Drug product	CRESTOR™	**SYNOPSIS**	
Drug substance	Rosuvastatin calcium tablets 10 mg, 20 mg		
Document No.	Not applicable		
Edition No.	Not applicable		
Study code	D3560L00027 (4522US/0007)		
Date	19 September 2005		

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 Hispanic Subjects (STARSHIP)

Coordinating investigator

Study centers

This study was conducted in the United States of America (USA). The dietary lead-in phase involved 98 centers; patients from 86 centers were randomized.

Publications

None

Study dates		**Phase of development**
First subject enrolled	23 May 2003	Therapeutic confirmatory (IIIb)
Last subject completed randomized treatment phase	30 November 2004	

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 reducing low-density lipoprotein cholesterol (LDL-C) after 6 weeks of treatment in Hispanic subjects with hypercholesterolemia.

Secondary objectives of the randomized treatment phase of the study were as follows: to compare the efficacy and safety of 2 doses of rosuvastatin (10 mg and 20 mg) with that of 2 doses of atorvastatin (10 mg and 20 mg) in modifying other lipids and lipoproteins in Hispanic subjects with hypercholesterolemia following 6 weeks of treatment; to compare the efficacy and safety of 2 doses of rosuvastatin (10 mg and 20 mg) with that of 2 doses of atorvastatin (10 mg and 20 mg) in achieving National Cholesterol Education Panel (NCEP) Adult Treatment Panel (ATP) III goals in Hispanic subjects with hypercholesterolemia; and to assess the safety of treatment with rosuvastatin and atorvastatin during the 6-week randomized treatment phase.

The pharmacokinetic objective of the study was to quantify systemic exposure to rosuvastatin by measuring the steady state plasma rosuvastatin concentrations in approximately 150 subjects randomized to rosuvastatin.

The secondary objective of the extension phase of the study was to assess the long-term safety of treatment with rosuvastatin during the extension phase.

Study design

This was an open-label, randomized, multicenter, Phase IIIb study to compare the efficacy and safety of rosuvastatin and atorvastatin in reducing LDL-C in Hispanic patients with hypercholesterolemia. *This clinical study report (CSR) reports on the 6-week randomized treatment phase of the study.* A final report providing cumulative (randomized treatment phase and extension phase) rosuvastatin safety data, as well as efficacy data collected during the extension phase, will be prepared separately.

Target subject population and sample size

Self-described Hispanic patients aged 18 or older with a diagnosis of hypercholesterolemia and moderate to high risk for coronary heart disease (CHD) events were randomized into this study.

A total of 592 evaluable patients (148 per treatment group) were required to test the hypothesis of superiority in terms of a 6% difference in the change from baseline in LDL-C levels for each of the treatment comparisons.

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

The investigational products were rosuvastatin calcium 10 mg (batch 2000046820) and 20 mg (batch 2000046822), and the comparators were commercially available tablets of atorvastatin 10 mg (batch numbers 2000046627 and 2000057030) and 20 mg (batch numbers 2000046629 and 2000057042). Study drug was taken once daily, orally.

Duration of treatment

After a 6-week dietary lead-in phase, eligible patients 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 phase. Eligible patients who completed the randomized treatment phase had the option to enter the extension phase for a minimum of 12 weeks during which they were treated with rosuvastatin.

Criteria for evaluation (main variables)

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

The primary efficacy variable was percent reduction in LDL-C from baseline after 6 weeks of treatment.

The secondary efficacy variables were

- Percent change from baseline in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TG, non-HDL-C (total cholesterol minus HDL-C), LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I), and ApoB/ApoA-I after 6 weeks of treatment.
- Percentage of patients, overall and by risk category, who achieved their NCEP ATP III LDL-C goal after 6 weeks.
- Percentage of patients who achieved their optimal LDL-C level (<100 mg/dL) after 6 weeks of treatment.
- Percentage of patients with TG ≥200 mg/dL at baseline who achieved both their NCEP ATP III LDL-C and non-HDL-C goals after 6 weeks of treatment.

The safety variables studied were frequency of adverse events (AEs) and abnormal laboratory values during 6 weeks of treatment.

The pharmacokinetic variable of steady state plasma rosuvastatin concentrations was examined in the randomized treatment phase and continued into the extension phase. Cumulative randomized and extension phase safety data and extension phase efficacy data will be reported separately.

Statistical methods

For efficacy, the Intent-to-Treat (ITT) population consisted of all randomized patients who received study treatment and had a baseline reading of at least 1 pre-randomization measurement and at least 1 post-baseline measurement for 1 or more lipid variables. The goal of the primary efficacy analysis was to show superiority (statistical separation at the $p < 0.017$ type I error level) following non-inferiority (6% test limit) of rosuvastatin in terms of percent reduction from baseline in LDL-C levels in the randomized treatment phase 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. The analysis of the primary efficacy variable was repeated for the secondary lipid variables, but without non-

inferiority testing. The number and percentage of patients who achieved NCEP ATP III goals at Week 6 were summarized, but not subjected to statistical testing.

The safety population contained all patients who had at least 1 dose of study treatment. Safety analyses included AEs, hematology, clinical chemistry, urinalysis, vital signs, weight, and physical exam. Tabulations of AEs focused on treatment-emergent AEs and included tabulations of serious adverse events (SAEs) and AEs leading to study discontinuation (DAEs). Elevations of alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN), creatine kinase (CK) >10 x ULN, and increases in serum creatinine >100% from baseline were highlighted and summarized by treatment dose group.

Patient population

In total, 2750 patients entered the dietary lead-in phase and 696 patients were randomized to treatment. The total study population was 49.6% male with a median age of 58 years, and the demographic and baseline characteristics were generally comparable across the treatment groups. The safety population included 692 patients, and data from 663 patients were analyzed for efficacy in the ITT population. The frequency of patients discontinuing from the randomized treatment phase was low (8.0%) and generally similar across the treatment dose groups. The most common reasons overall for discontinuations were withdrawal of consent (2.4%) and adverse events (2.3%).

Efficacy results

With regard to the primary efficacy variable, rosuvastatin 10 mg and 20 mg had statistically superior LDL-C reduction (44.3% and 49.2%, respectively) compared with the same doses of atorvastatin (35.1% and 41.5%, respectively) after 6 weeks of treatment. Rosuvastatin 10 mg achieved non-inferiority to atorvastatin 20 mg.

As with LDL-C, for all secondary measurements, all treatments achieved a mean change from baseline generally considered to be a clinically meaningful improvement. After 6 weeks of treatment, there was a statistically significant improvement for patients using rosuvastatin 10 mg or 20 mg compared with patients using the same dose of atorvastatin for the following secondary efficacy lipid parameters: TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB, and ApoB/ApoA-I. There were no statistically significant differences between rosuvastatin and atorvastatin for any comparison for HDL-C, TG, and ApoA-I. Variables concerning achievement of NCEP ATP III/optimal goals were not subjected to statistical testing. However, on the basis of descriptive statistics, a numerically higher percentage of patients using rosuvastatin, including those with elevated TG (≥200 mg/dL) at baseline, reached their target NCEP ATP III goals than those using atorvastatin at equivalent doses. Numerical improvements for rosuvastatin compared with atorvastatin in NCEP ATP III goal attainment were largest among high-risk patients.

Safety results

The frequencies of AEs associated with each treatment dose group were similar (rosuvastatin 10 mg, 29.5%; rosuvastatin 20 mg, 29.7%; atorvastatin 10 mg, 31.7%; atorvastatin 20 mg,

31.5%). The most common AEs across all treatment groups were myalgia (4.0%), headache (1.7%), hypertension (1.4%), and urinary tract infection (1.4%). The overall AE profile associated with each treatment dose group was similar. The majority of patients who had AEs had AEs that were mild to moderate in severity and were considered by the investigator to be unrelated to study treatment. No deaths occurred in this study. The frequency of SAEs and DAEs was low and no individual SAE or DAE occurred more than once in any treatment group, except the DAE myalgia, which occurred in no more than 2 patients in each treatment dose group. None of the AEs that occurred in this study was unexpected for this study population.

Changes in clinical laboratory results were generally small and showed no treatment-related trends. Of the 692 patients in the safety population, 1 patient (in the 20-mg atorvastatin group) had clinically important elevations in ALT (>3 x ULN on 2 consecutive visits) that resolved in the extension phase while on rosuvastatin. No patient had clinically important elevations of CK (ie, >10 x ULN) or of serum creatinine (ie, increase >100% from baseline). Six patients (5 rosuvastatin treated and 1 atorvastatin treated) had a shift in dipstick urine protein from none or trace at baseline to "++ or greater" at Week 6. Two of these patients (1 rosuvastatin treated and 1 atorvastatin treated) had a concomitant increase in urine blood. None of these 6 patients had an increase in serum creatinine >100% from baseline. Overall, the number of clinically notable laboratory abnormalities was low. Changes in vital signs and physical findings were small and showed no treatment-related trends.

Overall, rosuvastatin was well-tolerated in this Hispanic study population and its safety profile for rosuvastatin was similar to that of atorvastatin.

Date of the report

19 September 2005

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