Drug product:	Rosuvastatin calcium tablets 5 mg and 40 mg	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Rosuvastatin calcium		
Document No.:	Not applicable		
Edition No.:	Not applicable		
Study code:	D3560C0004 (4522IL/0044)		
Date:	18 October 2006		

Randomized, Double-blind, Multicenter Trial to Assess the Effect of High and Low doses of Rosuvastatin on Progression of Carotid Artery Atheroma in Moderately Hypercholesterolemic Patients with Asymptomatic Carotid Stenosis After 24 Months of Dosing (ORION)

International co-ordinating investigator

Study center(s)

This study was conducted in the United States (2 centers).

Publications

Chu B, Hatsukami TS, Polissar N, Waterton J, Raichlen J, Yuan C. Evaluation of carotid atherosclerotic lesion distribution in hypercholesterolemic patients using high-resolution magnetic resonance imaging [Abstract]. In: Radiological Society of North America Scientific Assembly and Annual Meeting Program. Oak Brook, IL: Radiological Society of North America, 2003.

Chu B, Hatsukami TS, Zhao X, Polissar NL, Kraiss LW, Parker DL, et al. Use of magnetic resonance imaging to assess carotid atherosclerotic lesion distribution [Abstract]. Atheroscler Suppl 2003;4(2):253 (3P-0871).

Chu B, Hatsukami TS, Polissar NL, Zhao X, Waterton JC, Raichlen J, et al. Reproducibility of carotid atherosclerotic lesion type determination using high-resolution magnetic resonance imaging [Abstract]. Atheroscler Suppl 2003;4(2):253 (3P-0872).

Chu B, Hatsukami TS, Polissar NL, Zhao X, Kraiss LW, Parker DL, et al. Determination of carotid artery atherosclerotic lesion type and distribution in hypercholesterolemic patients with moderate carotid stenosis using noninvasive magnetic resonance imaging. Stroke 2004;35:2444-48.

Chu B, Balu N, Underhill H, Saam T, Takaya N, Raichlen J, et al. Carotid magnetic resonance scans provide consistent signal-to-noise ratio and contrast-to-noise ratio in the ORION trial. J Cardiovasc Magn Reson 2006;8(1) (Abstract 211).

Hatsukami TS, Zhao X-Q, Yuan C, Tessier JJ, Miller E, Pears JS. Study Design for a Randomized, Double-Blind Trial to Assess the Effect of 24 Months of Dosing With rosuvastatin on Progression of Carotid Artery Atheroma in Moderately Hypercholesterolemic Patients With Asymptomatic Carotid Stenosis. Atherosclerosis 2001;Suppl 2(2):47-8 (Abstract P4).

Hatsukami TS, Zhao X, Kraiss LW, Parker DL, Waterton J, Cain V, et al. Assessment of rosuvastatin treatment on carotid atherosclerosis in moderately hypercholesterolemic subjects using high-resolution magnetic resonance imaging [Abstract]. Eur Heart J 2005;26(Abstract Supplement):626.

Underhill H, Yuan C, Kerwin W, Raichlen J, Waterton J, Hatsukami T. Automated magnetic resonance imaging assessment of common carotid artery wall changes after 2 years of statin therapy. J Cardiovasc Magn Reson 2006;8(1) (Abstract 338).

Study dates		**Phase of development**
First patient enrolled	6 January 2000	Therapeutic confirmatory (III)
Last patient completed	5 August 2004	

Objectives

The primary objective was to compare the change in the carotid artery wall volume after 24 months dosing with low and high doses of rosuvastatin as assessed by magnetic resonance imaging (MRI).

The secondary objectives of the study were to:

- compare the change in the carotid artery wall volume after all other time points
- measure change in composition (as assessed by index of lesion MRI signal)
- measure changes in intima media thickness of the carotid arteries by B-mode ultrasound
- measure concentrations of circulating markers of vascular inflammation (C-reactive protein [CRP] and interleukin-6 [IL-6])

- measure change in homocysteine and lipoprotein particle size
- measure levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)
- examine tissues of those subjects who progress to endarterectomy for cell infiltration, expression of markers of vascular inflammation (eg, intercellular adhesion molecule-1 [ICAM-1] and cluster of differentiation-40 [CD-40] ligand) and possible rosuvastatin content
- generate the hypothesis that other indices of lesion composition derived from other MRI images can be useful in monitoring functional response of a plaque to lipid-lowering with a statin
- determine the drug's safety and tolerability

Study design

This was a randomized, double-blind, parallel-group, multicenter, phase III study comparing low (5 mg) and high doses (40/80 mg) of rosuvastatin in adult patients with moderate hypercholesterolemia and with carotid stenosis or an atherosclerotic plaque with a lipid-rich necrotic core.

The study was 110 weeks in duration and comprised of the following 2 periods: a 6-week lead-in period and a 104-week (24-month) randomized treatment period.

Patients randomized to the low-dose group were to receive rosuvastatin 5 mg for the full 2-year period. Patients randomized to the high-dose group were to receive rosuvastatin 40 mg for the first 4 weeks and were then titrated up to rosuvastatin 80 mg for the duration of the study. Those patients who did not tolerate the 80-mg dose or achieved an LDL-C <50 mg/dL could be back-titrated to rosuvastatin 40 mg. A protocol amendment modified the study design in that all subsequent patients randomized to the high-dose group were to receive rosuvastatin 40 mg for the full 2-year period, requiring all rosuvastatin 80-mg patients to be back-titrated to rosuvastatin 40 mg.

Five additional visits were allowable during the lead-in period as necessary: Pre-screening, Visit 2.1, and Visits 3.1, 3.2, and 3.3.

Target patient population and sample size

Seventy-three patients entered the dietary lead in period and 43 were randomized (low-dose n=21; high-dose n=22). This study included men or women (aged 18 years and older) with moderate hypercholesterolemia and 16% to 79% stenosis of one or more carotid arteries, or an atherosclerotic plaque with a lipid-rich necrotic core as assessed by baseline duplex carotid ultrasound and MRI.

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

Rosuvastatin calcium (ZD4522, CRESTOR®) 5 mg (batch numbers: 2000000724, 2000015243, 2000017348, and 2000030289), 40 mg (batch number: 2000001033, 2000015241, 2000018188, and 2000030888), or 80 mg (batch number: 993151A, 2000015240, and 2000018189) encapsulated tablets were administered orally, with water if required, once daily before bedtime (ie, approximately 3 hours after the evening meal).

Duration of treatment

There were 2 periods in this study: a lead-in period of 6 weeks and a randomized treatment period of 104 weeks (24 months).

Criteria for evaluation (main variables)

Efficacy

- Primary variable: absolute change from baseline in the carotid artery wall volume after 24 months of dosing with rosuvastatin (bilateral)

Secondary measurements:

- Carotid artery wall composition (as assessed by index of lesion MRI signal) bilateral and unilateral measurements
- Minimal carotid lumen cross-sectional area, unilateral, and bilateral measurements
- Carotid artery wall volume, unilateral measurement
- Mean intima media thickness of the carotid arteries by B-mode ultrasound
- Cell infiltration, expression of markers of vascular inflammation (eg, ICAM-1 and cluster of differentiation-40 ligand) and possible rosuvastatin concentration in patients progressing to endarterectomy
- Circulating markers of inflammation (CRP, IL-6), homocysteine, and lipoprotein particle size
- Lipid parameters: TC, TG, LDL-C, and HDL-C
- Safety as determined by AEs, physical examination, vital signs, electrocardiogram (ECG), and laboratory data.

Safety

Standard safety assessments included AE reports, clinical laboratory data (hematology, hepatic and renal clinical chemistry, and urinalysis), vital signs, ECGs, and physical examination.

Statistical methods

Two analysis sets were used:

- **Full analysis set (ITT)**—all randomized patients who had taken at least 1 dose of study treatment and who had a baseline reading, and at least 1 post-baseline reading, for 1 or more MRI variables. This was the primary population for analysis of efficacy data and effectiveness endpoints.

- **PP analysis set**—all patients who did not have major deviations or violations of protocol requirements. As a change from the protocol, an analysis of the per protocol population was not conducted.

- **Safety analysis set**—all patients who entered the lead-in period at Visit 1 (Week -6) through the randomized treatment period and received at least 1 dose of study drug. Analysis was based on the actual treatment received.

Patient population

Overall, the patients in this study were representative of the target population of patients with coronary artery disease. In the safety population (N=43; low-dose [n=21] and high-dose [n=22]), the mean age was 64.8 years of age, with 53.5% ≥65 years of age; 67.4% were men; 97.7% were Caucasian; and 88.4% had normal or mildly impaired renal function. In regard to medical history, out of 43 total patients, 30 had atherosclerotic disease, 29 had hypertension, 9 were current cigarette smokers, and 8 had diabetes mellitus.

Efficacy results

For the primary efficacy variable, there was no significant difference between the low- and high-dose groups in the change from baseline in bilateral carotid artery wall volume at Week 104 and no significant change from baseline in bilateral carotid artery wall volume was present in either dose group at Week 104.

There were no clinically meaningful differences between dose groups or from baseline for the following secondary endpoints:

- Carotid artery wall volume and percent obstructive volume at all time points

- Total volume and percentage of total volume of each AHA lesion type

- Volume of plaque classified as lipid-rich necrotic core, calcification, or hemorrhage

- Percentage change from baseline in the common carotid far wall mean of maximum intima media thickness

- Percentage change from baseline in circulating markers of inflammation (CRP, IL-6)

- Percentage change from baseline in homocysteine and lipoprotein particle size parameters

There were significant differences between dose groups and from baseline for the following secondary endpoints:

- Percentage change from baseline in routine lipid parameters (TC, TG, HDL-C, LDL-C, nonHDL-C, TC/HDL-C, LDC-C/HDL-C, nonHDL-C/HDL-C) except for HDL-C, TG, and Apolipoprotein (Apo) A-I which did not show significant changes from baseline in the low-dose group

- Percentage change from baseline in specialty lipid parameters (Apolipoprotein [Apo] B, ApoA-I, lipoprotein [a] [Lp(a)], ApoB/ApoA-I) except for Lp(a) and ApoA-I, where there were no significant differences between the 2 dose groups

For patients in the NCEP III high-risk category, the majority of patients in both dose groups reached their target goals. No conclusions could be made regarding high-risk patients with baseline triglycerides ≥200 mg/dL because of the very small number of patients meeting these criteria.

Regarding cell infiltration, expression of markers of vascular inflammation (eg, ICAM-1 and CD-40 ligand) and possible rosuvastatin concentration in patients progressing to endarterectomy, no patients progressed to endarterectomy.

Safety results

Overall, treatment up to 2 years with low (5 mg) or high (40/80 mg) doses of rosuvastatin was safe and well tolerated. The percentage of patients with any AE was 76.2% for the low-dose group and 95.5% for the high-dose group. When examining the high-dose group by dose at onset, the percentages of patients with any AE were 72.7% at 40 mg and 73.3% at 80 mg. Most AEs were mild or moderate in severity. Of the 43 patients in the safety population, the most common AEs across all treatment groups were pain in extremity (n=7), hypertension (n=6), arthralgia (n=6), nasopharyngitis (n=5), and urinary tract infection (n=5). These AEs are not unexpected in this patient population. No treatment-related AE occurred in more than 1 patient for any dose (5 mg, 40 mg, or 80 mg). Most patients with AEs had AEs that were either mild or moderate in severity. There was 1 death (at 40 mg) due to myocardial infarction (this patient also had a brainstem infarction) which was not considered to be treatment-related by the investigator. There were 3 patients with an SAE at 5 mg (atrial fibrillation, urinary tract infection, arthritis, bladder neck obstruction), 1 at 40 mg (the patient with myocardial infarction and brain stem infarction mentioned previously) and none at 80 mg. There was 1 patient with a DAE (discontinuation due to an adverse event) at 5 mg (atrial fibrillation) and 1 at 40 mg (the patient with myocardial infarction and brain stem infarction mentioned previously), and 0 at 80 mg. None of the SAEs or DAEs was treatment-related. No patient had a clinically important elevation of ALT (>3 x ULN at 2 consecutive occasions), CK (>10 x ULN), or serum creatinine (>100% increase from baseline). Only 2 patients had shifts in urine protein or urine blood from none or trace at baseline to ≥++ that

persisted to the last study visit; for each of these there was a plausible explanation other than study drug. Overall, the safety profile was consistent with that previously reported for rosuvastatin and other statins. No new safety issues emerged.

Date of the report

18 October 2006