SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: Rosuvastatin

Trial title (number): A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial to Investigate the Effect of Rosuvastatin on Lipoproteins in Patients with Differing Atherogenic Lipoprotein Profiles (4522IL/0040).

Clinical phase: III

First subject recruited: 18 November 1999
Last subject completed: 2 August 2000
AstraZeneca approval date: 30 September 2001

Principal investigator and location:

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective was to understand better the mechanism of action of rosuvastatin on lipoproteins. This was to be achieved by causing a large decrease in low-density lipoprotein cholesterol (LDL-C) levels in three groups of subjects with different lipid profiles, so providing an opportunity to explore changes in lipoprotein subfractions and other related parameters of lipid metabolism.

METHODS

Design: This was a randomised, double-blind, placebo-controlled, crossover trial. After a 6- to 10-week screening period, subjects were randomised to one of two crossover treatment groups, using a stratified design: rosuvastatin 40 mg followed by placebo, or placebo followed by rosuvastatin 40 mg. Subjects received each treatment once daily for 8 weeks. There was a

5-week washout period between the crossover of treatments to allow sufficient time for LDL-C levels to return to pre-treatment values.
Randomisation was stratified by lipid profile groups, defined as follows:

- Group HC (denoting Type IIa hypercholesterolaemia): subjects had normal TG levels of <2.0 mmol/L (<177 mg/dL) with raised LDL-C levels of >4.2 mmol/L (>162 mg/dL).
- Group CHL (denoting Type IIb combined hyperlipidaemia): subjects had raised TG levels of 2.0 to 5.0 mmol/L (177 to 443 mg/dL) with raised LDL-C levels of >4.2 mmol/L (>162 mg/dL);
- Group HTG (denoting Type IV hypertriglyceridaemia): subjects had raised triglyceride (TG) levels of 2.0 to 5.0 mmol/L (177 to 443 mg/dL) with normal LDL-C levels of ≤4.2 mmol/L (≤162 mg/dL);

Population: A total of 45 males or postmenopausal females with Type IIa, IIb, or IV hyperlipidaemia, who satisfied the entry criteria, were to be recruited. Six subjects were required in each treatment sequence to have at least 90% power of detecting an absolute change of -2.2498 mmol/L in LDL-C from baseline in each lipid profile group; thus, 12 subjects were required in each lipid profile group. To allow for withdrawals, 15 subjects were recruited to each lipid profile group.
Although the aim of the trial was to investigate the mechanism of action of rosuvastatin, the trial was powered to detect a reduction in LDL-C of sufficient magnitude (-2.2498 mmol/L from baseline) to generate measurable differences in the various efficacy variables of exploratory interest in this trial.
Key inclusion criteria: Males or postmenopausal women, aged 18 years or older; discontinuation of all cholesterol-lowering drugs and dietary supplements; fasting LDL-C and TG levels that fitted one of the three categories specified in the design (i.e., subjects with hypertriglyceridaemia, combined hyperlipidaemia, or hypercholesterolaemia); an Eating Pattern Assessment Tool (EPAT) score of ≤28 to demonstrate dietary compliance; no evidence of active cardiopulmonary disease on chest X-ray; electrocardiogram (ECG) results that show no acute changes.
Key exclusion criteria: fasting lipoprotein (a) (Lp[a]) ≥100 mg/dL before randomisation; Type III hypercholesterolaemia or heterozygous familial hyperlipidaemia; presence of apolipoprotein E2E2 phenotype; history of hypersensitivity reactions to HMG-CoA reductase inhibitors; various concomitant illnesses, including active liver disease or hepatic dysfunction (defined by an alanine aminotransferase [ALT], aspartate aminotransferase [AST], or bilirubin concentration >1.5 x the upper limit of normal [ULN]), active arterial disease, history of malignancy (unless basal or squamous cell skin carcinoma), uncontrolled hypertension, and uncontrolled hypothyroidism; fasting serum glucose >9.99 mmol/L (>180 mg/dL) or glycated haemoglobin (HbA_{1C}) >9% recorded at any time during screening; serum creatine kinase (CK) concentration >3 x ULN; serum creatinine >220 µmol/L (>2.5 mg/dL) before randomisation; usage of concomitant medications known to affect the lipid profile or present a potential safety concern (e.g., through drug interaction).

Dosage: After a 6- to 10-week screening period, subjects took oral doses of encapsulated trial treatment once daily, approximately 3 hours after the evening meal. Doses of treatments were as follows: rosuvastatin 40 mg or matching placebo. The same dose of trial treatment was taken for 8 weeks, after which there was a 5-week washout period followed by a crossover in randomised treatment for a further 8 weeks. Formulation and batch numbers were as follows: rosuvastatin 40 mg (F12566, 65736B99), placebo (F12545, 65734H99).

Key assessments:

Efficacy: All analyses were performed on the PP population using the observed data. Descriptive summaries were also based on the PP population.

The main analysis of the primary endpoint (the absolute change from baseline in plasma LDL-C levels after 8 weeks of treatment with rosuvastatin or placebo) was performed on the observed data in the PP population using analysis of variance (ANOVA) appropriate for a 2-period crossover design. The ANOVA model was fitted separately to each of the three lipid profile groups, and included terms for subject, treatment, and crossover period. An additional ANOVA was carried out on the primary endpoint to explore the effect of plasma ApoB levels at baseline on reduction in LDL-C; these data were analysed as per primary endpoint, but also included a term for baseline ApoB (as a continuous covariate). The ApoB term was retained in this exploratory model for estimation of treatment effects regardless of its statistical significance. Least squares means and Standard errors obtained from the ANOVA models were used to perform t-tests. P-values and associated 95% confidence intervals for the difference in treatment least squares means for each comparison were also reported.

In the analyses described above, no formal assessment of the effect of carryover from the first treatment period to the second was carried out. Descriptive statistics were presented for absolute LDL-C levels, changes in LDL-C levels from baseline, and % change in LDL-C levels from baseline by treatment at each visit.

A large number of secondary endpoints was chosen deliberately with the view of generating information on the effects of rosuvastatin on different lipids. The key secondary analysis examined the absolute changes from baseline in plasma TG levels after 8 weeks of treatment with rosuvastatin or placebo. This analysis was performed on the observed data on the PP population using ANOVA; data were analysed as per the primary endpoint, although an additional exploratory analysis in which baseline ApoB was fitted as a covariate was not performed. Descriptive statistics were presented for absolute values and % changes from baseline by treatment group at each visit for levels of all other lipid and lipoprotein variables.

Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, haematology, urinalysis), vital signs, electrocardiograms (ECGs), and physical examination. All data were summarised.

RESULTS

Demography: A total of 135 subjects entered the screening period; of these, 35 subjects from 6 centres were randomised to treatment, of whom 34 received trial medication. This was the PP efficacy population at 8 weeks and the safety population, and comprised 5 subjects in the HTG group, 14 in the CHL group and 15 in the HC group. The required number of HTG subjects was not achieved due to difficulties in recruiting subjects with the appropriate lipid profile. There

were no protocol violations, but 5 protocol deviations due to non-compliance with trial medication led to exclusion from the PP population. All subjects were Caucasian and were aged between 40 and 78 years. All subjects in the HTG group and one-third of subjects in the HC group were male, while there was an even sex distribution in the CHL group. The first subject entered the trial on 18 November 1999 and the last subject completed the trial on 2 August 2000. Seven subjects withdrew during the randomised treatment period, the most common reason being withdrawal of informed consent.

Efficacy: A summary of the efficacy findings is presented in Table I.

Table I Summary of efficacy findings (PP population)

	Rosuvastatin compared with placebo after 8 weeks of treatment					
	Lipid profile groups					
	Type IV HTG		Type IIb CHL		Type IIa HC	
	Placebo (N = 5)	Rosuvastatin 40 mg (N = 5)	Placebo (N = 14)	Rosuvastatin 40 mg (N = 14)	Placebo (N = 15)	Rosuvastatin 40 mg (N = 15)
Primary endpoint						
lsmean of absolute change (mmol/L) from baseline after 8 weeks of treatment						
LDL-C	0.02[a]	2.09[a]	0.20	-2.66[b]	-0.14	-2.81[b]
LDL-C adjusted for ApoB	NC	NC	0.21	-2.66[b]	-0.11	-2.78[b]
Secondary endpoints						
lsmean of absolute change from baseline after 8 weeks of treatment						
TG	0.47[a]	0.81[a]	-0.10	-0.73[ns]	-0.12	-0.44[ns]
Mean % change from baseline after 8 weeks of treatment						
TC	0.70	-40.68	3.96	-44.74	-3.64	-44.32
VLDL-C	-11.92	-35.53	15.56	-29.22	14.38	2.65
HDL-C	10.75	14.89	4.69	11.19	3.91	9.45
ApoA-I	-3.98	4.95	0.98	7.92	-2.70	2.90
ApoB	-5.09	-44.19	2.90	-49.65	-3.22	-50.80
VLDL-TG	17.96	-49.30	11.39	-4.14	9.06	-5.00
VLDL1	103.09	-37.62	14.66	-10.68	-14.09	8.70
VLDL1-CE	5.28	-41.39	-1.34	-27.37	36.78	-15.32
VLDL1-TG	-1.21	-0.03	1.71	3.85	1.72	26.32
VLDL2	22.73	-38.34	-3.9	-45.07	8.54	-21.28
VLDL2-CE	-8.34	-7.00	14.22	-28.63	6.82	-28.41
VLDL2-TG	6.16	-3.04	-6.65	21.45	0.65	37.14
IDL	-3.16	-28.70	16.67	-55.39	-10.94	-54.26
IDL-CE	2.13	-21.62	5.67	-17.82	-3.69	-21.81
IDL-TG	-25.38	84.43	-9.82	69.54	22.34	116.81

[a] Values of difference from baseline mean to final mean for HTG group (not lsmean of absolute change), [b] $p \leq 0.001$, [ns] = not significant versus placebo

(continued)

Table I Summary of efficacy findings (PP population) (continued)

	Rosuvastatin compared with placebo after 8 weeks of treatment					
	Lipid profile groups					
	Type IV HTG		Type IIb CHL		Type IIa HC	
	Placebo (N = 5)	Rosuvastatin 40 mg (N = 5)	Placebo (N = 14)	Rosuvastatin 40 mg (N = 14)	Placebo (N = 15)	Rosuvastatin 40 mg (N = 15)
SQ-IDL-C	-39.11	-58.01	69.88	-44.61	9.58	-34.65
LDL	46.94	-49.73	6.95	-54.20	-7.58	-51.82
LDL-CE	0.98	-8.36	-2.61	-6.16	-1.57	-9.93
LDL-TG	-21.70	74.98	-2.86	30.94	11.71	132.85
HDL2	-27.99	-41.76	9.05	-4.33	-12.99	27.10
HDL2-FC	27.58	56.79	1.53	0.56	33.73	-7.33
HDL2-CE	-8.28	-33.11	22.38	-11.72	-22.83	20.08
HDL2-TG	-17.44	-36.00	7.14	4.04	23.67	-5.40
HDL3	-0.02	0.47	8.61	6.79	-4.85	3.24
HDL3-FC	9.18	30.66	6.55	0.70	19.22	-1.38
HDL3-CE	-13.38	2.84	5.79	2.93	-3.63	5.20
HDL3-TG	-13.95	-19.52	19.84	-6.99	36.83	-6.30
VLDL1-ApoB	81.13	-35.68	13.42	-16.01	11.09	227.03
VLDL1-ApoC-II	99.16	-53.01	16.48	-33.25	-7.82	49.46
VLDL1-ApoC-III	96.43	-45.24	13.86	7.15	-6.63	149.32
VLDL1-ApoE	161.79	-13.77	121.76	291.08	14.2	115.17
VLDL2-ApoB	1.69	-24.68	3.75	-40.44	9.75	-15.75
VLDL2-ApoC-II	265.70	-47.72	-21.40	-50.09	55.37	112.97
VLDL2-ApoC-III	62.90	-36.87	2.18	-12.37	5.71	54.28
VLDL2-ApoE	8.79	49.10	21.89	-24.36	21.62	-19.52
IDL-ApoB	-7.59	-27.38	22.59	-49.65	-12.35	-50.02
IDL-ApoE	45.69	216.83	153.39	-44.72	26.87	26.40
LDL-ApoB	42.57	-49.29	6.12	-52.08	-7.53	-49.89
LDL-ApoE	137.20	205.83	45.45	-14.09	-6.07	13.39
LDL-I	72.03	-70.99	53.98	-48.08	0.80	-67.77
LDL-II	35.29	159.38	-10.06	0.09	-2.62	-52.19
LDL-III	-21.85	-60.60	103.38	-46.52	-6.62	21.86
%LDL-III	-29.83	-12.93	90.44	19.96	-7.34	118.15
LDL-Lp(a)	-69.07	-56.99	-50.49	-9.76	-10.21	16.83
LDL-III-Lp(a)	16.90	261.54	58.28	50.65	99.44	88.50

[a] Values of difference from baseline mean to final mean for HTG group (not lsmean of absolute change), [b] $p \leq 0.001$, [ns] = not significant versus placebo (continued)

Table I Summary of efficacy findings (PP population) (continued)

	Rosuvastatin compared with placebo after 8 weeks of treatment					
	Lipid profile groups					
	Type IV HTG		Type IIb CHL		Type IIa HC	
	Placebo (N = 5)	Rosuvastatin 40 mg (N = 5)	Placebo (N = 14)	Rosuvastatin 40 mg (N = 14)	Placebo (N = 15)	Rosuvastatin 40 mg (N = 15)
HDL2	-27.99	-41.76	9.05	-4.33	-12.99	27.10
HDL3	-0.02	0.47	8.61	6.79	-4.85	3.24
HDL2/HDL3	-25.45	-40.32	-0.27	-9.79	-8.12	21.85
Efflux into plasma	46.88	16.34	30.16	6.73	26.60	15.74
Efflux into HDL3	1.24	-3.35	0.49	0.23	-4.01	6.11
ApoC-II	1.00	-37.22	2.14	-26.22	-1.32	-13.12
ApoC-III	-1.19	-10.51	0.17	-1.11	-14.12	4.32
ApoE	5.12	9.38	-4.80	-40.59	-11.68	-26.34
Plasma LDL-C	2.32	-54.26	5.53	-57.24	-2.40	-61.31
True LDL-C	7.77	-53.56	3.95	-56.70	-6.47	-61.20
CETP activity	2.76	47.80	66.56	-13.96	28.37	58.49
CETP concentration	-10.29	-29.26	14.29	-33.77	-3.01	-35.64
LDL oxidisability	55.00	168.42	205.81	1062.28	580.40	416.50

[a] Values of difference from baseline mean to final mean for HTG group (not lsmean of absolute change), [b] $p \leq 0.001$, [ns] = not significant versus placebo

Reductions in LDL-C levels were observed in response to treatment with rosuvastatin 40 mg in all subjects. Numbers of subjects in the HTG group were too small to permit analysis but in the CHL and HC lipid profile groups, rosuvastatin resulted in a statistically significantly greater decrease in LDL-C levels than did placebo.

The mean reduction in LDL-C levels by treatment with rosuvastatin 40 mg in the HC and CHL groups fulfilled the criterion of a reduction of 2.2498 mmol/L to allow exploration of secondary objectives. Endpoints for the HTG group, in which the reduction from baseline in LDL-C did not reach this target, continued to be monitored.

Among the secondary endpoints, the most notable changes in response to rosuvastatin treatment were decreases in all the lipid profile groups in TC, ApoB, LDL-ApoB, LDL, IDL and SQ-IDL-C, and increases in HDL-C.

There were some differences between the lipid profile groups in response to rosuvastatin. For example, reductions in VLDL-C and ApoC-II were noted in the HTG and CHL groups but to a lesser extent in the HC group. ApoE was observed to decrease in the HC and CHL groups but less so in the HTG group, while VLDL-TG and VLDL1 levels declined more markedly in the HTG group than in either of the HC or CHL groups. Changes in all other endpoints were more difficult to interpret owing to variability in the results.

Reductions in lipid parameters following rosuvastatin treatment were accompanied by a decrease in the CE to TG ratio. Thus, rosuvastatin resulted in a reduction in particle count, and the remaining particles were richer in TG than in CE.
No distinct effects of rosuvastatin could be detected on cholesterol efflux into plasma or to the acceptor HDL3. Decreases in CETP concentration were observed following rosuvastatin treatment in all groups, although changes in activity were more variable and there were discernible differences in baseline values between placebo and rosuvastatin in each subject group. In the assay for LDL oxidisability, there was a tendency for the conjugated diene lag phase to increase but the small sample sizes precluded meaningful conclusions being drawn.
Safety: Rosuvastatin 40 mg was generally well tolerated; the percentage of subjects with adverse events (including treatment-related adverse events) was similar to that in the placebo group. There were no deaths or serious adverse events in the trial, and two subjects withdrew due to adverse events. Pharyngitis and hypertension were the most commonly reported events. Overall, there were no apparent differences between rosuvastatin 40 mg and placebo in the incidences of individual adverse events, most of which occurred as isolated cases. No subject had an elevation of ALT that was >3 x ULN or an elevation in CK >10 x ULN on either rosuvastatin 40 mg or placebo treatment. There were no marked changes or treatment-related trends in clinical biochemistry parameters, vital signs or physical examinations.