AstraZeneca

Drug product	Rosuvastatin calcium tablets 10 mg and 20 mg	**SYNOPSIS**	
Drug substance	Rosuvastatin calcium		
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Report on the Randomized Treatment Phase

Study Title: A 6-Week, Randomized, Open-Label, Comparative Study to Evaluate the Efficacy and Safety of Rosuvastatin and Atorvastatin in the Treatment of Hypercholesterolemia in African-American Subjects

Coordinating investigator

Study centers

This study was conducted at 82 centers across the United States of America (USA).

Publications

Ferdinand K, Deedwania PC, Haffner S, Caplan RJ, Gold A. Designs of 3 trials comparing rosuvastatin and atorvastatin in African American, South Asian, and Hispanic patients: ARIES, IRIS, and STARSHIP trials [abstract]. Atheroscler Suppl 2003;4(2):83. Abstract 1P-0290.

Study dates		**Phase of development**
First subject enrolled	05 March 2002	Therapeutic confirmatory (IIIb)
Last subject completed randomized treatment phase	29 December 2003	

Objectives

The primary objective of the study was:

- To compare the efficacy of 2 doses of rosuvastatin (10 mg and 20 mg) with 2 doses of atorvastatin (10 mg and 20 mg) in African-American subjects with

hypercholesterolemia by measuring the percent change in low-density lipoprotein cholesterol (LDL-C) from baseline after 6 weeks of treatment.

Secondary objectives of the randomized treatment phase of the study were to compare the efficacy and safety of 2 doses of rosuvastatin (10 mg and 20 mg) with 2 doses of atorvastatin (10 mg and 20 mg) in African-American subjects with hypercholesterolemia by measuring:

- Percent change from baseline in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-high-density lipoprotein cholesterol (non-HDL-C), Apolipoprotein B (ApoB), Apolipoprotein A-I (ApoA-1), LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-I after 6 weeks of treatment

- Percentage of subjects, overall and by risk category, who achieve the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) LDL-C goals after 6 weeks of treatment

- Percentage of subjects with TG ≥200 mg/dL at baseline who achieve both their NCEP ATP III LDL-C and non-HDL-C goals after 6 weeks of treatment

- Safety and tolerability by evaluating the frequency and severity of adverse events (AEs) and abnormal laboratory values through 6 weeks of treatment

The pharmacokinetic objective of the study was:

- To quantify systemic exposure to rosuvastatin by measuring steady state plasma rosuvastatin concentration in approximately 150 subjects randomized to rosuvastatin.

The secondary objective of the extension phase of the study was:

- To assess safety and tolerability by evaluating the incidence and severity of AEs and abnormal laboratory values in rosuvastatin-treated subjects at the end of the open-label extension (OLE) phase

Study design

This was an open-label, randomized, multicenter, Phase IIIb study to compare the efficacy and safety of rosuvastatin and atorvastatin in African-American subjects with hypercholesterolemia. After a 6 week dietary lead-in period, eligible subjects were randomized to 1 of 4 treatment dose groups: rosuvastatin 10 mg or 20 mg or atorvastatin 10 mg or 20 mg for a 6 week treatment period. After successful completion of the randomized treatment phase, eligible subjects could elect to participate in the OLE phase.

This clinical study report (CSR) reports on the randomized treatment phase of the study.

Target subject population and sample size

African-Americans, aged 18 or older, with a diagnosis of hypercholesterolemia (Fredrickson Types IIa or IIb), fasting TG levels <400 mg/dL, fasting LDL-C ≥160 mg/dL and ≤300 mg/dL if not taking statins the previous 7 days or fasting LDL-C ≥130 mg/dL and ≤250mg/dL if taking statins within 7 days, but who agreed to discontinue all cholesterol-lowering drugs, were recruited for this study.

One-hundred-forty-eight (148) evaluable subjects per treatment dose group (a total of 592 subjects) were required to test the hypothesis of superiority in terms of percent change from baseline in LDL-C levels, based on power of 85%, for each of the comparisons between rosuvastatin and atorvastatin. A predicted screen-failure rate of 60% and a withdrawal rate of 15% during the randomized treatment phase were based on previous rosuvastatin studies.

Of the 2385 subjects who entered into the dietary lead-in period, with a screen-failure rate of 67.5%, a total of 774 subjects were randomized, with at least 178 evaluable subjects per treatment dose group, meeting the desired power for this study. (The withdrawal rate was 6.7% during the randomized treatment phase).

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

Rosuvastatin calcium (CRESTOR™) 10 mg and 20 mg and atorvastatin 10 mg and 20 mg. Doses were to be taken orally, once daily, as a single tablet. (Atorvastatin was supplied as commercially available tablets through the local retail pharmacy). Batch numbers for rosuvastatin 10 mg were 2000027606, 2000038729 and for rosuvastatin 20 mg were 2000027616, 2000036165. (A subject randomized to rosuvastatin 20 mg was incorrectly dispensed rosuvastatin 10 mg [batch number 200007606] at Visit 4, returned to the site later that same day, and was re-dispensed rosuvastatin 20 mg [batch number 2000027616]. This discrepancy is noted on page 7 of the CSR Appendix 12.1.6).

Duration of treatment

After a 6 week dietary lead-in period, eligible subjects were randomized to 1 of 4 treatment dose groups: rosuvastatin 10 mg or 20 mg or atorvastatin 10 mg or 20 mg for a 6 week treatment period. Eligible subjects who completed the randomized treatment phase had the option to enter the OLE phase for a minimum of 12 weeks; these results were reported in a separate CSR.

Criteria for evaluation (main variables)

Efficacy

The following efficacy variables were addressed in the randomized treatment phase:

(a) Primary variable

- Percent reduction in LDL-C from baseline to Week 6

(b) Secondary variables:

- Percent change from baseline in TC, HDL-C, TG, non-HDL-C, ApoB, ApoA-I, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-I at Week 6
- Percent of subjects, overall and by risk category, who achieved their NCEP ATP III LDL-C goal at Week 6
- Percent of subjects with TG ≥200 mg/dL at baseline who achieved both their NCEP ATP III LDL-C and non-HDL-C goals at Week 6

Pharmacokinetics

The following pharmacokinetic variable was examined in the randomized treatment phase (continuing into the extension phase):

- Steady state plasma rosuvastatin concentrations

Safety

The following safety variable was studied in the randomized treatment phase:

- Frequency of AEs and abnormal laboratory values at Week 6

Statistical methods

(a) Analysis of efficacy

The Intent-to-Treat (ITT) population consisted of all randomized subjects who received study treatment and had a baseline reading of at least 1 pre-randomization measurement and at least 1 post-baseline reading for 1 or more lipid variables. The Per-Protocol (PP) efficacy population contained all subjects included in the ITT population who did not have a major protocol deviation.

The goal of this analysis was to show superiority of rosuvastatin in terms of LDL-C lowering in any of the 3 comparisons of interest: rosuvastatin 10 mg and atorvastatin 10 mg; rosuvastatin 10 mg and atorvastatin 20 mg; and rosuvastatin 20 mg and atorvastatin 20 mg. Prior to testing for superiority, a non-inferiority test, with a 6% limit, was performed. Superiority was established for a comparison if that contrast showed statistical separation at the $p < 0.017$ type I error level. The above comparisons were made using a Bonferroni adjustment with a significance level of 0.017, to obtain an experiment-wise error rate of 0.05. The initial analysis of variance (ANOVA) model included terms for treatment and region (pooled centers). The results were presented as least squares means (lsmeans) with 98.3% confidence intervals (CIs) and p-values.

The assumptions of normality and homogeneity of variance were explored using probability and residual plots. If any of the assumptions were violated, an appropriate transformation of

the data was performed in an attempt to induce normality; if transformations failed to induce normality, then an appropriate non-parametric test was used.

The analysis of the primary efficacy variable was repeated for the secondary variables (TC, HDL-C, TG, non-HDL-C, TC/HDL-C, non-HDL-C/HDL-C, LDL-C/HDL-C, ApoB, ApoA-I, and ApoB/ApoA-I), although a meaningful difference was dependent on the parameter analyzed.

The number and percent of subjects who achieved their NCEP ATP III LDL-C goal, and non-HDL-C goal, if baseline TG was ≥200 mg/dL, at Week 6 was calculated and summarized, both overall and by NCEP ATP III risk category.

Details on the exploratory analyses are included in the Statistical Analysis Plan (SAP) for the randomized treatment phase (Appendix 12.1.9).

(b) Analysis of safety

Data from all subjects who entered the dietary lead-in period onwards was included in the evaluation of safety. Those subjects who withdrew during the dietary lead-in period and those who withdrew after randomization were summarized separately. The safety population for treatment-emergent AEs contained all subjects who had at least 1 dose of study treatment.

AEs were classified according to 3 definitions: reported during the dietary lead-in period, treatment-emergent (ie, either starting during the randomized treatment phase or ongoing from the dietary lead-in period and subsequently worsening during the randomized treatment phase), and observed during the randomized treatment phase (ie, all events that started, stopped, or were ongoing within the randomized treatment phase). The incidence of AEs was tabulated by treatment received according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term, and reported by treatment dose group for events occurring during the dietary lead-in period and those that were treatment-emergent. In the case of AEs leading to study discontinuation (DAEs), the incidence was also tabulated and reported by treatment dose group for all events observed during the randomized treatment phase. Summaries of all AEs, deaths, serious AEs (SAEs), DAEs, and treatment-related AEs were presented.

Hematology and clinical chemistry were summarized by mean, median, standard deviation (SD), minimum, maximum, and number of subjects at each visit. Hematology and clinical chemistry values outside the laboratory reference ranges were highlighted. Hepatic biochemistry and creatine kinase (CK) values, as well as their changes from baseline, were summarized using descriptive statistics at each visit. Elevations of alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN) and CK >10 x ULN were highlighted and summarized by treatment dose group.

Urinalysis results were also presented by mean, SD, minimum, maximum, and number of subjects at each visit, where appropriate. Qualitative urinalysis results were presented in

tabular format, summarizing the "shift" from qualitative category at baseline to qualitative category at a particular visit.

Vital signs and weight were summarized with descriptive statistics. Physical examination abnormalities at baseline and new or aggravated physical exam abnormalities at Week 6 were listed.

Subject population

In total, 2385 subjects entered the dietary lead-in period and 774 subjects from 76 centers were randomized to treatment. The first subject was enrolled in the study on 05 March 2002 and the last subject completed the randomized treatment phase of the study on 29 December 2003. The mean age was generally comparable across the treatment dose groups, with the age range of subjects in the study 18 to 87 years and the overall median age 54 years. More female subjects than male subjects participated in the study, 501/774 (64.7%) compared to 273/774 (35.3%), respectively; however, the male to female ratios in the rosuvastatin and atorvastatin groups were similar. Body mass index (BMI) was somewhat high but similar across all treatment dose groups, with a mean of 32.5 kg/m^2 overall. Other demographic and baseline characteristics were generally comparable across the treatment dose groups and the subject population enrolled in this study was representative of the target population for rosuvastatin (ie, had baseline lipid and lipoprotein levels consistent with hypercholesterolemia).

At Week 6, 765 subjects were included in the safety population; data from 732 subjects were analyzed for efficacy in the ITT population and from 582 subjects in the PP population.

The frequency of subjects discontinuing from the randomized treatment phase was low (6.7%) and generally similar across the treatment dose groups. The most common reasons for discontinuation were adverse events (2.3%) and protocol non-compliance (1.6%) overall. Protocol deviations considered serious enough to warrant exclusion of data from the PP population analysis were similar across the treatment dose groups and occurred most frequently (16.4%) in the category of non-compliance. The mean level of observed treatment compliance for the atorvastatin-treated subjects was slightly lower (93.1% for rosuvastatin-treated subjects vs 88.9% for atorvastatin-treated subjects) due to local pharmacy errors and also may have reflected delays in dispensing atorvastatin. The frequency of rosuvastatin-treated subjects with >90% compliance was 71.2% compared to 61.9% for atorvastatin-treated subjects.

Efficacy results

The analysis of the percent change in LDL-C, TC, HDL-C, TG, and non-HDL-C from baseline to Week 6, comparing rosuvastatin and atorvastatin for the LOCF on the ITT population, is summarized in Table S 1.

Table S 1 Analysis of percent change from baseline to Week 6 in LDL-C, TC, HDL-C, TG, and non-HDL-C comparing rosuvastatin and atorvastatin (LOCF on ITT population)

ANOVA for % change[a]	Rosuva 10 mg		Rosuva 20 mg		Atorva 10 mg		Atorva 20 mg		Rosuva 10 mg –Atorva 10 mg		Rosuva 10 mg –Atorva 20 mg		Rosuva 20 mg –Atorva 20 mg	
Week 6 LOCF for LDL-C														
N (%)	186		188		178		177							
Lsmean (SE)	-37.1	(1.28)	-45.7	(1.27)	-31.8	(1.32)	-38.5	(1.31)	-5.3	(1.63)	1.4	(1.63)	-7.2	(1.63)
LCL to UCL[b]									-9.2 to -1.4		-2.5 to 5.3		-11.1 to -3.3	
p-value									0.0013*		0.3806		<0.0001*	
Week 6 LOCF for TC														
N	186		188		178		178							
Lsmean (SE)	-26.6	(1.01)	-33.0	(1.00)	-23.1	(1.04)	-28.7	(1.03)	-3.4	(1.29)	2.1	(1.29)	-4.3	(1.28)
LCL to UCL[b]									-6.5 to -0.4		-1.0 to 5.2		-7.4 to -1.2	
p-value[c]									0.0076*		0.1022		0.0008*	
Week 6 LOCF for HDL-C														
N	186		188		178		178							
Lsmean (SE)	7.0	(0.94)	6.5	(0.94)	5.6	(0.97)	3.7	(0.96)	1.4	(1.20)	3.3	(1.20)	2.8	(1.20)
LCL to UCL[b]									-1.5 to 4.3		0.4 to 6.1		0 to 5.7	
p-value[c]									0.2489		0.0065*		0.0189	
Week 6 LOCF for TG														
N	186		188		178		178							
Lsmean (SE)	-16.0	(1.87)	-20.9	(1.87)	-17.1	(1.94)	-19.6	(1.91)	1.1	(2.39)	3.5	(2.39)	-1.3	(2.39)
LCL to UCL[b]									-4.6 to 6.8		-2.2 to 9.3		-7.0 to 4.4	
p-value[C]									0.6515		0.1394		0.5780	

Table S 1 Analysis of percent change from baseline to Week 6 in LDL-C, TC, HDL-C, TG, and non-HDL-C comparing rosuvastatin and atorvastatin (LOCF on ITT population)

ANOVA for % change[a]	Rosuva 10 mg		Rosuva 20 mg		Atorva 10 mg		Atorva 20 mg		Rosuva 10 mg –Atorva 10 mg		Rosuva 10 mg –Atorva 20 mg		Rosuva 20 mg –Atorva 20 mg	
Week 6 LOCF for non-HDL-C														
N	186		188		178		178							
Lsmean (SE)	-34.3	(1.22)	-42.3	(1.21)	-29.8	(1.26)	-35.6	(1.24)	-4.5	(1.55)	1.4	(1.55)	-6.7	(1.55)
LCL to UCL[b]									-8.2 to -0.8		-2.3 to 5.1		-10.4 to -3.0	
p-value[c]									0.0039*		0.3799		<0.0001*	
Week 6 LOCF for ApoB														
N	181		181		168		172							
Lsmean (SE)	-29.3	(1.23)	-37.2	(1.23)	-25.3	(1.30)	-31.4	(1.27)	-4.1	(1.58)	2.1	(1.57)	-5.8	(1.57)
LCL to UCL[b]									-7.8 to -0.3		-1.7 to 5.8		-9.6 to -2.1	
p-value[c]									0.0105*		0.1838		0.0002*	
Week 6 LOCF for ApoA-I														
N	181		181		168		172							
Lsmean (SE)	5.4	(0.99)	4.0	(0.99)	2.7	(1.04)	0.7	(1.02)	2.7	(1.27)	4.7	(1.26)	3.4	(1.26)
LCL to UCL[b]									-0.3 to 5.7		1.7 to 7.8		0.4 to 6.4	
p-value[c]									0.0340		0.0002*		0.0076*	

Data derived from Section 11, Table 11.2.1.1.3, Table 11.2.2.1.3, Table 11.2.3.1.3, Table 11.2.4.1.3, and Table 11.2.5.1.3.

[a] ANOVA included terms for treatment and region (pooled center).

[b] Upper and lower confidence interval limits set at 98.3%.

[c] The Bonferroni-adjusted critical p-value is 0.017; *denotes statistical significance.

ANOVA Analysis of variance; ApoA-I Apolipoprotein A-I; ApoB Apolipoprotein B; Atorva Atorvastatin; HDL-C High-density lipoprotein cholesterol; ITT Intent-to-Treat population; LCL Lower confidence interval limit; LDL-C Lower-density lipoprotein cholesterol; LOCF Last observation carried forward; Lsmean Least squares mean; Non-HDL-C Total cholesterol minus HDL-C; NR Not recorded; Rosuva Rosuvastatin; SE Standard error; TC Total cholesterol; TG Triglycerides; UCL Upper confidence interval limit.

The efficacy results of this study are based on the laboratory values of 732 African-American subjects with hypercholesterolemia after 6 weeks of treatment with rosuvastatin (10 mg or 20 mg) or atorvastatin (10 mg or 20 mg). Rosuvastatin 10 mg and rosuvastatin 20 mg had superior LDL-C reduction when compared to the same doses of atorvastatin. Rosuvastatin 10 mg achieved non-inferiority to atorvastatin 20 mg.

A statistically significantly greater reduction in TC was observed in subjects receiving rosuvastatin 10 mg and rosuvastatin 20 mg compared with subjects receiving the same doses of atorvastatin at Week 6. A statistically significantly greater increase in HDL-C was observed in subjects receiving rosuvastatin 10 mg compared with subjects receiving atorvastatin 20 mg at Week 6. While both the rosuvastatin and atorvastatin-treated subjects experienced reductions in TG after 6 weeks, no statistically significant difference was found between the treatment dose groups. A statistically significantly greater reduction in non-HDL-C was observed in subjects receiving rosuvastatin 10 mg and rosuvastatin 20 mg compared with subjects receiving the same doses of atorvastatin at Week 6.

Statistically significantly greater reductions in the ratios of LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C were observed in subjects receiving rosuvastatin 10 mg and rosuvastatin 20 mg compared with subjects receiving the same doses of atorvastatin at Week 6.

Statistically significantly greater reductions in ApoB and the ratio of ApoB/ApoA-I were observed in subjects receiving rosuvastatin 10 mg and rosuvastatin 20 mg compared with subjects receiving the same doses of atorvastatin after 6 weeks of treatment. Statistically significantly greater increases in ApoA-I were observed in subjects receiving rosuvastatin 10 mg compared with subjects receiving atorvastatin 20 mg and in subjects receiving rosuvastatin 20 mg compared with subjects receiving atorvastatin 20 mg at Week 6.

More subjects reached their target NCEP ATP III goals using rosuvastatin than atorvastatin at equivalent doses after 6 weeks of treatment. Differences in NCEP ATP III goal attainment were largest among high-risk subjects. High risk was considered having Coronary heart disease (CHD) or a CHD risk equivalent (clinical forms of atherosclerotic disease, diabetes), or 10 year risk for CHD >20%; target goal for LDL-C was <100 mg/dL and for non-HDL-C was <130 mg/dL.

These results showed that subjects treated with rosuvastatin 10mg and 20 mg had statistically significantly greater reductions in LDL-C, TC, non-HDL-C, and ApoB when compared to atorvastatin on a milligram-equivalent basis, and that subjects treated with rosuvastatin 10 mg had statistically significantly greater increases in HDL-C and ApoA-I when compared to subjects treated with atorvastatin 20 mg, in African-American subjects with hypercholesterolemia.

Pharmacokinetic results

The plasma rosuvastatin concentration data obtained in this study were incorporated into a population pharmacokinetic model for rosuvastatin. The results are reported separately by the Experimental Medicines Group (Wilmington, DE, USA).

Safety results

The frequency of AEs associated with each treatment dose group was similar. The most common AEs were myalgia (2.5%), headache (2.1%), nasopharyngitis (1.7%), constipation (1.7%), and arthralgia (1.6%). No deaths occurred in this study. The frequency of SAEs and DAEs was low; there were insufficient numbers of events to draw conclusions about possible treatment-related differences. The overall AE profile associated with each treatment dose group was similar. The majority of AEs were mild to moderate in severity and were considered by the investigator to be unrelated to study treatment. None of the AEs that occurred in this study was unexpected for this study population.

No events of hepatic dysfunction were found. The frequency of myalgia, a class effect of statins, was low (3.1% for rosuvastatin-treated subjects and 1.9% for atorvastatin-treated subjects). None of the cases were associated with a clinically important elevation in CK (>10 x ULN). Of 4 subjects with a treatment-emergent AE of blood creatine phosphokinase increased, only 1 subject in the atorvastatin 10 mg group had a laboratory value showing a CK elevation >5 x ULN. One subject in the rosuvastatin 10 mg group had a treatment-emergent AE of blood creatinine increased along with laboratory values indicating a >30% increase from baseline in serum creatinine.

Changes in clinical laboratory results were generally small and showed no treatment-related trends. No clinically important ALT elevations (ALT >3 x ULN) were found. No elevations in CK >5 x ULN occurred in rosuvastatin-treated subjects and 2 atorvastatin-treated subjects had CK elevations >5 x ULN (1 in each dose group). No subject had a clinically important CK elevation >10 x ULN. A >30% increase from baseline in serum creatinine was observed in 4 subjects, 3 rosuvastatin-treated subjects (0.8%) and 1 atorvastatin-treated subject (0.3%); no subject experienced a doubling in serum creatinine. Eight subjects, 3 rosuvastatin-treated (0.8%) and 5 atorvastatin-treated (1.3%) subjects, experienced an increase in dipstick urine protein from none or trace at baseline to "++ or greater" at Week 6. Fourteen subjects, 6 rosuvastatin-treated (1.6%) and 8 atorvastatin-treated (2.2%) subjects, had an increase in urine blood from none or trace at baseline to "++ or greater" at Week 6. Overall, the number of clinically notable elevations was low and similar across the treatment dose groups.

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

Rosuvastatin was well-tolerated in this African-American study population. The safety profile for rosuvastatin was similar to atorvastatin, and as expected for other statins.

Date of the report

07 July 2004