Drug product:	CRESTOR™	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium 10- and 20-mg tablet		
Document No.:	Not applicable		
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Final Report of Extension Phase and Overall Safety Data

An Open-label, Randomized, Multi-center, Phase IIIb, Parallel Group Switching Study to Compare the Efficacy and Safety of Lipid Lowering Agents Atorvastatin and Simvastatin with Rosuvastatin in High Risk Subjects with Type IIa and IIb Hypercholesterolemia (MERCURY II)

International co-ordinating investigator

Study center(s)

The randomized phase was conducted at 152 centers: US (117 centers), Canada (19 centers), Argentina (4 centers), Brazil (6 centers), and Mexico (6 centers). Of these, 145 centers enrolled patients into the extension phase: US (112 centers), Canada (18 centers), Argentina (4 centers), Brazil (6 centers), and Mexico (5 centers).

Publications

Ballantyne C, Raichlen JS, Cain VA, Sager PT. Effect of switching high- and very high-risk patients to rosuvastatin from atorvastatin or simvastatin on achievement of new ATP III goals: MERCURY II. Atheroscler Suppl 2005;6(1):101 (Abstract W16-P-003).
Ballantyne C, Raichlen JS, Cain VA, Sager PT. Achievement of non-HDL-C and apo B goals in high-risk patients who achieve their ATP III LDL-C goal: MERCURY II trial. Atheroscler Suppl 2005;6(1):101 (Abstract W16-P-004).

Study dates		**Phase of development**
First patient enrolled	28 November 2001	Therapeutic confirmatory (IIIb)
Last patient completed	24 October 2003 (Randomized phase) 15 September 2004 (Extension phase)	

Objectives

The primary objective of the study addressed in the randomized phase was:

- To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing patients at high risk for coronary heart disease (CHD) to their National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) low-density lipoprotein-cholesterol (LDL-C) target goal at Week 16. Patients were treated with atorvastatin or simvastatin for 16 weeks, or with rosuvastatin for 8 weeks following 8 weeks of comparator treatment.

Secondary objectives of the randomized phase of the study were aimed at comparing the efficacy of rosuvastatin with that of atorvastatin and simvastatin at 16 weeks in bringing patients to their LDL-C targets based on European Atherosclerosis Society (EAS) and Canadian Medical Association guidelines, in bringing patients with high triglyceride (TG) levels (≥200 mg/dL) to their NCEP ATP III LDL-C target, and in percentage changes from baseline in LDL-C and additional lipoproteins and lipids. Treatment effects at the 8-week time point were also evaluated. Rosuvastatin was compared with atorvastatin and simvastatin with respect to the incidence and severity of adverse events (AEs) and abnormal laboratory values, and the relationship between systemic exposure to rosuvastatin and calculated creatinine clearance (CrCl) and/or creatine kinase (CK) was assessed.

The extension phase of this study had a single objective, which was a secondary objective of the study. The objective was to:

- Assess the safety of extended treatment with rosuvastatin.

Although efficacy objectives were not specified for the extension phase of this study in the protocol, efficacy variables (see criteria for evaluation below) were summarized to address questions about efficacy for this open-label, titration-to-target extension phase.

Study design

This randomized, open-label, parallel-group, multi-center, study in patients at high risk for CHD events was designed to determine whether switching patients treated initially with atorvastatin or simvastatin to rosuvastatin is more effective than continued treatment with the comparator statins in bringing additional patients to goals. After a 6-week dietary lead-in period to stabilize baseline LDL-C values off lipid lowering therapy, eligible patients were randomly assigned to 1 of 5 treatments for 8 weeks (Period 1). At the end of Period 1, all patients were randomly assigned within each treatment arm to an additional 8 weeks of treatment (Period 2) with either the original comparator treatment or rosuvastatin:

Rosuvastatin 20 mg → rosuvastatin 20 mg
Atorvastatin 10 mg → atorvastatin 10 mg or rosuvastatin 10 mg
Atorvastatin 20 mg → atorvastatin 20 mg or rosuvastatin 20 mg
Simvastatin 20 mg → simvastatin 20 mg or rosuvastatin 10 mg
Simvastatin 40 mg → simvastatin 40 mg or rosuvastatin 20 mg

After successful completion of the randomized phase, eligible patients could elect to participate in an open-label extension phase examining the safety of rosuvastatin. During this time, patients were given an initial start dose of 10 mg or 20 mg of rosuvastatin based on their prior therapy during the randomized treatment period. At subsequent visits, the dose could be titrated up to 40 mg to attain their NCEP ATP III LDL-C target (<100 mg/dL).

This Clinical Study Report (CSR) presents cumulative (randomized phase and extension phase) rosuvastatin safety data, as well as efficacy data obtained during the extension phase. Efficacy and safety analyses for rosuvastatin and comparators during the randomized phase are reported in the CSR for the randomized phase of the study, located in an appendix to this report.

Target patient population and sample size

The target population of the randomized phase included male and non-pregnant female patients (aged 18 years or older) with primary hypercholesterolemia, Types IIa or IIb. At randomization, patients had fasting LDL-C concentrations ≥130 mg/dL but <250 mg/dL, a high risk for CHD events and fasting TG concentrations <400 mg/dL. No sample-size estimation was done for the extension phase. The sample size in the extension phase was limited to the number of available patients who successfully completed the randomized phase of the study.

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

In the randomized phase, the investigational products were rosuvastatin 10 mg or 20 mg once daily in oral tablet form and the comparators were atorvastatin 10 mg or 20 mg once daily and simvastatin 20 mg or 40 mg once daily, in commercially available tablets. These rosuvastatin batches were used: 10 mg: 2000026097, 2000030229, 2000030930, 2000031949, 2000034767, 80526J01, 84370A01, 90325E02; 20 mg: 2000026931, 2000021421, 2000025904, 2000030461, 2000030933, 2000031293, 2000033770, 2000034769, 80579C01, 82995F01. During the extension phase of the study, the investigational products were rosuvastatin 10 mg, 20 mg, or 40 mg once daily in oral tablet form. These rosuvastatin batches were used: 10 mg: 2000021394, 2000022481, 2000028929, 2000030229, 2000030231, 2000030930, 2000031949, 2000034767, 2000048685, 80526J01, 84370A01, 90325E02, 84370A01, 93626J02; 20 mg: 2000021421, 2000028931, 2000030461, 2000030933, 2000031293, 2000033770, 2000034769, 2000034861, 80579C01, 82995F01, 90530F02, 90528H02, 90541J02, 93623H02; 40 mg: 2000024320, 2000029112, 2000030047, 2000033803, 2000034126, 82994I01, 91683I02, 90556B02, 91684F02. Note that batch numbers are provided for US sites and ADM numbers are provided for non-US sites.

Duration of treatment

There were a minimum of 4 scheduled clinical visits for the extension period: Visits 6, 6.1, 7, and 8. The first visit in the extension phase was the same as the last day of the randomized phase (Visit 6). The first titration visit (Visit 6.1) took place 6 weeks after Visit 6 and was mandatory. An additional titration visit could take place 6 weeks after Visit 6.1 for patients

who had not achieved their NCEP ATP III LDL-C target. Once patients achieved their NCEP ATP III target or were receiving the maximum dose of rosuvastatin (40 mg), they entered the fixed-dose period (Visit 7). Thereafter, there could be extended visits attached to Visit 7 (ie, 7.1, 7.2, 7.3) scheduled at 12-week intervals. The final visit was designated Visit 8.

Criteria for evaluation (main variables)

Efficacy

The following efficacy variables were studied in the extension phase:

- Percentage change from baseline (prior to randomized treatment) in LDL-C, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), TG, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C at each visit.
- Percentage of patients who achieved their NCEP ATP III LDL-C target (<100 mg/dL) at each visit.
- Percentage of patients with baseline TG ≥200 mg/dL who achieved their NCEP ATP III LDL-C target (<100 mg/dL) and non-HDL-C target (<130 mg/dL) at each visit.

Safety

The following secondary safety variable was addressed cumulatively for rosuvastatin-treated patients in the randomized treatment and extension phases:

- Safety as determined by the incidence and severity of AEs, abnormal laboratory values, vital signs, and physical examination findings.

Statistical methods

Efficacy

Efficacy measures were summarized using descriptive statistics or frequency distributions (whichever was appropriate) for the raw data. No formal statistical analyses were performed.

Safety

Data from all patients who received at least 1 dose of rosuvastatin therapy in the randomized and/or extension phase of the study were included in the cumulative safety analysis. Summaries of all treatment-emergent AEs, AEs leading to death, serious AEs (SAEs), treatment-related AEs, and AEs leading to study discontinuation (DAEs) were presented for all patients on rosuvastatin therapy during the randomized and extension phases. Hematology, clinical chemistry, and vital signs were summarized descriptively. New or aggravated physical exam abnormalities at the final visit (Visit 8) were listed.

Patient population

The first of 1993 patients was enrolled in the randomized phase on 28 November 2001, and the last patient completed the randomized phase on 24 October 2003. A total of 1675 patients entered the extension phase of study, and the last patient completed the extension phase on 15 September 2004. The cumulative safety population (all patients who received rosuvastatin in the randomized or the extension phase) comprised 1797 patients, and 1649 patients were included in the extension intent-to-treat (ITT) efficacy population. A total of 410/1797 (22.8%) patients in the cumulative safety population discontinued the study, most commonly due to AE (152/1797 [8.5%] patients).

The demographic characteristics of the cumulative safety population were similar to those seen among the groups in the randomized phase. The age and sex balance in the study population are common in patients presenting with primary hypercholesterolemia in clinical practice, with 41.8% of patients 65 years of age or older and 56.5% male. In the cumulative safety population, 80.6% of the patients were Caucasian.

Efficacy results

During rosuvastatin treatment in the extension phase of the study, patients in the ITT population exhibited improvements from baseline in mean lipid values for all lipid parameters evaluated of a magnitude generally established to be clinically meaningful. Improvements from baseline were apparent at Visit 6.1 (first visit of the titration phase), and mean changes from baseline were similar from Visit 6.1 through the final visit (Visit 8). Mean percentage changes from baseline through Visit 8 were: -49.00% for LDL-C, -34.52% for TC, 7.16% for HDL-C, -18.27% for TG, and -43.73% for non-HDL-C.

A total of 1210/1527 (79.2%) rosuvastatin-treated patients achieved their NCEP ATP III LDL-C target (<100 mg/dL) at the final study visit. Of rosuvastatin-treated patients with baseline TG ≥200 mg/dL, 384/565 (68.0%) patients achieved their NCEP ATP III LDL-C target (<100 mg/dL) and non-HDL-C target (<130 mg/dL) at the final study visit (Visit 8).

Safety results

The mean and median durations of exposure during the extension phase for patients receiving rosuvastatin were 465.8 days and 498.0 days, respectively. The mean and median durations of exposure for the cumulative safety population (randomized plus extension phases) were 480.5 days and 513.5 days, respectively.

The numbers and percentages of patients with treatment-emergent AEs in the cumulative safety population (randomized and extension phases) by category and by dose at date of onset/worsening are summarized in Table S1.

Table S1 Number (%) of rosuvastatin-treated patients who had a treatment-emergent adverse event by category, by dose at date of onset/worsening, in the cumulative safety population (randomized treatment and extension phases)

	Rosuva 10 mg [a] (n=826)		Rosuva 20 mg [a] (n=1353)		Rosuva 40 mg [a] (n=314)		Rosuva total[a] (n=1797)	
	n	(%)	n	(%)	n	(%)	n	(%)
Any AE	547	(66.2)	942	(69.6)	213	(67.8)	1439	(80.1)
AEs leading to death	9	(1.1)	10[b]	(0.7)	2	(0.6)	21[b]	(1.2)
AEs leading to withdrawal	52	(6.3)	84[c]	(6.2)	13	(4.1)	147[c]	(8.2)
SAEs	86	(10.4)	127	(9.4)	28	(8.9)	234	(13.0)
Treatment-related AEs	79	(9.6)	141	(10.4)	39	(12.4)	242	(13.5)
Treatment-related AEs leading to death	0		0		0		0	
Treatment-related AEs leading to withdrawal	29	(3.5)	44[c]	(3.3)	6	(1.9)	78[c]	(4.3)
Treatment-related SAEs	1	(0.1)	1	(0.1)	0		2	(0.1)
OAEs[d]	0		0		0		0	

[a] Number of patients receiving dose at time of AE onset or AE worsening in intensity. Patients may have been included in more than 1 dose category, but are included only once in the total. Therefore, the total is not the sum of individual treatments. Summaries do not include the 5-mg dose; 1 patient (0702/0062) received 5 mg rosuvastatin in addition to other doses during the study and did not experience any AEs on this dose.

[b] One additional patient (0103/0036) died during the extension phase with the last rosuvastatin treatment being 20 mg. Since the onset of the AE that caused the death (lung cancer) was during randomized treatment with atorvastatin, this death is not included in this table.

[c] One additional patient (Patient 0195/0053) experienced an AE (urticaria, Day 144, on rosuvastatin 20 mg) that was also a DAE that was considered by the investigator to be treatment-related. However, due to an error in the database discovered after database lock, this AE was recorded as not related to study treatment. Therefore, this patient is summarized in this table as having an AE and DAE but not as having a treatment-related AE or DAE.

[d] OAEs were to include significant AEs of particular clinical importance, other than SAEs and DAEs.

AEs Adverse events; DAE Adverse event leading to discontinuation from the study; OAEs Other significant adverse events; Rosuva Rosuvastatin; SAEs Serious adverse events.

A total of 21 patients died due to an AE that occurred during rosuvastatin treatment; 1 additional patient died during the extension phase due to an AE that began while that patient was receiving atorvastatin during the randomized phase. None of these deaths was considered to be treatment-related. Treatment-emergent SAEs were reported in 13.0% of patients, 3 of which occurring in 2 patients were considered treatment-related by the investigator. The incidence of treatment-emergent AEs considered treatment-related by the investigator was generally low (13.5%). The most common AE was arthralgia (9.9%) and the most common AE considered by the investigator to be treatment-related was myalgia (2.4%). The majority of treatment-emergent AEs were mild to moderate in severity. The frequencies of treatment-emergent DAEs and treatment-emergent DAEs considered treatment-related by the investigator were generally low.

Mean changes in clinical laboratory results were generally small. A total of 7 patients had a clinically important elevation in alanine aminotransferase (ALT) (>3 × the upper limit of normal [ULN] on 2 consecutive visits), 7 patients had a clinically important elevation in CK values (>10 × the ULN), and there were no episodes of rhabdomyolysis. These clinically important abnormalities are consistent with the known effects of statins and did not raise any new safety concerns regarding the long-term treatment with rosuvastatin. A clinically important elevation (>100% increase from baseline) in serum creatinine occurred in 2 patients, both of which were judged unrelated to study treatment. Shifts in urine protein were low in frequency and did not appear to be associated with renal impairment. Changes in vital signs and physical findings were small.

Date of the report

16 June 2005