# SYNOPSIS

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|---|---|
| Drug product | Rosuvastatin tablets 10 and 20 mg |
| Drug substance(s) | Rosuvastatin calcium |
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An Open-label Randomised, Multicentre, Phase-IIIb, Parallel-group Switching Study to Compare the Efficacy and Safety of Lipid-lowering Agents Atorvastatin, Pravastatin, Simvastatin and Rosuvastatin in Subjects with Type IIa and IIb Hypercholesterolaemia

**International Co-ordinating Investigator**

**Study centres**

This study was conducted at 224 centres: UK (41 centres), France (7 centres), Germany (20 centres), the Netherlands (17 centres), Italy (8 centres), Spain (6 centres), Norway (28 centres), Denmark (1 centre), Finland (12 centres), Belgium (8 centres), Hungary (13 centres), the Czech Republic (13 centres), Slovakia (9 centres), Canada (25 centres), and Australia (16 centres).

**Publications**

None at the time of writing this report.

| **Study dates** | | **Phase of development** |
|---|---|---|
| First subject enrolled | 21 May 2001 | Therapeutic confirmatory (IIIb) |
| Last subject completed | 3 April 2002 | |

## Objectives

The primary objective of this study was to compare the efficacy of rosuvastatin with each of atorvastatin, simvastatin, and pravastatin in bringing subjects to their established European Atherosclerosis Society (EAS) (Wood et al, 1998) low-density lipoprotein cholesterol (LDL-C) target goal at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.

Secondary objectives were:

- To compare the efficacy of rosuvastatin with each of atorvastatin, simvastatin, and pravastatin in bringing subjects to their established National Cholesterol Education Program (NCEP) (Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults, 2001 [Adult Treatment Panel III]) LDL-C target goal at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.

- To compare the efficacy of rosuvastatin with each of atorvastatin, simvastatin, and pravastatin in bringing subjects to their established EAS LDL-C and total cholesterol (TC) target goal at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.

- To compare the efficacy of rosuvastatin with each of atorvastatin, simvastatin, and pravastatin in bringing subjects to their established EAS LDL-C target goal and their established NCEP LDL-C target goal at Week 8.

- To compare the efficacy of rosuvastatin with each of atorvastatin, simvastatin, and pravastatin in bringing subjects to their established EAS LDL-C and TC target goal at Week 8.

- To compare the efficacy of rosuvastatin with each of atorvastatin, simvastatin, and pravastatin in modifying lipids and lipoproteins at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.

- To compare the efficacy of rosuvastatin with each of atorvastatin, simvastatin, and pravastatin in modifying lipids and lipoproteins at Week 8.

- To compare effectiveness of treatment of rosuvastatin with atorvastatin, simvastatin, and pravastatin at 8 and 16 weeks of treatment.

- To compare rosuvastatin, atorvastatin, simvastatin, and pravastatin at 8 weeks and 16 weeks of treatment with respect to the incidence and severity of adverse events and abnormal laboratory values.

## Study design

This was an open-label, randomised, multicentre, 5-arm, parallel-group, 2-period study investigating the efficacy and safety of 8 weeks of treatment (rosuvastatin 10 mg/day [Arm 1], atorvastatin 10 mg/day [Arm 2] or 20 mg/day [Arm 3], simvastatin 20 mg/day [Arm 4], or pravastatin 40 mg/day [Arm 5]) in subjects with primary hypercholesterolaemia (Period 1), followed by a further 8 weeks of treatment when subjects were switched to rosuvastatin or remained on original treatment (Period 2). Treatments in each arm of Period 2 were as follows: Arm 1 (rosuvastatin 10 mg); Arm 2 (half switched to rosuvastatin 10 mg, half remained on atorvastatin 10 mg); Arm 3 (one-third switched to rosuvastatin 10 mg, one-third to rosuvastatin 20 mg, and one-third remained on atorvastatin 20 mg); Arm 4 (half switched to rosuvastatin 10 mg, half remained on simvastatin 20 mg); Arm 5 (half switched to rosuvastatin 10 mg, half remained on pravastatin 40 mg).

## Target subject population and sample size

Male and female subjects, aged 18 years or older, with primary hypercholesterolaemia (Types IIa or IIb), a history of coronary heart disease (CHD), Type 2 diabetes, CHD risk score of >20%/10 year, or other established atherosclerotic disease.

A total of 2022 evaluable subjects were required (630 for atorvastatin 20 mg; 348 for each of the other 4 treatment arms) – from 2260 randomised subjects (derived from approximately 5650 subjects) – for 80% power of detecting a 15% difference (between rosuvastatin and each comparator) in the % of subjects reaching EAS LDL-C target goal at Week 16 (the primary variable of this study). The 15% difference used for sizing this study was based on previous rosuvastatin comparator studies; it was recognised that not all comparisons in this study would show such a magnitude of difference.

## Investigational product and comparators: dosage, mode of administration and batch numbers

Rosuvastatin (ZD4522, CRESTOR™) 10 and 20 mg, atorvastatin 10 and 20 mg, simvastatin 20 mg, and pravastatin 40 mg. Doses were administered orally once daily as a single tablet. Batch numbers were: rosuvastatin (10 mg) TS1021R2; rosuvastatin (20 mg) TS1022R2; atorvastatin (10 mg) H1802372, and H1802404; atorvastatin (20 mg) 31800301, 071401W1, 032601W1, and 143501W2; simvastatin 205880, 212231, 212527, and 214694; and pravastatin A148, A161, A174, and A139.

## Duration of treatment

A 6-week dietary lead-in period, followed by 2 consecutive 8-week treatment periods (Periods 1 and 2). Eligible subjects then had the option to enter into an extension study (planned to run until March 2004 or until the launch of rosuvastatin in each country).

## Criteria for evaluation (main variables)

### Efficacy

- Primary variable:
  - Percentage of subjects reaching EAS LDL-C target goal at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.
- Secondary variables:
  - Percentage of subjects reaching NCEP LDL-C target goal at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.
  - Percentage of subjects reaching EAS LDL-C and TC target goal at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.
  - Percentage of subjects reaching EAS LDL-C target goal and % of subjects reaching NCEP LDL-C target goal at Week 8.
  - Percentage of subjects reaching EAS LDL-C and TC target goal at Week 8.
  - Percent change from baseline in lipids and lipoproteins at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment.
  - Percent change from baseline in lipids and lipoproteins at Week 8.
  - Percentage of subjects reaching EAS LDL-C, NCEP LDL-C, and EAS LDL-C and TC target goals at 16 weeks of treatment with rosuvastatin, atorvastatin, simvastatin, and pravastatin.
  - Percent change in lipids and lipoproteins at 16 weeks of treatment with rosuvastatin, atorvastatin, simvastatin, and pravastatin.

### Safety

- Secondary variable:
  - Safety evaluation as determined by the incidence of adverse events and abnormal laboratory data at Weeks 8 and 16.

## Statistical methods

Analyses were performed on last observations carried forward (LOCF) from an intention-to-treat (ITT) population. The numbers of subjects reaching target goals were compared using logistic regression analyses; % changes from baseline in lipids and lipoproteins were compared using analysis of variance (ANOVA) models. The Bonferroni correction was applied to significance levels to allow for multiple treatment comparisons. Safety data were not subject to formal statistical analysis.

## Subject population

In total, 6508 subjects entered the dietary lead-in period (of a planned 5650) and 3161 subjects were randomised to treatment (of a planned 2260). A lower than expected incidence of screen failures led to more subjects than planned being randomised to treatment.

The majority of randomised subjects were Caucasian (99%) and between 18 and 64 years of age (58%). The sex balance in the study population (58% males and 42% females) resembled that seen in subjects presenting with primary hypercholesterolaemia in clinical practice. Overall, the treatment groups were comparable for demographic characteristics and baseline lipid levels, and had baseline lipid levels similar to those seen in subjects presenting with primary hypercholesterolaemia in clinical practice.

Of the 3161 randomised subjects, 12 received no study treatment and were not included in the safety population. In Period 1, the following numbers of subjects actually received study treatment: rosuvastatin 10 mg n=550; atorvastatin 10 mg n=536; atorvastatin 20 mg n=948; simvastatin 20 mg n=557; and pravastatin 40 mg n=534. (There was also a cerivastatin treatment arm, which was subsequently removed from the protocol due to the withdrawal of cerivastatin from all markets, and 21 subjects actually received cerivastatin in Period 1. In addition, due to dispensing errors 2 subjects actually received more than 1 treatment, and 1 subject actually received rosuvastatin 20 mg, in Period 1.) In Period 2, the following numbers of subjects actually received study treatment: rosuvastatin 10 mg n=1646; rosuvastatin 20 mg n=306; atorvastatin 10 mg n=245; atorvastatin 20 mg n=310; simvastatin 20 mg n=254; and pravastatin 40 mg n=256.

Of the 3140 subjects randomised to treatment with rosuvastatin, atorvastatin, simvastatin, and pravastatin, 122 discontinued treatment in Period 1 (all of the cerivastatin subjects also discontinued) and 62 discontinued in Period 2; thus 2956 subjects completed both study periods. Overall, the total % of subjects discontinuing was similar between treatments, and the most common reason for discontinuation of treatment was adverse events.

There were 3149 subjects in the safety population; and 2967 and 2353, respectively, in the ITT and per-protocol (PP) populations for the primary variable at Week 16.

## Efficacy results

The results of the analysis of the % of subjects reaching EAS LDL-C target goal at Week 16, subjects having switched to rosuvastatin at Week 8 or having remained on original treatment (the primary variable of this study), are presented in Table 1.

## Table 1 Percentage of subjects reaching EAS LDL-C target goal at Week 16 (LOCF on ITT population)

| Statistic | | Treatment arm – Period 1/Period 2 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Arm 1** | **Arm 2** | | **Arm 3** | | | **Arm 4** | | **Arm 5** | |
| | | **R10/R10 (n=521)** | **A10/R10 (n=276)** | **A10/A10 (n=240)** | **A20/R10 (n=293)** | **A20/R20 (n=305)** | **A20/A20 (n=299)** | **S20/R10 (n=277)** | **S20/S20 (n=250)** | **P40/R10 (n=253)** | **P40/P40 (n=253)** |
| Baseline LDL-C: mean (SD) | mmol/L | 4.27 (0.80) | 4.21 (0.74) | 4.19 (0.69) | 4.32 (0.78) | 4.37 (0.79) | 4.32 (0.86) | 4.30 (0.76) | 4.28 (0.75) | 4.23 (0.77) | 4.26 (0.83) |
| | mg/dL | 164.9 (31.0) | 162.7 (28.7) | 161.6 (26.5) | 166.7 (30.1) | 168.9 (30.6) | 166.8 (33.2) | 165.8 (29.3) | 165.1 (28.9) | 163.1 (29.9) | 164.3 (31.9) |
| Reaching target: n/N[a] | | 457/521 | 237/276 | 193/240 | 251/293 | 275/305 | 252/299 | 238/277 | 180/250 | 222/251 | 166/252 |
| **Analysis** | | | | | | | | | | | |
| Proportion reaching target | | 0.88 | 0.86 | 0.80 | 0.86 | 0.90 | 0.84 | 0.86 | 0.72 | 0.88 | 0.66 |
| Difference (SE) | | NA | 0.06 (1.32)[b] | | 0.02 (1.31)[c] | 0.06 (1.34)[d] | | 0.14 (1.32)[b] | | 0.22 (1.36)[b] | |
| Odds ratio | | NA | 1.84 | | 1.13 | 2.27 | | 3.55 | | 7.78 | |
| 95% CI | | NA | 1.08 to 3.20 | | 0.62 to 2.07[e] | 1.20 to 4.42[e] | | 2.10 to 6.16 | | 4.34 to 14.65 | |
| p-value[f] | | NA | **0.0257** | | 0.6417[e] | **0.0039**[e] | | **<0.0001** | | **<0.0001** | |

[a] n/N represents the number of subjects reaching target / the number of subjects with recorded data; EAS target for LDL-C: <3.0 mmol/L (116 mg/dL).
[b] Relates to the difference in the proportion of subjects reaching target goal (rosuvastatin minus comparator) for the 2 Period-2 arms arising from the single Period-1 arm.
[c] Relates to the difference in the proportion of subjects reaching target goal (rosuvastatin 10 mg minus atorvastatin 20 mg) for the 2 relevant Period-2 arms arising from the single Period-1 arm.
[d] Relates to the difference in the proportion of subjects reaching target goal (rosuvastatin 20 mg minus atorvastatin 20 mg) for the 2 relevant Period-2 arms arising from the single Period-1 arm.
[e] 97.5% CI (p-values <0.025 are statistically significant due to application of Bonferroni corrections).
[f] p-value obtained using logistic regression analyses; values <0.05 are statistically significant (except[e]); values in bold are statistically significant.
A10 or A20 Atorvastatin 10 or 20 mg; CI Confidence interval; NA Not applicable; P40 Pravastatin 40 mg; R10 or R20 Rosuvastatin 10 or 20 mg; S20 Simvastatin 20 mg; SE Standard error. (For example, A10/R10 represents atorvastatin 10 mg in Period 1 followed by rosuvastatin 10 mg in Period 2.)

A statistically significant greater % of subjects who switched to rosuvastatin 10 mg at Week 8 reached EAS LDL-C target goal at Week 16 compared with subjects who remained on atorvastatin 10 mg (86% versus 80%, p=0.0257), simvastatin 20 mg (86% versus 72%, p<0.0001), or pravastatin 40 mg (88% versus 66%, p<0.0001). In addition, a statistically significant greater % of subjects who switched to rosuvastatin 20 mg at Week 8 reached EAS LDL-C target goal at Week 16 compared with subjects who remained on atorvastatin 20 mg (90% versus 84%, p=0.0039). Compared with subjects who remained on atorvastatin 20 mg, a numerically greater percentage of subjects who switched to rosuvastatin 10 mg at Week 8 reached EAS LDL-C target goal at Week 16 (86% versus 84%, p=0.6417). Therefore, a greater percentage of subjects who switched to rosuvastatin at Week 8 reached target at Week 16, and this is considered to indicate a clinical benefit of treatment with rosuvastatin.

Results for the secondary variables supported those for the primary variable: compared with the other statins, a greater % of subjects who switched to rosuvastatin at Week 8 reached EAS and NCEP target goals – and showed an improved lipid profile – at Week 16. The analyses of the Week-8 data and effectiveness of 16 weeks of treatment with rosuvastatin supported the clinical benefit of rosuvastatin 10 mg.

**Safety results**

Overall, the study treatments were well tolerated. In Periods 1 and 2, the incidence of AEs associated with each treatment was generally similar, the incidence of deaths, SAEs, and discontinuations due to AEs (DAEs) was low and there was no evidence of any treatment-related differences. None of the AEs that occurred in this study was unexpected given the age and underlying medical conditions of the subject population. There were no events indicative of hepatic dysfunction, which has been reported previously with other statins. Myalgia (also known to occur with statins) was reported by 1.9% of subjects in Period 1 and 0.9% of subjects in Period 2; none of the cases was associated with a clinically important elevation in CK (>10-times the ULN).

Changes in clinical laboratory results were generally small and showed no treatment-related trends. There were no clinically important elevations in ALT (>3-times the ULN on 2 consecutive visits). Two subjects (0.1%) had a clinically important elevation in CK (>10-times the ULN on at least 1 occasion): 1 on atorvastatin 20 mg in Period 1, the other on rosuvastatin 10 mg in Period 2; both subjects were asymptomatic. A >30% change from baseline in serum creatinine was reported by 38 subjects (1.2%).

Changes in vital signs and physical findings were small and showed no treatment-related trends.