt)	55 (45 - 68)***	64 (47 - 87)***

a, Conditions of the experiments, as in Table 4.
b, Mean values of four or more determinations
Significance of differences from rosuvastatin, ** $p<0.01$, *** $p<0.001$
(Study: PS06)

In vivo studies

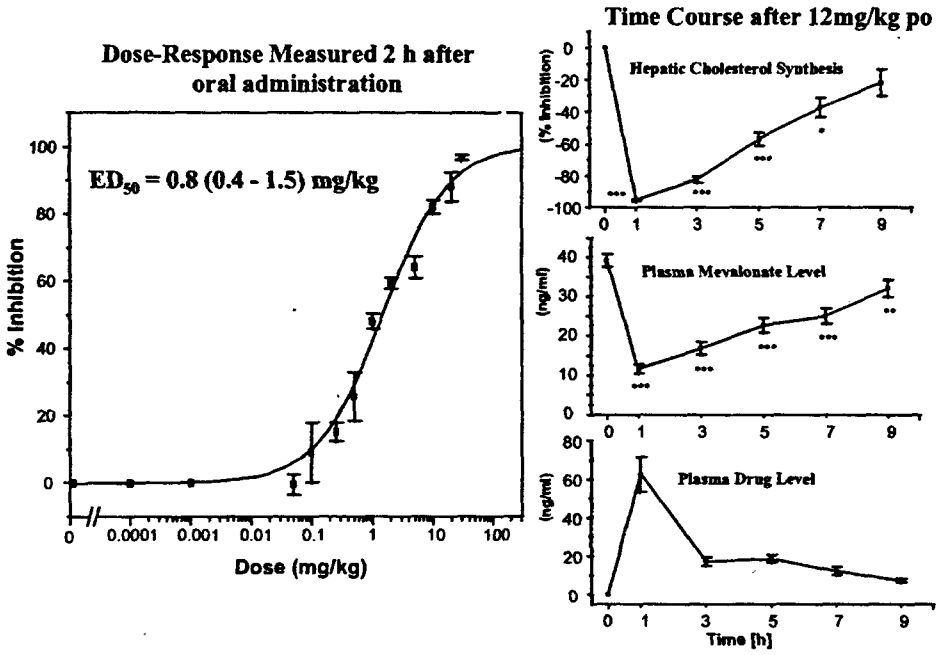
Rosuvastatin was shown to inhibit hepatic cholesterol synthesis after oral administration to the rat, with 50 to 80% inhibition of liver HMG-CoA reductase achieved at doses between 1 and 5 mg/kg. The rate of uptake of rosuvastatin from plasma was higher into liver than any other tissue. When statins were compared in the rat, there was evidence of a relatively long duration of action on liver cholesterol synthesis. In the dog, plasma mevalonate levels were rapidly reduced after oral administration of rosuvastatin. The ED_{50} for this effect, measured at 4 hours post-dose, was similar to the ED_{50} in rat.

Inhibition of cholesterol synthesis in rat liver by rosuvastatin and other statins[a]

Compound	ED_{50}[b] (mg/kg) with 95% confidence limits
rosuvastatin	0.8 (0.4 - 1.5)
cerivastatin (sodium salt)	0.01 (0.005 - 0.20)**
fluvastatin (sodium salt)	0.25 (0.12 - 0.53)*
simvastatin (lactone)	1.2 (0.7 - 2.1)
atorvastatin (calcium salt)	1.3 (0.7 - 2.5)
pravastatin (sodium salt)	22.3 (10.4 - 48.1)**

a Compounds were suspended in 0.5% polysorbate 80 and administered by oral gavage. Two hours later the animals were injected ip with [2-^{14}C] sodium acetate. After a further hour the animals were sacrificed and a section of the liver excised.
Labelled sterols were measured by flow scintillography after —— The data was expressed as mean percentage inhibition compared to controls and a dose response curve was constructed for each compound. The curve was fitted to the estimates of the means using a four parameter logistic model (ORIGIN Software).
b Mean results of at least 3 experiments in each case
Statistical calculations by analysis of variance. Significance of difference for rosuvastatin, * $p<0.05$, ** $p<0.01$.
(Study: PS21)

Inhibition of hepatic cholesterol synthesis after oral administration of rosuvastatin to the rat[a]



a, For experimental details, see footnotes to Table 13. The dose response curve is the combined result of 4 experiments.
Significance of difference from controls, * $p<0.05$, ** $p<0.01$ ***$p<0.001$
(Study: PS20)

Plasma lipid levels are low in wild type rodent species such as the mouse and rat and are resistant to reduction by statins. Dose-dependent reductions in cholesterol levels were observed with rosuvastatin in the dog and on prolonged oral administration of low doses (0.03 and 0.1 mg/kg), significant and stable cholesterol-lowering effects were observed. Moreover, rosuvastatin has been shown to reduce serum cholesterol and lipoprotein levels in the Cynomolgus monkey. These observations are in line with literature results with other statins and are consistent with inhibition of hepatic cholesterol synthesis in these species.

Rosuvastatin dose-dependently reduced VLDL and LDL in two strains of transgenic mice and reduced VLDL production rates. In a genetically hyperlipidaemic rabbit, rosuvastatin reduced total and LDL-cholesterol and reduced the extent and degree of atherosclerotic lesions in the aorta.

Secondary pharmacodynamics:

Oral dosing with rosuvastatin is not expected to produce significant secondary pharmacological effects in humans within the effective therapeutic dose range. The ED_{50} for the inhibition of cholesterol in liver was generally less than 1 mg/kg, that was lower than the NOAEL observed in toxicologic studies. In the toxicologic studies, major target organs include liver, gallbladder, eye, testis and forestomach. Renal and muscle toxicity was noted in rabbits at dose of 3 mg/kg (lethal dose).

The following pharmacology studies were submitted in this NDA:

Title	Species	Duration	Route of Administration	Concentration/ Dose
In Vitro Studies:				
Determination of the physico-chemical properties of ZD4522 Dissociation constants, logP, logD		na	in vitro	na
The time- and concentration-dependent effect of ZD4522 on the activity of HMG-CoA reductase in isolated rat hepatic microsomes	rat isolated hepatic microsomes	0 - 30 min 30 min	in vitro	20 nM up to 300 nM
The concentration-dependent effect of ZD4522, and five reference inhibitors, on the activity of HMG-CoA reductase in isolated rat hepatic microsomes	rat isolated hepatic microsomes	30 min	in vitro	up to 1000 nM
Competition between ZD4522 and HMG-CoA substrate and NADPH co-substrate for HMG-CoA reductase in isolated rat hepatic microsomes	rat isolated hepatic microsomes	30 min	in vitro	up to 3000 nM
The concentration-dependent effect of ZD4522 on the activity of HMG-CoA reductase in rat and human hepatic microsomes	rat and human isolated hepatic microsomes	30 min	in vitro sodium salt used in some studies	up to 100 nM
Determination of enzyme kinetics for ZD4522 utilizing recombinant soluble catalytic domain of human HMG-CoA reductase	Human isolated enzyme recombinant catalytic domain of HMG-CoA reductase	0 - 30 min	in vitro	up to 100 nM
The concentration-dependent effect of ZD4522, and five reference inhibitors, on the activity of a recombinant soluble catalytic domain of human HMG-CoA reductase	human isolated enzyme recombinant catalytic domain of HMG-CoA reductase	30 min	in vitro	up to 1000 nM
The concentration-dependent effect of ZD4522, and five reference inhibitors, on the activity of HMG-CoA reductase in isolated human hepatic microsomes	human isolated hepatic microsomes	30 min	in vitro	up to 1000 nM

Title	Species	Duration	Route of Administration	Concentration/ Dose
The concentration-dependent effect of ZD4522, — on enzyme activity in rat liver microsomes and recombinant soluble catalytic domain of human HMG-CoA reductase	rat isolated hepatic microsomes Human isolated enzyme, recombinant catalytic domain of HMG-CoA reductase	30 min	in vitro	up to 300 nM rat microsomes: up to 100 mM catalytic domain: up to 15 mM
The concentration-dependent effect of ZD4522, and it's des-methyl metabolite (M534905), on rat hepatic microsomal HMG-CoA reductase activity, and on recombinant soluble catalytic domain of human HMG-CoA reductase	rat isolated hepatic microsomes human isolated enzyme recombinant catalytic domain of HMG-CoA reductase	30 min	in vitro	ZD4522 and metabolite: rat microsomes up to 1000 nM catalytic domain: up to 200 nM
The concentration-dependent effect of ZD4522 on cholesterol and triglyceride synthesis in isolated rat hepatocytes in suspension culture	rat isolated primary hepatocytes	3 h	in vitro	up to 100 nM
The concentration-dependent effect of ZD4522, and five reference inhibitors, on cholesterol synthesis in the isolated rat hepatocyte monolayer culture	rat isolated primary hepatocytes	3 h	in vitro	up to 100 nM
To measure the kinetics of uptake of ZD4522 and pravastatin into hepatocytes and to study the effects of ion substitutions, organic anions and metabolic inhibitors on the high affinity uptakes	rat isolated rat primary hepatocytes	20 s	in vitro	up to 200 mM
The concentration-dependent effect of ZD4522, and five reference inhibitors, on Cholesterol synthesis in rat and human fibroblast monolayer culture	rat NRK fibroblastic cell line human CCD50SK fibroblastic cell line	3 h	in vitro	up to 100 mM

Title	Species	Duration	Route of Administration	Concentration/ Dose
The concentration-dependent effect of ZD4522, and five reference inhibitors, on cholesterol synthesis in human umbilical vein endothelial cells.	human Primary HUVEC's isolated from fresh human cords	3 h	in vitro	up to 3000 nM
The concentration-dependent effect of ZD4522 on cholesterol synthesis in Monolayers of cultured human vascular endothelial cells, human myoblasts and human vascular smooth muscle cells	human isolated human myoblasts, vascular smooth muscle cells and HUVEC's	3 h	in vitro	up to 20 mM
The concentration-dependent effects of ZD4522 on the induction of receptors for low density lipoprotein (LDL-R) in a human hepatoma cell line (HepG2)	human hepatoma cell line HepG2	24 h	in vitro	up to 10 mM
The concentration-dependent effects of ZD4522 on the levels of mRNA for the receptor for low density lipoprotein (LDL-R) and on the LDL-R promoter activity in a human hepatoma cell line (HepG2)	human hepatoma cell line HepG2	24 h	in vitro	up to 10 mM
The concentration-dependent effect of ZD4522 on the induction of the low-density lipoprotein receptor in the human hepatoma cell line (HepG2)	human hepatoma cell line HepG2	24 h	in vitro	up to 10 mM
In Vivo Studies:				
The dose-dependent effect of ZD4522 after a single oral administration on rat liver cholesterol synthesis, and the time-dependent inhibitory effect and plasma drug and mevalonate levels	rat intact male	dose response 3 h time-course 9 h	single oral gavage dose single oral gavage dose	0 - 30 mg/kg 12 mg/kg
The dose-dependent effect of ZD4522, and five reference inhibitors, on hepatic Cholesterol synthesis in the rat	rat male	3 h	single oral gavage dose	0 - 30 mg/kg

Title	Species	Duration	Route of Administration	Concentration/ Dose
The time-dependent effect of ZD4522, and three reference inhibitors, on rat hepatic cholesterol synthesis following a single oral administration	rat male	1 - 9 h	single oral gavage dose	12 mg/kg
The dose-dependent effect of ZD4522 on rat liver cholesterol synthesis following a single intraperitoneal dose	rat male	30 min	single intraperitoneal dose	0.001 - 5 mg/kg
Uptake clearance of ZD4522 and pravastatin into liver and other tissues of the rat	rat male	0.25 - 5 min	Single iv dose (radiolabelled ZD4522)	5 mg/kg
The dose-dependent effect of oral Administration of ZD4522 (sodium salt) on sterol synthesis in liver and a number of non-hepatic tissues in the rat	rat male	3 h	single oral gavage dose sodium salt of ZD4522	0.1, 1, 10 and 25 mg/kg
The dose-dependent effects of oral Administration of ZD4522 on sterol Synthesis in liver and a number of non-hepatic tissues in the rat	rat male	3 h	single oral gavage dose	0 - 30 mg/kg
The dose-dependent effects of oral Administration of ZD4522 on sterol Synthesis in slices of rat liver and adrenal Glands studied ex vivo	rat male	2 h (+ 2 h)	2 h in vivo phase; tissues incubated ex vivo 2 h	0.1, 1 and 10 mg/kg
Effect of ZD4522 on hyperlipidemia in APOE*3Leiden mice	Mouse female transgenic for the mutated human form of apoE3 (apoE*3Leiden) on the mouse apoE-deficient background	4 weeks	administered admixed into diet to deliver the required daily dose	Final concentration of ZD4522 in diet 0.00125%, 0.0025% and 0.005% (equivalent to 1.5, 3 and 6 mg/kg/day)
The dose-dependent effect of ZD4522 on plasma lipid levels in the apoB/CETP double transgenic mouse	Mouse female transgenic for both the human apoB100 and cholesteryl ester transfer protein	2 weeks	administered admixed into diet to deliver the required daily dose	Final concentration of ZD4522 in diet 0.005 to 0.07% (equivalent to 8 - 104 mg/kg/day)

Title	Species	Duration	Route of Administration	Concentration/ Dose
The effect of ZD4522 (calcium salt) on serum lipoproteins and the extent of development of aortic and coronary atherosclerosis in Watanabe Heritable Hyperlipidaemic (WHHL) rabbits	WHHL rabbit male and female	26 weeks	administered admixed into diet to deliver the required daily dose	3 and 10 mg/kg/day
The dose-dependent effect of ZD4522, when administered in capsules once daily for four days, on plasma cholesterol and triglyceride in the dog	beagle dog male	4 days	daily oral dose administered in capsule, sodium salt	0.1, 0.3, 1.0 and 3 mg/kg/day
The dose-dependent effect of ZD4522 on plasma cholesterol and triglyceride levels in the dog when administered in capsules once daily for four days	beagle dog male	4 days	daily oral dose administered in capsule, sodium salt	0.3, 1.0 and 3 mg/kg/day
The dose-dependent effect of ZD4522 on serum cholesterol in the dog when administered in capsules once daily for fourteen days	beagle dog male	14 days	daily oral dose administered in capsule	3 mg/kg/day
Effect of ZD4522 on serum cholesterol level in the dog when administered in capsules once daily for 13 weeks	beagle dog male	13 weeks	daily oral dose administered in capsule	0.03 and 0.1 mg/kg/day
Effect of ZD4522 on serum cholesterol levels in the Cynomolgus monkey following five days of oral administration	Cynomolgus monkey male	5 days	oral gavage, twice per day at 0900 and 1600 h	12.5, 25 and 50 mg/kg/day

Pharmacology summary:

Currently, 6 statins are available for use to treat dyslipidemias. Rosuvastatin, as a new statin, is expected to have similar effects as other statins. Rosuvastatin was shown to inhibit HMG-CoA reductase *in vitro*, and inhibit cholesterol synthesis *in vivo* at doses less than 1 mg/kg in rats and dogs.

Comparison of statins with rosuvastatin

Parameter	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin	Cerivastatin	Fluvastatin	Lovastatin
Dose range (mg/day)	10 - 80	10 - 80	5 - 80	10 - 40	0.2 to 0.8	20 - 80	10 - 80
LDL-C reduction (%)[a]	51 - 65	39 - 60	26 - 47	22 - 34	25 - 42	22 - 35	21 - 42
Prodrug	No	No	Yes (lactone)	No	No	No	Yes (lactone)
Lipophilicity	Hydrophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic
Tmax (hr)	3 - 5	1 - 2	1.3 - 2.4	1 - 1.5	2	1	2 - 4
$T_{1/2}$ (hr)[b]	18	14	1.9	1 - 3	2 - 4	2.7	2.9
Bioavailability (%)	20	14	<5	17	60	24	<5
Protein binding (%)	88	98	95	50	>99	98	>95
P450 metabolism	2C9	3A4	3A4	No	3A4;2C8	2C9;2C8;3A4	3A4
Active metabolites	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Metabolite important contributor to therapeutic effect	No	Yes	Yes	No	Yes	No	Yes
Route of excretion[c]	Feces 10% urine	Feces <2% urine	Feces 13% urine	Feces 20% urine	Feces 24% urine	Feces 5% urine	Feces 10% urine

[a] LDL-C changes are mean changes except for fluvastatin where median changes are listed.
[b] Atorvastatin active metabolites have a half-life of 20 to 30 hours; data shown for simvastatin and lovastatin are for the hydroxy acid compounds.
[c] Data represents recovery of drug following an oral dose.
(ref: Knopp 1999, Lennernas and Fager 1997, Physician's Desk Reference 2001.)

Pharmacology conclusions:

The pharmacology of rosuvastatin and the similar pharmacologic activity of other statins support the proposed indication of rosuvastatin.

APPEARS THIS WAY
ON ORIGINAL

II. SAFETY PHARMACOLOGY:

Neurological effects:

Slight effects were seen in behavioral tests (slight hypothermia and weight loss) in mice (dosed at 0, 30, 100, 300, and 1000 mg/kg) following a single oral dose of 300 and 1000 mg/kg, but not in mice or dogs (dosed at 10 and 100 mg/kg) after a single oral dose ≤ 100 mg/kg.

Single oral doses to mice (doses of 30, 100, and 300 mg/kg) had no statistically significant effects on spontaneous motor activity, induced anesthesia, electroshock, convulsion induction or pain reaction.

Single oral dose to dogs at doses of 10 and 100 mg/kg had no significant effect on sleep-wakefulness cycles and the EEG patterns.

Cardiovascular effects:

Reductions in blood pressure and increased heart rates were seen at high doses in anaesthetized rats (300 mg/kg) following intraduodenal dosing (id) and reductions in blood pressure were observed in anaesthetized cats following a single 100 mg/kg id. There were no cardiovascular effects (heart rate, ECG) in conscious dogs following 100 mg/kg orally. In an *in vitro* study using canine Purkinje fibres, rosuvastatin had no effect on action potential duration at concentrations of 1, 10, 100, and 1000 ng/ml.

Pulmonary effects:

No effects in dogs (dosed at 10 and 100 mg/kg) on respiratory and circulation systems was observed.

Renal effects:

In a single dose study in male rats with doses of 0, 30, 100 and 300 mg/kg, no effect was observed in urine volume or electrolyte excretion at doses up to 300 mg/kg.

Gastrointestinal effects:

A single oral dose of 300 mg/kg inhibited gastric emptying in mice and intestinal transit time in rats (following oral doses of 0, 30, 100 and 300 mg/kg). Repeat (5 days) dosing of 100 mg/kg had no effect on intestinal transit time.

In the isolated rabbit ileum, a concentration of 10^{-4} M caused weak, spontaneous contractions. No significant effects were observed at 10^{-4} M on the contractile responses of isolated guinea pig ileum to histamine, acetylcholine, serotonin or barium chloride.

The following safety pharmacology studies were submitted in this NDA:

Title	Species	Duration	Route of Administration	Concentration/ Dose
Evaluation of effect on cardiac action potential duration in isolated canine Purkinje fibres	Isolated canine purkinje fibres	In vitro	Not applicable	1, 10, 100 and 1000 ng/ml
Assessment of effects on general activity and behavior	Mouse (male)	Single dose	Oral	0, 30, 100, 300 and 1000 mg/kg
Assessment of effects on the central nervous system (effect on spontaneous motor activity)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (influence on thiopental induced anesthesia)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (influence on pentobarbital induced anesthesia)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (anti-convulsive (electroshock induced) activity)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (anti-convulsive (pentylenetetrazol induced) activity)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central Nervous system (proconvulsive (electroshock induced) activity	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (pro-convulsive (pentylenetetrazol induced) activity)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (analgesic activity)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (anti-analgesic activity)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the central nervous system (effect on body temperature)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the respiratory and cardiovascular systems	Cat (males and females) (anaesthetised)	Single dose	Oral	0, 30 and 100 mg/kg
Assessment of effects on renal function	Rat (SD, male)	Single dose	Oral	0, 30, 100 and 300 mg/kg

Title	Species	Duration	Route of Administration	Concentration/ Dose
Assessment of effects on respiration and cardiovascular parameters	Rat (SD, male) (anaesthetised)	Single dose	Intra-duodenal	0, 30, 100 and 300 mg/kg
Assessment of effects on the digestive system (small intestinal transit of charcoal meal)	Mouse (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the digestive system (gastric emptying)	Rat (male)	Single dose	Oral	0, 30, 100 and 300 mg/kg
Assessment of effects on the digestive system (spontaneous motility of the ileum)	Isolated rabbit ileum	In-vitro	Not applicable	10^{-6}, 10^{-5} and 10^{-4} M
Assessment of effects on the contractile response of isolated ileum to histamine, acetylcholine, serotonin creatinine sulfate and barium chloride	Isolated guinea-pig ileum	In-vitro	Not applicable	10^{-6},10^{-5} and 10^{-4} M
Assessment of the central (especially EEG), respiratory and cardiovascular effects. Comparison with lovastatin and pravastatin	Dog (male and female beagles)	Single dose	Oral	10 and 100 mg/kg

Safety pharmacology summary:

Based on the results of above experiments, no significant safety pharmacologic concern was noted at single dose of 100 mg/kg, that was much higher than the NOAEL in repeat dose toxicologic studies. Therefore, oral single dosing with rosuvastatin is not expected to produce significant secondary pharmacological effects in humans within the therapeutic dose range of less than 10 mg/day based on the comparison of the estimated AUC values at 100 mg/kg in animal studies and the human exposure at 10 mg/day.

Safety pharmacology conclusions:

Rosuvastatin does not have significant concern in safety pharmacology following single dose treatment at ≥ 100 mg/kg.

III. PHARMACOKINETICS/TOXICOKINETICS:

Analytical methods

Validated radioimmunoassay (RIA) assays have been developed for the measurement of rosuvastatin concentrations in biological matrices.

assays were used to determine rosuvastatin concentrations in rat, rabbit and dog plasma in early studies. Methods were based on The limit of quantification (LOQ) was ng/ml in rat, rabbit and dog respectively. The working range was the LOQ. Two of the methods also allowed measurement of rosuvastatin lactone in dog, with similar sensitivity and precision to that for parent compound.

The RIA method was used to determine rosuvastatin concentrations in mouse, rat, dog and Cynomolgus monkey plasma. The assay was based on anti-rosuvastatin antibodies, raised in rabbits, with a ^{125}I-labelled tyramine derivative of rosuvastatin as competitor. The LOQ of the RIA procedure was ng/ml in mouse, rat, dog, and Cynomolgus monkey, respectively. Inter-assay variability was generally less than 15%.

The assay was used to determine rosuvastatin concentrations in mouse, rat, rabbit, dog and Cynomolgus monkey plasma; in rat and rabbit fetal homogenate; in rat milk; and in phosphate buffered saline. The LOQ was g/ml in mouse, dog and Cynomolgus monkey plasma, ng/ml in rat plasma, ng/g in fetal tissue, ng/ml in rat milk and ng/ml in PBS.

PK parameters:

Animal studies: since the metabolites only accounted a small proportion of the total plasma concentration, and they are either not active or much less active than the parent compound, therefore, only PK values for the parent compound are listed.

APPEARS THIS WAY
ON ORIGINAL

C_{max} and AUC values observed at the NOAELs established in the toxicology studies with rosuvastatin

Species	NOAEL (mg/kg/day)	Study duration	Reference	C_{max} (ng/mL)		AUC_{0-24} (ng.hr/mL)	
Mouse	20	13 Weeks	F-15-L	Day 1 Day 89	25.7/195* 57.1/114	Day 1 Day 89	213/550*† 145/322†
Rat	2	6 Months	F-13-L	Day 1 Day 91 Day 182	12.5 15.5 33.6	Day 1 Day 91 Day 182	79.1 96.7 149
Dog	3	12 Months	B-46-L	Day 0 Day 184 Day 365	61.5 63.3 88.3	Day 0 Day 184 Day 365	303 446 703
Monkey	10	6 Months	F-14-L	Day 0 Day 90 Day 181	25.9/33.0* 32.3/21.1 24.8/58.7	Day 0 Day 90 Day 181	352/469* 313/246 342/818

* Male/Female
† AUC(0-12)

APPEARS THIS WAY
ON ORIGINAL

PK in different animal species:

Toxicokinetic Data in the Rat

Sampling occasion	Sex	Parameter	Dose level (mg/kg/day)			
S-4522-F-16-L	Rat sighting oncogenicity study					
			6	20	60	
Day 1	m+f	C_{max} (ng/ml)	19.0	82.2	381	
	m+f	AUC(0-24) (ng.h/ml)	122	340	1350	
Day 90	m+f	C_{max} (ng/ml)	30.4	389	3490	
	m+f	AUC(0-24) (ng.h/ml)	240	1130	6720	
S-4522-F-13-L	Rat 6 month toxicity study					
			2	6	20	
Day 1	m+f	C_{max} (ng/ml)	12.5	60.6	475	
	m+f	AUC(0-24) (ng.h/ml)	79.1	239	1310	
Day 91	m+f	C_{max} (ng/ml)	15.6	66.1	708	
	m+f	AUC(0-24) (ng.h/ml)	96.7	254	1950	
Day 182	m+f	C_{max} (ng/ml)	33.6	130	885	
	m+f	AUC(0-24) (ng.h/ml)	149	424	2410	
D4522 TCR2852 (KPR009)	Rat main oncogenicity study					
			2	20	60	80
Day 1	m	C_{max} (ng/ml)	2.92	51.0*	569	944
	m	AUC(0-t) (ng.h/ml)	NC	290	2560	3558
	f	C_{max} (ng/ml)	385	161	1156	4407
	f	AUC(0-t) (ng.h/ml)	308	318	2380	5805
1 Month	m	C_{max} (ng/ml)	7.38	224	1435	7975
	m	AUC(0-t) (ng.h/ml)	20.5	465	2910	9836
	f	C_{max} (ng/ml)	NC	188	691	828
	f	AUC(0-t) (ng.h/ml)	NC	211	2135	1801
1 Year	m	C_{max} (ng/ml)	16.1	284	1052	1976
	m	AUC(0-t) (ng.h/ml)	59.6	659	2021	3903
	f	C_{max} (ng/ml)	34.6*	312	1757	2990
	f	AUC(0-t) (ng.h/ml)	88.5	565	2968	4636

* t_{max} was 1.5 hours post-dose, for all other animals t_{max} was 0.5 hours
NC Not calculated
AUC(0-t) Area under plasma concentration time curve from zero to time of last quantifiable concentration

Toxicokinetic Data in the Mouse

Sampling occasion	Sex	Parameter	Dose level (mg/kg/day)		
S-4522-F-15-L Mouse sighting oncogenicity study					
			20	60	200
Day 1	m	C_{max} (ng/ml)	25.7	1230	13400
	m	AUC(0-12) (ng.h/ml)	213	1480	19000
Day 1	f	C_{max} (ng/ml)	195	1930	7060
	f	AUC(0-12) (ng.h/ml)	550	2870	19700
Day 89	m	C_{max} (ng/ml)	57.1	494	2520
	m	AUC(0-12) (ng.h/ml)	145	722	3080
Day 89	f	C_{max} (ng/ml)	114	393	2860
	f	AUC(0-12) (ng.h/ml)	322	969	5610
D4522 KPM010 Main oncogenicity study					
			10	60	200
Week 52	m	C_{max} (ng/ml)	87.8	273	3180
	m	AUC(0-24) (ng.h/ml)	120	580	4270
	f	C_{max} (ng/ml)	38.9	165	3320
	f	AUC(0-24) (ng.h/ml)	158	779	4900

Toxicokinetics in male rabbits (mean ± SD, n = 5, from S-4522-B-52-N)

Sampling occasion	Parameter	Dose level (mg/kg/day)	
		5	10
Day 0	C_{max} (ng/ml)	140 ± 50	340 ± 180
Day 6		300 ± 180	500 ± 200
Day 13		310 ± 150	730 ± 120#
Day 0	C_{max} (ng/ml)	180 ± 30*	410 ± 310*
Day 6		200 ± 80*	500 ± 100*
Day 13		290 ± 130*#	480 ± 120*#

* In the presence of mevalonic acid, # n = 4,
SD Standard deviation

Toxicokinetics in the dog (mean ± SD, n = 3)

Sampling occasion	Sex	Parameter	Dose level (mg/kg/day)			
S-4522-B-20-L Dog 1 month toxicity study						
			10	30	90#	
Day 0	m	C_{max} (ng/ml)	290 ± 160	550 ±390	2630 ± 1140	
	m	AUC(0-24) (ng.h/ml)	1520 ± 240	3520 ± 1810	19900 ± 2770	
	f	C_{max} (ng/ml)	200 ± 40	840 ± 380	4770 ± 4940	
	f	AUC(0-24) (ng.h/ml)	1110 ± 240	3890 ± 1030	23900 ± 18000	
Day 29	m	C_{max} (ng/ml)	270 ± 120	720 ± 220	8990 ± 8280	
	f	C_{max} (ng/ml)	180 ± 80	500 ± 330	4380 ± 4720	
S-4522-B-21-L Dog 3 month toxicity study						
			7.5	15	30S	
Day 0	m	C_{max} (ng/ml)	260 ± 80	340 ± 130	1300 ± 770	
	f	C_{max} (ng/ml)	250 ± 200	750 ± 240	1710 ± 880	
Day 41	m	C_{max} (ng/ml)	320 ± 250	270 ± 60	2600 ± 2300	
	f	C_{max} (ng/ml)	210 ± 70	750 ± 340	1830 ± 1000	
Day 82	m	C_{max} (ng/ml)	350 ± 280	410 ± 210	1420 ± 700	
	f	C_{max} (ng/ml)	150 ± 20	440 ± 170	1280 ± 460	
S-4522-B-33-L Dog 3 month toxicity study						
			1S	2S	4S	
Day 0	m+f	C_{max} (ng/ml)	19.4 ± 5.3	46.0 ± 20.2	88.5 ± 40.9	
Day 43	m+f	C_{max} (ng/ml)	17.1 ± 6.0	25.5 ± 7.5	64.8 ± 34.3	
Day 82	m+f	C_{max} (ng/ml)	22.8 ± 6.9	22.2 ± 12.4	49.0 ± 21.7	
S-4522-B-37-L Dog 6 month toxicity study						
			1S	4S		
Day 0	m+f	C_{max} (ng/ml)	16.7 ± 9.3	120 ± 63.9		
	m+f	AUC(0-24) (ng.h/ml)	95.6 ± 45.3	639 ± 317		
Day 89	m+f	C_{max} (ng/ml)	13.1 ± 7.1	61.2 ± 18.8		
	m+f	AUC(0-24) (ng.h/ml)	76.4 ± 35.4	384 ± 146		
Day 179	m+f	C_{max} (ng/ml)	18.0 ± 7.8	111 ± 69.8		
	m+f	AUC(0-24) (ng.h/ml)	122 ± 56.5	661 ± 198		
S-4522-B-46-L Dog 12 month toxicity study						
			1@	3@	6b	6*
Day 0	m+f	C_{max} (ng/ml)	16.6 ± 4.0	61.5 ± 26.6	267 ± 393	156 ± 74
	m+f	AUC(0-24) (ng.h/ml)	85.8 ± 25.6	303 ± 59	1230 ± 1750	767 ± 384
Day 184	m+f	C_{max} (ng/ml)	25.8 ± 14.4	63.3 ± 22.1	658 ± 1300	195 ± 85
	m+f	AUC(0-24) (ng.h/ml)	154 ± 72	446 ± 137	2130 ± 2520	1170 ± 360
Day 363	m+f	C_{max} (ng/ml)	27.1 ± 10.4	88.3 ± 27.2	816 ± 1860	236 ± 114
	m+f	AUC(0-24) (ng.h/ml)	237 ± 92	703 ± 158	3120 ± 3820	1700 ± 776

* Parameters at 6 mg/kg/day after exclusion of 2 outliers (n = 12)
# n = 5, S n = 6, @ n = 8, b n = 14

Pharmacokinetic parameters in the Cynomolgus monkey

Sampling occasion	Sex	Parameter	Dose level (mg/kg/day)	
S-4522-F-10-N Cynomolgus monkey 1 month toxicity study				
			10 (n = 1)	30 (n = 1)
Day 0	m	C_{max} (ng/ml)	37.4	22.2
	m	AUC(0-24) (ng.h/ml)	132	315
	f	C_{max} (ng/ml)	14.2	26.2
	f	AUC(0-24) (ng.h/ml)	201	305
Day 28	m	C_{max} (ng/ml)	12.6	27.7
	m	AUC(0-24) (ng.h/ml)	132	243
	f	C_{max} (ng/ml)	14.0	17.8
	f	AUC(0-24) (ng.h/ml)	72.8	247
S-4522-F-14-L Cynomolgus monkey 6 months toxicity study*				
			10 (n = 6)	30 (n = 6)
Day 0	m+f	C_{max} (ng/ml)	29.4 ± 19.9	71.2 ± 43.7
	m+f	AUC(0-24) (ng.h/ml)	410 ± 260	1020 ± 540
Day 90	m+f	C_{max} (ng/ml)	26.7 ± 13.3	105 ± 44.5
	m+f	AUC(0-24) (ng.h/ml)	279 ± 175	1430 ± 394
Day 181	m+f	C_{max} (ng/ml)	41.8 ± 38.7	207 ± 170
	m+f	AUC(0-24) (ng.h/ml)	580 ± 520	2640 ± 2080
D4522 KKP011 Cynomolgus monkey disposition single dose study*				
			10 (n = 4)	
Day 1	m	C_{max} (ng/ml)	13.0 ± 8.64	
	m	AUC (ng.h/ml)	85.5 ± 36.6	
D4522 KKP064 Cynomolgus monkey pharmacokinetic multiple dose study*				
			10 (n = 4)	30 (n = 4)
Day 1	m	C_{max} (ng/ml)	33.7 ± 12.7	103 ± 72.0
	m	AUC(0-24) (ng.h/ml)	223 ± 86.4	459 ± 151
Day 10	m	C_{max} (ng/ml)	62.8 ±9.51	194 ± 83.0
	m	AUC(0-24) (ng.h/ml)	415 ± 117	908 ± 306

* Mean ± standard deviation

Clinical studies:

Absorption of rosuvastatin in man is in excess of 20% of the dose. In-vitro studies indicate that absorption across the intestinal epithelium is a complex process involving simple diffusion and active transport.

In blood, rosuvastatin was distributed in favor of plasma, with 35% of blood concentration being associated with blood cells. Eighty-eight percent of the plasma concentration was bound to plasma proteins (principally albumin). Binding was reversible and independent of concentration.

Rosuvastatin was only slowly metabolized in human hepatocytes (in vitro). Rosuvastatin did not induce cytochrome P450s in animals - nor inhibit the P450 isoforms in human hepatic microsomes (in vitro). CYP2C9 was the principal P450 involved in rosuvastatin metabolism (2C19, 3A4, and 2D6 were implicated to a lesser extent). These data indicate little potential for interaction of rosuvastatin with co-administered drugs that are metabolized by cytochrome P450s.

In vivo, rosuvastatin was not extensively metabolized and was excreted predominantly as parent compound; metabolism was a minor route of clearance. N-desmethyl rosuvastatin was identified in excreta and plasma, and rosuvastatin-lactone was identified in plasma - both metabolites have also been observed in toxicology species, and therefore form part of the safety assessment of the compound. Rosuvastatin was the principal circulating drug-related species and was responsible for all circulating active HMG-CoA reductase inhibitor activity, and over 85% of circulating total HMG-CoA reductase inhibitor activity.

One hundred percent of a 20-mg dose of [^{14}C]-rosuvastatin was recovered in excreta: 90% in feces and 10% in urine. The fecal route is, therefore, the most important route of elimination.

Rosuvastatin was cleared by both renal and non-renal routes. Renal clearance accounted for approximately 28% of total plasma clearance (48.9 L/h), with tubular secretion the dominant renal process. The volume of distribution at steady state was estimated as 134 L; hepatic-extraction ratio was estimated as 0.63. The absolute bioavailability of rosuvastatin in man was 20.1%.

Typical rosuvastatin pharmacokinetic profiles exhibited a T_{max} of 3- to 5-h post-dose. Following peak plasma concentration, there was a bi-exponential decline with a terminal T½ of approximately 18.6 h. Both T_{max} and T½ were independent of dose. Dose proportionality of C_{max} and $AUC_{(0-t)}$ was established in healthy volunteers over the dose range 10 to 80 mg. However, marked variation in exposure was observed in all dose levels and overlaps of concentration were noted across dose range 10 to 80 mg. On multiple dosing, steady state was reached within 5 days. Pharmacokinetics were unchanged by multiple dosing and accumulation was minimal. When volunteers were dosed fed (instead of fasted) the rate - but not the extent - of absorption was decreased. Increases of exposure were observed in patients with renal or hepatic impairment.

Pharmacokinetic parameters after administration of multiple oral-dose rosuvastatin to healthy volunteers (pooled data)

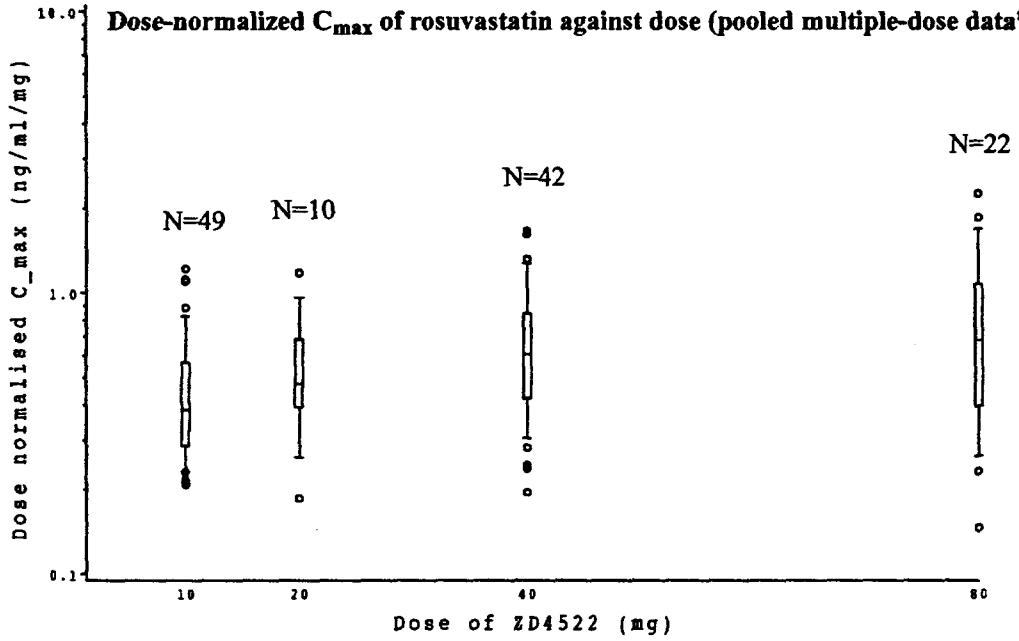
Dose mg	N	C_{max} ng/ml gmean (CV%)		t_{max} h Median (range)		AUC(0-24) ng.h/ml gmean (CV%)		$t_{½}$ h Mean (SD)	
10[a]	49	4.09	(49.3)	3.0	(1.0 to 6.0)	40.1	(46.7)	29.7[b]	(14.0)
20[c]	10	9.87	(53.3)	3.0	(3.0 to 12.0)	87.9	(50.0)	14.5[d]	(2.63)
40[e]	42	24.1	(57.0)	4.0	(1.0 to 6.0)	201	(47.0)	20.8[f]	(12.8)
80[g]	22	53.1	(79.3)	4.5	(1.0 to 8.0)	436	(70.7)	13.4[f]	(2.04)

Data derived from Summary Table T2.3.

[a] Trials 4, 5, 18; [b] N = 27; [c] Trials 2, 17; [d] N = 7; [e] Trials 2, 13, 14, [f] N = 6; [g] Trials 11, 56. (See Table 44 for individual trial information.)

Mean = Arithmetic mean.

Dose-normalized C_{max} of rosuvastatin against dose (pooled multiple-dose data[a])



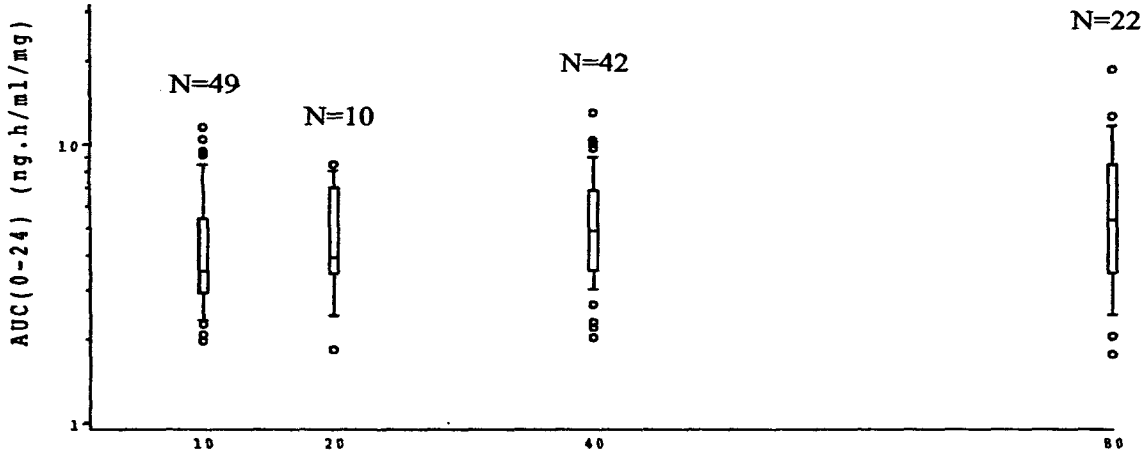
Data from HPB analyses.

[a] Trials 2, 4, 5 (fasted only), 11, 13, 14, 17 and 18 (normal subjects only), and 56.

The median, inter-quartile range, and 10th and 90th percentiles are shown.

ZD4522 = Rosuvastatin.

Dose-normalized AUC(0-24) of rosuvastatin against dose (pooled multiple-dose data[a])



Data from HPB analyses.

[a] Trials 2, 4, 5 (fasted only), 11, 13, 14, 17 and 18 (normal subjects only), and 56.
The median, inter-quartile range, and 10th and 90th percentiles are shown.

Pharmacokinetic parameters of subjects with hepatic impairment (Maddrey classification) and healthy volunteers after administration of multiple oral-dose rosuvastatin 10 mg (Trial 18)

Parameter (units)	Summary statistic		Healthy volunteers N = 6		Maddrey 'not severe' N = 10		Maddrey 'severe' N = 2[a]
C_{max} (ng/ml)	gmean	(CV%)	6.02	(63.1)	8.14	(51.9)	23.4 and 96.7
	Mean[b]	(SD)	6.86	(3.60)	8.93	(3.65)	(As above)
AUC(0-24) (ng.h/ml)	gmean	(CV%)	60.7	(76)	56.6	(56.0)	128 and 242
	Mean[b]	(SD)	71.7	(39.1)	63.2	(28.6)	(As above)
C_{min} (ng/ml)[c]	gmean	(CV%)	0.7	(114)	0.6	(64.1)	0.9 and 0.5
t_{max} (h)	Median	(Range)	3.5	(2.0 to 4.0)	2.5	(0.5 to 4.0)	2.0 and 0.5
CL_r (ml/min)	gmean	(CV%)	153	(35)	112	(59.8)	124 and 132
	Mean[b]	(SD)	160	(49.1)	126	(56.6)	(As above)
f_e (%)	gmean	(CV%)	5.81	(56.0)	4	(103)	9.89 and 19.9
	Mean[b]	(SD)	6.52	(3.51)	4.9	(2.7)	(As above)

Data derived from Table 27 (healthy volunteers), Summary Tables T2.7.1 and T2.7.2 (Maddrey 'not severe'), and Clinical Trial Report (Tables G5.2, G5.4 and G5.5) (Maddrey 'severe').
[a] Individual data - rather than means - are presented (data is always presented in the same subject order - Subject 0109 followed by Subject 0110); [b] Arithmetic mean; [c] C_{min} based on 24-h assessment following Day-15 dose.
CL_r = Renal clearance; f_e = fraction of drug excreted unchanged in the urine; Maddrey 'not severe' = Child-Pugh scores of 5 to 7; Maddrey 'severe' = Child-Pugh scores of 8 and 9.

Pharmacokinetic parameters of subjects with renal impairment and normal renal function after administration of multiple oral-dose rosuvastatin 20 mg

Parameter (units)	Summary statistic		Renal status based on creatinine clearance[a]							
			Normal renal function N = 4		Mild renal impairment N = 8		Moderate renal impairment N = 4		Severe renal impairment N = 6	
C_{max} (ng/ml)	gmean	(CV%)	10.1	(32.3)	17.7	(118)	11.4	(58.8)	31.5	(39.0)
	Mean[b]	(SD)	10.5	(3.07)	24.1	(17.3)	12.8	(7.21)	33.3	(11.3)
AUC(0–24) (ng.h/ml)	gmean	(CV%)	98.0	(35.3)	139	(91.7)	105	(59.6)	309	(19.2)
	Mean[b]	(SD)	103	36.7	177	(117)	117	(60.3)	314	(60.3)
t_{max} (h)	Median	(range)	4.00	(3.00 to 12.0)	3.50	(0.50 to 6.00)	3.00	(0.50 to 4.00)	3.00	(0.50 to 8.00)
$t_{½}$ (h)	Mean[b]	(SD)	12.0	(NC)	17.1	(5.22)	20.2	(5.05)	20.4	(5.38)

Data derived from Clinical Trial Report (see Trial 17, Section 4.1.1, and T5.3) - also see Table 44.
[a] Subjects were stratified based on creatinine clearance. The renal status categories are as follows: normal renal function: CrCl >80 ml/min/1.73 m^2); mild impairment (CrCl 50 to 80 ml/min/1.73 m^2); moderate impairment (CrCl 30 to <50 ml/min/1.73 m^2); severe impairment (CrCl <30 ml/min/1.73 m^2); [b] Arithmetic mean.

Absorption:

ZD4522 can be absorbed after oral administration. T_{max} ranged from 0.25 to 6 hour depending on animal species and dose. C_{max} and AUC increased with ZD4522 proportionally at lower doses and more than proportionally at higher doses. The absolute bioavailability is 32% in dogs. The absorption is at least 56% in the rat and 74% in the dog. Fasting, low calcium diet increases absorption. The dog has higher C_{max} and $AUC_{(0-24)}$ than other species, which correlated with the greater sensitivity to toxicity.

In the mouse, the absorption of rosuvastatin was rapid, as evidenced by the C_{max} at 0.5 hours after dosing (the first sampling point) in most animals. C_{max} and AUC values increased more than in proportion to increasing dose. The elimination half-life, determined following 52 weeks of dosing at 10 to 200 mg/kg/day, ranged from 2.4 to 6.8 hours.

In the rat, the plasma concentrations of rosuvastatin increased more than proportionately with increasing dose. C_{max} occurred at 0.5 hours after dosing (the first sampling point) in most animals. The elimination half-life ranged from 3 to 11 hours.

In the male rabbit, the absorption of rosuvastatin was rapid, as evidenced by the C_{max} occurring by 0.5 hours after dosing in all animals. C_{max} values increased broadly in proportion to increasing dose. Based on C_{max}, multiple dosing resulted in approximately 2-fold accumulation.

In the dog, C_{max} and AUC increased in proportion to dose at lower doses (1 to 6 mg/kg). At higher doses C_{max} increased more than proportionately with dose. The rate of absorption was variable; with T_{max} ranging from 1 to 4 hours after dosing. There was no consistent effect of multiple dosing on the plasma concentrations. In most of the studies no accumulation was observed, whereas in the 12-month study the concentrations appeared to increase at successive sampling days. These differences are interpreted as a consequence of the high variability in plasma concentrations.

In the monkey, T_{max} ranged from 0.25 to 4 hours post-dose, and mean half-life of the terminal phase ranged from 5.7 to 6.9 hours. Plasma concentrations appeared to reach steady state and showed up to a 2-fold accumulation after 10 days of dosing. The extent of systemic exposure, between 10 and 30 mg/kg, increased in a less than dose proportional manner.

Distribution:

The quantitative tissue distribution of total radioactivity in the albino rat was investigated after single or 14-day repeated oral administration of 5 mg/kg of [^{14}C]-rosuvastatin. The studies demonstrated that concentrations of radioactivity in the liver were about 10-fold higher than those in plasma. The concentrations in most other tissues were at, or below, the plasma concentrations. After repeated daily administration, the pattern of distribution was similar but the liver and plasma concentrations were about 2 to 3-fold higher than those seen after a single dose. Radioactivity accumulated in the plasma, Harderian gland, mandibular gland, heart, lung, kidney and liver over the 14-days dosing period, without apparently reaching steady state. In fat, brown fat, pancreas, spleen, epididymis, mesenteric lymph node and skin, steady state seemed to be achieved within 6 days. Tissue concentrations declined approximately in parallel with plasma concentrations after single and repeated administration,