Drug product:	CRESTOR™	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium tablets 10, 20, 40 mg		
Document No.:			
Edition No.:			
Study code:	D3560L00026_OLE/ 4522US0006_OLE_OLE		
Date:	01February 06		

Final Report with Extension Phase Data

A 6-week, Randomized, Open-Label, Comparative Study to Evaluate the Efficacy and Safety of Rosuvastatin and Atorvastatin in the Treatment of Hypercholesterolemia in South Asian Subjects (IRIS)

Coordinating investigator

Study centers

This study was conducted at 76 centers across the United States of America (USA) and Canada.

Publications from Final Report with Extension Phase Data

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 subjects: ARIES, IRIS, and STARSHIP trials. Atheroscler Suppl 2003;4(2):83 (IP-0290).

Study dates		**Phase of development**
First patient enrolled	07 November 2002	Therapeutic confirmatory (Phase IIIb)
Last patient completed randomized treatment phase	06 December 2004	
Last patient completed extension phase	04 March 2005	

Objectives

The primary objective of the study (addressed in the randomized treatment phase) 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) in South Asian patients with hypercholesterolemia after 6 weeks of treatment.

The 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 South Asian patients with hypercholesterolemia by assessing:

- Percent change from baseline in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-high-density lipoprotein cholesterol (non-HDL-C), LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C after 6 weeks of treatment.
- Percent of patients, overall and by risk category, who achieved their National Cholesterol Education Center (NCEP) Adult Treatment Panel III (ATP III) LDL-C goals after 6 weeks of treatment.
- Percent of patients who achieved optimal LDL-C (<100 mg/dL) level, as defined by ATP III, after 6 weeks of treatment.
- Percent of patients with TG ≥200 mg/dL who achieved both their NCEP ATP III LDL-C and non-HDL-C goals after 6 weeks of treatment.
- Safety and tolerability of treatment with rosuvastatin and atorvastatin during the 6-week treatment period.

The pharmacokinetic objective of the study was:

- To quantify systemic exposure to rosuvastatin by measuring plasma rosuvastatin concentrations in approximately 150 patients randomized to rosuvastatin.

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

- Safety and tolerability of treatment with rosuvastatin during the 12-week extension period.

Study design

This was an open-label, randomized, multicenter, Phase IIIb study to compare the efficacy and safety of rosuvastatin and atorvastatin in South Asian patients with hypercholesterolemia. After a 6-week dietary lead-in period, 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 period. Of these, 3 comparison groups (rosuvastatin 10 mg vs atorvastatin 10 mg, rosuvastatin 10 mg vs atorvastatin 20 mg, and rosuvastatin 20 mg vs atorvastatin 20 mg) were used to test the hypothesis of superiority in terms of percentage change from baseline in LDL-C levels in the randomized treatment phase.

After successful completion of the randomized treatment phase, eligible patients could elect to participate in the extension phase. The extension phase consisted of an open-label, titration-to-target period followed by a fixed-dose period. Patients were given an initial start dose of either 10 mg or 20 mg of rosuvastatin based on their prior treatment during the 6 week randomized phase. At subsequent visits, doses were titrated up to 40 mg to attain NCEP ATP III target LDL-C and non-HDL-C goals. The final safety evaluation was performed at the end of the extension phase.

This clinical study report (CSR) presents cumulative (randomized treatment phase and extension phase) rosuvastatin safety data, as well as efficacy data obtained during the extension phase. Efficacy and safety analyses for rosuvastatin and comparator during the randomized treatment phase were reported in the IRIS randomized treatment phase CSR.

Target patient population and sample size

In order to enter the extension phase of this study, patients had to successfully complete the randomized treatment phase. The target population of the randomized treatment phase included self-described South Asian (origin of India, Pakistan, Bangladesh, Sri Lanka, Nepal, or Bhutan) men or non-pregnant women who were 18 years of age or older with hypercholesterolemia (Fredrickson Types IIA and IIB), with LDL-C values ≤300 mg/dL and fasting TG <500 mg/dL, who met one of the following criteria at Visit 1: 1) coronary heart disease (CHD) or CHD risk equivalents and LDL-C ≥100 mg/dL; 2) 2 or more major risk factors and a Framingham 10-year risk ≥10% to ≤20% and LDL-C ≥130 mg/dL; or 3) 0-1 major risk factor or with 2+ major risk factors and a Framingham 10-year risk <10% and LDL-C ≥160 mg/dL, and who agreed to discontinue all cholesterol-lowering drugs at Week -6 (Visit 1).

No sample size estimation was calculated for the extension phase, as sample size was by design limited to the available patients who completed the randomized phase of the study.

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

During the open-label, randomized treatment phase, the investigational products were rosuvastatin calcium (CRESTOR™) 10 and 20 mg and the comparators were atorvastatin 10 and 20 mg. In the extension phase, 10, 20, and 40 mg rosuvastatin were used. Atorvastatin was supplied as commercially available tablets through the local retail pharmacy. Rosuvastatin was supplied by AstraZeneca. During both phases, doses were to be taken orally, once daily, as a single tablet. During the randomized treatment phase, the following rosuvastatin batches were used: 10 mg: 2000052365, 2000047899, and 2000034895, and 20 mg: 2000052373, 2000048606, and 2000034897. During the extension phase, the following rosuvastatin batches were used: 10 mg: 2000034895, 2000047899, and

2000052365, 20 mg: 2000034897, 2000048606, 2000063557, and 2000052373; and, 40 mg: 2000052381 and 2000063572.

Duration of treatment

After a 6-week dietary lead-in period, eligible patients were randomized to 1 of 4 treatment groups: rosuvastatin 10 mg or 20 mg or atorvastatin 10 mg or 20 mg for a 6-week treatment period. Patients who completed the randomized treatment period had the option to enter the extension phase for a minimum of 12 weeks.

Upon entry into the extension phase, patients who received rosuvastatin during the randomized treatment period remained on their assigned dose. Patients who received either dose of atorvastatin during the randomized treatment phase were switched to rosuvastatin 10 mg. During each scheduled visit of the extension phase, lipid levels were assessed, and the investigator could initiate dose changes based on his or her medical judgment. Beginning at Visit 6, patients who had not achieved their LDL-C or non-HDL-C goal were asked to return to the clinic within 4 to 7 days for a dose-titration to the next appropriate dose (doubling of the previous dose) until they achieved their LDL-C or non-HDL-C goal or the maximum dose of rosuvastatin (40 mg) was reached, whichever occurred earlier. At the time that the extension phase was terminated, the study drug was commercially available.

Criteria for evaluation (main variables)

The following efficacy variables were addressed in the extension phase:

- Percent change from baseline in LDL-C, TC, HDL-C, TG, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C at each extension visit
- Percent of patients, overall and by risk category, who achieved their NCEP ATP III LDL-C goals at each extension visit
- Percent of patients who achieved optimal LDL-C (<100 mg/dL) level, as defined by NCEP ATP III, at each extension visit
- Percent of patients with baseline TG ≥200 mg/dL who achieved both their NCEP ATP III LDL-C and non-HDL-C goals at each extension visit

The following pharmacokinetic variable was examined in the randomized treatment and extension phases:

- Steady state plasma rosuvastatin concentrations

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

- Incidence of adverse events (AEs) and abnormal laboratory values during 6 weeks of treatment

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

- Incidence of AEs and abnormal laboratory values during the OLE (open-label extension) period

Statistical methods

Although efficacy objectives were not specified in the protocol for the extension phase, efficacy analyses were performed on the intent-to-treat (ITT) population in the extension phase, comprising all patients in the database who received study treatment in the extension phase, had a baseline lipid reading from the randomized treatment phase of the study, and had at least 1 scheduled lipid reading after entry into the extension phase (Week 6). Baseline lipid values for the extension phase were the same as for the randomized treatment phase: the average of the last 3 measurements made prior to randomization.

Efficacy measures were summarized using descriptive statistics or frequency distributions (whichever was appropriate) for the raw data. No formal statistical analyses were performed. The Friedewald value was the primary efficacy measure for LDL-C except at those visits where TG was >400 mg/dL (4.52 mmol/L), when the β quantification measurement was used. Descriptive statistics of percentage change from baseline in lipid variables were presented by final dose of rosuvastatin at each extension visit. Visit data (descriptive statistics on the percentage of patients in the extension ITT population reaching NCEP ATP III target goals) were summarized at each extension visit.

Data from all patients who received at least 1 dose of rosuvastatin therapy in the randomized treatment and/or extension phases of the study were included in the cumulative safety analysis. AEs were classified according to observed events (all events that started, stopped, or were ongoing on rosuvastatin therapy) and treatment-emergent events (observed events that either started during rosuvastatin therapy or were present when rosuvastatin therapy began and worsened during rosuvastatin therapy). AEs occurring prior to randomization, where patients were randomized to rosuvastatin, and prior to entry in the extension study, for patients not randomized to rosuvastatin, were not summarized. An AE that started on 1 dose of rosuvastatin and increased on a subsequent dose of rosuvastatin was considered to be treatment-emergent on both rosuvastatin doses. 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. In addition, these AEs were reported by dose at time of onset or worsening. Summaries of all AEs, AEs leading to death, serious adverse events (SAEs), AEs leading to study discontinuation (DAEs), and treatment-related AEs were presented for all patients on rosuvastatin therapy during the randomized treatment and extension phases. AEs that began prior to the extension phase, but were reported during the extension phase, were listed.

Hematology and clinical chemistry were summarized using descriptive statistics at each visit. Hepatic biochemistry, creatine kinase (CK), and serum creatinine values, as well as their changes from baseline, were summarized using descriptive statistics at each visit. Laboratory

values outside the reference ranges for rosuvastatin patients at any timepoint during the randomized treatment or extension phases were highlighted and clinically significant elevations in alanine aminotransferase (ALT), CK, and serum creatinine were summarized. Urinalysis results were summarized using descriptive statistics; qualitative urinalysis results summarized the shift from qualitative category at baseline to qualitative category at a particular visit.

Vital signs and weight were summarized using descriptive statistics. New or aggravated physical examination abnormalities at the final visit were also listed.

Patient population

The first patient was enrolled in the study on 07 November 2002, 740 patients participated in the randomized treatment phase, and the last patient completed the randomized treatment phase of the study on 06 December 2004. For the long-term extension phase, 568 patients entered and the last patient completed the extension phase on 04 March 2005. The patients in the randomized treatment phase and those participating in the extension were generally similar.

The study included only self-described South Asian patients. The majority (approximately 79%) fell between 18 and 64 years of age, with a mean age of 55.7 years, and approximately 68% being men and 32% women. The demographics, CHD and CHD risk equivalents, major CHD risk factors, Framingham 10-year risk percentage, and the NCEP ATP III risk categories for patients entering the extension phase were generally similar to those of the population in the randomized treatment phase of the study.

A total of 554 patients were included in the extension ITT population for efficacy analysis in the extension phase. The cumulative safety population was used for safety analyses and included 648 patients (all patients who had received rosuvastatin in the randomized or the extension phase). A total of 124 (19.1%) of the patients included in the cumulative safety population discontinued the study. The most common reason for discontinuation was protocol non-compliance (6.5%).

Efficacy results

A clinically meaningful reduction in LDL-C was observed in rosuvastatin patients over time. Mean LDL-C was 155.6 mg/dL at baseline and was 83.6 mg/dL at the final extension visit. The mean reduction in LDL-C from baseline to the final extension visit was 46.2%.

For the secondary efficacy variables, mean decreases from baseline to the final visit of the extension phase were: TC (32.2%), TG (20.7 %), non-HDL-C (41.6%), LDL-C/HDL-C (50.0%), TC/HDL-C (37.1%), and non-HDL-C/HDL-C (45.7%). HDL-C increased by 8.8%.

On the basis of descriptive statistics, the majority of rosuvastatin patients (85.4%) met their NCEP ATP III LDL-C target goals at the final extension visit. The high-risk patients had more aggressive goals for LDL-C reduction, yet percentages of high-risk patients with goal attainment were comparable to other risk groups (for all doses: 85.3% high-risk,

86.2% medium-risk, and 83.0% low-risk patients met goal). The majority of rosuvastatin patients (78.7%) numerically met their NCEP ATP III optimal LDL-C (<100 mg/dL) goal. The percentage of high-risk patients reaching their NCEP ATP III optimal LDL-C (<100 mg/dL) level at the final visit of the extension phase was higher when compared to other risk groups (for all doses: 85.3% high-risk, 71.0% medium-risk, and 48.9% low-risk patients met goal). The majority (60.5%) of rosuvastatin patients with TG ≥200 mg/dL numerically achieved both their target NCEP ATP III LDL-C and non-HDL-C goals at the final extension visit.

The above results are similar to the efficacy results reached by rosuvastatin-treated patients in the randomized treatment phase of the study. South Asian patients with hypercholesterolemia experienced a clinically meaningful improvement in their lipid profile over time.

Pharmacokinetic results

The plasma rosuvastatin concentration data obtained in this study will be incorporated into a population pharmacokinetic model for rosuvastatin. The results will be reported separately by Clinical Pharmacology (Wilmington, DE, USA).

Safety results

Overall, rosuvastatin was well tolerated in this South Asian study population of patients with hypercholesterolemia. Over the extended exposure period, no new safety signals were noted.

The treatment-emergent AE profiles for rosuvastatin patients in the cumulative safety population were consistent with those noted in the randomized treatment phase. The most common treatment-emergent AEs were myalgia (4.2%), arthralgia (3.1%), constipation (2.3%), headache (2.2%), and dizziness (1.9%). The frequencies of deaths, SAEs, DAEs, and treatment-related AEs for rosuvastatin patients were low. None of the AEs that occurred in this study was unexpected given the underlying medical conditions of the patient population.

The number of hepatic events was low; only 2 of these events had corresponding ALT values considered clinically important (>3 times upper limit of normal [ULN] on 2 consecutive occasions). The overall frequency of myalgia (a known class effect of statins) was low (4.2%); none of the cases was associated with a clinically important elevation in CK (>10 x ULN). One patient (0.2%) had an AE of acute renal failure concomitant with multi-system organ failure, considered by the investigator to be not related to treatment. There were no AEs of proteinuria; 1 patient with an AE of hematuria (not considered related to the study drug by the investigator) experienced an increase in dipstick urine blood from none at baseline to +++ at the final visit.

Changes in clinical laboratory results were generally small for rosuvastatin patients in the cumulative safety population. Three rosuvastatin patients (0.5%) had clinically important ALT elevations (>3 x ULN on 2 consecutive visits); 2 of the patients had ALT elevations that decreased by the final visit and the remaining patient's elevation was not considered to be treatment-related by the investigator. No rosuvastatin patient had a clinically important elevation in CK (>10 x ULN) or in serum creatinine (>100% from baseline). Five

rosuvastatin patients (0.8%) experienced an increase in dipstick urine protein from none or trace at baseline to "++ or greater" at any visit. Eleven rosuvastatin patients (1.8%) experienced an increase in dipstick urine blood from none or trace at baseline to "++ or greater" at any visit. Overall, the number of clinically notable elevations was low.

Changes in vital signs and physical findings were small and similar across the rosuvastatin dose groups.

Date of the report

01 February 2006