CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-366 / S-010

Trade Name: Crestor

Generic Name: Rosuvastatin calcium

Sponsor: AstraZeneca Pharmaceuticals, LP

Approval Date: November 8, 2007

Indications: For adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	X
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-366/S-010

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
US Agent for IPR Pharmaceuticals, Inc.
Attention: Patricia A. DeFeo, MS
Director, Regulatory Affairs
1800 Concord Pike, P. O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. DeFeo:

Please refer to your supplemental new drug application dated January 5, 2007, received January 8, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets.

We acknowledge receipt of your submissions dated April 26, May 17 and 23, August 22 (2), September 14 and 27, and November 8 (email), 2007.

This supplemental new drug application provides for a new indication for Crestor as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert submitted November 8, 2007, by email.) Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-366/S-010.**"

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
11/8/2007 06:24:21 PM
Eric Colman for Mary Parks

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CRESTOR safely and effectively. See full prescribing information for CRESTOR.

CRESTOR (rosuvastatin calcium) tablets
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Indications and Usage, Slowing of the Progression of Atherosclerosis (1.4)	11/2007
Dosage and Administration, Slowing of the Progression of Atherosclerosis (2.2)	11/2007
Use with Cyclosporine or Lopinavir/Ritonavir (2.5)	07/2007
Warnings and Precautions, Skeletal Muscle Effects (5.1)	07/2007

INDICATIONS AND USAGE

CRESTOR is an HMG Co-A reductase inhibitor indicated for:
- patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C (1.1)
- patients with hypertriglyceridemia as an adjunct to diet (1.2)
- patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB (1.3)
- slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet (1.4)

Limitations of use (1.5):
- Effect of CRESTOR on cardiovascular morbidity and mortality has not been determined.
- CRESTOR has not been studied in Fredrickson Type I, III, and V dyslipidemias.

DOSAGE AND ADMINISTRATION
- CRESTOR can be taken with or without food, at any time of day. (2.1)
- Dose range: 5-40 mg once daily. Use 40 mg dose only for patients not reaching LDL-C goal with 20 mg. (2.1)
- **Hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, and atherosclerosis:** Starting dose 10 mg. Consider 20 mg starting dose for patients with LDL-C>190 mg/dL and aggressive lipid targets. (2.2)
- **HoFH:** Starting dose 20 mg. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg, 20 mg, and 40 mg (3)

CONTRAINDICATIONS
- Known hypersensitivity to product components (4)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)

WARNINGS AND PRECAUTIONS
- **Skeletal muscle effects (e.g., myopathy and rhabdomyolysis):** Risks increase with use of 40 mg dose, advanced age (≥65), hypothyroidism, renal impairment, and combination use with cyclosporine, lopinavir/ritonavir, or certain other lipid-lowering drugs. Advise patients to promptly report unexplained muscle pain, tenderness, or weakness and discontinue CRESTOR if signs or symptoms appear (5.1)
- **Liver enzyme abnormalities and monitoring:** Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment. (5.2)

ADVERSE REACTIONS

Most frequent adverse reactions (rate≥2%) are headache, myalgia, abdominal pain, asthenia, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS
- **Cyclosporine:** Combination increases rosuvastatin exposure. Limit CRESTOR to 5 mg once daily. (2.5, 7.1)
- **Gemfibrozil:** Combination should be avoided. If used together, limit CRESTOR dose to 10 mg once daily. (2.6, 5.1, 7.2)
- **Lopinavir/Ritonavir:** Combination increases rosuvastatin exposure. Limit CRESTOR dose to 10 mg once daily. (2.5, 5.1, 7.3)
- **Coumarin anti-coagulants:** Combination prolongs INR. Achieve stable INR prior to starting CRESTOR. Monitor INR frequently until stable upon initiation or alteration of CRESTOR therapy. (5.3, 7.4)
- **Concomitant lipid-lowering therapies:** Use with fibrates and niacin products may increase the risk of skeletal muscle effects. (2.6, 5.1, 7.5, 7.6)

USE IN SPECIFIC POPULATIONS
- **Pediatric use:** Safety and effectiveness not established. (8.4)
- **Severe renal impairment (not on hemodialysis):** Starting dose is 5 mg, not to exceed 10 mg. (2.7, 5.1, 8.6)
- **Asian population:** Consider 5 mg starting dose. (2.4, 8.8)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2007

***FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE
1.1 Hyperlipidemia and Mixed Dyslipidemia
1.2 Hypertriglyceridemia
1.3 Homozygous Familial Hypercholesterolemia
1.4 Slowing of the Progression of Atherosclerosis
1.5 Limitations of Use

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Hyperlipidemia, Mixed Dyslipidemia, Hypertriglyceridemia, and Slowing of the Progression of Atherosclerosis
2.3 Homozygous Familial Hypercholesterolemia
2.4 Dosage in Asian Patients
2.5 Use with Cyclosporine or Lopinavir/Rotonavir
2.6 Concomitant Lipid-Lowering Therapy
2.7 Dosage in Patients With Severe Renal Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
5.1 Skeletal Muscle Effects
5.2 Liver Enzyme Abnormalities and Monitoring
5.3 Concomitant Coumarin Anticoagulants
5.4 Proteinuria and Hematuria
5.5 Endocrine Effects

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience

7 DRUG INTERACTIONS
7.1 Cyclosporine
7.2 Gemfibrozil
7.3 Lopinavir/Ritonavir
7.4 Coumarin Anticoagulants
7.5 Niacin
7.6 Fenofibrate

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
8.8 Asian Patients

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
14.1 Hyperlipidemia and Mixed Dyslipidemia
14.2 Heterozygous Familial Hypercholesterolemia
14.3 Hypertriglyceridemia
14.4 Homozygous Familial Hypercholesterolemia
14.5 Slowing of the Progression of Atherosclerosis

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
17.1 Skeletal Muscle Effects
17.2 Concomitant Use of Antacids
17.3 Pregnancy
17.4 Liver Enzymes

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hyperlipidemia and Mixed Dyslipidemia

CRESTOR is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate.

1.2 Hypertriglyceridemia

CRESTOR is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

1.3 Homozygous Familial Hypercholesterolemia

CRESTOR is indicated as adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia.

1.4 Slowing of the Progression of Atherosclerosis

CRESTOR is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

1.5 Limitations of Use

The effect of CRESTOR on cardiovascular morbidity and mortality has not been determined.

CRESTOR has not been studied in Fredrickson Type I, III, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The dose range for CRESTOR is 5 to 40 mg orally once daily.

CRESTOR can be administered as a single dose at any time of day, with or without food.

When initiating CRESTOR therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy.

The 40 mg dose of CRESTOR should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose [*see Warnings and Precautions* (5.1)].

2.2 Hyperlipidemia, Mixed Dyslipidemia, Hypertriglyceridemia and Slowing of the Progression of Atherosclerosis

The recommended starting dose of CRESTOR is 10 mg once daily. For patients with marked hyperlipidemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20 mg starting dose may be considered.

After initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

2.3 Homozygous Familial Hypercholesterolemia

The recommended starting dose of CRESTOR is 20 mg once daily. Response to therapy should be estimated from pre-apheresis LDL-C levels.

2.4 Dosage in Asian Patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. [*see Use in Specific Populations* (8.8) *and Clinical Pharmacology* (12.3)].

2.5 Use with Cyclosporine or Lopinavir/Ritonavir

In patients taking cyclosporine, the dose of CRESTOR should be limited to 5 mg once daily [see *Warnings and Precautions* (5.1) *and Drug Interactions* (7.1)]. In patients taking a combination of lopinavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily [*see Warnings and Precautions* (5.1) *and Drug Interactions* (7.3)].

2.6 Concomitant Lipid-Lowering Therapy

The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with niacin or fenofibrate; a reduction in CRESTOR dosage should be considered in this setting. [*see Warnings and Precautions* (5.1) *and Drug Interactions* (7.5, 7.6)]

Combination therapy with gemfibrozil should be avoided because of an increase in CRESTOR exposure with concomitant use; if CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily [*see Warnings and Precautions* (5.1) *and Drug Interactions* (7.2)].

2.7 Dosage in Patients With Severe Renal Impairment

For patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily [*see Use in Specific Populations* (8.6) *and Clinical Pharmacology* (12.3)].

3 DOSAGE FORMS AND STRENGTHS

5 mg: Yellow, round, biconvex, coated tablets. Debossed "CRESTOR" and "5" on one side of the tablet.

10 mg: Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "10" on one side of the tablet.

20 mg: Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "20" on one side of the tablet.

40 mg: Pink, oval, biconvex, coated tablets. Debossed "CRESTOR" on one side and "40" on the other side of the tablet.

4 CONTRAINDICATIONS

CRESTOR is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, urticaria and angioedema have been reported with CRESTOR [*see Adverse Reactions* (6.1)].
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels [*see Warnings and Precautions* (5.2)].
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, CRESTOR may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy. [*see Use in Specific Populations* (8.1) *and Nonclinical Toxicology* (13.2)]
- Nursing mothers. Because another drug in this class passes into breast milk, and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants. [*see Use in Specific Populations* (8.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including CRESTOR. These risks can occur at any dose level, but are increased at the highest dose (40 mg).

CRESTOR should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age $\geq$ 65 years, inadequately treated hypothyroidism, renal impairment).

The risk of myopathy during treatment with CRESTOR may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, or lopinavir/ritonavir. [*see Dosage and Administration* (2) *and Drug Interactions* (7)].

CRESTOR therapy should be discontinued if markedly elevated creatinine kinase levels occur or myopathy is diagnosed or suspected. CRESTOR therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or

predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Enzyme Abnormalities and Monitoring

It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including CRESTOR. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to CRESTOR therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking CRESTOR versus 0.5% of patients treated with placebo.

Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CRESTOR is recommended.

CRESTOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease [*see Clinical Pharmacology* (12.3)]. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of CRESTOR. [*see Contraindications* (4)]

5.3 Concomitant Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with CRESTOR because of the potentiation of coumarin-type anti-coagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs. [*see Drug Interactions* (7.4)]

5.4 Proteinuria and Hematuria

In the CRESTOR clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among CRESTOR treated patients. This finding was more frequent in patients taking CRESTOR 40 mg, when compared to lower doses of CRESTOR or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on CRESTOR therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

5.5 Endocrine Effects

Although clinical studies have shown that CRESTOR alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if CRESTOR is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis). [*see Warnings and Precautions* (5.1)]
- Liver enzyme abnormalities [*see Warnings and Precautions* (5.2)]

In the CRESTOR controlled clinical trials database (placebo or active-controlled) of 5,394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were:

- myalgia
- abdominal pain
- nausea

The most commonly reported adverse reactions (incidence $\geq$ 2%) in the CRESTOR controlled clinical trial database of 5,394 patients were:

- headache
- myalgia
- abdominal pain
- asthenia
- nausea

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Adverse reactions reported in $\geq$ 2% of patients in placebo-controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had a treatment duration of up to 12 weeks.

Table 1. Adverse Reactions* Reported by ≥ 2% of Patients Treated with CRESTOR and ≥ Placebo in Placebo-Controlled Trials (% of Patients)

Adverse Reactions	CRESTOR 5 mg N=291	CRESTOR 10 mg N=283	CRESTOR 20 mg N=64	CRESTOR 40 mg N=106	Total CRESTOR 5 mg – 40mg N=744	Placebo N=382
Headache	5.5	4.9	3.1	8.5	5.5	5.0
Nausea	3.8	3.5	6.3	0	3.4	3.1
Myalgia	3.1	2.1	6.3	1.9	2.8	1.3
Asthenia	2.4	3.2	4.7	0.9	2.7	2.6
Constipation	2.1	2.1	4.7	2.8	2.4	2.4

* Adverse reactions by COSTART preferred term.

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis. The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria [*see Warnings and Precautions* (5.4)]; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

In the METEOR study, involving 981 participants treated with rosuvastatin 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years, 5.6% of CRESTOR-treated subjects versus 2.8% of placebo-treated subjects discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: myalgia, hepatic enzyme increased, headache, and nausea [*see Clinical Studies* (14.5)]

Adverse reactions reported in ≥ 2% of patients and at a rate greater than or equal to placebo are shown in Table 2.

Table 2. Adverse Reactions* Reported by ≥ 2% of Patients Treated with CRESTOR and ≥ Placebo in the METEOR Trial (% of Patients)

Adverse Reactions	CRESTOR 40 mg N=700	Placebo N=281
Myalgia	12.7	12.1
Arthralgia	10.1	7.1
Headache	6.4	5.3

Dizziness	4.0	2.8
Blood CPK	2.6	0.7
Abdominal pain	2.4	1.8
ALT >3x ULN	2.2	0.7

* Adverse reactions by MedDRA preferred term.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CRESTOR: arthralgia, hepatitis, jaundice and memory loss. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Cyclosporine

Cyclosporine significantly increased rosuvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily. [*see Dosage and Administration* (2.5), *Warnings and Precautions* (5.1), *and Clinical Pharmacology* (12.3)].

7.2 Gemfibrozil

Gemfibrozil significantly increased rosuvastatin exposure. Therefore, combination therapy with CRESTOR and gemfibrozil should be avoided. If used, do not exceed CRESTOR 10 mg once daily. [*see Dosage and Administration* (2.6) *and Clinical Pharmacology* (12.3)].

7.3 Lopinavir/Ritonavir

The combination of lopinavir and ritonavir significantly increased rosuvastatin exposure. Therefore, in patients taking a combination of lopinavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily. The effect of other protease inhibitors on rosuvastatin pharmacokinetics has not been examined. [*see Dosage and Administration* (2.5), *Warnings and Precautions* (5.1) *and Clinical Pharmacology* (12.3)]

7.4 Coumarin Anticoagulants

CRESTOR significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with CRESTOR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs. [*see Warnings and Precautions* (5.3) *and Clinical Pharmacology* (12.3)]

7.5 Niacin

The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with niacin; a reduction in CRESTOR dosage should be considered in this setting [*see Warnings and Precautions* (5.1)]

7.6 Fenofibrate

When CRESTOR was coadministered with fenofibrate no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. The benefit of further alterations in lipid levels by the combined use of CRESTOR with fibrates should be carefully weighed against the potential risks of this combination. [*see Warnings and Precautions* (5.1) *and Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category X.

CRESTOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy. [*see Contraindications* (4)]

There are no adequate and well-controlled studies of CRESTOR in pregnant women. There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Rosuvastatin crosses the placenta in rats and rabbits. In rats, CRESTOR was not teratogenic at systemic exposures equivalent to a human therapeutic dose of 40 mg/day. At 10-12 times the human dose of 40 mg/day, there was decreased pup survival, decreased fetal body weight among female pups, and delayed ossification. In rabbits, pup viability decreased and maternal mortality increased at doses equivalent to the human dose of 40 mg/day. [*see Nonclinical Toxicology* (13.2)]

CRESTOR may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking CRESTOR, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are three times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class

passes into human milk and because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants. [*see Contraindication* (4)]

8.4 Pediatric Use

The safety and effectiveness of CRESTOR in pediatric patients have not been established.

Treatment experience with CRESTOR in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age.

In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of CRESTOR. Both C_{max} and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

8.5 Geriatric Use

Of the 10,275 patients in clinical studies with CRESTOR, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients are at higher risk of myopathy and CRESTOR should be prescribed with caution in the elderly. [*see Warnings and Precautions,* (5.1) *and Clinical Pharmacology,* (12.3)]

8.6 Renal Impairment

Rosuvastatin exposure is not influenced by mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 m^2); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. CRESTOR dosing should be adjusted in patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not requiring hemodialysis. [*see Dosage and Administration* (2.7) *and Warnings and Precautions* (5.1) *and Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

CRESTOR is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is known to increase rosuvastatin exposure; CRESTOR should be used with caution in these patients. [*see Contraindications* (4) *and Warning and Precautions* (5.2) *and Clinical Pharmacology* (12.3)].

8.8 Asian Patients

Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. CRESTOR dosage should be adjusted in Asian patients. [*see Dosage and Administration* (2.4) *and Clinical Pharmacology* (12.3)]

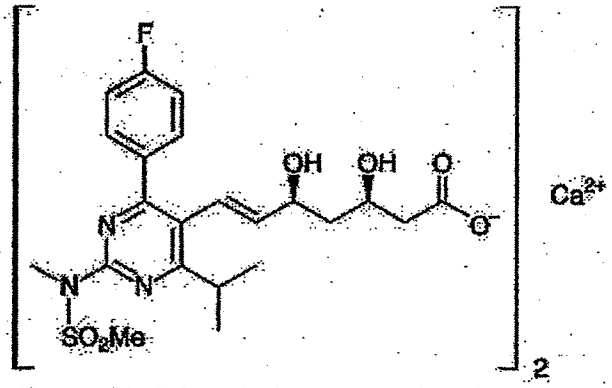
10 OVERDOSAGE

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

11 DESCRIPTION

CRESTOR (rosuvastatin calcium) is a synthetic lipid-lowering agent for oral administration.

The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

Inactive Ingredients: Each tablet contains: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CRESTOR is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

12.3 Pharmacokinetics

- ***Absorption:*** In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both C_{max} and AUC increased in approximate proportion to CRESTOR dose. The absolute bioavailability of rosuvastatin is approximately 20%.

  Administration of CRESTOR with food did not affect the AUC of rosuvastatin.

  The AUC of rosuvastatin does not differ following evening or morning drug administration.

- ***Distribution:*** Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

- ***Metabolism:*** Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

- ***Excretion:*** Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.

  After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

- ***Race:*** A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group.

- ***Gender:*** There were no differences in plasma concentrations of rosuvastatin between men and women.

- ***Geriatric:*** There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

- ***Renal Impairment:*** Mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects ($CL_{cr} > 80$ mL/min/1.73 m^2).

- ***Hemodialysis:*** Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

- ***Hepatic Impairment:*** In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased.

  In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function

Drug-Drug Interactions:

Cytochrome P450 3A4

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

Table 3. Effect of Co-administered Drugs on Rosuvastatin Systemic Exposure

Co-administered drug and dosing regimen	Rosuvastatin		
	Dose (mg)*	Change in AUC	Change in C_{max}
Cyclosporine – stable dose required (75 mg – 200 mg BID)	10 mg QD for 10 days	↑ 7-fold†	↑11-fold†
Gemfibrozil 600 mg BID for 7 days	80 mg	↑ 1.9-fold†	↑ 2.2-fold†
Lopinavir/ritonavir combination 400 mg/100 mg BID for 10 days	20 mg QD for 7 days	↑ 5-fold†	↑ 2-fold†
Fenofibrate 67 mg TID for 7 days	10 mg	↑ 7%	↑21%
Aluminum & magnesium hydroxide combination antacid			
Administered simultaneously	40 mg	↓ 54%†	↓ 50%†
Administered 2 hours apart	40 mg	↓ 22%	↓ 16%
Erythromycin 500 mg QID for 7 days	80 mg	↓ 20%	↓ 31%
Ketoconazole 200 mg BID for 7 days	80 mg	↑ 2%	↓ 5%
Itraconazole 200 mg QD for 5 days	10 mg 80 mg	↑ 39% ↑ 28%	↑ 36% ↑ 15%
Fluconazole 200 mg QD for 11 days	80 mg	↑ 14%	↑ 9%

* Single dose unless otherwise noted

† Clinically significant [*see Dosage and Administration* (2) *and Warnings and Precautions* (5)]

Table 4. Effect of Rosuvastatin Co-Administration on Systemic Exposure To Other Drugs

Rosuvastatin Dosage Regimen	Co-administered Drug		
	Name and Dose	Change in AUC	Change in C_{max}
40 mg QD for 10 days	Warfarin* 25 mg single dose	R-Warfarin ↑4% S-Warfarin ↑6%	R-Warfarin ↓ 1% S-Warfarin 0%
40 mg QD for 12 days	Digoxin 0.5 mg single dose	↑ 4%	↑ 4%
40 mg QD for 28 days	Oral Contraceptive (ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days	EE ↑ 26% NG ↑ 34%	EE ↑ 25% NG ↑ 23%

EE = ethinyl estradiol, NG = norgestrel

*Clinically significant pharmacodynamic effects [See *Warnings and Precautions* (5.4)]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human

exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class.

13.2 Animal Toxicology and/or Pharmacology

Embryo-fetal Development

Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times the human exposure at 40 mg/day based on AUC).

In pregnant rats given oral gavage doses of 2, 10, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures $\geq$ 12 times the human exposure at 40 mg/day based on body surface area.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to the human exposure at 40 mg/day based on body surface area, decreased fetal viability and maternal mortality was observed.

Rosuvastatin was not teratogenic in rats at $\leq$ 25 mg/kg/day or in rabbits $\leq$ 3 mg/kg/day (systemic exposures equivalent to the human exposure at 40 mg/day based on AUC or body surface area, respectively).

Central Nervous System Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses $\leq$30 mg/kg/day (systemic exposures $\leq$60 times the human exposure at 40 mg/day based on AUC) did not reveal retinal findings during treatment for up to one year.

14 CLINICAL STUDIES

14.1 Hyperlipidemia and Mixed Dyslipidemia

CRESTOR reduces total-C, LDL-C, ApoB, nonHDL-C, and TG, and increases HDL-C, in adult patients with hyperlipidemia and mixed dyslipidemia.

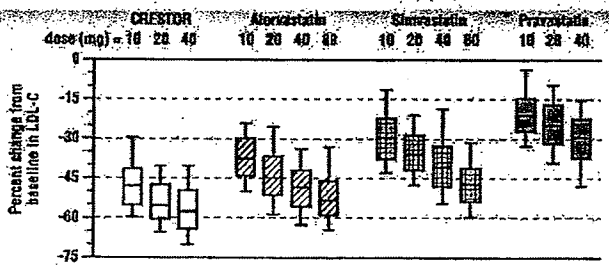
Dose-Ranging Study: In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hyperlipidemia CRESTOR given as a single daily dose for 6 weeks significantly reduced total-C, LDL-C, nonHDL-C, and ApoB, across the dose range (Table 5).

Table 5. Dose-Response in Patients With Hyperlipidemia (Adjusted Mean % Change From Baseline at Week 6)

Dose	N	Total-C	LDL-C	Non-HDL-C	ApoB	TG	HDL-C
Placebo	13	-5	-7	-7	-3	-3	3
CRESTOR 5 mg	17	-33	-45	-44	-38	-35	13
CRESTOR 10 mg	17	-36	-52	-48	-42	-10	14
CRESTOR 20 mg	17	-40	-55	-51	-46	-23	8
CRESTOR 40 mg	18	-46	-63	-60	-54	-28	10

Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study of 2,240 patients with hyperlipidemia or mixed dyslipidemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin (Figure 1 and Table 6).

Figure 1. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Patients with Hyperlipidemia or Mixed Dyslipidemia



Box plots are a representation of the 25th, 50th, and 75th percentile values, with whiskers representing the 10th and 90th percentile values.

Mean baseline LDL-C: 189 mg/dL

Table 6. Percent Change in LDL-C From Baseline to Week 6 (LS Mean*) by Treatment Group (sample sizes ranging from 156–157 patients per group)

	Treatment Daily Dose			
Treatment	**10 mg**	**20 mg**	**40 mg**	**80 mg**
CRESTOR	-46†	-52‡	-55§	—
Atorvastatin	-37	-43	-48	-51
Simvastatin	-28	-35	-39	-46
Pravastatin	-20	-24	-30	—

* Corresponding standard errors are approximately 1.00
† CRESTOR 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. ($p<0.002$)
‡ CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. ($p<0.002$)
§ CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg ($p<0.002$)

14.2 Heterozygous Familial Hypercholesterolemia

Active-Controlled Study: In a study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased by 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (Table 7).

Table 7. Mean LDL-C Percentage Change from Baseline

		CRESTOR (n=435) *LS Mean 95% CI	Atorvastatin (n=187) LS Mean 95% CI
Week 6	20 mg	-47% (-49%, -46%)	-38% (-40%, -36%)
Week 12	40 mg	-55% (-57%, -54%)	-47% (-49%, -45%)
Week 18	80 mg	NA	-52% (-54%, -50%)

*LS Means are least square means adjusted for baseline LDL

14.3 Hypertriglyceridemia

Dose-Response Study: In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 8).

Table 8. Dose-Response in Patients With Primary Hypertriglyceridemia Over 6 Weeks Dosing Median (Min, Max) Percent Change From Baseline

Dose	Placebo (n=26)	CRESTOR 5 mg (n=25)	CRESTOR 10 mg (n=23)	CRESTOR 20 mg (n=27)	CRESTOR 40 mg (n=25)
Triglycerides	1 (-40, 72)	-21 (-58, 38)	-37 (-65, 5)	-37 (-72, 11)	-43 (-80, -7)
nonHDL-C	2 (-13, 19)	-29 (-43, -8)	-49 (-59, -20)	-43 (-74, 12)	-51 (-62, -6)
VLDL-C	2 (-36, 53)	-25 (-62, 49)	-48 (-72, 14)	-49 (-83, 20)	-56 (-83, 10)
Total-C	1 (-13, 17)	-24 (-40, -4)	-40 (-51, -14)	-34 (-61, -11)	-40 (-51, -4)
LDL-C	5 (-30, 52)	-28 (-71, 2)	-45 (-59, 7)	-31 (-66, 34)	-43 (-61, -3)
HDL-C	-3 (-25, 18)	3 (-38, 33)	8 (-8, 24)	22 (-5, 50)	17 (-14, 63)

14.4 Homozygous Familial Hypercholesterolemia

Dose-Titration Study: In an open-label, forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.

14.5 Slowing of the Progression of Atherosclerosis

In the *Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR)* study, the effect of therapy with CRESTOR on carotid atherosclerosis was assessed by B-mode ultrasonography in patients with elevated LDL-C, at low risk (Framingham risk ≤10% over ten years) for symptomatic coronary artery disease and with subclinical atherosclerosis as evidenced by carotid intimal-medial thickness (cIMT). In this double-blind, placebo-controlled clinical study 984 patients were randomized (of whom 876 were analyzed) in a 5:2 ratio to CRESTOR 40 mg or placebo once daily. Ultrasonograms of the carotid walls were used to determine the annualized rate of change per patient from baseline to two years in mean maximum cIMT of 12 measured segments. The estimated difference in the rate of change in the maximum cIMT analyzed over all 12 carotid artery sites between CRESTOR-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI –0.0196, –0.0093; p<0.0001).

The annualized rate of change from baseline for the placebo group was +0.0131 mm/year (p<0.0001). The annualized rate of change from baseline for the CRESTOR group was -0.0014 mm/year (p=0.32).

At an individual patient level in the CRESTOR group, 52.1% of patients demonstrated an absence of disease progression (defined as a negative annualized rate of change), compared to 37.7% of patients in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

CRESTOR® (rosuvastatin calcium) Tablets are supplied as:

- NDC 0310-0755-90: 5 mg. Yellow, round, biconvex, coated tablets. Debossed "CRESTOR" and "5" on one side; bottle of 90 tablets
- NDC 0310-0751-90: 10 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "10" on one side; bottle of 90 tablets
- NDC 0310-0751-39: 10 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "10" on one side; unit dose packages of 100
- NDC 0310-0752-90: 20 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "20" on one side; bottles of 90
- NDC 0310-0752-39: 20 mg. Pink, round, biconvex, coated tablets. Debossed "CRESTOR" and "20"on one side; unit dose packages of 100
- NDC 0310-0754-30: 40 mg. Pink, oval, biconvex, coated tablets. Debossed "CRESTOR" on one side and "40" on the other side; bottles of 30

Storage

Store at controlled room temperature, 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Skeletal Muscle Effects

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

17.2 Concomitant Use of Antacids

When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after CRESTOR administration.

17.3 Pregnancy

If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy.

17.4 Liver Enzymes

It is recommended that liver enzymes be checked before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

CRESTOR is a trademark of the AstraZeneca group of companies
© AstraZeneca 2003, 2005, 2007
Licensed from SHIONOGI & CO., LTD., Osaka, Japan

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: IPR Pharmaceuticals, Inc.
Carolina, PR 00984

ASTRAZENECA

Rev XX/XX XXXX-XX
XXXXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	21-366
Submission Number	010
Submission Code	SE1
Letter Date	January 5, 2007
Stamp Date	January 9, 2007
PDUFA Goal Date	November 8, 2007
Reviewer Name	Amy G. Egan, M.D., M.P.H.
Review Completion Date	November 8, 2007
Established Name	Rosuvastatin calcium
(Proposed) Trade Name	CRESTOR®
Therapeutic Class	Lipid lowering
Applicant	AstraZeneca LP
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	Once daily
Indication	Slowing the progression of atherosclerosis
Intended Population	Patients in whom lipid-lowering therapy is indicated

Table of Contents

1 EXECUTIVE SUMMARY 6

1.1 RECOMMENDATION ON REGULATORY ACTION 6
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 6
1.2.1 Risk Management Activity 6
1.2.2 Required Phase 4 Commitments 6
1.2.3 Other Phase 4 Requests 6
1.3 SUMMARY OF CLINICAL FINDINGS 7
1.3.1 Brief Overview of Clinical Program 7
1.3.2 Efficacy 7
1.3.3 Safety 10
1.3.4 Dosing Regimen and Administration 12
1.3.5 Drug-Drug Interactions 13
1.3.6 Special Populations 14

2 INTRODUCTION AND BACKGROUND 15

2.1 PRODUCT INFORMATION 15
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 16
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 18
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 19
2.5 PRESUBMISSION REGULATORY ACTIVITY 19

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 20

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) 20
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 20

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 20

4.1 SOURCES OF CLINICAL DATA 20
4.2 TABLES OF CLINICAL STUDIES 20
4.3 REVIEW STRATEGY 21
4.4 DATA QUALITY AND INTEGRITY 22
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 22
4.6 FINANCIAL DISCLOSURES 22

5 CLINICAL PHARMACOLOGY 23

5.1 PHARMACOKINETICS 23
5.2 PHARMACODYNAMICS 24
5.3 EXPOSURE-RESPONSE RELATIONSHIPS 24

6 INTEGRATED REVIEW OF EFFICACY 24

6.1 INDICATION 24
6.1.1 Methods 24
6.1.2 General Discussion of Endpoints 25
6.1.3 Study Design 25
6.1.4 Efficacy Findings 25
6.1.6 Efficacy Conclusions 33

7 INTEGRATED REVIEW OF SAFETY 34

7.1 METHODS AND FINDINGS 34
7.1.1 Deaths 34
7.1.2 Other Serious Adverse Events 35
7.1.3 Dropouts and Other Significant Adverse Events 36
7.1.4 Other Search Strategies 41

7.1.5 Common Adverse Events 43
7.1.7 Laboratory Findings 47
7.1.8 Vital Signs 53
7.1.9 Electrocardiograms (ECGs) 53
7.1.12 Special Safety Studies 54
7.1.14 Human Reproduction and Pregnancy Data 54
7.1.16 Overdose Experience 55
7.1.17 Postmarketing Experience 55
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 55
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 55
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 59
7.2.3 Adequacy of Overall Clinical Experience 60
7.2.8 Assessment of Quality and Completeness of Data 61
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS 61
7.4 GENERAL METHODOLOGY 62
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence 62

8 ADDITIONAL CLINICAL ISSUES 62

8.1 DOSING REGIMEN AND ADMINISTRATION 62
8.2 DRUG-DRUG INTERACTIONS 62
8.3 SPECIAL POPULATIONS 63
8.4 PEDIATRICS 66
8.6 LITERATURE REVIEW 55

9 OVERALL ASSESSMENT 67

9.1 CONCLUSIONS 67
9.2 RECOMMENDATION ON REGULATORY ACTION 68
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 66
9.3.1 Risk Management Activity 68
9.3.2 Required Phase 4 Commitments 69
9.3.3 Other Phase 4 Requests 69
9.4 LABELING REVIEW 69
9.5 COMMENTS TO APPLICANT 69

10 APPENDICES 71

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS 71
10.2 LINE-BY-LINE LABELING REVIEW 152

REFERENCES 153

TABLE OF TABLES:

Table 1: Summary of slope (mm/year) by weighted average LDL-C (ITT population) 8
Table 2: Common adverse events (≥ 2%) - pooled safety population 11
Table 3: Atherosclerosis indications in the labels of lipid-lowering drugs 17
Table 4: U.S. Retail Prescription Data for Rosuvastatin 18
Table 5: Description of and key objectives in the rosuvastatin clinical efficacy studies for the treatment of atherosclerosis 20
Table 6: Annualized changes from baseline values to the end of the treatment period (Week 104) in cIMT for the secondary variables (ITT population) 27
Table 7: Percent change from baseline to end of study in lipid values – LOCF 27
Table 8: Percent change from baseline to end of study in CRP – LOCF 28
Table 9: Summary of annualized rate of change (slope) in mm/year for the treatment groups by selected pre-specified subgroups - ITT population 28
Table 10: Annualized rate of change in maximum cIMT of the 12 carotid artery sites by baselione mean maximum cIMT quartiles (ITT population) 30
Table 11: Summary of slope (mm/year) by weighted average LDL-C (ITT population) 31
Table 12: Number (percent) of patients in the METEOR ITT population who were concomitantly treated with anti-hypertensives 32
Table 13: Mean maximum cIMT of the 12 carotid artery sites (METEOR, ITT population excluding patients concomitantly treated with anti-hypertensives) 32
Table 14: Deaths occurring in rosuvastatin atherosclerosis trials 34
Table 15: Number (%) of subjects with SAEs 35
Table 16: Demographics of subjects who experienced SAE - safety population 36
Table 17: Demographics of withdrawn subjects - safety population 37
Table 18: TEAEs leading to study discontinuation (safety population) 37
Table 19: Data Mining for Renal Impairment for Statins 43
Table 20: Data Mining for Renal Failure and Acute Renal Failure for Statins 43
Table 21: Common adverse events (≥ 2%) - pooled safety population 45
Table 22: Treatment related adverse events occurring in ≥ 1% of patients - ISS safety population 47
Table 23: ALT elevations >3x ULN during treatment - pooled safety population 48
Table 24: CK elevations during treatment - pooled safety population 48
Table 25: Maximum serum creatinine elevations by category during treatment - pooled safety population 49
Table 26: ALT elevations >3x ULN on 2 or more consecutive occasions - pooled safety population 50
Table 27: Patients with abnormal platelet findings - pooled safety population 52
Table 28: Dropouts due to laboratory abnormalities - pooled safety population 53
Table 29: METEOR and ASTEROID demographic and selected baseline characteristics 57
Table 30: METEOR and ASTEROID baseline lipids, lipoproteins and CRP (METEOR ITT and ASTEROID IEV populations) 58
Table 31: Overview of exposure - METEOR safety population 58
Table 32: Overview of exposure - ASTEROID safety population 59
Table 33: Overview of exposure - ORION safety population 59

Table 34: Cumulative spontaneous reporting rates of ADRs associated with CRESTOR , by dose 60
Table 35: Most common adverse events by sex during randomized treatment - pooled safety population 64
Table 36: Most common adverse events by ethnic origin by treatment - METEOR and ASTEROID pooled 65
Table 37: 2007 Monthly Prescriptions for Rosuvastatin by dose 69

TABLE OF FIGURES:

Figure 1: Annualized rate of change in mean maximum cIMT of the near wall of the left internal carotid artery 26
Figure 2: Data Mining Results for Rhabdomyolysis with Statins 42
Figure 3: Relationship between LDL-C reduction and carotid IMT change 67

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that rosuvastatin be approved for the following indication: As adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

It is recommended that a summary of the METEOR trial be allowed in the Clinical Studies section of the label.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. This Reviewer is concerned with the potential for increased use of the 40 mg dose of rosuvastatin. The sponsor should be advised to monitor utilization of the 40 mg dose and to closely monitor patients on the 40 mg dose for rhabdomyolysis and myopathy during the initial 2 years following the approval of this sNDA.

While the cumulative reporting rates of renal failure and renal impairment combined (44 per million patients) is below the estimated annual incidence of 200 cases per million for acute renal failure in the community, the higher reporting rates for reported events of renal failure/renal impairment for rosuvastatin 40 mg are of concern and should also be closely monitored during the initial 2 years following this approval.

The sponsor should be required to submit Periodic Safety Update Reports semi-annually for the next 2 years to allow for such monitoring to occur.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

One pivotal study and two supportive studies were submitted in this sNDA to support the efficacy of rosuvastatin in slowing the progression of atherosclerosis and the safety of the long-term use of rosuvastatin 40 mg.

METEOR, the pivotal efficacy study, was a randomized, double-blind, placebo-controlled study of 984 subjects randomized in a 5:2 ratio into 2 parallel treatment arms over a period of 104 weeks. This study assessed the efficacy of rosuvastatin 40 mg in altering the natural history of carotid intimal-media thickness (cIMT) as compared to placebo.

ASTEROID, a supportive study, was a 104-week, open-label, multi-center, Phase IIIb study in 507 patients, evaluating whether treatment with rosuvastatin 40 mg resulted in regression of coronary artery atheroma volume as measured by intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) in patients with coronary artery disease undergoing coronary angiography.

ORION, an exploratory study, was a randomized, double-blind, parallel-group, multicenter, phase III study in 43 patients, 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. ORION employed MRI and B-mode ultrasound of the carotid arteries.

1.3.2 Efficacy

In METEOR, the primary efficacy variable was the annualized rate of change (as assessed by a multi-level mixed effects regression model) in the mean maximum cIMT of 12 carotid artery sites - near and far wall of the right and left common carotid artery; near and far wall of the right and left carotid bulb; and near and far wall of the right and left internal carotid artery. METEOR showed that rosuvastatin 40 mg significantly slowed the progression of carotid atherosclerosis compared to placebo. The difference in the annualized rate of change in the mean maximum cIMT analyzed over all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI: -0.0196, -0.0093; $p<0.001$).

The annualized change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI: -0.0041, 0.0014), but was not significantly different from zero ($p=0.32$). This was associated with a 45% decrease in LDL-C in the rosuvastatin group. There was significant progression in the placebo group (+0.131 mm/year; 95% CI: 0.0087, 0.0174; $p<0.0001$). This was associated with a 0.6% decrease in LDL-C in the placebo group.

Relative to placebo, rosuvastatin 40 mg achieved statistically significant differences in the annualized rate of change in all 4 of the secondary cIMT endpoints: the change from baseline in mean maximum cIMT of the near and far walls of the right and left common carotid artery:

-0.0122 mm/year (CI: -0.0170, -0.0074; p<0.0001); the change from baseline in mean maximum cIMT of the near and far walls of the right and left carotid bulb: -0.0212 mm/year (CI: -0.0306, -0.0119; p<0.0001); the change from baseline in mean maximum cIMT of the near and far walls of the right and left internal carotid: -0.0105 mm/year (CI: -0.0196, -0.015; p<0.0228); and the mean change from baseline in the near and far walls of the right and left CCA: -0.0085 mm/year (CI: -0.0113, -0.0056; p<0.0001). However, it is notable that there was no statistically significant treatment difference in 3 of the 4 walls of the internal carotid artery and that the statistically significant treatment difference observed in the 1 wall (the near wall of the left internal carotid) was due to an unusual "spike" in the placebo rate of change that occurred between baseline and 6 months.

Despite some variability in the data by country (in the rosuvastatin treated patients, the mean change from baseline in the European contingent [n=407] was +0.0002 mm/year while in the U.S. contingent [n=217] was -0.0047 mm/year; in the placebo group, the mean change from baseline in the European contingent [n=172] was +0.0146 mm/year while in the U.S. contingent [n=80] was +0.0088 mm/year), the overall treatment effect (rosuvastatin vs. placebo) was similar, -0.0144 mm/year for the European group and -0.0135 mm/year for the U.S. group.

When the annualized rates of change were analyzed by average percent change in LDL-C, the annualized rate of change in mean cIMT was -0.0021 mm/year in the group that achieved an average percentage change in LDL-C less than the mean (n=383) versus an annualized rate of change of -0.0003 mm/year in the group that achieved an average percentage change in LDL-C ≥ the mean.

The table below summarizes the annualized rate of change in mean maximum cIMT by on-treatment level of LDL-C achieved. The group that showed the greatest effect was the group that achieved an on-treatment LDL-C of ≥ 70 mg/dL but < 100 mg/dL; the annualized rate of change in mean maximum cIMT for this group (n=228) was -0.0024 mm/year.

Table 1: Summary of slope (mm/year) by weighted average LDL-C (ITT population)

CATEGORY	SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=624
Weighted average LDL-C < Mean	N	389
	Slope mean	-0.0023
	Slope SE	0.0016
	Slope 95% CI	(-0.0055, 0.0008)
Weighted average LDL-C ≥ Mean	N	233
	Slope mean	0.0004
	Slope SE	0.0024
	Slope 95% CI	(-0.0043, 0.0051)
Weighted average LDL-C < 100 mg/dL	N	518
	Slope mean	-0.0018
	Slope SE	0.0014
	Slope 95% CI	(-0.0045, 0.0009)
Weighted average LDL-C ≥ 100 mg/dL	N	104
	Slope mean	0.0010

CATEGORY	SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=624
	Slope SE	0.0044
	Slope 95% CI	(-0.0076, 0.0096)
Weighted average LDL-C < 70 mg/dL	N	290
	Slope mean	-0.0014
	Slope SE	0.0019
	Slope 95% CI	(-0.0051, 0.0023)
Weighted average LDL-C ≥ 70 mg/dL	N	332
	Slope mean	-0.0014
	Slope SE	0.0019
	Slope 95% CI	(-0.0050, 0.0023)

Annualized rate of change of cIMT was summarized by quartile of baseline cIMT (Quartiles: first, 0.6976167 to 1.02467 mm; second, >1.02467 to 1.124958 mm; third, >1.24958 to 1.26029 mm; fourth, >1.26029 to 1.904 mm). The rosuvastatin/placebo difference in annualized rate of change for each quartile was directionally and quantitatively consistent with the results of the all patients' primary analysis (-0.0094 mm/year, -0.0128 mm/year, -0.0188 mm/year and -0.0171 mm/year, respectively).

Because of the relatively large number of subjects on anti-hypertensive medications known to have an effect on cIMT progression (16% of rosuvastatin subjects and 18% of placebo subjects), annualized rate of change of cIMT was analyzed excluding these subjects. The treatment difference, rosuvastatin versus placebo was essentially unchanged, -0.0140 mm/year ($p<0.0001$).

Despite the complexity of the statistical model employed by the sponsor, results obtained by the Agency's statistician (please see Dr. David Hoberman's review) using a less complicated model documented the consistent and robust results obtained by the sponsor.

While it is difficult to compare results across studies, one comparison warrants mentioning. METEOR was modeled on ACAPS (Asymptomatic Carotid Artery Progression Study) which was a 3-year study in 919 subjects with asymptomatic atherosclerosis to assess the effect of lovastatin 20 mg or 40 mg versus placebo on atherosclerosis progression as assessed by B-mode ultrasound of the carotid arteries. In ACAPS, where a linear regression model was used in the primary analysis, the annualized rate of change in mean maximum carotid IMT (the composite of the same 12 sites as used in METEOR) in the lovastatin 20/40 mg group was -0.009 mm/year; an increase of 0.006 mm/year was seen in the placebo group. This was associated with a 28% reduction in LDL-C in the lovastatin group; the mean LDL-C level achieved in ACAPS was 113.1 mg/dL.

It is unclear why rosuvastatin 40 mg, clearly the most potent of the marketed statins, which achieved a greater reduction in LDL-C than did lovastatin in ACAPS achieved inferior results to lovastatin in the rate of change from baseline in mean maximum carotid IMT (-0.009 mm/year vs. -0.0014 mm/year), despite a comparable treatment difference (-0.0145 mm/year vs. -0.015 mm/year) especially in light of the current literature which would suggest that the cIMT is simply a surrogate for LDL-C and that the greater the reduction in LDL-C, the greater the

slowing of progression of atherosclerosis. This discrepancy between the results of the two trials could not be explained by differences in baseline cIMT, age, gender, co-morbid conditions, or baseline cholesterol levels.

The clinical meaning of the small improvements in carotid intimal-media thickness observed in the METEOR trial is unclear. The predictive value of changes in IMT for stroke or cardiovascular events has not been established. Only one study has studied prospectively the relationship between IMT progression rate and coronary events. A long-term follow-up study (8.8 years) of a cohort of patients enrolled in the NIASPAN study CLAS (The Cholesterol Lowering Atherosclerosis Study) showed that a yearly cIMT progression rate of 0.03 mm was associated with a relative risk of 2.2 for MI or coronary death and a relative risk of 3.1 for any coronary event.

The effect of rosuvastatin on cardiovascular morbidity and mortality has not yet been determined.

1.3.3 Safety

There were a total of 6 deaths that occurred during treatment in the 3 submitted studies – 1 in ORION, 4 in ASTEROID, and 1 in METEOR. All deaths occurred in rosuvastatin 40 mg treatment arms.

In the 3 submitted studies, SAEs occurred in 19/281 (6.8%) subjects on placebo, 3/21 (14.3%) subjects on rosuvastatin 5 mg and 235/1229 (19.1%) subjects on rosuvastatin 40 mg.

The discontinuation rate for treatment-related adverse reactions (myalgia, constipation, asthenia, abdominal pain, and nausea) in the 3 studies comprising the current submission was 3.5%. For METEOR, the only placebo-controlled trial of the 3, the discontinuation rate for these treatment-related AEs was 3.3%. These rates are similar to the rates reported in the current product label – 3.7%.

During these 2 year trials involving over 1200 subjects, there were no cases of rhabdomyolysis, nor were there any adverse events compatible with hepatic dysfunction. There was one case of renal failure in a patient with concomitant congestive heart failure.

Elevations in CK >10x ULN occurred in 4 (0.3%) rosuvastatin treated subjects in the trials, and in no placebo subjects; creatinine increase of > 100% occurred in 2 (0.2%) of rosuvastatin treated subjects and in no placebo subjects; and ALT >3x ULN on 2 consecutive occasions occurred in 5 (0.4%) rosuvastatin treated subjects and in 1 (0.4%) placebo subject.

The following table provides a summary of the most common (≥2%) adverse events in the pooled data:

Table 2: Common adverse events (≥ 2%) - pooled safety population

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229	ROSUVASTATIN 5 MG N=21	PLACEBO N=281
Total # subjects with AE	**1027 (83.6)**	**16 (76.2)**	**226 (80.4)**
Musculoskeletal and Connective Tissue Disorders	**498 (40.5)**	**7 (33.3)**	**117 (41.6)**
Myalgia	163 (13.3)	0	34 (12.1)
Arthralgia	103 (8.4)	2 (9.5)	20 (7.1)
Back pain	91 (7.4)	1 (4.8)	29 (10.3)
Muscle spasms	47 (3.8)	0	9 (3.2)
Pain in extremity	37 (3.0)	2 (9.5)	6 (2.1)
Osteoarthritis	33 (2.7)	1 (4.8)	8 (2.8)
Shoulder pain	29 (2.4)	0	8 (2.8)
Tendonitis	24 (2.0)	1 (4.8)	6 (2.1)
Infections and Infestations	**461 (37.5)**	**5 (23.8)**	**118 (42.0)**
Nasopharyngitis	106 (8.6)	2 (9.5)	31 (11.0)
Influenza	95 (7.7)	11 (52.4)	29 (10.3)
URI	67 (5.5)	1 (4.8)	13 (4.6)
Sinusitis	48 (3.9)	0	15 (5.)
Bronchitis	45 (3.7)	0	13 (4.6)
UTI	36 (2.9)	1 (4.8)	7 (2.5)
Gastrointestinal Disorders	**299 (24.3)**	**4 (19.0)**	**72 (25.6)**
Diarrhea	44 (3.6)	1 (4.8)	11 (3.9)
Constipation	42 (3.4)	0	12 (4.3)
Abdominal pain upper	36 (2.9)	0	12 (4.3)
Nausea	35 (2.8)	1 (4.8)	7 (2.5)
Abdominal pain	29 (2.4)	0	5 (1.8)
Dyspepsia	29 (2.4)	0	6 (2.1)
GERD	28 (2.3)	0	6 (2.1)
Nervous System Disorders	**241 (19.6)**	**2 (9.5)**	**44 (15.7)**
Dizziness	57 (4.6)	0	8 (2.8)
Hypoaesthesia	25 (2.0)	0	10 (3.6)
General Disorders and Administration Site Conditions	**201 (16.4)**	**4 (19.0)**	**32 (11.4)**
Fatigue	70 (5.7)	1 (4.8)	16 (5.7)
Non-cardiac chest pain	56 (4.6)	0	1 (0.36)
Peripheral edema	39 (3.2)	1 (4.8)	3 (1.1)
Cardiac Disorders	**199 (16.2)**	**2 (9.5)**	**9 (3.2)**
Angina pectoris	95 (7.7)	1 (4.8)	0
Injury, Poisoning and Procedural Complications	**180 (14.6)**	**4 (19.0)**	**43 (15.3)**
Respiratory, Thoracic and Mediastinal Disorders	**178 (14.5)**	**0**	**31 (11.0)**
Cough	50 (4.1)	0	8 (2.8)
Pharyngolaryngeal pain	26 (2.1)	0	7 (2.5)

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229	ROSUVASTATIN 5 MG N=21	PLACEBO N=281
Dyspnea	25 (2.0)	0	3 (1.1)
Investigations	**163**	**1 (4.8)**	**21 ((7.5)**
Blood CK increased	36 (2.9)	0	2 (0.71)
ALT increased	27 (2.2)	0	0
Skin and Subcutaneous Tissue Disorders	**128**	**0**	**34 (12.1)**
Rash	26 (2.1)	0	7 (2.5)
Vascular Disorders	**124**	**7 (33.3)**	**14 (5.0)**
Hypertension	79 (6.4)	4 (19.0)	7 (2.5)
Psychiatric Disorders	**113 (9.2)**	**1 (4.8)**	**23 (8.2)**
Insomnia	39 (3.2)	0	11 (3.9)
Depression	32 (2.6)	0	3 (1.1)
Anxiety	31 (2.5)	0	5 (1.8)
Eye Disorders	**69 (5.6)**	**0**	**20 (7.1)**
Renal and Urinary Disorders	**67 (5.5)**	**2 (9.5)**	**20 (7.1)**
Reproductive System and Breast Disorders	**61 (5.0)**	**0**	**14 (5.0)**
Metabolism and Nutrition Disorders	**60 (4.9)**	**1 (4.8)**	**10 (3.6)**
Neoplasms Benign, Malignant and Unspecified	**52 (4.2)**	**1 (4.8)**	**11 (3.9)**
Ear and Labyrinth Disorders	**47 (3.8)**	**1 (4.8)**	**6 (2.1)**
Immune System Disorders	**27 (2.2)**	**0**	**5 (1.8)**

1.3.4 Dosing Regimen and Administration

According to the sponsor, a 40 mg dose was chosen for METEOR in order to maximize the chances of demonstrating regression versus baseline and was based on the findings of the ASAP (Atorvastatin vs. Simvastatin on Atherosclerotic Progression) study. In ASAP, regression of cIMT occurred in the atorvastatin 80 mg treated patients and was associated with a 50.5% decrease in LDL-C.

The rosuvastatin dose in ASTEROID was also 40 mg. The use of the 40 mg dose was again chosen to demonstrate regression of coronary atheroma over the 2-year course of the study. Angiographic studies have demonstrated that lowering LDL-C slows the progression of coronary atherosclerosis and have suggested that at least a 40% decrease in LDL-C is needed to arrest progression of the atherosclerosis process. REVERSAL (Reversing Atherosclerosis with Aggressive Lipid-Lowering Study) demonstrated that intensive lipid-lowering with atorvastatin 80 mg was insufficient, however, to achieve regression in IVUS endpoints measured across the total vessel segment despite an LDL-C reduction of 46.3%.

The sponsor acknowledges the lack of a definitive demonstration of the anti-atherosclerotic effects of lower doses of rosuvastatin. The sponsor further acknowledges that *it remains appropriate to initiate therapy within the currently recommended rosuvastatin product dosing guidelines for the treatment of hypercholesterolemia.*

1.3.5 Drug-Drug Interactions

No new data were submitted.

Rosuvastatin has no significant interaction with cytochrome P450 3A4 isoenzymes. Of the known drug-drug interactions listed in the current product label, the following observations were made in the current submission:

- No patient concomitantly took cyclosporine and rosuvastatin in any of the 3 submitted studies.
- A total of 42 patients concomitantly took rosuvastatin and Vitamin K antagonist anticoagulants. Only one possible treatment related AE ("hemoglobin decreased") occurred.
- No patient concomitantly took fenofibrate and rosuvastatin in any of the 3 submitted studies.
- No patient concomitantly took gemfibrozil and rosuvastatin in any of the 3 submitted studies.
- Three patients received concomitant oral contraceptive medication and rosuvastatin. There were no treatment related AEs in any of these patients.

In the submitted studies, possible adverse interactions with other medications likely to be co-administered with rosuvastatin were also considered. These drugs included other non-statin lipid-modifying medications (e.g., niacin, ezetimibe, and bile acid sequestrants), anti-diabetics, anti-hypertensives, and hormone replacement therapy. The following observations were made:

- Four patients in ASTEROID received concomitant rosuvastatin plus niacin. The percentage of patients with "any AE" while receiving rosuvastatin plus niacin was 25%, while the percentage of patients with "any AE" while receiving rosuvastatin without niacin was 83%.
- One patient concomitantly took ezetimibe and rosuvastatin. No AE was reported.
- Forty-one patients concomitantly took a bile acid sequestrant and rosuvastatin. In METEOR, of the patients receiving rosuvastatin 40 mg plus a BAS, 38.9% had "any AE", while 83.7% of patients receiving rosuvastatin 40 mg without BAS had "any AE". (50% of patients receiving placebo plus BAS experienced "any AE", while 79.6% of patients receiving placebo without BAS had "any AE".) In ASTEROID, the incidence of "any AE" was 87% in patients who received the BAS, and 83% in patients who did not.
- In ASTEROID, 69 out of the 507 patients receiving rosuvastatin 40 mg, received antidiabetic medication. The adverse event profiles were similar between patients on concomitant anti-diabetic medication and those not with the exception of a higher incidence of angina pectoris – 23.2% of patients on anti-diabetic medications versus 16.9% of patients not on anti-diabetic medications.

- In METEOR, 130 patients out of 700 treated with rosuvastatin 40 mg and 51 patients out of 281 treated with placebo received concomitant anti-hypertensive medication. With the exception of hypertension which was seen in more patients receiving anti-hypertensive medication in both the rosuvastatin and placebo groups, the AE profiles of the groups receiving study drug plus anti-hypertensive agents was similar to the patients who did not. In ASTEROID, 482 out of the 507 patients receiving rosuvastatin 40 mg received concomitant anti-hypertensive medication. With the exception of differences in the incidence of angina pectoris (17.2% of patients on concomitant anti-hypertensives vs. 24% of patients not on concomitant anti-hypertensives) and myalgia (13.3% of patients on concomitant anti-hypertensives vs. 28% of patients not on concomitant anti-hypertensives), the pattern of AEs in the 2 groups was similar.
- In METEOR, 100 female patients out of 281 female rosuvastatin treated patients and 37 female patients out of 114 female placebo treated patients received concomitant HRT. There were no clinically relevant differences in the occurrence of treatment related AEs. In ASTEROID, 23 female patients out of 147 received concomitant rosuvastatin and HRT. Peripheral edema occurred in 6 (26.1%) of the women receiving concomitant HRT, while occurring in 11 (8.9%) of women not receiving HRT.

1.3.6 Special Populations

In the current studies, there was a slightly greater frequency of "any AE" in women than in men during rosuvastatin treatment (METEOR 89% vs. 80%; ASTEROID 88% vs. 82%; and ORION 93% vs. 83%, respectively). In METEOR, there was a slightly greater incidence of AEs in women than men in the placebo group (85% vs. 77%).

The METEOR protocol excluded patients >70 years of age. In METEOR, the frequency of "any AE" was higher in patients ≥ 65 years of age for both the rosuvastatin (90% vs. 82%, respectively) and placebo groups (89% vs. 79%, respectively). However, for myalgia, the frequencies were higher in the <65 years of age patients for both rosuvastatin (13% vs. 10%) and placebo (13% vs. 8%). In ASTEROID, myalgia occurred in 14.6% of subjects < 65 years of age, 13.3% of subjects ≥ 65 years of age, 13.9% of subjects < 70 years of age, and 18.2% of subjects ≥ 75 years of age.

There were too few non-Caucasian patients in any of the 3 studies to permit meaningful comparisons. There were only 10 Asian patients in all 3 studies combined.

The incidence of "any AE" was slightly higher in subjects with mild to moderate renal impairment at baseline than in those subjects who had normal renal function at baseline. In METEOR, the frequency of "any AE" was 82.9% in subjects who had normal renal function at baseline; 88.8% in subjects with mild renal impairment; and 100% in patients with moderate renal impairment.

Patients with impaired hepatic function at baseline who were receiving rosuvastatin 40 mg had a somewhat higher frequency of myalgia than patients with normal hepatic function in METEOR (16.7% vs. 13.0%) but not in ASTEROID (9.6% vs. 15.5%).

2 INTRODUCTION AND BACKGROUND

Rosuvastatin is a member of the statin class of lipid-lowering compounds, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and reduce cholesterol synthesis. It is presently approved at once daily doses of 5, 10, 20, or 40 mg. It is indicated:

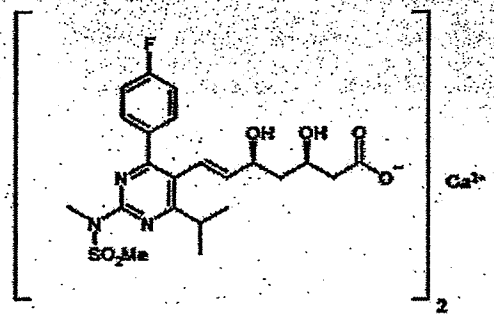
1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non-HDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

This NDA supplement presents data from one pivotal efficacy study, Study D3562C00088 (**METEOR**: "A Randomized, Double-blind, Placebo-controlled, Multicenter Parallel Group Phase III Study Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin 40 mg") and two additional studies D3562C0076 (**ASTEROID**: "A 104-Week, Open-label, Multi-center, Phase 3b Study Evaluating the Effect of Treatment with Rosuvastatin 40 mg on Atherosclerotic Disease as Measured by Intravascular Ultrasound and Quantitative Coronary Angiography in Subjects Undergoing Coronary Angiography who have Coronary Artery Disease") and D3560C00044 (**ORION**: "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") to support an indication "to slow (b) (4) the progression of atherosclerosis."

The sponsor is further seeking the addition of a summary of the METEOR study in the Clinical Studies section of the label.

2.1 Product Information

Rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)- 6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14. Its structural formula is:



Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Rosuvastatin reduces total cholesterol (total-C), LDL-C, ApoB, and nonHDL-C (total cholesterol minus HDL-C) in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Rosuvastatin also reduces TG and produces increases in HDL-C. Rosuvastatin reduces total-C, LDL-C, VLDL-cholesterol (VLDL-C), ApoB, nonHDL-C, and TG, and increases HDL-C in patients with isolated hypertriglyceridemia. The effect of rosuvastatin on cardiovascular morbidity and mortality has not been determined.

2.2 Currently Available Treatment for Indications

Currently, four of the 6 commercially available statins contain atherosclerosis trials in their labels. These are summarized in the table below:

Table 3: Atherosclerosis indications in the labels of lipid-lowering drugs

STATIN	ATHEROSCLEROSIS TRIALS IN LABEL	PATIENT POPULATION STUDIED	DURATION OF STUDY	SURROGATE MARKER USED	INDICATION IN LABEL
CRESTOR	None	N.A.	N.A.	N.A.	None
LESCOL	Lipoprotein and Coronary Atherosclerosis Study (LCAS)	Patients with coronary artery disease and LDL-C 115-190 mg/dL (N=429)	2.5 years	Quantitative coronary angiography (QCA)	*Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels*
LIPITOR	None	N.A.	N.A.	N.A.	None
MEVACOR	1. Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)	1.Hyperlipidemic patients	1. 2 years	1. QCA	*MEVACOR is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels*
	2. Monitored Atherosclerosis Regression Study (MARS)	2.Hyperlipidemic patients with at least 2 coronary artery lesions	2. 4 years	2. QCA	
	3. Familial Atherosclerosis Treatment Study (FATS)	3.Hyperlipidemic patients (N=146)	3. 2.5 years	3. QCA	
	4. Asymptomatic Carotid Artery Progression Study (ACAPS)	4.Hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline	4. 3 years	4. cIMT	
PRAVACHOL	1. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)	1. Patients with coronary disease and LDL-C 130-190 mg/dL (N=264)	1. 3 years	1. Coronary angiography	*In patients with clinically evident coronary heart disease, PRAVACHOL is indicated to slow the progression of coronary atherosclerosis*
	2. Regression Growth Evaluation Statin Study (REGRESS)	2. Patients with angina, angiographically documented coronary artery disease, and TC 160-310 mg/Dl (N=653)	2. 2 years	2. Coronary angiography	

STATIN	ATHEROSCLEROSIS TRIALS IN LABEL	PATIENT POPULATION STUDIED	DURATION OF STUDY	SURROGATE MARKER USED	INDICATION IN LABEL
ZOCOR	Multicenter Anti-Atheroma Study (MAAS)	Hypercholesterolemic patients with coronary heart disease	4 years	QCA	None
NIASPAN	1.The Cholesterol-Lowering Atherosclerosis Study (CLAS) 2.The Familial Atherosclerosis Treatment Study (FATS)	1. Male patients with previous coronary bypass surgery (N=162) 2. Male patients with Apo B levels ≥ 125 mg/dL, established CAD and FH of vascular disease (N=146)	1. 2 years 2. 2.5 years	1. QCA 2. QCA	*In patients with a history of coronary artery disease (CAD) and hypercholesterol-emia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.*
VYTORIN	None	N.A.	N.A.	N.A.	None
ADVICOR	None	N.A.	N.A.	N.A.	None
ZETIA	None	N.A.	N.A.	N.A.	None

2.3 Availability of Proposed Active Ingredient in the United States

The rosuvastatin clinical study program has involved over 55,000 patients. The first marketing approval for rosuvastatin was in the Netherlands on November 6, 2002 and the drug was first launched in Canada on February 19, 2003. It was approved in the U.S. on August 12, 2003. As of December 1, 2006, rosuvastatin has been approved in 86 countries and, according to the sponsor, there is estimated to be more than (b) (4) patient-years of post marketing experience.

A summary of U.S retail prescriptions for rosuvastatin from launch through June, 2007 is provided below:

Table 4: U.S. Retail Prescription Data for Rosuvastatin

YEAR	NUMBER OF ROSUVASTATIN PRESCRIPTIONS (IN MILLIONS)
2003	(b) (4)
2004	
2005	
2006	
2007 (through June 2007)	

2.4 Important Issues With Pharmacologically Related Products

Over the last several years, multiple studies, notably of lipid altering agents, have been conducted to examine effects on anatomically defined arterial disease. In this regard, several statin package inserts include study summaries and indications based on the results of trials utilizing arterial anatomic assessments of disease as measures of drug effect. Specifically, the labels for lovastatin, simvastatin, pravastatin, and fluvastatin all describe the results of placebo-controlled trials showing apparent slowing of the progression of atherosclerosis by drug compared to placebo. These findings are obviously consistent with the known role of LDL-cholesterol in atherosclerotic disease and are "validated" by the results of now multiple trials showing reductions in cardiovascular disease events (fatal and non-fatal myocardial infarctions, unstable angina, strokes, revascularizations, etc.) in patients treated with statins compared to placebo.

However, while ultrasound of the carotid arteries, MRI and CT of the coronaries and carotids, and intravascular ultrasound of the coronaries have been studied, variably, for their utility in predicting cardiovascular disease risk and in assessing the effects of anti-atherosclerotic therapies, none stands as a fully validated "surrogate" measure of anti-atherosclerosis efficacy. Specifically, as for coronary angiography itself, there are inadequate data to permit a calculation of the extent of cardiovascular disease risk reduction as a function of a given degree of change in anatomic parameters as assessed by these methods.

2.5 Presubmission Regulatory Activity

In developing its program on atherosclerosis, AstraZeneca sought guidance from the Agency from the summer of 2001 until spring 2002. The design features of a single pivotal study were discussed such as: measurement of atherosclerosis by cIMT; asymptomatic patients with subclinical atherosclerosis; rosuvastatin 40 mg versus placebo; and a primary endpoint of mean maximum cIMT from 12 sites over time as estimated by a statistical model. The final version of the METEOR study was developed based on these discussions.

Important agreements made during these discussions include:

- The Agency's acknowledgement that Carotid Intimal Media Thickness (cIMT) is predictive of Coronary Artery Disease (CAD).
- The Division's agreement that one trial could support the target or the alternate indication.
- Acceptance of the hierarchical mixed-effects model for the primary efficacy analysis.

On October 5, 2006, AstraZeneca submitted a meeting request/questions to the Division in anticipation of its submission of this sNDA. At that time, the Division indicated that the proposed submission appeared adequate for filing and the one trial could support the target or the alternate indication if the data were sufficiently robust.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new data were submitted.

3.2 Animal Pharmacology/Toxicology

No new data were submitted.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In this NDA supplement the sponsor has submitted three studies in support of the anti-atherosclerotic effects of rosuvastatin. METEOR, the pivotal study included in this submission, evaluated the effects of 2 years of treatment with rosuvastatin 40 mg on the natural history of atherosclerosis in the carotid arteries as assessed by carotid ultrasound (cIMT). ASTEROID provides evidence in support of the proposed indication; it evaluated the effects of 2 years of treatment with rosuvastatin 40 mg on the progression of atherosclerosis in the coronary arteries, as assessed by intravascular ultrasound (IVUS) and by quantitative coronary angiography (QCA). Also included is ORION, which was an exploratory study to examine the effects of low-dose (5 mg) versus high-dose (40/80 mg) rosuvastatin on carotid atherosclerosis as assessed by both magnetic resonance imaging (MRI) and cIMT.

4.2 Tables of Clinical Studies

Table 5: Description of and key objectives in the rosuvastatin clinical efficacy studies for the treatment of atherosclerosis

STUDY AND LOCATION	STUDY DESIGN DOSE DURATION	PATIENT POPULATION	KEY OBJECTIVES
METEOR 61 centers in U.S. and Europe	Randomized, double-blind, placebo-controlled, parallel-group Rosuvastatin 40 mg 104 weeks	Males aged ≥ 45 and ≤ 70 and females aged ≥ 55 and ≤ 70 with ↑ LDL-C and 10-year CHD risk < 10% by FRI. Max IMT of ≥ 1.2 mm and < 3.5 mm at baseline	Primary: Effects of rosuva 40 mg on the change in the mean maximum cIMT of the 12 vessel segments Secondary: Effects of rosuva 40 mg on the change in the mean maximum cIMT of the near and far walls of the right and left CCA, of the carotid bulb and of the ICA, and change in the mean IMT of the near and far walls of the right and left CCA. Percent change from baseline in

STUDY AND LOCATION	STUDY DESIGN DOSE DURATION	PATIENT POPULATION	KEY OBJECTIVES
			lipid and lipoprotein levels and CRP.
ASTEROID 53 centers in North America, Europe and Australia	Open-label, single-arm Rosuvastatin 40 mg 104 weeks	Males or females ≥ 18 years of age with angiographic evidence of CAD. No restriction on baseline LDL-C.	Primary: Whether treatment with rosuva 40 mg results in regression of coronary artery atheroma burden as assessed by the TAV in the most severely diseased segment or the PAV in the total segment. Secondary: IVUS: To evaluate the nominal change in TAV in the total segment. QCA: Percent change in the MLD within all measured coronary segments Percent change from baseline in lipid and lipoprotein levels.
ORION 2 centers in U.S.	Randomized, double-blind, parallel-group, multicenter study Rosuvastatin 5 mg, 40/80 mg 104 weeks	Males and females ≥ 18 years of age with hypercholesterolemia with either 16% to 79% stenosis of one or more carotid arteries, or an atherosclerotic plaque with a lipid-rich necrotic core.	Primary: Change in the carotid artery wall volume after 24 months dosing with low and high doses of rosuvastatin as assessed by MRI. Secondary: Change in the carotid artery wall volume after all other time points; change in composition (by index lesion MRI images); change in mean IMT of the right and left carotid arteries by B-mode ultrasound; percent change from baseline in lipid and lipoprotein levels.

4.3 Review Strategy

The three submitted studies, ORION, ASTEROID and METEOR were similar only in duration – all were 104 week studies. Neither ASTEROID nor ORION was placebo controlled – ORION was active controlled (5 mg vs. 40/80 mg) and ASTEROID was a single arm (40 mg) study. All of the studies employed different modalities of atherosclerosis assessment – ORION used MRI; ASTEROID used IVUS and QCA; and METEOR used cIMT by B mode ultrasound. The patient populations studied were different – METEOR was conducted in low cardiovascular risk patients with subclinical carotid atherosclerosis who did not meet current guidelines for statin therapy, whereas ASTEROID and ORION were conducted in patients with established cardiovascular disease who did meet current guidelines for statin therapy. For these reasons, METEOR, which was the most scientifically rigorous of the submitted studies (double-blind, placebo-controlled, and using an accepted measure of atherosclerosis) was the focus of the review for the proposed

indication. ASTEROID and ORION were reviewed especially for their contribution to the long-term safety profile of rosuvastatin, specifically the highest marketed dose, 40 mg.

4.4 Data Quality and Integrity

A review was conducted at 2 clinical sites (Site #101 and Site #108) to assess adherence to FDA regulatory requirements and if possible, to determine a reason for the treatment difference between the 2 sites. Overall, data from these 2 sites appeared acceptable in support of this NDA supplement. There was no reason identified to account for the treatment difference between the 2 sites.

Please see full DSI report by Andrea Slavin.

4.5 Compliance with Good Clinical Practice

METEOR, ASTEROID, and ORION were conducted by AstraZeneca in compliance with Good Clinical Practice (GCP) requirements. As certified in the submission, no debarred investigators were used in the conduct of these studies.

The following sites were identified by this Reviewer for inspection:

Site 101 in Winston-Salem, NC, USA
Study D3562C00088-METEOR
33 Randomized/100 Not Randomized

Site 108 in Minneapolis, MN USA
Study D3562C00088-METEOR
65 Randomized/253 Not Randomized

These sites were chosen for their discrepant results. Site 101 showed the largest treatment effect for a site of "reasonable size"; this site also had numerous (n=26) protocol deviations. Site 108 was the largest U.S. site and showed no treatment effect.

4.6 Financial Disclosures

The sponsor indicated that the following investigators received more than $25,000 from AstraZeneca. (It should be noted that exact amounts were requested from the sponsor, but were not provided.)

- (b) (6)
-
-

(b) (6) was listed as a (b) (6) subjects were enrolled. Dr. Financial Disclosure Form was not archived in the study file. Attempts by the sponsor to locate Dr. (b) (6) were unsuccessful

It is the opinion of this Medical Reviewer that given the relatively small number of subjects enrolled by these investigators and given Dr. (b) (6) role as a sub-investigator, that the integrity of the studies was not compromised.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new data were submitted. A brief summary of the PK of rosuvastatin is provided below:

- Peak plasma concentrations of rosuvastatin are reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increase in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.
- Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by C_{max}, but there was no effect on the extent of absorption as assessed by AUC.
- Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration.
- There are no differences in plasma concentrations of rosuvastatin between men and women.
- There are no differences in plasma concentrations of rosuvastatin between the non-elderly and elderly populations (age ≥ 65 years).
- Rosuvastatin is not extensively metabolized; approximately 10% of a radio-labeled dose is recovered as metabolite.
- The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9. Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.
- Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%).
- The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.
- There are no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, there is an approximate 2-fold

elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group

- Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.
- Mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min/1.73m ^{2}) has no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increase about 3-fold in patients with severe renal impairment (CL_{cr} < 30 mL/min/1.73m ^{2}) compared with healthy subjects (CL_{cr} > 80 mL/min/1.73m ^{2}).
- In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin are modestly increased.

5.2 Pharmacodynamics

No new data were submitted.

5.3 Exposure-Response Relationships

No new data were submitted.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication being sought by the sponsor is "to slow (b) (4) the progression of atherosclerosis".

6.1.1 Methods

To support the efficacy of rosuvastatin in slowing (b) (4) the progression of atherosclerosis, data from three 2-year Phase 3 studies were submitted. Because of the different modalities of assessing atherosclerosis employed in the studies, pooling of the data was not possible. In terms of the labeling revision requested, only METEOR was considered to be relevant in the efficacy analysis.

METEOR employed carotid intimal-media thickness as assessed by B-mode ultrasound. In order to standardize results at the 61 international centers involved in METEOR, a standardized protocol for the ultrasound process was developed and employed, and 2 core laboratories were employed for the reading of all scans – 1 in the U.S. and 1 in Europe. All readers participated in a uniform training and certification program. Reader differences were accounted for by including a factor for reader in the statistical model. Similarly, 3 different types of ultrasound machines were employed in the trial. No patient changed between these scanners during the course of the study. An analysis of variance was carried out based on the model for the primary

efficacy variable (which included scanner as a fixed effect) using all cIMT data. There was no significant effect of scanner (p=0.76).

6.1.2 General Discussion of Endpoints

The primary variable for METEOR was change from baseline values to end of treatment in maximum carotid intimal-media thickness (cIMT) over 12 carotid artery sites (near and far walls of the left and right CCA; near and far walls of the left and right carotid bulb; and near and far walls of the left and right ICA). This was determined using a multi-level mixed effects regression model that estimated mean annualized rate of change (mm/year) over the 2-year study period for each treatment group. This allowed for imputation of missing values and also weighted each individual's contribution to the overall mean based on the amount of missing data that existed for each individual patient.

Secondary cIMT efficacy variables were segment-specific and measured as change from baseline values to end of treatment in the following, with the same statistical analyses applied as for the primary variable:

- Maximum cIMT over the 4 CCA sites
- Maximum cIMT over the 4 carotid bulb sites
- Maximum cIMT over the 4 ICA sites
- Mean cIMT over the 4 CCA sites

Secondary laboratory variables included:

- Percentage change from baseline to Week 104 in lipid parameters: LDL-C, TC, HDL-C, TG, nonHDL-C, and TC/HDL-C, LDL-C/HDL-C, and nonHDL-C/HDL-C ratios (observed and LOCF data in the ITT population)
- Percentage change from baseline in apolipoproteins (ApoB, ApoA-I, ApoB/Apo-A-I) (observed and LOCF data in the ITT population)
- Percentage change from baseline to Week 104 in a circulating marker of inflammation: CRP (observed and LOCF data in the ITT population)

6.1.3 Study Design

METEOR was a double-blind, placebo-controlled study of 984 subjects randomized in a 5:2 fashion into 2 parallel treatment arms over a period of 104 weeks. The study was designed to assess the efficacy of rosuvastatin 40 mg in altering the natural history of cIMT as compared to placebo.

6.1.4 Efficacy Findings

It is important to note that there was essentially no difference in the drop-out rates between rosuvastatin treated subjects and placebo treated subjects. Furthermore, there was no issue with too many drop-outs occuring too early in the study for drug versus placebo. And the frequency of missing data, i.e. scans where it was not possible to measure carotid artery thickness in a

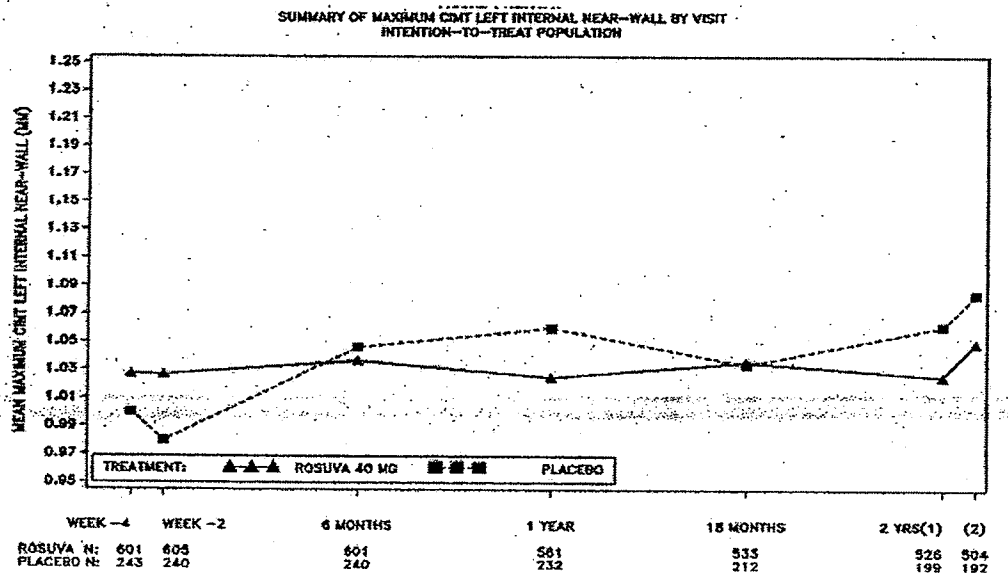
particular carotid site, was not different between treatment groups. Missing data was < 1% for common and bulb sites, but up to 6.7% for the internal sites. However, 11% of the subjects randomized never underwent a post-baseline scan and are therefore "unaccounted" for. Their impact on the analyses is unknown.

For the primary endpoint, the difference in the annualized rate of change in the maximum cIMT analyzed over all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI -0.0196, -0.0093); this difference was statistically significant (p<0.0001).

The annualized change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI -0.0041, 0.0014), but was not significantly different from zero (p=0.32). There was significant progression in the placebo group (+0.0131 mm/year; 95% CI 0.0087, 0.0174; p<0.0001).

For the secondary cIMT endpoints the differences in the annualized rate of change were statistically significant for all 4 endpoints; however, it should be noted that the difference achieved in the internal carotid artery was based on 1 wall (the near wall of the left internal carotid) where there was a "spike" in the placebo progression rate (see Figure below).

Figure 1: Annualized rate of change in mean maximum cIMT of the near wall of the left internal carotid artery



The table below summarizes the differences in the annualized rate of change observed in the secondary cIMT endpoints:

Table 6: Annualized changes from baseline values to the end of the treatment period (Week 104) in cIMT for the secondary variables (ITT population)

VARIABLE	ROSUVASTATIN 40 MG N=624 (MM/YEAR)	PLACEBO N=252 (MM/YEAR)	ROSUVASTATIN 40 MG VS. PLACEBO (P-VALUE)
Maximum cIMT of CCA	-0.0038	0.0084	<0.0001
Maximum cIMT of the carotid bulb	-0.0040	0.0172	<0.0001
Maximum cIMT of ICA	0.0039	0.0145	0.0228
Mean cIMT of CCA	0.0004	0.0088	<0.0001

The tables below summarize the results of the secondary laboratory endpoints – both the lipid endpoints and CRP.

Table 7: Percent change from baseline to end of study in lipid values – LOCF

PARAMETER	ROSUVASTATIN 40 MG N=622	PLACEBO N=251	ROSUVASTATIN 40 MG VS. PLACEBO
LDL-C (mg/dL)			
LSmean % change	-45.3	-0.6	-44.7
SE	0.89	1.39	1.65
CI	-47.0, -43.6	-3.3, 2.1	-47.9, -41.5
p-value			<0.0001
TC (md/dL)			
LSmean % change	-31.0	0.2	-31.2
SE	0.66	1.05	1.24
CI	-32.3, -29.7	-1.8, 2.3	-33.7, -28.8
p-value			<0.0001
HDL-C (mg/dL)			
LSmean % change	8.9	3.7	5.2
SE	0.67	1.06	1.26
CI	7.5, 10.2	1.6, 5.8	2.7, 7.6
p-value			<0.0001
TG (md/dL)			
LSmean % change	-14.1	9.2	-23.3
SE	1.74	2.73	3.24
CI	-17.6, -10.7	3.8, 14.6	-29.7, -17.0
p-value			<0.0001
Non-HDL-C (mg/dL)			
LSmean % change	-41.9	-0.4	-41.6
SE	0.83	1.31	1.55
CI	-43.6, -40.3	-2.9, 2.2	-44.6, -38.5
p-value			<0.0001
LDL-C/HDL-C ratio			
LSmean % change	-48.3	-2.7	-45.6
SE	0.94	1.48	1.75
CI	-50.1, -46.4	-5.6, 0.2	-49.0, -42.1
p-value			<0.0001
TC/HDL-C ratio			
LSmean % change	-35.3	-2.0	-33.3

PARAMETER	ROSUVASTATIN 40 MG N=622	PLACEBO N=251	ROSUVASTATIN 40 MG VS. PLACEBO
SE	0.74	1.16	1.37
CI	-36.7, -33.8	-4.2, 0.3	-36.0, -30.6
p-value			<0.0001
Non-HDL-C/HDL-C			
LSmean % change	-45.0	-2.1	-42.8
SE	0.93	1.47	1.74
CI	-46.8, -43.2	-5.0, 0.7	-46.3, -39.4
p-value ratio			<0.0001
Apo B (mg/dL)			
LSmean % change	-38.4	-1.9	-36.5
SE	0.78	1.24	1.46
CI	-39.9, -36.9	-4.3, 0.6	-39.4, -33.7
p-value			<0.0001
Apo A-I (mg/dL)			
LSmean % change	6.7	3.4	3.3
SE	0.52	0.83	0.98
CI	5.7, 7.7	1.8, 5.1	1.3, 5.2
p-value			<0.0001
Apo B/Apo A-I ratio			
LSmean % change	-41.5	-4.5	-37.0
SE	0.79	1.26	1.49
CI	-43.1, -40.0	-7.0, -2.0	-39.9, -34.1
p-value			<0.0001

Table 8: Percent change from baseline to end of study in CRP – LOCF

STATISTICAL PARAMETER	ROSUVASTATIN 40 MG N=624	PLACEBO N=252	ROSUVASTATIN 40 MG VS. PLACEBO
N	505	203	
Median, (%)	-36.2	-2.9	
Range, (%)	-98.6, 1994.4	-90.3, 1715.0	
p-value (LOCF)			<0.0001

Pre-specified subgroups were analyzed and a summary of annualized rate of change (slope) in mm/year for the treatment groups by pre-specified subgroups is provided below. There is an apparent regional difference in results in both the rosuvastatin and placebo groups. However, statistical analyses did not reveal any evidence of heterogeneity of effect over primary subgroups, including gender, age category (above and below the median), center, or country.

Table 9: Summary of annualized rate of change (slope) in mm/year for the treatment groups by selected pre-specified subgroups - ITT population

SUBGROUP CATEGORY	SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=624	PLACEBO N=252
Region			
European centers	N	407	172
	Slope mean	0.0002	0.0146
	Slope 95% CI	(-0.0031, 0.0035)	(0.0094, 0.0199)

SUBGROUP CATEGORY	SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=624	PLACEBO N=252
U.S. centers	N	217	80
	Slope mean	-0.0047	0.0088
	Slope 95% CI	(-0.0097, 0.0002)	(0.0010, 0.0166)
Age			
<Median	N	303	127
	Slope mean	-0.0005	0.0096
	Slope 95% CI	(-0.0044, 0.0034)	(0.0034, 0.0157)
≥Median	N	321	125
	Slope mean	-0.0022	0.0164
	Slope 95% CI	(-0.0061, 0.0016)	(0.0103, 0.0225)
Sex			
Female	N	244	99
	Slope mean	-0.0025	0.0154
	Slope 95% CI	(-0.0069, 0.0019)	(0.0084, 0.0224
Male	N	380	153
	Slope mean	-0.0007	0.0114
	Slope 95% CI	(-0.0042, 0.0028)	(0.0059, 0.0170)
Race	N	30	12
Nonwhite	Slope mean	-0.0104	0.0091
	Slope 95% CI	(-0.0268, 0.0060)	(-0.0168, 0.0350)
	N	594	240
White	Slope mean	-0.0012	0.0130
	Slope 95% CI	(-0.0039, 0.0016)	(0.0086, 0.0175)
BMI			
<30 kg/m^2	N	498	196
	Slope mean	-0.0016	0.0127
	Slope 95% CI	(-0.0046, 0.0014)	(0.0079, 0.0175)
≥30 kg/m^2	N	124	56
	Slope mean	-0.0014	0.0139
	Slope 95% CI	(-0.0082, 0.0052)	(0.0033, 0.0246)
NCEP risk factors			
2+ risk factors	N	189	98
	Slope mean	-0.0045	0.0148
	Slope 95% CI	(-0.0097, 0.0007)	(0.0065, 0.0230)
<2 risk factors	N	435	154
	Slope mean	-0.0001	0.0119
	Slope 95% CI	(-0.0034, 0.0031)	(0.0068, 0.0170)
History of hypertension			
History	N	117	54
	Slope mean	-0.0041	0.0155
	Slope 95% CI	(-0.1041, 0.0022)	(0.0056, 0.0254)
No history	N	507	198
	Slope mean	-0.0008	0.0124
	Slope 95% CI	(-0.0039, 0.0023)	(0.0075, 0.0172)

SUBGROUP CATEGORY	SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=624	PLACEBO N=252
Baseline LDL-C			
<Mean	N	331	133
	Slope mean	-0.0002	0.0117
	Slope 95% CI	(-0.0040, 0.0035)	(0.0057, 0.0176)
≥Mean	N	293	119
	Slope mean	-0.0029	0.0145
	Slope 95% CI	(-0.0069, 0.0012)	(0.0081, 0.0209)
Baseline CRP			
<Median	N	284	105
	Slope mean	-0.0006	0.0174
	Slope 95% CI	(-0.0048, 0.0036)	(0.0108, 0.0240)
≥Median	N	272	117
	Slope mean	-0.0020	0.0083
	Slope 95% CI	(-0.0063, 0.0023)	(0.0016, 0.0151)

Despite some variability in the data by country, the overall treatment effect (rosuvastatin vs. placebo) was similar, -0.0144 mm/year for the European group and -0.0135 mm/year for the U.S. group.

Annualized rate of change of cIMT were summarized by quartile of baseline cIMT (Quartiles: first, 0.6976167 to 1.02467 mm; second, >1.02467 to 1.124958 mm; third, >1.24958 to 1.26029 mm; fourth, >1.26029 to 1.904 mm). As summarized in the table below, the rosuvastatin/placebo difference in annualized rate of change for each quartile was directionally and quantitatively consistent with the results of the all patients' primary analysis.

Table 10: Annualized rate of change in maximum cIMT of the 12 carotid artery sites by baselione mean maximum cIMT quartiles (ITT population)

STATISTICAL PARAMETER	ROSUVASTATIN 40 MG	PLACEBO	ROSUVASTATIN VS. PLACEBO
All patients			
N	624	252	876
Annualized rate of change (mm/yr)	-0.0014	0.0131	-0.0145
95% CI	-0.0041, 0.0014	0.0087, 0.0174	-0.0196, -0.0093
p-value	0.3224	<0.0001	<0.0001
First quartile			
N	156	63	219
Annualized rate of change (mm/yr)	0.0062	0.0156	-0.0094
95% CI	0.0022, 0.0102	0.0093, 0.0219	-0.0168, -0.0020
Second quartile			
N	156	63	219
Annualized rate of change (mm/yr)	0.0004	0.0132	-0.0128
95% CI	-0.0043, 0.0052	0.0057, 0.0208	-0.0218, -0.0038
Third quartile			
N	161	58	219
Annualized rate of change (mm/yr)	-0.0039	0.0149	-0.0188
95% CI	-0.0093, 0.0016	0.0062, 0.0235	-0.0294, -0.0081
Fourth quartile			

N	151	68	219
Annualized rate of change (mm/yr)	-0.0084	0.0087	-0.0171
95% CI	-0.0158, -0.0010	-0.0030, 0.0203	-0.0303, -0.0038

When the annualized rates of change were analyzed by average percent change in LDL-C, the mean rate of change in mean cIMT was -0.0021 mm/year in the group that achieved an average percentage change in LDL-C less than the mean (n=383) versus a mean rate of change of -0.0003 mm/year in the group that achieved an average percentage change in LDL-C ≥ the mean.

However, in terms of the level of LDL-C achieved, the group that achieved the best results was the group that achieved an on-treatment LDL-C of ≥ 70 mg/dL but < 100 mg/dL; the rate of change in mean cIMT in this group (n=228) was -0.0024 mm/year. For subjects who achieved an LDL-C < 70 mg/dL (n=290), the rate of change in mean cIMT was -0.0014 mm/year; for those who achieved an LDL-C ≥ 100 mg/dL, the rate of change was +0.0010 mm/year. This is summarized in tabular format below:

Table 11: Summary of slope (mm/year) by weighted average LDL-C (ITT population)

CATEGORY	SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=624
Weighted average LDL-C < Mean	N	389
	Slope mean	-0.0023
	Slope SE	0.0016
	Slope 95% CI	(-0.0055, 0.0008)
Weighted average LDL-C ≥ Mean	N	233
	Slope mean	0.0004
	Slope SE	0.0024
	Slope 95% CI	(-0.0043, 0.0051)
Weighted average LDL-C < 100 mg/dL	N	518
	Slope mean	-0.0018
	Slope SE	0.0014
	Slope 95% CI	(-0.0045, 0.0009)
Weighted average LDL-C ≥ 100 mg/dL	N	104
	Slope mean	0.0010
	Slope SE	0.0044
	Slope 95% CI	(-0.0076, 0.0096)
Weighted average LDL-C < 70 mg/dL	N	290
	Slope mean	-0.0014
	Slope SE	0.0019
	Slope 95% CI	(-0.0051, 0.0023)
Weighted average LDL-C ≥ 70 mg/dL	N	332
	Slope mean	-0.0014
	Slope SE	0.0019
	Slope 95% CI	(-0.0050, 0.0023)

Curiously, despite a 45% reduction in LDL-C achieved with rosuvastatin 40 mg, the percentage reduction in cIMT for the rosuvastatin group was only 0.12%. This is in contrast to a 0.7%

decrease in cIMT in ACAPS, where lovastatin 20/40 mg achieved a 28% reduction in LDL-C. The literature would suggest that more intensive lipid lowering is associated with more dramatic reductions of cIMT progression. Furthermore, the literature suggests that each 10% reduction in LDL-C is estimated to reduce the carotid IMT by 0.73%.

Numerous clinical trials have evaluated the effects of antihypertensive therapy on IMT progression compared with diuretic or placebo. In general, these trials have shown that antihypertensive treatment slows progression; however, these trials are more difficult to interpret than lipid-lowering trials because antihypertensive therapy often acutely changes intravascular volume. Because IMT varies inversely with acute changes in intravascular volume, it becomes difficult to distinguish between acute changes in IMT caused by physiologic alterations in blood volume and long-term changes in atherosclerosis burden.[1] For this reason, and because a significant number of the participants in METEOR were on concomitant anti-hypertensives, the sponsor was asked to perform the primary analysis excluding these patients. The following tables summarize the concomitant anti-hypertensives used by subjects in METEOR by treatment and the annualized rate of change in the mean maximum cIMT of the 12 carotid artery sites excluding these subjects.

Table 12: Number (percent) of patients in the METEOR ITT population who were concomitantly treated with anti-hypertensives

DRUG CLASS	ROSUVASTATIN 40 MG N=624	PLACEBO N=252
Any specified concomitant medication	**101 (16)**	**45 (18)**
Calcium channel blockers	20 (3)	8 (3)
Beta-blockers	52 (8)	22 (9)
ACE inhibitors	29 (5)	17 (7)
Angiotensin II receptor blockers	28 (4)	11 (4)

Table 13: Mean maximum cIMT of the 12 carotid artery sites (METEOR, ITT population excluding patients concomitantly treated with anti-hypertensives)

STATISTICAL PARAMETER	ROSUVASTATIN 40 MG N=523	PLACEBO N=207	ROSUVASTATIN VS. PLACEBO
Annualized rate of change (mm/year)	-0.0009	0.0131	-0.0140
95% confidence interval	-0.0039, 0.0021	0.0083, 0.0179	-0.0197, -0.0083
p-value	0.5582	<0.0001	<0.0001

The annualized rate of change from baseline for the rosuvastatin group drops from -0.0014 mm/year to -0.0009 mm/year when patients concomitantly taking anti-hypertensives are excluded from the analysis. The annualized rate of change from baseline for the placebo group remains the same, suggesting a possible interaction between rosuvastatin and the anti-hypertensive medications. The treatment difference however remains statistically significant and similar to the results of the primary analysis.

[1] Crouse, JR. Imaging atherosclerosis: state of the art. *Journal of Lipid Research*. 2006;47:1677-1699.

6.1.6 Efficacy Conclusions

In an asymptomatic population with elevated LDL-C, at low risk (<10%) for symptomatic CAD, and with subclinical atherosclerosis as evidenced by cIMT:

- Rosuvastatin 40 mg produced a statistically significant difference in annualized rate of change in maximum cIMT analyzed over all 12 carotid sites (-0145 mm/year; 95% CI -0.0196, -0.0093; p<0.0001). The difference in rosuvastatin annualized change versus zero was not significant (-0.0014 mm/year; 95% CI -0.0041, 0.0014; p=0.32).
- Rosuvastatin 40 mg produced a statistically significant difference in annualized rate of change in maximum cIMT of the near and far walls of the right and left CCA (-0.0122 mm/year; 95% CI -0.0170, -0.0074; p<0.0001). The difference in rosuvastatin annualized change versus zero was also statistically significant (-0.0038 mm/year; 95% CI -0.0064, -0.0013; p=0.0036),
- Rosuvastatin 40 mg produced a statistically significant difference in annualized rate of change in maximum cIMT of the near and far walls of the right and left carotid bulb (-0.0212 mm/year; 95% CI -0.0306, -0.0119; p<0.0001). The difference in rosuvastatin annualized change versus zero was not significant (-0.0040 mm/year; 95% CI -0.0090, 0.0010; p=0.1139)
- Rosuvastatin 40 mg produced a statistically significant difference in annualized rate of change in maximum cIMT of the near and far walls of the right and left internal carotid artery (-0.0105 mm/year; 95% CI -0.0196, -0.0015; p=0.0228). The difference in rosuvastatin annualized change versus zero was not significant (0.0039 mm/year; 95% CI -0.0009, 0.0088; p=0.1101). These results must be viewed with caution given that there was no statistically significant difference in 3 of the 4 walls of the ICA and the one wall that produced the difference (the near wall of the left internal carotid) was driven by an unusual spike in the rate of progression in the placebo group between baseline and 6 months.
- Rosuvastatin 40 mg produced a statistically significant difference in annualized rate of change in mean cIMT of the near and far walls of the right and left CCA (-0.0085 mm/year; 95% CI -0.0113, -0.0056; p<0.0001). The difference in rosuvastatin annualized change versus zero was not significant (0.0004 mm/year; 95% CI -0.0011, 0.0019; p=0.6375).

It should be noted, however, that several issues may have affected the efficacy results:

- 11% of the subjects randomized never had a post baseline scan performed.
- The study population was overwhelmingly (94.2%) Caucasian and the majority of patients were male (59.8%). Patients completing the two-year treatment period were even more predominantly white (97-98%) than the randomized population (94%) and relatively fewer were from U.S. centres (RSV 33%, placebo 25%) compared with the randomized population (35%).
- The frequency of patients with protocol deviations leading to exclusion of data from the PP analysis set was higher in the placebo group (30.0% for patients receiving rosuvastatin and 36.1% for patients receiving placebo). Overall, 10.9% of patients in the rosuvastatin group and 16.5% of patients in the placebo group received a concomitant medication disallowed by the protocol.

- A multi-level repeated-measures linear mixed effects model was used for the analysis of primary and secondary cIMT endpoints which was a regression approach and assumed that cIMT values were expected to change in a linear fashion over time. The sponsor performed analyses to confirm the linearity of the rate of change of cIMT over time. There was weak evidence of non-linearity in the RSV group, however, it did not achieve statistical significance.
- There were residuals from the main analysis which were more extreme than would be expected from a normal distribution of residuals. The sponsor explains that "this is probably due to imprecise measures from carotid sites that are difficult for the sonographer to image and for the reader to measure. Because positive and negative residuals occurred with similar frequency, and in both treatment groups, the effect on estimates of slopes was neutral, but reported confidence intervals and p-values were larger than they would be in the absence of extreme residuals".
- There were baseline differences that existed regionally (between Europe and the U.S.), although the treatment difference in annualized rate of change, rosuvastatin versus placebo was similar.
- The annualized rate of change in mean maximum cIMT from baseline to end of study for the rosuvastatin group was significantly less than what would have been predicted based on the literature and the achieved percentage reduction in LDL-C.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were a total of 6 deaths that occurred during treatment in the 3 submitted studies – 1 in ORION, 4 in ASTEROID, and 1 in METEOR. All deaths occurred in rosuvastatin 40 mg treatment arms. The deaths are summarized in the table below:

Table 14: Deaths occurring in rosuvastatin atherosclerosis trials

TRIAL SUBJECT NUMBER	AGE/GENDER	TREATMENT RECEIVED	DAYS ON TREATMENT	CAUSE OF DEATH
ORION 026/0001	73/Male	Rosuvastatin 40 mg	252 days	Acute MI
ASTEROID 0008/0042	72/Male	Rosuvastatin 40 mg	9 days	Acute MI
ASTEROID 0072/0002	59/Female	Rosuvastatin 40 mg	24 days	Ventricular fibrillation
ASTEROID 0130/0047	79/Male	Rosuvastatin 40 mg	35 days	Renal failure, pneumonia, septic shock
ASTEROID	61/Male	Rosuvastatin 40 mg	198 days	Gastric cancer

TRIAL SUBJECT NUMBER	AGE/GENDER	TREATMENT RECEIVED	DAYS ON TREATMENT	CAUSE OF DEATH
0161/0025				
METEOR 0458/0803	64/Male	Rosuvastatin 40 mg	163 days	Creutzfeldt-Jakob disease

Patient narratives for all deaths can be found in the individual study reports in the appendices.

7.1.2 Other Serious Adverse Events

In the 3 submitted studies, SAEs occurred in 19/281 (6.8%) subjects on placebo, 3/21 (14.3%) subjects on rosuvastatin 5 mg and 235/1229 (19.1%) subjects on rosuvastatin 40 mg. The table below summarizes the SAEs by primary SOC and treatment.

Table 15: Number (%) of subjects with SAEs

PRIMARY SOC	ROSUVASTATIN 40 MG N=1229 N (%)	ROSUVASTATIN 5 MG N=21 N (%)	PLACEBO N=281 N (%)
Total subjects with SAE	**235 (19.1)**	**3 (14.3)**	**19 (6.8)**
Cardiac Disorders	110 (9.0)	1 (4.8)	0
Injury, Poisoning and Procedural Complications	36 (2.9)	0	3 (1.1)
Infections and Infestations	22 (1.8)	1 (4.8)	4 (1.4)
Musculoskeletal and Connective Tissue Disorders	21 (1.7)	1 (4.8)	3 (1.1)
General Disorders and Administration Site Conditions	20 (1.6)	0	1 (0.36)
Neoplasms Benign, Malignant and Unspecified	20 (1.6)	1 (4.8)	3 (1.1)
Nervous System Disorders	20 (1.6)	0	3 (1.1)
Gastrointestinal Disorders	19 (1.5)	0	1(0.4)
Vascular Disorders	12 (1.0)	0	4 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	8 (0.7)	0	0
Renal and Urinary Disorders	7 (0.6)	1 (4.8)	4 (1.4)
Psychiatric Disorders	4 (0.3)	0	0
Blood and Lymphatic System Disorders	3 (0.2)	0	0
Eye Disorders	3 (0.2)	0	0
Hepatobiliary Disorders	3 (0.2)	0	1 (0.4)
Investigations	3 (0.2)	0	3 (1.1)
Congenital, Familial and Genetic Disorders	2 (0.2)	0	0
Reproductive System and Breast Disorders	2 (0.2)	0	2 (0.7)
Skin and Subcutaneous Tissue Disorders	2(0.2)	0	1 (0.4)

PRIMARY SOC	ROSUVASTATIN 40 MG N=1229 N (%)	ROSUVASTATIN 5 MG N=21 N (%)	PLACEBO N=281 N (%)
Metabolism and Nutrition Disorders	1 (0.1)	0	0
Immune System Disorders	1 (0.1)	0	0

It should be noted that a majority of the Cardiac Disorders SAEs (99/110; 90%) that occurred with rosuvastatin 40 mg came from the ASTEROID trial where there was no control group. Subjects in the ASTEROID trial were at higher risk for cardiovascular events by virtue of their having established coronary artery disease as a criterion for entry.

The table below provides demographics on those subjects who experienced an SAE:

Table 16: Demographics of subjects who experienced SAE - safety population

VARIABLE	ROSUVASTATIN 40 MG N=235	ROSUVASTATIN 5 MG N=3	PLACEBO N=19
Age			
Mean	59.5	68.3	59.4
Min, max	37, 85	65, 72	49, 68
Median	59	68	61
Gender [n(%)]			
Male	159 (67.7)	1 (33.3)	10 (52.6)
Female	76 (32.3)	2 (66.7)	9 (47.4)
Race [n(%)]			
Caucasian	229 (97.4)	2 (66.7	19 (100)
Black	3 (1.3)	0	0
Asian	0	1 (33.3)	0
Hispanic	2 (0.9)	0	0
Other	1 (0.4)	0	0
BMI			
Mean	28.5	29.8	27.6
Min, max	16.6, 53.8	21.5, 34.6	20.2, 38.1
Median	27.5	33.4	26.7

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The table below summarizes the demographics of the dropouts:

Table 17: Demographics of withdrawn subjects - safety population

VARIABLE	ROSUVASTATIN 40 MG N=143	ROSUVASTATIN 5 MG N=1	PLACEBO N=22
Age			
Mean	57.2	68	59.7
Min, max	40, 80	68	52, 69
Median	57	68	58.5
Gender [n(%)]			
Male	86 (60.1)	0	6 (27.3)
Female	57 (39.9)	1 (100)	16 (72.7)
Race [n(%)]			
Caucasian	133 (93.0)	0	19 (86.4)
Black	4 (2.8)	0	0
Asian	3 (2.1)	1 (100)	0
Hispanic	2 (1.4)	0	1 (4.5)
Other	1 (0.7)	0	2 (9.1)
BMI			
Mean	28.2	21.5	27.0
Min, max	19.4, 40.0	21.5	20.3, 37.6
Median	27.6	21.5	25.7

7.1.3.2 Adverse events associated with dropouts

Discontinuation due to AEs was higher in the rosuvastatin 40 mg group (11.4%) than in the placebo group (7.8%). The greatest percentage of discontinuations due to AEs was in the primary SOC Musculoskeletal and Connective Tissue Disorders which was the cause of discontinuation in 4.0% of rosuvastatin 40 mg treated patients versus 2.8% of placebo patients.

Table 18: TEAEs leading to study discontinuation (safety population)

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229 N (%)	ROSUVASTATIN 5 MG N=21 N (%)	PLACEBO N=281 N (%)
Total subjects with DAE	**140 (11.4)**	**1 (4.8)**	**22 (7.8)**
Cardiac disorders	**27 (2.2)**	**1 (4.8)**	**0**
Angina pectoris	9 (0.7)	0	0
Angina unstable	4 (0.3)	0	0
Coronary artery disease	3 (0.2)	0	0
Coronary artery stenosis	3 (0.2)	0	0
Acute coronary syndrome	2 (0.2)	0	0
Arrhythmia	1 (0.1)	0	0
Myocardial ischemia	1 (0.1)	0	0
Ventricular extrasystoles	1 (0.1)	0	0
Ventricular fibrillation	1 (0.1)	0	0
Atrial fibrillation	0	1 (4.8)	0
Ear and labyrinth disorders	**1 (0.1)**	**0**	**0**
Tinnitus	1 (0.1)	0	0
Gastrointestinal disorders	**14 (1.1)**	**0**	**2 (0.7)**
Abdominal pain upper	4 (0.3)	0	0

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229 N (%)	ROSUVASTATIN 5 MG N=21 N (%)	PLACEBO N=281 N (%)
Nausea	4 (0.3)	0	0
Diarrhea	2 (0.2)	0	1 (0.4)
Constipation	1 (0.1)	0	1 (0.4)
Abdominal distension	1 (0.1)	0	0
Abdominal pain	1 (0.1)	0	0
Abdominal pain lower	1 (0.1)	0	0
Breath odor	1 (0.1)	0	0
Change of bowel habit	1 (0.1)	0	0
General disorders and administration site conditions	**7 (0.6)**	**0**	**3 (1.1)**
Fatigue	5 (0.4)	0	3 (1.1)
Non-cardiac chest pain	1 (0.1)	0	0
Pain	1 (0.1)	0	0
Pyrexia	0	0	1 (0.4)
Infections and infestations	**4 (0.3)**	**0**	**2 (0.7)**
Bronchitis	1 (0.1)	0	0
Creutzfeldt-Jakob disease	1 (0.1)	0	0
Parvovirus infection	1 (0.1)	0	0
Hepatitis C	1 (0.1)	0	0
Pneumonia	0	0	1 (0.4)
Viral infection	0	0	1 (0.4)
Injury, poisoning and procedural complications	**2 (0.2)**	**0**	**0**
Polytraumatism	1 (0.1)	0	0
Coronary artery restenosis	1 (0.1)		
Investigations	**14 (1.1)**	**0**	**5 (1.8)**
Hepatic enzyme increased	5 (0.4)	0	0
Blood CPK increased	4 (0.3)	0	0
ALT increased	3 (0.2)	0	0
AST increased	2 (0.2)	0	0
Liver function test abn.	1 (0.1)	0	2 (0.7)
GGT increased	1 (0.1)	0	0
Hepatic enzyme increased	1 (0.1)	0	0
Blood bilirubin increased	1 (0.1)	0	1 (0.4)
Blood TG increased	1 (0.1)	0	0
ESR increased	0	0	1 (0.4)
Transaminases increased	0	0	1 (0.4)
Virus serology test +	0	0	1 (0.4)
Metabolism and nutrition disorders	**0**	**0**	**1 (0.4)**
NIDDM	0	0	1 (0.4)
Musculoskeletal and connective tissue disorders	**49 (4.0)**	**0**	**8 (2.8)**
Myalgia	32 (2.6)	0	5 (1.8)
Muscular weakness	3 (0.2)	0	0
Neck pain	2 (0.2)	0	0
Arthralgia	2 (0.2)	0	0
Musculoskeletal pain	2 (0.2)	0	0

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229 N (%)	ROSUVASTATIN 5 MG N=21 N (%)	PLACEBO N=281 N (%)
Pain in extremity	2 (0.2)	0	0
Musculoskeletal stiffness	1 (0.1)	0	2 (0.7)
Pain in extremity	1 (0.1)	0	1 (0.4)
Back pain	1 (0.1)	0	0
Muscle spasms	1 (0.1)	0	0
Polymyalgia	1 (0.1)	0	0
Polymyalgia rheumatica	1 (0.1)	0	0
Tendonitis	1 (0.1)	0	0
Fibromyalgia	1 (0.1)	0	0
Bursitis	0	0	1 (0.4)
Joint stiffness	0	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (0.3)**	**0**	**1 (0.4)**
Prostate cancer	1 (0.1)	0	0
Thyroid gland cancer	1 (0.1)	0	0
Gastric cancer	1 (0.1)	0	0
SCC of lung	1 (0.1)	0	0
Ovarian cancer	0	0	1 (0.4)
Nervous system disorders	**14 (1.1)**	**0**	**2 (0.7)**
Headache	4 (0.3)	0	0
Hypoaesthesia	3 (0.2)	0	0
Dizziness	2 (0.2)	0	1 (0.4)
Balance disorder	1 (0.1)	0	0
Brainstem infarct	1 (0.1)	0	0
Neuralgia	1 (0.1)	0	0
Subarachnoid hemorrhage	1 (0.1)	0	0
Tension headache	1 (0.1)	0	0
Tremor	0	0	1 (0.4)
Psychiatric disorders	**1 (0.1)**	**0**	**2 (0.7)**
Disorientation	1 (0.1)	0	0
Depression	0	0	1 (0.4)
Insomnia	0	0	1 (0.4)
Renal and urinary disorders	**2 (0.2)**	**0**	**1 (0.4)**
Chromaturia	1 (0.1)	0	0
Renal failure	1 (0.1)	0	0
Hematuria	0	0	1 (0.4)
Proteinuria	0	0	1 (0.4)
Reproductive system and breast disorders	**0**	**0**	**1 (0.4)**
Menopausal symptoms	0	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**1 (0.1)**	**0**	**0**
Wheezing	0	0	0
Skin and subcutaneous tissue disorders	**4 (0.3)**	**0**	**2 (0.7)**
Alopecia	1 (0.1)	0	1 (0.4)

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229 N (%)	ROSUVASTATIN 5 MG N=21 N (%)	PLACEBO N=281 N (%)
Rash	1 (0.1)	0	0
Rash morbilliform	1 (018)	0	0
Urticaria	1 (0.1)	0	0
Night sweats	0	0	1 (0.4)
Vascular disorders	**0**	**0**	**1 (0.4)**
Hypotension	0	0	1 (0.4)

These discontinuation rates are consistent with previous clinical studies with rosuvastatin as reported in the product label. The current product label notes that "In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse reactions attributable to rosuvastatin. The most frequent adverse reactions thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea." In the 3 studies comprising the current submission, the discontinuation rate for these treatment-related AEs is 3.5%. Similarly, if one looks exclusively at METEOR, the only placebo-controlled study of the 3, the discontinuation rate for these treatment-related AEs was 3.3%.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Hepatic adverse events

The only adverse event relating to the hepato-biliary system was a case of chronic cholecystitis with cholelithiasis and hepatic steatosis reported in a METEOR placebo patient (0103/2122). No cases of hepatitis, jaundice, or other AEs suggestive of hepatic dysfunction were reported in any rosuvastatin 40 mg patient in METEOR, ASTEROID or ORION.

7.1.3.3.2 Skeletal muscle adverse events

During the 3 studies there was 1 transient muscle-related adverse event. In METEOR, 1 patient (0601/0415) in the rosuvastatin 40 mg group experienced transient exercise-induced muscle pain associated with a clinically important CK elevation of 3059 U/L (>10 x ULN), meeting a pre-specified case definition of myopathy in the clinical study program. The patient was noted to have participated in a rowing contest and had performed extreme physical exercise in preparation for the contest prior to blood testing. The investigator related the increased CK to the vigorous exercise. Study medication was not interrupted; the elevated CK returned to normal and the patient completed the study as planned

There were no cases of skeletal muscle adverse events in either ASTEROID or ORION.

7.1.3.3.3 Renal adverse events

There were no renal adverse events in METEOR or ORION.

In ASTEROID, there was 1 report (0103/0004) of renal failure. The investigator's reported

term was renal insufficiency. This patient had cardiac failure at the same time as the renal insufficiency. The central laboratory did not measure serum creatinine until the recorded day of resolution, when serum creatinine was normal.

Another patient (0001/0010) had an adverse event of proteinuria associated with a clinically important increase in serum creatinine of 301 µmol/L (>100% increase from baseline and greater than ULN). This patient recovered during continued treatment with rosuvastatin and the adverse event was not considered by the investigator to be related to treatment but rather to treatment with diuretic and ACE-inhibitor, and partial obstruction of the left kidney.

7.1.3.3.4 Ischemic CV events

Cardiovascular and cerebrovascular events were not adjudicated in METEOR. The number of treatment-emergent ischemic CV events (defined as angina pectoris, acute coronary syndrome, myocardial infarction, or unstable angina) reported as adverse events over the 2 years of the METEOR study was 0.9% in the rosuvastatin 40 mg group and 0 in the placebo group. There were 0 events of cerebrovascular accident or transient ischemic attack reported during the randomized treatment period of METEOR; however, one patient in the rosuvastatin treatment group was diagnosed with a stenosis of the right carotid artery at the final study visit on Day 736. While the disparity in the number of ischemic CV events between rosuvastatin-treated patients and placebo-treated patients may simply be due to chance, its occurrence in this low-risk population is certainly notable.

Cardiovascular events occurred commonly in ASTEROID – the number of treatment-emergent ischemic CV events (defined as angina pectoris, acute coronary syndrome, myocardial infarction, or unstable angina) recorded as adverse events over the 2 years of the ASTEROID study was 23.1% in the rosuvastatin treated patients.

7.1.4 Other Search Strategies

The following other sources were searched for safety issues associated with the use of rosuvastatin:

- The June 28, 2007 PSUR submitted by AstraZeneca.
- The medical literature.
- The AERS database.

For a discussion of the results of the June 28, 2007 PSUR, please see Section 7.2.2.

For a discussion of the medical literature, please see Section 8.6.

A search of the AERS database was performed specifically for the adverse reactions of rhabdomyolysis and acute renal failure associated with the use of CRESTOR. The following is a summary of reports where CRESTOR was listed as the "suspect drug".

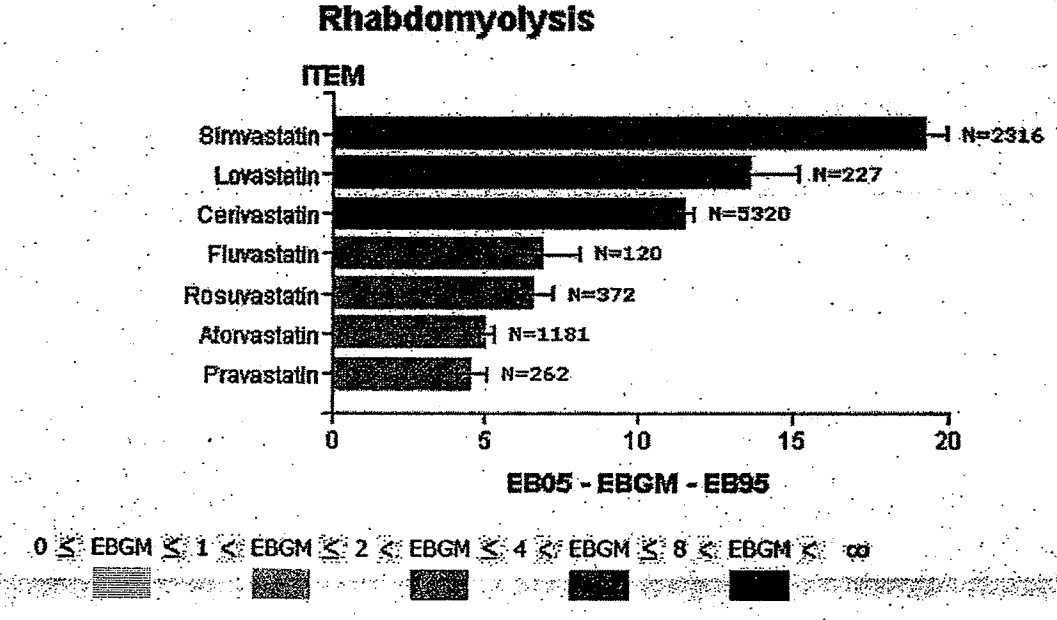
Rhabdomyolysis

From launch to present, there have been 355 reports of rhabdomyolysis entered into the AERS database where CRESTOR was listed as the "suspect drug". The breakdown by year follows:

2003	1
2004	95
2005	128
2006	92
2007	39

Data mining was performed by the Office of Surveillance and Epidemiology (OSE) for signal detection for rhabdomyolysis for all of the currently approved statins. Using a lower bound estimate (EB05) value of 2.0 or greater for signal detection (which signifies that the signal strength is at least twice what is expected), all statins were found to signal.

Figure 2: Data Mining Results for Rhabdomyolysis with Statins



Acute renal failure

From launch to present, there have been 129 reports of acute renal failure entered into the AERS database where CRESTOR was listed as the "suspect drug". The breakdown by year follows:

2003	1
2004	36
2005	54
2006	28
2007	10

Data mining was also performed for renal impairment and renal failure and acute renal failure. Again using the DDRE's working definition of considering the lower bound estimate (EB05) value of 2.0 or greater for signal detection, cerivastatin signaled for renal impairment and renal failure, and cerivastatin and simvastatin signaled for acute renal failure.

Table 19: Data Mining for Renal Impairment for Statins

Ingredient	N	EB05	EB95	EBGM	PT
Cerivastatin	1251	5.711	6.268	5.985	Renal impairment
Simvastatin	165	1.445	1.865	1.644	Renal impairment
Fluvastatin	19	0.947	1.99	1.393	Renal impairment
Lovastatin	54	0.846	1.32	1.062	Renal impairment
Atorvastatin	142	0.824	1.085	0.947	Renal impairment
Pravastatin	45	0.802	1.305	1.029	Renal impairment
Rosuvastatin	31	0.656	1.177	0.886	Renal impairment

Source: Data Mining, WebVDME V6.0, Run 827, Ingredient (S), CBAERS from CBER Extract 9/2/2007

Table 20: Data Mining for Renal Failure and Acute Renal Failure for Statins

Ingredient	N	EB05	EB95	EBGM	PT
Cerivastatin	1918	6.229	6.715	6.469	Renal failure
Simvastatin	336	1.616	1.933	1.769	Renal failure
Rosuvastatin	136	1.13	1.497	1.304	Renal failure
Fluvastatin	34	1.042	1.822	1.389	Renal failure
Cerivastatin	464	3.288	3.83	3.551	Renal failure acute
Simvastatin	520	2.503	2.891	2.691	Renal failure acute
Fluvastatin	53	1.65	2.586	2.076	Renal failure acute
Rosuvastatin	151	1.279	1.671	1.465	Renal failure acute
Atorvastatin	290	1.045	1.268	1.152	Renal failure acute

Source: Data Mining, WebVDME V6.0, Run 827, Ingredient (S), CBAERS from CBER Extract 9/2/2007

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In all 3 studies, adverse events were identified by instructing patients to report any adverse experience that developed between study visits and interviewing patients for symptoms at each

visit (including the dietary lead-in period). A description of the event was recorded, together with its severity and duration, any action taken, its outcome, and the investigator's assessment of the relationship of the event to study treatment.

A treatment-emergent adverse event was defined as the development of a new medical condition or the deterioration of a pre-existing medical condition during exposure to or following treatment with the study drug. Events were reported by study treatment received at the time the adverse event was reported.

Clinically significant abnormal laboratory values, vital signs, or physical examinations were also recorded as adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

A review of the ISS dataset did not reveal any apparent discrepancies between the investigator text for the adverse event and the preferred term. As part of the protocol, "to avoid colloquial expressions, the AE term was reported in standard medical terminology whenever possible." Therefore, no verbatim terms were provided.

7.1.5.3 Incidence of common adverse events

Adverse events occurred slightly more commonly in the rosuvastatin 40 mg group (83.2%) than in the placebo group (80.8%). The most common adverse events were in the primary SOC Musculoskeletal and Connective Tissue Disorders where the incidence was 40.5% among the rosuvastatin 40 mg group and 41.6% among the placebo group. The other notable adverse events were in the primary SOC Cardiac Disorders where the incidence of adverse events was 16.2% among the rosuvastatin 40 mg group and 3.2% among the placebo group. This was driven predominantly by the adverse event angina pectoris where the occurrence was 7.7% among the rosuvastatin 40 mg group and 0 among the placebo group. Again, the majority of these events occurred in the ASTEROID trial which was a single arm (rosuvastatin 40 mg) trial in a patient population with established cardiovascular disease.

7.1.5.4 Common adverse event tables

The following table provides a summary of the most common (≥2%) adverse events in the pooled data:

Table 21: Common adverse events (≥ 2%) - pooled safety population

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229	ROSUVASTATIN 5 MG N=21	PLACEBO N=281
Total # subjects with AE	**1027 (83.6)**	**16 (76.2)**	**226 (80.4)**
Musculoskeletal and Connective Tissue Disorders	**498 (40.5)**	**7 (33.3)**	**117 (41.6)**
Myalgia	163 (13.3)	0	34 (12.1)
Arthralgia	103 (8.4)	2 (9.5)	20 (7.1)
Back pain	91 (7.4)	1 (4.8)	29 (10.3)
Muscle spasms	47 (3.8)	0	9 (3.2)
Pain in extremity	37 (3.0)	2 (9.5)	6 (2.1)
Osteoarthritis	33 (2.7)	1 (4.8)	8 (2.8)
Shoulder pain	29 (2.4)	0	8 (2.8)
Tendonitis	24 (2.0)	1 (4.8)	6 (2.1)
Infections and Infestations	**461 (37.5)**	**5 (23.8)**	**118 (42.0)**
Nasopharyngitis	106 (8.6)	2 (9.5)	31 (11.0)
Influenza	95 (7.7)	11 (52.4)	29 (10.3)
URI	67 (5.5)	1 (4.8)	13 (4.6)
Sinusitis	48 (3.9)	0	15 (5.)
Bronchitis	45 (3.7)	0	13 (4.6)
UTI	36 (2.9)	1 (4.8)	7 (2.5)
Gastrointestinal Disorders	**299 (24.3)**	**4 (19.0)**	**72 (25.6)**
Diarrhea	44 (3.6)	1 (4.8)	11 (3.9)
Constipation	42 (3.4)	0	12 (4.3)
Abdominal pain upper	36 (2.9)	0	12 (4.3)
Nausea	35 (2.8)	1 (4.8)	7 (2.5)
Abdominal pain	29 (2.4)	0	5 (1.8)
Dyspepsia	29 (2.4)	0	6 (2.1)
GERD	28 (2.3)	0	6 (2.1)
Nervous System Disorders	**241 (19.6)**	**2 (9.5)**	**44 (15.7)**
Dizziness	57 (4.6)	0	8 (2.8)
Hypoaesthesia	25 (2.0)	0	10 (3.6)
General Disorders and Administration Site Conditions	**201 (16.4)**	**4 (19.0)**	**32 (11.4)**
Fatigue	70 (5.7)	1 (4.8)	16 (5.7)
Non-cardiac chest pain	56 (4.6)	0	1 (0.36)
Peripheral edema	39 (3.2)	1 (4.8)	3 (1.1)
Cardiac Disorders	**199 (16.2)**	**2 (9.5)**	**9 (3.2)**
Angina pectoris	95 (7.7)	1 (4.8)	0
Injury, Poisoning and Procedural Complications	**180 (14.6)**	**4 (19.0)**	**43 (15.3)**
Respiratory, Thoracic and Mediastinal Disorders	**178 (14.5)**	**0**	**31 (11.0)**
Cough	50 (4.1)	0	8 (2.8)
Pharyngolaryngeal pain	26 (2.1)	0	7 (2.5)
Dyspnea	25 (2.0)	0	3 (1.1)

PRIMARY SOC PREFERRED TERM	ROSUVASTATIN 40 MG N=1229	ROSUVASTATIN 5 MG N=21	PLACEBO N=281
Investigations	**163**	**1 (4.8)**	**21 ((7.5)**
Blood CK increased	36 (2.9)	0	2 (0.71)
ALT increased	27 (2.2)	0	0
Skin and Subcutaneous Tissue Disorders	**128**	**0**	**34 (12.1)**
Rash	26 (2.1)	0	7 (2.5)
Vascular Disorders	**124**	**7 (33.3)**	**14 (5.0)**
Hypertension	79 (6.4)	4 (19.0)	7 (2.5)
Psychiatric Disorders	**113 (9.2)**	**1 (4.8)**	**23 (8.2)**
Insomnia	39 (3.2)	0	11 (3.9)
Depression	32 (2.6)	0	3 (1.1)
Anxiety	31 (2.5)	0	5 (1.8)
Eye Disorders	**69 (5.6)**	**0**	**20 (7.1)**
Renal and Urinary Disorders	**67 (5.5)**	**2 (9.5)**	**20 (7.1)**
Reproductive System and Breast Disorders	**61 (5.0)**	**0**	**14 (5.0)**
Metabolism and Nutrition Disorders	**60 (4.9)**	**1 (4.8)**	**10 (3.6)**
Neoplasms Benign, Malignant and Unspecified	**52 (4.2)**	**1 (4.8)**	**11 (3.9)**
Ear and Labyrinth Disorders	**47 (3.8)**	**1 (4.8)**	**6 (2.1)**
Immune System Disorders	**27 (2.2)**	**0**	**5 (1.8)**

When the event rates for METEOR (the only placebo controlled study submitted) are compared with the event rates for placebo-controlled studies noted in the product label, one observes that two AEs (myalgia and back pain) are particularly notable for their discrepant results. The product label notes an occurrence of myalgia in 2.8% of rosuvastatin subjects versus 1.3% of placebo subjects, while METEOR reports rates of 12.7% and 12.1%, respectively. In the product label, back pain is reported in 2.6% of rosuvastatin subjects versus 2.4% of placebo subjects, while METEOR reports rates of 8.4% and 10.3%, respectively.

This is likely due to the significantly longer duration of the METEOR trial (2 years) versus the cholesterol-lowering trials (≤ 12 weeks), as well as the exclusive use of the 40 mg dose in the METEOR trial.

In METEOR, the mean age of patients who experienced myalgia was similar for the rosuvastatin and placebo groups, 56.3 and 57.1, respectively.

7.1.5.5 Identifying common and drug-related adverse events

Common drug-related adverse events are summarized in the table below by primary SOC and Preferred Term. Treatment related adverse events occurred in approximately the same percentage of subjects in the placebo group and the rosuvastatin 40 mg group - 17.1% vs. 17.0%, respectively.

Table 22: Treatment related adverse events occurring in ≥ 1% of patients - ISS safety population

SOC NAME PREFERRED TERM	ROSUVASTATIN 40 MG N=1229	PLACEBO N=281
Total # with AEs	**209 (17.0)**	**48 (17.1)**
Musculoskeletal and Connective Tissue Disorders	**101 (8.2)**	**22 (7.8)**
Myalgia	66 (5.4)	12 (4.3)
Investigations	**57 (4.6)**	**6 (2.1)**
ALT increased	20 (1.6)	0
Blood CK increased	17 (1.4)	1 (0.36)
Gastrointestinal Disorders	**52 (4.2)**	**9 (3.2)**
Constipation	17 (1.4)	5 (1.8)
Nervous System Disorders	**33 (2.7)**	**11 (3.9)**
Headache	16 (1.3)	6 (2.1)
General Disorders and Administration Site Conditions	**18 (1.5)**	**7 (2.5)**

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was done according to different schedules for each of the 3 studies. In ORION, full chemistry screen and hematology were performed at baseline and weeks 28, 52, 78, and 104. Urinalysis was performed at baseline and weeks 8, 20, 28, 40, 52, 65, 78, 91, and 104. Liver function tests, CPK, and serum creatinine were performed at baseline and weeks 2, 4, 8, 12, 20, 40, 65, and 91.

In ASTEROID, full chemistry screen was performed at baseline and weeks 13, 26, 52, 78, and 104; urinalysis was performed at baseline and weeks 13, 26, 52, and 104; and hematology was performed at baseline and week 104.

In METEOR, full chemistry screen and urinalysis were performed at baseline and weeks 6, 13, 39, 65, 91, and 104; and hematology was performed at baseline and week 104.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

METEOR was the only study which employed a placebo control. ASTEROID was a single arm study and ORION had an active control. Nonetheless, the data have been pooled to try and maximize our understanding of the long-term safety of the 40 mg dose of rosuvastatin. It should, however, be noted that this approach will portray the drug in a more unfavorable light.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.1.1 Hepatic biochemistry

There was a higher frequency of isolated ALT elevations >3x ULN in the rosuvastatin 40 mg group than placebo. The table below summarizes the number of ALT elevations >3x ULN in isolated observations, along with the number of ALT elevations >3x ULN on 2 consecutive occasions. The frequency of ALT elevations >3x ULN on 2 consecutive occasions was the same in the rosuvastatin 40 mg group and the placebo group, 0.4%.

Table 23: ALT elevations >3x ULN during treatment - pooled safety population

	ROSUVASTATIN 40 MG N=1202	ROSUVASTATIN 5 MG N=21	PLACEBO N=276
ALT >3x ULN at any visit, n (%)	25 (2.1)	0	2 (0.7)
ALT >3x ULN at 2 consecutive visits, n (%)	5 (0.4)	0	1 (0.4)

There were no true Hy's cases in any of the 3 submitted clinical studies. One subject (0601/0447) from the METEOR trial, who had a baseline elevation in total bilirubin (=30 U/L) experienced an ALT > 3xULN (=156 U/L) on Day 91 with total bilirubin > 2xULN (=45 U/L). Coincident with these abnormalities were an elevated AST of 104 U/L and an elevated CK of 501 U/L; alkaline phosphatase and GGT were normal. Laboratories were repeated on Day 105 and while ALT and total bilirubin were still elevated, they no longer met Hy's Law. The patient remained on study through Day 731 at which time ALT was slightly elevated (=45 U/L) and total bilirubin had normalized (=21 U/L). The subject was a 46 year old male with Posner Schlossman Syndrome (also known as Glaucomatocyclitic Crisis, an uncommon inflammatory eye condition which typically affects young to middle-aged adults who develop recurrent episodes of high pressure inside the eye accompanied by mild inflammation.) The subject experienced 2 SAEs of acute exacerbations of PSS, both requiring hospitalization – one on Day 51 and one on Day 126.

7.1.7.3.1.2 Muscle biochemistry

There was a higher frequency of CK elevation >5x ULN and >10x ULN in the rosuvastatin 40 mg group than in the placebo group. The results are summarized in the table below:

Table 24: CK elevations during treatment - pooled safety population

	ROSUVASTATIN 40 MG N=1202	ROSUVASTATIN 5 MG N=21	PLACEBO N=276
CK >5x ULN at any visit, n (%)	14 (1.2)	0	2 (0.7)

CK >10 x ULN at any visit, n (%)	4 (0.3)	0	0

7.1.7.3.1.3 Renal biochemistry

There was a higher frequency of serum creatinine increase of >50% and >100% in the rosuvastatin 40 mg group than in the placebo group. The results are summarized in the table below:

Table 25: Maximum serum creatinine elevations by category during treatment - pooled safety population

	ROSUVASTATIN 40 MG N=1133	ROSUVASTATIN 5 MG N=21	PLACEBO N=249
>50% increase in creatinine from baseline, n (%)	20 (1.8)	0	2 (0.8)
>100% increase in creatinine from baseline, n (%)	2 (0.2)	0	0

In METEOR, increases from baseline in serum creatinine to the final study visit were slightly higher in the placebo group (mean changes were 3.3 µmol/L in the rosuvastatin 40 mg group and 4.1 µmol/L in the placebo group).

In ASTEROID, increases from baseline in serum creatinine to the final study visit were small; the mean change was 1.61 µmol/L.

7.1.7.3.1.4 Hematology

In each of the 3 studies, drops in mean platelet counts from baseline were noted for the rosuvastatin patients, METEOR -27x10^9/L; ASTEROID -7x10^9/L; and ORION low-dose -9x10^9/L, ORION high-dose -34 x10^9/L; while in the METEOR placebo group the mean change in platelet count from baseline was -4 x10^9/L. Thrombocytopenia is listed in the current CRESTOR label as a rare event (< 1%) as part of a "hypersensitivity reaction"; it is kept under review by the sponsor and is reported in the periodic safety update report.

7.1.7.3.1.5 Urinalysis

The number and percent of patients with proteinuria, hematuria, and proteinuria and hematuria at any visit and at the final visit are shown in the table below:

	ROSUVASTATIN 40 MG N=1157	ROSUVASTATIN 5 MG N=21	PLACEBO N=245
At any time during the study			
Patients with proteinuria	32 (2.8)	0	2 (0.8)
Patients with hemturia	41 (3.5)	1 (4.8)	5 (2.0)
Patients with both	7 (0.6)	0	1 (0.4)

	ROSUVASTATIN 40 MG N=1157	ROSUVASTATIN 5 MG N=21	PLACEBO N=245
At final visit			
Patients with proteinuria	18 (1.6)	0	1 (0.4)
Patients with hemturia	19 (1.6)	0	1 (0.4)
Patients with both	2 (0.2)	0	0

An analysis of subjects who experienced proteinuria or hematuria during the METEOR trial revealed that the mean age of patients experiencing hematuria in the rosuvastatin group was higher (58.1 years) than in the placebo group (54.8 years). Similarly, the mean age of patients experiencing proteinuria in the rosuvastatin group was higher (58.5 years) than in the placebo group (49 years).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Five patients in the rosuvastatin 40 mg group and 1 patient in the placebo group had clinically important elevations in ALT (defined as >3x ULN on 2 consecutive visits greater than 48 hours apart). The patients are described in the table below:

Table 26: ALT elevations >3x ULN on 2 or more consecutive occasions - pooled safety population

STUDY/ PATIENT #	AGE/ SEX/ RACE	TREATMENT	BASELINE ALT	ALT ELEVATIONS	WITHDRAWN (YES/NO)	OUTCOME
METEOR 0501/0228	65/F/C	Rosuvastatin 40 mg	77 U/L	219 U/L – D40 175 U/L – D44	Yes	At final visit (D133), ALT had decreased, but remained elevated at 46 U/L
METEOR 0601/0460	60/F/C	Rosuvastatin 40 mg	33 U/L	173 U/L – D91 124 U/L – D99	Yes	At final visit (D139), ALT was decreased, but remained elevated at 44 U/L
METEOR 0801/0367	60/M/C	Rosuvastatin 40 mg	35 U/L	273 U/L – D36 295 U/L – D43	Yes	At final visit (D79), ALT had returned to within normal range
METEOR 0801/0381	60/F/C	Rosuvastatin 40 mg	33 U/L	157 U/L – D279 139 U/L – D287	No	On D343 ALT had returned to within normal range
ASTEROID 0005/0055	40/M/C	Rosuvastatin 40 mg	16 U/L	520 U/L – D371 396 U/L – D376	Yes	Subject was positive for Hepatitis C Ab
METEOR 0103/2122	67/M/C	Placebo	45 U/L	99 U/L – D505 124 U/L – D595	Yes	Subject with chronic

STUDY/ PATIENT #	AGE/ SEX/ RACE	TREATMENT	BASELINE ALT	ALT ELEVATIONS	WITHDRAWN (YES/NO)	OUTCOME
						cholecystitis, cholelithiasis, and hepatic steatosis

Four patients in the rosuvastatin 40 mg group had a clinically important elevation of CK (defined as >10x ULN). Brief narratives are provided below:

- METEOR Patient 0601/0415, a 57 year-old white male, treated with rosuvastatin 40 mg, experienced muscle pain associated with a clinically important CK elevation (>10x ULN). Baseline CK was 159 U/L. On D43, the patient had an elevated CK of 877 U/L, and on D52, follow-up CK was 3059 U/L. This patient was a competitive rower and performed extreme physical exercise in preparation for a competition prior to blood testing. The elevated CK returned to normal without study drug interruption and the patient completed the study.
- ASTEROID Patient 0083/0001, a 53 year-old Caucasian male, treated with rosuvastatin 40 mg experienced elevated CK to >5x ULN on D267. He had just been diagnosed with hypothyroidism with a TSH of 124 mIU/L and complained of muscle cramping and diffuse swelling. Study drug was continued and cramping improved. On D244 the patient was asymptomatic and there was less swelling; however, on D274, CK was >10x ULN and the study drug was discontinued. On D281, the CK was 5.9x ULN. Subsequently, CK was normal and remained normal.
- ASTEROID Patient 0026/0002, a 78 year-old Caucasian male, treated with rosuvastatin 40 mg was hospitalized for a syncopal episode. During the hospitalization, his initial CK was 2060 U/L with normal CK-MB and on repeat testing was 1750 and 1460 U/L. Study drug was halted during the hospitalization, but was resumed after his discharge. Subsequent CK values were normal.
- ASTEROID Patient 0130/0047, a 79 year-old Caucasian male, treated with rosuvastatin 40 mg developed back pain following lifting heavy materials on D26. On D35, the general practitioner was consulted because the patient had experienced drowsiness and muscle weakness for 3 days. The following morning, the patient had a blood test which showed a CK of 6841 U/L, creatinine 870 µmol/L and potassium 7.8 mmol/L. The patient developed renal failure, bronchopneumonia, and atelectasis, which deteriorated to septic shock, leading to hypotension and death on D37. Postmortem exam included multiple muscle biopsies which found no evidence of rhabdomyolysis and pathology of the kidneys did not reveal any specific defect.

Thrombocytopenia, is listed in the current CRESTOR label as a rare event (< 1%) as part of "hypersensitivity reactions"; it is kept under review by the sponsor. Sixteen patients in the 3 studies had a platelet count <100 x 10^9/L at some point during the study. Of these 16 patients, 8 had platelets <100 x 10^9/L at baseline; of these 8, 4 patients recovered while on rosuvastatin treatment, 2 had missing follow-up values, 1 had improvement in the platelet count but remained <LLN and 1 had platelet count increase but remained <100 x 10^9/L. These patients are summarized below:

Table 27: Patients with abnormal platelet findings - pooled safety population

STUDY/ PATIENT NUMBER	TREATMENT	AGE/SEX/RACE	PLATELET COUNT (X 10^9/L)	ADVERSE EVENT	CONCOMITANT MEDICATIONS
ASTEROID 0166/0009	RSV 40 mg	51/M/C	B: 25 F: 219		Plavix, Tenormin
ASTEROID 0030/0012	RSV 40 mg	52/F/C	B: 274 F: 44		Aspirin, Toprol XL
ASTEROID 00002/0046	RSV 40 mg	49/M/C	B: 273 F: 56	GERD, arthralgia, insomnia	Lisinopril, ASA, Plavix
ASTEROID 0014/0003	RSV 40 mg	54/F/C	B: 230 F: 56	Gravitational edema, cough, fatigue, amnesia, toothache	Plavix, aspirin
ASTEROID 0002/0042	RSV 40 mg	56/M/C	B: 57 F: 96	Myalgia	ASA, Plavix
ASTEROID 0142/0029	RSV 40 mg	59/M/C	B: 59 B (retest): 191 F: 221		Cardioaspirin
ASTEROID 0001/0037	RSV 40 mg	73/M/C	B: 62 F: 119	Brainstem infarct	ASA, Norvasc, Zestril, Plavix
ASTEROID 0005/0057	RSV 40 mg	53/M/C	B: 64 F: Unk		Aspirin, Plavix
ASTEROID 0008/0032	RSV 40 mg	61/M/C	B: 181 B (retest): 129 F: 77	Arthralgia, HTN, shoulder pain	Aspirin, Lotensin, HCTZ
ASTEROID 0013/0030	RSV 40 mg	66/F/C	B: 120 F: 90		Aspirin, HCTZ, atenolol
ASTEROID 0062/0015	RSV 40 mg	67/M/C	B: 149 F: 90	Fatigue, libido decreased, hemoglobin decreased, platelet count decreased	Aspirin
ORION 0216/0031	RSV 40/80 mg	76/M/C	B: 164 F: 92		Aspirin, Enalapril, HCTZ, Zyban
ASTEROID 0004/0004	RSV 40 mg	42/F/C	B: 94 F: Unk		Zestril
ASTEROID 0003/0003	RSV 40 mg	54/F/C	B: 194 F: 96	Pain in extremity, osteopenia, back pain, sinusitis	Aspirin, Prinivil, Toprol XL, Zyban
ASTEROID 0018/0035	RSV 40 mg	64/F/C	B: 97 F: 175		Asprirn, Atenolol
METEOR 0302/0644	RSV 40 mg	57/F/C	B: 97 F: 207	Thrombocytopenia D1-367, recovered at final visit	Ranitidine

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

The following is a summary of the dropouts for laboratory abnormalities by Preferred Term and treatment:

Table 28: Dropouts due to laboratory abnormalities - pooled safety population

PREFERRED TERM	ROSUVASTATIN 40 MG N=1229 N (%)	PLACEBO N=281 N (%)
Total # patients who withdrew	**14 (1.1)**	**5 (1.8)**
Hepatic enzyme increased	5 (0.4)	0
Blood CK increased	4 (0.3)	0
ALT increased	3 (0.2)	0
AST increased	2 (0.2)	0
Liver function test abnormal	1 (0.1)	2 (0.7)
Blood bilirubin increased	1 (0.1)	1 (0.4)
Blood TG increased	1 (0.1)	0
Chromaturia	1 (0.1)	0
GGT increased	1 (0.1)	0
Renal failure	1 (0.1)	0
Hematuria	0	1 (0.4)
Proteinuria	0	1 (0.4)
ESR increased	0	1 (0.4)
Transaminases increased	0	1 (0.4)
Virus serology test positive	0	1 (0.4)

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs data, including systolic blood pressure, diastolic blood pressure and pulse rate, were recorded at each visit throughout the METEOR (except for Visits 7, 9, and 11) and ORION studies, and at baseline and end of study in ASTEROID.

There were no clinically relevant changes in vital signs over time in any of the 3 studies.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were measured in METEOR (Visits 4 and 13) and ORION (Visits 2, 12, and 16). ECGs were not collected in ASTEROID.

A brief review of preclinical studies is provided:

There were no cardiovascular effects (heart rate, ECG) in conscious

dogs following 100 mg/kg orally. In an in vitro study using canine Purkinje fibres, rosuvastatin had no effect on action potential duration at concentrations of 1, 10, 100, and 1000 ng/ml.

Reductions in blood pressure and increased heart rates were seen at high doses in anaesthetized rats (300 mg/kg) following intraduodenal dosing (id) and reductions in blood pressure were observed in anaesthetized cats following a single 100 mg/kg id. There were no cardiovascular effects (heart rate, ECG) in conscious dogs following 100 mg/kg orally. In an in vitro study using canine Purkinje fibres, rosuvastatin had no effect on action potential duration at concentrations of 1, 10, 100, and 1000 ng/ml.

7.1.9.3 Standard analyses and explorations of ECG data

There were no clinically significant changes in ECG in METEOR. In ORION, one patient in the high-dose rosuvastatin group had a clinically meaningful change in ECG (inferior ischemia) from baseline at Week 52 which was not present at Week 104; no CRF was submitted for this patient. No patient had a clinically meaningful change in ECG at Week 104.

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There was no indication of a withdrawal and/or rebound phenomenon in any clinical studies, including the 3 studies reported in this submission; however, withdrawal and/or rebound have not been evaluated specifically.

7.1.14 Human Reproduction and Pregnancy Data

According to the sponsor, as of 6 May 2006, cumulatively, there were 44 reports of pregnancy with reported exposure to rosuvastatin. Of these 44 reports, 17 were study reports and 27 were spontaneous reports. Of the spontaneous reports, 20 were medically confirmed (2 serious, 18 non-serious) and 7 were non-serious, non-medically confirmed.

There were 3 cumulative reports of rosuvastatin exposure during lactation (all non-serious, non-medically confirmed, spontaneous).

The cumulative review of all reports of rosuvastatin exposure during pregnancy or lactation did not identify "an association between rosuvastatin exposure and the occurrence of any pattern of adverse outcomes."

7.1.16 Overdose Experience

There is no specific treatment in the event of overdoses with rosuvastatin. In the event of overdose, the patient is to be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance the clearance of rosuvastatin.

7.1.17 Postmarketing Experience

From the start of the clinical development program to 30 April 2006 it was estimated that approximately 55000 patients were exposed to rosuvastatin in the clinical study program. As of 30 April 2006, the cumulative worldwide market exposure was calculated to be approximately (b) (4) patients, representing over (b) (4) patient years.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 1207 patients who received rosuvastatin 40 mg were evaluated for safety in the METEOR and ASTEROID studies. An additional 281 placebo patients in the METEOR study were also evaluated for safety. Also included in the safety evaluation were 21 patients who received 5 mg rosuvastatin and 22 patients who received 40/80 mg rosuvastatin in the ORION study.

In METEOR, 700 patients were exposed to 40 mg rosuvastatin for 621.7 days and 281 received placebo for 620.8 days. In ASTEROID, the mean duration of exposure was 630.4 days for the rosuvastatin 40 mg group (N=507). In ORION, the mean duration of exposure was 685.6 days for the rosuvastatin 5 mg group (N=21) and 679.1 days for the rosuvastatin 40/80 mg group (N=22).

7.2.1.1 Study type and design/patient enumeration

A total of 5751 patients entered the METEOR screening period. Of these, 4767 (82.9%) were withdrawn and 984 (17.1%) completed screening. All patients completing the screening period were randomized to receive study treatment (702 patients received rosuvastatin and 282 patients received placebo). The study was sized with the expectation that up to 30% of randomized patients would withdraw from the study before 2 years. The overall percentage of patients who discontinued during the study was 25.0% and was similar between the 2 treatment groups (24.5% for the rosuvastatin group versus 26.2% for the placebo group). A larger percentage of patients treated with rosuvastatin withdrew due to an AE as compared with patients treated with placebo (11.3% versus 7.8%, respectively).

In METEOR, a post-hoc analysis examined the relationship between reported AEs in the days prior to withdrawal and withdrawals reported for reasons of "withdrew consent", "lost-to

follow-up", "investigator's discretion" and "informed consent withdrawn". Among METEOR patients treated with rosuvastatin 40 mg, 11% of withdrawals in these categories reported an AE <30 days prior to withdrawal, 5% reported an AE 30 to 60 days prior to withdrawal, and 44% reported an AE >60 days prior to withdrawal. Among patients treated with placebo, the percentages were 21% reporting an AE <30 days prior to withdrawal, 8% reporting an AE 30 to 60 days prior to withdrawal, and 44% reporting an AE >60 days prior to withdrawal

A total of 1183 patients were screened for ASTEROID. Of these, 507 patients entered the treatment period in ASTEROID. Subsequently, 125 (24.7%) patients withdrew from treatment. The most common reason for study discontinuation was AE (12.4%). Fourteen (2.8%) patients were lost to follow-up.

In ASTEROID, a post-hoc analysis examined the relationship between reported AEs in the days prior to withdrawal and withdrawals reported for reasons of "withdrew consent", "lost-to follow-up", "investigator's discretion" and "informed consent withdrawn". Among ASTEROID patients treated with rosuvastatin 40 mg, 23% of withdrawals in these categories reported an AE <30 days prior to withdrawal, 6% reported an AE 30 to 60 days prior to withdrawal, and 46% reported an AE >60 days prior to withdrawal.

A total of 73 patients entered the dietary lead-in period for ORION. Of these, 43 patients entered the treatment period in ORION. Subsequently, 2 patients in each treatment group withdrew from treatment.

7.2.1.2 Demographics

METEOR was conducted in low cardiovascular risk patients with subclinical carotid atherosclerosis who did not meet current guidelines for statin therapy (so that placebo could be given), whereas ASTEROID and ORION were conducted in patients with established cardiovascular disease who did meet current guidelines for statin therapy.

Patients in all 3 studies were predominately Caucasian (>94%) and male (METEOR 59.8%, ASTEROID 71.0%, and ORION 67.4%). The mean age was 56.7 years in METEOR, 58.5 years in ASTEROID, and 64.8 years in ORION with an adequate percentage of patients ≥ 65 years of age in each study (METEOR 13.1%, ASTEROID 29.4%, and ORION 53.5%). Patients enrolled in ASTEROID weighed (85.7 kg) more and had a greater BMI (29.2 kg/m2) than patients enrolled in METEOR (80.5 kg and 27.2 kg/m2). Patients in ORION weighed less and had slightly lower BMIs than patients in ASTEROID (82.9 kg and 28.1 kg/m2). Approximately 1.7% of patients in METEOR had a moderate decrease in renal function based on eGFR compared to 12.4% of the ASTEROID patients. Estimated GFR measurements were not made in ORION, however, 9.3% of patients had moderate baseline renal impairment based on calculated creatinine clearance.

The patient population enrolled in METEOR was at low 10-year risk for CHD according to the NCEP ATP III guidelines published in 2001. Overall, 98.3% of patients entering the METEOR study were considered, on the basis of the 2001 NCEP ATP III guidelines (Expert

panel NCEP 2001), to be at low risk due to the presence of either 0 to 1 risk factor or ≥ 2 risk factors and a Framingham 10-year risk of < 10%; 1.6% of patients were considered moderate risk with ≥ 2 risk factors with a Framingham 10-year risk of 10% to 20%. One patient in the rosuvastatin group was diabetic and with the exception of 1 patient (Patient 0302/0188), there were no patients with symptomatic atherosclerotic disease. (This latter patient [Patient 0302/0188] had a history of cardiac chest pain, which was not known at the time of randomization to rosuvastatin. This history was disclosed at Visit 5 and became relevant as the patient had multiple ischemic adverse events during the study. The patient was later withdrawn.)

Overall, the patients studied in ASTEROID were representative of the population of patients with atherosclerotic CAD. Inclusion criteria for ASTEROID required documented CAD; patients enrolled in this study were by definition high risk according to the NCEP ATP III guidelines published in 2001.

Table 29: METEOR and ASTEROID demographic and selected baseline characteristics

CHARACTERISTIC	METEOR		ASTEROID
	ROSUVASTATIN 40 MG (N=702)	PLACEBO (N=282)	ROSUVASTATIN 40 MG (N=507
Age (years)			
Mean (SD)	56.7 (6.2)	56.9 (6.03)	58.5 (10.06)
Range	45, 70	45, 70	33, 85
Sex, n (%)			
Male	421 (60.0)	167 (59.2)	360 (71.0)
Female	281 (40.0)	115 (40.8)	147 (29.0)
Race, n (%)			
Caucasian	659 (93.9)	268 (95.0)	477 (94.1)
Black	11 (1.6)	2 (0.7)	17 (3.4)
Asian	8 (1.1)	0	1 (0.2)
Hispanic	23 (3.3)	10 (3.5)	8 (1.6)
Other	1 (0.1)	2 (0.7)	4 (0.8)
Weight (kg)			
N	699	282	502
Mean (SD)	80.4 (14.38)	80.7 (13.68)	85.7 (16.74)
Range	40, 125	46, 125	40, 143
BMI (kg/m^2)			
N	699	282	501
Mean (SD)	27.1 (3.99)	27.5 (4.04)	29.2 (5.08)
Range	16, 47	19, 42	17, 54
Renal function (CrCL), n (%)			
Normal	523 (39.9)	97 (34.4)	111 (21.9)
Mild impairment	350 (49.9)	156 (55.3)	326 (64.3)
Moderate impairment	15 (2.1)	2 (0.7)	63 (12.4)
Severe impairment	0	0	0
NR	0	0	7 (1.4)
Estimated GFR, n (%)			
Normal	280 (39.9)	97 (34.4)	111 (21.9)
Mild impairment	350 (49.9)	156 (55.3)	326 (64.3)
Moderate impairment	15 (2.1)	2 (0.7)	63 (12.4)
Severe impairment	0	0	0

CHARACTERISTIC	METEOR		ASTEROID
	ROSUVASTATIN 40 MG (N=702)	PLACEBO (N=282)	ROSUVASTATIN 40 MG (N=507
NR	0	0	7 (1.4)

Table 30: METEOR and ASTEROID baseline lipids, lipoproteins and CRP (METEOR ITT and ASTEROID IEV populations)

LABORATORY VARIABLE (MG/DL)	METEOR		ASTEROID
	ROSUVASTATIN 40 MG (N=624)	PLACEBO (N=252)	ROSUVASTATIN 40 MG (N=346)
LDL-C	154.5	154.3	130.4
TC	229.2	230.2	204.0
HDL-C	49.7	49.0	43.1
TG	125.8	134.4	152.2
nonHDL-C	179.6	181.2	160.9
Apo B	115.7	117.4	127.9
Apo A-I	152.2	151.5	138.6
CRP	0.302	0.276	NR

7.2.1.3 Extent of exposure (dose/duration)

Table 31: Overview of exposure - METEOR safety population

	ROSUVASTATIN 40 MG (N=700)	PLACEBO (N=281)
Randomized treatment period (days)		
N	688	272
Mean (SD)	621.7 (225.78)	620.8 (227.18)
Minimum, maximum	2, 792	3, 790
Not recorded	12	9
Weeks		
0 to < 13	50 (7.1)	20 (7.1)
13 to < 26	22 (3.1)	10 (3.6)
26 to < 39	21 (3.0)	6 (2.1)
39 to < 52	15 (2.1)	7 (2.5)
52 to < 65	15 (2.1)	6 (2.1)
65 to < 78	11 (1.6)	5 (1.8)
78 to < 91	15 (2.1)	6 (2.1)
91 to < 104	130 (18.6)	46 (16.4)
104 +	409 (58.4)	166 (59.1)
Not calculated	12 (1.7)	9 (3.2)

Table 32: Overview of exposure - ASTEROID safety population

	ROSUVASTATIN 40 MG (N=507)
Randomized treatment period (days)	
N	503
Mean (SD)	630.4 (209.87)
Median	727.0
Minimum, maximum	1, 863
Not recorded	4
Weeks	
0 to < 13	24 (4.7)
13 to < 26	18 (3.6)
26 to < 39	18 (3.6)
39 to < 52	7 (1.4)
52 to < 65	9 (1.8)
65 to < 78	19 (3.7)
78 to < 91	16 (3.2)
91 to < 104	146 (28.8)
104 +	246 (48.5)
Not calculated	4 (0.8)

Table 33: Overview of exposure - ORION safety population

	ROSUVASTATIN 5 MG (N=21)	ROSUVASTATIN 40/80 MG (N=22)
Randomized treatment period (days)		
N	685.6	679.1
Mean (SD)	144.08	167.95
Minimum, maximum	728	729
Not recorded	114	104
	739	747
Weeks		
0 to < 12	0	0
12 to < 20	1 (4.8)	1 (4.5)
20 to < 28	0	0
28 to < 40	0	1 (4.5)
40 to < 52	0	0
52 to < 65	1 (4.8)	0
65 to < 78	0	0
78 to < 91	0	0
91 to < 104	7 (33.3)	5 (22.7)
104 +	12 (57.1)	15 (68.2)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The following other sources were searched for safety issues associated with the use of rosuvastatin:

- The June 28, 2007 PSUR submitted by AstraZeneca.
- The medical literature.
- The AERS database.

For a discussion of the results of the results of the review of the AERS database, please see Section 7.1.4.

For a discussion of the medical literature, please see Section 8.6.

7.2.2.2 Postmarketing experience

A PSUR submitted June 28, 2007 covering the time period 07 November 2006 to 06 May 2007 was reviewed. The following is a summary of the cumulative reporting rates by dose of adverse reactions associated with the use CRESTOR that are kept under review. A dose response is evident in the occurrence of all SAEs, as well as the clinically relevant AEs of rhabdomyolysis, renal failure, and renal impairment. The risk of these AEs is particularly pronounced at the 40 mg dose.

Table 34: Cumulative spontaneous reporting rates of ADRs associated with CRESTOR , by dose

EVENT	CRESTOR DOSAGE (RR PER MILLION PATIENTS)			
	5 MG	10 MG	20 MG	40 MG
All SAEs	119.3	241.9	296	737.3
All AEs	1664.1	1981.3	1442.4	2216.5
Rhabdomyolysis	19.1	34.8	53.7	273.1
Myopathy	10.0	10.8	16.8	13.7
Myositis	7.3	9.4	10.9	41.0
CK increase	62.9	91.9	81.3	150.2
Hepatic events	83.8	126.3	107.3	191.2
Renal failure	8.2	13.0	20.1	77.4
Renal impairment	11.8	16.1	32.7	100.1
Proteinuria	4.6	6.8	12.6	36.4

7.2.3 Adequacy of Overall Clinical Experience

The submitted studies, in particular METEOR, do little to assuage this Reviewer's concern regarding the use of cIMT as a surrogate endpoint. The tremendous variability and inconsistency in the data, despite measures to control for variability (i.e., standardized sonography methods, centralized reading, repetition of scans at baseline and end of study, etc.) highlight a concern with adopting these measures and trying to assign clinical benefit to the results. In approving an indication for slowing the progression, we are relying as much on the known LDL-lowering capability of rosuvastatin and the presumed improvement that conveys on cardiovascular morbidity and mortality as on the study itself. Furthermore, it must be kept in mind that the

sponsor is seeking an indication for a population that was not studied (subjects in whom statin therapy is not indicated based on current NCEP guidelines) and for dosages that were not used.

These studies do, however, provide additional support to the overall safety profile of the 40 mg dose of rosuvastatin.

7.2.8 Assessment of Quality and Completeness of Data

In METEOR, the frequency of patients with protocol deviations leading to exclusion of data from the PP analysis set was higher in the placebo group (30.0% for patients receiving rosuvastatin and 36.1% for patients receiving placebo). Overall, 10.9% of patients in the rosuvastatin group and 16.5% of patients in the placebo group received a concomitant medication disallowed by the protocol.

Overall, for 91.4% of rosuvastatin-treated patient scans and 89.6% of placebo-treated patient scans all 12 carotid sites could be visualized and measured. The frequency of missing data was approximately 1% for all carotid sites, except for the right ICA near wall, which had a maximum frequency of 5.1%. The frequency of this missing data was independent of treatment group and visit.

In the ITT population, 13.8% in the rosuvastatin group and 16.3% in the placebo group withdrew from the study after Week 26 and before Week 104. The sponsor claims that "Conservative analyses were carried out in which patients were given imputed values after withdrawal. The results of these analyses showed that the results from the main analysis were insensitive to a range of conservative assumptions about the effects of missing data due to premature withdrawal".

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. This Reviewer is concerned with the potential for increased use of the 40 mg dose of rosuvastatin. The sponsor will need to monitor utilization of the 40 mg dose and closely monitor patients on the 40 mg dose for rhabdomyolysis and myopathy during the initial 2 years following this approval.

While the cumulative reporting rates of renal failure and renal impairment combined (44 per million patients) is below the estimated annual incidence of 200 cases per million for acute renal failure in the community, the higher reporting rates for reported events of renal failure/renal impairment for rosuvastatin 40 mg are of concern and should also be closely monitored during the initial 2 years following this approval.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

To support the efficacy of rosuvastatin in slowing (b) (4) the progression of atherosclerosis, only data from METEOR was considered to be relevant; due to the different modalities of assessing atherosclerosis employed in the 3 submitted studies, pooling of the data was not possible.

Safety data, however, were pooled across the 3 studies. This was done despite the lack of placebo arms in ASTEROID and ORION and despite the different populations studied in order to enhance the overall database of exposure to the 40 mg dose. It should be noted, however, that this approach will tend to portray the drug in a less favorable light, given that the placebo rates in the pooled analysis are drawn exclusively from the METEOR trial.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions

No new data were submitted. The following drug-drug interactions were commented on in the current submission:

- **Cyclosporine:** *Co-administration of cyclosporine with rosuvastatin resulted in no significant changes in cyclosporine plasma concentrations. However, C_{max} and AUC of rosuvastatin increased 11- and 7-fold, respectively, compared with historical data in healthy subjects. These increases are considered to be clinically significant.*

  One patient in METEOR received concomitant cyclosporine. This patient was in the placebo group, and had an AE of anxiety. No patient in either ASTEROID or ORION received concomitant cyclosporine.

- **Warfarin:** *Co-administration of warfarin (25 mg) with rosuvastatin (40 mg) did not change warfarin plasma concentrations but increased the International Normalized Ratio (INR).*

  In METEOR 9 patients in the rosuvastatin 40 mg group received concomitant Vitamin K antagonist anticoagulants; of these, 4 patients had AEs, 1 of which was hemoglobin decreased. In METEOR placebo patients, 6 patients received concomitant Vitamin K antagonist anticoagulants; of these, 3 patients had AEs, 1 of which was anemia. In ASTEROID, 31 rosuvastatin 40 mg patients received concomitant Vitamin K antagonist

anticoagulant with 24 having adverse events. In ORION, 1 patient in each treatment group received concomitant Vitamin K antagonist anticoagulants and both of these patients had adverse events.

- **Fenofibrate:** *Co-administration of fenofibrate (67 mg three times daily) with rosuvastatin (10 mg) resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate.*

  None of the patients in METEOR, ASTEROID, or ORION received concomitant fibrates excluding gemfibrozil.

- **Gemfibrozil:** *Co-administration of gemfibrozil (600 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in a 90% and 120% increase for AUC and C_{max} of rosuvastatin, respectively. This increase is considered to be clinically significant.*

  There was 1 patient (placebo group) who received gemfibrozil in the METEOR study but experienced no AEs. No patients in the ASTEROID or ORION studies received gemfibrozil.

- **Oral contraceptives:** *Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.*

  In METEOR, 1 patient treated with rosuvastatin received concomitant oral contraceptive medication compared with no patient treated with placebo. In ASTEROID, 2 patients received concomitant rosuvastatin plus oral contraceptive medication. No patients in ORION received oral contraceptive medication. These numbers were too small to permit an assessment of tolerability of rosuvastatin plus oral contraceptive medication.

8.3 Special Populations

A summary of the special populations highlighted in the current CRESTOR label is provided, along with data from the 3 current studies:

- *There are no differences in plasma concentrations of rosuvastatin between men and women.*

  In the current studies, there was a slightly greater frequency of "any AE" in women than in men during rosuvastatin treatment (METEOR 89% vs. 80%; ASTEROID 88% vs. 82%; and ORION 93% vs. 83%, respectively). In METEOR, there was a slightly greater incidence of AEs in women than men in the placebo group (85% vs. 77%).

  The most common adverse events in the pooled safety population by sex and treatment are summarized in the table below:

Table 35: Most common adverse events by sex during randomized treatment - pooled safety population

PREFERRED TERM	ROSUVASTATIN 40 MG (N= 1229)		PLACEBO (N-281)	
	Males (N=795)	Females (N=434)	Males (N=167)	Females (N=114)
Any adverse event	**642 (80.8)**	**379 (87.3)**	**129 (77.2)**	**97 (85.1)**
Myalgia	105 (13.2)	58 (13.4)	16 (9.6)	18 (15.8)
Influenza	62 (7.8)	33 (7.6)	17 (10.2)	12 (10.5)
Arthralgia	60 (7.5)	45 (10.4)	10 (6.0)	10 (8.8)
Back pain	57 (7.2)	33 (7.6)	14 (8.4)	15 (13.2)
Nasopharyngitis	51 (6.4)	33 (7.6)	16 (9.6)	14 (12.3)
Fatigue	36 (4.5)	33 (7.6)	11 (6.6)	5 (4.4)
Blood CK increased	32 (4.0)	4 (0.9)	2 (1.2)	0
URI	21 (2.6)	29 (6.7)	4 (2.4)	8 (7.0)
Headache	20 (2.5)	25 (5.8)	6 (3.6)	9 (7.9)
Cough	17 (2.1)	15 (3.5)	3 (1.1)	5 (4.4)

- *There are no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years).*

  The METEOR protocol excluded patient >70 years of age. In METEOR, the frequency of "any AE" was higher in patients ≥ 65 years of age compared to patients < 65 years of age for both the rosuvastatin (90% vs. 82%, respectively) and placebo groups (89% vs. 79%, respectively). However, for myalgia, the frequencies were higher in the < 65 year of age patients for both rosuvastatin (13% vs. 10%) and placebo (13% vs. 8%).

  In ASTEROID, the most common AE in all 4 age groups < 65 year of age, ≥ 65 year of age, < 75 years of age and ≥ 75 year of age) was angina pectoris occurring in a slightly greater frequency in the older patients; 16.5% of patients < 65 years of age, 21.3% of patients ≥ 65 years of age; 17.1% of patients < 75 years of age, and 30.3% of patients ≥ 75 years of age. Myalgia was the second most commonly reported AE in the < 65 year of age (14.6%), ≥ 65 years of age (13.3%), < 75 years of age (13.9%), and ≥ 75 years of age (18.2%) groups. The most striking differences were in some lower frequency AEs in the contrasted < 75 and ≥ 75 years of age groups where atrial fibrillation was 1.9% in the <75 years of age group and 24.2% in the ≥ 75 years of age group.

- *There are no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, there is an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group.*

  There were too few non-Caucasian patients in any of the 3 studies to permit meaningful comparisons. There were only 10 Asian patients in all 3 studies combined. The table below provides a summary of the most common adverse events by ethnicity and treatment:

Table 36: Most common adverse events by ethnic origin by treatment - METEOR and ASTEROID pooled

PREFERRED TERM	ROSUVASTATIN 40 MG (N=1207)				PLACEBO (N=281)			
	Caucasian (N=1134) N (%)	Black (N=28) N (%)	Asian (N=8) N (%)	Hispanic (N=31) N (%)	Caucasian (N=267) N (%)	Black (N=2) N (%)	Asian (N=0) N (%)	Hispanic (N=10) N (%)
Any AE	958 (84.5)	22 (78.6)	6 (75)	15 (48.4)	218 (81.6)	2 (100)	0	4 (40)
Myalgia	153 (13.5)	4 (14.3)	2 (25)	2 (6.5)	34 (12.7)	0	0	0
Arthralgia	97 (8.6)	3 (10.7)	0	0	20 (7.5)	0	0	0
Influenza	89 (7.8)	2 (7.1)	0	1 (3.2)	29 (10.9)	0	0	0
Back pain	83 (7.3)	3 (10.7)	1 (12.5)	3 (9.7)	29 (10.9)	0	0	0
Nasopharyngitis	78 (6.9)	2 (7.1)	0	1 (3.2)	29 (10.9)	0	0	1 (10)
Fatigue	65 (5.7)	2 (7.1)	1 (12.5)	1 (3.2)	15 (5.6)	0	0	0
URI	49 (4.3)	0	0	1 (3.2)	12 (4.5)	0	0	0
Headache	45 (4.0)	0	0	0	15 (5.6)	0	0	0
Sinusitis	33 (2.9)	0	0	0	14 (5.3)	0	0	0

- *Mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min/1.73m ^{2}) has no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increase about 3-fold in patients with severe renal impairment (CL_{cr} < 30 mL/min/1.73m ^{2}) compared with healthy subjects (CL_{cr} > 80 mL/min/1.73m ^{2}).*

  In METEOR, in the group of 700 patients receiving rosuvastatin 40 mg, there were 521 patients with normal renal function, 116 with mild renal impairment (CrCl 50 to ≤ 80 mL/min), and 6 with moderate renal impairment (CrCl 30 to < 50 mL/min). In the group of 281 patients receiving placebo there were 217 with normal renal function, 37 with mild renal impairment, and none with moderate renal impairment.

  In the 521/700 METEOR rosuvastatin 40 mg patients with normal renal function at entry, the frequency of "any AE" was 82.9% compared with 88.8% for the 116/700 METEOR rosuvastatin 40 mg patients with mild renal impairment. In the 6 rosuvastatin 40 mg patients with moderate renal impairment, the frequency of "any AE" was 100%.

  In the 334/507 ASTEROID rosuvastatin 40 mg patients with normal renal function, the frequency of "any AE" was 84.7%; in the 142 rosuvastatin 40 mg patients with mild renal impairment it was 79.6%, and in the 19 rosuvastatin with moderate renal impairment it was 94.7%.

- *In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin are modestly increased.*

  Review of the most common AEs shows that patients receiving rosuvastatin 40 mg with impaired hepatic function had a somewhat higher frequency of myalgia than patients with normal hepatic function in METEOR (16.7% vs. 13.0%) but not in ASTEROID (9.6% vs. 15.5%).

  In the 570/700 METEOR rosuvastatin 40 mg patients with normal hepatic function at entry, the frequency of "any AE" was 83.9%, whereas in the 66/700 METEOR

rosuvastatin 40 mg patients who did not have normal hepatic function, the frequency of "any AE" was 84.8%. In the 232/281 METEOR placebo patients with normal liver function, the frequency of "any AEs" was 80.2% compared to 82.4% for the 17 placebo patients with moderately impaired liver function at baseline.

In the 413/507 ASTEROID rosuvastatin 40 mg patients with normal hepatic function at entry the frequency of "any AE" was 85.0% compared to 79.5% in the 83 ASTEROID 40 mg patients with moderately impaired hepatic function.

8.4 Pediatrics

In accordance with 21 CFR § 314.55(c)(2)(i), AstraZeneca has certified that CRESTOR does not represent a meaningful therapeutic benefit for pediatric patients with atherosclerosis and is not likely to be used in a substantial number of pediatric patients specifically for this indication. Consequently, they have requested that a full waiver be granted from the requirement to conduct 'anti-atherosclerosis' studies in pediatric patients. This Reviewer is in agreement with granting the sponsor the requested full waiver.

8.6 Literature Review

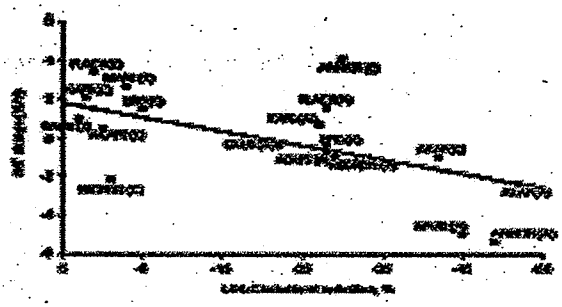
The pathophysiology of atherosclerosis is complex, comprised of a multi-faceted process apparently initiated and perpetuated by lipid accumulation in the arterial wall, involving inflammation, cellular proliferation, disruption of tissue integrity, and ultimate friability of the arterial intima leading to thrombosis at sites of intimal injury. As such, methods, both invasive and non-invasive, of imaging the arterial wall have come into favor in the assessment of atherosclerotic disease. Ultrasound of the carotid arteries, MRI and CT of the coronaries and carotids, and intravascular ultrasound of the coronaries have been studied, variably, for their utility in predicting cardiovascular disease risk, in assessing the effects of anti-atherosclerotic therapies, and for directing surgical intervention to address arterial disease. Strictly speaking, none stands as a fully validated "surrogate" measure of anti-atherosclerosis efficacy. Specifically, as for coronary angiography itself, there are inadequate data to permit a calculation of the extent of cardiovascular disease risk reduction as a function of a given degree of change in anatomic parameters as assessed by these methods.

Over the last several years, multiple studies, notably of lipid-lowering drugs, anti-hypertensive agents, and hormone replacement therapy (HRT) have been conducted to examine effects on anatomically defined arterial disease. In this regard, several statin package inserts include study summaries and indications based on the results of trials utilizing arterial anatomic assessments of disease as measures of drug effect. Specifically, the labels for lovastatin, simvastatin, pravastatin, and fluvastatin all describe the results of placebo-controlled trials showing apparent slowing of the progression of atherosclerosis by drug compared to placebo. These findings are obviously consistent with the known role of LDL-cholesterol in atherosclerotic disease and are "validated" by the results of now multiple trials showing reductions in cardiovascular disease events (fatal and non-fatal myocardial infarctions, unstable angina, strokes, revascularizations, etc.) in

patients treated with statins compared to placebo.

While there has been some debate as to whether the effect of HMG CoA reductase inhibitors on atherosclerosis is attributable to a reduction in LDL-C or to other pleiotropic effects of statins, Amarenco et al in a review of statins in carotid atherosclerosis found that there was a strong correlation between LDL reduction and carotid IMT reduction (r=0.65; p=0.004). Each 10% reduction in LDL-C was estimated to reduce the carotid IMT by 0.73% per year (95% CI: 0.27 to 1.19). The figure below depicts their results and shows the relationship between LDL-C reduction and carotid IMT change.[2]

Figure 3: Relationship between LDL-C reduction and carotid IMT change



9 OVERALL ASSESSMENT

9.1 Conclusions

Despite this Reviewer's reluctance to accept cIMT as a surrogate endpoint for a drug that has yet to complete a cardiovascular outcomes study, I acknowledge that the sponsor designed and conducted this study in consultation with the Agency and that the study has produced significant and robust results to support the addition of an indication to slow the progression of atherosclerosis. But there remain some inexplicable aspects to the findings of this study that can only be answered by a clinical outcomes study. Specifically, this Reviewer was struck by the small change in cIMT achieved relative to the degree of LDL-C lowering achieved. Also bothersome was the disparity in ischemic cardiovascular events occurring among subjects on rosuvastatin versus placebo, 6/700 (0.9%) vs. 0, respectively.

The sponsor has requested an indication "to slow (b) (4) the progression of atherosclerosis". The sponsor is basing the term (b) (4) observed in 52.1% of rosuvastatin-treated subjects versus 37.7% of placebo-treated subjects. This Medical Reviewer does not support the use of the

[2] Amarenco, P et al. Statins in Stroke Prevention and Carotid Atherosclerosis: Systematic Review and Up-to-Date Meta-Analysis. *Stroke*. 2004;35:2902-2909.

term [(b) (4)] progression of atherosclerosis" in the indication for this drug. The sponsor designed the METEOR trial to show regression of atherosclerosis and had initially proposed an indication "to slow the progression [(b) (4)] of atherosclerosis":

The primary objective of the study was to assess the effects of rosuvastatin 40 mg treatment for 104 weeks on the change in the mean maximum IMT of the 12 carotid artery segments: near and far walls of the right and left CCA, carotid bulb, and the internal carotid artery (ICA). The rosuvastatin-treated patients, in whom the IMT was expected to regress over time, were compared to the placebo-treated patients, in whom the IMT was expected to progress over time. If there was a significant difference between these treatment groups, then the rosuvastatin-treated patients were examined further to determine whether there was significant regression in IMT between the beginning and the end of the treatment period.

When the study results failed to show regression, the sponsor performed a post-hoc analysis looking at the percentage of patients who had an absence of progression and modified the indication to suggest that this translated into [(b) (4)] the progression of atherosclerosis. It is the belief of this Medical Reviewer that the sponsor is not being true to the design of the clinical study and that the clinical meaningfulness of this finding, especially in light of the fact that ~50% of rosuvastatin-treated subjects did not show an absence of progression, is unclear. Apart from mentioning these results in the Clinical Studies section, no use of the concept "[(b) (4)] progression of atherosclerosis" should be allowed in the label.

9.3 Recommendation on Regulatory Action

It is recommended that rosuvastatin be approved for the following indication: As adjunctive therapy to diet to slow the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C to target levels.

It is recommended that a summary of the METEOR trial be allowed in the Clinical Studies section of the label.

9.3.1 Risk Management Activity

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. This Reviewer is concerned with the potential for increased use of the 40 mg dose of rosuvastatin. The table below highlights this trend; the data were compiled by OSE and reflect the number of U.S. retail prescriptions written monthly for rosuvastatin by dose.

Table 37: 2007 Monthly Prescriptions for Rosuvastatin by dose

DOSE	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	% INCREASE JAN-AUG
									(b) (4)

The sponsor should be advised to monitor utilization of the 40 mg dose and to closely monitor patients on the 40 mg dose for rhabdomyolysis and myopathy during the initial 2 years following this approval. This should take the form of requiring the sponsor to submit Periodic Safety Update Reports semi-annually for the next 2 years.

While the cumulative reporting rates of renal failure and renal impairment combined (44 per million patients) is below the estimated annual incidence of 200 cases per million for acute renal failure in the community, the higher reporting rates for reported events of renal failure/renal impairment for rosuvastatin 40 mg are of concern and should also be closely monitored during the initial 2 years following this approval.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

See Section 10.2 for changes to the current label referable to the current submission.

CRESTOR is the first HMG CoA reductase inhibitor to be in Physician Labeling Rule format. Extensive labeling negotiations were conducted with the sponsor. Please refer to the Approval letter for a copy of the final agreed upon PLR label.

9.5 Comments to Applicant

Because of the effect of HMG-CoA reductase inhibitors on skeletal muscle and because the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose (40 mg) the sponsor should be advised to monitor utilization of the 40 mg dose and to closely monitor patients on the 40 mg dose for rhabdomyolysis and myopathy during the initial 2 years following this approval.

Because of a possible association between rosuvastatin and renal failure/renal impairment and because of the higher reporting rates for events of renal failure/renal impairment for rosuvastatin 40 mg are, the sponsor should be advised to closely monitor patients for events of renal failure/renal impairment during the initial 2 years following this approval.

This monitoring should take the form of requiring the sponsor to submit Periodic Safety Update Reports semi-annually for the next 2 years.

APPEARS THIS WAY ON ORIGINAL

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.2 Appendix A:

Study D3560C00044 (4522IL/0044) ORION

A 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

Study initiation date: 6 January 2000
Study completion date: 5 August 2004

10.1.2.1 Objectives

Primary

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).

Secondary

The secondary objectives of the study were to:

- Compare the change in the carotid artery wall volume after all other time points
- Measure change 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 (e.g., 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

10.1.2.2 Endpoints

Primary efficacy measures

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

Secondary efficacy measures

- 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 (e.g., 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 measures

- Adverse events
- Physical examination
- Vital signs
- ECG
- Clinical laboratory data (hematology, hepatic and renal clinical chemistry, and urinalysis)

10.1.2.3 Statistical and Analytical Plans

Analysis population:

- **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

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 randomized treatment period. Patients enrolled to the lead-in were

counseled on the National Institute of Health (NIH) NCEP Step-I diet. Patients were required to be on the diet for at least 4 weeks prior to randomization.

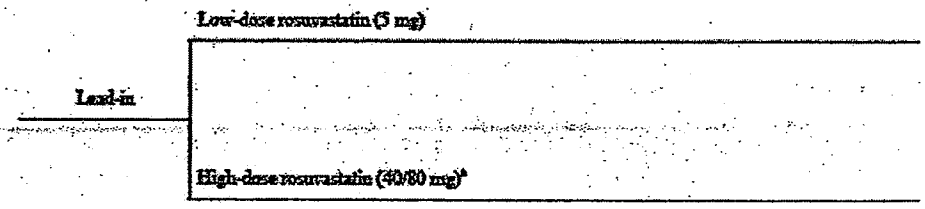
In addition, patients were required to discontinue any cholesterol-lowering medication, to ensure that no residual effect on lipids carried forward into the randomized treatment period.

The treatment period began at randomization at Visit 4 and continued through Visit 16 for a total duration of 104 weeks. The initial visits of the randomized treatment period, Visits 4, 5, and 6, occurred at 2-week intervals. Following Visit 6 up to and including Visit 8, scheduled visits occurred at 4-week intervals. Following Visit 8 up to and including Visit 10, scheduled visits occurred at 8-week intervals. Thereafter, scheduled visits up to and including Visit 16 occurred at 3-month intervals.

Randomization: Eligible patients were randomized in a 1:1 ratio to low-dose (5 mg) or high-dose (40/80 mg) rosuvastatin. 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 40 mg for the full 2-year period, requiring all rosuvastatin 80-mg patients to be back-titrated to rosuvastatin 40 mg.)

Figure 10.1.2.3.1 Study design

	Lead-in period			Randomized treatment												
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
(Week)	(-6)	(-2)	(-1)	(0)	(2)	(4)	(8)	(12)	(20)	(28)	(40)	(52)	(65)	(78)	(91)	(104)
Month										6	9	12	15	18	21	24



10.1.2.4 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Provided signed informed consent prior to performance of any tests or assessments.
2. Males and non-pregnant/nursing females, who were ≥ 18 years of age at Visit 1, and who were able to attend office visits.
3. Had moderate hypercholesterolemia. Patients not on a lipid-lowering therapy at Visit 1 had a fasting LDL-C concentration of ≥ 100 mg/dL (2.59 mmol/L) and < 250 mg/dL (6.47 mmol/L). Patients whose lipid-lowering drugs were discontinued at Visit 1 had to satisfy LDL-C inclusion criteria at randomization.
4. All cholesterol-lowering drugs (including lipid-lowering dietary supplements or food additives) had to be discontinued at Visit 1 (Week -6). Patients taking probucol had to discontinue usage 12 months prior to inclusion in this study.
5. Had 16% to 79% stenosis of one or more carotid arteries or had an atherosclerotic plaque identified on the B-mode image as assessed at Visit 1, by baseline duplex carotid ultrasound, and were unlikely to require endarterectomy during the study. In the latter circumstance, the patient had a pre-screening carotid MRI which confirmed the presence of an atherosclerotic plaque with a lipid-rich necrotic core.
6. Had a confirmatory baseline MRI (preferably at Visit 2, but prior to Visit 4) showing an image quality score of ≥ 3 with an identifiable lesion.
7. Had < 50% of MRI segments showing major calcification (preferably at Visit 2, but prior to Visit 4)
8. Had no contraindications to MRI such as pacemakers, occupations in which metal fragments in the eyes/head are common (unless computed tomography of the head shows no metal foreign bodies), and had a suitable body habitus for ease of entering the scanner

For inclusion into the randomized treatment period of the study, the protocol required that patients had to fulfill the following criteria:

1. Fasting LDL-C concentrations were ≥ 100 mg/dL (2.59 mmol/L) and < 250 mg/dL (6.47 mmol/L), and LDL-C values from Visits 2 and 3 or Visit 2.1 and 3 were within 18% of each other (the higher value was used as the denominator in this calculation). If the percentage was >18%, additional lead-in visits (Visits 3.1, 3.2, and 3.3) could be scheduled to obtain another LDL-C determination. If an additional assessment was made, then the 2 most recent values were used for evaluation of eligibility. The additional assessment(s) was to be approximately 1 week after the Visit 3 or the most recent assessment.
2. Patients should be on the NCEP Step-I diet for at least 4 weeks.

Exclusion Criteria:

1. Use of cholesterol-lowering drugs or lipid-lowering dietary supplements or food additives after Visit 1.
2. History of serious or hypersensitivity reactions to other HMG-CoA reductase inhibitors.
3. Pregnant women, women who were breast-feeding, or women of childbearing potential who were not using chemical or mechanical means of contraception, or who had a positive serum pregnancy test (serum β-human chorionic gonadotropin [β-HCG] analysis).
4. Active arterial disease such as unstable angina, MI, transient ischemic attack (TIA), cerebrovascular accident, coronary artery bypass graft surgery, or angioplasty within 3 months of study entry.
5. History of malignancy, with the exception of patients whose only malignancy was basal- or squamous-cell skin carcinoma or patients who were disease-free for at least 10 years (excluding women with a history of cervical dysplasia unless they had 3 consecutive normal cervical smears recorded prior to entry into the lead-in period).
6. Uncontrolled hypertension, defined as either a mean resting diastolic blood pressure (BP) of > 95 mmHg or a mean resting systolic BP of > 200 mmHg, recorded at any visit during the lead-in period.
7. Fasting serum glucose of > 150 mg/dL (8.33 mmol/L) recorded at any time during the lead-in period, or glycosylated hemoglobin (HgbA1c) > 8% recorded at Visit 1 (patients with a history of diabetes were to be well-controlled).
8. Uncontrolled hypothyroidism, defined as a thyroid-stimulating hormone (TSH) value >1.5 times the upper limits of normal (ULN) at Visit 1 (Week 6) or patients whose thyroid replacement therapy was initiated within the last 3 months.
9. Total occlusion or heavy calcifications on the index side of the carotid artery as assessed via ultrasound.
10. Endarterectomy on the index side performed after Visit 1.
11. History of homozygous familial hypercholesterolemia or known Type III hyperlipoproteinemia (familial dysbetalipoproteinemia).
12. Use of concomitant medications (including astemizole, atorvastatin, azathioprine, carbamazepine, cerivastatin, cholestyramine, cisapride, clofibrate, colestipol, cyclosporine, erythromycin, fenofibrate, fluconazole, fluvastatin, gemfibrozil, itraconazole, ketoconazole, lovastatin, fish oils, immune globulin, niacin, orlistat, phenobarbital, phenytoin, pravastatin, probucol, psyllium, rifampin, simvastatin, sulfisoxazole, terfenadine, troglitazone, pioglitazone, rosiglitazone, and warfarin).
13. History of alcohol and/or drug abuse.
14. Active liver disease or hepatic dysfunction, as defined by elevations ≥ 1.5 times the ULN of any of the following liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin at any visit prior to randomization.
15. Elevations in serum creatine kinase (CK) > 3 times the ULN prior to randomization.
16. Elevations in serum creatinine ≥ 2.5 mg/dL (220 µmol/L) prior to randomization.
17. Participation in another investigational study, < 4 weeks before enrollment in the

lead-in period.

18. Any patient randomized to treatment who subsequently withdrew from this or a previous rosuvastatin study.
19. Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would have compromised the patient's safety or successful participation in the study.
20. Treatment with lipid-lowering therapy for ≥ 1 year, with on-therapy LDL-C < 100 mg/dL (2.59 mmol/L).
21. Fasting TG > 400 mg/dL (4.52 mmol/L).

10.1.2.5 Amendments and Post Hoc Changes

Amendment 1 (28 September 1999)

The following changes and corrections were made to the protocol before the start of patient recruitment:

- the interim analysis was removed
- changes in MRI schedule. MRI data from Visits, 2, 4, 10 (Month 6), 12 (Month 12), and 16 (Month 24) were to be analyzed

Amendment 2 (December 8, 1999)

The following changes and corrections were made to the protocol before the start of patient recruitment:

- Hepatic lipase test replaced with lipoprotein particle size assessment
- Procedural change – subjects whose LDL-C is ≤ 50 mg/dL will remain at the 40 mg dose level or be titrated down from 80 mg.
- Prescreening visit allowed for lipid assessment.
- The period between Visit 1 and Visit 2 may have been reduced from 4 weeks to 2 weeks if subjects were on Step-I therapy and not currently receiving any lipid-lowering medication.
- Inclusion criteria were amended to include the following – all cholesterol-lowering drugs (including lipid-lowering dietary supplements or food additives) must be discontinued at Visit 1. Subjects taking probucol should have discontinued its use 12 months before inclusion in this trial.
- Digoxin removed as an excluded medication; orlistat added as an excluded medication.

Amendment 3 (30 March 2000)

The following changes were made to the protocol after the start of patient recruitment:

- The investigator was allowed to perform lipid determination for up to 3 weeks prior to Visit 1 instead of the previous 1 week before Visit 1.
- After Visit 6, subjects who had LDL-C concentrations > 50mg/dL for 2-3 subsequent visits or presented no safety or tolerability issues were permitted to have the blood draw at the time of the scheduled visit.
- Duplex ultrasounds of the carotid arteries were to be performed at the pre-screening visit for some patients. A pre-screen carotid ultrasound can be performed at anytime between the pre-screen visit and Visit 1 for those subjects who never had a carotid artery ultrasound performed in the past or have not had an ultrasound in the previous 2 years.

This pre-screen ultrasound will be considered as the Visit 1 ultrasound. For all others, the Visit 1 carotid ultrasound can be performed at anytime between Visit 1 and Visit 2.

Amendment 4 (5 July 2000)
The following change was made to the protocol after the start of patient recruitment:

- Change to the inclusion criteria to allow subjects with LDL-C < 100 mg/dL or with < 16% stenosis provided the presence of atherosclerotic plaque is confirmed by both ultrasound and pre-screen procedures.

Amendment 5 (21 May 2001)
The following change was made to the protocol after the start of patient recruitment:

- Added an additional investigator site and extended study timelines.

Amendment 6 (28 May 2002)
The following changes were made to the protocol after the start of patient recruitment:

- Subjects receiving 40 mg in the high-dose group were to receive 40 mg for the full 2-year study period. Subjects who were previously randomized to 80 mg were to be back titrated to the 40 mg dose.
- Language was added to the informed consent concerning a possible side effect of myopathy.
- History of serious hypersensitivity reactions to other HMG-CoA reductase inhibitors was added to the exclusion criteria.
- Clinical chemistry tests were expanded to include the determination of the concentration of creatinine.
- Urinalysis was performed at additional visit – Visits 1, 3, 7, 9, 10, 11, 12, 13, 14, 15, and 16.

Changes to planned analyses – before database lock:

- Non-compliance with trial medication would be based on 2 consecutive visits rather than the first occurrence. Changed to non-compliance will be based on the first occurrence.
- "Carotid near wall and far wall intima media thickness data would be analyzed in a blinded fashion at the end of the study". Only far wall intima media thickness data were obtained from the carotid ultrasound procedure.
- An analysis on the PP population would be carried out to confirm results from the primary analysis. The analysis on the PP population was not to be carried out. However, protocol violations and deviations were to be identified programmatically, the protocol violation/deviation log was to be reviewed, and protocol violations and deviations were to be flagged in the analysis dataset. If there were significant numbers of patients with protocol violations and/or deviations of the type that would exclude data from per-protocol analyses, consideration was to be given to carrying out analyses on the PP-observed populations in addition to pre-planned analyses on the ITT population.
- ANCOVA was to be used as the primary method of analysis for percent change in lesion volume with degree of stenosis at baseline, center, and treatment group terms in the model. Inclusion criterion 5 stated that patients had to "have either 16% to 79% stenosis

of ≥ 1 carotid arteries, or have an atherosclerotic plaque identified on the B-mode image as assessed at Visit 1 by baseline duplex carotid ultrasound". The study team removed degree of stenosis from the statistical model.

- The effect of center was not to be included as a factor in the statistical model, although it was stipulated in the protocol. The original protocol proposed a single research site, but the 5th protocol amendment permitted the initiation of a 2nd center. It was argued that the effect of center should not be included in the statistical model, but was to be explored to ensure that the effect of center was not significant.
- Indicated that the primary endpoint would be "percent change" in carotid artery wall volume; however, the study team decided to use the "absolute change" in carotid artery wall volume as the primary endpoint and to explore "percentage change" in carotid artery wall volume separately. Baseline was used as a covariate.
- A secondary endpoint was added to analyze the change from baseline in "percent obstructive volume".
- The secondary endpoints involving the percentage of patients reaching NCEP III were not specifically specified in the current protocol, but were summarized for all applicable time points as specified in the SAP.

Changes to planned analyses – after database lock:

- Additional presentations of MRI data including only patients with data at all 4 visits.
- Calculating an average baseline rather than using only Visit 4 for MRI data for summaries including all 4 visits.
- For compositional indices, additional presentations for patients with the composition present at baseline.
- Summary of numbers of patients that regressed, progressed or stayed the same for changes in MRI parameters.
- For ultrasound data calculating an average baseline rather than using only Visit 4 for far wall mean of mean intima media thickness.
- For ultrasound data, only presenting baseline and Month 24 and data for patients with all 4 visits for far wall mean of mean intima media thickness.
- Calculating time-weighted average lipid values in addition to LOCF.
- For percent change from baseline in lipid and lipoprotein analyses, ANOVA was used to calculate differences between the groups instead of ANCOVA.

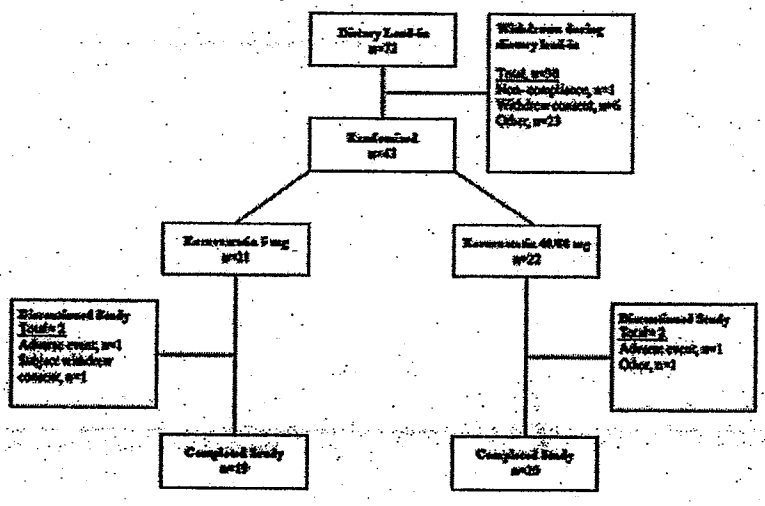
10.1.2.6 Results

10.1.2.6.1 Disposition

A total of 73 patients entered the dietary lead-in period, and 43 patients from 2 centers were randomized to treatment, of whom 42 were analyzed for efficacy. Of those subjects who were withdrawn during dietary lead-in (n=30), 1 was withdrawn due to non-compliance, 6 withdrew consent, and 23 were withdrawn due to "other". This included: carotid stenosis of an artery < 16% bilaterally; subject was claustrophobic and could not have MRI; TSH greater than 1.5 x ULN; abnormal lab values; LDL-C < 100 mg/dL at Visit 3; glucose > 150 mg/dL; sponsor's request due to subject's high statin dosage (atorvastatin 80 mg). For sixteen of the 23 subjects who were withdrawn for "other", no specific explanation for their withdrawal was given.

Of the 43 patients who were randomized, 21 were randomized to rosuvastatin 5 mg and 22 were randomized to rosuvastatin 40/80 mg. Treatment discontinuation rates were similar in the 2 groups – two patients discontinued from the rosuvastatin 5 mg group, one for adverse event and one who withdrew consent; two patients discontinued from the rosuvastatin 40/80 mg group, one for adverse event and one for other ("sponsor request for withdrawal"). Nineteen subjects from the rosuvastatin 5 mg group and 20 subjects from the rosuvastatin 40/80 mg group completed the study.

Figure 10.1.2.6.1.1: Summary of patients' disposition



10.1.2.6.2 Demographics

Table 10.1.2.6.2.1: Demographic and baseline characteristics of the full data set

DEMOGRAPHIC OR BASELINE CHARACTERISTIC	TREATMENT GROUP		
	Rosuvastatin 5 mg (N=21)	Rosuvastatin 40/80 mg (N=22)	Total (N=43)
Gender			
Male	13 (61.9)	16 (72.7)	29 (67.4)
Female	8 (38.1)	6 (27.3)	14 (32.6)
Age			
Mean (SD)	65.0 (6.5)	64.6 (12.4)	64.8 (9.8)
Range	53, 75	40, 78	40, 78
18-64 (%)	10 (47.6)	10 (45.5)	20 (46.5)
≥ 65 (%)	11 (52.4)	12 (54.5)	23 (53.5)
Race			
Caucasian	20 (95.2)	22 (100.0)	42 (97.7)
Asian	1 (4.8)	0	1 (2.3)
Weight (kg)			
Mean (SD)	85.05 (19.01)	80.75 (16.59)	82.85 (17.73)
Range	54.9, 124.9	52.2, 112.6	52.2, 124.9
BMI (kg/m^2)			
N	19	21	40
Mean (SD)	28.73 (4.97)	27.45 (4.51)	28.06 (4.72)
Range	19.8, 36.3	22.0, 40.6	19.8, 40.6
Not calculated	2	1	3
Renal function, n (%)			
Normal	9 (47.6)	7 (31.8)	17 (39.5)
Mild	10 9 (42.9)	12 (54.5)	21 (48.8)
Moderate	11 1 (4.8)	3 (13.6)	4 (9.3)
Severe	12 0	0	0
Missing	13 1 (4.8)	0	1 (2.3)
CHD risk factors, n			
Atherosclerotic disease	14	16	30
Male ≥ 45; female ≥ 55	21	20	41
Premature menopause w/o estrogen	1	0	1
Family history of premature CHD/PVD	2	5	7
Current cigarette smoker	4	5	9
Hypertension	15	14	29
Diabetes mellitus	3	5	8
HDL-C < 40 mg/dL	6	8	14
HDL-C ≥ 60 mg/dL	2	2	4
Atherosclerosis history, n	14	15	29
Family history of HeFH, n	3	4	7

Concomitant medication use was comparable between treatment groups, with the exception of slightly more subjects on low dose rosuvastatin who were also taking calcium channel blockers and/or beta blockers:

Table 10.1.2.6.2.2: Concomitant medication use

MEDICATION	ROSUVASTATIN 5 MG (N=21)	ROSUVASTATIN 40/80 MG (N=22)
Calcium channel blocker	4	2
Beta blocker	7	4
Aspirin	19	19
ACE inhibitor	5	12
ARB	2	1
NSAID	12	8
Organic nitrates	1	1
Niacin	0	1
Plavix	0	1

10.1.2.6.3 Efficacy Findings

10.1.2.6.3.1 Primary Endpoint – Change from baseline in bilateral carotid artery volume at Week 104

There was no significant difference between the 2 dose groups in the change from baseline in bilateral carotid artery 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.

Table 10.1.2.6.3.1: MRI morphological indices – change from baseline in bilateral carotid artery wall volume (mm^3)

WEEK	STATISTIC	TREATMENT GROUP	
		Rosuvastatin 5 mg	Rosuvastatin 40/80 mg
104	N	15	20
	Mean (SD)	3.90 (39.5)	1.28 (43.9)
	Median	7.2	-6.2
	Min/Max	-59.1/69.4	-97.5/90.9
	t-test p-value	0.708	0.898

Table 10.1.2.6.3.2: MRI morphological indices – ANCOVA for change from baseline in bilateral carotid artery wall volume

WEEK	STATISTIC	TREATMENT GROUP	
		Rosuvastatin 5 mg	Rosuvastatin 40/80 mg
104	N	15	20
	LSMeans	3.89	1.29
	SE	11.12	9.61
	Difference in LSMean	NA	-2.59
	SE of difference	NA	14.79
	LCL	NA	-32.72
	UCL	NA	27.53
	p-value	NA	0.862

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, LDL-C/HDL-C, nonHDL-C/HDL-C) except for HDL-C, TG, and Apo A-1 which did not show significant changes from baseline in the low-dose group.
- Percentage change from baseline in specialty lipid parameters (ApoB, ApoA-1, Lp[a], ApoB/ApoA-1) except for lipoprotein (a) and ApoA-1, where there were no significant differences between the 2 dose groups.

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

Table 10.1.2.6.3.3: Results for secondary efficacy variables

VARIABLE	ROSUVASTATIN 5 MG (N=15)	ROSUVASTATIN 40/80 MG (N=20)
Change in carotid artery wall volume (mm^3) (baseline to week 104)		
Mean (SD)	-3.71 (29.08)	2.55 (36.53)
Median	1.5	-5.2
Min, max	-57.2, 36.2	-63.9, 90.9
t-test p-value	0.629	0.758
LS Mean change	-3.43 (8.96)	2.35 (7.72)
Treatment comparisons		
LSMeans (SE) of difference		5.78 (12.00)
LCL, UCL		-18.67, 30.23
Treatment p-value		0.633
Change in carotid artery % obstructive volume (baseline to week 104)		
Mean (SD)	0.05 (3.62)	0.07 (3.81)
Median	0.6	-0.4
Min, max	-9.0, 3.8	-6.7, 10.1

VARIABLE	ROSUVASTATIN 5 MG (N=15)	ROSUVASTATIN 40/80 MG (N=20)
t-test p-value	0.954	0.931
LS Mean change	0.01 (0.98)	0.11 (0.84)
Treatment comparisons		
LSMeans (SE) of difference		0.1 (1.3)
LCL, UCL		-2.53, 2.73
Treatment p-value		0.939
Change in carotid artery maximum wall thickness (baseline to week 104)		
Mean	-0.09 (0.52)	0.22 (0.47)
Median	-0.1	0.2
Min, max	-0.9, 1.2	-0.8, 1.1
t-test p-value	0.500	0.047
LS Mean change	-0.1 (0.1)	0.21 (0.11)
Treatment comparisons		
LSMeans (SE) of difference		0.29 (0.17)
LCL, UCL		-0.06, 0.64
Treatment p-value		0.106
Change in carotid artery minimum lumen area (baseline to week 104)		
Mean	-0.40 (3.51)	-0.84 (3.79)
Median	-0.5	0.1
Min, max	-7.7, 7.3	-10.4, 6.9
t-test p-value	0.666	0.337
LS Mean change	-0.37 (0.94)	-0.86 (0.81)
Treatment comparisons		
LSMeans (SE) of difference		-0.50 (1.24)
LCL, UCL		-3.02, 2.03
Treatment p-value		0.692
Change in bilateral common carotid far wall mean IMT (mm) (baseline to week 104)		
N	12	16
Mean	-0.007 (0.098)	-0.007 (0.052)
Median	0.010	-0.002
Min, max	-0.30, 0.08	-0.09, 0.10
Within group p-value	0.819	0.613
LS Mean change	-0.006 (0.021)	-0.007 (0.018)
Treatment comparisons		
LSMeans (SE) of difference		-0.001 (0.028)
LCL, UCL		-0.057, 0.056
Treatment p-value		0.981

Table 10.1.2.6.3.4: Percent change in lipid values from baseline (LOCF)

PARAMETER	ROSUVASTATIN 5 MG (N=20)	ROSUVASTATIN 40/80 MG (N=22)
LDL-C (mg/dL) (baseline to week 104)		
Mean (SD)	-38.3 (9.6)	-56.0 (23.9)
p-value	<0.001	<0.001

PARAMETER	ROSUVASTATIN 5 MG (N=20)	ROSUVASTATIN 40/80 MG (N=22)
Treatment comparisons		
LSMeans (SE) of difference		-21.7 (4.1)
Treatment p-value		<0.001
TC (mg/dL)		
(baseline to week 104)		
Mean (SD)	-26.1 (8.7)	-37.7 (17.8)
p-value	<0.001	<0.001
Treatment comparisons		
LSMeans (SE) of difference		-15.50 (3.4)
Treatment p-value		<0.001
HDL-C (mg/dL)		
(baseline to week 104)		
Mean (SD)	0.28 (12.3)	9.8 (19.1)
p-value	0.920	0.025
Treatment comparisons		
LSMeans (SE) of difference		6.5 (3.1)
Treatment p-value		0.041
TG (mg/dL)		
(baseline to week 104)		
Mean (SD)	-5.7 (25.3)	-16.5 (29.4)
p-value	0.329	0.016
Treatment comparisons		
LSMeans (SE) of difference		-15.3 (5.2)
Treatment p-value		0.006
Non-HDL-C (mg/dL)		
(baseline to week 104)		
Mean (SD)	-32.4 (9.2)	-49.6 (21.5)
p-value	<0.001	<0.001
Treatment comparisons		
LSMeans (SE) of difference		-21.3 (4.0)
Treatment p-value		<0.001
LDL-C/HDL-C ratio		
(baseline to week 104)		
Mean (SD)	-38.0 (9.6)	-59.4 (21.3)
p-value	<0.001	<0.001
Treatment comparisons		
LSMeans (SE) of difference		-23.9 (3.8)
Treatment p-value		<0.001
TC/HDL-C ratio		
(baseline to week 104)		
Mean (SD)	-25.8 (10.1)	-42.38 (16.6)
p-value	<0.001	<0.001
Treatment comparisons		
LSMeans (SE) of difference		-18.9 (3.4)
Treatment p-value		<0.001

10.1.2.6.4.1 Deaths

There was one death that occurred during randomized treatment.

Subject 0216/0001 was a 73 year-old Caucasian male with hypercholesterolemia. The subject was enrolled and randomized to rosuvastatin 40 mg. On Day 39 of treatment, the subject experienced a pontine stroke which required hospitalization. The subject was taken off study drug for 9 days during hospitalization and was treated with aspirin 81 mg and clopidogrel. Concomitant medication before the episode included isosorbide, atenolol, amlodipine, and aspirin 325 mg.

The subject experienced a second episode of pontine stroke on Day 221 requiring prolonged hospitalization. The subject was withdrawn from the study and was to be treated with warfarin indefinitely.

The subject was readmitted to the hospital approximately one month after withdrawal from study with a myocardial infarction. He developed respiratory distress and died 3 days after admission. Diagnoses were acute respiratory failure, acute myocardial infarction, critical aortic stenosis and super therapeutic INR.

10.1.2.6.4.2 Other Serious Adverse Events

During the randomized treatment phase, 3 (14.3%) patients in the low-dose group and 1 (4.5%) patient in the high-dose group had a treatment-emergent SAE (the subject from the high-dose group is the same patient who died and is discussed above).

Table 10.1.2.6.4-1: Serious adverse events by Preferred Term

PREFERRED TERM	ROSUVASTATIN 5 MG (N=21) N (%)	ROSUVASTATIN 40/80 MG (N=22) N (%)
Total # with SAE	**3 (14.3)**	**1 (4.5)**
Arthritis	1 (4.8)	0
UTI	1 (4.8)	0
Bladder neck obstruction	1 (4.8)	0
Atrial fibrillation	1 (4.8)	0
Brainstem infarction	0	1 (4.5)
Myocardial infarction	0	1 (4.5)

A brief summary of the narratives that were provided for the SAEs is shown in the table below:

Table 10.1.2.6.4-2: Patient narratives for SAEs

PATIENT ID#	AGE	SEX	RELEVANT HISTORY	PREFERRED TERM	TREATMENT DAY	OUTCOME
Low-dose rosuvastatin						
0216/0003	66	Female	Hypercholesterolemia; DJD	Arthritis; knee replacement	257	Recovered
0216/0024	72	Male	None	Urinary tract infection	94	Recovered
				Bladder neck obstruction	378	Recovered
0216/0029	70	Female	Heart disease with atrial fibrillation; breast cancer; cigarette smoking	Atrial fibrillation	385	Recovered
High-dose rosuvastatin						
0216/001	73	Male	Hypercholesterolemia	Brainstem infarction	39, 221	Recovered Ongoing
				Myocardial infarction	252	Died

10.1.2.6.4.3 Dropouts and Other Significant Adverse Events

During the randomized treatment phase, 1 patient in the low-dose group and 1 patient in the high-dose group had a discontinuation due to adverse event. Both of these DAEs were also categorized as SAEs.

Table 10.1.2.6.4.3-1 presents a summary of adverse events leading to withdrawal.

Table 10.1.2.6.4.3-1: Adverse events leading to permanent treatment discontinuation

PATIENT ID#	AGE	SEX	RELEVANT HISTORY	PREFERRED TERM	TREATMENT DAY	OUTCOME
Low-dose rosuvastatin						
0216/0029	70	Female	Heart disease with atrial fibrillation; breast cancer; cigarette smoking	Atrial fibrillation	385	Recovered
High-dose rosuvastatin						
0216/001	73	Male	Hypercholesterolemia	Brainstem infarction	221	Patient died

10.1.2.6.4.4 All Treatment Emergent Adverse Events Reported

The most common treatment-emergent AEs, summarized by SOC and preferred term for both treatment groups are shown in Table 10.1.2.6.4.4-1 below:

Table 10.1.2.6.4.4-1: Number and percent of rosuvastatin patients who had a treatment-emergent adverse event

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 5 MG (N=21) N (%)	ROSUVASTATIN 40/80 MG (N=22) N (%)
Any AE	**17 (81.0)**	**21 (95.5)**
Blood and lymphatic system disorders	**0**	**1 (4.5)**
Anemia		1 (4.5)
Cardiac disorders	**2 (9.5)**	**3 (13.6)**
Angina pectoris	1 (4.8)	2 (9.1)
Atrial fibrillation	1 (4.8)	
Myocardial infarction		1 (4.5)
Myocardial ischemia		1 (4.5)
Ear and labyrinth disorders	**1 (4.8)**	**3 (13.6)**
Cerumen impaction		1 (4.5)
Meniere's disease		1 (4.5)
Vertigo	1 (4.8)	1 (4.5)
Endocrine disorders	**0**	**1 (4.5)**
Thyroid nodule		1 (4.5)
Eye disorders	**1 (4.8)**	**3 (13.6)**
Cataract	1 (4.8)	1 (4.5)
Eye pruritus		1 (4.5)
Macular degeneration		1 (4.5)
Gastrointestinal disorders	**4 (19.0)**	**9 (40.9)**
Colonic polyp		1 (4.5)
Diarrhea	1 (4.8)	1 (4.5)
Dyspepsia		1 (4.5)
Gastritis		1 (4.5)
Gastrointestinal discomfort		2 (9.1)
Hemorrhoids	1 (4.8)	1 (4.5)
Inguinal hernia		2 (9.1)
Nausea		1 (4.5)
Periodontal disease	2 (9.5)	
Reflux gastritis	1 (4.8)	1 (4.5)
General disorders and administration site conditions	**4**	**4 (18.2)**
Asthenia	1 (4.8)	
Fatigue	1 (4.8)	2 (9.1)
Peripheral edema	1 (4.8)	
Pyrexia	1 (4.8)	
Rigors	1 (4.8)	
Thirst		2 (9.1)
Infections and infestations	**5 (23.8)**	**13 (59.1)**
Arthritis infective		1 (4.5)
Bronchitis	1 (4.8)	1 (4.5)
Diverticulitis		1 (4.5)

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 5 MG (N=21) N (%)	ROSUVASTATIN 40/80 MG (N=22) N (%)
Gingival infection	1 (4.8)	
Influenza	1 (4.8)	4 (18.2)
Laryngitis		1 (4.5)
Localized infection		1 (4.5)
Nasopharyngitis	2 (9.5)	3 (13.6)
Pneumonia		1 (4.5)
Pneumonia (RSV)		1 (4.5)
Respiratory tract infection		1 (4.5)
Sinusitis		1 (4.5)
Tooth infection		1 (4.5)
Upper respiratory tract infection	1 (4.8)	1 (4.5)
Urinary tract infection	1 (4.8)	4 (18.2)
Injury, poisoning and procedural complications	**4**	**1 (4.5)**
Cartilage injury	1 (4.8)	
Clavicle fracture	1 (4.8)	
Meniscus lesion	1 (4.8)	
Muscle strain	1 (4.8)	
Periorbital hematoma		1 (4.5)
Investigations	**1 (4.8)**	**5 (22.7)**
ALT increased		1 (4.5)
Bacteria urine	1 (4.8)	
Blood creatinine increased		1 (4.5)
Blood glucose increased		1 (4.5)
Cardiac murmur		1 (4.5)
HbA1c increased		1 (4.5)
Heart rate irregular		1 (4.5)
PSA increased		1 (4.5)
Protein urine present		1 (4.5)
Metabolism and nutrition disorders	**1 (4.8)**	**2 (9.1)**
Diabetes mellitus	1 (4.8)	
Gout		1 (4.5)
Increased appetite		1 (4.5)
Musculoskeletal and connective tissue disorders	**8 (38.1)**	**13 (59.1)**
Arthralgia	2 (9.5)	4 (18.2)
Arthritis	1 (4.8)	
Back pain	1 (4.8)	
Buttock pain	1 (4.8)	
Dupuytren's contracture		1 (4.5)
Exostosis	1 (4.8)	
Groin pain		1 (4.5)
Intervertebral disc protrusion	1 (4.8)	1 (4.5)
Localized osteoarthritis	1 (4.8)	
Muscle cramp		1 (4.5)
Muscle fatigue		1 (4.5)
Musculoskeletal stiffness		1 (4.5)
Myalgia		2 (9.1)
Neck pain		1 (4.5)
Osteoarthritis	1 (4.8)	1 (4.5)

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 5 MG (N=21) N (%)	ROSUVASTATIN 40/80 MG (N=22) N (%)
Osteoporosis		1 (4.5)
Pain in extremity	2 (9.5)	5 (22.7)
Periarthritis		1 (4.5)
Tendonitis	1 (4.8)	
Neoplasms	**2 (9.5)**	**0**
Prostate cancer	2 (9.5)	
Nervous system disorders	**3 (14.3)**	**6**
Brain stem infarction		1 (4.5)
Headache	1 (4.8)	2 (9.1)
Hypoaesthesia		1 (4.5)
Nerve compression	1 (4.8)	
Sciatica	1 (4.8)	
Sinus headache		1 (4.5)
Somnolence		1 (4.5)
Psychiatric disorders	**1 (4.8)**	**4 (18.2)**
Anxiety		1 (4.5)
Depression		2 (9.1)
Stress symptoms	1 (4.8)	1 (4.5)
Renal and urinary disorders	**2 (9.5)**	**1 (4.5)**
Bladder neck obstruction	1 (4.8)	
Hematuria	1 (4.8)	1 (4.5)
Urinary incontinence	1 (4.8)	
Respiratory, thoracic and mediastinal disorders	**0**	**2 (9.1)**
Hoarseness		1 (4.5)
Postnasal drip		1 (4.5)
Upper respiratory tract congestion		1 (4.5)
Skin and subcutaneous tissue disorders	**0**	**3 (13.6)**
Face edema		1 (4.5)
Rash		1 (4.5)
Urticaria		1 (4.5)
Vascular disorders	**7 (33.3)**	**3 (13.6)**
Hot flush	1 (4.8)	
Hypertension	4 (19.0)	2 (9.1)
Hypotension	1 (4.8)	
Intermittent claudication	1 (4.8)	1 (4.5)
Varicose vein	1 (4.8)	

Some patients (n=15) randomized to the high-dose group received both 40 mg and 80 mg. The only treatment-emergent AEs that occurred in 2 or more patients on 80 mg were pain in extremity (n=3), angina pectoris (n=2), arthralgia (n=2), headache (n=2), depression (n=2), and urinary tract infection (n=2).

10.1.2.6.4.5 Other significant adverse events

Other significant adverse events include hepatic, skeletal muscle, and renal events. Examination of AEs suggestive of liver disturbances, such as elevations in ALT and hepatic dysfunction revealed no clinically significant symptom complex. No muscle-related AEs associated with CK >10 x ULN occurred. No AEs suggestive of clinically significant renal dysfunction occurred.

10.1.2.6.4.6 Laboratory values

Hematology

Table 10.1.2.6.4.6-1: Hematology values outside of reference range

		HB	HCT	RBC	WBC	PLATE	NEUTR	EOSIN	LYMPH	BASO
TREATMENT										
ROSUVA 5 MG	NO. OF PATIENTS	6	11	18	6	2	2	0	10	0
	NO. ABOVE REFERENCE RANGE	0	1	0	1	1	0	0	1	0
	% ABOVE REFERENCE RANGE	0.0	9.1	0.0	16.7	50.0	100.0	0	10.0	0
	NO. BELOW REFERENCE RANGE	6	10	18	5	1	0	0	0	0
	% BELOW REFERENCE RANGE	100.0	90.9	100.0	83.3	50.0	0.0	0	90.0	0
ROSUVA 40/80 MG	NO. OF PATIENTS	9	11	18	5	5	10	0	11	0
	NO. ABOVE REFERENCE RANGE	0	0	0	2	1	9	0	3	0
	% ABOVE REFERENCE RANGE	0.0	0.0	0.0	40.0	20.0	90.0	0	27.3	0
	NO. BELOW REFERENCE RANGE	9	11	18	3	4	1	0	8	0
	% BELOW REFERENCE RANGE	100.0	100.0	100.0	60.0	80.0	10.0	0	72.7	0

		EOSINO	MONO	MCV	MCH	MCHC	RDW	BASOC
TREATMENT								
ROSUVA 5 MG	NO. OF PATIENTS	3	0	5	15	4	5	2
	NO. ABOVE REFERENCE RANGE	3	0	4	14	0	5	2
	% ABOVE REFERENCE RANGE	100.0	0	80.0	93.3	0.0	100.0	100.0
	NO. BELOW REFERENCE RANGE	0	0	1	1	4	0	0
	% BELOW REFERENCE RANGE	0.0	0	20.0	6.7	100.0	0.0	0.0
ROSUVA 40/80 MG	NO. OF PATIENTS	0	0	5	35	6	5	6
	NO. ABOVE REFERENCE RANGE	0	0	5	35	0	5	6
	% ABOVE REFERENCE RANGE	0	0	100.0	100.0	0.0	100.0	100.0
	NO. BELOW REFERENCE RANGE	0	0	0	0	6	0	0
	% BELOW REFERENCE RANGE	0	0	0.0	0.0	100.0	0.0	0.0

Table 10.1.2.6.4.6-2: Clinically significant elevations of ALT by rosuvastatin dose

		ROSUVA 5 MG	ROSUVA 40 MG	ROSUVA 80 MG
ALT >3 X ULN	NO. OF PATIENTS	21	22	15
	NO. WITH SIG. ELEVATION IN RANDOM PHASE	0	0	1
	% WITH SIG. ELEVATION IN RANDOM PHASE	0	0	6.7
	NO. WITH SIG. ELEV. AT BASE & IN RANDOM PHASE	0	0	0

Table 10.1.2.6.4.6-3: Clinically significant elevations of CK by rosuvastatin dose

CK >5 X ULN	NO. OF PATIENTS	21	22	15
	NO. WITH SIG. ELEVATION IN RANDOM PHASE	0	0	0
	% WITH SIG. ELEVATION IN RANDOM PHASE	0	0	0
	NO. WITH SIG. ELEV. AT BASE & IN RANDOM PHASE	0	0	0
CK >10 X ULN	NO. OF PATIENTS	21	22	15
	NO. WITH SIG. ELEVATION IN RANDOM PHASE	0	0	0

Table 10.1.2.6.4.6-4: Number (% of rosuvastatin-treated patients who had elevations in serum creatinine

	Rosuvastatin 5 mg (n=21)		Rosuvastatin 40/80 mg* (n=22)	
	N	(%)	n	(%)
>30% increase from baseline	0	0	1	4.5
>100% increase from baseline	0	0	0	0

The patient in the high-dose group (patient 0216/0018) had an increase of >50% from baseline while on 80 mg and greater than 30% while on 40 mg. He had persistent, moderate elevations of AST and ALT from Week 10 onward, which were reported as AEs. This patient was treated for infectious arthritis during the study. He had a history of hypothyroidism (treated), frozen shoulder, and depression. He also had intermittent proteinuria, not present on his last visit.

Urinalysis

Five patients had a shift in urine protein from none or trace at baseline to ≥ ++ at any time during the study (Patients 0216/0002, 0216/0018, 0216/0030, 0216/0040, 0216/0041). All 5 of these patients were in the high-dose (40/80 mg) group. Of these, 3 did not have proteinuria

at the end of the study. Two had ≥ ++ urine protein at the last study visit.

- Patient 0216/0002 was a 77-year-old female with a history of UTI. She showed proteinuria during randomized treatment. Her creatinine remained normal. Her final urinalysis also showed + blood.
- Patient 0216/0041 was a 72-year-old male. He had + to +++ proteinuria from Week 20 onward in association with similar amounts of blood. Creatinine remained normal. Medical history was unremarkable; there was no diabetes or hypertension, and no history of bladder or prostate disease that might have accounted for the urinary findings.

Three patients had a shift in urine blood from none or trace at baseline to ≥ ++ at any time during the study. Of these patients, 1 (Patient 0216/0024) was in the low-dose group and 2 (patients 0216/0033 and 0216/0041) were in the high-dose group. Only patient 0216/0041 had urinary blood present at the last visit; this patient is discussed above.

10.1.2.6.4.6 Vital signs

There were no clinically meaningful changes in mean systolic BP, mean diastolic BP or heart rate throughout the study.

10.1.2.6.4.7 ECG

One patient (0216/0009) had a clinically meaningful ECG change (inferior ischemia) at 52 weeks which was not present at 104 weeks.

10.1.2.6.4.8 Extent of exposure

Table 10.1.2.6.4.8-1: Summary of extent of exposure

	Rosuvastatin 5 mg (n=21)	Rosuvastatin 40/80 mg (n=22)
Duration of treatment in days		
Mean	685.6	679.1
Standard deviation	144.02	167.95
Median	728	729
Min	114	104
Max	739	747
Duration of treatment in weeks; n (%)		
0<12	0	0
12<20	1 (4.8)	1 (4.5)
20<28	0	0
28<40	0	1 (4.5)
40<52	0	0
52<65	1 (4.8)	0
65<78	0	0
78<91	0	0
91<104	7 (33.3)	5 (22.7)
104+	12 (57.1)	15 (68.2)

10.1.2.6.4.9 Study schedule

Table 10.1.2.6.4.9-1: Study schedule

	Lead-in period			Randomized treatment period												
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Month										6	9	12	15	18	21	24
Week No.	-6	-2	-1	0	2	4	8	12	20	28	40	52	65	78	91	104
Entry criteria	X			X												
Informed consent	X															
Dietary counsel	X			X			X	X	X	X	X	X	X	X	X	X
Medical history	X															
Chest X-ray film[a]	X															
Physical exam and vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standard lipids: fasting TC, TG, LDL-C, and HDL-C[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specialty lipids ApoB, ApoA-I, LP(a)				X					X			X				X
Full clinical chemistry[d]	X		X							X		X		X		X
Liver function tests, CK, creatinine[e]				X	X	X	X	X	X		X		X		X	
Hematology	X		X							X		X		X		X
Urinalysis	X		X				X		X	X	X	X	X	X	X	X
HgbA1c[f]	X											X		X		X
Lipoprotein particle size				X								X				X
Homocysteine				X								X				X
C-reactive protein				X						X		X				X
IL-6				X						X		X				X

	Lead-in period			Randomized treatment period												
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Month										6	9	12	15	18	21	24
Week No.	-6	-2	-1	0	2	4	8	12	20	28	40	52	65	78	91	104
Pregnancy test[g]	X		X							X		X		X		X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12 lead)		X										X				X
Drug dispensing				X	X	X	X	X	X	X	X	X	X	X	X	
Compliance check					X	X	X	X	X	X	X	X	X	X	X	X
Carotid ultrasound[h]	X			X						X		X				X
MRI[i]		X		X						X		X				X
Carotid lesion biopsy[j]																

Patients who at Visit 1 were not currently on any lipid-lowering therapy and were on a stable diet had the period between Visit 1 and Visit 2 shortened by 2 weeks.

[a] Optional for patients ≥50 years of age, and who did not have a chest X-ray film in the previous 12 months.

[b] Physical exam was performed at Visits 2, 12, and 16. Height was measured at Visit 2. Vital signs: weight, blood pressure, and resting pulse were taken at every visit.

[c] Additional lipid determinations were allowed: A Pre-screen Visit was performed up to 3 weeks before Visit 1, a Visit 2.1 for patients previously on a lipid-lowering therapy with an LDL-C <100 mg/dl at Visit 2, and Visits 3.1 to 3.3 for patients whose LDL-C values were not within 18% of each other at Visit 3. A reserve sample from the chemistry or lipid assessments at Visits 4, 6, 8, 12, and 16 was maintained at the central laboratory.

[d] Serum T_4 and TSH were also determined at Visit 1.

[e] AST, ALT, CK, and creatinine were performed from the full chemistry sample at appropriate visits.

[f] Patients with a history of diabetes mellitus or a fasting blood glucose concentration of >120 mg/dL at Visit 1, had their concentration of Hemoglobin A1c (HgbA1c) measured at Visits 1, 12, 14, and 16.

[g] Required for women of childbearing potential. No additional blood was to be drawn; the full chemistry sample was to be utilized.

[h] Pre-screen carotid ultrasound was performed anytime between Pre-screen Visit and Visit 1 for those patients who never had a carotid artery ultrasound performed in the past or did not have an ultrasound in the previous 2 years. This pre-screen carotid ultrasound was considered as the Visit 1 ultrasound. For all others, Visit 1 carotid ultrasound was performed anytime between Visit 1 and Visit 2. Ultrasound must be completed before doing MRI.

10.1.3 Appendix B:

Study D3562C00076 (4522IL/0076) ASTEROID

A 104-Week, Open-label, Multi-center, Phase IIIb Study Evaluating the Effect of Treatment with Rosuvastatin 40 mg on Atherosclerotic Disease as Measured by Intravascular Ultrasound and Quantitative Coronary Angiography in Subjects Undergoing Coronary Angiography who have Coronary Artery Disease

Study initiation date: 8 November 2002
Study completion date: 18 November 2005

10.1.3.1 Objectives

Primary

The primary objective of this study was:

- To evaluate whether 104 weeks of treatment with rosuvastatin (40 mg) resulted in regression of coronary artery atheroma burden as assessed by the total atheroma volume (TAV) in the most severely diseased segment or the percent atheroma volume (PAV), as measured by intravascular ultrasound (IVUS) imaging.

Secondary

The secondary objectives of the study were:

- To evaluate whether 104 weeks of treatment with rosuvastatin (40 mg) resulted in regression of coronary artery atheroma burden, as assessed by TAV in the total segment as measured by IVUS.
- To evaluate whether 104 weeks of treatment with rosuvastatin (40 mg) resulted in regression of CAD as measured by QCA.
- To evaluate the change in lipid and lipoprotein levels after 104 weeks of treatment with rosuvastatin (40 mg) as assessed by percent change from baseline.
- To evaluate the safety of rosuvastatin (40 mg) through the 104 weeks of treatment.

10.1.3.2 Endpoints

Primary efficacy measures

- The nominal change (end of treatment minus baseline) in TAV in the 10 mm segment of the coronary artery with the largest plaque volume at baseline (termed the most diseased subsegment) as measured by IVUS.
- The nominal change (end of treatment minus baseline) in PAV in the total segment where the total segment is the 30 to 80 mm segment of the targeted (imaged) coronary artery for all anatomically comparable slices (matched images at end of treatment and baseline with data) as measured by IVUS.

Secondary efficacy measures

- The nominal change (end of treatment minus baseline) in TAV in the total segment where the total segment is the 30 to 80 mm segment of the targeted (imaged) coronary artery for

all anatomically comparable slices (matched images at end of treatment and baseline with data), normalized for segment length (IVUS).

- The mean change in the percent diameter stenosis for all lesions with >25% stenosis severity (QCA).
- The percent change in the minimum luminal diameter (MLD) within all measured coronary segments (QCA).
- The percent change from baseline in lipid parameters (LDL-C, TC, TG, HDL-C, non-HDL-C, VLDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C).
- The percent change from baseline in lipoprotein parameters (Apo B, Apo A-I, Apo B/Apo A-I).
- The number and percent of patients reaching NCEP ATP III target goals.
- Incidence and severity of AEs and abnormal laboratory values.

10.1.3.3 Statistical and Analytical Plans

Analysis population: The following analysis sets were defined and utilized in the analysis and presentation of data:

- **IVUS evaluable analysis set (IEV):** The IEV analysis set consisted of patients who took at least 1 dose of study drug and had an evaluable pre-treatment IVUS and an evaluable post-treatment IVUS examination at Week 78 or later.
- **Per-protocol analysis set (PP):** The PP analysis set consisted of patients from the IEV analysis set who were not major deviators or violators of the protocol requirements as defined in the SAP.
- **QCA evaluable analysis set (QEV):** The QEV analysis set consisted of patients who took at least 1 dose of study drug and had a pre-treatment and a post-treatment QCA examination at Week 78 or later. This analysis set was only used to perform percent diameter stenosis and MLD analyses.
- **Safety analysis set:** Patients who received at least one dose of study drug were included in the safety population.

Study design: This was a 104-week, open-label, multi-center, Phase IIIb study evaluating whether treatment with rosuvastatin (40 mg) resulted in regression of coronary artery atheroma volume as measured by IVUS and QCA in patients with CAD undergoing coronary angiography.

The overall study design comprised the screening period and the treatment period.

During the 6-week screening period, patients were identified for possible enrollment in the study if they met angiographic inclusion criteria. Patients who satisfied all available inclusion and exclusion criteria were to have IVUS performed immediately following the qualifying angiography. IVUS was to be performed within 2 weeks after qualifying angiography but within 4 weeks prior to start of treatment.

Patients should not have been treated with lipid lowering medication for more than 3 months in the 12 months prior to screening. Any patient receiving such medication in the 4 weeks prior to screen could be enrolled into the study if they discontinued their current lipid-lowering therapy and waited 4 weeks before being allocated to study drug.

Patients who entered the Screening Period were instructed to follow current NCEP or regional dietary guidelines for the duration of the study.

All inclusion and exclusion criteria were to be satisfied before patients entered the Treatment Period. QCA and IVUS recordings were reviewed by the Angiographic and IVUS Core Laboratories, respectively, before patients returned for Visit 2 to be provided with study drug.

Eligible patients were provided with rosuvastatin 40 mg (Visit 2). Patients began treatment with study drug within 4 weeks after the qualifying IVUS. Treatment was administered from Visit 2 once daily for 104 weeks. Patients had follow-up visits (Visits 2 through 10) every 13 weeks for 104 weeks after starting treatment with study drug.

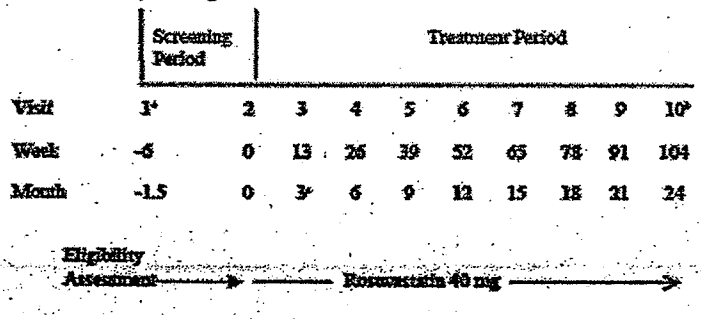
If LDL-C levels were not below 100 mg/dL at Visit 3 (Week 13), or any subsequent visit, a cholesterol binding resin was added to the treatment regimen.

IVUS and angiography were to be performed at baseline (screening, Visit 1) and at Week 104 (final visit, Visit 10).

All patients who required PCI for clinically indicated reasons at Week 78 (Visit 8) or later had QCA and IVUS examination of the target vessel performed at that time, as well as all other end of study assessments, and the patients were then withdrawn.

Randomization: No randomization was performed. All eligible patients were treated with rosuvastatin 40 mg.

Figure 10.1.3.3-1: Study design



[a]Qualifying QCA and IVUS
[b]Follow-up QCA and IVUS
[c]If LDL-C ≥ 100 mg/dL at Visit 3, or any subsequent visit thereafter, colestevelam or equivalent will be added to treatment regimen

QCA = Quantitative coronary angiography; IVUS = Intravascular ultrasound

10.1.2.4 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Signed written informed consent to participate in the study.
2. Men or women 18 years of age or older.
3. Women had to be non-lactating, not of childbearing potential (1 year post-menopausal or surgically sterilized [total hysterectomy, bilateral tubal ligation, bilateral oophorectomy]) or using a reliable method of birth control (condoms with spermicide) considered suitable by the investigator.
4. Clinical indication for coronary catheterization.
5. Willing to follow all study procedures including adherence to lipid-lowering diet, study visits, fasting blood draws and compliance with study drug regimen.

Angiographic inclusion criteria:

1. Entire coronary circulation: Had to have angiographic evidence of CAD, as defined by at least 1 lesion in a native coronary artery that has > 20% reduction in lumen diameter by angiographic visual estimation.
2. Left main coronary artery: Had to have ≤ 50% reduction in lumen diameter by visual estimation.
3. Target coronary artery: The target vessel had to have ≤ 50% reduction in lumen diameter by angiographic visual estimation throughout a segment of at least 40 mm in length (the target segment) and the vessel had to be large enough to accommodate the IVUS catheter. A lesion of up to 60% was permitted distal to the target segment. Side branches of the target (imaged) vessel may have been narrowed up to 70% by visual estimation, provided the target segment contained no lesion greater than 50%. This vessel may have been designated the target vessel if it was accessible to the IVUS catheter and if it:
   - Had not undergone prior PCI or coronary artery bypass graft surgery (CABG)
   - Had not sustained a myocardial infarction (MI)
   - Was not currently a candidate for intervention or a likely candidate for intervention over the next 104 weeks
   - Was not a bypass graft.
4. IVUS examination performed within 4 weeks prior to start of study drug (and within 2 weeks after angiography) that had been judged by the Cleveland Clinic IVUS Core Laboratory to be of acceptable quality.

Exclusion Criteria:

1. Use of lipid-lowering medication for more than 3 months within the previous 12 months. Longer periods of treatment were not permitted because of the potential effects of such therapy on coronary atherosclerosis. Patients receiving treatment with a lipid-lowering medication within the past 4 weeks required a 4-

week wash-out period following which a baseline lipid profile was taken at visit 2.

2. Patients who had symptoms consistent with moderate or greater severity of congestive heart failure (New York Heart Association Class III or IV), or whose most recent determination of left ventricular ejection fraction was < 0.35, by contrast left ventriculography, radionuclide ventriculography or echocardiography. The absence of left ventricular ejection fraction measurement did not prohibit entry into the study. Excluding patients with moderate or severe heart failure avoided confounding the safety profile of rosuvastatin with possible non-drug-related cardiovascular events.
3. Clinically significant heart disease which, in the opinion of the Principal Investigator (or designee), was likely to require coronary bypass surgery, cardiac transplantation, surgical repair and/or replacement during the course of the study.
4. Uncontrolled hypertension defined as either a resting diastolic blood pressure (DBP) of ≥ 100 mm Hg or a resting systolic blood pressure (SBP) of ≥ 200 mm Hg recorded at screening. Excluding such patients avoided confounding the safety profile of rosuvastatin with possible non-drug-related cardiovascular events.
5. Known serious or hypersensitivity reactions to HMG-CoA reductase inhibitors.
6. Triglyceride (TG) level ≥ 500 mg/dL (5.65 mmol/L) at screening because patients with very high triglyceride levels may have warranted treatment with agents that could increase the risk of side effects associated with statin drugs.
7. Creatine kinase (CK) >3 times the upper limit of normal (ULN) range at screening because of the potential of statins to cause muscle abnormalities.
8. Known major hematologic, neoplastic, metabolic, gastrointestinal or endocrine dysfunction, which in the judgment of the investigator may have affected the patient's ability to complete the study.
9. History of malignancy, except in patients who had been disease-free > 5 years or whose only malignancy had been basal or squamous cell skin carcinoma.
10. Life-threatening illness indicating the patient was not expected to survive for 104 weeks.
11. Unreliability as a study participant based on the investigator's knowledge of the patient, such as drug or alcohol abuse.
12. Participation in any investigational drug or device study within 30 days prior to study entry or expectation to participate in any other investigational drug or device study during the course of this study. Patients who withdrew from this study for any reason could not re-enter the study.
13. Use of any medication listed in the Prohibited Medications Section of the study protocol (including HMG-CoA reductase inhibitors, fibric acid derivatives, niacin, bile acid sequestrants [except where LDL-C ≥ 100 mg/dL at Visit 3], any other prescription medicine given to treat dyslipidemia, cyclosporine).
14. Uncontrolled diabetes, defined as glycosylated hemoglobin (HbA_{1c}) ≥ 10% at screening. Excluding such patients avoided confounding the safety profile of rosuvastatin with possible non-drug-related cardiovascular events.
15. Active liver disease or hepatic dysfunction, as determined by aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]) or

bilirubin levels ≥ 1.5x ULN at screening, because of the potential of statins to cause disturbances in liver function.

16. Secondary causes of hyperlipoproteinemia, such as uncontrolled primary hypothyroidism (defined as thyroid stimulating hormone [TSH] 1.5x ULN), nephrotic syndrome, and/or renal dysfunction (serum creatinine ≥2.0 mg/dL [177 µmol/L]) at screening.
17. Coronary artery bypass surgery < 6 weeks prior to the qualifying IVUS.
18. Significant medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study.

10.1.3.5 Amendments and Post Hoc Changes

Amendment 1 (23 May 2003)

This amendment was not implemented because it was discovered that some text that was no longer applicable had not been deleted. Amendment 2 included all of the applicable changes from Amendment 1.

Amendment 2 (3 July 2003)

The following changes and corrections were made to the protocol after the start of subject recruitment:

- Visit 2 window changed from ± 7 days to ± 3 days
- Clarified that a patient who met all inclusion/exclusion criteria could have the IVUS performed immediately following the qualifying angiography
- Clarified requirement of patients who have been treated with lipid-lowering therapy in the 3 months within the past 12 months
- Clarified that LDL-C levels of patients are expected to be < 100 mg/dL
- Added additional lab draw verbiage for patients who consent to Version 2 of the protocol only.
- Clarified that only SAEs will be tracked until event has resolved, stabilized and no further change is expected
- Clarification that non-SAE will be collected if event is still ongoing at Visit 2.
- "Study drug should not be frozen" was removed from the protocol.
- Clarified the thresholds of significance (CK > 10x ULN and ALT > 3x ULN).
- HIPAA text included.

Amendment 3 (1 June 2005)

The following changes and corrections were made to the protocol after the start of subject recruitment:

- Primary objective changed from "regression of coronary artery atheroma volume" to "regression of coronary artery atheroma as assessed by the total atheroma volume (TAV) in the most severely diseased segment or the percent atheroma volume (PAV)".
- Secondary objectives regarding TAV added, as well as secondary objectives regarding lipids and safety.

- Primary endpoint was changed from TAV in total segment to dual primary endpoints TAV in the most diseased subsegment and PAV. New lipid and lipoprotein secondary endpoints were added. New safety secondary endpoints were also added.
- Introduction and rationale sections updated to account for new objectives and endpoints.
- An optional genetic research section has been included as Appendix Q of the protocol.
- The use of oral contraceptives as a reliable method of birth control has been deleted.
- The shipment of laboratory samples within 24 hours was amended to allow the sites to have ample shipping time.
- The addition of Central laboratory storage for leftover serum/plasma that had been previously collected at Visits 1 (and Visit 2 if performed), 3, 6, and 10 was added because few patients were enrolled under Amendment 2 of the protocol.
- 'Ethics Review' and 'Study Timetable and Termination' sections were also revised as per the EU Clinical Trials Directive Requirements.
- Clarification was made that the use of colesevelam or an equivalent at Visit 3 can also be given at any subsequent visit in study regimen if a patient's LDL-C is ≥ 100 mg/dL or at any subsequent visit thereafter, at the investigator's discretion.
- "Overdose" reporting was clarified per the revised AstraZeneca SOP.
- Recording of AEs was clarified with regard to reporting of coronary related disease as adverse events.
- The criteria of laboratory parameters of clinical significance were also updated.
- Clarified that the lipoprotein analysis results would not be available on an ongoing basis.
- IVUS definitions and analyses updated in protocol Appendix I.
- QCA definitions and analysis updated in protocol Appendix H.

Post Hoc Changes
Changes to the analyses, made before database lock

The following changes to the planned analyses were made prior to database lock and prior to the unblinding of the primary endpoints:

- The term used to describe the ITT analysis set was renamed the IVUS Evaluable (IEV) analysis set since patients must have a baseline and post baseline (at least 78 weeks) IVUS examination to be in this analysis set.
- The calculations for the primary and secondary IVUS and QCA endpoints were clarified.
- A time-weighted average was added to the lipid analyses in addition to the LOCF.
- Noted that the numbers of patients reaching the NCEP ATP III LDL-C and LDL-C and non-HDL-C target goals will be summarized.
- A QEV analysis set was defined to be patients with a baseline and post baseline QCA examination. Exploratory analyses were added to analyze the secondary QCA endpoints on the QEV analysis set.

Changes to the analyses, made after database lock

The following changes to the planned analyses were made after the database lock and after the unblinding of the primary endpoints:

- Summaries of selected medical histories and concomitant medications of interest for the safety and IEV population.
- Number of patients regressing and progressing according to IVUS.
- MLD mean change
- Demographic, medical history, concomitant medications, and AE summaries for the non-IEV population (n=158)
- Removal of bile acid sequestrant group from AE tables.
- Analysis of estimated glomerular filtration rate.
- Analyses of MLD-minimum in addition to the MLD average. The MLD-minimum is the minimum MLD of all non-occluded segments at baseline.
- Additional subgroup analyses for IVUS and QCA parameters.
- Summaries of changes in primary endpoints by decile and category.
- Summary of numbers of patients that regressed, progressed or stayed the same for changes in QCA endpoints.
- Sensitivity analyses on the primary endpoints.
- Change in lumen as a ratio of external elastic membrane (EEM).
- Summary of % stenosis for specified intervals of reference diameters.
- Correlations between IVUS and QCA parameters.
- Analysis of creatinine clearance.

10.1.3.6 Results

10.1.3.6.1 Disposition

A total of 1183 patients were screened. Of the 1183, 507 patients took at least 1 dose of study drug (rosuvastatin 40 mg) and comprised the safety analysis set (safety population). Over this 104-week study, 125 (24.7%) withdrew from treatment; the most common reasons for withdrawal were adverse event (12.4%) and "withdrew consent" (6.3%). Of the 507 patients in the safety population, 349 (68.8%) had IVUS evaluation at baseline and after at least 78 weeks, and comprise the IVUS evaluable analysis set (IEV population). Of the 349 patients in the IEV population, 319 had an evaluable most diseased subsegment (for calculating one of the primary endpoints). The per-protocol (PP) population was a subset of the IEV and consisted of 259 patients (51.1%) who did not have major protocol violations or deviations. The QCA evaluable population was only used to perform percent diameter stenosis and MLD analyses. All decisions on the inclusion or exclusion of patients from the rosuvastatin-treated analysis populations described above were made before database lock.

10.1.3.6.2 Demographics

Table 10.1.3.6.2-1: Demographic and key baseline characteristics – safety and IEV population

CHARACTERISTIC VARIABLE	SAFETY POPULATION (N=507)	IEV POPULATION (N=349)
Age (years)		
Mean (SD)	58.5 (10.1)	58.5 (9.98)
Median	58.0	58.0
Range	33, 85	33, 85
Sex [n (%)]		
Male	360 (71.0)	245 (70.2)
Female	147 (29.0)	104 (29.8)
Weight (kg)		
Mean (SD)	85.7 (16.74)	85.5 (16.77)
Median	84.0	83.0
Range	40, 143	40, 143
BMI (kg/m^2)		
Mean	29.2 (5.1)	29.1 (4.9)
Median	28.4	28.4
Range	16.7, 53.8	16.7, 53.8
Race [n (%)]		
Caucasian	477 (94.1)	338 (96.8)
Hispanic	8 (1.6)	3 (0.9)
Black	17 (3.4)	7 (2.0)
Asian	1 (0.2)	1 (0.3)
Other	4 (0.8)	0
Baseline renal function [n (%)]		
Normal	334 (65.9)	235 (67.3)
Mild	142 (28.0)	97 (27.8)
Moderate	19 (3.7)	11 (3.2)
Severe	0	0
NR	12 (2.4)	6 (1.7)
Baseline estimated GFR [n (%)]		
Normal	111 (21.9)	72 (20.6)
Mild	326 (64.3)	229 (65.6)
Moderate	63 (12.4)	43 (12.3)
Severe	0	0
NR	7 (1.4)	5 (1.4)

Table 10.1.3.6.2-2: Co-morbidities - safety and IEV population

CO-MORBIDITY	SAFETY POPULATION N=507 N (%)	IEV POPULATION N=349 N (%)
Hypertension	483 (95.3)	335 (96.0)
Diabetes mellitus	64 (12.6)	46 (13.2)
Acute coronary syndrome*	84 (16.6)	60 (17.2)
Prior myocardial infarction**	121 (23.9)	86 (24.6)

*Includes the following preferred terms: acute coronary syndrome, acute myocardial infarction and angina unstable
**Includes the following preferred terms: myocardial infarction and silent myocardial infarction

Table 10.1.3.6.2-3: Concomitant medication use – safety and IEV population

MEDICATION	SAFETY POPULATION N=507 N (%)	IEV POPULATION N=349 N (%)
Calcium channel blocker	190 (37.5)	144 (41.3)
Beta blocker	410 (81.0)	294 (84.2)
ASA	424 (83.6)	292 (83.7)
Statin	178 (35.1)	122 (35.0)
ACE inhibitor	258 (50.9)	186 (53.3)
Organic nitrates	435 (85.8)	297 (85.1)
ARB	80 (15.8)	64 (18.3)

10.1.3.6.3 Efficacy Findings

10.1.3.6.3.1 Co-Primary Endpoints – TAV in most diseased subsegment; PAV in total segment

The 2 primary endpoints showed statistically significant ($p<0.001$) regression of coronary atheroma volume following 104 weeks of treatment with rosuvastatin (40 mg). Percent atheroma volume (PAV) in the total segment decreased with a median change from baseline of -0.8%. A decrease in PAV was observed in 222/349 (63.6%) of IEV subjects. Total atheroma volume (TAV) in the most diseased subsegment decreased with a median change from baseline of -5.6 mm^3. A decrease in TAV was observed in 249/319 (78.1%) evaluable subjects.

Table 10.1.3.6.3.1-1: Summary of change from baseline in co-primary endpoints – IEV population

PARAMETERS	TAV (MOST DISEASED SUBSEGMENT) N=319	PAV (TOTAL SEGMENT) N=349
Mean (SD)	-6.101 (10.0748)	-0.978 (3.1518)
Median	-5.640	-0.789
Min, max	-43.47, 37.48	-10.82, 13.95
p-value	p<0.001	p<0.001

For the primary IVUS endpoints, statistically significant regression of coronary artery atheroma volume was consistently found across sub-groups.

Table 10.1.3.6.3.1-2: Change from baseline for the primary efficacy variables in pre-specified subgroups – IEV population

SUB-GROUP	PERCENT ATHEROMA VOLUME IN TOTAL SEGMENT (%)			TOTAL ATHEROMA VOLUME IN TOTAL SEGMENT (MM^3)		
	N	Median change (IQR)	p-value	N	Median change (IQR)	p-value
Age						
≤ median	180	-0.8 (-3.0, 0.4)	<0.001	163	-6.1 (-11.3, -1.1)	<0.001
> median	169	-0.6 (-2.8, 1.1)	<0.001	156	-4.4 (-10.8, -0.4)	<0.001
Sex						
Male	245	-0.8 (-2.8, 0.8)	<0.001	221	-6.1 (-11.2, -0.4)	<0.001
Female	104	-0.7 (-3.1, 0.9)	<0.001	98	-4.2 (-10.5, -0.4)	<0.001
BMI						
≤ median	174	-0.9 (-3.2, 0.5)	<0.001	161	-6.5 (-11.6, -0.8)	<0.001
> median	173	-0.7 (-2.6, 1.0)	<0.001	156	-5.0 (-10.6, -0.3)	<0.001
History of DM						
Yes	46	-0.9 (-2.8, 0.9)	0.03	44	-6.4 (-11.1, -1.5)	<0.001
No	303	-0.8 (-3.0, 0.8)	<0.001	275	-5.4 (-10.9, -0.3)	<0.001
Average LDL-C during treatment						
≤ mean	192	-1.1 (-3.1, 0.7)	<0.001	177	-4.8 (-11.3, -0.4)	<0.001
> mean	157	-0.6 (-2.3, 1.0)	0.001	142	-5.8 (-10.2, -0.7)	<0.001
< 70	254	-0.9 (-3.1, 0.7)	<0.001	231	-5.6 (-11.4, -0.4)	<0.001
70 to <100	78	-0.3 (-2.2, 1.2)	0.09	72	-5.3 (-9.4, 0.4)	<0.001
≥ 100	17	-0.2 (-2.5, 0.6)	0.22	16	-6.9 (-11.9, -1.5)	0.004
LDL-C at baseline						
≤ mean	187	-0.6 (-2.5, 0.9)	<0.001	171	-4.8 (-10.1, 0.0)	<0.001
> mean	159	-1.0 (-3.2, 0.5)	<0.001	145	-6.2 (-12.3, -1.3)	<0.001
Average HDL-C during treatment						
≤ mean	197	-0.9 (-2.9, 0.9)	<0.001	179	-6.2 (-11.0, -0.7)	<0.001
> mean	152	-0.7 (-2.9, 0.8)	<0.001	140	-4.7 (-11.0, -0.2)	<0.001
> 45	205	-0.7 (-2.9, 0.7)	<0.001	190	-5.3 (-11.5, -0.4)	<0.001
≤ 45	144	-0.8 (-2.9, 1.1)	<0.001	129	-5.9 (-10.6, -0.4)	<0.001
< 40	80	-1.3 (-2.8, 0.4)	<0.001	71	-5.9 (-10.1, -0.1)	<0.001
≥ 40	269	-0.7 (-2.9, 0.9)	<0.001	248	-5.6 (-11.3, -0.5)	<0.001
< 35	34	-1.5 (-2.6, 0.1)	0.008	29	-5.9 (-9.0, -0.1)	<0.001
≥ 35	315	-0.7 (-2.9, 0.9)	<0.001	290	-5.6 (-11.2, -0.4)	<0.001
HDL-C at baseline						
≤ mean	206	-0.9 (-3.1, 0.8)	<0.001	187	-6.1 (-11.0, -0.7)	<0.001
> mean	140	-0.7 (-2.7, 0.8)	<0.001	129	-5.2 (-10.9, 0.1)	<0.001

10.1.3.6.3.2 Secondary Endpoints

For the secondary IVUS endpoint, TAV in the total segment decreased with a median change of -12.5 mm^3 (mean change of -14.7 mm^3). The median percent change from baseline in TAV of the total segment was -6.8% (mean -6.7%), with a decrease observed in 272/349 (77.9%) of the IEV patients.

Table 10.1.3.6.3.2-1: Change from baseline in the TAV in the total segment – IEV population (N=349)

	MEAN (SD)	MEDIAN (IQR)	MEDIAN CHANGE (CI)	P-VALUE	PATIENTS REGRESSING N (%)
Baseline (mm^3)	212.2 (81.3)	204.7 (146.0, 259.8)	NA	NA	NA
Final (mm^3)	197.5 (79.1)	186.8 (135.1, 243.8)	-12.5 (-15.08, -10.48)	<0.001	272 (77.9)

Two secondary variables examined the effect of treatment on the coronary arteries using QCA. In the largest population of patients having final coronary angiograms (the QCA evaluable population), the percent diameter stenosis decreased by an average of -1.30%. The median change was a decrease of -0.50% with a decrease observed in 156/292 (53.4%) of QEV subjects. The MLD measured by QCA decreased by an average of -0.021 mm. The median change was -0.010 mm, with a median decrease of -0.38%. Overall, 351/371 (94.6%) of the QEV patients were clinically unchanged, with 18 (4.9%) progressing and 2 (0.5%) regressing.

Table 10.1.3.6.3.2-2: Change from baseline in the percent diameter of stenosis – QEV population (N=292)

	MEAN (SD)	MEDIAN	MEAN CHANGE (SD)	MEDIAN CHANGE (CI)	P-VALUE
Baseline (mm^3)	37.301 (8.414)	35.708	NA	NA	NA
Final (mm^3)	36.005 (10.070)	34.450	-1.295 (8.002)	-0.500 (-1.000, 0.000)	<0.001

Table 10.1.3.6.3.2-3: Percent change from baseline in the minimum luminal diameter – QEV population (N=371)

	MEAN (SD)	MEDIAN	MEAN CHANGE (SD)	MEDIAN CHANGE (CI)	P-VALUE
Baseline (mm^3)	2.237 (0.361)	2.227	NA	NA	NA
Final (mm^3)	2.216 (0.370)	2.207	-0.021 (0.096)	-0.010 (-0.013, -0.003)	<0.001

The secondary QCA endpoints did not consistently reach statistical significance across subgroups.

Table 10.1.3.6.3.2-4: Change from baseline for the QCA efficacy variables in pre-specified subgroups – IEV population

SUB-GROUP	MINIMUM LUMINAL DIAMETER (MM)			PERCENT DIAMETER STENOSIS (%)		
	N	Median change (IQR)	p-value	N	Median change (IQR)	p-value
Age						
≤ median	174	-0.43 (-2.3, 0.9)	0.0072	138	-1.0 (-4.0, 2.0)	0.0218
> median	166	-0.38 (-2.1, 1.4)	0.0395	132	0.0 (-3.6, 2.0)	0.0524
Sex						
Male	237	-0.45 (-2.4, 0.9)	0.0008	197	-0.5 (-4.0, 2.0)	0.0202
Female	103	-0.34 (-1.8, 1.7)	0.3346	73	-0.5 (-3.3, 1.0)	0.0519
BMI						
≤ median	171	-0.27 (-2.1, 1.6)	0.2151	139	-1.0 (-4.3, 1.0)	0.0013
> median	167	-0.62 (-2.4, 0.8)	0.0004	129	0.0 (-3.0, 2.0)	0.2395
History of DM						
Yes	45	-1.17 (-4.0, -0.2)	0.0003	37	-0.5 (-3.5, 1.4)	0.4299
No	295	-0.62 (-2.1, 1.4)	0.0217	233	-0.5 (-3.6, 2.0)	0.0030
Average LDL-C during treatment						
≤ mean	187	-0.38 (-1.8, 1.5)	0.1125	148	-0.5 (-4.0, 2.0)	0.0144
> mean	153	-0.43 (-3.3, 0.9)	0.0012	122	-0.5 (-3.3, 2.0)	0.0710
< 70	248	-0.35 (-1.9, 1.5)	0.0659	195	-0.5 (-4.0, 2.0)	0.0019
70 to <100	75	-0.39 (-3.6, 0.9)	0.0117	63	-1.0 (-3.0, 2.0)	0.2388
≥ 100	17	-2.47 (-4.9, 0.0	0.0232	12	0.9 (-3.0, 5.8)	0.6377
LDL-C at baseline						
≤ mean	181	-0.37 (-2.1, 1.1)	0.0212	142	-0.6 (-4.0, 2.0)	0.0169
> mean	156	-0.44 (-2.3, 1.2)	0.0196	126	0.0 (-3.0, 2.0)	0.0642
Average HDL-C during treatment						
≤ mean	191	-0.64 (-2.5, 0.9)	0.0003	163	-0.5 (-4.0, 2.0)	0.0208
> mean	149	-0.30 (-2.0, 1.6)	0.3704	107	-0.5 (-3.0, 1.3)	0.0483
> 45	200	-0.29 (-1.9, 1.5)	0.2266	153	-0.5 (-3.6, 1.0)	0.0028
≤ 45	140	-0.71 (-2.9, 0.7)	0.0002	117	0.0 (-3.5, 2.3)	0.2239
< 40	77	-1.15 (-2.9, 0.7)	0.0015	64	0.0 (-2.8, 2.5)	0.5900
≥ 40	263	-0.30 (-2.1, 1.5)	0.0355	206	-0.6 (-4.0, 1.3)	0.0015
< 35	33	-1.47 (-2.3, 0.8)	0.0880	27	0.0 (-3.0, 3.0	0.6566
≥ 35	307	-0.34 (-2.2, 1.2)	0.0040	243	-0.5 (-4.0, 2.0)	0.0022
HDL-C at baseline						
≤ mean	201	-0.68 (-2.5, 0.8)	<0.0001	160	-0.5 (-4.0, 2.0)	0.0387
> mean	136	0.04 (-1.4, 2.0)	0.9897	108	-0.4 (-3.3, 1.2)	0.0277

For all lipids and lipoproteins, there was a statistically significant improvement from baseline following treatment with rosuvastatin 40 mg.

Table 10.1.3.6.3.2-5: Percent change from baseline in lipid values

PARAMETER	BASELINE MEAN (SD)	FINAL VISIT MEAN (SD)	LSMEAN % CHANGE (CI)
LDL-C (mg/dL)	130.4 (34.25)	60.5 (25.00)	-53.10 (-56.098, -50.100)
TC (md/dL)	204.0 (41.22)	131.6 (31.81)	-34.38 (-36.580, -32.179)
HDL-C (mg/dL)	43.1 (11.09)	48.0 (13.83)	12.82 (9.999, 15.635)
TG (md/dL)	152.2 (81.73)	116.9 (69.19)	-17.80 (-23.094, -12.504)
Non-HDL-C (mg/dL)	160.9 (40.16)	83.7 (29.45)	-47.55 (-50.225, -44.876)
VLDL-C (mg/dL)	30.4 (16.36)	23.4 (13.83)	-17.79 (-23.117, -12.464)
LDL-C/HDL-C ratio	3.19 (1.058)	1.34 (0.631)	-57.49 (-60.466, -54.510)
TC/HDL-C ratio	4.97 (1.415)	2.88 (0.866)	-40.71 (-42.898, -38.530)
Non-HDL-C/HDL-C ratio	3.97 (1.415)	1.88 (0.866)	-52.14 (-54.941, -49.344)
Apo B (mg/dL)	127.90 (29.156)	74.61 (22.326)	-41.52 (-43.762, -39.271)
Apo A-I (mg/dL)	138.55 (27.117)	150.16 (31.256)	8.83 (6.411, 11.259)
Apo B/Apo A-I ratio	0.95 (0.268)	0.51 (0.167)	-45.52 (-47.617, -43.420)

10.1.3.6.4 Safety Findings

10.1.3.6.4.1 Deaths
Four (0.8%) patients who received rosuvastatin died during the study.

Patient 0008/0042 was a 72 year-old male with a history of CAD, GERD, BPH, HTN, myalgia, migraine headaches, and sexual dysfunction who felt dizzy and collapsed while barbecuing at home on Day 9. An autopsy was performed and causes of death were acute myocardial ischemia and hypertrophic cardiovascular disease.

Patient 0072/0002 was a 59 year-old female with a history of COPD who suffered from ventricular fibrillation and cardiopulmonary arrest on Day 24 and was successfully resuscitated at home. She was hospitalized but died 4 days later. The cause of death was considered to be ventricular fibrillation. Study drug was stopped on the day of event onset.

Patient 0130/0047 was a 79 year-old male with a history of cholecystitis, gastric ulcer, hypertension, and CHD who developed back pain following heavy lifting on Day 26 and was prescribed an NSAID (diclofenac). On Day 35, the general practitioner was consulted because the patient had experienced drowsiness and muscle weakness for 3 days. Arthrotec as well as study drug were stopped. The following morning, the patient fell in the bathroom and had trouble getting up. The blood test showed a CK of 6841 U/L, creatinine of 870 µmol/L and potassium of 7.8 mmol/L. Repeat CK the next day was 11881 U/L and serum creatinine was 870 µmol/L. The patient developed renal failure, bronchopneumonia which deteriorated to septic shock and death on Day 37. Postmortem examination revealed a fracture of the T11 vertebral body with local muscle hemorrhage. Multiple muscle biopsies found no evidence of rhabdomyolysis and results from micropathology did not show any specific kidney defects.

Patient 0161/0025 was a 61 year-old male with a history of CAD, RBBB, duodenal ulcer who experienced a gastric disorder on Day 162, which was confirmed as gastric cancer on Day 198;

study drug was stopped on the same day. The patient died from gastric cancer 89 days later on Day 287.

10.1.3.6.4.2 Other Serious Adverse Events

The percent of patients who experienced non-fatal SAEs was 32.7%. The most common SAEs were angina pectoris (7.9%), CAD (3.6%), non-cardiac chest pain (3.0%), unstable angina (2.6%) and stent occlusion (2.0%).

Table 10.1.3.6.4.2-1: Serious adverse events by Primary SOC and Preferred Term

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG (N=507) N (%)
Any SAE	**166 (32.7)**
Blood and lymphatic system disorders	**1 (0.4)**
Anemia	1 (0.2)
ITP	1 (0.2)
Cardiac disorders	**99 (19.5)**
Angina pectoris	38 (7.5)
Coronary artery disease	18 (3.6)
Angina unstable	13 (2.6)
Coronary artery stenosis	7 (1.4)
Myocardial infarction	7 (1.4)
Acute coronary syndrome	4 (0.8)
Atrial fibrillation	4 (0.8)
Myocardial ischemia	5 (1.0)
Acute myocardial infarction	2 (0.4)
Atrial flutter	2 (0.4)
Cardiac failure	2 (0.4)
Coronary artery dissection	2 (0.4)
Arrythmia	1 (0.2)
Atrioventricular block	1 (0.2)
Bradycardia	1 (0.2)
Cardiac failure congestive	1 (0.2)
Congestive cardiomyopathy	1 (0.2)
Mitral valve incompetence	1 (0.2)
SVT	1 (0.2)
Tachycardia	1 (0.2)
Ventricular fibrillation	1 (0.2)
Congenital, familial and genetic disorders	**2 (0.4)**
ASD	1 (0.2)
Gastrointesinal AVM	1 (0.2)
Gastrointestinal disorders	**11 (2.2)**
Abdominal pain	2 (0.4)
Colitis ulcerative	2 (0.4)
Duodenal ulcer hemorrhage	1 (0.2)
Erosive esophagitis	1 (0.2)
Gastric ulcer	1 (0.2)
GERD	1 (0.2)
Inguinal hernia	1 (0.2)
Intestinal obstruction	1 (0.2)
Rectal hemorrhage	1 (0.2)
General disorders and administrative site conditions	**17 (3.4)**

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG (N=507) N (%)
Non-cardiac chest pain	15 (3.0)
Chest discomfort	1 (0.2)
Chest pain	1 (0.2)
Peripheral edema	1 (0.2)
Hepatobiliary disorders	**3 (0.6)**
Bile duct stone	2 (0.4)
Acute cholecystitis	1 (0.2)
Cholelithiasis	1 (0.2)
Immune system dsorders	**1 (0.2)**
Drug hypersensitivity	1 (0.2)
Infections and infestations	**15 (3.0)**
Appendicitis	2 (0.4)
Postoperative infection	2 (0.4)
Abscess jaw	1 (0.2)
Bronchiectasis	1 (0.2)
Acute bronchitis	1 (0.2)
Bronchopneumonia	1 (0.2)
Cystitis	1 (0.2)
Gastroenteritis	1 (0.2)
Groin infection	1 (0.2)
Pneumonia	1 (0.2)
Sepsis syndrome	1 (0.2)
Sinusitis	1 (0.2)
UTI	1 (0.2)
Viral labyrinthitis	1 (0.2)
Injury, poisoning, and procedural complications	**26 (5.1)**
Stent occlusion	10 (2.0)
Coronary artery restenosis	7 (1.4)
Polytraumatism	2 (0.4)
Arterial injury	1 (0.2)
Concussion	1 (0.2)
Incisional hernia	1 (0.2)
Pneumonitis chemical	1 (0.2)
Splenic injury	1 (0.2)
Tendon rupture	1 (0.2)
Thoracic vertebral fracture	1 (0.2)
Upper limb fracture	1 (0.2)
Investigations	**3 (0.6)**
ALT increased	1 (0.2)
AST increased	1 (0.2)
Blood CK increased	1 (0.2)
INR increased	1 (0.2)
Metabolism and nutrition disorders	**1 (0.2)**
Diabetes mellitus	1 (0.2)
Musculoskeletal and connective tissue disorders	**10 (2.0)**
Osteoarthritis	2 (0.4)
Aseptic necrosis bone	1 (0.2)
Back pain	1 (0.2)
Intervertebral disc protrusion	1 (0.2)
Joint effusion	1 (0.2)
Rotator cuff syndrome	1 (0.2)
Spinal column stenosis	1 (0.2)

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG (N=507) N (%)
Spinal osteoarthritis	1 (0.2)
SLE	1 (0.2)
Neoplasms benign, malignant and unspecified	**8 (1.6)**
Colon cancer	2 (0.4)
Breast cancer (male)	1 (0.2)
Gastric cancer	1 (0.2)
Lung squamous cell carcinoma	1 (0.2)
Lymphocytic lymphoma	1 (0.2)
Lymphoma	1 (0.2)
Non-Hodgkin's lymphoma	1 (0.2)
Nervous system disorders	**16 (3.2)**
Syncope	6 (1.2)
Cerebrovascular accident	2 (0.4)
Cervical cord compression	1 (0.2)
Dysarthria	1 (0.2)
Hemorrhage intracranial	1 (0.2)
Lumbar radiculopathy	1 (0.2)
Migraine	1 (0.2)
Subarachnoid hemorrhage	1 (0.2)
Syncope vasovagal	1 (0.2)
TIA	1 (0.2)
Psychiatric disorders	**3 (0.6)**
Delirium	1 (0.2)
Depression	1 (0.2)
Suicide attempt	1 (0.2)
Renal and urinary disorders	**6 (1.2)**
Hematuria	1 (0.2)
Nephrolithiasis	1 (0.2)
Renal artery stenosis	1 (0.2)
Renal failure	1 (0.2)
Urethral stricture	1 (0.2)
Urge incontinence	1 (0.2)
Reproductive system and breast disorders	**1 (0.2)**
Breast mass	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	**6 (1.2)**
Chronic obstructive airways disease exacerbated	2 (0.4)
Acute respiratory failure	1 (0.2)
Laryngeal edema	1 (0.2)
Pulmonary embolism	1 (0.2)
Sleep apnea syndrome	1 (0.2)
Skin and subcutaneous tissue disorders	**1 (0.1)**
Skin fibrosis	1 (0.2)
Vascular disorders	**10 (2.0)**
Deep vein thrombosis	2 (0.4)
Hypotension	2 (0.4)
Aneurysm	1 (0.2)
Aortic aneurysm	1 (0.2)
Femoral artery occlusion	1 (0.2)
Hypertension	1 (0.2)
Orthostatic hypotension	1 (0.2)
Peripheral vascular disease	1 (0.2)

10.1.3.6.4.3 Dropouts and Other Significant Adverse Events

Overall, there were 61 rosuvastatin-treated patients with treatment-emergent AEs leading to study discontinuation. These are summarized in the table below:

Table 10.1.3.6.4.3-1: TEAEs leading to study discontinuation (safety population)

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG (N=507) N (%)
Any DAE	**61 (12.0)**
Cardiac disorders	**21 (4.1)**
Angina pectoris	9 (1.8)
Angina unstable	4 (0.8)
Coronary artery disease	3 (0.6)
Coronary artery stenosis	3 (0.6)
Myocardial ischemia	1 (0.2)
Ventricular fibrillation	1 (0.2)
Gastrointestinal disorders	**2 (0.4)**
Abdominal pain upper	1 (0.2)
Nausea	1 (0.2)
General disorders and administration site conditions	**3 (0.6)**
Fatigue	1 (0.2)
Non-cardiac chest pain	1 (0.2)
Pain	1 (0.2)
Infections and infestations	**1 (0.2)**
Hepatitis C	1 (0.2)
Injury, poisoning, and procedural complications	**2 (0.4)**
Coronary artery restenosis	1 (0.2)
Polytraumatism	1 (0.2)
Investigations	**5 (1.0)**
ALT increased	1 (0.2)
Blood bilirubin increased	1 (0.2)
Blood CK increased	2 (0.4)
Blood triglycerides increased	1 (0.2)
Musculoskelatal and connective tissue disorders	**19 (3.7)**
Arthralgia	1 (0.2)
Fibromyalgia	1 (0.2)
Muscular weakness	1 (0.2)
Musculoskeletal pain	1 (0.2)
Myalgia	15 (3.0)
Pain in extremity	1 (0.2)
Neoplasms benign, malignant and unspecified	**2 (0.4)**
Gastric cancer	1 (0.2)
Lung squamous cell carcinoma	1 (0.2)
Nervous system disorders	**2 (0.4)**
Dizziness	1 (0.2)
Hypoaesthesia	1 (0.2)
Renal and urinary disorders	**2 (0.4)**
Chromaturia	1 (0.2)
Renal failure	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**1 (0.2)**
Wheezing	1 (0.2)
Skin and subcutaneous tissue disorders	**1 (0.2)**
Urticaria	1 (0.2)

10.1.3.6.4.4 All Treatment Emergent Adverse Events Reported

Of 507 rosuvastatin-treated patients in the safety population, 423 (83.4%) had a treatment emergent AE. The most common (≥ 2%) treatment-emergent AEs, summarized by SOC and preferred term are shown in Table 10.1.3.6.4.4-1 below:

Table 10.1.3.6.4.4-1: Number and percent of rosuvastatin patients who had a treatment-emergent adverse event

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG (N=507) N (%)
Any adverse event	**423 (83.4)**
Cardiac disorders	**170 (33.5)**
Angina pectoris	91 (17.9)
Coronary artery disease	20 (3.9)
Palpitations	19 (3.7)
Atrial fibrillation	17 (3.4)
Angina unstable	13 (2.6)
Bradycardia	10 (2.0)
Gastrointestinal disorders	**135 (26.6)**
Constipation	26 (5.1)
Diarrhea	19 (3.7)
Nausea	18 (3.6)
Abdominal pain upper	17 (3.4)
GERD	16 (3.2)
Dyspepsia	14 (2.8)
Abdominal pain	12 (2.4)
General disorders and administration site conditions	**125 (24.7)**
Non-cardiac chest pain	52 (10.3)
Fatigue	30 (5.9)
Peripheral edema	25 (4.9)
Infections and infestations	**148 (29.2)**
Influenza	26 (5.1)
Nasopharyngitis	22 (4.3)
Bronchitis	16 (3.2)
Upper respiratory tract infection	15 (3.0)
Sinusitis	14 (2.8)
Urinary tract infection	10 (2.0)
Injury, poisoning and procedural complications	**91 (17.9)**
Post procedural pain	15 (3.0)
Contusion	12 (2.4)
Stent occlusion	10 (2.0)
Investigations	**76 (15.0)**
Blood CK increased	18 (3.6)
ALT increased	17 (3.4)
Metabolism and nutrition disorders	**47 (9.3)**
Diabetes mellitus	19 (3.7)
Musculoskeletal and connective tissue disorders	**189 (37.3)**
Myalgia	72 (14.2)
Back pain	31 (6.1)
Arthralgia	30 (5.9)
Muscle spasms	21 (4.1)
Shoulder pain	15 (3.0)

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG (N=507) N (%)
Pain in extremity	14 (2.8)
Musculoskeletal pain	10 (2.0)
Neck pain	10 (2.0)
Nervous system disorders	**102 (20.1)**
Dizziness	29 (5.7)
Headache	24 (4.7)
Hypoesthesia	13 (2.6)
Syncope	13 (2.6)
Psychiatric disorders	**58 (11.4)**
Anxiety	24 (4.7)
Depression	21 (4.1)
Insomnia	18 (3.6)
Respiratory, thoracic and mediastinal disorders	**95 (18.7)**
Dyspnea	21 (4.1)
Cough	18 (3.6)
Dyspnea exertional	12 (2.4)
Pharyngolaryngeal pain	10 (2.0)
Skin and subcutaneous tissue disorders	**56 (11.0)**
Rash	12 (2.4)
Vascular disorders	**85 (16.8)**
Hypertension	58 (11.4)
Hypotension	11 (2.2)

10.1.3.6.4.5 Other significant adverse events

Significant AEs of particular clinical importance include hepatic, skeletal muscle, and renal events. Clinically important laboratory abnormalities associated with hepatic, skeletal muscle, or renal systems are reported separately.

In addition to abnormal hepatic laboratory values reported as AEs, there were no hepatic AEs associated with clinically important elevations of ALT (> 3x ULN on 2 consecutive occasions greater than 48 hours apart).

In addition to elevated CK values reported as AEs, there were no skeletal muscle AEs associated with a clinically important elevation of CK (> 10x ULN).

In addition to abnormal serum creatinine values reported as AEs, there was 1 report of renal failure not considered an SAE or a DAE. The investigator's reported term was renal insufficiency (from Day 678 to Day 732). The patient (0103/0004) had cardiac failure and experienced cardiac decompensation at the same time as the renal insufficiency.

Another patient (0001/0010) had an AE of proteinuria associated with a clinically important increase in serum creatinine (> 100% increase from baseline and greater than ULN). This patient with the AE of proteinuria recovered on treatment.

10.1.3.6.4.6 Laboratory values

Hematology

There were no clinically meaningful changes in values of hematology parameters over time.

Table 10.1.3.6.4.6-1: Hematology values outside of reference range – safety population

PARAMETER (UNIT)	WEEK	RELATION TO REFERENCE RANGE	ROSUVASTATIN ALL PATIENTS (N=507)
PLATELETS (X10**9/L)	BASELINE	NO. OF PATIENTS	45
		NO. ABOVE REFERENCE RANGE	3
		% ABOVE REFERENCE RANGE	6.7%
		NO. BELOW REFERENCE RANGE	42
		% BELOW REFERENCE RANGE	93.3%
	FINAL	NO. OF PATIENTS	36
		NO. ABOVE REFERENCE RANGE	1
		% ABOVE REFERENCE RANGE	2.8%
		NO. BELOW REFERENCE RANGE	35
		% BELOW REFERENCE RANGE	97.2%
HAEMOGLOBIN (G/DL)	BASELINE	NO. OF PATIENTS	212
		NO. ABOVE REFERENCE RANGE	0
		% ABOVE REFERENCE RANGE	0%
		NO. BELOW REFERENCE RANGE	212
		% BELOW REFERENCE RANGE	100.0%
	FINAL	NO. OF PATIENTS	130
		NO. ABOVE REFERENCE RANGE	1
		% ABOVE REFERENCE RANGE	0.8%
		NO. BELOW REFERENCE RANGE	129
		% BELOW REFERENCE RANGE	99.2%
HAEMATOCRIT (%VOL FRACTION)	BASELINE	NO. OF PATIENTS	257
		NO. ABOVE REFERENCE RANGE	4
		% ABOVE REFERENCE RANGE	1.6%
		NO. BELOW REFERENCE RANGE	253
		% BELOW REFERENCE RANGE	98.4%
	FINAL	NO. OF PATIENTS	162
		NO. ABOVE REFERENCE RANGE	6
		% ABOVE REFERENCE RANGE	3.7%
		NO. BELOW REFERENCE RANGE	157
		% BELOW REFERENCE RANGE	96.3%

PARAMETER (UNIT)	WEEK	RELATION TO REFERENCE RANGE	ROSUVASTATIN ALL PATIENTS (N=507)
ERYTHROCYTES (X10**12/L)	BASELINE	NO. OF PATIENTS	331
		NO. ABOVE REFERENCE RANGE	1
		% ABOVE REFERENCE RANGE	0.3%
		NO. BELOW REFERENCE RANGE	330
		% BELOW REFERENCE RANGE	99.7%
	FINAL	NO. OF PATIENTS	219
		NO. ABOVE REFERENCE RANGE	2
		% ABOVE REFERENCE RANGE	0.9%
		NO. BELOW REFERENCE RANGE	217
		% BELOW REFERENCE RANGE	99.1%
RED CELL DIST WIDTH (%)	BASELINE	NO. OF PATIENTS	94
		NO. ABOVE REFERENCE RANGE	94
		% ABOVE REFERENCE RANGE	100.0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
	FINAL	NO. OF PATIENTS	92
		NO. ABOVE REFERENCE RANGE	92
		% ABOVE REFERENCE RANGE	100.0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
MEAN CORPUSCULAR VOLUME (FL)	BASELINE	NO. OF PATIENTS	136
		NO. ABOVE REFERENCE RANGE	127
		% ABOVE REFERENCE RANGE	93.4%
		NO. BELOW REFERENCE RANGE	9
		% BELOW REFERENCE RANGE	6.6%
	FINAL	NO. OF PATIENTS	110
		NO. ABOVE REFERENCE RANGE	98
		% ABOVE REFERENCE RANGE	89.1%
		NO. BELOW REFERENCE RANGE	12
		% BELOW REFERENCE RANGE	10.9%

PARAMETER (UNIT)	WEEK	RELATION TO REFERENCE RANGE	ROSUVASTATIN ALL PATIENTS (N=507)
MEAN CORPUSCULAR HB (PMOL/CELL)	BASELINE	NO. OF PATIENTS	120
		NO. ABOVE REFERENCE RANGE	114
		% ABOVE REFERENCE RANGE	95.2%
		NO. BELOW REFERENCE RANGE	16
		% BELOW REFERENCE RANGE	4.8%
	FINAL	NO. OF PATIENTS	275
		NO. ABOVE REFERENCE RANGE	254
		% ABOVE REFERENCE RANGE	92.4%
		NO. BELOW REFERENCE RANGE	21
		% BELOW REFERENCE RANGE	7.6%
MEAN CORPUSCULAR HB CONC (MMOL HB/L RB)	BASELINE	NO. OF PATIENTS	89
		NO. ABOVE REFERENCE RANGE	0
		% ABOVE REFERENCE RANGE	0%
		NO. BELOW REFERENCE RANGE	89
		% BELOW REFERENCE RANGE	100.0%
	FINAL	NO. OF PATIENTS	71
		NO. ABOVE REFERENCE RANGE	0
		% ABOVE REFERENCE RANGE	0%
		NO. BELOW REFERENCE RANGE	71
		% BELOW REFERENCE RANGE	100.0%
LEUCOCYTES (X10**9/L)	BASELINE	NO. OF PATIENTS	73
		NO. ABOVE REFERENCE RANGE	31
		% ABOVE REFERENCE RANGE	42.5%
		NO. BELOW REFERENCE RANGE	42
		% BELOW REFERENCE RANGE	57.5%
	FINAL	NO. OF PATIENTS	71
		NO. ABOVE REFERENCE RANGE	20
		% ABOVE REFERENCE RANGE	28.2%
		NO. BELOW REFERENCE RANGE	51
		% BELOW REFERENCE RANGE	71.8%

PARAMETER (UNIT)	WEEK	RELATION TO REFERENCE RANGE	ROSUVASTATIN ALL PATIENTS (N=507)
NEUTROPHILS - BANDS (%)	BASELINE	NO. OF PATIENTS	0
		NO. ABOVE REFERENCE RANGE	0
		% ABOVE REFERENCE RANGE	0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
	FINAL	NO. OF PATIENTS	0
		NO. ABOVE REFERENCE RANGE	0
		% ABOVE REFERENCE RANGE	0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
NEUTROPHILS - SEGMENTED (%)	BASELINE	NO. OF PATIENTS	149
		NO. ABOVE REFERENCE RANGE	148
		% ABOVE REFERENCE RANGE	99.3%
		NO. BELOW REFERENCE RANGE	1
		% BELOW REFERENCE RANGE	0.7%
	FINAL	NO. OF PATIENTS	94
		NO. ABOVE REFERENCE RANGE	90
		% ABOVE REFERENCE RANGE	95.7%
		NO. BELOW REFERENCE RANGE	4
		% BELOW REFERENCE RANGE	4.3%
LYMPHOCYTES (%)	BASELINE	NO. OF PATIENTS	155
		NO. ABOVE REFERENCE RANGE	13
		% ABOVE REFERENCE RANGE	8.4%
		NO. BELOW REFERENCE RANGE	142
		% BELOW REFERENCE RANGE	91.6%
	FINAL	NO. OF PATIENTS	112
		NO. ABOVE REFERENCE RANGE	13
		% ABOVE REFERENCE RANGE	11.6%
		NO. BELOW REFERENCE RANGE	99
		% BELOW REFERENCE RANGE	88.4%

PARAMETER (UNIT)	WEEK	RELATION TO REFERENCE RANGE	ROSUVASTATIN ALL PATIENTS (N=507)
MONOCYTES (%)	BASELINE	NO. OF PATIENTS	11
		NO. ABOVE REFERENCE RANGE	11
		% ABOVE REFERENCE RANGE	100.0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
	FINAL	NO. OF PATIENTS	5
		NO. ABOVE REFERENCE RANGE	5
		% ABOVE REFERENCE RANGE	100.0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
EOSINOPHILS (%)	BASELINE	NO. OF PATIENTS	11
		NO. ABOVE REFERENCE RANGE	11
		% ABOVE REFERENCE RANGE	100.0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
	FINAL	NO. OF PATIENTS	19
		NO. ABOVE REFERENCE RANGE	19
		% ABOVE REFERENCE RANGE	100.0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
BASOPHILS (%)	BASELINE	NO. OF PATIENTS	0
		NO. ABOVE REFERENCE RANGE	0
		% ABOVE REFERENCE RANGE	0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%
	FINAL	NO. OF PATIENTS	0
		NO. ABOVE REFERENCE RANGE	0
		% ABOVE REFERENCE RANGE	0%
		NO. BELOW REFERENCE RANGE	0
		% BELOW REFERENCE RANGE	0%

Clinical Chemistry

Clinically significant changes in values of ALT over time are summarized below.

Table 10.1.3.6.4.6-2: Clinically significant elevations of ALT (> 3x ULN) – safety population

	Rosuvastatin 40 mg (N=507)	
Patients with baseline and subsequent measurement, n (%)	491	(100.0)
>3x ULN at any visit, n (%)	9	(1.8)
>3x ULN at 2 consecutive visits, n (%)	1	(0.2)

One patient (005/0055) had clinically important elevations in ALT (> 3x ULN on 2 consecutive visits greater than 48 hours apart). The patient was a 40 year-old Caucasian male with a history of angina pectoris, CAD and arthritis who had elevated ALT to 21x ULN at Week 52 (Day 371). He was asymptomatic. The study drug was discontinued on Day 375. The elevated ALT had improved slightly at repeat testing on Days 376 and 382. Serological tests revealed positive hepatitis C antibody. On Day 403, the ALT had increased to 26x ULN, but the patient remained

asymptomatic and had normal bilirubin. On Day 410, the patient was seen by a hepatologist who made the diagnosis "mildly active chronic hepatitis C with patchy periportal fibrosis." The ALT was 33x ULN at this time.

There were no clinically meaningful changes in mean values over time in other hepatic biochemistry parameters (total bilirubin, alkaline phosphatase, AST).

Clinically significant changes in values of CK over time are summarized below.

Table 10.1.3.6.4.6-3: Clinically significant elevations of CK (> 5x and > 10x ULN) – safety population

	Rosuvastatin 40 mg (N=507)	
Patients with baseline and subsequent measurement, n (%)	491	(100.0)
>5x ULN at any visit, n (%)	6	(1.2)
>10x ULN at any visit, n (%)	3*	(0.61)

Three patients (0083/0001, 0026/0002, and 0130/0047) had clinically important increases in CK (> 10x ULN). None of the patients had rhabdomyholysis or myopathy.

Subject 0083/0001
A 53-year-old Caucasian male with a history of ischemic heart disease, hypertension, dyslipidemia, and chronic left-sided neck swelling experienced elevated creatine phosphokinase (CK) to > 5x ULN on Day 267 (measured at a local laboratory, i.e., other than a central laboratory). He had just been diagnosed with hypothyroidism with a TSH of 124 mIU/L and complained of muscle cramping and diffuse swelling. Study drug was continued and cramping improved. On Day 244 the patient was asymptomatic and there was less swelling; however, on Day 274, CK measured at a local laboratory was > 10x ULN. The same sample analyzed at the central laboratory had a CK value 9.7x ULN. The study drug was discontinued at this time (Day 274). On Day 281, the CK was 5.9x ULN. Subsequently, CK was normal and remained normal when rechecked (at a local laboratory).

The patient had been treated with aspirin and ramipril and had been started on levothyroxine a few days (Day 263) before the AE of elevated CK (Day 267) was reported.

Subject 0026/0002
A 78-year-old Caucasian male with a history of sleep apnea, hypertension, hyperlipidemia, obesity and syncopal episodes was hospitalized for another syncopal episode on Day 589. During the hospitalization, his initial CK (at a local laboratory) was 2060 U/L with normal MB fraction of CK and on repeat testing was 1750 and 1460 U/L. When questioned, the patient denied having any symptoms, such as muscle aches, pains, flu-like symptoms, fever, nausea or emesis. Study drug was halted during the hospitalization, but the patient resumed study drug immediately after his discharge against the advice of the treating physicians.

On Day 659, during the regular study visit, CK was normal. The patient never reported muscle symptoms, and throughout the study, his CK and creatinine had been normal at scheduled visits.

The patient had been treated with atenolol, hydrochlorothiazide and lisinopril during the study.

Subject 0130/0047 was previously discussed under deaths.

Changes in mean and median serum creatinine values over time are summarized in the table below, followed by a summary of the maximum elevations in serum creatinine for treated patients.

Table 10.1.3.6.4.6-4: Change from baseline to final visit in serum creatinine – safety population

	Rosuvastatin 40 mg (N=507)		
Serum creatinine (µmol/L)	**Baseline**	**Final visit**	**Change from baseline to final visit**
N	500	447	440
Mean (SD)	88.86 (15.79)	90.56 (15.37)	1.61 (13.73)
Median	88.40	88.40	0.00
Range	44.20 to 141.44	61.88 to 159.12	-44.20 to 53.04

Table 10.1.3.6.4.6-5: Maximum serum creatinine elevations by category during treatment – safety population

	Rosuvastatin 40 mg (N=507)	
Patients with baseline and subsequent measurement, n (%)	501	(100.0)
>50% increase from baseline, n (%)	16	(3.2)
>100% increase from baseline, n (%)	3[a]	(0.6)

Three patients had a doubling of serum creatinine from baseline, but the elevated value was greater than ULN in only 2 (0.6%) of these patients. One of the patients (0001/0010) is described below. The other (0130/0047) was described under deaths.

Subject 0001/0010
A 72-year-old black male with a history of hypertension, stroke, peripheral vascular disease, and peripheral edema experienced an AE of mild proteinuria from Day 96 to 361; the corresponding dipstick protein finding from central laboratory was ++ on Days 96 and 172 (a shift from none or trace at baseline). The proteinuria then changed to moderate (protein dipstick from central laboratory +++ on Day 361) and was present until Day 502 when it

resolved on treatment. No further central laboratory urine dipstick results are available. On Day 498 the patient developed an elevated creatinine of 301 µmol/L, a > 100% increase from the baseline value of 80 µmol/L, that was identified at a laboratory other than the central laboratory. The patient was complaining of pain and swelling in the right leg. Furosemide and lisinopril were discontinued. The study drug was not interrupted and the patient continued in the study. The creatinine improved to 133 µmol/L at Day 509 and by Day 598 it was normal at 106 µmol/L (all measured in local laboratory). The patient was noted to have dehydration, a hypotensive episode and partial obstruction of the left kidney.

The patient stopped taking study drug on Day 529, while lost to follow-up (after Visit 7 [Day 466]). When information on the patient was subsequently obtained, the investigator reported that the patient was withdrawn from the study on Day 630 due to an AE (myocardial infarction). Because this DAE occurred greater than 30 days after the end of study drug treatment, it is not included in the summary tables of treatment-emergent AEs.

Other medical history included glaucoma, mitral valve regurgitation, prostate cancer, radiation cystitis with resultant cystectomy and ileostomy, chronic obstructive pulmonary disease, gynecomastia, blindness of the left eye, asthma and right leg weakness due to complication of angiography. The patient had been treated with clonidine, aspirin, folic acid, warfarin, potassium, lisinopril, clopidogrel, furosemide and cilostazol during the study. Both proteinuria and elevated serum creatinine resolved while on rosuvastatin.

The number and percent of patients with creatinine values outside of the reference range are summarized in the table below:

Table 10.1.3.6.4.6-6: Number and percent of patients with creatinine values outside of reference range – safety population

PARAMETER (UNIT)	WEEK	RELATION TO REFERENCE RANGE	ROSUVASTATIN ALL PATIENTS (N=507)
CREATININE (UMOL/L)	BASELINE	NO. OF PATIENTS	41
		NO. ABOVE REFERENCE RANGE	8
		% ABOVE REFERENCE RANGE	19.5%
		NO. BELOW REFERENCE RANGE	33
		% BELOW REFERENCE RANGE	80.5%
	FINAL	NO. OF PATIENTS	22
		NO. ABOVE REFERENCE RANGE	11
		% ABOVE REFERENCE RANGE	50.0%
		NO. BELOW REFERENCE RANGE	11
		% BELOW REFERENCE RANGE	50.0%

Urinalysis

The number and percent of patients with proteinuria or hematuria is shown in the table below.

Table 10.1.3.6.4.6-6: Number and percent of patients with proteinuria or hematuria – safety population

	Rosuvastatin 40 mg (N=507)			
	At any time during the study		At final visit	
	N	%	N	%
Patients with proteinuria[a]	23	5.0	14	3.0
Patients with hematuria[b]	23	5.0	12	2.6
Patients with proteinuria and hematuria	6	1.3	1	0.2

None of the 23 patients who had proteinuria had a clinically important increase of serum creatinine (> 100% from baseline and > ULN) or an AE indicating renal dysfunction such as renal failure. Twelve of the 14 patients with proteinuria at final visit showed no clinically relevant increase in serum creatinine or had creatinines remaining within normal range. The other two are described below:

- **Subject 0015/0042** entered the study with current medical history consisting of angina pectoris, anxiety, CAD, diabetes mellitus, dizziness, factor V Leiden mutation, gastroesophageal reflux disease, hyperlipidaemia, hypertension, obesity, skin ulcer and tinnitus. On study Day 89, serum creatinine increased from a baseline of 88 µmol/L to 124 µmol/L. At that time, concomitant medication included l-carnitine, Prilosec, Climara patch, ASA, atenolol, Glucophage, hydrochlorothiazide, Isordil, Ativan, nitroglycerine, Plavix, and Zestril. Urine dipstick revealed trace protein and no blood. Serum creatinine fluctuated from that visit between 106 µmol/L and 133 µmol/L, until Day 722 when the final serum creatinine was 124 µmol/L. The patient completed the study on Day 722. At that time urine dipstick revealed 2+ protein and 1+ blood.
- **Subject 0020/0007** entered the study with current medical history consisting of angina pectoris, CAD, depression, diabetes mellitus, hypertension, musculoskeletal discomfort, sinusitis, smoking and ventricular hypertrophy. Concomitant medications included Glucotrol, Klonopin, Neurontin, Norvasc, trazodone, Vasotec, aspirin, metoprolol, Plavix, and Vicodin. On study Day 100 serum creatinine increased from a baseline of 97 µmol/L to 124 µmol/L. Urine dipstick revealed 2+ protein and no blood. The patient was lost to follow-up at study Day 100.

One (0.2%) patient (0081/0024) had both proteinuria and hematuria at the final visit. This patient is described below:

- **Patient 0081/0024** had elevated creatinine of 141 µmol/L on Day 183 of

treatment, a > 30% increase from the baseline value of 80 µmol/L. The subject was asymptomatic. No treatment was provided for this laboratory abnormality. The creatinine returned to within normal range on Day 201. The creatinine remained in the normal range at Day 366. On Day 458, the subject came for Visit 7 and was complaining of anorexia and weight loss of 20 pounds, now stating that the symptoms started at the beginning of the study. The investigator discontinued the study drug and the subject had blood work. The CK was elevated to 652 (5.4x ULN) and the creatinine was 133 µmol/L. On day 462, the subject had repeat blood studies done. The CK was now 145 (1.2x ULN) and the creatinine had returned to within normal limits. The subject had a prior medical history of type 2 diabetes, hypertension, thoracic scoliosis, angina, menopause and gout. This subject underwent percutaneous transluminal coronary angioplasty of the left anterior descending artery approximately 7 months before entering the study and percutaneous transluminal coronary angioplasty of the right coronary artery on Day -17. The subject was treated with metformin, diltiazem, temazepam, atenolol, enalapril, glyburide, allopurinol, aspirin and domperidone during the study.

10.1.3.6.4.7 Vital signs

There were no clinically meaningful changes in mean systolic BP, mean diastolic BP or heart rate throughout the study.

10.1.3.6.4.8 Extent of exposure

Table 10.1.3.6.4.8-1: Summary of treatment duration (weeks) on rosuvastatin 40 mg – safety population

	Rosuvastatin 40 mg (N=507)	
	N	%
0 to <13 weeks	24	4.7
13 to <26 weeks	18	3.6
26 to <39 weeks	18	3.6
39 to <52 weeks	7	1.4
52 to <65 weeks	9	1.8
65 to <78 weeks	19	3.7
78 to <91 weeks	16	3.2
91 to <104 weeks	146	28.8
104+ weeks	246	48.5
NR, N (%)	4	0.8

10.1.3.6.4.9 Study schedule

	Screening	Treatment period[a]							
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Elapsed time (weeks)	**-6 to 0**	**0**	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**
Routine assessments:										
Signed informed consent	√									
History	√									
Physical examination, vital signs	√									√
Fasting lipid panel[b]	√	√[c]	√			√				√
Lipoprotein panel[b]	√									√
Hematology	√									√
Clinical chemistry	√		√[d]	√[d]		√[d]		√[d]		√
Thyroid stimulating hormone	√									
Additional parameters[b,e]	√					√				√
Urine sample	√		√	√		√				√
Glycosylated hemoglobin (HbA_{1C})[f]	√									
Quantitative coronary angiography[g]	√									√
Intravascular ultrasound[h]	√									√
Inclusion/exclusion criteria review	√	√								
Dietary counseling	√	√	√	√	√	√	√	√	√	
Adverse event review		√	√	√	√	√	√	√	√	√
Review of concomitant medications	√	√	√	√	√	√	√	√	√	√
Dispense study drug		√	√	√	√	√	√	√	√	
Compliance check/tablet count			√	√	√	√	√	√	√	√

10.1.4 Appendix C:

Study D3562C00088 (4522IL/0088) METEOR

A Randomized, Double-blind, Placebo-controlled, Multicenter Parallel Group Phase III Study Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg

Study initiation date: 8 August 2002
Study completion date: 17 May 2006

10.1.4.1 Objectives

Primary

The primary objective of the study was to assess the effects of rosuvastatin 40 mg treatment for 104 weeks on the change in the mean maximum IMT of the 12 carotid artery segments: near and far walls of the right and left CCA, carotid bulb, and the internal carotid artery (ICA). The rosuvastatin-treated patients, in whom the IMT was expected to regress over time, were compared to the placebo-treated patients, in whom the IMT was expected to progress over time. If there was a significant difference between these treatment groups, then the rosuvastatin-treated patients were examined further to determine whether there was significant regression in IMT between the beginning and the end of the treatment period.

Secondary

The secondary objectives of the study were to assess the effects of rosuvastatin 40 mg for 104 weeks on the following variables:

- Change in the mean maximum IMT of the near and far walls of the right and left CCA
- Change in the mean maximum IMT of the near and far walls of the right and left carotid bulb
- Change in the mean maximum IMT of the near and far walls of the right and left ICA
- Change in the mean IMT of the near and far walls of the right and left CCA
- Change in LDL-C, TC, HDL-C, TG, nonHDL-C, Apolipoprotein (Apo) B, ApoA-I, nonHDL-C/HDL-C, and ApoB/ApoA-I
- Change in the inflammatory marker: C-reactive protein (CRP)
- Safety was assessed by evaluations of vital signs, adverse events (AEs), clinical laboratory analyses, and electrocardiograms (ECGs)

10.1.4.2 Endpoints

Primary efficacy measures

The primary variable was change from baseline values to end of treatment in maximum cIMT over the 12 carotid artery sites. This was determined using a multi-level mixed effects regression model that estimated mean annualized rate of change (mm/year) over the 2-year study period for each treatment group (summarized by treatment group in the ITT and PP populations). The statistical significance of the maximum cIMT annualized rate of change (slope) between

rosuvastatin and placebo was evaluated using the time-by-treatment interaction term in the model.

Secondary efficacy measures
Secondary efficacy variables were segment-specific and measured as a change from baseline values to end of treatment in the following, with the same statistical analyses (as for the primary variable) applied (summarized by treatment group in the ITT and PP populations):

- Maximum cIMT over the 4 CCA sites (near and far walls of the right and left CCA)
- Maximum cIMT over the 4 carotid bulb sites (near and far walls of the right and left carotid bulb)
- Maximum cIMT over the 4 ICA sites (near and far walls of the right and left ICA)
- Mean cIMT over the 4 CCA sites (near and far walls of the right and left CCA)

Secondary laboratory variables include:

- Percentage change from baseline to Week 104 in lipid parameters: LDL-C, TC, HDL-C, TG, nonHDL-C, and TC/HDL-C, LDL-C/HDL-C, and nonHDL-C/HDL-C ratios (observed and LOCF data in the ITT population)
- Percentage change from baseline in apolipoproteins (ApoB, ApoA-I, ApoB/Apo-A-I) (observed and LOCF data in the ITT population)
- Percentage change from baseline to Week 104 in a circulating marker of inflammation: CRP (observed and LOCF data in the ITT population)

Safety variables include:

- Safety and tolerability, by evaluating the incidence and severity of AEs, abnormal laboratory values (hematology, clinical chemistry, GFR, and urinalysis), vital signs and weight, ECGs, and PE (Randomized safety population)

10.1.4.3 Statistical and Analytical Plans
Analysis population: The following analysis sets were defined and used in the analysis and/or presentation of data:

- **Intent-to-Treat (ITT) population:** The ITT population consisted of all randomized patients who received at least 1 dose of study medication and had a baseline reading, and at least 1 post-baseline assessment of cIMT.
- **Per-Protocol (PP) population:** The PP population consisted of patients in the ITT population who were not major protocol violators or major deviators.
- **Safety population:** The randomized safety population consisted of all patients who were randomized and took at least 1 dose of study medication and had at least 1 safety assessment.

Study design: This was a randomized, double-blind, placebo-controlled study of 984 SUBJECTS randomized in a 5:2 ratio into 2 parallel treatment arms over a period of 104 weeks. This study assessed the efficacy of rosuvastatin in altering the natural history of cIMT as compared to placebo.

There was 1 optional pre-screening visit and 13 visits during the course of the study. During the optional pre-screening visit, the study outline was explained to patients. If the patient was interested in the study, he/she signed a pre-screening informed consent form. Lipid values were checked using a finger-stick test. Patients who had values within ± 15% of the lipid values specified by the entry eligibility criteria were referred to the PI for Visit 1.

Medical history and height were also recorded at Visit 1 (Week -6). Following assessment of eligibility based on lipid level, Framingham risk score, and determination of IMT by carotid ultrasound, patients were randomly assigned to either the rosuvastatin or placebo group at Visit 4 (Week 0). A full physical examination was carried out at Visit 4 (Week 0) and Visit 13 (Week 104). Nutritional counseling was performed at randomizationVisit 4 (Week 0) and reinforced at each patient contact.

Carotid ultrasound scans were performed within 2 weeks of Visit 2 (Week -4) and Visit 3 (Week -2), and within 1 week of Visits 7 (Week 26), 9 (Week 52), 11 (Week 78), and 13 (Week 104). A second IMT ultrasound was performed within 2 weeks of the IMT procedure completed for the final visit. Final IMT procedures were scheduled before discontinuation of the study treatment. The second and final IMT procedure was scheduled at or before Visit 13 (Week 104), at which time study treatment was terminated. The 2 IMT procedures for Visit 13 were performed on different days, whenever possible. IMT readings were performed centrally in 1 of the 2 IMT core laboratories.

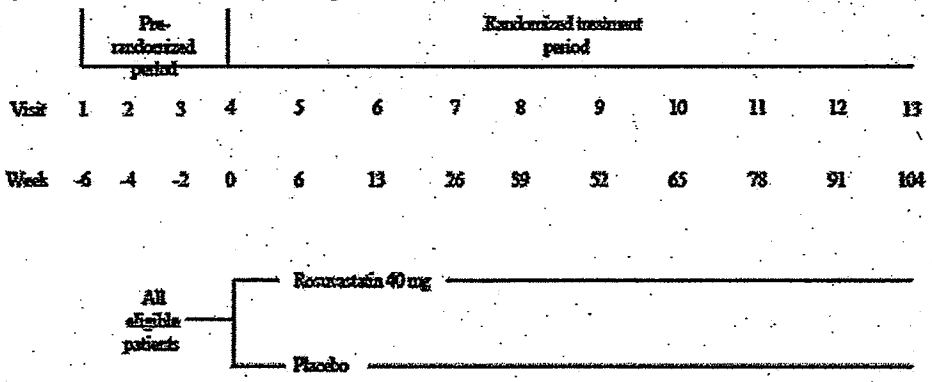
A bile acid sequestrant (BAS) was added to the blinded study drug based on LDL-C values. In the placebo group, a BAS was added in 1 of 2 circumstances based on a patient's inclusion criteria: 1) in patients with only age as a risk factor, a BAS was added if their LDL-C levels were ≥ 190 mg/dL on 2 consecutive protocol-specified lipid draws during the study; and, 2) in patients with 2 risk factors and a FRI of < 10% over 10 years, a BAS was added if the LDL-C levels were ≥ 160 mg/dL on 2 consecutive protocol-specified lipid draws during the study. In the rosuvastatin group, a BAS was added in patients with LDL-C levels ≥ 100 mg/dL on 2 consecutive protocol-specified lipid draws during the study.

The results of the LDL-C determinations were known to the central laboratory, but remained concealed to the investigator and study center personnel. A flag on the central laboratory report notified the investigator that BAS therapy was required. If LDL_C levels continued to be ≥ 190 mg/dL for those patients with only age as a risk factor, or ≥ 160 mg/dL for those with ≥ 2 risk factors and a < 10% FRI, despite continuation of diet, blinded study medication, and a BAS, the patient's primary care physician was notified of this occurrence and advised to manage the patient's treatment regimen. If a statin was added to the patient's regimen, blinded study medication and the BAS were discontinued. These patients had all end-of study procedures completed and were discontinued from the study.

Randomization: At the end of the screening period, patients who satisfied the entry criteria were randomly assigned to 1 of the following 2 treatment groups: rosuvastatin 40 mg or placebo. Patients were allocated to treatment in balanced blocks. A block of random numbers was assigned to each treatment center. Centers allocated patient numbers strictly sequentially. All

study personnel, except in the case of emergency unblinding, were unaware of the randomization code until all study data had been analyzed.

Figure 10.1.4.3-1: Study design



10.1.4.4 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Provide a written informed consent
2. Men between the ages of ≥ 45 and ≤ 70 years or women between the ages of ≥ 55 and ≤ 70 years
3. Patients with 2 or more risk factors and a 10-year Framingham CHD risk <10%:

   Fasting LDL-C at Visit 1 (Week -6) was ≥ 120 mg/dL (3.1 mmol/L) and < 160 mg/dL (4.1 mmol/L)

   An additional visit (Visit 1.1) may have been scheduled within 1 week to obtain another LDL-C determination if lipid levels were 114 mg/dL (2.95 mmol/L) to 119 mg/dL (<3.1 mmol/L), inclusive, or 160 mg/dL (4.1 mmol/L) to 168 mg/dL (4.3 mmol/L), inclusive

   Patients with age and no other risk factor:

   Fasting LDL-C at Visit 1 (Week -6) was ≥ 120 mg/dL (3.1mmol/L) and < 190 mg/dL (4.9 mmol/L)

   An additional visit (Visit 1.1) may have been scheduled within 1 week to obtain another LDL-C determination if lipid levels were 114 mg/dL (2.95 mmol/L) to 119 mg/dL (<3.1 mmol/L), inclusive, or 190 mg/dL (4.9 mmol/L) to 199 mg/dL (5.1 mmol/L), inclusive.

   If an additional assessment was made, the values from Visit 1 (Week -6) and

Visit 1.1 (Week -6 + 1 week) could be averaged and used for the evaluation of eligibility.

4. TG < 500 mg/dL (5.65 mmol/L) at Visit 1 (Week -6)
5. HDL-C levels ≤ 60 mg/dL (1.6 mmol/L) at Visit 1 (Week -6)
6. Maximum IMT ≥ 1.2 mm and < 3.5 mm at any location in the carotid ultrasound scans conducted at both Visit 2 (Week -4) and Visit 3 (Week -2)
7. Willing to follow all study procedures including study visits, fasting blood draws, and compliance with study treatment regimen

Exclusion Criteria:

1. Use of pharmacologic lipid-lowering medications (e.g., HMG-CoA reductase inhibitors, fibrate derivatives, bile acid binding resins, niacin or its analogues at doses > 400 mg) within 12 months prior to Visit 1 (Week -6)
2. History of hypersensitivity reactions to other HMG-CoA reductase inhibitors
3. Pregnant women, women who were breast-feeding, and women of childbearing potential who were not using chemical or mechanical contraception, or had a positive serum pregnancy test
4. Clinical evidence of CAD or any other atherosclerotic disease such as angina, MI, transient ischemic attack (TIA), symptomatic CAD, cerebrovascular accident (CVA), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), peripheral arterial disease, abdominal aortic aneurysm (AAA)
5. History of malignancy, except in patients who had been disease free for > 10 years or whose only malignancy had been basal or squamous cell skin carcinoma. Women with a history of cervical dysplasia would be excluded unless 3 consecutive normal cervical smears had subsequently been recorded before entry into the screening period.
6. Uncontrolled hypertension defined as either a mean resting diastolic blood pressure (DBP) of ≥ 100 mm Hg or a resting systolic blood pressure (SBP) of ≥ 200 mm Hg recorded at any time during the screening period
7. History of diabetes mellitus or current diabetes mellitus
8. Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) > 1.5 times the upper limit of normal (ULN) at Visit 1 or patients whose thyroid replacement therapy was initiated within the last 3 months
9. History of heterozygous or homozygous familial hypercholesterolemia or known hyperlipoproteinemia Types I, III, IV, or V (familial dysbetalipoproteinemia)
10. Use of concomitant medications, including statins, fibrates, niacin, BAS, other medication given to treat dyslipidemia, lymphocyte immune globulin, Rhogam, azathioprine, muromonab-CD3, cyclosporine, tacrolimus
11. History of alcohol and/or drug abuse within the past 5 years
12. Active liver disease or hepatic dysfunction as defined by elevations of ≥ 1.5 x ULN at Visit 1 in any of the following liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin
13. Serum creatine kinase (CK) > 3 x ULN at Visit 1 (Week -6)

14. Serum creatinine > 2.0 mg/dL (177 mmol/L) recorded during the screening period
15. Participation in another investigational drug study, and having ingested investigational drug ≤ 4 weeks before enrollment in the screening period
16. Randomized patient in this study who subsequently withdrew
17. History of a significant medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study

The following restrictions were applied to patients in this study:

1. Patients who were blood donors were not to have donated blood during the study and for 3 months following their last dose of study treatment
2. Patients must have fasted (water was permitted) and refrained from alcohol consumption for 8 hours before visits requiring blood collection
3. Patients were to have refrained from cigarette smoking on the morning of each visit
4. Patients were to have been advised to maintain their normal physical activities or exercise routines during the study
5. Patients were to have alerted the investigator regarding any elective planned surgery or extended travel.

10.1.4.5 Amendments and Post Hoc Changes

Amendment 1 (16 April 2003)

- Extended patient enrollment period to May 2006
- Lower limit of LDL-C at screening decreased from 130 mg/dL to ≥ 120 mg/dL
- Added 1 optional pre-screening visit to review study outline and check lipid values
- Stipulated that final IMT procedures be scheduled before the discontinuation of study treatment
- Additional interrogation angles were permitted when performing screening IMT measurements at Visits 2 and 3, if the image appeared to show a thicker region of the arterial site.
- Patients who did not successfully complete screening were not to be re-screened, with the exception of patients who had previously failed the LDL-C criteria in the range of 120 mg/dL to < 130 mg/dL. Such patients may have been re-screened.
- Decreased the lower limit of LDL-C at screening from 130 mg/dL to ≥ 120mg/dL and decreased the limits of LDL-C from 123 mg/dL to 129 mg/dL to > 114 mg/dL to119 mg/dL for an additional visit.
- Maximum IMT ≥ 1.2 mm and < 3.5 mm measurements specified "at any location".
- If a patients was removed from treatment for ≥ 2 weeks, the AstraZeneca physician or designee was to be contacted prior to any decision to withdraw or resume treatment.
- Laboratory specimens analyzed would not be frozen and stored, but analyzed on an ongoing basis. Removed references to plasma.
- SAEs were to be recorded for 30 days following the last dose of study drug.
- Added serum creatinine to abbreviated chemistry panel.

Amendment 2 (17 November 2004)

- Added that database lock would define the end of the study, and was anticipated in August 2006.
- Added that AstraZeneca would provide safety updates and reports according to local requirements and that the investigator was responsible for providing the IRB with any serious and unexpected AEs from any other study connected with the IP
- Added provision to meet HIPPA compliance.
- The 2 IMT procedures for Visit 13 were to be performed on different days whenever possible. All non-IMT procedures would be conducted and a single IMT would be performed on any patient withdrawing after 26 weeks.
- Added as a discontinuation criterion the development of a high-risk medical condition.
- Added that after the patient completed or discontinued the study, they were treated according to local medical practice.
- Added an optional genetic sample collection and separate informed consent form if participating.

Local Amendment (Belgium) (28 January 2003)

- Made provision for an optional pre-screening visit. Study procedures and timelines would be explained by the sub-investigator and if the patients was interested, would sign a pre-screening informed consent. Lipid values would be checked using a finger prick test and patients found to be in the lipid range of the study inclusion criteria ±15% would be referred to the PI for Visit 1.

Local Amendment (France) (14 April 2003)

- Made provision for an optional pre-screening visit. A specific informed consent was collected from the patient after having explained study procedures and timelines. Lipid values were checked using a finger prick test and patients found to be in the range of the inclusion criteria ± 15% entered the study. This optional pre-screening visit was to be performed in fasted patients within 7 days of Visit 1.

Local Amendment (Czech Republic) (24 April 2003)

- Made provision for an optional pre-screening visit. Lipid values would be checked using a finger prick test or from 1 blood sample collection and patients found to be in the lipid range of the study inclusion criteria ±15% would be referred to the pre-IMT evaluation.

Changes to Planned Analyses (before database lock)

- A time-weighted average was added to the lipid analyses in addition to the LOCF in the SAP
- Many subgroup analyses were added to the SAP
- Estimated GFR was added to the safety data collection in the SAP

Post-hoc Changes to Planned Analyses (after database lock)

- The SAP specified fixed effects for intercept, site, and TIME. This was changed to fixed effects for intercept and TIME.

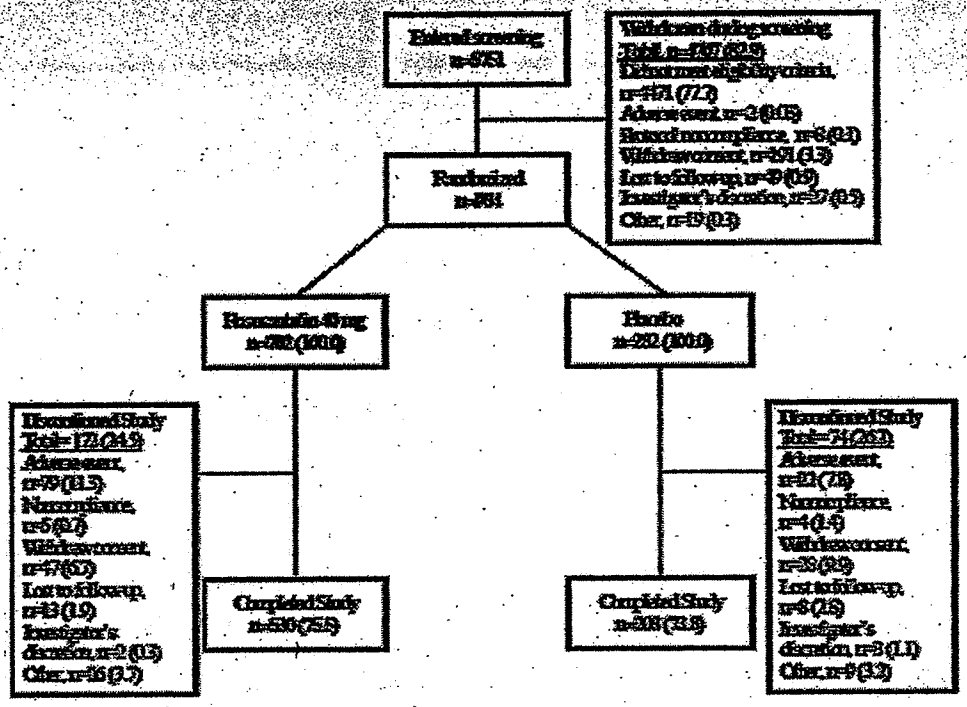
- The analysis of CRP data was changed from the planned ANCOVA to use of the Wilcoxon Rank Sum test, as the analysis of percent change in CRP provides a skewed data distribution.
- An analysis of AE status relative to the date of patient withdrawal was conducted
- In addition to the planned analysis to obtain a p-value for difference in rosuvastatin annualized change vs. zero, an analysis obtained p-values for the difference in placebo annualized change vs. zero.
- A p-value for the chi square comparison between the 2 tratment groups for maximum cIMT of the 12 carotid artery sites was obtained.
- Sensitivity analyses were conducted.
- Non-serious and serious ischemic treatment-emergent CV events were examined in a post-hoc analysis.

10.1.4.6 Results

10.1.4.6.1 Disposition

A total of 5751 patients entered the screening period. Of these, 984 (17.1%) were randomized to study treatment – 702 patients were randomized to rosuvastatin 40 mg and 282 patients were randomized to placebo). Of 984 randomized patients, 246 (25.0%) withdrew from treatment over the 2-year period. The most common reason for study discontinuation was AEs (10.3%). Three randomized patients (2 in the rosuvastatin group and 1 in the placebo group) received no study treatment and were not included in the safety population; thus, 981 patients were evaluated for safety. Of these, 876 were analyzed for efficacy in the ITT population, and 863 were analyzed for efficacy in the PP population.

Figure 10.1.4.6.1-1: Patient disposition, N (%)



10.1.4.6.2 Demographics

Table 10.1.4.6.2-1: Demographic and baseline characteristics – randomized patients

BASELINE CHARACTERISTIC SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=702	PLACEBO N=282
Age		
Mean (SD)	56.7 (6.2)	56.9 (6.03)
Min, max	45, 70	45, 70
Age group		
18 – 64 [N (%)]	611 (87.0)	244 (86.5)
≥ 65 [N (%)]	91 (13.0)	38 (13.5)
Sex		
Male [N (%)]	421 (60.0)	167 (59.2)
Female [N (%)]	281 (40.0)	115 (40.8)
BMI (kg/m^2)		
Mean (SD)	27.1 (3.99)	27.5 (4.04)
Min, max	16, 47	19, 42
BMI group		
< 20 kg/m^2 [N (%)]	10 (1.4)	4 (1.4)
20 - < 25 kg/m^2 [N (%)]	224 (31.9)	75 (26.6)
25 - < 30 kg/m^2 [N (%)]	324 (46.2)	143 (50.7)
≥30 kg/m^2 [N (%)]	141 (20.1)	60 (21.3)
Race		
Caucasian [N (%)]	659 (93.9)	268 (95.0)

BASELINE CHARACTERISTIC SUMMARY STATISTIC	ROSUVASTATIN 40 MG N=702	PLACEBO N=282
Black [N (%)]	11 (1.6)	2 (0.7)
Asian [N (%)]	8 (1.1)	0
Hispanic [N (%)]	23 (3.3)	10 (3.5)
Other [N (%)]	1 (0.1)	2 (0.7
Maximum cIMT (mm) (Week -2)		
Mean (SD)	1.869 (0.511)	1.932 (0.562)
Range	1.185, 5.122	1.201, 3.478

Table 10.1.4.6.2-2: Co-morbidities

CO-MORBIDITY	ROSUVASTATIN 40 MG N=702 N (%)	PLACEBO N=282 N (%)
Smoking	22 (3.1)	16 (5.7)
Hypertension	138 (19.7)	58 (20.6)
HDL-C < 40 mg/dL	64 (9.1)	36 (12.8)
HDL-C ≥ 60 mg/dL	46 (6.6)	12 (4.3)
Male age ≥ 45 years; Female age ≥ 55 years	702 (100.0)	282 (100.0)
Family history of premature CHD	65 (9.3)	31 (11.0)
Diabetes	1 (0.1)	0
Total number of risk factors:		
0	31 (4.4)	7 (2.5)
1	448 (63.8)	164 (58.2)
2	175 (24.9)	90 (31.9)
3	45 (6.4)	17 (6.0)
4	3 (0.4)	4 (1.4)
5	0	0
NCEP ATP III risk category		
Low (<10%)	690 (98.3)	277 (98.2)
Moderate (10-20%)	11 (1.6)	5 (1.8)
High (>20%)	1 (0.1)	0

Table 10.1.4.6.2-3: Concomitant medication use

MEDICATION	ROSUVASTATIN 40 MG N=702 N (%)	PLACEBO N=282 N (%)
ASA	139 (19.8)	66 (23.4)
Beta blocker	52 (7.4)	22 (7.8)
ACE inhibitors	29 (4.1)	17 (6.0)
ARB	28 (4.0)	11 (3.9)
Calcium channel blocker	20 (2.8)	8 (2.8)

10.1.4.6.3 Efficacy Findings

10.1.4.6.3.1 Primary Endpoint – For the primary endpoint, rosuvastatin slowed the progression of carotid atherosclerosis compared to placebo. The difference in the annualized rate of change in the maximum cIMT of all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI: -0.0196, -0.0093); this difference was

statistically significant (p<0.001). The annualized change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI: -0.0041, 0.0014), but was not significantly different from zero (p=0.3224). There was significant progression in the placebo group (+0.131 mm/year; 95% CI: 0.0087, 0.0174; p<0.0001).

Table 10.1.4.6.3.1-1: Changes from baseline values to the end of treatment (Week 104) in maximum cIMT of the 12 carotid artery sites - ITT population

STATISTICAL PARAMETER	ROSUVASTATIN 40MG N=624	PLACEBO N=252
Annualized change (mm/year)	-0.0014	0.0131
Absolute change from 0 to 2 years (mm)	-0.0028	0.0261
SE of annualized change (mm/year)	0.00140	0.00222
95% CI for annualized change (mm/year)	-0.0041, 0.0014	0.0087, 0.0174

Table 10.1.4.6.3.1-2: Analysis of between-group and within-rosuvastatin group comparisons of change in maximum cIMT of the 12 carotid artery sites from baseline values to the end of treatment – ITT population

STATISTICAL PARAMETER	ROSUVASTATIN 40MG VS. PLACEBO
Difference in annualized change (mm/year)	-0.145
Difference at 2 years (mm)	-0.0289
SE of difference in annualized change (mm/year)	0.00263
95% CI for difference in annualized change (mm/year)	-0.0196, -0.0093
p-value for difference in annualized change	<0.0001
	Rosuvastatin 40 mg vs. zero
p-value for difference in rosuvastatin annualized change vs. zero	0.3224

10.1.4.6.3.2 Secondary Endpoints

Table 10.1.4.6.3.2-1: Changes from baseline values to the end of the treatment period (Week 104) in maximum cIMT of the individual sites – ITT population

STATISTICAL PARAMETER	ROSUVASTATIN 40MG N=624	PLACEBO N=252
Near and far walls of the right and left CCA		
Annualized change (mm/year)	-0.0038	0.0084
Absolute change from 0 to 2 years (mm)	-0.0077	0.0167
SE of annualized change (mm/year)	0.00132	0.00208
95% CI for annualized change (mm/year)	-0.0064, -0.0013	0.0043, 0.0124
Near and far walls of the right and left carotid bulb		
Annualized change (mm/year)	-0.0040	0.0172
Absolute change from 0 to 2 years (mm)	-0.0080	0.0344
SE of annualized change (mm/year)	0.00254	0.00401
95% CI for annualized change (mm/year)	-0.0090, 0.0010	0.0094, 0.0251

Near and far walls of the right and left ICA		
Annualized change (mm/year)	0.0039	0.0145
Absolute change from 0 to 2 years (mm)	0.0079	0.0289
SE of annualized change (mm/year)	0.00246	0.00389
95% CI for annualized change (mm/year)	-0.0009, 0.0088	0.0068, 0.0221

Table 10.1.4.6.3.2-2: Analysis of between-group and within-rosuvastatin group comparisons of change in maximum cIMT of the individual sites from baseline values to the end of treatment – ITT population

STATISTICAL PARAMETER	ROSUVASTATIN 40MG VS. PLACEBO
Near and far wall of the right and left CCA	
Difference in annualized change (mm/year)	-0.0122
Difference at 2 years (mm)	-0.0244
SE of difference in annualized change (mm/year)	0.00247
95% CI for difference in annualized change (mm/year)	-0.0170, -0.0074
p-value for difference in annualized change	<0.0001
	Rosuvastatin 40 mg vs. zero
p-value for difference in rosuvastatin annualized change vs. zero	0.0036
Near and far wall of the right and left carotid bulb	
Difference in annualized change (mm/year)	-0.0212
Difference at 2 years (mm)	-0.0425
SE of difference in annualized change (mm/year)	0.00475
95% CI for difference in annualized change (mm/year)	-0.0306, -0.0119
p-value for difference in annualized change	<0.0001
	Rosuvastatin 40 mg vs. zero
p-value for difference in rosuvastatin annualized change vs. zero	0.1139
Near and far wall of the right and left internal carotid	
Difference in annualized change (mm/year)	-0.0105
Difference at 2 years (mm)	-0.0210
SE of difference in annualized change (mm/year)	0.00462
95% CI for difference in annualized change (mm/year)	-0.0196, -0.015
p-value for difference in annualized change	0.0228
	Rosuvastatin 40 mg vs. zero
p-value for difference in rosuvastatin annualized change vs. zero	0.1101

Table 10.1.4.6.3.2-3: Changes from baseline values to the end of the treatment period (Week 104) in mean cIMT of the near and far walls of the right and left CCA – ITT population

STATISTICAL PARAMETER	ROSUVASTATIN 40MG N=624	PLACEBO N=252
Annualized change (mm/year)	0.0004	0.0088
Absolute change from 0 to 2 years (mm)	0.0007	0.0176
SE of annualized change (mm/year)	0.00077	0.00121

STATISTICAL PARAMETER	ROSUVASTATIN 40MG N=624	PLACEBO N=252
95% CI for annualized change (mm/year)	-0.0011, 0.0019	0.0064, 0.0112

Table 10.1.4.6.3.2-4: Analysis of between-group and within-rosuvastatin group comparisons of change in mean cIMT of the near and far walls of the right and left CCA from baseline values to end of treatment – ITT population

STATISTICAL PARAMETER	ROSUVASTATIN 40MG VS. PLACEBO
Difference in annualized change (mm/year)	-0.0085
Difference at 2 years (mm)	-0.0169
SE of difference in annualized change (mm/year)	0.00144
95% CI for difference in annualized change (mm/year)	-0.0113, -0.0056
p-value for difference in annualized change	<0.0001
	Rosuvastatin 40 mg vs. zero
p-value for difference in rosuvastatin annualized change vs. zero	0.6375

Table 10.1.4.6.3.2-5: Percent change from baseline in lipid values - LOCF

PARAMETER	ROSUVASTATIN 40 MG N=622	PLACEBO N=251	ROSUVASTATIN 40 MG VS. PLACEBO
LDL-C (mg/dL)			
LSmean % change	-45.3	-0.6	-44.7
SE	0.89	1.39	1.65
CI	-47.0, -43.6	-3.3, 2.1	-47.9, -41.5
p-value			<0.0001
TC (md/dL)			
LSmean % change	-31.0	0.2	-31.2
SE	0.66	1.05	1.24
CI	-32.3, -29.7	-1.8, 2.3	-33.7, -28.8
p-value			<0.0001
HDL-C (mg/dL)			
LSmean % change	8.9	3.7	5.2
SE	0.67	1.06	1.26
CI	7.5, 10.2	1.6, 5.8	2.7, 7.6
p-value			<0.0001
TG (md/dL)			
LSmean % change	-14.1	9.2	-23.3
SE	1.74	2.73	3.24
CI	-17.6, -10.7	3.8, 14.6	-29.7, -17.0
p-value			<0.0001
Non-HDL-C (mg/dL)			
LSmean % change	-41.9	-0.4	-41.6
SE	0.83	1.31	1.55
CI	-43.6, -40.3	-2.9, 2.2	-44.6, -38.5
p-value			<0.0001
LDL-C/HDL-C ratio			
LSmean % change	-48.3	-2.7	-45.6
SE	0.94	1.48	1.75
CI	-50.1, -46.4	-5.6, 0.2	-49.0, -42.1
p-value			<0.0001

PARAMETER	ROSUVASTATIN 40 MG N=622	PLACEBO N=251	ROSUVASTATIN 40 MG VS. PLACEBO
TC/HDL-C ratio			
LSmean % change	-35.3	-2.0	-33.3
SE	0.74	1.16	1.37
CI	-36.7, -33.8	-4.2, 0.3	-36.0, -30.6
p-value			<0.0001
Non-HDL-C/HDL-C			
LSmean % change	-45.0	-2.1	-42.8
SE	0.93	1.47	1.74
CI	-46.8, -43.2	-5.0, 0.7	-46.3, -39.4
p-value ratio			<0.0001
Apo B (mg/dL)			
LSmean % change	-38.4	-1.9	-36.5
SE	0.78	1.24	1.46
CI	-39.9, -36.9	-4.3, 0.6	-39.4, -33.7
p-value			<0.0001
Apo A-I (mg/dL)			
LSmean % change	6.7	3.4	3.3
SE	0.52	0.83	0.98
CI	5.7, 7.7	1.8, 5.1	1.3, 5.2
p-value			<0.0001
Apo B/Apo A-I ratio			
LSmean % change	-41.5	-4.5	-37.0
SE	0.79	1.26	1.49
CI	-43.1, -40.0	-7.0, -2.0	-39.9, -34.1
p-value			<0.0001

Table 10.1.4.6.3.2-6: Analysis of percent change from baseline in CRP to the final visit – ITT population

STATISTICAL PARAMETER	ROSUVASTATIN 40 MG N=624	PLACEBO N=252	ROSUVASTATIN 40 MG VS. PLACEBO
N	505	203	
Median, (%)	-36.2	-2.9	
Range, (%)	-98.6, 1994.4	-90.3, 1715.0	
p-value (LOCF)			<0.0001

10.1.4.6.4 Safety Findings

10.1.4.6.4.1 Deaths
One patient died during the study.

Patient 0458/0803, a 64-year-old white male in the rosuvastatin group, died approximately 2 months post study treatment. He experienced an AE of paresthesia of the right hand before start of study medication from Day -7 and an AE of amnesia from Day 113. From Day 125, the patient experienced visual disturbance and he experienced blindness from Day 147. Study medication was withdrawn on Day 147. Creutzfeldt-Jakob disease, a rapidly progressive dementia, was diagnosed on Day 163 and the patient was admitted to the hospital. Magnetic resonance imaging (MRI) on Day 171 showed parieto-occipital cortical abnormality and an

electroencephalogram (EEG) later showed diffuse encephalopathy. The patient died on Day 207, reportedly due to Creutzfeldt-Jakob disease. An autopsy was not performed. Concomitant medications included a multivitamin for nutritional supplementation, ginkgo biloba (Tebonin) for aging prophylaxis, magnesium for muscle cramping, acetylsalicylic acid for circulation, oxymetazoline HCL (Nasivin), and cough syrup for a cold.

10.1.4.6.4.2 Other Serious Adverse Events

The frequency of nonfatal treatment-emergent SAEs was higher in the rosuvastatin group compared to the placebo group (9.0% vs. 6.8%, respectively). There were no cases of hepatitis, rhabdomyolysis, or renal failure during the course of the study.

Table 10.1.4.6.4.2-1: Number (%) of patients with the most commonly reported nonfatal treatment-emergent SAEs – Safety population

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Any SAE	**65 (9.3)**	**19 (6.8)**
Blood and lymphatic disorders	**1 (0.1)**	**0**
Lymphadenopathy	1 (0.1)	
Cardiac disorders	**8 (1.1)**	**0**
Acute coronary syndrome	2 (0.3)	0
Angina pectoris	2 (0.3)	0
Angina unstable	1 (0.1)	0
Atrial fibrillation	1 (0.1)	0
Atrial flutter	1 (0.1)	0
AV block	1 (0.1)	0
Ventricular tachycardia	1 (0.1)	0
Eye disorders	**3 (0.4)**	**0**
Cataract	1 (0.1)	0
Glaucomatocyclitic crises	1 (0.1)	0
Retinal detachment	1 (0.1)	0
Gastrointestinal disorders	**8 (1.1)**	**1 (0.4)**
Inguinal hernia	3 (0.4)	0
Abdominal pain	1 (0.1)	
Colitis ulcerative	1 (0.1)	
Duodenal ulcer	1 (0.1)	
Intestinal obstruction	1 (0.1)	
Mechanical ileus	1 (0.1)	
Esophagitis	1 (0.1)	
Impaired gastric emptying	0	1 (0.4)
General disorders and administration site conditions	**3 (0.4)**	**1 (0.4)**
Chest pain	1 (0.1)	0
Hyperplasia	1 (0.1)	0
Non-cardiac chest pain	1 (0.1)	0
Fatigue	0	1 (0.4)
Pyrexia	0	1 (0.4)
Hepatobiliary disorders	**0**	**1 (0.4)**
Cholecystitis	0	1 (0.4)
Cholelithiasis	0	1 (0.4)

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Infections and infestations	**7 (1.0)**	**4 (1.4)**
Diverticulitis	2 (0.3)	0
Bursitis infective	1 (0.1)	0
Cellulitis	1 (0.1)	0
Sinusitis	1 (0.1)	0
Pneumonia	1 (0.1)	1 (0.4)
Creutzfeldt-Jakob disease	1 (0.1)	0
Urinary tract infection	1 (0.1)	0
Epidemic nephropathy	0	1 (0.4)
Gastroenteritis	0	1 (0.4)
Pleurisy viral	0	1 (0.4)
Postoperative wound infection	0	1 (0.4)
Injury, poisoning, and procedural complications	**9 (1.3)**	**3 (1.1)**
Joint injury	2 (0.3)	0
Tendon rupture	2 (0.3)	1 (0.4)
Ankle fracture	1 (0.1)	0
Concussion	1 (0.1)	0
Ligament injury	1 (0.1)	0
Patella fracture	1 (0.1)	0
Radius fracture	1 (0.1)	0
Ureteric injury	1 (0.1)	0
Hip fracture	0	1 (0.4)
Procedural pain	0	1 (0.4)
Investigations	**0**	**3 (1.1)**
Liver function test abnormal	0	1 (0.4)
RBC ESR increased	0	1 (0.4)
Transaminases increased	0	1 (0.4)
Virus serology test positive	0	1 (0.4)
Musculoskeletal and connective tissue disorders	**11 (1.6)**	**3 (1.1)**
Osteoarthritis	3 (0.4)	1 (0.4)
Arthritis	2 (0.3)	0
Myalgia	1 (0.1)	1 (0.4)
Rotator cuff syndrome	1 (0.1)	1 (0.4)
Bursitis	1 (0.1)	0
Intervertebral disc protrusion	1 (0.1)	0
Musculoskeletal chest pain	1 (0.1)	0
Osteonecrosis	1 (0.1)	0
Polymyalgia rheumatica	1 (0.1)	0
Synovitis	1 (0.1)	0
Musculoskeletal stiffness	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**12 (1.7)**	**3 (1.1)**
Prostate cancer	3 (0.4)	0
Breast cancer	2 (0.3)	0
Basal cell carcinoma	1 (0.1)	0
Bronchial carcinoma	1 (0.1)	0
Lung neoplasm malignant	1 (0.1)	0
Malignant melanoma	1 (0.1)	0
Renal neoplasm	1 (0.1)	0

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Squamous cell carcinoma	1 (0.1)	0
Thyroid gland cancer	1 (0.1)	0
Colon cancer	0	1 (0.4)
Lymphoma	0	1 (0.4)
Ovarian cancer	0	1 (0.4)
Nervous system disorders	**3 (0.4)**	**3 (1.1)**
Headache	1 (0.1)	0
Subarachnoid hemorrhage	1 (0.1)	0
Syncope	1 (0.1)	0
Dizziness	0	1 (0.4)
Epilepsy	0	1 (0.4)
Syncope vasovagal	0	1 (0.4)
Psychiatric disorders	**1 (0.1)**	**0**
Depression	1 (0.1	0
Renal and urinary disorders	**1 (0.1)**	**4 (1.4)**
Hematuria	1 (0.1)	1 (0.4)
Bladder prolapse	0	1 (0.4)
Nephrolithiasis	0	1 (0.4)
Proteinuria	0	1 (0.4)
Renal colic	0	1 (0.4)
Reproductive system and breast disorders	**1 (0.1)**	**2 (0.7)**
Ovarian cyst	1 (0.1)	0
BPH	0	1 (0.4)
Rectocele	0	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	**2 (0.3)**	**0**
Asthma	1 (0.1)	0
Nasal septum deviation	1 (0.1)	0
Skin and subcutaneous tissue disorders	**1 (0.1)**	**1 (0.4)**
Pemphigoid	1 (0.1)	0
Night sweats	0	1 (0.4)
Vascular disorders	**2 (0.3)**	**4 (1.4)**
Aortic stenosis	1 (0.1)	0
DVT	1 (0.1)	0
Hematoma	0	1 (0.4)
Hypotension	0	1 (0.4)
Thrombosis	0	1 (0.4)
Venous thrombosis	0	1 (0.4)

10.1.4.6.4.3 Dropouts and Other Significant Adverse Events

The frequency of treatment-emergent DAEs was higher in the rosuvastatin group compared to the placebo group (11.3% vs. 7.8%, respectively). The most frequent treatment-emergent DAEs were in the primary SOC "Musculoskeletal and connective tissue disorders" where there were 30 subjects (4.3%) in the rosuvastatin group who discontinued and 8 subjects (2.8%) in the placebo group.

Table 10.1.4.6.4.3-1: Number (%) of patients with the most commonly reported treatment-emergent DAEs – Safety population

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Any DAE	**78 (11.1)**	**22 (7.8)**
Cardiac disorders	**4 (0.6)**	**0**
Acute coronary syndrome	2 (0.3)	0
Arrhythmia	1 (0.1)	0
Ventricular extrasystoles	1 (0.1)	0
Ear and labyrinth disorders	**1 (0.1)**	**0**
Tinnitus	1 (0.1)	0
Gastrointestinal disorders	**12 (1.7)**	**2 (0.7)**
Abdominal pain upper	3 (0.4)	0
Nausea	3 (0.4)	0
Diarrhea	2 (0.3)	1 (0.4)
Constipation	1 (0.1)	1 (0.4)
Abdominal distension	1 (0.1)	0
Abdominal pain	1 (0.1)	0
Abdominal pain lower	1 (0.1)	0
Breath odor	1 (0.1)	0
Change of bowel habit	1 (0.1)	0
General disorders and administration site conditions	**4 (0.6)**	**3 (1.1)**
Fatigue	4 (0.6)	3 (1.1)
Pyrexia	0	1 (0.4)
Infections and infestations	**3 (0.4)**	**2 (0.7)**
Bronchitis	1 (0.1)	0
Creutzfeldt-Jakob disease	1 (0.1)	0
Parvovirus infection	1 (0.1)	0
Pneumonia	0	1 (0.4)
Viral infection	0	1 (0.4)
Investigations	**9 (1.3)**	**5 (1.8)**
Hepatic enzyme increased	5 (0.7)	0
ALT increased	2 (0.3)	0
AST increased	2 (0.3)	0
Blood CPK increased	2 (0.3)	0
Liver function test abnormal	1 (0.1)	2 (0.7)
GGT increased	1 (0.1)	0
Hepatic enzyme increased	1 (0.1)	0
Blood bilirubin increased	0	1 (0.4)
RBC sedimentation rate increased	0	1 (0.4)
Transaminases increased	0	1 (0.4)
Virus serology test positive	0	1 (0.4)
Metabolism and nutrition disorders	**0**	**1 (0.4)**
NIDDM	0	1 (0.4)
Musculoskeletal and connective tissue disorders	**30 (4.3)**	**8 (2.8)**
Myalgia	17 (2.4)	5 (1.8)
Muscular weakness	2 (0.3)	0
Neck pain	2 (0.3)	0

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Musculoskeletal stiffness	1 (0.1)	2 (0.7)
Pain in extremity	1 (0.1)	1 (0.4)
Arthralgia	1 (0.1)	0
Back pain	1 (0.1)	0
Muscle spasms	1 (0.1)	0
Musculoskeletal pain	1 (0.1)	0
Pain in extremity	1 (0.1)	0
Polymyalgia	1 (0.1)	0
Polymyalgia rheumatica	1 (0.1)	0
Tendonitis	1 (0.1)	0
Bursitis	0	1 (0.4)
Joint stiffness	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.3)**	**1 (0.4)**
Prostate cancer	1 (0.1)	0
Thyroid gland cancer	1 (0.1)	0
Ovarian cancer	0	1 (0.4)
Nervous system disorders	**11 (1.6)**	**2 (0.7)**
Headache	4 (0.6)	0
Hypoaesthesia	2 (0.3)	0
Dizziness	1 (0.1)	1 (0.4)
Balance disorder	1 (0.1)	0
Neuralgia	1 (0.1)	0
Subarachnoid hemorrhage	1 (0.1)	0
Tension headache	1 (0.1)	0
Tremor	0	1 (0.4)
Psychiatric disorders	**1 (0.1)**	**2 (0.7)**
Disorientation	1 (0.1)	0
Depression	0	1 (0.4)
Insomnia	0	1 (0.4)
Renal and urinary disorders	**0**	**1 (0.4)**
Hematuria	0	1 (0.4)
Proteinuria	0	1 (0.4)
Reproductive system and breast disorders	**0**	**1 (0.4)**
Menopausal symptoms	0	1 (0.4)
Skin and subcutaneous tissue disorders	**3 (0.4)**	**2 (0.7)**
Alopecia	1 (0.1)	1 (0.4)
Rash	1 (0.1)	0
Rash morbilliform	1 (0.1)	0
Night sweats	0	1 (0.4)
Vascular disorders	**0**	**1 (0.4)**
Hypotension	0	1 (0.4)

10.1.4.6.4.4 All Treatment Emergent Adverse Events Reported

Of the 700 rosuvastatin-treated patients in the safety population, 583 (83.3%) had a treatment emergent AE, vs. 22/281 (80.4%) of placebo-treated patients. The most common (≥ 1%)

treatment-emergent AEs, summarized by SOC and preferred term are shown in Table 10.1.4.6.4.4-1 below:

Table 10.1.4.6.4.4-1: Number (%) of patients with the most commonly reported treatment-emergent adverse events – Safety population

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Any AE	**583 (83.3)**	**226 (80.4)**
Blood and lymphatic system disorders	**7 (1.0)**	**1 (0.4)**
Cardiac disorders	**27 (3.9)**	**9 (3.2)**
Palpitations	4 (0.6)	4 (1.4)
Ear and labyrinth disorders	**30 (4.3)**	**6 (2.1)**
Vertigo	14 (2.0)	3 (1.1)
Endocrine disorders	**5 (0.7)**	**3 (1.1)**
Hypothyroidism	1 (0.1)	3 (1.1)
Eye disorders	**36 (5.1)**	**20 (7.1)**
Cataract	6 (0.9)	5 (1.8)
Visual disturbance	1 (0.1)	3 (1.1)
Gastrointestinal disorders	**156 (22.3)**	**72 (25.6)**
Diarrhea	24 (3.4)	11 (3.9)
Abdominal pain upper	19 (2.7)	12 (4.3)
Abdominal pain	17 (2.4)	5 (1.8)
Constipation	16 (2.3)	12 (4.3)
Nausea	16 (2.3)	7 (2.5)
Dyspepsia	15 (2.1)	6 (2.1)
GERD	11 (1.6)	6 (2.1)
Flatulence	9 (1.3)	3 (1.1)
Toothache	7 (1.0)	3 (1.1)
Vomiting	6 (0.9)	6 (2.1)
Inguinal hernia	5 (0.7)	3 (1.1)
Abdominal pain lower	3 (0.4)	3 (1.1)
Gingivitis	0	3 (1.1)
General disorders and administration site conditions	**72 (10.3)**	**32 (11.4)**
Fatigue	39 (5.6)	16 (5.7)
Edema peripheral	13 (1.9)	3 (1.1)
Pyrexia	1 (0.1)	5 (1.8)
Hepatobiliary disorders	**3 (0.4)**	**5 (1.8)**
Cholelithiasis	1 (0.1)	5 (1.8)
Immune system disorders	**13 (1.9)**	**4 (1.4)**
Seasonal allergy	10 (1.4)	2 (0.7)
Infections and infestations	**303 (43.3)**	**116 (41.3)**
Nasopharyngitis	81 (11.6)	30 (10.7)
Influenza	66 (9.4)	29 (10.3)
Upper respiratory tract infection	50 (7.1)	12 (4.3)
Sinusitis	33 (4.7)	14 (5.0)
Bronchitis	29 (4.1)	13 (4.6)
Urinary tract infection	24 (3.4)	7 (2.5)
Gastroenteritis	13 (1.9)	9 (3.2)
Pneumonia	11 (1.6)	5 (1.8)
Gastroenteritis viral	10 (1.4)	5 (1.8)

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Pharyngitis	10 (1.4)	3 (1.1)
Cystitis	9 (1.3)	8 (2.8)
Tooth infection	6 (0.9)	3 (1.1)
Skin infection	2 (0.3)	3 (1.1)
Herpes simplex	1 (0.1)	3 (1.1)
Injury, poisoning, and procedural complications	**88 (12.6)**	**43 (15.3)**
Joint injury	12 (1.7)	1 (0.4)
Muscle strain	9 (1.3)	3 (1.1)
Contusion	8 (1.1)	6 (2.1)
Joint sprain	5 (0.7)	3 (1.1)
Meniscus lesion	2 (0.3)	3 (1.1)
Procedural pain	2 (0.3)	4 (1.4)
Arthropod bite	1 (0.1)	3 (1.1)
Investigations	**81 (11.6)**	**21 (7.5)**
Blood CPK increased	18 (2.6)	2 (0.7)
Hepatic enzyme increased	11 (1.6)	2 (0.7)
ALT increased	10 (1.4)	0
CRP increased	8 (1.1)	1 (0.4)
AST increased	7 (1.0)	0
Metabolism and nutrition disorders	**12 (1.7)**	**10 (3.6)**
Diabetes mellitus	1 (0.1)	4 (1.4)
Musculoskeletal and connective tissue disorders	**300 (42.9)**	**117 (41.6)**
Myalgia	89 (12.7)	34 (12.1)
Arthralgia	71 (10.1)	20 (7.1)
Back pain	59 (8.4)	29 (10.3)
Muscle spasms	26 (3.7)	8 (2.8)
Osteoarthritis	25 (3.6)	8 (2.8)
Tendonitis	23 (3.3)	6 (2.1)
Pain in extremity	20 (2.9)	6 (2.1)
Shoulder pain	14 (2.0)	8 (2.8)
Arthritis	11 (1.6)	2 (0.7)
Neck pain	11 (1.6)	3 (1.1)
Musculoskeletal stiffness	8 (1.1)	10 (3.6)
Bone pain	7 (1.0)	3 (1.1)
Muscular weakness	5 (0.7)	3 (1.1)
Musculoskeletal chest pain	5 (0.7)	3 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**33 (4.7)**	**11 (3.9)**
Basal cell carcinoma	7 (1.0)	0
Thyroid neoplasm	4 (0.6)	3 (1.1)
Nervous system disorders	**134 (19.1)**	**44 (15.7)**
Headache	45 (6.4)	15 (5.3)
Dizziness	28 (4.0)	8 (2.8)
Hypoaesthesia	11 (1.6)	10 (3.6)
Paresthesia	10 (1.4)	1 (0.4)
Sciatica	10 (1.4)	1 (0.4)
Migraine	7 (1.0)	1 (0.4)
Psychiatric disorders	**53 (7.6)**	**23 (8.2)**

SYSTEM ORGAN CLASS PREFERRED TERM	ROSUVASTATIN 40 MG N=700 N (%)	PLACEBO N=281 N (%)
Insomnia	21 (3.0)	11 (3.9)
Depression	11 (1.6)	3 (1.1)
Anxiety	6 (0.9)	5 (1.8)
Sleep disorder	4 (0.6)	3 (1.1)
Renal and urinary disorders	**41 (5.9)**	**20 (7.1)**
Hematuria	16 (2.3)	8 (2.8)
Proteinuria	6 (0.9)	3 (1.1)
Urinary incontinence	2 (0.3)	3 (1.1)
Reproductive system and breast disorders	**32 (4.6)**	**20 (7.1)**
Prostatitis	7 (1.0)	1 (0.4)
BPH	2 (0.3)	3 (1.1)
Respiratory, thoracic, and mediastinal disorders	**81 (11.6)**	**31 (11.0)**
Cough	32 (4.6)	8 (2.8)
Pharyngolaryngeal pain	16 (2.3)	7 (2.5)
Rhinitis allergic	9 (1.3)	1 (0.4)
Epistaxis	6 (0.9)	4 (1.4)
Dyspnea	4 (0.6)	3 (1.1)
Sinus congestion	4 (0.6)	3 (1.1)
Skin and subcutaneous tissue disorders	**69 (9.9)**	**34 (12.1)**
Rash	13 (1.9)	7 (2.5)
Pruritus	9 (1.3)	6 (2.1)
Eczema	6 (0.9)	4 (1.4)
Alopecia	4 (0.6)	3 (1.1)
Dermatitis contact	4 (0.6)	3 (1.1)
Night sweats	0	3 (1.1)
Vascular disorders	**36 (5.1)**	**14 (5.0)**
Hypertension	19 (2.7)	7 (2.5)

10.1.4.6.4.5 Other significant adverse events

Cardiovascular and cerebrovascular events were not adjudicated in METEOR. Six patients (0.9%) in the rosuvastatin group versus no patients in the placebo group experienced treatment-emergent ischemic CV events (serious and non-serious) defined as angina pectoris, acute coronary syndrome, myocardial infarction, or unstable angina (p=0.12).

The 6 patients in the rosuvastatin group with ischemic CV events were as follows:

- **Patient 0201/0008** experienced an AE of angina pectoris on D631. The patient continued in the study.
  Patient 0203/0132 had a SAE of acute coronary syndrome on D278. The patient was withdrawn from the study due to the SAE.
  Patient 0301/0601 experienced an AE of angina pectoris on D725. The patient continued in the study.

- **Patient 0302/0188,** experienced an MI during the study – on D29; the MI was not reported as serious nor was it a DAE. This patient also had 4 discrete events of angina pectoris (D25, 32, 64, and 131), 1 AE of unstable angina (D45), and 1 SAE each of angina pectoris (D132) and unstable angina (D49). This patient had pre-existing CAD, although that was not known at the time of randomization to rosuvastatin (as the patient did not disclose this history until Visit 5). This history became relevant because of the above multiple ischemic AEs during the course of the study. Symptomatic CAD was considered a CHD risk equivalent, denoting that this patient should have been categorized as high-risk at baseline according to NCEP ATP III guidelines. The patient was later discontinued from the study at the investigator's discretion.
- **Patient 0458/0825** had a SAE of acute coronary syndrome on D246. The patient was withdrawn from the study due to the SAE.
- **Patient 0801/0390** experienced an AE (D24) and a SAE (D126) of angina pectoris. The patient was later discontinued from the study at the investigator's discretion.

A synopsis of the narratives for the SAEs of ventricular tachycardia, atrial fibrillation, AV block, and atrial flutter are provided below:

- **Patient 0215/0059:** 48 year-old Caucasian male with no significant medical history was diagnosed with aortic stenosis on Day 10 of the study and with sleep apnea syndrome on Day 452. On Day 224, the patient developed ventricular tachycardia which was treated with cordarone (on day 438) and metoprolol (on day 466). The patient completed the study as planned. Ventricular tachycardia was reported as recovered on Day 576.

- **Patient 0301/0534:** 58 year-old Caucasian male with no significant medical history developed atrial fibrillation on Day 1. This was treated with metropolol on Day 258, then sotalol on Day 657. The patient completed the study as planned. Atrial fibrillation was reported as ongoing at end of study.

- **Patient 0242/0086:** 66 year-old Caucasian female with history of "arrhythmia" and hypothyroidism, and arthrosis and osteoporosis for which she was started on Vioxx on Day 107 (until Day 116), Actonel and Calcium/D3 on Day 134, and Foxamax on Day 176. On Day 116, the patient was reported as developing peripheral (leg) edema which was reported as resolved on Day 134. On Day 133, the patient developed AB block which resolved on Day 150. The patient completed the study as planned.

- **Patient 0108/2239:** 63 year-old Caucasian male with no significant medical history was diagnosed with atrial flutter on Day 1 of the study. The patient was treated with coumadin (started on Day 3 and ongoing at study end) and lanoxin (started on Day 7; stopped on Day 12) and sotalol (started on Day 54 and ongoing at study end). The patient completed the study as planned. Atrial flutter was reported as recovered on Day 46.

There were no events of cerebrovascular accident or transient ischemic attack reported during the randomized treatment period of the study. **Patient 0458/0829,** in the rosuvastatin treatment group, was diagnosed with a stenosis of the right carotid artery at the final study visit on Day 736.

In addition to abnormal hepatic laboratory values reported as AEs, one patient **(0103/2122)** in the placebo group had chronic cholecystitis with cholelithiasis and hepatic steatosis (D274) associated with clinically important elevations of ALT (>3 x ULN on 2 consecutive occasions greater than 48 hours apart) (D505).

In addition to elevated CK values reported as AEs, one patient **(0601/0415)** in the rosuvastatin group experienced exercise-induced muscle pain associated with a clinically important CK elevation (>10 x ULN) (D93). The patient completed the study.

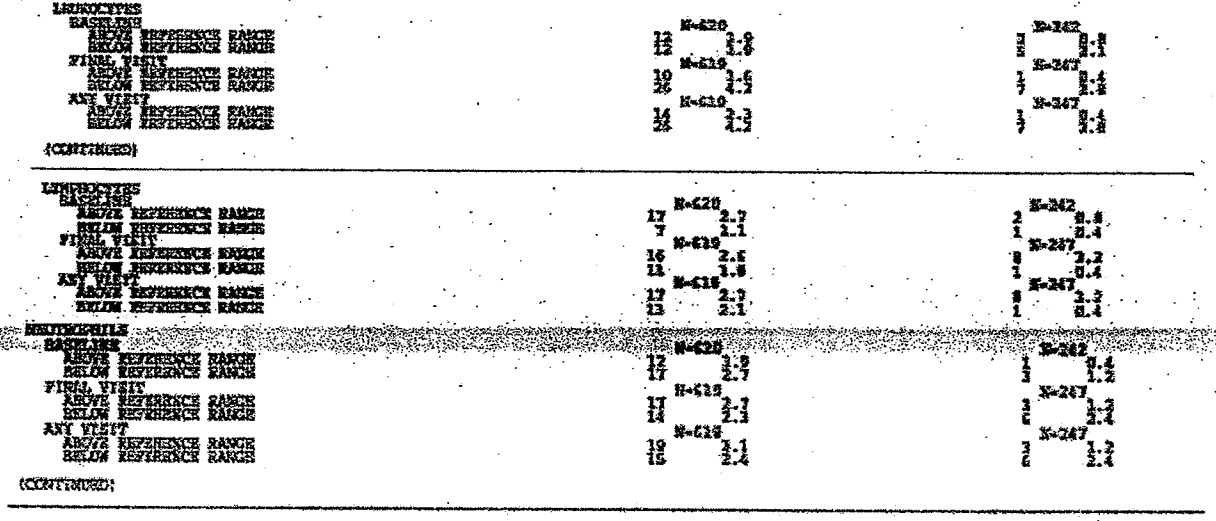
In addition to abnormal serum creatinine values reported as AEs, no patient had a clinically important elevation of serum creatinine that was >100% increase from baseline.

10.1.4.6.4.6 Laboratory values

Hematology

There were no clinically meaningful changes in values of hematology parameters over time

Table 10.1.4.6.4.6-1: Hematology values outside of reference range – safety population



Clinically significant changes in values of ALT over time are summarized below.

Table 10.1.4.6.4.6-2: Clinically significant elevations of ALT (> 3x ULN) – safety population

	Rosuvastatin 40 mg (N=700)	Placebo (N=281)
Patients with baseline and subsequent measurement, n (%)	689 (100.0)	276 (100.0)
>3 x ULN at any visit, n (%)	15 (2.2)	2 (0.7)
>3 x ULN at 2 consecutive visits, n (%)	4 (0.6)	1 (0.4)

Overall, 2.2% of patients in the rosuvastatin group and 0.7% of patients in the placebo group experienced elevations in ALT > 3 x ULN. Of these patients, 0.6% in the rosuvastatin group and 0.4% in the placebo group experienced an elevation in ALT > 3 x ULN on 2 consecutive visits at least 48 hours apart. These patients are described below:

- **Patient 0501/0228**, a 65-year-old white female treated with **rosuvastatin**, had an ALT value of 25 U/L at Week -6 and an elevated baseline (Week 0) ALT of 77 U/L. On Day 40, the patient had an ALT value of 219 U/L (> 3 x ULN), an AST of 117 U/L, and a GGT of 233 U/L; on (follow-up) Day 44, ALT was 175 U/L (> 3 x ULN on 2 consecutive visits greater than 48 hours apart), AST was 88 U/L, and GGT was 251 U/L. The patient had AEs of ALT, AST, and GGT increased reported from Day 40 to Day 92 and was withdrawn from the study due to ALT and AST elevation. No associated symptoms were reported. Study drug was stopped on Day 43. An ultrasound of the liver and biliary tree was performed on Day 44 of study treatment and was normal. Serology testing from Day 56 for possible hepatitis was negative. On final visit (Day 133), the patient's ALT had decreased below the baseline value, but remained above ULN at 46 U/L; AST was 37 U/L and GGT was 92 U/L.
- **Patient 0601/0460**, a 60-year-old white female treated with **rosuvastatin**, had a baseline ALT of 33 U/L. On Day 91, ALT was 173 U/L (> 3 x ULN) and AST was 91 U/L; on (follow-up) Day 99, ALT was 124 U/L (> 3 x ULN on 2 consecutive visits greater than 48 hours apart) and AST was 81 U/L. Study medication was stopped at this time (Day 104). The patient's CK values were elevated throughout the study, ranging from a maximum CK value of 424 U/L at Week -6 to a CK value of 264 U/L at final visit; GGT values remained within normal limits (WNL). The patient had an AE of hepatic enzymes increased from Day 91 and was withdrawn from the study due to this AE. No associated symptoms or complaints were reported. On the final follow-up visit (Day 139), ALT was decreased, but remained slightly elevated at 44 U/L and AST was 42 U/L.
- **Patient 0801/0367**, a 60-year-old white male treated with **rosuvastatin**, had an elevated ALT value of 47 U/L at Week -6 and a baseline (Week 0) ALT of 35 U/L. On Day 36, the patient had an ALT value of 273 U/L (> 3 x ULN), an AST of 129 U/L, and a GGT of 162 U/L; on (follow-up) Day 43, ALT was 295 U/L (> 3 x ULN on 2 consecutive visits greater than 48 hours apart), AST was 119 U/L, and GGT was 199 U/L. Study drug was

stopped on Day 43. The patient had AEs of ALT, AST, and GGT increased from Day 43 to Day 85 and was withdrawn from the study. No associated symptoms or complaints were reported. On the final visit (Day 79), ALT and AST returned to WNL and GGT had decreased, but remained elevated at 85 U/L.

- **Patient 0801/0381**, a 60-year-old white female treated with **rosuvastatin**, had an ALT of 33 U/L at baseline (Week 0). On Day 279, the patient had an ALT of 157 U/L (> 3 x ULN) and an AST of 111 U/L; on (follow-up) Day 287, ALT was 139 U/L and AST was 78 U/L. GGT values were WNL. The patient had an AE of liver function test abnormal from Day 285 to Day 323. No associated symptoms or complaints were reported. Study medication was interrupted on Day 285 due to the elevations. On Day 349, study medication was restarted and the patient completed the study without further liver disturbances.
- **Patient 0103/2122**, a 67-year-old white male in the **placebo** group, had an elevated Week -6 ALT of 50 U/L and a baseline (Week 0) ALT of 45 U/L. The patient was diagnosed with chronic cholecystitis, cholelithiasis, and hepatic steatosis on Day 274, associated with clinically important elevations of ALT (> 3 x ULN on 2 consecutive occasions greater than 48 hours apart). From Day 505, the patient had an AE of abnormal liver function test and was withdrawn from the study. The corresponding ALT value on Day 505 was 99 U/L. On (follow-up) Day 595, the patient had an ALT of 124 U/L (> 3 x ULN), an AST of 108 U/L, and a GGT of 104 U/L; on Day 617, the ALT value was 122 U/L, AST was 105 U/L, and GGT was 108 U/L. Study medication was stopped on Day 623. On the final follow-up visit (Day 704), the ALT value had decreased, but remained elevated at 69 U/L; AST was 47 U/L and GGT was 54 U/L.

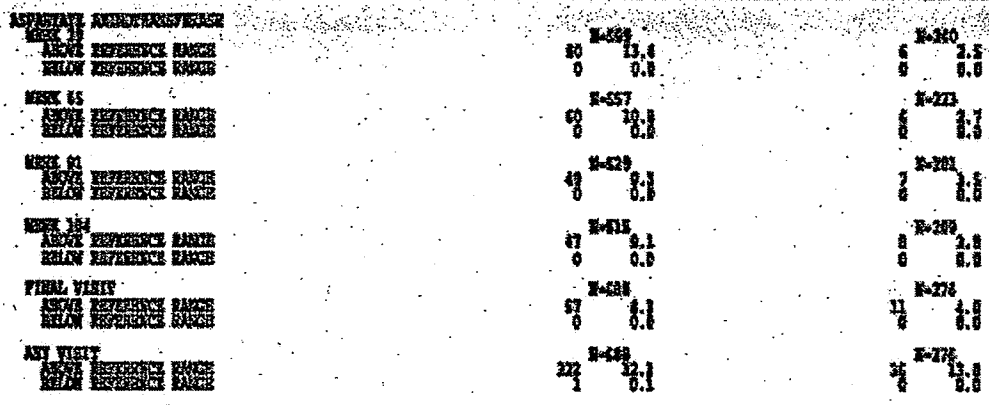
Two patients in the **rosuvastatin** group had ALT values 2.9 x ULN on 2 consecutive occasions greater than 48 hours apart (not meeting criteria in the clinical study program for clinically important).

- **Patient 0108/2351** had ALT elevations of 123 U/L on Day 261 and 142 U/L on Day 275; ALT returned to WNL by Day 449.
- **Patient 0601/0447** had ALT elevations of 156 U/L on Day 91 and 127 U/L on Day 105; at the final visit (Day 731), ALT had decreased, but remained elevated at 45 U/L. In both cases, bilirubin levels were elevated throughout the study. Both patients completed the study.

There were no clinically meaningful changes in mean values over time in other hepatic biochemistry parameters (total bilirubin, alkaline phosphatase, AST). Mean AST values increased in the rosuvastatin group from baseline 23.2 U/L to the final visit (26.4 U/L. Change from baseline to the final visit was 3.6 U/L for the rosuvastatin group and -1.2 U/L for the placebo group.

The percentage of patients in the rosuvastatin group with AST values outside the reference range increased from baseline (4.4%) to the final visit (8.3%), while the percent of patient in the placebo group with AST values outside the reference range was stable over time.

Table 10.1.4.6.4.6-3: Number (%) of patients with values outside of reference range (AST) – Safety population



The number of patients with a CK elevation > 10 x ULN is shown below:

Table 10.1.3.6.4.6-4: Clinically significant elevations of CK (> 5x and > 10x ULN) – safety population

	Rosuvastatin 40 mg (N=700)	Placebo (N=281)
Patients with baseline and subsequent measurement, n (%)	659 (100.0)	276 (100.0)
>5 x ULN at any visit, n (%)	8 (1.2)	2 (0.7)
>10 x ULN at any visit, n (%)	1 (0.1)	0

Overall, 1 patient (0.1%) in the rosuvastatin group and no patient in the placebo group had a clinically important elevation of CK (> 10 x ULN). This patient is described below:

- One patient (**0601/0415**), a 57-year-old white male, treated with **rosuvastatin,** experienced exercise-induced muscle pain associated with a clinically important CK elevation (>10 x ULN), meeting a pre-specified case definition of myopathy in the clinical study program, although not reported as myopathy by the investigator. Baseline (Week 0) CK was 159 U/L. On Day 43, the patient had an elevated CK of 877 U/L, and on Day 52 (follow-up visit), CK was 3059 U/L (> 10 x ULN). The patient was noted to have participated in a rowing contest and had performed extreme physical exercise in preparation for the contest prior to blood testing. Study medication was not interrupted; the elevated CK returned to normal on Day 93 (136 U/L) and the patient completed the study as planned.

One patient (**0201/0005**) in the **rosuvastatin** group had a baseline CK value of 85 U/L. On Day 49, the patient had an AE of creatine phosphokinase increased; CK was elevated at 1969 U/L (9.9 x ULN, not meeting criteria in the clinical study program for clinically important). Study drug was stopped on Day 52 and restarted on Day 56 when the CK level decreased to 384 U/L. The patient was noted to have engaged in heavy physical activity the

day prior to testing. The next visit (Day 91) CK was WNL at 101 U/L. The patient completed the study as planned.

Changes in mean and median serum creatinine values over time are summarized in the table below, followed by a summary of the maximum elevations in serum creatinine for treated patients.

Table 10.1.4.6.4.6-5: Change from baseline to final visit in serum creatinine – safety population

Change from baseline to final visit, µmol/L		
N	476	187
Mean (SD)	3.3 (9.32)	4.1 (8.76)
Median	3.0	4.0
Range	-73 to 45	-18 to 35

Table 10.1.4.6.4.6-6: Maximum serum creatinine elevations by category during treatment – safety population

	Rosuvastatin 40 mg (N=700)	Placebo (N=281)
Patients with baseline and subsequent measurement, n (%)	632 (90.3)	249 (88.6)
>50% increase from baseline, n (%)	4 (0.6)	2 (0.7)
>100% increase from baseline, n (%)	0	0

Overall, 0.6% of patients in the rosuvastatin group and 0.7% of patients in the placebo group had an increase in serum creatinine > 50% from baseline. No patients in the study had a doubling of serum creatinine from baseline.

There were no clinically meaningful changes in other renal biochemistry parameters.

Urinalysis

The number and percent of patients with proteinuria or hematuria is shown in the table below:

Table 10.1.4.6.4.6-7: Number and percent of patients with proteinuria or hematuria – safety population

	Rosuvastatin 40 mg (N=700) N (%)	Placebo (N=281) N (%)
At any time during the study		
N (%)	628 (100)	245 (100)
Patients with proteinuria[a]	4 (0.6)	2 (0.8)
Patients with hematuria[b]	16 (2.5)	5 (2.0)
Patients with proteinuria and hematuria	1 (0.2)	1 (0.4)
At final visit		
N (%)	628 (100)	245 (100)
Patients with proteinuria[a]	2 (0.3)	1 (0.4)
Patients with hematuria[b]	6 (1.0)	1 (0.4)
Patients with proteinuria and hematuria	1 (0.2)	0

None of the patients who had proteinuria had a clinically important increase of serum creatinine (> 100% from baseline and > ULN) or had an AE indicating renal dysfunction such as renal failure.

One patient (0.2%) in the **rosuvastatin** group and 1 patient (0.4%) in the **placebo** group had combined proteinuria and hematuria at any time during the study, and 1 patient (0.2%) in the rosuvastatin group and no patients in the placebo group had combined proteinuria and hematuria at final visit.

10.1.4.6.4.7 Vital signs

There were no clinically meaningful changes in vital signs, ECG, weight, or physical findings.

10.1.4.6.4.8 Extent of exposure

Table 10.1.4.6.4.8-1: Summary of treatment duration (weeks) on rosuvastatin 40 mg – safety population

Weeks, N (%)		
0 to <13	50 (7.1)	20 (7.1)
13 to <26	22 (3.1)	10 (3.6)
26 to <39	21 (3.0)	6 (2.1)
39 to <52	15 (2.1)	7 (2.5)
52 to <65	15 (2.1)	6 (2.1)
65 to <78	11 (1.6)	5 (1.8)
78 to <91	15 (2.1)	6 (2.1)
91 to <104	130 (18.6)	46 (16.4)
≥104	409 (58.4)	165 (59.1)
Not calculated	12 (1.7)	9 (3.2)

10.1.4.6.4.9 Study schedule

Study plan	Screening			Treatment									
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13[a]
Week number	-6	-4	-2	0	4	13	26	39	52	65	78	91	104
Informed consent	√												
Randomization				√									
Vital signs	√			√	√	√		√		√		√	√
Height	√												
Body weight	√			√	√	√	√	√	√	√	√	√	√
Adverse events		√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medications	√			√	√	√	√	√	√	√	√	√	√
Medical history	√												
Physical examination				√									√
ECG				√									√
Chemistry panel	√[b]			√	√	√		√[c]		√[c]		√[c]	√
Pregnancy test	√[d]												
Hematology				√									√
Urine sample[e]				√	√	√		√		√		√	√
Serum lipid profile	√[f]			√		√				√			√
ApoAI and ApoB				√									√
Inflammatory marker				√[g]									√
FRI	√												
IMT		√[h]	√[h]				√		√		√		√[i]
Dispense study drug				√		√	√	√	√	√	√	√	
Study medication compliance					√	√	√	√	√	√	√	√	√
Nutritional counseling[j]				√	√	√	√	√	√	√	√	√	

Note: Visit windows of ±14 days applied for Visits 1 to Visits 4. Visit windows of ±7 days applied for Visits 5 to 13.

[a] In the event of early withdrawal, all non-IMT procedures scheduled for Visit 13 (Week 104) were conducted. A single IMT was performed on any patient who withdrew after 26 weeks.

[b] Chemistry panel included TSH at Visit 1.

[c] Abbreviated chemistry panel included liver function tests (ALT, AST, bilirubin, ALP), serum creatinine, and CK only.

[d] Serum pregnancy test was required only for premenopausal females. Those with amenorrhea for at least 1 year were exempt.

[e] Urine sample for complete urinalysis.

[f] If lipid values for labs drawn at Visit 1 (Week -6) did not meet the inclusion criteria, but were within 5% of the range for LDL-C, ie, 123 mg/dL (3.2 mmol/L) to 129 mg/dL (3.3 mmol/L) inclusive or 160 mg/dL (4.1 mmol/L) to 166 mg/dL (4.3 mmol/L) inclusive for patients with a 10-year CHD risk <10%; or 123 mg/dL (3.2 mmol/L) to 129 mg/dL (3.3 mmol/L) inclusive or 190 mg/dL (4.9 mmol/L) to 199 mg/dL (5.1 mmol/L), inclusive, for patients with only age as a risk factor, blood was redrawn at Visit 1.1 (Week -4±1).

[g] Inflammatory marker CRP only.

[h] IMT measurements at Visit 2 (Week -4) and Visit 3 (Week -2) must have met inclusion criteria of maximum IMT ≥1.2 mm and <3.5 mm.

[i] Final IMT procedures were scheduled before discontinuation of study treatment. The second and final IMT procedure should have occurred at or before Visit 13 (Week 104), at the time of discontinuation of the study treatment. The 2 IMT procedures for Visit 13 should have been performed on different days, wherever possible.

[j] Nutritional counseling was reinforced at each clinic visit.

ALP Alkaline phosphatase; ALT Alanine aminotransferase; Apo Apolipoprotein; AST Aspartate aminotransferase; CHD Coronary heart disease; CK Creatine kinase; CRP C-reactive protein; ECG Electrocardiogram; FRI Framingham Risk Index; IMT Intima media thickness; LDL-C Low-density lipoprotein cholesterol; TSH Thyroid stimulating hormone.

10.2 Line-by-Line Labeling Review

CRESTOR will be the first HMG CoA reductase inhibitor to be in Physician Labeling Rule format. A detailed labeling review will be conducted separately from this document.

Sponsor's request:

1 INDICATIONS AND USAGE
To slow (b) (4) *the progression of atherosclerosis*

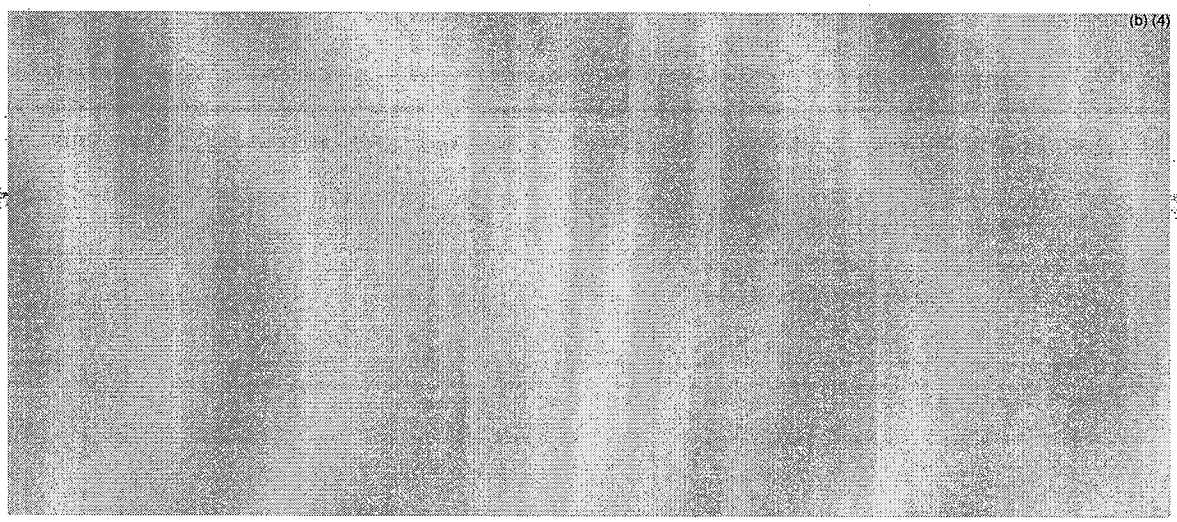
Medical Reviewer's recommendation:
Summary Page:

INDICATIONS AND USAGE
To slow the progression of atherosclerosis as part of a treatment strategy to lower TC and LDL-C to target levels.

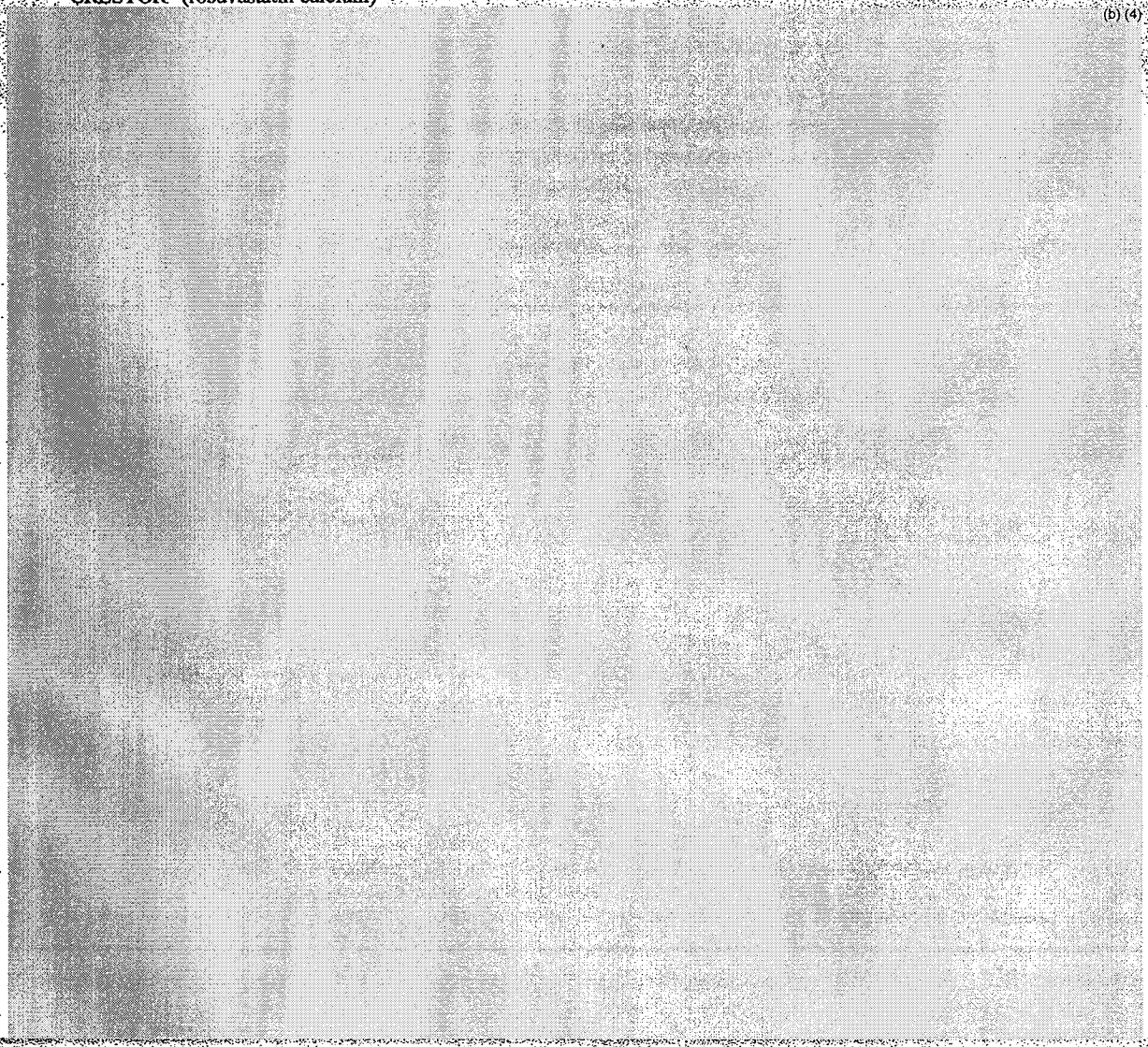
Full Prescribing Information page

1 INDICATIONS AND USAGE
1.4 Slowing of the Progression of Atherosclerosis
CRESTOR is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

Sponsor's request:
14 CLINICAL STUDIES
14.5 Atherosclerosis



(b) (4)



Medical Reviewer's recommendation:

14 CLINICAL STUDIES

14.5 Slowing of the Progression of Atherosclerosis

In the *Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR)* study, the effect of therapy with CRESTOR on carotid atherosclerosis was assessed by B-mode ultrasonography in patients with elevated LDL-C, at low risk (Framingham risk <10% over ten years) for symptomatic CAD and with subclinical atherosclerosis as evidenced by carotid intimal-medial thickness (cIMT). In this double-blind, placebo-controlled clinical study 984 patients were randomized (of whom 876 were analyzed) in a 5:2 ratio to CRESTOR 40 mg or placebo once daily. Ultrasonograms of the carotid walls were used to determine the annualized rate of change per patient from baseline to two years in mean maximum cIMT of 12

measured segments. The estimated difference in the rate of change in the maximum cIMT analyzed over all 12 carotid artery sites between CRESTOR-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI –0.0196, –0.0093; p<0.0001).

The annualized rate of change from baseline for the placebo group was +0.0131 mm/year (p<0.0001). The annualized rate of change from baseline for the CRESTOR group was -0.0014 mm/year (p=0.32).

At an individual patient level in the CRESTOR group, 52.1% of patients demonstrated an absence of disease progression (defined as a negative annualized rate of change), compared to 37.7% of patients in the placebo group.

APPEARS THIS WAY ON ORIGINAL

REFERENCES

1. Amarenco, P et al. Statins in Stroke Prevention and Carotid Atherosclerosis: Systematic Review and Up-to-Date Meta-Analysis. *Stroke*. 2004;35:2902-2909.
2. Crouse, JR. Imaging atherosclerosis: state of the art. *Journal of Lipid Research*. 2006;47:1677-1699.
3. Bots, ML et al. Carotid Intima-Media Thickness Measurements in Intervention Studies: Design Options, Progression Rates, and Sample Size Considerations: A Point of View. *Stroke*. 2003;34:2985-2994.
4. Mancini, GB et al. Surrogate Markers for Cardiovascular Disease: Structural Markers. *Circulation*. 2004;109:IV-22-IV-30.
5. Balk, EM et al. Effects of Statins on Nonlipid Serum Markers Associated with Cardiovascular Disease, A Systematic Review. *Ann Intern Med*. 2003;139:670-682.
6. Corvol, JC et al. Differential Effects of Lipid-Lowering Therapies on Stroke Prevention, a Meta-analysis of Randomized Trials. *Arch Intern Med*. 2003;163:669-676.
7. Furberg, CD et al. Coronary Heart Disease/Myocardial Infarction: Effect of Lovastatin on Early Carotid Atherosclerosis and Cardiovascular Events. *Circulation*. 1994;90:1679-1687.
8. Revkin, JH et al. Biomarkers in the Prevention and Treatment of Atherosclerosis: Need, Validation, and Future. *Pharmacological Reviews*. 2007;59:40-53.
9. Grobbee, DE and Bots, ML. Atherosclerotic dfisease regression with statins: studies using vascular markers. *International Journal of Cardiology*. 2004;96:447-459.
10. Ubels, FL et al. Carotid intima-media thickness: influence of drug treatment and clinical implications. *The Netherlands Journal of Medicine*. 1999;55:188-195.
11. Espeland, MA et al. Analysis Strategies for Serial Multivariate Ultrasonographic Data that are Incomplete. *Statistics in Medicine*. 1992;11:1041-1056.
12. Kastelein, JP et al. Atherosclerosis Measured by B-Mode Ultrasonography: Effect of Statin Therapy on Disease Progression. *Am J Med*. 2004;116:31S-36S.
13. Smilde, TJ et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomized, double-blind trial. *Lancet*. 2001;357:577-581.
14. Smilde, TJ et al. Rationale, Design and Baseline Characteristics of a Clinical Trial Comparing the Effects of Robust vs Conventional Cholesterol Lowering and Intima Media Thickness in Patients with Familial Hypercholesterolaemia, The Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) Study. *Clin Drug Invest*. 2000;2:67-79.
15. Kastelein, JP et al. Surrogate markers of atherosclerosis: impact of statins. *Atherosclerosis Supplements*. 2003;4:31-36.
16. Nissen, SE et al. Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis, The ASTEROID Trial. *JAMA*. 2006;295:E1-E10.
17. Kablak-Ziembicka, A et al. Gender Differences in Carotid Intima-Media Thickness in Patients With Suspected Coronary Artery Disease. *Am J Cardiol*. 2005;96:1217-1222.
18. Nichols, SJ et al Statins, High-Density Lipoprotein Cholesterol, and Regression of Coronary Atherosclerosis. *JAMA*. 2007;297:499-507.

19. Nissen, SE. Halting the progression of atherosclerosis with intensive lipid lowering: results from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. *Am J Med.* 2005;118:22S-27S.
20. Schartl, M et al. Use of Intravascular Ultrasound to Compare Effects of Different Strategies of Lipid-Lowering Therapy on Plaque Volume and Composition in Patients With Coronary Artery Disease. *Circulation.* 2001;104:387-392.
21. Bots, ML et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomized, double-blind trial. *Lancet.* 2007;370:153-160.
22. Espeland, MA et al. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. *Current Controlled Trials in Cardiovascular Medicine.* 2005;6:1-6.
23. Jones, PH et al. Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR Trial). *Am J Cardiol.* 2003;92:152-160.
24. Kastelein, JP et al. Atherosclerosis Measured by B-Mode Ultrasonography: Effect of Statin Therapy on Disease Progression. *Am J Med.* 2004;116:31S-36S.
25. Salonen, R et al. Kuopio Atherosclerosis Prevention Study (KAPS): A Population-Based Primary Preventive Trial of the Effect of LDL Lowering on Atherosclerotic Progression in Carotid and Femoral Arteries. *Circulation.* 1995;92:1758-1764.
26. Kapur, N. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. *Expert Rev Cardiovasc Ther.* 2007;5:161-175.
27. Cannon, CP et al. Meta-Analysis of Cardiovascular Outcomes Trials Comparing Intensive Versus Moderate Statin Therapy. *J Am Coll Cardiol.* 2006;48:438-445.
28. Bots, ML et al. Carotid Intima-Media Thickness Measurements in Intervention Studies: Design Options, Progression Rates, and Sample Size Considerations: A Point of View. *Stroke.* 2003;34:2985-2994.
29. Kang, S et al. Effects of statin therapy on the progression of carotid atherosclerosis: a systematic review and meta-analysis. *Atherosclerosis.* 2004;177:433-442.
30. Cheung, BMY et al. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol.* 2003;57:640-651.
31. Furberg, CD et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation.* 1994;90:1679-1687.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Egan
11/8/2007 05:51:38 PM
MEDICAL OFFICER

Eric Colman
11/8/2007 05:53:35 PM
MEDICAL OFFICER

Team Leader Review Memo

Date	October 4, 2007
From	Eric Colman, MD
Subject	Efficacy Supplement
NDA/Supp	21-366/s-010
Drug	Crestor/Rosuvastatin
Dosages	5mg, 10mg, 20mg and 40mg Tablets
Proposed Indication	To slow the progression of atherosclerosis
Recommendation	*Approve*

1. Introduction to Review

This efficacy supplement provides data on carotid intima-media thickness (cIMT) in support of an indication to slow (b) (4) progression of atherosclerosis. The primary efficacy data come from the METEOR trial. Safety, and supportive efficacy, data come from two additional clinical studies. This memo focuses on interpretation of the cIMT data.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Lovastatin, fluvastatin, pravastatin, and long-acting niacin have indications for the slowing of progression of atherosclerosis. Lovastatin's indication is based on cIMT data. The other drug's indications are based on quantitative coronary angiography data.

Following discussion between the Division and AstraZeneca (AZ) in 2001 and 2002, it was mutually agreed that robust results from a single trial using cIMT as a surrogate endpoint would potentially support approval of Rosuvastatin to slow progression of atherosclerosis (or a similarly worded indication).

3. CMC/Microbiology/Device

None.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology data were included in this efficacy supplement.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data, including the results a thorough QT study, were submitted in this supplement.

6. Clinical Microbiology

N/A

7. Clinical/Statistical

Three clinical studies were submitted in this efficacy supplement: METEOR, ASTEROID, and ORION. METEOR was a randomized, double-blind, placebo-controlled 2-year trial which compared the effect of 40 mg daily Rosuvastatin to placebo on cIMT in patients with a 10-year absolute risk for cardiovascular events < 10%. ASTEROID was an open-label, single-arm, 2-year trial of 40 mg daily Rosuvastatin which examined total atherosclerotic volume (TAV) using intravascular ultrasound (IVUS) in patients with angiographic evidence of coronary artery disease (CAD). ORION was a randomized, double-blind 2-year trial which compared the effect of 5 mg vs. 40/80 mg daily Rosuvastatin on MRI-measured carotid artery wall volume in patients with documented CAD.

Given its design characteristics, METEOR provides the most reliable estimate of Rosuvastatin's effect on the progression of atherosclerosis. As such, efficacy (and safety) data from this trial will be addressed in greater detail than the data from ASTEROID and ORION.

7.1. Efficacy – METEOR

This was a randomized, double-blind, placebo-controlled 2-year trial of 984 low-risk patients randomized 5:2 to 40 mg Rosuvastatin or placebo daily. The primary efficacy endpoint was the change from baseline to endpoint in maximum cIMT over 12 carotid artery sites. This was done using a multi-level, mixed-effects regression model was used to estimate the mean annualized rate of change (mm/year) for each treatment group. Secondary endpoint included changes in other cIMT landmarks, lipoprotein lipid levels, and CRP.

The Intent-to-Treat (ITT) population comprised 702 Rosuvastatin and 282 placebo subjects. The groups were well-matched at baseline. The mean age was 57 years; 60% were male, 95% were Caucasian, the average BMI was 27 kg/m^2, 20% had hypertension, and roughly 20% were taking aspirin. Approximately 20% of the subjects withdrew prematurely from the study.

In the primary efficacy analysis, the annualized change in cIMT was -0.0014 mm in the Rosuvastatin group and 0.0131 mm in the placebo group ($p<0.0001$). The changes in the secondary cIMT endpoints were favorable for the Rosuvastatin compared with the placebo-treated subjects. The mean LDL-C levels in the Rosuvastatin group decreased by 45% and by 0.6% in the placebo group ($p<0.0001$). The mean HDL-C levels in the Rosuvastatin group increased by 9% and by 5% in the placebo group ($p<0.0001$). The changes in other lipoprotein lipid parameters in the Rosuvastatin and placebo groups were as expected. The median concentrations of CRP decreased by 36% and 3% in the Rosuvastatin and placebo groups, respectively ($p<0.0001$).

Dr. Egan rightly points out that the change in cIMT observed in the Rosuvastatin group from METEOR appears small relative to the magnitude of the reduction in LDL-C. In

trials using mid-range doses of lovastatin, pravastatin, and fluvastatin, cIMT has been shown to change by an average of -0.012 mm/year.[1] This is very similar to the -0.0014 noted in METEOR. However, the average reduction in LDL-C in METEOR was 45%, significantly larger than the 25% to 35% reductions typically observed with mid-range doses of lovastatin, pravastatin, and fluvastatin.[2] The inclusion of individuals at low risk for heart disease in METEOR may explain the discrepancy.

7.2. Safety

The safety data for this supplemental NDA come primarily from METEOR. Of the three clinical trials submitted, METEOR was the only one that was double-blind and placebo-controlled.

There were no new or unexpected safety findings in the three clinical trials.

As will all statins, there is a risk for myopathy and rhabdomyolysis with Rosuvastatin. No serious muscle adverse events were reported in any of the patients exposed to Rosuvastatin. When approved there was also concern that Rosuvastatin may be associated with renal toxicity. There were no renal adverse events in METEOR or ORION. In ASTEROID one patient who developed renal insufficiency which was thought to be secondary to congestive heart failure. Another participant in ASTEROID had proteinuria and an elevation in serum creatinine. These abnormalities resolved while the subject continued on treatment with Rosuvastatin. The investigator attributed these adverse evens to concomitant treatment with a diuretic and an ACE-inhibitor.

There were no cases of hepatitis, jaundice, or other adverse events related to the hepatobiliary system in patients randomized to Rosuvastatin.

In METEOR, there were 8 (1.1%) serious cardiac adverse events reported in the Rosuvastatin group compared with 0 in the placebo group (nominal p=0.12). Two of the events, atrial fibrillation and atrial flutter, occurred on Day 1 of treatment and can therefore be discounted as drug-related. The remaining events were: acute coronary syndrome, angina pectoris, unstable angina, AV block, and ventricular tachycardia. Given the wealth of data on the cardiovascular benefits of statins and the favorable changes in cardiovascular surrogate endpoints reported in this supplemental NDA, the imbalance in serious cardiac disorders between Rosuvastatin and placebo groups is most likely a chance finding.

8. Advisory Committee Meeting

There was no advisory committee meeting for this efficacy supplement.

---

[1] Epseland MA, et al. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. Current Controlled Trials in Cardiovascular Medicine 2005:6;1-6.

[2] Drug Class Review on HMG-CoA Reductase Inhibitors. The Agency for Healthcare Research and Quality. September 2005.

9. Other Relevant Regulatory Issues

None.

10. Financial Disclosure

Dr. Egan has reviewed the relevant financial disclosure information and did not uncover anything of note.

11. Labeling

With the assistance of the SEALD team, we have transformed the Rosuvastatin labeling to the PLR format. There were three key labeling issues that we discussed with the company. The first was the wording of the indication. Given that the within-group change from baseline to Year 2 in cIMT was not significant in the Rosuvastatin group, we believed that the indication should include a statement about slowing the progression of atherosclerosis. The company pushed for the use of "(b) (4) the progression of atherosclerosis," but we were not willing to compromise on this point. The second issue was related to (b) (4) We agreed with the request. This was an open-label, single-arm study in which the effect of 40 mg of Rosuvastatin on atherosclerosis was assessed by intravascular ultrasound of the coronary arteries. Although there was a statistically significant reduction in the atheroma volume following 2 years of treatment, (b) (4) (b) (4). The company eventually acquiesced.

12. DSI Audits

The Division of Scientific Investigations inspected two clinical sites and did not find any notable deficiencies or irregularities.

13. Conclusions and Recommendations

The company has provided sufficient data to support granting an indication for the slowing of the progression of atherosclerosis. I agree with Dr. Egan that the supplement should be approved.

_____

Eric Colman, MD
DMEP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
11/8/2007 08:57:49 PM
MEDICAL OFFICER

MEMORANDUM

Primary Medical Officer sNDA 21-366 SE1 Filing Memo:

To: DFS for sNDA 21-366

From: Amy G. Egan, M.D., M.P.H.

RE: sNDA 21-366

CRESTOR™	Rosuvastatin calcium is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor, for oral use.
Sponsor:	AstraZeneca LP
Letter date:	January 5, 2007
Date received:	January 9, 2007
PDUFA date:	November 4, 2007

BACKGROUND:

Rosuvastatin is a member of the statin class of lipid-lowering compounds, which inhibit 3- hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and reduce cholesterol synthesis. It is presently approved at once daily doses of 5, 10, 20, or 40 mg. It is indicated:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non-HDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

This NDA supplement presents data from one pivotal efficacy study, Study D3562C00088 (4522IL/0088, METEOR: "A Randomized, Double-blind, Placebo-controlled, Multicenter Parallel Group Phase III Study Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin 40 mg") and two additional studies D3562C0076 (4522IL/0076, ASTEROID: "A 104-Week, Open-label, Multi-center, Phase 3b Study Evaluating the Effect of Treatment with Rosuvastatin 40 mg on Atherosclerotic Disease as Measured by Intravascular Ultrasound and Quantitative Coronary Angiography in Subjects Undergoing Coronary Angiography who have Coronary Artery Disease") and D3560C00044 (4522IL/0044, ORION: "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") to support an indication "to slow [redacted] (b)(4) the progression of atherosclerosis in patients in whom lipid-lowering therapy is indicated." The sponsor is further seeking the addition of a summary of the METEOR study in the Clinical Studies section of the label. (See Appendix C.)

The rosuvastatin clinical study program has involved over 55,000 patients. The first marketing approval for rosuvastatin was in the Netherlands on November 6, 2002 and the drug was first launched in Canada on February 19, 2003. It was approved in the U.S. on August 12, 2003. As

of December 1, 2006, rosuvastatin has been approved in 86 countries and there is estimated to be more than [redacted] (b) (4) patient-years of post marketing experience.

REGULATORY HISTORY/RELEVANT NDA's/LABELING:

The pathophysiology of atherosclerosis is complex, comprised of a multi-faceted process apparently initiated and perpetuated by lipid accumulation in the arterial wall, involving inflammation, cellular proliferation, disruption of tissue integrity, and ultimate friability of the arterial intima leading to thrombosis at sites of intimal injury. As such, methods, both invasive and non-invasive, of imaging the arterial wall have come into favor in the assessment of atherosclerotic disease. Ultrasound of the carotid arteries, MRI and CT of the coronaries and carotids, and intravascular ultrasound of the coronaries have been studied, variably, for their utility in predicting cardiovascular disease risk, in assessing the effects of anti-atherosclerotic therapies, and for directing surgical intervention to address arterial disease. Strictly speaking, none stands as a fully validated "surrogate" measure of anti-atherosclerosis efficacy. Specifically, as for coronary angiography itself, there are inadequate data to permit a calculation of the extent of cardiovascular disease risk reduction as a function of a given degree of change in anatomic parameters as assessed by these methods.

Over the last several years, multiple studies, notably of lipid altering agents, have been conducted to examine effects on anatomically defined arterial disease. In this regard, several statin package inserts include study summaries and indications based on the results of trials utilizing arterial anatomic assessments of disease as measures of drug effect. Specifically, the labels for lovastatin, simvastatin, pravastatin, and fluvastatin all describe the results of placebo-controlled trials showing apparent slowing of the progression of atherosclerosis by drug compared to placebo. These findings are obviously consistent with the known role of LDL-cholesterol in atherosclerotic disease and are "validated" by the results of now multiple trials showing reductions in cardiovascular disease events (fatal and non-fatal myocardial infarctions, unstable angina, strokes, revascularizations, etc.) in patients treated with statins compared to placebo.

Table 1: Currently approved labeling for lipid-lowering agents and atherosclerosis

Statin	Atherosclerosis trials in label	Patient population studied	Duration of study	Surrogate marker used	Indication in label
CRESTOR	None	N.A.	N.A.	N.A.	None
LESCOL	Lipoprotein and Coronary Atherosclerosis Study (LCAS)	Patients with coronary artery disease and LDL-C 115-190 mg/dL	2.5 years	Quantitative coronary angiography (QCA)	*Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels*
LIPITOR	None	N.A.	N.A.	N.A.	None
MEVACOR	1. Canadian Coronary Atherosclerosis	1.Hyperlipidemic patients	1. 2 years	1. QCA	*MEVACOR is indicated to slow the progression of*

Statin	Atherosclerosis trials in label	Patient population studied	Duration of study	Surrogate marker used	Indication in label
	Intervention Trial (CCAIT) 2. Monitored Atherosclerosis Regression Study (MARS) 3. Familial Atherosclerosis Treatment Study (FATS) 4.Asymptomatic Carotid Artery Progression Study (ACAPS)	2.Hyperlipidemic patients with at least 2 coronary artery lesions 3.Hyperlipidemic patients 4.Hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline	2. 4 years 3. 2.5 years 4. 3 years	2. QCA 3. QCA 4. cIMT	*coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels*
PRAVACHOL	1. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) 2. Regression Growth Evaluation Statin Study (REGRESS)	1. Patients with coronary disease and LDL-C 130-190 mg/dL 2. Patients with angina, angiographically documented coronary artery disease, and TC 160-310 mg/dL	1. 3 years 2. 2 years	1. Coronary angiography 2. Coronary angiography	*In patients with clinically evident coronary heart disease, PRAVACHOL is indicated to slow the progression of coronary atherosclerosis*
ZOCOR	Multicenter Anti-Atheroma Study	Hypercholesterolemic patients with coronary heart disease	4 years	QCA	None
Other lipid-lowering agents:					
NIASPAN	1.The Cholesterol-Lowering Atherosclerosis Study (CLAS) 2.The Familial Atherosclerosis Treatment Study (FATS) 3.The Harvard Atherosclerosis Reversibility Project (HARP)	1. Male patients with previous coronary bypass surgery 2. Male patients with Apo B levels ≥ 125 mg/dL, established CAD and FH of vascular disease 3. Male and female patients with CHD and TC < 250 mg/dL and TC/HDL-C > 4	1. 2 years 2. 2.5 years 3. 2.5 years	1. QCA 2. QCA 3. Not indicated	*In patients with a history of coronary artery disease (CAD) and hypercholesterolemia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.*
VYTORIN	None	N.A.	N.A.	N.A.	None

Statin	Atherosclerosis trials in label	Patient population studied	Duration of study	Surrogate marker used	Indication in label
ADVICOR	None	N.A.	N.A.	N.A.	None
ZETIA	None	N.A.	N.A.	N.A.	None

PEDIATRIC WAIVER:

In accordance with 21 CFR § 314.55©(2)(i), AstraZeneca has certified that CRESTOR does not represent a meaningful therapeutic benefit for pediatric patients with atherosclerosis and is not likely to be used in a substantial number of pediatric patients specifically for this indication. Consequently, they have requested that a full waiver be granted from the requirement to conduct 'anti-atherosclerosis' studies in pediatric patients.

PDUFA FEE:

The Prescription Drug User Fee cover sheet (Form FDA 3397) was submitted and dated December 14, 2006 and indicated payment in the amount of $448,100.00.

EFFICACY DATA:

METEOR serves as the pivotal study to support efficacy. METEOR was a randomized, double-blind, placebo-controlled, parallel group study of 104 weeks duration using cIMT. The study was conducted in 61 centers in the U.S. and Europe. The participants were males aged ≥45 and ≤70 and females aged ≥55 and ≤70; HDL-C ≤60mg/dL; LDL-C either between ≥120 mg/dL and <160 mg/dL with 10-year CHD risk below 10% on the Framingham risk score, or with LDL-C between ≥120 mg/dL and <190 mg/dL but no additional CHD risk factor other than age; TG <500mg/d; and a maximum IMT of between ≥1.2 mm and <3.5 mm.

The primary objective was to assess the effects of rosuvastatin 40 mg on the change in the mean maximum IMT of the 12 vessel segments: the near and far walls of the CCA, the carotid bulb and the ICA segments for both right and left carotid arteries. The secondary objectives were to assess the effects of rosuvastatin 40 mg on: the change in the mean maximum IMT of the near and far walls of the right and left CCA, of the carotid bulb and of the ICA, and change in the mean IMT of the near and far walls of the right and left CCA; the percent change from baseline in lipid and lipoprotein levels and CRP; and safety as evaluated by the incidence and severity of AEs and by abnormal lab values.

The first patient was enrolled in the study on August 8, 2002 and the last patient completed the randomized treatment phase of the study on May 17, 2006. A total of 5751 patients entered the screening period. Of these, 984 (17.1%) were randomized to study treatment (702 patients were randomized to rosuvastatin and 282 patients were randomized to placebo). Of 984 randomized patients, 246 (25.0%) withdrew from treatment over the 2-year period. For the total randomized population, the most common reason for study discontinuation was adverse event (10.3%).

The majority of randomized patients were Caucasian (94.2%) and were male (59.8%). The age range of patients in the study was 45 to 70 years; 129 patients (13.1%) were ≥65 years of age. A summary of the primary analysis, as presented by the sponsor, is provided below:

For the primary endpoint, the difference in the annualized rate of change in the Maximum cIMT of all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients

was -0.0145 mm/year (95% CI -0.0196, -0.0093); this difference was statistically significant ($p<0.001$). Overall, during the 2 years of the study, there was a negative annualized rate of change, in 52.1% of patients in the rosuvastatin group compared to 37.7% of patients in the placebo group ($p=0.0002$). The annualized change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI: -0.0041, 0.0014), but was not significantly different from zero ($p=0.3224$). There was significant progression in the placebo group (+0.0131 mm/year; 95% CI: 0.0087, 0.0174; $p<0.0001$).

There was a significant difference between rosuvastatin and placebo in annualized rate of change in maximum cIMT of the following segments: CCA ($p<0.0001$), carotid bulb ($p<0.0001$), ICA ($p=0.0228$), and in the mean cIMT of the CCA ($p<0.001$). There was significant regression in maximum cIMT of the CCA in the rosuvastatin group (-0.0038 mm/year; 95% CI: -0.0064, -0.0013; $p=0.0036$). The annualized change was not significantly different from zero in the rosuvastatin group for the other 3 secondary IMT variables. There was significant progression in all 4 secondary IMT endpoints in the placebo group ($p=0.0002$ for maximum cIMT of the ICA; $p<0.0001$ for other endpoints). Results were consistent across all pre-specified subgroups, including age, gender, and lipid levels.

Table 2: Annualized changes from baseline values to the end of the treatment period (Week 104) in cIMT for the primary and secondary variables (ITT populations)

ANNUALIZED CHANGE (MM/YEAR)	ROSUVASTATIN 40 MG (N=624)	PLACEBO (N=252)	ROSUVASTATIN 40 MG VS. PLACEBO (P-VALUE)
Primary variable: Maximum cIMT of the 12 carotid artery sites	-0.0014	0.0131	<0.0001
Secondary variables:			
Maximum cIMT of the CCA	-0.0038	0.0084	<0.0001
Maximum cIMT of the carotid bulb	-0.0040	0.0172	<0.0001
Maximum cIMT of the ICA	0.0039	0.0145	0.0228
Mean cIMT of the CCA	0.0004	0.0088	<0.0001

It should be noted that the literature suggests that far wall IMT measurements are more sensitive than near wall in detecting change, and because the rate of IMT progression varies significantly depending on the arterial site used for measurement (IMT progression is greater at the internal carotid compared with either the common carotid or the bifurcation) and because ICA-cIMT progression is the only site correlated with the full range of baseline vascular risk factors (age, male gender, hypertension, diabetes, and current smoking), the analyses of the individual sites is key. A summary of the sponsor's analysis of the mean-max internal cIMT is provided below:

TABLE 11.2.1.7.2
SUMMARY OF MEANMAX INTERNAL CIMT (MM) BY SITE AND VISIT
INTENTION-TO-TREAT POPULATION

VISIT / SUMMARY STATISTIC	MEANMAX INTERNAL CIMT = LEFT FAR WALL = ROSUVA N=624	PLACEBO N=252	ROSUVA N=624	PLACEBO N=253	= RIGHT FAR WALL = ROSUVA N=624	PLACEBO N=252	= LEFT NEAR WALL = ROSUVA N=624	PLACEBO N=252	= RIGHT NEAR WALL = ROSUVA N=624	PLACEBO N=252
WEEK -4										
N	624	252	621	251	620	249	601	243	586	238
MEAN	1.064	1.071	1.086	1.095	1.156	1.184	1.027	1.000	0.980	0.996
MEDIAN	1.008	1.010	0.979	1.004	1.037	1.057	0.977	0.979	0.909	0.909
STANDARD DEVIATION	0.271	0.288	0.421	0.411	0.452	0.507	0.376	0.358	0.373	0.369
MIN	0.496	0.495	0.469	0.482	0.495	0.488	0.407	0.407	0.325	0.325
MAX	2.225	2.114	3.246	3.008	3.596	3.659	3.080	2.303	3.139	3.044
WEEK -2										
N	624	252	623	249	620	251	605	240	593	235
MEAN	1.059	1.063	1.074	1.095	1.143	1.179	1.027	0.985	0.991	0.993
MEDIAN	1.017	1.007	0.978	1.000	1.022	1.057	0.947	0.909	0.909	0.898
STANDARD DEVIATION	0.264	0.275	0.421	0.420	0.442	0.502	0.376	0.353	0.365	0.341
MIN	0.477	0.523	0.384	0.415	0.495	0.488	0.344	0.407	0.343	0.244
MAX	2.155	2.113	3.456	3.165	3.547	3.237	3.187	3.303	2.446	2.273
6 MONTHS										
N	618	252	615	251	614	249	601	240	585	243
MEAN	1.056	1.084	1.082	1.128	1.143	1.185	1.037	1.016	0.998	0.982
MEDIAN	1.028	1.030	0.978	1.000	1.052	1.063	0.949	0.976	0.909	0.909
STANDARD DEVIATION	0.255	0.298	0.421	0.459	0.432	0.498	0.383	0.370	0.375	0.352
MIN	0.547	0.558	0.488	0.488	0.455	0.488	0.349	0.318	0.364	0.407
MAX	2.372	2.384	4.059	3.349	3.539	3.324	3.182	2.826	2.921	2.822

(CONTINUED)

NOTE: MEANMAX INTERNAL CIMT IS CALCULATED AS THE MEAN OF THE LEFT FAR WALL, RIGHT FAR WALL, LEFT NEAR WALL AND RIGHT NEAR WALL MAX INTERNAL CIMT.

TABLE 11.2.1.7.2
SUMMARY OF MEANMAX INTERNAL CIMT (MM) BY SITE AND VISIT
INTENTION-TO-TREAT POPULATION

VISIT / SUMMARY STATISTIC	MEANMAX INTERNAL CIMT = LEFT FAR WALL = ROSUVA N=624	PLACEBO N=252	ROSUVA N=624	PLACEBO N=252	= RIGHT FAR WALL = ROSUVA N=624	PLACEBO N=252	= LEFT NEAR WALL = ROSUVA N=624	PLACEBO N=252	= RIGHT NEAR WALL = ROSUVA N=624	PLACEBO N=252
1 YEAR										
N	594	239	589	238	591	239	581	232	565	226
MEAN	1.075	1.089	1.104	1.112	1.168	1.184	1.025	1.049	0.999	0.995
MEDIAN	1.027	1.038	0.979	1.000	1.058	1.087	0.976	0.964	0.909	0.909
STANDARD DEVIATION	0.274	0.292	0.436	0.436	0.465	0.478	0.370	0.405	0.367	0.353
MIN	0.525	0.522	0.464	0.546	0.488	0.488	0.407	0.455	0.364	0.448
MAX	2.572	2.527	3.455	2.909	3.480	3.364	3.285	2.609	2.921	2.822
18 MONTHS										
N	554	232	546	221	550	229	533	212	525	212
MEAN	1.074	1.087	1.106	1.118	1.153	1.195	1.036	1.034	0.987	0.998
MEDIAN	1.029	1.042	0.995	1.000	1.048	1.076	0.976	0.989	0.909	0.909
STANDARD DEVIATION	0.269	0.300	0.443	0.446	0.452	0.515	0.382	0.390	0.357	0.340
MIN	0.509	0.527	0.407	0.456	0.515	0.456	0.449	0.455	0.438	0.421
MAX	2.391	2.608	4.009	3.691	4.146	3.550	4.093	2.684	2.947	2.182

(CONTINUED)

NOTE: MEANMAX INTERNAL CIMT IS CALCULATED AS THE MEAN OF THE LEFT FAR WALL, RIGHT FAR WALL, LEFT NEAR WALL AND RIGHT NEAR WALL MAX INTERNAL CIMT.

TABLE 11.2.1.7.2
SUMMARY OF MEANMAX INTERNAL CIMT (MM) BY SITE AND VISIT
INTENTION-TO-TREAT POPULATION

VISIT / SUMMARY STATISTIC	MEANMAX INTERNAL CIMT = LEFT FAR WALL = ROSUVA N=624	PLACEBO N=252	ROSUVA N=624	PLACEBO N=252	= RIGHT FAR WALL = ROSUVA N=624	PLACEBO N=252	= LEFT NEAR WALL = ROSUVA N=624	PLACEBO N=252	= RIGHT NEAR WALL = ROSUVA N=624	PLACEBO N=252
2 YEARS (1)										
N	536	211	525	210	538	209	526	199	512	201
MEAN	1.074	1.108	1.110	1.138	1.159	1.226	1.025	1.061	1.005	1.002
MEDIAN	1.035	1.045	1.000	1.005	1.031	1.069	0.947	0.976	0.909	0.914
STANDARD DEVIATION	0.275	0.309	0.446	0.474	0.457	0.539	0.389	0.415	0.379	0.354
MIN	0.457	0.550	0.455	0.455	0.544	0.488	0.364	0.407	0.407	0.455
MAX	2.266	2.728	3.909	4.000	3.655	3.818	3.859	2.874	3.499	2.283
2 YEARS (2)										
N	514	202	509	199	513	199	504	192	494	192
MEAN	1.084	1.113	1.111	1.145	1.173	1.208	1.049	1.084	1.008	1.018
MEDIAN	1.034	1.045	0.998	1.057	1.057	1.057	0.953	0.964	0.909	0.909
STANDARD DEVIATION	0.288	0.315	0.466	0.492	0.495	0.532	0.411	0.417	0.391	0.373
MIN	0.466	0.515	0.455	0.488	0.455	0.488	0.407	0.438	0.364	0.466
MAX	2.473	2.523	3.873	3.909	3.619	3.546	3.925	2.961	3.589	2.439

NOTE: MEANMAX INTERNAL CIMT IS CALCULATED AS THE MEAN OF THE LEFT FAR WALL, RIGHT FAR WALL, LEFT NEAR WALL AND RIGHT NEAR WALL MAX INTERNAL CIMT.

The analysis of percent change from baseline to final visit in key lipid values for the ITT population is summarized below:

Table 3: Analysis of percent change from baseline to final visit in key lipid values (ITT population)

	FINAL VISIT (LOCF)		
	ROSUVASTATIN 40 MG (N=624)	PLACEBO (N=252)	ROSUVASTATIN 40 MG VS. PLACEBO
LDL-C (mg/dL)			
n	622	251	
LSmean % change	-45.3	-0.6	-44.7

	FINAL VISIT (LOCF)		
	ROSUVASTATIN 40 MG (N=624)	PLACEBO (N=252)	ROSUVASTATIN 40 MG VS. PLACEBO
p-value			<0.0001
TC (mg/dL)			
n	622	251	
LSmean % change	-31.0	0.2	-31.2
p-value			<0.0001
HDL-C (mg/dL)			
n	622	251	
LSmean % change	8.9	3.7	5.2
p-value			<0.0001
TG (mg/dL)			
n	622	251	
LSmean % change	-14.1	9.2	-23.3
p-value			<0.0001
Non-HDL-C (mg/dL)			
n	622	251	
LSmean % change	-41.9	-0.4	-41.6
p-value			<0.0001

Baseline CRP values were 0.135 mg/dL (median) for the rosuvastatin group and 0.148 mg/dL (median) for the placebo group. Median change from baseline was -36.2% in the rosuvastatin group and -2.9% in the placebo group ($p<0.0001$).

The sponsor concluded:

- *The effect of rosuvastatin on the atherosclerotic process is a slowing, and in the majority of cases, a delaying of disease progression.*

- *For the primary endpoint, rosuvastatin significantly slowed the progression of carotid atherosclerosis compared to placebo. The difference in the annualized rate of change in the maximum CIMT of all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI -0.0196, -0.0093); this difference was statistically significant ($p<0.0001$).*

  - *Overall, there was an absence of disease progression during the 2 years of the study, as evidenced by a negative annualized rate of change, in 52.1% of patients in the rosuvastatin group compared to 37.7% of patients in the placebo group ($p=0.0002$).*

  - *These results were consistent across all pre-specified subgroups. The results from the main analyses were also insensitive to a range of conservative assumptions about the effects of missing data due to premature withdrawal from the study.*

- *The annualized change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI -0.0041, 0.0014), but was not significantly different from zero ($p=0.3224$). There was significant progression in the placebo group (+0.0131 mm/year; 95% CI 0.0087, 0.0174; $p<0.0001$).*

- *The beneficial effects of rosuvastatin were consistent across all 4 secondary IMT endpoints.*

  - ❖ *Rosuvastatin significantly slowed the progression of carotid atherosclerosis compared to placebo, as evidenced by a significant difference in annualized rate of change in maximum CIMT of the following segments: CCA ($p<0.0001$), carotid bulb ($p<0.0001$), ICA ($p=0.0228$), and in the mean CIMT of the CCA ($p<0.0001$).*

  - ❖ *There was significant regression in maximum CIMT of the CCA in the rosuvastatin group (-0.0038 mm/year; 95% CI -0.0064, -0.0013; $p=0.0036$). The annualized change was not significantly different from zero in the rosuvastatin group for the other 3 secondary IMT variables.*

  - ❖ *There was significant progression in all 4 secondary IMT endpoints in the placebo group ($p=0.0002$ for maximum CIMT of the ICA; $p<0.0001$ for other endpoints).*

- *Following treatment with rosuvastatin, there was significant improvement ($p<0.0001$) compared to placebo for all lipids, lipoproteins, and their ratios, as well as for CRP. For the rosuvastatin group, there was a LDL-C reduction of 48.5% compared to the placebo group, based on time-weighted averages.*

ASTEROID was provided as a supportive study. ASTEROID was an open-label, single-arm study of 104 weeks duration using intravascular ultrasound (IVUS). The study was conducted in 53 centers in North America, Europe and Australia. The participants were males or females 18 years or older with angiographic evidence of CAD; there was no restriction on baseline LDL-C.

The primary objective was to determine whether treatment with rosuvastatin 40 mg would result in regression of coronary artery atheroma burden as assessed by the total atheroma volume (TAV) in the most severely diseased segment or the percent atheroma volume (PAV) in the total segment, as measured by IVUS. The secondary objectives were: to evaluate the nominal change in TAV in the total segment by IVUS; to evaluate the percent change in the minimum luminal diameter (MLD) within all measured coronary segments; to evaluate the change in the percent diameter stenosis for all lesions with >25% stenosis severity at baseline; and to evaluate the percent change from baseline in lipid and lipoprotein levels.

The first patient was enrolled in the study on November 8, 2002 and the last patient completed the randomized treatment phase of the study on November 18, 2005. A total of 1183 patients were screened. Of these, 507 patients took at least 1 dose of study drug (rosuvastatin 40 mg). In this 104-week study 24.7% of patients withdrew from treatment; the most common reason for withdrawal was AE (12.4%). Of the 507 patients in the safety population, 349 (68.8%) were included in the IVUS evaluable population.

In the safety population, the mean age was 58.5 years, with 29.4% ≥65 years of age; 71.0% were men; 94.1% were Caucasian; and 93.9% had normal or mildly impaired renal function. All patients had a history of CAD and were considered high risk by NCEP criteria. In regard to medical history, 95.3% had a history of hypertension, 23.9% had prior myocardial infarction, 16.6% had acute coronary syndrome, and 12.6% had diabetes mellitus.

Efficacy data were evaluated in 349 patients (IEV population) all of whom were treated with rosuvastatin 40 mg. For patients to be included in the efficacy analysis, they must have had the final IVUS examination at least 78 weeks after start of treatment. It should be noted that 17/349 (4.9%) received a bile acid sequestrant in addition to rosuvastatin for some portion of the treatment period.

Percent atheroma volume (PAV) in the total segment decreased with a median change of -0.8% from a median baseline of 39.9% (mean change of -1.0%), with a decrease in PAV observed in 222 (63.6%) of the 349 IEV patients. Total atheroma volume in the most diseased subsegment decreased with a median change of -5.6 mm^3 from a median baseline of 65.1 mm^3 (mean change of -6.1 mm^3). The median percent change from baseline in TAV of the most diseased subsegment was -9.1% (mean -8.5%), with a decrease in TAV observed in 249 (78.1%) of the 319 patients evaluable for this endpoint. For the secondary IVUS endpoint, TAV in the total segment decreased with a median change of -12.5 mm^3 (mean change of -14.7 mm^3), from a median baseline of 204.7 mm^3. The median percent change from baseline in TAV of the total segment was -6.8% (mean -6.7%), with a decrease observed in 272 (77.9%) of the 349 IEV patients. The findings are summarized in the table below:

Table 4: Change from baseline in the atheroma volume (IVUS evaluable population)

PERCENT ATHEROMA VOLUME IN THE TOTAL SEGMENT								
	N	**Mean**	**SD**	**Median**	**IQR**	**Median change (CI)**	**p-value**	**Subjects regressing n (%)**
Baseline (%)	349	39.6	8.5	39.9	33.8, 45.3	NA	NA	NA
Final (%)	349	38.6	8.5	38.5	32.6, 44.3	-0.8 (-1.20, -0.53)	<0.001	222 (63.6)
TOTAL ATHEROMA VOLUME IN THE MOST DISEASED SUBSEGMENT								
	N	**Mean**	**SD**	**Median**	**IQR**	**Median change (CI)**	**p-value**	**Subjects regressing n (%)**
Baseline (mm^3)	319	65.1	27.0	65.1	45.3, 82.2	NA	NA	NA
Final (mm^3)	319	59.0	24.5	58.4	40.6, 76.3	-5.6 (-6.8, -4.0)	<0.001	249 (78.1)

Two secondary variables examined the effect of treatment on the coronary arteries using QCA. In the largest population of patients having final coronary angiograms, the percent diameter stenosis decreased by an average of -1.30%. The median change was a decrease of -0.50% (95% confidence interval [CI]: -1.00, 0.00) from a median baseline of 35.7% ($p<0.001$), with a decrease observed in 156 (53.4%) of the 292 QCA evaluable patients. The MLD measured by QCA decreased by an average of -0.021 mm. The median change was -0.010 mm (95% CI: -0.013, -0.003) from a median baseline of 2.23 mm ($p<0.001$), with a median decrease of -0.38%. Overall, 351 (94.6%) of the 371 QCA evaluable patients were clinically unchanged, with 18 (4.9%) progressing and 2 (0.5%) regressing. These results are summarized below:

Table 5: Percent change from baseline in the minimum luminal diameter and change from baseline in the percent diameter of stenosis (QCA evaluable populations)

	N	MEAN	SD	MEDIAN	MEAN CHANGE (SD)	MEDIAN CHANGE (CI)	MEDIAN PERCENT CHANGE (CI)	P-VALUE
Percent change from baseline in the minimum luminal diameter								
Baseline (mm)	371	2.237	0.361	2.227	NA	NA	NA	NA
Final (mm)	371	2.216	0.370	2.207	-0.021 (0.096)	-0.010 (-0.013, -0.003)	-0.38 (-0.564, -0.128)	<0.001
Change from baseline in the percent diameter of stenosis								
Baseline (%)	292	37.301	8.414	35.708	NA	NA		NA
Final (%)	292	36.005	10.070	34.450	-1.295 (8.002)	-0.500 (-1.00, 0.000)		<0.001

Table 6 summarizes lipid and lipoprotein values at baseline and final visit (LOCF) and presents the percent change from baseline.

Table 6: Lipid values and percent change from baseline (IVUS evaluable population)

	N	MEAN	SD	MEDIAN	LSMEAN % CHANGE (CI)
LDL-C (mg/dL)					
Baseline	346	130.4	34.25	127.0	NA
Final visit (LOCF)	349	60.5	25.00	56.0	-53.10 (-56.098, -50.100)
TC (mg/dL)					
Baseline	346	204.0	41.22	197.0	NA
Final visit (LOCF)	349	131.6	31.81	126.0	-34.38 (-36.580, -32.179)
HDL-C (mg/dL)					
Baseline	346	43.1	11.09	41.0	NA
Final visit (LOCF)	349	48.0	13.83	46.0	12.82 (9.999, 15.635)
TG (md/dL)					
Baseline	346	152.2	81.73	135.0	NA
Final visit (LOCF)	349	116.9	69.19	102.0	-17.80 (-23.094, -12.504)

The sponsor concluded:

- *There was a statistically significant ($p<0.001$) regression of coronary atheroma volume as measured by all IVUS endpoints, including the primary variables (total atheroma*

volume in themost diseased subsegment and percent atheroma volume in the total segment) in the IVUS evaluable patients.

- *The regression of coronary atheroma observed by IVUS following 104 weeks of treatment was supported by a statistically significant ($p<0.001$) decrease in the percent diameter stenosis measured by QCA in the QCA evaluable patients. MLD measured by QCA showed a statistically significant ($p<0.001$) decrease in percent change and median change, with 94.6% of patients meeting clinical criteria for unchanged values. This is consistent with a slowing or delaying of progression of atherosclerotic disease in association with atheroma regression by IVUS in response to long-term rosuvastatin effects on the lipid profile.*
- *There was a significant and substantial improvement in all lipid and lipoprotein parameters.*

ORION was provided as a supportive study as well. ORION was a randomized, double-blind, parallel-group study of 104 weeks duration using MRI and ultrasound and comparing low (5 mg) and high doses (40/80 mg) of rosuvastatin. The study was conducted in 2 centers in the U.S. The participants were males or females 18 years or older with moderate hypercholesterolemia (LDL-C of ≥100 mg/dL and <250 mg/dL) and 16% to 79% stenosis of one or more carotid arteries, or had an atherosclerotic plaque identified on the B-mode image.

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 MRI. The secondary objectives 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 TC TG, LDL-C, and HDL-C; examine tissues of those subjects who progress to endarterectomy for cell infiltration, expression of markers of vascular inflammation (e.g. intercellular adhesion molecule-1 [ICAM-1] and cluster of differentiation-40 [CD-40] ligand) and possible rosuvastatin content; generate the hypothesis that other inidices 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.
The first patients was enrolled in the study on January 6, 2000 and the last patient completed the randomized treatment phase of the study on August 5, 2004. A total of 73 patients entered the dietary lead-in period, and 43 were randomized to treatment – 21 patients to rosuvastatin 5 mg and 22 to rosuvastatin 40/80 mg. Of those, 43 were analyzed for safety and 42 were analyzed for efficacy. There were 2 discontinuations from the rosuvastatin 5 mg group (1 due to AE; 1 withdrew consent); there were 2 discontinuations from the rosuvastatin 40/80 mg group (1 due to AE; 1 due to "other").

More male patients (67.4%) than female patients (32.6%) were randomized into the study. The age range of patients in the study was 40 to78 year; the overall mean age was 64.8 years, with 53.5% of patients being over 65 years of age. 97.7% of patients were Caucasian; 88.4% had normal or mildly impaired renal function. In regard to medical history, 29 patients had hypertension, 9 were current cigarette smokers, and 8 had diabetes mellitus.

For the primary variable, the change from baseline in bilateral carotid artery volume at Week 104, the high-dose minus low-dose difference was -2.6 mm^3, and for the change from baseline in bilateral carotid artery wall volume at Week 104, the high-dose was 1.3 mm^3 and the low-dose was 3.9 mm^3. These results are summarized in the table below:

Table 7: Bilateral carotid artery wall volume (mm3) using matched locations between the baseline and Month 24 visit

		BASELINE	WEEK 104 (OBS)
Low-dose rosuvastatin (N=15)			
Observed value	Mean (SD)	588.5 (239.7)	592.4 (251.3)
Change from baseline	Mean (SD)		3.90 (39.55)
	Median		7.2
	Min, max		-59.1, 69.4
	t-test p-value		0.708
	WSR p-value		0.524
LS Mean of change	Mean (SE)		3.89 (11.12)
High-dose rosuvastatin (N=20)			
Observed value	Mean (SD)	515.6 (235.9)	516.9 (233.6)
Change from baseline	Mean (SD)		1.28 (43.92)
	Median		-6.2
	Min, max		-97.5, 90.9
	t-test p-value		0.898
	WSR p-value		1.000
LS Mean of change	Mean (SE)		1.3 (9.6)
Treatment comparisons	LSMeans (SE) of difference		-2.59 (14.79)
	LCL, UCL		-32.72, 27.53
	Treatment p-value		0,862

Baseline lipid values and percent change from baseline at Week 104 (LOCF) are presented in the table below:

Table 8: Lipid values and percent change from baseline

LIPID MEASUREMENT TREATMENT	PERCENT CHANGE FROM BASELINE	
	Baseline Mean (SD)	Week 104 (LOCF)
LDL-C (mg/dL)		
Low-dose rosuva (N=20)	163.9 (38.1)	-38.3 (9.6)
High-dose rosuva (N=22)	148.9 (26.3)	-56.0 (23.9)
TC (mg/dL)		
Low-dose rosuva (N=20)	253.2 (47.8)	-26.1 (8.7)
High-dose rosuva (N=22)	224.3 (35.1)	-37.7 (17.8)
HDL-C (mg/dL)		
Low-dose rosuva (N=20)	48.6 (12.9)	0.28 (12.3)
High-dose rosuva (N=22)	45.2 (12.5)	9.8 (19.1)
TG (mg/dL)		
Low-dose rosuva (N=20)	209.8 (112.7)	-5.7 (25.3)
High-dose rosuva (N=22)	151.4 (42.3)	-16.5 (29.4)

The sponsor concluded that:

- *There was no significant difference between the 2 dose groups in the change from baseline in bilateral carotid artery volume at Week 104.*
- *There was no significant change from baseline in bilateral carotid artery wall volume in either dose group at Week 104.*
- *There was no significant difference between the 2 dose groups in the change from baseline in carotid artery volume at any of the measured time points. There was no significant change from baseline in carotid artery wall volume in either dose group at any of the measured time points.*
- *There were no significant differences between the dose groups for any of the morphological indices at any of the measured time points. No clinically important changes from baseline were present for any of the morphological indices measured at any of the time points.*
- *These were exploratory measurements using an unvalidated method. No results have been presented within the CSR but tables are available in the appendix.*
- *There were no clinically important changes from baseline in total bilateral volume or in percentage of total volume, for any of the lesion types. There were no significant differences between the dose groups.*
- *There were no significant differences between the dose groups for the compositional indices at any of the measured time points. No clinically important changess from baseline were present for compositional indices measured at any of the time points.*
- *The numbers were too small (n=1) to make any definitive conclusion regarding change from baseline in the volume of plaque classified as hemorrhages.*
- *The numbers were too small (n=4) to make any definitive conclusions regarding change from baseline in the volume of plaque classified as loose matrix.*
- *There were no significant differences between the dose groups at any of the measured time points. No clinically important changes from baseline were present for common carotid far wall intima media thickness at any of the time points.*
- *There were no significant differences between the dose groups at any of the measured time points. There were no significant changes from baseline for any time point, for either dose group.*
- *There were no significant changes from baseline in homocysteine levels or lipoprotein particle size at any time point for either dose group.*
- *No significant change from baseline in the percentage change in the diameter of major LDL particles was seen in either dose group for any of the time points.*
- *The distribution of LDL-C subclass phenotype was significantly different between the low and high-dose groups at Week 104 observed and Week 104 LOCF. Type B was more prevalent in the low-dose group while Type A was more prevalent in the high-dose group.*
- *With the exception of Lp[a]and ApoA-I, there were significant differences between the 2 dose groups for all measured lipid parameters using time-weighted averages.*
- *Significant clinically positive changes from baseline in time-weighted averages were noted in both dose groups except for HDL-C, TG, and Apo A-I which did not show significant changes from baseline in the low-dose group.*
- *For patients in the high-risk category, the majority of patients in both dose groups reached their target goals.*
- *No patients progressed to endarterectomy.*

SAFETY DATA:

Of the 984 subjects in **METEOR** who were randomized to study treatment, 3 subjects (2 randomized to rosuvastatin and 1 randomized to placebo) never received study drug and were not included in the safety population. Therefore, the safety population consisted of 702 subjects on rosuvastatin 40 mg and 208 subjects on placebo. Within the rosuvastatin group, 172 (24.5%) subjects discontinued the study – 79 (11.3%) of these were due to adverse events. The next largest group discontinuing were listed as "withdrew consent" – n=47 (6.7%). Within the placebo group, 74 (26.2%) discontinued the study – 22 (7.8%) of these were due to adverse events. The largest group discontinuing were listed as "withdrew consent" – n=28 (9.9%).

In METEOR, there was one death which occurred in the rosuvastatin group approximately 2 months post study treatment; the cause of death was reported as Creutzfeldt-Jakob disease and is not considered to be treatment –related.

The incidence of SAEs was higher in the rosuvastatin group than in the placebo group (63/700 [9.0%] versus 19/281 [6.8%]). The overall frequency of patients with AEs was similar between the treatment groups: 583/700 (83.3%) for the rosuvastatin group and 226/281 (80.4%) for the placebo group. The most commonly reported AE was myalgia, reported in 89/700 (12.7%) in the rosuvastatin group and 34/281 (12.1%) in the placebo group. One patient receiving rosuvastatin experienced exercise-induced muscle pain associated with a clinically important CK elevation (>10xULN) meeting a pre-specified case definition of myopathy in the clinical study program. CK returned to normal levels while the patient continued on study treatment. No other patient had clinically important CK elevation (>10xULN) during the course of the study. There were no cases of hepatitis, rhabdomyolysis, or renal failure.

Overall, 4/689 patients (0.6%) in the rosuvastatin group and 1/276 patients (0.4%) in the placebo group experienced an elevation in ALT >3xULN on 2 consecutive visits at least 48 hours apart. No patient in the study had a doubling of serum creatinine from baseline. The frequency of patients with proteinuria (defined as a shift in dipstick urine protein from none or trace at baseline to ≥2+ post-baseline) at any time during the study was low and similar for the 2 treatment groups; 16/628 patients (2.5%) in the rosuvastatin group and 5/245 patients (2.0%) in the placebo group at any time during the study, decreasing to 6/628 patients (1.0%) in the rosuvastatin group and 1/245 patients (0.4%) in the placebo group at the final visit. One patient in the rosuvastatin group and 1 patient in the placebo group had combined proteinuria and hematuria at any time during the study, and 1 patient in the rosuvastatin group and no patient in the placebo group had combined proteinuria and hematuria at the final visit. There was a small decrease in GFR for both treatment groups; absolute change from baseline to final visit was -3.82 mL/min/1.73 m^2 for the rosuvastatin group and 87.58 mL/min/1.73 m^2 for the placebo group.

Changes in vital signs, ECG, weight, and physical findings were small, and no clinically important patterns were identified.

The sponsor concluded that:

> *Rosuvastatin 40 mg was well-tolerated in this long-term, placebo-controlled study. There were no cases of hepatitis, rhabdomyolysis, or renal failure. Safety data were consistent with the established safety profile for rosuvastatin.*

All patients in **ASTEROID** received rosuvastatin 40 mg. There were 4 deaths in this study while on treatment (the 4 deaths were due to: myocardial ischemia; ventricular fibrillation; septic shock

following bronchopneumonia; and gastric cancer). None of these deaths was considered to be treatment-related.

The incidence of SAEs in ASTEROID was greater than the incidence of SAEs during rosuvastatin treatment in METEOR. There were 165 patients (32.5%) who experienced SAEs in ASTEROID, although only 1 SAE (elevated CK) was considered treatment-related by the study investigator. The most common SAEs were angina pectoris (7.5%), CAD (3.6%), non-cardiac chest pain (3.0%), unstable angina (2.6%) and stent occlusion (2.0%). The sponsor surmises that the higher rate of SAEs in this study was attributable to the higher CV risk patient population studied in ASTEROID.

Sixty-one patients (12.0%) discontinued due to an AE, of which 24 (4.7%) were considered by the investigator to be drug related. The most common AEs leading to discontinuation were myalgia (3.0%) and angina pectoris (1.8%).

Of the 507 patients comprising the safety population, 423 (83.4%) had a treatment-emergent AE. The most common SOCs with AEs were musculoskeletal (37.3%), cardiac (33.5%), infections and infestations (29.2%) and gastrointestinal (26.6%). The most common AEs were angina pectoris (17.9%), myalgia (14.2%), hypertension (11.4%), non-cardiac chest pain (10.3%), and back pain (6.1%).

One patient had ALT >3xULN on 2 consecutive occasions more than 48 hours apart. The patient was subsequently diagnosed with mildly active chronic hepatitis C. Three patients had CK>10xULN. None had muscle symptoms suggesting myopathy or rhabdomyolysis. There were 2 patients with an increase in serum creatinine >100% from baseline, and greater than ULN. Both cases were judged not related to study drug.

Proteinuria (a shift in urine protein from none/trace at baseline to ≥2+) was infrequent and less at the final visit (3.0%) than at any visit (5.0%). Six (1.3%) patients had both proteinuria and hematuria (a shift in urine blood from none/trace at baseline to ≥2+), at some time during the study, with only 1 (0.2%) patient having both at final visit. One patient who had proteinuria had a doubling of serum creatinine that resolved while on rosuvastatin. There was 1 case of renal insufficiency and one case of renal failure – both were deemed unrelated to treatment.

The sponsor concluded that:

> *Overall, rosuvastatin 40 mg was well-tolerated during this 104-week study in patients with CAD. This study identified no new safety issues. The pattern of AEs and abnormal laboratory findings (including muscle and liver symptomatology, and renal and urinalysis data) were consistent with findings from previous rosuvastatin clinical studies and the known safety profile of the drug.*

The safety population in **ORION** consisted of 43 patients – 21 on rosuvastatin 5 mg and 22 on rosuvastatin 40/80 mg. There was 1 patient in the 5 mg group who discontinued due to an AE (atrial fibrillation) and 1 patient on 40 mg who discontinued due to an AE (myocardial infarction and brainstem infarction) and no patients on 80 mg discontinued due to an AE.

In ORION, there was one death which occurred on rosuvastatin 40 mg – the patient with myocardial infarction and brainstem infarction mentioned previously. This was not considered treatment-related by the investigator.

There were 3 patients with SAEs at 5 mg (atrial fibrillation, urinary tract infection, arthritis, bladder neck obstruction), 1 at 40 mg (myocardial infarction and brainstem infarction) and none at 80 mg. The percentage of patients with any AE was 76.2% for the low-dose group and 95.5% for the high-dose group. Of those in the high-dose group, the percentages of patients with any AE were 72.7% at 40 mg and 73.3% at 80 mg. 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).

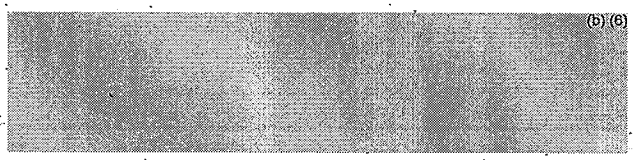
No patients had a clinically important elevation of ALT (>3xULN at 2 consecutive occasions), CK (>10xULN), or serum creatinine (>100% increase from baseline). Only 2 patients had shifts in urine protein or urine blood from non or trace at baseline to ≥++ that persisted to the last study visit.

The sponsor concluded that:

> *Long-term treatment (up to 24 months) with low-dose or high-dose rosuvastatin was well tolerated. The total number of patients in this study was small and the overall number of adverse events was low for the 2-year duration of the study. The frequency, character, and severity of AEs was not unexpected in this patient population treated for this duration (up to 24 months). The percentage of patients with any AE was 76.2% for the low-dose group and 95.5% for the high-dose group (72.7% at 40 mg and 73.3% at 80 mg). Most patients that had AEs, had AEs that were mild or moderate in severity and not unexpected in this patient.*

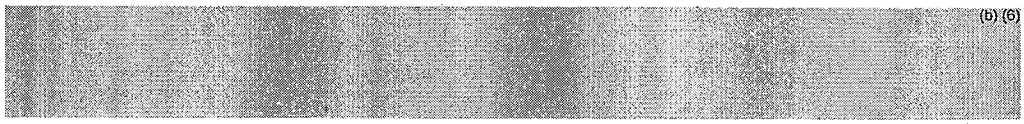
SITE INSPECTION:

See Appendix B for a comprehensive list of primary investigators, sites, number of subjects randomized, number of subjects not randomized, and number of protocol deviations and violations. The sponsor was asked to provide the names and financial disclosure forms for the primary investigators in the following studies at the following sites:



The sponsor provided the information in an e-mail dated February 28, 2007.

The sponsor has indicated the following investigators who have received more than $25,000 from AstraZeneca. (It should be noted that exact amounts were not provided by the sponsor.)



The sponsor will be asked to provide the exact amounts received, although the number of subjects enrolled by these investigators is small and should not likely impact the overall results of the trials.

There were several other sites of potential concern which are summarized below:

- (b) (6)
-
-
-
-

All of these sites represent a potential concern to the integrity of the trials, although given the supportive role of the ASTEROID trial in the current submission, it is felt that only METEOR sites warrant any kind of investigation. It is felt that the primary analysis should be performed with and without (b) (6) Site (b) (6). (b) (6) Sites (b) (6) warrant DSI investigations to see if there are obvious reasons why these two sites report opposite results.

ASSESSMENT:

From a clinical standpoint, this sNDA is fileable. See Appendix A for the filing checklist.

RECOMMENDATIONS:

- Instruct DSI to carry out investigations on the 2 sites indicated above.
- Have the sponsor submit the exact amounts of compensation received by the primary investigators indicated above.
- Have the sponsor clarify the enrollment number at (b) (6) Site (b) (6) in (b) (6). The dataset indicates (b) (6) subjects were randomized at this site, while the sponsor state that (b) (6) subjects were randomized at this site.

APPENDIX A:

NDA 21-366

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA adequately indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e. appropriately designed dose-ranging studies)?	X		Sponsor has chosen the highest marketed dose to gain more information on safety, as well as to enhance efficacy
5) On its face, do there appear to be the requisite number of adequate and well-controlled studies submitted in the application?	X		This will be a review issue. The sponsor was told prior to undertaking this pivotal study that the results would need to be robust in order for them to support the label change.
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		
7) Are all data sets for pivotal efficacy studies complete for all indications requested?	X		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X	This shouldn't be an issue.
11) Has the applicant submitted all additional required case report forms (beyond deaths and, drop-outs) previously requested by the Division)?	X		
12) Has the applicant presented the safety data in a manner consistent with center guideline and/or in a manner previously agreed to by the Division?	X		
13) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	X		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	X		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor submitted?	X		
16) From a clinical perspective, is this NDA fileable? If not, please state in item #17 below why it is not.	X		
17) Reasons for refusal to file: Not applicable.			

APPENDIX B:

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
For Study D3560C00044 (ORION)						
0216	Thomas S. Hatsukami MD	Seattle WA USA	41	31 (in placebo run-in)	21/14	16/5
0558	Larry W. Kraiss MD	Salt Lake City UT USA	2	3 (in placebo run-in)	1/3	
For Study D3562C00076 (ASTEROID)						
0001	Vincent Aquino MD	Houston TX USA	20	6	14/4	48/5
0002	Kenneth Baran MD	St. Paul MN USA	19	7	16/	32
0003	James C. Blankenship MD	Danville PA USA	11	1	4/	9
0004	John C. Messenger MD	Denver CO USA	4	2	3/	3
0005	Louis A. Cannon D.O.	Petoskey MI USA	29	7	17/	37/3
0006	Jeffrey W. Chambers MD	Minneapolis MN USA				4
0008	Patrick S. Colemari MD	Santa Rosa CA USA	22	8	11/	32/1
0009	Christopher J. Cooper MD	Toledo OH USA	12	5	11/1	9/1
0010	John C. Corbelli MD	Williamsville NY USA	3	2	1/	8
0012	Ira M. Dauber MD	Littleton CO USA	9	5	9/3	16/1
0013	Mark Rothenberg MD	Atlantis FL USA	4	1	2/	28/1
0014	Anthony C. DeFranco MD	Flint MI USA	9	3	7/	26
0015	Albert J. Deibele III, MD	Duluth MN USA	20	7	20/	28/1
0016	Riley D. Foreman D.O.	Ft. Smith AR USA				1
0017	Magdi G.H. Ghali MD	Des Moines IA USA	11		3/1	24/3
0018	Navin Gupta MD	Greensboro NC USA	21	5	15/3	72/9

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
0020	Paul C. Gordon MD	Providence RI USA	8	2	3/	5
0022	Joseph L. Gelormini MD	Buffalo NY USA	5		1/	16/2
0023	Steven R. Steinhubl MD	Chapel Hill NC USA				6
0024	Brigitta C. Brott MD	Birmingham AL USA	2	2	3/	3/1
0025	Craig Hjemdahl-Monsen MD	Valhalla NY USA				3
0026	Debabrata Mukherjee MD	Ann Arbor MI USA	5	3	5/	14
0027	Yoseph Shalev MD	Milwaukee WI USA	11	7	12/	24
0029	Jeffrey Snell MD	Chicago IL USA	2	1		11
0030	Paul D. Thompson MD*	Hartford CT USA	4			26/4
0031	Robert J. Weiss MD	Auburn ME USA				4
0034	Hooman Madyoon MD	Manteca CA USA				1
0060	Ian Meredith MD	Clayton VIC Australia				2
0061	David Colquhoun MD	Auchenflower QLD Australia	7		4/	5
0062	Greg R. Bellamy M.B.B.S., F.R.A.C.P.	New Lambton NSW Australia	9		3/	8
0063	Mark C.G. Horrigan M.B.B.S., F.R.A.C.P.	Heidelberg VIC Australia	6	1	3/2	3
0070	Stephane Carlier	Aalst Belgium	12	3	7/1	3
0071	Jean Renkin	Bruxelles Belgium	8	1	2/1	
0072	Pierre Materne	Liège Belgium	11	5	10/1	2
0073	Chris Vrints	Edegem Belgium	6	2	4/6	3

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
0080	Olivier F. Bertrand MD	Ste-Foy Quebec Canada	1			
0081	Francois Reeves MD	Montreal Quebec Canada	14	4	6/	20
0082	Jean-Claude Tardif MD	Montreal Quebec Canada	5	1	5/	7
0083	Michael Love MD	Halifax Nova Scotia Canada	2	2	2/1	6
0084	Christian Constance	Montreal Quebec Canada	4		2/	
0100	Jacques Puel	Toulouse France	6		2/	8
0101	Antoine Lefont	PARIS France	1	1	2/	/1
0103	Pierre Coste'	Pessac France	12	1	3/2	2
0104	Marie-Claude Morice	Massy France	2	1	2/	2
0109	Christophe Caussin	Paris France				1
0130	Jean-Paul R. Herrman MD	Amsterdam Netherlands	32	6	20/2	33/1
0131	Bernard J.W.M. Rensing MD	Nieuwegein Netherlands	4	2	2/	5
0132	Marcel Grosselink MD	Zwolle Netherlands	1			3
0133	Fredericus W.H.M. Bar MD	Maastricht Netherlands				3
0140	Francesco Prati	Rome Italy	4	1	4/	4
0141	Antonio Colombo	Milan Italy	5	1	3/	4
0142	Guglielmo Bernardi	Udine Italy	51	3	5/1	18
0143	Patrizia Presbitero	Milan Italy	12		6/1	7
0146	Achille Bravi	Siena Italy	7	1	3/	3
0147	Bernard Reimers	Venezia Italy	1	1	2/	
0148	Ezio Bramucci	Pavia Italy	2		1/	
0160	Javier Botas Rodriguez	Madrid Spain	5		2/1	1

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
0161	Carlos Macaya Miguel MD	Madrid Spain	22	7	28/	2/4
0164	Amadeo Betriu Gibert MD	Barcelona Spain	3	1	3/	
0165	Enrique Esplugas Oliveras MD	Barcelona Spain	7	1	4/	5
0166	José Maria Hernadez MD	Malaga Spain	9	4	8/	2
0180	Neal G. Uren MD	Edinburgh Scotland UK	5	1	2/	3
0181	Jamil Mayet MD	London UK				4
For Study D3562C00088 - METEOR						
0101	John M. Crouse MD	Winston-Salem NC USA	33	8	26/1	100
0102	Thomas W. Littlejohn III, MD	Winston-Salem NC USA	9	4	4/	35
0103	John M. Morgan MD	Philadelphia PA USA	6	1		32
0104	Mohammed F. Saad MD	Alhambra CA USA	29	29	19/1	235
0105	Robert M. Davidson MD	Los Angeles CA USA	5	1	6/	24
0107	Michael H. Davidson MD	Chicago IL USA	9	4	3/1	50
0108	Stephen P. Glasser MD	Minneapolis MN USA	65	9	22/2	253
0110	Leslie W. Miller MD	Minneapolis MN USA	12	5	9/	27
0112	Robert H. Knopp MD	Seattle WA USA	29	9	21/1	75
0113	Christie Ballantyne MD*	Houston TX USA	16	5	10/	68
0114	William Insull Jr., MD	Houston TX US	4	1	1/	17
0117	Daniel Edmundowicz MD	Pittsburgh PA USA	1			
0118	Alan H. Gradman MD*	Pittsburgh PA USA	1	1	/	29
0119	Danny H.	Chicago IL			/	11

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
	Sugimoto MD	USA				
0124	Neville Bittar MD	Madison WI USA	6	2	3/1	15
0125	Laurence G. Yellen MD	San Diego CA USA	5	2	3/1	31
0126	J.David Cameron MD	Kirkland WA USA	13	2	5/1	32
0127	Evan A. Stein MD, PhD	Cincinnati OH USA	9	4	6/1	9
0128	Eli M. Roth MD	Cincinnati OH USA	18	2	6/	27
0129	Tasneem Z. Naqvi MD	Los Angeles CA USA	4	1	2/	53
0130	Cecil M. Farrington MD	Salisbury NC USA	4		/	77
0131	Steven P. Schmidt DO	Philadelphia PA USA			/	2
0132	Bernard J. Mizock MD Zane P. Osborne MD	Chicago IL USA	27	12	15/1	352
0133	Margaret Drehobl MD	LaJolla CA USA	19	8	11/	106
0134	Dean J. Kereiakes MD	Cincinnati OH USA	14	4	3/	56
0136	Norman M. Lunde MD	Brooklyn Center MN USA	3	2	2/	19
0201	Alain Simon	Paris France	6		1/	32
0202	Patrick Audouy	Paris France	6	4	6/	27
0203	Charles Baranes	Paris France	44	3	17/3	163
0205	Jean-Phillipe Brugnaux	Paris France	1	1	/	34
0206	Eric Chabaud	Ivry sur Seine France	5		1/	13
0207	Phillippe Cahmbraud	Paris France				1
0209	Daniel Delbecq	Paris France	21	4	16/1	124
0211	Jean Claud Mouchet	Meudon France	3	2	4/	41
0212	Marc Pitoun	Paris France				5
0213	Andre Sebbah	Paris France	1			8
0214	Jacques	Paris France				5

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
	Tordjman					
0215	Gilles Bertrand	Metz France	5			9
0217	Marcel Frohn	Moutiers France	5			18
0219	Jean-Luc Jacques	Mars la Tour France	1			8
0220	Claude Kropka	Marange Silvange France				1
0222	Richter Dominique	Jarny France	4			6
0223	Patrick Wach	Briey France				3
0226	Jean -Louis Doubet	Thionville France	1			
0227	Christophe Herfeld	Thionville France				1
0229	Phillippe Martin	Yutz France	1			12
0232	Philippe Lauvray	Delme France				1
0234	Alain Prochasson	Metz France	1		1/	2
0237	Eric De Ste Lorette	Paris France	6	2	3/	23
0239	Jean-Claude Ingrand MD	Les Lilas France	10	2	6/	47
0240	Amin Bekerraz	Billancourt France				4
0241	Denis Smila MD	Yerres France	2	1	2	15
0242	Genevieve Arcizet	Bangolet France	4	1	1/2	24
0244	Pascal Didi MD	Paris France	1		1/	2
0245	Albert Cohen MD	Les Lilas France	4	1	1/	43
0246	Abner Hamou MD	Paris France				1
0248	Mohamad Oulmekki	Drancy France	4	1		20
0249	Karima Allouache	Bangolet France	6	1	2/	22
0301	Annette Bak MD, PhD	Utrecht CJ Holland	98	15	46/1	399
0302	Jan J. Jonker	Rotterdam HC Holland	77	18	31/1	619
0457	Raimond Erbel	Essen Germany	30 (37 per	10	8/1	194

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
			sponsor)			
0458	C. von Schacky	Munich Germany	78	24	54/2	372
0501	Leiv Ose MD, PhD	Oslo Norway	39	7	20/2	114
0502	Helge Istad MD	Oslo Norway				1
0503	Knut Risberg	Skedsmokorset Norway	14	2	2/	14
0505	Andreas Tandberg	Bekkestua Norway	1		1/	13
0506	Oyvind Aabo	Oslo Norway	2		2/	1
0510	Trond Daae-Johansen	Oslo Norway				5
0511	Jon Christiensen MD	Oslo Norway	1			4
0514	Anne C. Poole MD	Oslo Norway	2	1	2	11
0515	Sturla Haugsbo MD	Oslo Norway				
0518	Troels Dano MD	Oslo Norway				1
0601	Leila Antikainen	Kuopi Finland	79	15	19/1	324
0701	M. Goldstein	Bruxelles Belgium	17	5	8/2	59
0702	Guy Marchal Jan Staessen	Leuven Belgium	14	3	4/1	55
0801	Ales Linhart	Prague Czech Republic	49	7	10/1	127
0802	Ondrej Cermak MD	Slany Czech Republic				4
0900	Ward A. Riley PhD	Winston-Salem NC USA				
0901	Daniel O'Leary MD	Boston MA USA				
0902	Laurence Needleman MD	Philadelphia PA USA				
0904		Chicago IL USA				
0906	Kirk Beach MD	Seattle WA USA				
0907	Charles McCollum MD	Houston TX USA				
0909	Paolo Raggi	New Orleans				

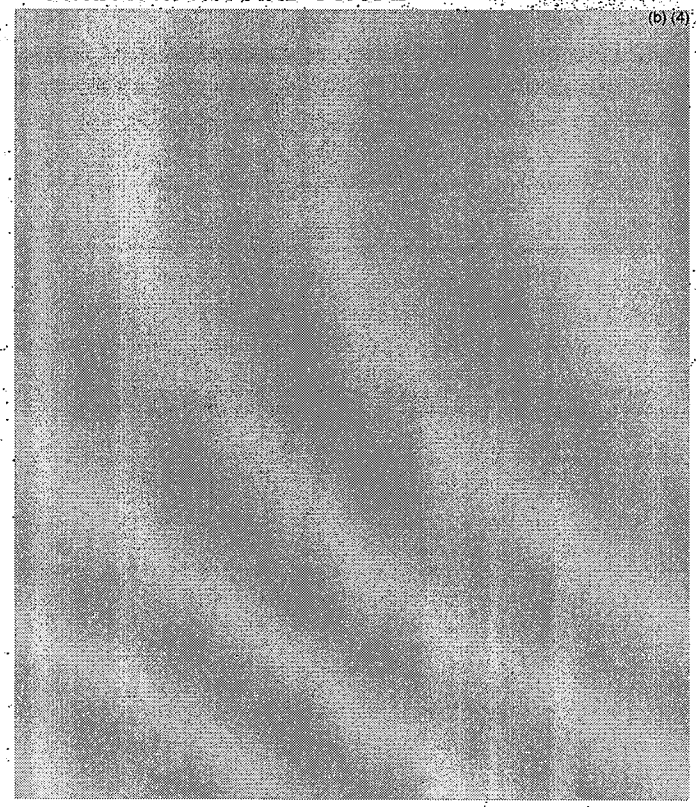
Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
	MD	LA USA				
0910	Kim Sutton-Tyrrell	Pittsburgh PA USA				
0911	James H. Stein MD	Madison WI USA				
0912	Tasneem Z. Naqvi MD	Los Angeles CA USA				
0914	Stephen J. Pomeranz-MD	Cincinnati OH USA				
0915	Shirley M. Otis MD	La Jolla CA USA				
0955	Ales Linhart MD,PhD	Prague Czech Republic				
0956	David Russell	Oslo Norway				
0957	Raimund Erbel	Essen Germany				
0958		Munchen Germany				
0960	Serge Kownator MD	Thoinville France				

*Indicates investigators who received >$25,000 by AstraZeneca

Appendix C: Labeling Change Proposals

1 INDICATIONS AND USAGE

(b) (4)



11 Pages of Draft Labeling have been Withheld as b4 (TS/CCI) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Egan
3/2/2007 04:21:06 PM
MEDICAL OFFICER

Eric Colman
3/2/2007 04:27:21 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT

POST-MARKETING EVALUATION
CMC ASSESSMENT FORM

APPLICANT: ASTRAZENECA PHARMS	NDA NUMBER: 021366	DOC TYPE: SE1	SEQ NUMBER: 010	SUBMISSION TYPE: ORIGINAL
PROPRIETARY NAME: CRESTOR(ROSUVASTATIN CALCIUM)10/20/40 (b) (4)	ESTABLISHED NAME: ROSUVASTATIN CALCIUM TABLETS			
DOSAGE FORM: TAB	STRENGTH/POTENCY: 10, 20, 40, (b) (4) MG	PHARMACOLOGICAL CATEGORY:		
LETTER DATE: 1/5/2007	STAMP DATE: 1/8/2007	PDUFA GOAL DATE: 11/8/2007	SUBMISSION (CHECK ONE) FIRM: PA FINAL: PA	
DIVISION IV BRANCH: VII	OND DIVISION: 510	MANAGED BY: OND	PAL: Brown	
			MEDIA SUBMISSION: Electronic	
SUPPLEMENT PROVIDES FOR: efficacy studies that support the use of CRESTOR in the treatment of atherosclerosis.				
BUNDLED: No				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: No	PAT: No	COMPARABILITY PROTOCOL: No	PHASE 4 COMMITMENT:	
REVIEW PATH: 3 - Moderate Risk - Minimal Review				
CONSULTS:				

JUSTIFICATION/COMMENTS: 2/16/2007 - BROWNJA

1. AstraZeneca has requested a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (a) or (b). To the best of the applicant's knowledge, no extraordinary circumstances exist relative to this action.

2. There are no CMC labeling changes.

3. From a CMC standpoint, this supplement can be approved.

PAL ACTION: From a CMC standpoint, this supplement can be approved.

BRANCH CHIEF: James Vidra

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Brown
2/16/2007 09:43:25 AM
CHEMIST

Jim Vidra
2/19/2007 04:11:50 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

ENVIRONMENTAL ASSESSMENT

AstraZeneca requests a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (a) or (b). To the best of the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-366/SE1-010

Drug Name: Crestor (rosuvastatin calcium)
Indication(s): Treatment of atherosclerosis
Applicant: AstraZeneca
Date(s): Submitted Jan. 5, 2007
Goal date Nov. 8, 2007
Review Priority: Standard

Biometrics Division: Biometrics 2 (HFD-715)
Statistical Reviewer: David Hoberman, Ph.D. (SGE)
Concurring Reviewers: J. Todd Sahlroot, Ph.D. (Deputy Director)

Medical Division: Metabolic and Endocrine Products (HFD-510)
Clinical Team: Amy Egan, M.D. (primary reviewer)
Eric Colman, M.D. (Deputy Director)
Project Manager: Margaret Simoneau

Keywords: Clinical studies, NDA review, mixed models

Table of Contents

Background and Design	3
Results	5
Discussion of Results	6
Interactions	7
Comments	8
Figures	9

Background and Design

The METEOR (Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin) trial sought to demonstrate the efficacy and safety of 40 mg rosuvastatin (R) in the slowing and/or regression of carotid artery thickening compared to placebo (P). Over the course of 2 years, measurements of carotid intima media thickness (CIMT) were made at the following time points relative to randomization: -4 weeks, -2 weeks, 26 weeks, 52 weeks, 78 weeks, and two measurements within a short interval at 104 weeks, for a total of 2 'baseline' and 5 post-randomization' measurements (7 total). To qualify for randomization, patients had to be asymptomatic with a 10-year coronary heart disease risk of less than 10% according to the Framingham Risk Index. Men were to be between the ages of 45-70, and women 55-70. LDL-C was to be between 120 and 160 mg/dL. Randomization was done with a 5:2 ratio (R to P) within a center. Sample size calculations served two purposes: 1) to find statistical evidence of 'regression' from baseline (a negative slope) within the R group and 2) statistical evidence of a difference in group slopes between R and P. For 1) the sponsor used a decrease of .008 mm/yr with a standard deviation of .058 mm/yr, data derived from other studies. For 80% power, this scenario required 415 patients treated with R. For 2) the sponsor used an increase of .012 mm/yr in the P group with the same standard deviation, again using data from other trials. The resulting P sample size is 166 for a power of 90%. The sponsor then assumes an attrition rate of 30%, resulting in a total target sample size of 840 subjects from up to 30 centers in Europe and North America.

A total of 12 thickness measurements (sites) were made on each patient: the near and far walls of the right and left Common Carotid artery, Carotid bulb and the Internal Carotid Artery (2 x 2 x 3=12 sites). The primary efficacy variable was 'change from baseline' values to the end of treatment in *maximum* CIMT (maximum of 5 images at a site) over the two year study period. It is important to point out that this 'change from baseline' is not the usual idea of subtracting a baseline value from the last observation on study. The statistical analysis plan (SAP) specifies that the 2 pre-randomization values will be used, not as covariates, but as *dependent* observations along with the post-randomization observations in a hierarchical mixed model which models site-specific values (within patient) over time. Each patient contributes at most 7 observations over time per site. Thus, the idea is to estimate and compare 'population' slopes across the treatment groups. The correlation of the 12 sites within each patient is modeled by using the following random effects in the model: intercepts at both the site level and patient level. Correlation over time points is modeled using random slopes at both the site level and patient level. The SAP then specifies an unstructured covariance matrix for the random effects, thus generating ten separate parameters (4 variance components and 6 covariances) to be estimated for that matrix. Fixed covariates in the model include age, sex, reader, and ultrasound machine. The p-value for the difference between slopes is derived from the treatment by time interaction term in the model.

As a technical aside, the sponsor oddly 'justifies' a 'model-based approach' by stating the following:

"...an important feature of the model is that regression lines will be fit to site-specific CIMT values, rather than directly to the means over carotid sites. The reason is that some carotid artery sites are consistently found to be more difficult to visualize than others, giving rise to missing data for between one and about 10% of scans depending on the site. In addition sites are known to differ in average thickness. Thus the probability of a CIMT being missing is likely to be related to its unobserved magnitude, thus violating the assumption of "missing completely at random [MCAR]". Average CIMT values over the 12 carotid sites would therefore be biassed [sic] and regression lines fit to such data would exhibit additional variability, and result in an inefficient analysis."

Three comments:

First, saying that "an important feature of the model is that regression lines will be fit to site-specific CIMT values", is confusing because it seems to indicate fitting least squares lines over time for each site separately, when, in fact, the sponsor must mean that the **model** will fit 'site-specific CIMT values'.

Second, the sponsor errs in focusing on MCAR when the issue using a likelihood-based approach (i.e. their mixed effects model) is MAR. But according to the sponsor, the data are not even MAR because the probability of being missing is related to unknown outcomes. Thus, the sponsor ignores the fact that estimates could be biased using their own likelihood-based mixed effects model.

Third, the sponsor has directly emulated the literature dealing with the estimation of population parameters and model fitting, whereas the real purpose of the trial should be to control Type I error while comparing treatments with respect to a parameter which clearly has no 'population' value. Recall that the eventual result is the comparison of two slopes which are derived by data from 3 different carotid arteries, any of which may show 'regression', 'progression' or 'no change' within the same patient at any of 12 sites. Thus, there is no such thing as a clinically relevant population slope being estimated by a model. The emphasis should be on 'proof of principal,' not the theory of estimation using complicated models. The sponsor has not addressed the issue of preservation of Type I error when estimating so many unknown model parameters.

The sponsor specifies the *primary endpoint* to be result using all 12 sites within patients. Four *secondary endpoints* include parallel results (maximum CIMT) for each of the 3 carotid arteries and the *mean* CIMT over the common carotid artery.

Results

In all, 984 patients were randomized, 702 to R and 282 to P among 59 centers in Europe and the United States. The ITT population consisted of patients who had at least one post-baseline observation. In that case, there were 624 assigned to R and 252 to P for a total of 876 patients in the ITT population. These 876 ITT patients were randomized among 59 centers among 8 countries in Europe and North America. However, 15 of these centers have an empty cell (either no P patient or R patient). For purposes of this reviewer's analyses, these 15 centers have been combined into one, resulting in 45 centers. Thus a total of 108 (11%) of randomized patients are not included in any analysis.

As noted earlier, each patient contributes a maximum of 7 data points over time. The table below displays the fraction of ITT patients contributing various numbers of data points:

	Number of Data Points				
	3	4	5	6	7
Placebo	4%	7%	7%	3%	79%
Rosuvastatin	5%	6%	4%	5%	80%

Figure 1 displays the cohorts of **placebo** patients who dropped out at different times over the course of the trial. **Figure 2** displays the cohorts of **rosuvastatin** patients who dropped out at different times over the course of the trial.

Using the supplied data base of 876 patients, the most common reason for discontinuation was adverse event (5.7%, 4.2% in the P group and 6.3% in the R group). However, the Clinical Study Report Synopsis (p.6) states that "for the total randomized population, the most common reason for study discontinuation was adverse events (10.3%)", thus raising the possibility that patients who dropped out before had as higher probability of dropping due to adverse events than patients who had at least one post-baseline observation. Nevertheless, the available data do not indicate any evidence of substantial 'bias' in group comparisons that may be due to missing data at the *patient* level. At the *site* level, the sponsor has supplied data which suggest similar comparability between the groups in terms of missing scans. The sponsor has done sensitivity analyses using data imputation for the 20% of patients who did not have complete data. This review does not address data imputation because it is unnecessary and does not provide additional insight into the questions at hand.

Table I below displays the fundamental results of the trial.

	Rous slope	Placebo slope	p-value
Primary variable:			
Maximum CIMT of the 12 carotid artery sites	-0.0014	0.0131	<0.0001
Secondary variables:			
Maximum CIMT of the CCA	-0.0038	0.0084	<0.0001
Maximum CIMT of the carotid bulb	-0.0040	0.0172	<0.0001
Maximum CIMT of the ICA	0.0039	0.0145	0.0228
Mean CIMT of the CCA	0.0004	0.0088	<0.0001

CCA Common carotid artery; CIMT Carotid intima media thickness; ICA Internal carotid artery; ITT Intent-to-Treat; Rosuva Rosuvastatin.

Although the sponsor reports that all 5 between group comparisons in the table are statistically significant at the .05 level, it also reports that the within R slope is not significantly different from zero: 95% confidence interval (-0.0041, 0014), p=.3224. However, 'progression' (i.e. positive slope) within the P group was significant: 95% confidence interval (0.0087, .0174), p<.0001. The sponsor states that "Results were robust, and consistent across all pre-specified subgroups, including age, gender, and lipid levels."

Discussion of Results

The sponsor's hierarchical mixed model approach is more complicated than need be and, albeit based on a substantial number of observations, raises the issue of potentially pitting the estimation of many parameters against an assurance of Type I error control. For that reason, this reviewer has elected to examine the results using two alternative methods: 1) fitting least squares slopes to the mean of all available site measurements within each patient and then using ANOVA with center and treatment to compare group slopes, and 2) using a mixed model on the same means within patient with random intercept and slope for each patient, using treatment, time, and time by treatment interaction as fixed effects with no covariates. The point is to make analyses as simple as possible (avoid 'black box' computation as much as possible) while still addressing the sponsor's purposes. In addition, this reviewer examined whether statistically significantly different slopes are found when using only post-randomization observations in the analyses. This serves as a check to see whether treatment effect is substantially due to a change from the 'baseline' measurements to 26 weeks, rather than a sustained difference in the rate of change over an extended period since the beginning of treatment.

Using both alternative methods, 4 of the 5 reported outcomes in the above table are robustly sustained. Only the marginal result (p=.0228) for the *internal carotid artery* requires further examination. For one thing, the usual 'change from baseline to last observation of study' result yields p=.14, not an encouraging result. Further, using all observations over time within patient, the analysis of fitted slopes yields p=.27, while the alternative mixed model approach yields p=.037. Note that this latter result is essentially the same as the sponsor's p= .0228 suggesting that 1) the complicated hierarchical site-specific analysis and 2) the use of covariates are unnecessary. When only post-randomization values are used (requiring patients with at least 3 post-randomization observations), the fitted slopes analysis yields p=.80, yielding no evidence of a difference in the rate of thickness change over time-after-treatment, unlike the cases of the bulb and common carotid arteries. When patients with at least 2 post-randomization observations per patient are used in the alternative mixed model, the p-value is .32, again a negative result for a difference in post baseline slopes. In the light of these results, the reason for the overall statistically significant difference between treatment slopes is easy to see. **Figure 3** indicates that there is a sharp increase in the P slope between –2 and 26 weeks at the left near wall of the internal carotid artery. This isolated result in time and space serves as the only evidence that rosuvastatin has its desired effect on the internal carotid artery. When this site is excluded from the mixed model analysis, the p-value rises from .037 to .47, while the accompanying difference in treatment slopes decreases from .01 to .004. The p-value for the left near wall is .0003 while the other 3 sites have p-values greater than .40. Only the combination of all 4 of these sites produces a p-value in the .02 to .03 range, and that only with a mixed model.

Interactions

The sponsor indicated no evidence of heterogeneity of effect over primary subgroups. Fitting least squares slopes to all data on each patient, two-way ANOVA's were used by this reviewer to search for treatment by covariate heterogeneity using the mean maximum over the 12 sites within patient. The results are below:

Treatment by Center: p=.28
Treatment by Country: p=.67
Treatment by age category (above and below median of 57 years): p=.13
Treatment by gender: p=.82

Further investigating the p=.13 result, this reviewer found that, using fitted slopes to all observations within a patient for the carotid bulb, patients below the median age of 57 derived no benefit, while those older than 57 did, p=.0006 for interaction. The table below displays the mean slope for each treatment by age category.

	younger than 57	older than 57
Placebo	0.0	.04
Rosuvastatin	-0.003	-.005

Comments

I. There is ample statistical evidence that, in two of the three carotid arteries (common and bulb), statistical significance was reached at the 5% level. The internal carotid presents a problem because the nominally significant result provided by the sponsor derives from an extreme p-value (.0003) in only one of the 4 sites. In other words, the sponsor's reported p-value of .0228 is only as low as it is because the .0003 is 'diluted' by the other 3 sites which do not achieve p-values below .40. In contrast, there are only 2 other instances of non-significant sites: the near wall of the right bulb and the far wall of the right common. The gross heterogeneity of 'effect' in the internal artery raises the question of whether the sponsor's result even applies to an entity called the 'internal carotid artery', for we now know that any possible 'positive' statistical finding (by whatever methodology) applies only to one anatomical site within what the sponsor calls 'the internal carotid artery'.

II. With regard to the plot in the proposed label, the straight lines depicting 95% confidence intervals result from the sponsor dropping the 'intercept term' of the fitted model, thus artificially making both groups start from 'baseline'. Since the only term in the model is thus the slope*time, then it follows that the standard error (and thus confidence interval width) of the 'predicted' difference from baseline is a simple function of time. The result is something that looks *as if* the sponsor did a 'regression through the origin', but really did not. Since the graphic depiction is not part of either the structural or analytic design, it should not be in the label. Any graphic should be consistent with the design of the study.

Figure 1

4522IL/0088

FIGURE 11.2.1.1.2.2
SUMMARY OF MEANMAX CIMT (MM) BY VISIT AND PLACEBO COHORTS OF ASSESSMENT COMPLETED
INTENTION-TO-TREAT POPULATION

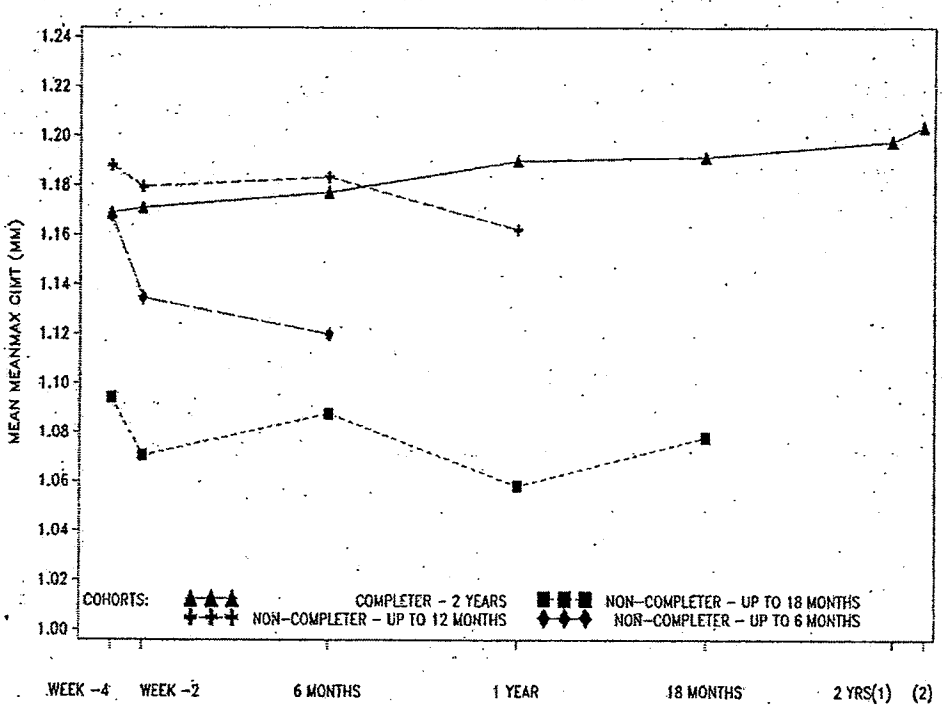


Figure 2

4522IL/0088

FIGURE 11.2.1.1.2.1
SUMMARY OF MEANMAX CIMT (MM) BY VISIT AND ROSUVASTATIN COHORTS OF ASSESSMENT COMPLETED
INTENTION-TO-TREAT POPULATION

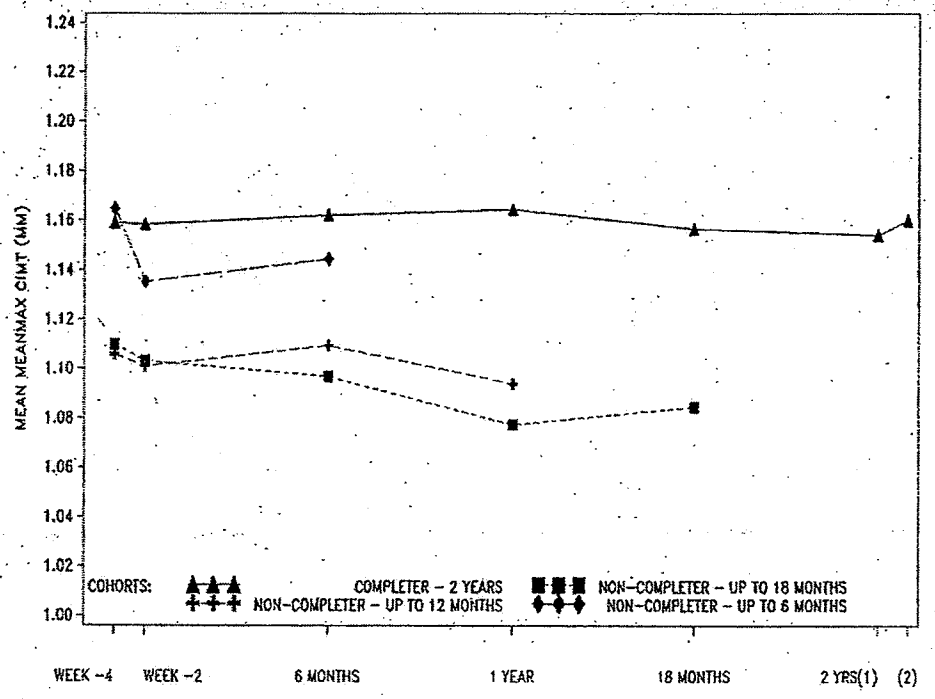
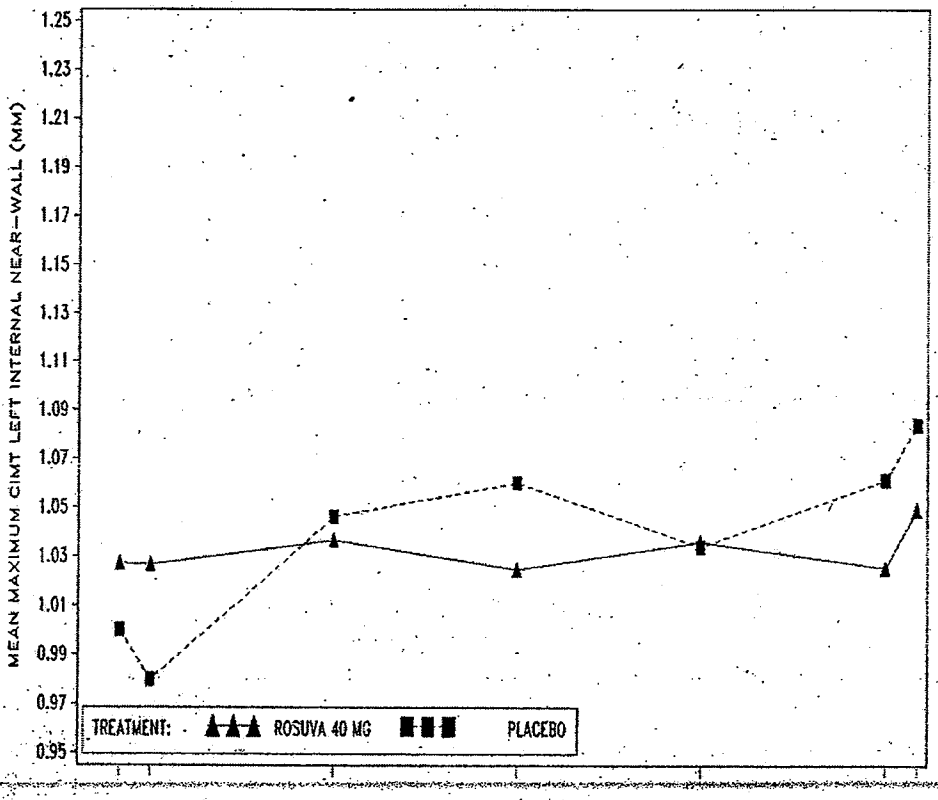


Figure 3

4522IL/0088

FIGURE 11.2.1.7.7
SUMMARY OF MAXIMUM CIMT LEFT INTERNAL NEAR-WALL BY VISIT
INTENTION-TO-TREAT POPULATION



	WEEK -4	WEEK -2	6 MONTHS	1 YEAR	18 MONTHS	2 YRS(1)	(2)
ROSUVA N:	601	605	601	581	533	526	504
PLACEBO N:	243	240	240	232	212	199	192

Y:\ZDA88\ANALYSIS\OUTPUT\MT\F11.2.1.7.7.CGM PLOT_MEANMAX.SAS 21SEP2006

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Todd Sahlroot
10/23/2007 11:04:23 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Metabolism and Endocrinology Products

Application Number: 21-366/S-010

Name of Drug: Crestor (rosuvastatin calcium) Tablets

Applicant: AstraZeneca

Material Reviewed:

Submission Date(s): January 5, 2007

Receipt Date(s): January 8, 2007

Submission Date of Structure Product Labeling (SPL): January 5, 2007

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review/Recommendations

The following issues have been identified in your proposed labeling.

General:

- Please revise your highlights using the Sample Tool Illustrating the Format for Highlights and Contents located at http://www.fda.gov/cder/regulatory/physLabel/default.htm. In addition, inspect the example PLR labels on this web site carefully to correct your other format deficiencies throughout the FPI.

- There should be only one line of white space between the section headings (i.e., Dosage and Administration, etc.) and the end of the previous sections (e.g., Indications and Usage). Delete the other white space. In addition, delete the white space below these section headings.

- Throughout the "Highlights of Prescribing Information" page, all sections including, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions Drug Interactions, and Use in Specific Populations have lines through the words.

Highlights of Prescribing Information:

- Highlights of Prescribing Information should be bolded and the line after should be deleted.
- The drug name, dosage form, route of administration and initial U.S. approval require bolding.
- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
- Add a Recent Major Changes section to Highlights. In addition, for recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:
  "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
- Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights. Also see the draft guidance at http://www.fda.gov/cder/guidance/7472dft.pdf." The pharmacologic class draft guidance was recently published.
- Under Indications and Usage, major limitations of use must be briefly noted.
- Under Contraindications, regarding hypersensitivity. List only known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.
- Delete the general company web site from the Adverse Reactions section statement. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]." AND "Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription

Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.

- Under Drug Interactions, requires bulleting and indentation.
- The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
- A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval. "12/2006" should be modified.
- A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Full Prescribing Information:

General:

- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]"

- Delete the revision date at the end of labeling. The revision date in Highlights makes this redundant and unnecessary.

- All lines after the sections listed (i.e. Indication and Usage, Dosage and Administration, etc.) need to be deleted.
- Under Indications and Usage, bullet the indications instead of assigning each indication a subsection number. There is no reason to assign subsection numbers for cross referencing back to the Indications and Usage section since there is no additional text.
- Under Contraindications, each contradiction should be identified by its own subheading. Pregnancy Category X translates to a Contraindication.
- Under Use in Specific Populations, additional subsections should include patients with renal insufficiency and dosage in Asian patients.

CSO LABELING REVIEW OF PLR FORMAT
Margaret Simoneau 6.18. 2007
Format comments: William Pierce 6.29.07

23 Pages of Draft Labeling have been Withheld as b4 (TS/CCI) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
7/2/2007 03:13:37 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366 / S-010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-366

NAME OF APPLICANT / NDA HOLDER
IPR Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
CRESTOR® (rosuvastatin calcium) tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
Rosuvastatin calcium	5mg, 10mg, 20mg, 40mg

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
RE 37,314	8/7/2001	06/12/2012

d. Name of Patent Owner
Shionogi Seiyaku Kabushiki Kaisha

Address *(of Patent Owner)*
1-8 Doshomachi 3-chome Chuo-Ku

City/State
Osaka 541-0045

ZIP Code
Japan

FAX Number *(if available)*

Telephone Number
06-6202-2161

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Glenn M. Engelmann, Vice President, Policy, Legal & Scientific Affairs & General Counsel
AstraZeneca Pharmaceuticals LP

Address *(of agent or representative named in 1.e.)*
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code
19850-5437

FAX Number *(if available)*

Telephone Number
(800) 456-3669

E-Mail Address *(if available)*

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? * Certain claims may cover at least one additional polymorph in addition to claiming the drug substance of the pending NDA, amendment or supplement, but the patent is not being listed on that basis.	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

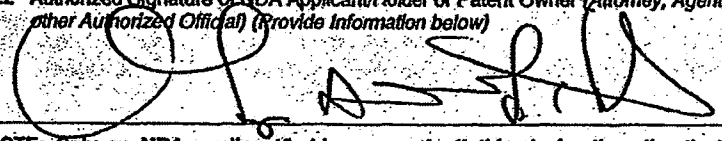
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

PSC Media Arts (301) 443-1090 EF

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	12-18-06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name George A. Gilbert, Director Patent Operations, Wilmington and Neuroscience TA	
Address 1800 Concord Pike	City/State Wilmington, DE
ZIP Code 19803	Telephone Number (302) 886-3887
FAX Number *(if available)* (302) 886-8221	E-Mail Address *(if available)* george.gilbert@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
~~Expiration Date: 07/31/06~~
See OMB Statement on Page 3.

NDA NUMBER
21-366

NAME OF APPLICANT / NDA HOLDER
IPR Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
CRESTOR® (rosuvastatin calcium) tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
Rosuvastatin calcium	5mg, 10mg, 20mg, 40mg

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,316,460	11/13/2001	08/04/2020

d. Name of Patent Owner	Address *(of Patent Owner)*	
AstraZeneca AB	SE 151 85	
	City/State: Södertälje	
	ZIP Code: Sweden	FAX Number *(if available)*
	Telephone Number: 01146855326000	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Glenn M. Engelmann, ~~Vice President,~~ Policy, Legal & Scientific Affairs & General Counsel AstraZeneca Pharmaceuticals LP	1800 Concord Pike	
	City/State: Wilmington, DE	
	ZIP Code: 19850-5437	FAX Number *(if available)*
	Telephone Number: (800) 456-3669	E-Mail Address *(if available)*

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

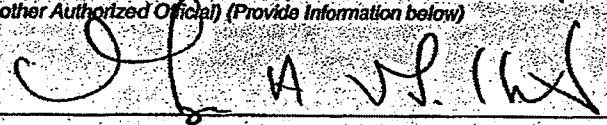
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

PSC Media Arts (301) 443-1090 EF

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	12-18-06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name George A. Gilbert, Director Patent Operations, Wilmington and Neuroscience TA	
Address 1800 Concord Pike	City/State Wilmington, DE
ZIP Code 19803	Telephone Number (302) 886-3887
FAX Number *(if available)* (302) 886-8221	E-Mail Address *(if available)* george.gilbert@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-366

NAME OF APPLICANT / NDA HOLDER
IPR Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
CRESTOR® (rosuvastatin calcium) tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
Rosuvastatin calcium	5mg, 10mg, 20mg, 40mg

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,858,618	02/22/2005	12/17/2021

d. Name of Patent Owner	Address *(of Patent Owner)*	
AstraZeneca AB	SE 151 85	
	City/State: Södertälje	
	ZIP Code: Sweden	FAX Number *(if available)*
	Telephone Number: 01146855326000	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Glenn M. Engelmann, Vice President, Policy, Legal & Scientific Affairs & General Counsel AstraZeneca Pharmaceuticals LP	1800 Concord Pike	
	City/State: Wilmington, DE	
	ZIP Code: 19850-5437	FAX Number *(if available)*
	Telephone Number: (800) 456-3669	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
1,2,3,4,5,6,9 and 10		☒ Yes	☐ No

PSC Media Arts (301) 443-1090 EF

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

DESCRIPTION

Rosuvastatin calcium is bis[(*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

INDICATIONS AND USAGE

In patients with hyperlipidemia,CRESTOR is indicated:

1. as an adjunct to diet to reduce elevated total cholesterol (total-C), low-density-lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), total cholesterol minus high-density lipoprotein cholesterol (nonHDL-C), and tryglycerides (TG) levels and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial and mixed dyslipidemia (Fredrickson Type IIa and IIb);...

4. to slow (b) (4) the progression of atherosclerosis

According to NCEP-ATPIII guidelines, therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for coronary heart disease due to hypercholesterolemia. The two major modalities of LDL-lowering therapy are therapeutic lifestyle changes (TLC) and drug therapy. The TLC Diet stresses reductions in saturated fat and cholesterol intake. Table 1 defines LDL-C goals and cutpoints for initiation of TLC and for drug consideration.

Table 1. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL level at which to initiate TLC	LDL level at which to consider drug therapy
CHD* or CHD Risk Equivalent (10-year risk > 20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL:drug optional)†
2+ Risk Factors (10-year risk ≤ 20%)	<130 mg/dL	≥130 mg/dL	≥130 mg/dL 10-year risk 10-20% ≥160 mg/dL 10-year risk <10%
0-1 Risk Factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL) (LDL-lowering drug optional)

*CHD = coronary heart disease.

Dosage and administration

CRESTOR can be administered as a single dose at any time of day, with or without food.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)

The dose range for CRESTOR is 5 to 40 mg once daily.

CLINICAL PHARMACOLOGY

Clinical Studies

Heterozygous Familial Hypercholesterolemia

In a study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased by 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups...

Hypertriglyceridemia

(Fredrickson Type IIb & IV)

In a double blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels....

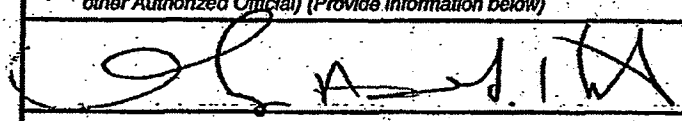
No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	12-18-06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name	
George A. Gilbert, Director Patent Operations, Wilmington and Neuroscience TA	
Address	**City/State**
1800 Concord Pike	Wilmington, DE
ZIP Code	**Telephone Number**
19803	(302) 886-3887
FAX Number *(if available)*	**E-Mail Address *(if available)***
(302) 886-8221	george.gilbert@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

PSC Media Arts (301) 443-1090 EF

EXCLUSIVITY SUMMARY

NDA # 21-366 SUPPL # 010 HFD # 510

Trade Name Crestor

Generic Name Rosuvastatin calcium tablets

Applicant Name AstraZeneca Pharmaceuticals, US agent for IPR Pharmaceuticals

Approval Date, If Known November 8, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study D3562C00088(4522IL/0088, METEOR) and 2 additional studies D3562C00076 (4522IL/076 ASTEROID) and D3560C00044 (4522IL/0044, ORION); METEOR was the efficacy trial and ASTEROID and ORION were studies to support the safety.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

METEOR, ASTEROID AND ORION

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
IND # 56,385	YES ☒	! NO ☐ ! Explain:
Investigation #2		!
IND #	YES ☐	! NO ☐ ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 ! !

YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Margaret Simoneau
Title: RPM
Date: 11.8.07

Name of Office/Division Director signing form: Colman, MD
Title: Deputy Division Director/Team Leader

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
11/8/2007 06:25:15 PM

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

CRESTOR® (rosuvastatin calcium) Tablets
NDA 21-366

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

EXCLUSIVITY INFORMATION

1. Exclusivity Claim

   AstraZeneca Pharmaceuticals LP claims an exclusivity period of three years for this supplemental new drug application.

2. Authority for Exclusivity Claim

   Exclusivity for this supplemental new drug application is being claimed pursuant to 21 CFR 314.108(b)(5).

3. Information Demonstrating this Supplemental Application Contains New Clinical Investigations Conducted or Sponsored by the Applicant that are Essential to the Approval of this Supplemental New Drug Application.

   (a) Certification of New Clinical Investigations

   AstraZeneca Pharmaceuticals LP certifies that to the best of its knowledge, each of the clinical investigation(s) included in this supplemental new drug application meets the definition of "new clinical investigation" set forth in 21 CFR Section 314.108(a).

Joel Raichlen, MD

(b) Essential to Approval

(i) Literature Search

Attached as Exhibit A is a list of all published studies and publicly available reports of clinical investigations known to AstraZeneca Pharmaceuticals LP through a literature search that are relevant to the conditions for which approval is being sought.

(ii) Certification

AstraZeneca Pharmaceuticals LP certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, the list of relevant published studies and/or publicly available reports is complete and accurate, and in its opinion, such published studies and/or publicly available reports do not provide a sufficient basis for the approval of the conditions for which approval is being sought without reference to the new clinical investigation(s) in this supplemental new drug application.

Joel Raichlen, MD

(iii) Explanation

The listed published studies and/or publicly available reports of clinical investigations do not provide sufficient basis for the approval of the conditions for which the Applicant is seeking approval, without reference to the new clinical investigations in this supplemental new drug application.

The new clinical investigation(s) provide safety and efficacy data regarding the use of CRESTOR® (rosuvastatin calcium) Tablets for the treatment of atherosclerosis that could not be gleaned from published information. Accordingly, these new clinical investigations are essential to the approval of this supplemental new drug application.

(c) Conducted or Sponsored by the Applicant.

AstraZeneca Pharmaceuticals LP, the agent and subsidiary of IPR Pharmaceuticals Inc., is the sponsor named in Form FDA 1571 for IND 56,385 under which the new clinical investigation[s] essential to the approval of this supplemental new drug application were conducted. We believe this fact is sufficient under 21 CFR 314.50(j)(4)(iii) to establish that the clinical investigations were conducted or sponsored by the Applicant.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-366 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** S-010

Stamp Date: January 8, 2007 **PDUFA Goal Date:** November 8, 2007

HFD 510 **Trade and generic names/dosage form:** Crestor (rosuvastatin calcium) Tablets

Applicant: AstraZenecaPharmaceuticals, US Agent for IPR **Therapeutic Class:** lipid altering agent

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ❖ **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only):

- patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C (1.1)
- patients with hypertriglyceridemia as an adjunct to diet (1.2)
- patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB (1.3)

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: As adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ❖ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❖ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❖ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Margaret Simoneau

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
11/8/2007 11:32:59 AM

1.6 Request for Waiver of the Pediatric Study

CRESTOR®(rosuvastatin calcium) for the Treatment of Atherosclerosis

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

CRESTOR is a registered trademark, property of the AstraZeneca group of companies

TABLE OF CONTENTS

PAGE

TABLE OF CONTENTS 2
1. REQUEST FOR WAIVER OF THE PEDIATRIC STUDY 3
1.1 Requirements for a Waiver from Pediatric Use Information 3
1.2 Analysis of Meaningful Therapeutic Benefit 3
1.3 Conclusion 4
2. REFERENCES 4

NDA 21-366: CRESTOR ® (rosuvastatin calcium) for the Treatment of Atherosclerosis

1. REQUEST FOR WAIVER OF THE PEDIATRIC STUDY

Sponsor: AstraZeneca Pharmaceuticals LP (AstraZeneca)

AstraZeneca is hereby providing a request for waiver of the pediatric study for this CRESTOR®(rosuvastatin calcium) Tablets supplemental New Drug Application (sNDA).

1.1 Requirements for a Waiver from Pediatric Use Information

Under 21 CFR § 314.55(c)(2), a full waiver may be granted if the applicant certifies that the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. Under 21 CFR § 314.55(c)(5), a drug will be considered to offer a meaningful therapeutic benefit over existing therapies for pediatric patients if FDA estimates that: (i) if approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in pediatric population; or (ii) the drug is in a class of drugs for an indication for which there is a need for additional therapeutic options. The preamble of the final rule indicates that FDA uses the "Priority" definition, with some modifications specific for pediatric patients, in determining whether a product offers a meaningful therapeutic benefit such as: (1) the comparison will be made only to other products that are already adequately labeled for use in the relevant pediatric population, (2) it is often therapeutically necessary to have two or more therapeutic options available, because some patients will be unresponsive to a given therapy (Federal Register, December 2, 1998). A "substantial number of patients" is defined as 50,000 pediatric patients (Federal Register, December 2, 1998). In addition, a partial waiver for a pediatric age group may be granted in the case of 15,000 or less pediatric patients in a particular age group when there are a substantial number of pediatric patients in total (Federal Register, December 2, 1998).

1.2 Analysis of Meaningful Therapeutic Benefit

Hypertension, dyslipidemia, insulin resistance, and even Type II diabetes are increasingly frequent in school-aged children (Sorof 2002), (Sanders 2006). As with adults, the recommendations for the management of these patients start with lifestyle modification (e.g., weight loss) followed by treatments that target specific cardiovascular risk factors (e.g., antihypertensive therapy) (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Although an emerging body of data suggests that the atherosclerotic process begins in the 2nd and 3rd decade of life (Groner 2006), actual symptomatic atherosclerotic cardiovascular disease is extremely rare in this age group. When atherosclerosis does occur, it is typically specific to relatively rare high risk subpopulations of children such as those with familial hypercholesterolemia, diabetes mellitus, type 1 and type 2, chronic kidney disease, heart transplantation, Kawasaki disease, congenital heart disease, chronic inflammatory disease, and childhood cancer (Kavey, 2006).

In contrast to the normal pediatric population, children with these specific underlying conditions experience accelerated atherosclerosis that can lead to premature coronary artery disease. In each of these diseases, therapeutic recommendations are directed at achieving control of the underlying metabolic conditions that lead to accelerated atherosclerosis. With the exception of children with familial hypercholesterolemia, statins are not currently indicated for the treatment of the hyperlipidemia in children, although guidelines list statin therapy as recommended treatment (Kavey, 2006). The only randomized controlled clinical trial in children to address whether statin treatment can alter the course of atherosclerosis in heterozygous familial hypercholesterolemia children failed to show a difference in intima-media thickness after 2-years treatment with pravastatin as compared to placebo (Wiegman, 2004). Thus, even in high risk pediatric patients there is little current evidence that atherosclerosis in and of itself is an appropriate proximate specific target for intervention.

Rosuvastatin is not currently indicated for the treatment of hyperlipidemia in children, although an ongoing dose ranging, efficacy and safety study was requested and agreed upon by FDA in official correspondence dated 7 March 2006 (NDA 21-366), to be submitted by AstraZeneca on or before 31 December 2009. If approved rosuvastatin could be used specifically to lower LDL in these severely hyperlipidemic children. It is reasonable to expect that these data on lipid modification would be relevant to effects on sub-clinical atherosclerosis. However, substantial evidence does not exist that statin treatment indicated for atherosclerosis in adults would offer meaningful proximate therapeutic benefit in the pediatric age group.

1.3 Conclusion

In accordance with 21 CFR § 314.55(c)(2)(i), AstraZeneca certifies that CRESTOR does not represent a meaningful therapeutic benefit for pediatric patients with atherosclerosis and is not likely to be used in a substantial number of pediatric patients specifically for this indication. Consequently, we respectfully request that a full waiver be granted from the requirement to conduct 'anti-atherosclerosis' studies in pediatric patients.

2. REFERENCES

Sorof J, Daniels S. Obesity hypertension in children: a problem of epidemic proportions. Hypertension. 2002 Oct;40(4):441-7.

Sanders BH, Lubsch LM, West DS. Prevalence and treatment of metabolic syndrome in adolescents with type 2 diabetes. Ann Pharmacother. 2006 Sep;40(9):1517-21.

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004;114;555-576

Groner JA, Joshi M, Bauer JA. Pediatric precursors of adult cardiovascular disease: noninvasive assessment of early vascular changes in children and adolescents.

Pediatrics. 2006 Oct;118(4):1683-91.

Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J. Cardiovascular Risk Reduction in High-Risk Pediatric Patients. A Scientific Statement From the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Circulation. 2006 (In press)

Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Buller HR, Sijbrands EJ, Kastelein JJ. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. JAMA. 2004 Jul 21;292(3):331-7.

DEBARMENT CERTIFICATION

Re: **NDA 21-366**

CRESTOR® (rosuvastatin calcium) Tablets

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

Donna M. Dea, Vice President
Regulatory Affairs
AstraZeneca

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

Crestor (b) (6)

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. (b) (6) _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study (b) (6)
Name of

_____, is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

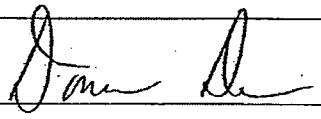
☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Donna Dea	Vice President, Regulatory Affairs
FIRM / ORGANIZATION	
AstraZeneca Pharmaceuticals	
SIGNATURE	**DATE**
	12/6/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

PSC Graphics: (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009
Crestor (b) (6)

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. (b) (6) *Name of clinical investigator*, who participated as a clinical investigator in the submitted study (b) (6) *Name of clinical study*, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Donna Dea	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: AstraZeneca Pharmaceuticals	
SIGNATURE: Donna Dea	DATE: 12/6/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

FORM FDA 3455 (4/06)

PSC Graphics: (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.
Crestor (b) (6)

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	SEE ATTACHED REPORT (S)	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Donna Dea	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: AstraZeneca Pharmaceuticals	
SIGNATURE: Donna Dea	DATE: 12/6/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

PSC Graphics (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009
Crestor (b) (6)

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. (b) (6) (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study (b) (6) (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Donna Dea	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: AstraZeneca Pharmaceuticals	
SIGNATURE	DATE: 12/6/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

FORM FDA 3455 (4/06)

PSC Graphics (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.
Crestor (b) (6)

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Donna Dea	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: AstraZeneca Pharmaceuticals	
SIGNATURE: Donna Dea	DATE: 12/6/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

PSC Graphics (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

Crestor (b) (6)

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Donna Dea	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: AstraZeneca Pharmaceuticals	
SIGNATURE	DATE: 12/6/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing ...uctions, searching existing data sources, gathering and maintaining the necessary data, and ...pleting and reviewing the collection of information. Send comments regarding this burden ...imate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (4/06)

PSC Graphics (301) 443-1090 EF

AstraZeneca

Date:05 December 2007

Mary Parks, MD, Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366 /S-010
CRESTOR® (rosuvastatin calcium) Tablets
TIME SENSITIVE PATENT INFORMATION - for Orange Book Listing

Dear Dr. Parks:

Reference is made to NDA 21-366 /S-010 for CRESTOR® (rosuvastatin calcium) Tablets submitted on 05 January 2007. Reference is also made to the 08 November 2007 FDA Approval Letter for this sNDA.

This submission is providing patent information in accordance with 21 CFR 314.53(c)(2)(ii) which requires that a completed and signed Form FDA 3542 for each patent that claims the drug substance, drug product, or approved method of use, be submitted within 30 days after the approval of a new drug application or a supplement.

This submission is being provided via the FDA Electronic Submission Gateway and includes:

- A Cover Letter
- A completed and signed Form FDA 356h
- Three completed and signed FDA 3542 form(s).

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.5.5001 (Corporate Edition), with a virus definition file dated 04 December 2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manager, at (302) 885-7969.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

AM/PD

Desk Copy: Margaret Simoneau, WO22, RM 3372 (Cover Letter Only)

Technical Review Jacket: Mary A. Holovac, Director, Drug Information
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs / HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

Simoneau, Margaret A

From: Addy, Rosemary
Sent: Friday, November 09, 2007 1:22 PM
To: Simoneau, Margaret A
Cc: Mathis, Lisa; Carmouze, Grace N
Subject: RE: NDA

Hi Margaret,

Please send me the sponsor's request for a waiver and your pediatric page. If the sponsor did not provide adequate justification for the waiver, please send a paragraph explaining why the waiver is necessary.

Thanks!
Rosemary

From: Mathis, Lisa
Sent: Tuesday, November 06, 2007 2:39 PM
To: Carmouze, Grace N; Addy, Rosemary
Cc: Simoneau, Margaret A
Subject: NDA

I just got a call from Margaret Simoneau in 510. She has an application that has a due date of tomorrow. It is for NDA 21-366 and the indication of arthrosclerosis, a condition seen only in adults (b) (5). They are waiving the pediatric studies. I told her that she was good to (b) (5)

She also gave me a heads up that there were (b) (4)

Lisa

Lisa L. Mathis, M.D.
CDR, USPHS
OND Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs
White Oak Complex, Bldg 21, Rm 1633
10903 New Hampshire Ave.
Silver Spring, MD 20993
(301) 796-1704
fax (301) 796-9744
email: Lisa.Mathis@fda.hhs.gov
(Note this is a new e-mail address)

Simoneau, Margaret A

From: Masucci, Iris
Sent: Thursday, November 08, 2007 3:08 PM
To: Simoneau, Margaret A
Subject: RE: NDA 21-366/S-010 CRESTOR

I looked it over, of course. No major issues outstanding.
:)

From: Simoneau, Margaret A
Sent: Thursday, November 08, 2007 3:08 PM
To: Masucci, Iris
Subject: RE: NDA 21-366/S-010 CRESTOR

Really, are you serious?

From: Masucci, Iris
Sent: Thursday, November 08, 2007 3:02 PM
To: Simoneau, Margaret A
Cc: Egan, Amy
Subject: RE: NDA 21-366/S-010 CRESTOR

Good enough for me. I can't look at it anymore!

Thanks to you both. Well done!

Iris

From: Simoneau, Margaret A
Sent: Thursday, November 08, 2007 2:56 PM
To: Masucci, Iris
Cc: Egan, Amy
Subject: FW: NDA 21-366/S-010 CRESTOR
Importance: High

From: DeFeo, Pat A [mailto:pat.defeo@astrazeneca.com]
Sent: Thursday, November 08, 2007 2:52 PM
To: Simoneau, Margaret A
Cc: Egan, Amy
Subject: NDA 21-366/S-010 CRESTOR
Importance: High

Dear Margaret,

Attached please find 2 documents. The first is a clean WORD version of the CRESTOR

label with the requested changes incorporated. The second is a pdf version of the WORD document. Please note that for the comment regarding Section 12.4, Table 4, two interaction studies were conducted. The first was a traditional PK/PD drug-drug interaction study utilizing 40 mg CRESTOR. The PK information in Table 4 was derived from that study. The second was a PD study which utilized 10 and 80 mg of CRESTOR. We have created a footnote beneath the table to refer back to the PD information in the *Warnings and Precautions* section of the label. We hope this is acceptable. If you require additional information on this, please do not hesitate to let me know.

Please do not hesitate to contact me with any questions.

Thank you,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

<<Crestor PI 11 08 07 noon_v2.doc>>

<<Crestor PI 11 08 07 noon_v2.pdf>>

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-366	BLA STN# NDA Supplement # 010	If NDA, Efficacy Supplement Type SE-1
Proprietary Name: Crestor Established Name: rosuvastatin calcium Dosage Form: tablets		Applicant: AstraZeneca Pharmaceuticals LP, Agent for IPR
RPM: M. Simoneau	Division: DMEP	Phone # 6-1295

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	November 8, 2007
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
- ☐ Fast Track
- ☐ Rolling Review
- ☐ CMA Pilot 1
- ☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

NDAs and NDA Supplements:
- ☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☐ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*.	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "Yes," skip to question (4) below. If "No," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below* (Summary Reviews). *If "No," continue with question (3).*	☐ Yes ☐ No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	☐ Yes ☐ No
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below* (Summary Reviews). *If "No," continue with question (5).*	☐ Yes ☐ No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced	☐ Yes ☐ No

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Colman, MD/11.8.07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	11.08.07
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	11.08.07
• Original applicant-proposed labeling	1.05.07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	First in PLR format
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	None
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	None
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	None
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☐ DMETS ☐ DSRCS ☐ DDMAC ☒ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	3.16.07
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	included
❖ Internal memoranda, telecons, email, etc.	included
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	Janice Brown 2.19.07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Statistical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NN
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	A.Egan 11.08.07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	In MO review
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None SEALD
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	In MO review
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	NN
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	Andrea Slavin 10.2.07
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None D. Hoberman 10.23.07
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☒ None

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
11/8/2007 09:36:31 AM

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Thursday, November 08, 2007 6:42 PM
To: Simoneau, Margaret A
Subject: RE: Scanned document from SIMONEAUM
Attachments: emfalert.txt

Dear Margaret,

We have received and acknowledge the attached letter for NDA 21-366/S-010 CRESTOR.

Thank you,

Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

-----Original Message-----
From: Simoneau, Margaret A [mailto:margaret.simoneau@fda.hhs.gov]
Sent: Thursday, November 08, 2007 6:38 PM
To: DeFeo, Pat A
Subject: FW: Scanned document from SIMONEAUM

Crestor S-010 Approval letter

From: SIMONEAUM [mailto:margaret.simoneau@fda.hhs.gov]
Sent: Thursday, November 08, 2007 6:35 PM
To: Simoneau, Margaret A
Subject: Scanned document from SIMONEAUM

<<ScanDoc.pdf>>

Simoneau, Margaret A

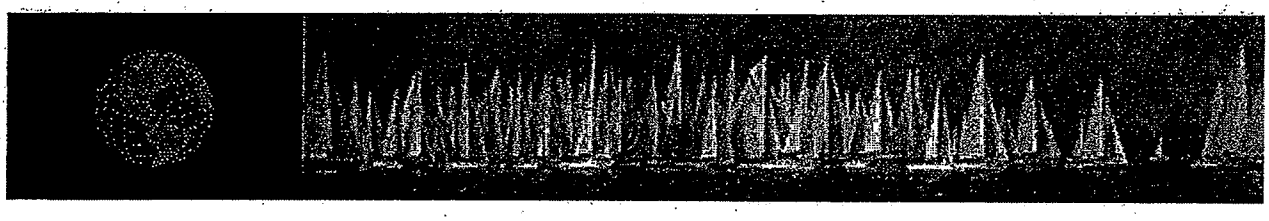
Subject:	NDA 21-366/S-010 Crestor/ Final PLR Discussions/ 1:30 to 2 PM Internal/ AND 2 -3 PM T-con with AZ
Location:	CDER WO 3157 conf rm Bldg22
Start:	Wed 11/7/2007 1:30 PM
End:	Wed 11/7/2007 3:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Egan, Amy; Masucci, Iris; Choe, Sally; Chung, Sang
Resources:	CDER WO 3157 conf rm Bldg22

Amy

5926993*

Simoneau, Margaret A

From: confirmations@mymeetings.com
Sent: Wednesday, November 07, 2007 10:55 AM
To: Simoneau, Margaret A
Subject: Conference Details (NOV 07, 2007--02:00 PM ET--Conf# (b) (4))



PLEASE DO NOT REPLY TO THIS E-MAIL.

- To reschedule/cancel this reservation click here.
- For additional customer service, call us at 877-855-4797.
- Calls must be canceled at least 30 minutes prior to the start time to avoid cancellation fees.
- Meeting leaders are responsible for all charges associated with this conference, so please use discretion when giving out passcodes and other conference-related information.



MEETING INFORMATION

CONFIRMATION #:	(b) (4)
COMPANY:	FTS-HHS FDA CDER
LEADER:	MS MARGARET SIMONEAU
PHONE #:	1-301-796-1295
DAY OF CALL PHONE #:	1-301-796-1295
CRC:	
CONTACT:	MS MARGARET SIMONEAU
PHONE #:	1-301-796-1295
SERVICE LEVEL:	UNATTENDED
CALL ACCESS TYPE:	MEET ME
# OF LINES:	Total=4 Dialout=0 Meet Me=4 Meet Me Toll=0

CALL DATE:	NOV-07-2007 (Wednesday)
CALL TIME:	02:00 PM EASTERN TIME
DURATION:	1 hr

DIAL-IN NUMBERS

PARTICIPANT PASSCODE: (b)(5)

For security reasons, the passcode and the leader's name will be required to join your call.

Country	Toll Numbers	Freephone/ Toll Free Number
USA		(b)(4)

Restrictions may exist when accessing freephone/toll free numbers using a mobile telephone.

IN-CONFERENCE FEATURES

All participants must use a touch-tone phone to participate in an Audio Conference. The follo features are available for you to use on your phone during an active conference:

- Press *0 operator assistance (small fee may apply).
- Press *6 mute/unmute individual line.

AUDIO FEATURES

Tones

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Tuesday, November 06, 2007 8:40 PM
To: Simoneau, Margaret A
Cc: Egan, Amy
Subject: NDA 21-366/S-10 Crestor
Attachments: CRESTOR; Comments for Sections 4, 5 and 6.doc; emfalert.txt

Dear Margaret,

Below please find 2 WORD documents. The first is an annotated copy of the draft CRESTOR label sent to AstraZeneca on Monday, November 5, 2007 by the FDA. In the right margin of this copy, AstraZeneca's comments to FDA's proposed changes can be found. The second document is an addendum, referred to within the comments area of the label, which gives a more detailed discussion of AstraZeneca's concerns as related to Sections 4, 5, and 6 of the November 5 label.

We look forward to meeting with you tomorrow, Wednesday, November 7, at 2 PM EST to discuss these comments. I have not yet received dial-in information for this teleconference but will look for it tomorrow prior to the meeting.

Please do not hesitate to contact me with any questions or concerns.

<<CRESTOR PI 11 06 07 715pm.doc>> <<Comments for Sections 4, 5 and 6.doc>>
Best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

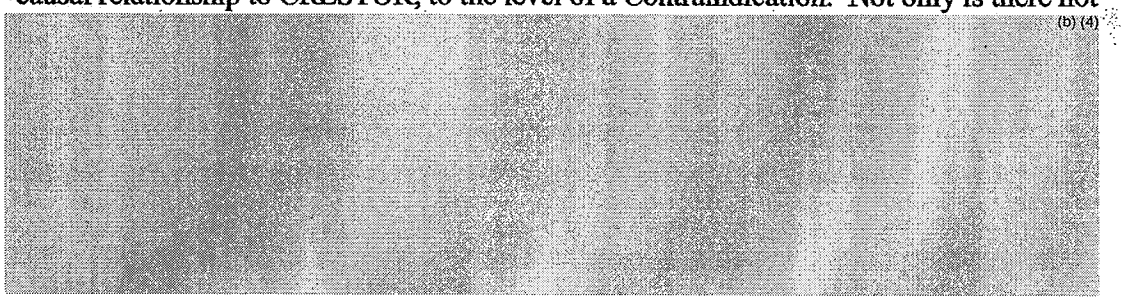
AstraZeneca has made diligent efforts to revise the CRESTOR label in accordance with the FDA's new Physician Labeling Rule (PLR) format. In particular, the enclosed labeling has been revised based on FDA's January 2006 *Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format* ("Guidance") and with specific direction from FDA in the labeling discussions. The Guidance makes a distinction between "Adverse Reactions", which are "undesirable effect[s], reasonably associated with the use of a drug...*for which there is some basis to believe there is a causal relationship*" to the drug, and "Adverse Events," which are "untoward medical event(s) associated with the use of a drug in humans, whether or not considered drug-related." (See *Guidance*, Glossary (emphasis added)). AstraZeneca understands, based on the *Guidance* and specific direction from the FDA, that the ADVERSE REACTIONS section is only to include those adverse clinical experiences for which there is some basis to believe there is a "plausible causal relationship" to drug therapy. (Teleconference with FDA on November 2, 2007). In addition, we understand that, other than postmarketing events, the ADVERSE REACTIONS section should include only those Adverse Reactions reported in controlled clinical trials. (Teleconference with FDA on October 18, 2007; comments on label received October 30, 2007; and teleconference with FDA on November 2, 2007). We further understand that the FDA does not view AstraZeneca's listing of Adverse Reactions in the labeling as an acknowledgment of a causal connection equivalent to the level of proof that would apply in private legal actions related to drug labeling. (See 67 Fed. Reg. 72555, 72556 (December 6, 2002).

With the above in mind, we have several comments on the changes FDA has made to the CRESTOR label in the Division's communication of November 5, 2007.

CONTRAINDICATIONS (Section 4):

The Division has revised the first Contraindication in Section 4 to state that CRESTOR is contraindicated in "Patients with a known hypersensitivity to any component of this product. Acute hypersensitivity reactions including face edema, thrombocytopenia, leukopenia, and vesiculobullous rash have occurred during treatment with CRESTOR." As discussed in our teleconference on November 2, 2006, (b) (4)

causal relationship to CRESTOR, to the level of a Contraindication. Not only is there not (b) (4)



[redacted] (b) (4)

WARNINGS AND PRECAUTIONS (Section 5):

The Division has included the following new Section 5.6 in WARNINGS AND PRECAUTIONS: "Hypersensitivity Reactions: Acute hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash) have occurred during treatment with CRESTOR. CRESTOR therapy should therefore be discontinued if an acute hypersensitivity reaction is suspected." As noted above with respect to the CONTRAINDICATIONS section, AstraZeneca does not believe these adverse events are causally related to CRESTOR or that including them in the WARNINGS AND PRECAUTIONS section will provide useful information to healthcare providers to help them in prescribing. As noted in the discussion on CONTRAINDICATIONS, we believe that it is sufficient to list any hypersensitivity reactions that might be plausibly causally related to CRESTOR in the ADVERSE REACTIONS section of the label. Therefore, we have removed Section 5.6 from the label.

ADVERSE REACTIONS (6)

AstraZeneca has several comments on FDA's revision to the ADVERSE REACTIONS section of the label. We have agreed, at FDA's specific direction, to remove those Adverse *Events* that were listed in the October 27, 2007 submission to FDA. However, FDA has now added kidney failure and hepatitis as Adverse *Reactions* in Section 6.1 of the label. AstraZeneca [redacted] (b) (4) . With respect to hepatitis, it should have been included in the label in Section 6.2 as an Adverse Reaction identified during postmarketing experience with CRESTOR and was omitted as an oversight. We have now included it in Section 6.2, POSTMARKETING EXPERIENCE.

FDA has revised the description of the METEOR trial in Section 6.1 to include "[redacted] (b) (4) ", as "serious adverse reactions ... reported more commonly on rosuvastatin than placebo." As discussed in our teleconference on November 2, 2007, AstraZeneca does not believe these events were plausibly causally related to CRESTOR treatment in METEOR. To include [redacted] (b) (4) events, which were adverse *events* reported in the METEOR trial -- events as to which there is not a "reasonable suspicion" of a causal relationship -- is inconsistent with FDA guidance and could be misleading to prescribers. As such, we respectfully disagree that these events should be listed in the label. Further, we have revised the reference to "[redacted] (b) (4)" in that section of the label to refer to "myopathy" to be consistent with the specificity included in other sections of the label. A reference to "[redacted] (b) (4)" is extremely broad and could imply that we saw events such as rhabdomyolysis in the

METEOR trial. To be consistent with FDA's guidance for the remainder of the ADVERSE REACTIONS section, we are also proposing including a list of those Adverse Reactions from the METEOR trial that led to discontinuation.

Finally, we note that FDA has removed the following Adverse Reactions from the label: "abdominal pain, dizziness, rash, pruritis, and urticaria." AstraZeneca selected these adverse clinical experiences, together with the others listed in Section 6.1, for inclusion as Adverse Reactions based on a comparison of the current U.S. labeling and the Core Data Sheet (CDS) for CRESTOR. The CDS was developed in accordance with the CIOMS guidelines for preparing core clinical safety information on drugs and, although pharmacovigilance is ongoing, the CDS reflects the current known safety profile of the drug based upon the determination of the company's global labeling team. These particular Adverse Reactions were included because they are listed in the CDS and there is some basis to believe there may be a causal relationship to CRESTOR. We believe they should be listed as Adverse Reactions in 6.1 and therefore have included them.

Simoneau, Margaret A

From: Masucci, Iris
Sent: Tuesday, November 06, 2007 1:57 PM
To: Simoneau, Margaret A
Subject: RE: NDA 21-366/S-10 Crestor

A few minor things to fix:

- The very first line in Highlights "HIGHLIGHTS OF PRESCRIBING INFORMATION" should be left-justified, not centered.
- Ask them to delete the trademark symbol from the drug name near the top of HL. Although some PLR labels have included these, (b) (5)
- The first line in Contents "*Full Prescribing Information: Contents" should be in all upper case lettering.
- The section titles in HL (with the dashed lines around them) should be centered within the column. The dashes should run from end to end, across the whole line.
- The margins in the FPI should be reduced, perhaps to 1" all around.
- Under "6 Adverse Reactions," in the very beginning of the section where we list (and then cross-reference) the most serious adverse reactions, I see that only skeletal muscle effects is listed. Shouldn't we also include the liver one here too, especially since we listed both in Highlights?
- Because there is no PPI, the last line in HL should read just "See 17 for PATIENT COUNSELING INFORMATION" and the rest deleted. And, the whole sentence should be bolded. Then, in section 17 of the FPI, the first line referring the reader to the PPI should be deleted, as should the entire section 17.5.

Again, as I said, I'd be happy to do a final once-over as we get down to the wire.

Iris

From: Simoneau, Margaret A
Sent: Monday, November 05, 2007 12:52 PM
To: 'DeFeo, Pat A'
Cc: Colman, Eric C; Egan, Amy; Masucci, Iris
Subject: NDA 21-366/S-10 Crestor

Ms. DeFeo,

Attached you will find the most current version of the proposed PLR PI. The areas that are highlighted in yellow are either "recent major changes" which require a vertical line next to them (atherosclerosis and lopinavir/ritonavir); or parts of the label that you need to complete; or areas which are still up for discussion (hypersensitivity, METEOR AR's). Please feel free to contact me if you have any questions.

Thank you,

Margaret

<< File: CrestorS10110507.doc >>

Simoneau, Margaret A

From: Hankin, Joan E
Sent: Friday, November 02, 2007 2:24 PM
To: Simoneau, Margaret A
Subject: RE: NDA 21-366/S-010 Crestor

Peg:

Thanks for the update. I will stay tuned.

Joan

From: Simoneau, Margaret A
Sent: Friday, November 02, 2007 2:20 PM
To: Hankin, Joan E
Cc: Egan, Amy; Colman, Eric C
Subject: RE: NDA 21-366/S-010 Crestor

Hi Joan,
Thank you for the information regarding the planned AZ consult. The Crestor S-010 efficacy supplement requires the implementation of the new PLR package insert and we have not come to any agreement on labeling. Therefore, the MOR would not be finalized and in DFS until labeling is complete. Amy Egan is the MO for this supplement, but lipid consults are assigned by the team leader. I will include you on the action letter, which may or may not, be on the UF date.

Thanks

From: Hankin, Joan E
Sent: Friday, November 02, 2007 1:41 PM
To: Simoneau, Margaret A
Cc: Hankin, Joan E
Subject: FW: NDA 21-366/S-010 Crestor

Peg:

Today I got a voice message from Linda Wolff at AZ giving me a heads-up that they will be sending DDMAC a request(s) for review of a launch TV ad under the DTC TV User Fee program for the new indication for Crestor the week of 11/19 (following approval the week of 11/8). They would be sending in a storyboard for a 60 second and/or 75 second ads for comment under the 45 calendar day clock.

I know there was controversy about use of the term (b) (4) rather than "slow" the progression of atherosclerosis.

(1) Would you mind passing along the denial of the term (b) (4) for background purposes?

(2) Is there anything else I should know about the labeling negotiations?

(3) Is the MOR in DFS, it wasn't really clear to me?

(4) I assume Amy Egan would be the MO for any consultation, is that correct?

Any info would be appreciated for gearing up.

From: Vij, Kanika
Sent: Friday, November 02, 2007 1:34 PM
To: Hankin, Joan E
Subject: RE: NDA 21-366/S-010 Crestor

There absolutely was and I'm sure it has a lot to do with wanted to use that in advertising. They got a capital "No" from the review division on this!

From: Hankin, Joan E
Sent: Friday, November 02, 2007 1:32 PM
To: Vij, Kanika
Subject: RE: NDA 21-366/S-010 Crestor

Kanika:

I only see AZ's response to FDA's resistance to use of the term (b) (4) not FDA's rejection of their request for reconsideration.

From: Vij, Kanika
Sent: Friday, November 02, 2007 1:27 PM
To: Hankin, Joan E
Subject: FW: NDA 21-366/S-010 Crestor

Hi Joan,

See if you can access this, this was the review division's response to AZ.

Thanks,
Kanika

From: Simoneau, Margaret A
Sent: Wednesday, October 24, 2007 12:18 PM
To: Vij, Kanika
Subject: FW: NDA 21-366/S-010 Crestor

From: DeFeo, Pat A [mailto:pat.defeo@astrazeneca.com]
Sent: Tuesday, October 23, 2007 4:37 PM
To: Simoneau, Margaret A
Cc: Egan, Amy; Colman, Eric C; Sahlroot, Jon T
Subject: NDA 21-366/S-010 Crestor

Dear Ms. Simoneau,

We greatly appreciate the opportunity to talk with you and the other members of the review team yesterday regarding the addition of the Atherosclerosis data to the CRESTOR label. As discussed, AstraZeneca is forwarding an alternate suggestion for the graphical presentation of the METEOR

data for inclusion in the Clinical Studies section of the label. We have also provided in the attached document some additional points which we respectfully request the FDA to consider in regards to the label.

<<Response to FDA_final draft.doc>>
Reference is made to 2 publications which were included in the Atherosclerosis sNDA CTD application. If need be, I can forward those articles to you as .pdf files. Please do not hesitate to contact me for anything further.

Thank you and best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

MEMORANDUM

To: **Margaret Simoneau**
Division of Metabolism and Endocrinology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **October 25, 2007**

Re: **Comments on draft labeling for Crestor (rosuvastatin)**
NDA 21-366/S-010

We have reviewed the proposed label for Crestor (FDA version dated 10/22/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- When doses are expressed throughout the label, please use only a space between the number and the units instead of a dash (i.e., use "20 mg" instead of "20-mg").
- For the new information listed under Recent Major Changes, the corresponding text in the Full Prescribing Information must have a vertical line next to it in the left margin to alert the reader to the new information.
- Throughout the label, sometimes the trade name is presented in all upper case lettering, and sometimes it is mixed case. The preferred presentation is mixed case, but please ensures consistency throughout the label.
- The width of the margins in the Full Prescribing Information (FPI) is unusually wide. While a 1/2" margin is used on all sides for the page containing Highlights and Contents, there is no required margin size for the FPI. We recommend, however, reducing it to 1" all around for ease of reading.
- We note that nearly all instances of "rosuvastatin" in the FPI have been changed to "Crestor." There are times, however, when using the generic name seems more appropriate. For example, we should probably talk about excretion of rosuvastatin into breast milk, not Crestor. Similar changes seem appropriate for the Description section. If we are specifically discussing use of the marketed formulation (as in Clinical Studies or Pharmacokinetics, if correct), then we should use the brand name. Please consider revisions.

- Throughout the label, we sometimes refer to other drugs in this class as "statins" and sometimes as "HMG-CoA reductase inhibitors." Is "statins" now an acceptable term, or should we use the more formal HMG term? Please revise for consistency throughout the label once the appropriate term is selected.

HIGHLIGHTS

- We note that the Highlights section uses several different. Please revise this section to a single font for ease of reading.

- There are several places in Highlights where hard return (i.e., white space) is needed to improve readability. Hard returns should be inserted both before the line with the brand/generic name and after the line with the initial U.S. approval date. Additionally, a hard return should be inserted at the end of each section within Highlights, so white space appears before the next section header.

- With the addition of the atherosclerosis information, lines must be added for Recent Major Changes (for both Indications and Usage and Dosage and Administration), Indications and Usage, and Dosage and Administration.

- To preserve lines in Highlights, the indenting of the bullets and their text can be decreased.

Indications and Usage

- Please consider if the indications would be presented more clearly if the condition were presented first, followed by what lipid changes the drug causes. As written, the reader has to wade through all the altered lipid parameters to get to the indicated condition. We suggest something similar to:

  CRESTOR is a HMG-CoA reductase inhibitor indicated for:
  - patients with primary hypercholesterolemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C (1)
  - patients with hypertrigylceridemia as an adjunct to diet (1)
  - patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB (1)
  - slowing the progression of atherosclerosis... (1)

- We note that only one of the three "limitations of use" appears in Highlights. Should the other two as well? In general, all known limitations discussed in the FPI appear in Highlights.

Dosage and Administration

- Please omit the intending from the initial text in this section.

- This initial paragraph is too wordy for Highlights and should be pared down. We also recommend revising the bulleted information for ease of reading. We recommend:

For all patients:

- Crestor can be taken with or without food, at any time of day. (2.1)
- Use 40 mg dose only for patients not reaching LDL-C goal with 20 mg. (2.1)
- Use recommended starting doses for initial therapy or for patients switched from another HMG-CoA reductase inhibitor (2.1)

- Hypercholesterolemia, mixed dyslipidemia, or hypertriglyceridemia: Starting dose 10 mg. Consider 20 mg starting dose for patients with LDL-C >190 mg/dL and aggressive lipid targets (2.1)
- HoFH: Starting dose 20 mg. (2.1, 2.2)
- Slowing of progression of atherosclerosis: 40 mg ??? (2.X)

- The information that current appears in this section on Asian patients, renal impairment, myopathy, and concomitant therapy is all repeated elsewhere in Highlights (e.g., under Drug Interactions or Use in Specific Populations). While the same topic is often discussed in multiple places in the FPI (in varying levels of detail), we try to avoid repeating information in Highlights. Therefore, we recommend that these be deleted from Dosage and Administration in Highlights.

- The recommendation to use [redacted] (b) (4) for myopathy does not appear anywhere in the FPI. Should it? If not, it should be deleted from Highlights.

Contraindications

- The contraindication in pregnancy and nursing mothers should not be combined because they are distinct patient populations.

Warnings and Precautions

- Once the ordering of this section in the FPI has been finalized, a decision must be made as to how many of the warnings/precautions warrant inclusion in Highlights.

- The topics discussed in this section should state the risk, followed by what the clinician should do about it. We can assist with revisions.

- We suggest changing "Myopathy/Rhabdomyolysis" to "Skeletal Muscle Effects" to reflect recommend changes in the FPI heading.

- The information presented under "Myopathy/Rhabdomyolysis" is overly wordy for Highlights and should be pared down. We recommend:

  Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with use of 40 mg dose, advanced age (>65 years), hypothyroidism, renal impairment, and combination use with cyclosporine, lopinavir/ritonavir, fibrates, or niacin. Discontinue Crestor if signs or symptoms appear (5.1).

- As noted above, the discussion of liver effects should include the monitoring recommendations. We recommend:

Liver dysfunction: Transaminase elevations can occur. Monitor liver function before and during therapy (5.2)

Adverse Reactions

- This sentence can be pared down to:

  Most frequent adverse reactions (>4%) are:.

  Why does the list presented here not match the reactions listed in Table 2? Please verify. In addition, please ensure that the appropriate cut-off incidence rate is used here.

- *"To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch"*

  Extra hard returns should be inserted both before and after this sentence.

Drug Interactions

- As in Warnings and Precautions, these interactions should be ordered by importance and should match the final ordering in the FPI.
- As in Warnings and Precautions, this section should succinctly state what the concern is, and then how to manage it. The current wording is overly lengthy. We can assist with revisions.
- We recommend adding the antacid interaction here because it is important enough to warrant inclusion in Highlights.

Use in Specific Populations

- The ordering here should reflect the ordering in section 8 of the FPI. Therefore, it should be: Pediatric Use, Renal Impairment, and then Asian Patients. The pregnancy/nursing line can be omitted because it is discussed in Contraindications. We recommend:

- Pediatric use: Safety and effectiveness not established. (8.4)
- Severe renal impairment (not on hemodialysis): Start dose is 5 mg, not to exceed 10 mg daily. (2.7, 8.6)
- Asian patients: Consider 5 mg start dose. (2.4, 8.8)

Patient Counseling Statement

- *"See 17 for PATIENT COUNSELING INFORMATION"*

  This entire line should be bolded.

- Is there an FDA-approved patient label (e.g., PPI)? If so, this line must read, "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling."

Revision Date

- Please ensure that the date/month at the end of Highlights is filled in upon approval of this label. The entire line should be flush right within the column.

CONTENTS

- The line "Full Prescribing Information: Contents" should appear in all upper case lettering.
- All numbered sections and subsections of the FPI must be listed in Contents. Some are missing (e.g., those under "1 Indications and Usage). Please ensure that all are included.
- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.

FULL PRESCRIBING INFORMATION

- Please ensure that all numbered subsection titles are in bolded type, as is done for the main section titles.

1.2 Hypertriglyceridemia

- *"Crestor is also indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia."*

  Please delete the "also" from this sentence because it is unnecessary.

1.3 Homozygous Familial Hypercholesterolemia

- (b) (4) ."

  Are we trying to say that Crestor can be used with other treatment modalities or alone if these other modalities are unavailiable? The current wording is not entirely clear. Should we add the word "alone" and say, " ... or alone if such treatments are unavailable..."? Please consider revising.

1.4 Atherosclerosis

- As above, please delete "also" from the indication.

1.5 General Guidelines

- We recommend changing this section title to more accurately reflect what is presented here. These are not really guidelines, but are instead "limitations of use." This term is what is commonly used in the Indications and Usage section to explain situations in which the drug should not be used or for which data are unavailable. We therefore recommend revising the section title to "Limitations of Use."

2 Dosage and Administration

- We note that there is currently no subsection here for dosing for the atherosclerosis indication. Please revise to insert it before the subsection on dosing in Asian patients.

2.1 General Dosing Information

- *"When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy."*

  Should we say "... titrated according to the patient's response and individualized goal of therapy" instead?

- *"The 40-mg dose of CRESTOR is* (b)(4) *only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose."*

  Please consider revising this sentence to avoid saying (b)(4) which seems somewhat awkward for labeling. Should we say, "... should be used only for..." or something similar?

2.2 Hyperlipidemia, Mixed Dyslipidemia and Hypertriglyceridemia

- *"The* (b)(4) *recommended starting dose of CRESTOR is 10 mg once daily."*

  Do we need the word (b)(4) in this sentence?

- *"After initiation* (b)(4) *or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly."*

  The use of "(b)(4) or" here seems unnecessary. Wouldn't just "or" suffice here?

  Please insert "the" before "dosage adjusted accordingly."

2.3 Homozygous Familial Hypercholesterolemia

- *"The [redacted] recommended starting dose of CRESTOR is 20 mg once daily."*

  Again, is the word "[redacted]" needed here?

  Please delete the extra period at the end of this sentence.

- [redacted]

  [redacted] but the preceding section does not. Please consider deleting this sentence. It is unnecessary here because the full dosage range is given under General Dosing Information at the beginning of this section.

2.5 Dosage in Patients Taking Cyclosporine or Combination of Lopinavir and Ritonavir

- Because this section is cited in Recent Major Changes in Highlights and the title must appear in Highlights, please consider shortening the section title so it fits more easily in Highlights. We suggest "Use with Cyclosporine or Lopinavir/Ritonavir" or something similar.

- *"In patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily [see, Warnings and Precautions (5.1) and Drug Interactions (7)]."*

  The phrase "therapy should be limited to" seems a bit awkward. We suggest revising to "the dose of Crestor should be limited to..." as is done in the next sentence about lopinavir/ritonavir.

- *"In patients [redacted] taking a combination of lopinavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily."*

  We suggest deleting [redacted] from this sentence because it is unnecessary.

2.6 Concomitant Lipid-Lowering Therapy

- [redacted]

  We note that this interaction is not mentioned in "7 Drug Interactions." Should it be added there, with a cross-reference from here to there as is done for the gemfibrozil paragraph that follows?

- *"Combination therapy with gemfibrozil should generally be avoided;"*

  Should we explain why here, instead of just referring the reader to Warnings and Precautions (e.g., "... should generally be avoided because of an increased risk for skeletal muscle effects from combination use" or something similar)?

4 Contraindications

- *"Patients with a known hypersensitivity to any component of this product."*

  Because hypersensitivity reactions have been observed with Crestor, the type and nature of these reactions should be described briefly here in a brief second sentence.

  Has cross-sensitivity been demonstrated among statins? Could a patient with a severe hypersensitivity reaction to one statin safely receive another? If not, please consider revising this statement to say that it is contraindicated in patients with hypersensitivity to this or any other statin.

- Please see this reviewer's email correspondence of October 25, 2007 for further details on recommended revisions to the pregnancy and nursing mothers contraindications.

5 Warnings and Precautions

- Please review this section to ensure that the warnings/precautions discussed here are in decreasing order of importance.

5.1 Skeletal Muscle

- We suggest revising this section title to "Skeletal Muscle Effects" or something similar. "Skeletal Muscle" alone is not a "risk."

- "(b) (4) *cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with Crestor."*

  We recommend deleted the bolded type from this sentence. The use of bolded type is being discouraged in labeling and should be used sparingly (e.g., when an explicit direction is being given to the reader such as "Do not inject intramuscularly"). Having this sentence as the first paragraph in the first warning gives it adequate emphasis.

  Please consider deleting the word (b) (4) from this sentence. It is rather vague and can be seen as (b) (4).

- The first two paragraphs in this section are somewhat choppy and could benefit from revision. The first paragraph is a single sentence about observed cases of rhabdomyolysis. Then, the next two sentences say that Crestor increases the risks of myopathy and rhabdomyolysis. Please consider revising to a more broad discussion that can be applied to the whole statin class. We suggest something similar to:

  Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Crestor. These risks can occur at any dose level, but are increased at the highest dose (40 mg). Crestor should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age >65 years, hypothyroidism, renal impairment).

- *"The risk of myopathy during treatment with Crestor may be increased with concurrent administration of other lipid-lowering therapies, cyclosporine, or lopinavir/ritonavir."*

Please consider expanding this sentence to explain why this is true (e.g., because these combinations all increase plasma levels of Crestor?).

Please consider saying "some other lipid-lowering therapies" instead of implying that this is true for all.

- *"The benefit of further alterations in lipid levels by the combined use of Crestor with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with Crestor rosuvastatin and gemfibrozil should generally be avoided."*

  This paragraph seems out of place because it includes no explanation of why these combinations should be avoided. If it is because of increased risks of myopathies from higher Crestor levels, then this entire paragraph should be merged with the preceding paragraph that explains why certain drug combinations increase these risks.

  In addition, please consider if bolded type if truly necessary here.

- [redacted] (b) (4)

  This paragraph seems to repeat the same information in the preceding paragraphs and can be deleted if the others are revised.

- We suggest merging and slightly reorganizing the last two paragraphs in this section to improve flow. We recommend something similar to:

  Crestor therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. CRESTOR therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Tests

- We suggest revising this section title to better reflect that it discusses recommended liver test monitoring and how/not to use in patients with hepatic impairment.

- We suggest putting the bolded paragraph about the recommended monitoring schedule first in this section (without the bolded type) to improve its prominence.

- As with the section on skeletal muscle effects, please consider introducing this topic with a "class labeling" sentence to replace the current first sentence. We suggest something similar to the recommendation under Skeletal Muscle Effects stating that this is a risk with all statins, including Crestor, and then go on to give the Crestor-specific findings.

5.3 Proteinuria and Hematuria

- *"Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on Crestor therapy with unexplained persistent proteinuria during routine urinalysis testing."*

  This sentence advises the clinician about what to do for a patient with proteinuria, but there is no recommendation about what to do for hematuria. Is it the same recommendation? Please consider revising for clarity.

5.4 Cortisol Levels

- Has the combination of Crestor (or other statins) and these drugs actually been shown to reduce cortisol levels? It is not entirely clear what this recommendation is based on. Additionally, does it truly warrant a warning/precaution, or would it be better suited for the Drug Interactions section?

- If it remains a warning/precaution, please consider revising the subsection title to better reflect the risk. Just saying "cortisol levels" is not informative for the reader.

5.5 Concomitant Coumarin Anticoagulants

- We note that "coumarin" is misspelled in the section title.

- Please add a cross-reference to the appropriate subsection in Drug Interactions to the end of this section to point the reader to the more detailed discussion.

5.6 Concomitant Lipid-Lowering Therapies

- We suggest that this subsection be deleted entirely. The risks of combination use of Crestor with gemfibrozil are adequately covered under "5.1 Skeletal Muscle" and "7 Drug Interactions." To give it its own warning/precaution is unnecessary.

5.6 Hypersensitivity Reactions

- As noted under Contraindications, please consider if a discussion of statin cross-sensitivity is appropriate here.

- Please consider adding more information on what the clinician should do if such a reaction occurs (e.g., discontinue immediately and permanently, not give other statins if appropriate, etc.).

6 Adverse Reactions

- This section should be revised to comply with the recommended organization from the guidance on the Adverse Reactions section of labeling. Section 6 should begin with a listing of the most serious adverse events discussed elsewhere in the label (with cross-

referencing), and then list the most common adverse reactions (similar to the list that appears in Highlights), and then the most common reasons for discontinuation. We can assist with revisions.

6.1 Clinical Studies Experience

- Table 2

  Although probably obvious to the reader, we should clarify in the table title or within the table that the numbers in the cells are percentages.

7 Drug Interactions

- As with Warnings and Precautions, the drug interactions listed in this section should be presented in order of importance. Those which require some intervention should appear first (and those will be the ones that appear in Highlights). Putting the lack of CYP450 interactions first seems inappropriate and promotional (i.e., other statins interact, but Crestor doesn't). Please ensure proper ordering.

- We note that there is no listing here for bile acid resin agents or niacin. Please consider if they should be added.

7.2 Cyclosporine

- *"When Crestor 10 mg was co-administered with cyclosporine in cardiac transplant patients, clinically significant increases in Cmax and AUC were observed (11-fold and 7-fold, respectively) compared with healthy subjects."*

  For clarity, we suggest revising this sentence to, "... clinically significant increases in Crestor Cmax and AUC..."

7.4 Lopinavir/Ritonavir

- *"In patients* (b) (4) *taking a combination of lopinavir and ritonavir, the dose of Crestor should be limited to 10 mg once daily."*

  As above, we suggest deleting (b) (4) from this sentence.

7.5 Coumarin Anticoagulants – Warfarin

- *"When Crestor was coadministered with warfarin in patients clinically significant increases in INR were observed (>4, baseline 2-3)"*

  Please add a period to the end of this sentence.

7.7 Antacid

- Please consider if this interaction and dosing recommendations should be discussed under Dosage and Administration, where other interactions that result in dosing modifications are discussed. It could easily be overlooked if it appears only here.

7.8 Oral Contraceptives

- Are these changes in AUC clinically significant? Should the clinician do anything when these are used together with Crestor? Please consider adding a clinical recommendation as appears in most of the other drug interaction discussions.

8 Use in Specific Populations

- Please consider adding a subsection here (e.g., 8.8) for Asian patients, noting the need for dosage adjustments and cross-referencing elsewhere in the label.

8.1 Pregnancy and 8.3 Nursing Mothers

- Please see this reviewer's email correspondence of October 25, 2007 for further details on recommended revisions to the pregnancy and nursing mothers sections.

8.5 Geriatric Use

- Please see the labeling regulations at CFR 201.57 for the required statements for this section.

8.6 Renal Impairment

- This language is nearly identical to what appears in "12.3 Pharmacokinetics." Please consider summarizing here, focusing on the clinical recommendations, and then cross-referencing to the full discussion in Pharmacokinetics.
- *"Crestor therapy should be adjusted in patients with severe renal impairment."*

We suggest rewording "Crestor therapy" to "Crestor dosing" or something similar.

8.7 Hepatic Impairment

- *"Crestor is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels."*

We suggest that this sentence come first in this section, instead of at the end.

12.1 Mechanism of Action

- *"Crestor is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol."*

  Are the terms "selective" and "competitive inhibitor" supported or are they promotional? If the latter, we recommend deletion.

12.3 Pharmacokinetics

- We recommend that the first two sentences about taking Crestor with food and time of administration be moved under the Absorption section.
- Because Crestor is not approved in pediatric patients, the section on pharmacokinetics findings in children should be moved to "8.4 Pediatric Use." If a drug is approved in children, then all information on use in children appears in the usual sections (Dosage and Administration, Clinical Studies, Adverse Reactions, Clinical Pharmacology, etc.). If it is not approved in children, the information should all appear in Pediatric Use.
- The subheading "Renal (b) (4) should be changed to the preferred term "Renal Impairment." The same recommendation applies to "hepatic (b) (4) ."
- In general, the detailed findings of pharmacokinetic drug interaction studies are described in this section. However, because the drug interactions descriptions under section 7 briefly describe the relevant pharmacokinetic parameters, a drug interactions section in Pharmacokinetics seems unnecessary. Alternatively, it could say simply "Drug-Drug Interactions *[see Drug Interactions (7)]*. The current listing of drug interactions seems inadequate.

13.2 Animal Toxicology and/or Pharmacology

- Please see this reviewer's email correspondence of October 25, 2007 for further details on recommended revisions to the Nonclinical Toxicology section.
- The subheading "13.2.1" must be deleted. Numbered subheading can only go to one decimal place. Instead, if subheadings are needed within a numbered subsection, the headings can be underlined and/or italicized.
- We also recommend spelling out "CNS" upon its first use here in the label.

14.1 Hyperlipidemia and Mixed Dyslipidemia

- (b) (4)

  This sentence seems unnecessary and out of place here. Should it be deleted entirely, or should it be moved to Dosage and Administration? The (b) (4) onset claim also seems inconsistent with the recommendation under Dosage and Administration to (b) (4)

- Please delete the numbers 1 and 2 that are used to introduce the dose-ranging study and the active-controlled study. These can be confusing with the use of numbers in the section and subsection titles.

- Table 3

  In the "Dose" column, please insert "Crestor" before and "mg" after each dose clarity (e.g., Crestor 5 mg, Crestor 10 mg, etc.).

- Figure 1

  Should the figure title say "Mixed Dyslipidemia" instead of "Type IIa/IIB"?

  In the footnote under the figure, please replace the colon in "Mean baseline LDL-C; 189 mg/dL" with a colon.

- Table 4

  Please consider if it would be helpful to make the order of the comparator drugs the same in Figure 1 and Table 4. This would require switching pravastatin and simvastatin in one place.

  Did the study design and data analysis plan for this study allow for the inclusion of statistics for all these pair-wise multiple comparisons presented in the footnotes? If not, we recommend deletion.

14.2 Heterozygous Familial Hypercholesterolemia

- Please consider if this study should have its own numbered subsection or if it should be a subheading under 14.1 to reflect how the indications are presented.

14.5 Atherosclerosis

- Please consider revising the title of this section to more accurately reflect the approved indication – slowing of the progression of atherosclerosis.

- *"In the METEOR study, the effect of therapy with Crestor on carotid atherosclerosis was assessed by B-mode ultrasonography in patients with elevated LDL-C, at low risk (Framingham risk <10% over ten years) for symptomatic CAD and with subclinical atherosclerosis as evidenced by carotid intimal-medial thickness (cIMT)."*

- Please consider deleting the acronym "METEOR" unless meaningful to clinicians.

- Please spell out "CAD" upon its first use here in the label.

- *"The annualized rate of change from baseline for the Crestor group was -0.0014 mm/year (p=0.32)."*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Iris Masucci
10/30/2007 09:07:52 AM
DDMAC REVIEWER

Laurie Burke
10/30/2007 11:50:59 AM
INTERDISCIPLINARY

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Monday, October 29, 2007 4:49 PM
To: Simoneau, Margaret A
Subject: NDA 21-366/S-010 CRESTOR
Attachments: emfalert.txt

Dear Ms. Simoneau,

We have received the FDA's response to our October 23, 2007 submission. We sincerely appreciate the review team's consideration of our proposal. AstraZeneca understands and acknowledges the Division's position on inclusion of the term (b) (4) in the Indications and Usage section of the label, as well as the (b) (4)

We also are grateful for the team's consideration of the alternate figure and have taken into account the comments the FDA has made. We appreciate the limitations on being able to provide contextual information for a graphic representation in the label. However, AstraZeneca believes that with appropriate context and clarification, a graph of the type proposed in the original sNDA submission of the label is an appropriate representation of the METEOR results and has value as a part of a balanced description of those results.

With this in mind, for the purposes of the CRESTOR package insert, AstraZeneca respectfully declines the opportunity to include a graphic representation of the METEOR data in the Clinical Studies section.

We look forward to hearing from you regarding the next steps in the completion of this process by the PDUFA action date of November 8, 2007. Please do not hesitate to contact me should there be a need.

Best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Saturday, October 27, 2007 6:08 PM
To: Simoneau, Margaret A
Subject: NDA 21-366/S-010 CRESTOR - Adverse Reaction Tables
Attachments: AE; emfalert.txt

Dear Ms. Simoneau:

As requested during the October 22, 2007 teleconference, AstraZeneca is sending an updated version of the Adverse Reactions section of the CRESTOR label. The attached section has been updated in accordance with communications with the Agency and taking into account the "*Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance*" issued in January 2006 ("Guidance). In teleconferences on August 9, 2007 and October 18, 2007, the Agency advised that the Adverse Reactions section may only include adverse reactions occurring with CRESTOR at a frequency of ≥2% and at a rate greater than or equal to placebo. In accordance with that direction, we have removed those previously listed events that occurred at a frequency of <2% in the CRESTOR clinical trial program. Table 2 reflects these changes. In text format below Table 2, we included a list of adverse reactions that occurred below the specified rate in placebo controlled trials, but for which there is some basis to believe there may be a causal relationship with the drug (see Guidance, Section V, subsection I). This list is followed by a list of rare adverse reactions consistent with the statin drug class, together with appropriate cross references as provided in the Guidance.

As requested during the October 22, 2007 teleconference, the Adverse Reactions section has been updated to include a description of the overall METEOR clinical trial. A textual description advising that the adverse reactions reported in METEOR were similar to those reported in other clinical trials has been added. This data has not been combined with the data in Table 2 for several reasons, consistent with Section V, Subsection A of the Guidance. The study design of the METEOR trial was very different than that of the trials listed in Table 2 in that it was of a 2-year duration, while the studies included in Table 2 had a treatment duration of up to 12 weeks. In addition, the adverse reactions from the METEOR study were coded in MedDRA while those of all the other studies in the label were coded in COSTART, which makes pooling the data difficult. The information regarding the METEOR study is consistent with the data in the summary of clinical safety document submitted with the January 5, 2007 sNDA submission.

An Adverse Events section has also been included with this revision. AstraZeneca believes that it is important to inform clinicians of those most common events reported in clinical studies. In accordance with direction from the Agency regarding the frequency rates, however, we have revised the list to include only those events that occurred in greater than or equal to 2% of the patients in the clinical trial database.

<<AE Proposal FINAL2.doc>>

Please do not hesitate to contact me via telephone, mobile phone, or e-mail should you have any questions.

Thank you,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)

2 Pages of Draft Labeling have been Withheld as b4 (TS/CCI) immediately following this page

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Tuesday, September 25, 2007 5:16 PM
To: Simoneau, Margaret A
Subject: voice mail message of September 23, 2007
Attachments: emfalert.txt

Dear Margaret,

I hope you are well. I apologize for any confusion in contacting a member of the CRESTOR team last week. (b) (6) was supposed to be my contact while I was out but (b) (6). I hope this did not create too much of a problem.

I received your voice mail message of Monday, September 23. I will be in the office all day tomorrow and for the rest of the week (and next) so please feel free to call or e-mail with any questions you might have.

Best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

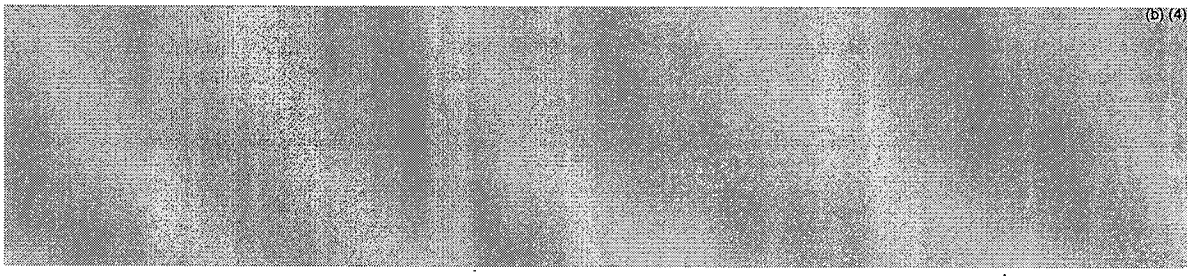
Simoneau, Margaret A

From: Simoneau, Margaret A
Sent: Thursday, October 25, 2007 8:55 AM
To: 'DeFeo, Pat A'
Cc: Colman, Eric C; Egan, Amy; Sahlroot, Jon T
Subject: NDA 21-366/S-010 Proposed labeling comments

Ms. DeFeo,

We have considered your "Response to FDA regarding the CRESTOR Atherosclerosis label" and have the following comments:

1. The figure (Figure 2) which you submitted would be acceptable with the following changes:

   a. 

   b.

   c.

2. We have reconsidered your request to add (b) (4) the progression of atherosclerosis" to the Indications and Usage section and information about ASTEROID to the Clinical Studies section of the label. We continue to maintain our position as stated during the October 22 teleconference.

3. With regard to today's voice mail message regarding the table of PK interactions requested by the Agency, please use the template below and submit the table to us as soon as possible:

Co-administered drug		Rosuvastatin dose	Rosuvastatin PK change	
Name	Dosing		AUC	C_{max}
Erythromycin	500 mg QID for 7 days	80 mg	-20%	-31%
Gemfibrozil	600 mg bid for 7 days	80 mg	+90%	+120%

4. Please complete and submit the Adverse Reaction Tables as requested previously as soon as possible.

Thank you,

Margaret

Simoneau, Margaret A

From: Vij, Kanika
Sent: Wednesday, October 24, 2007 4:01 PM
To: Simoneau, Margaret A
Subject: RE: NDA 21-366/S-010 Crestor

Hi Margaret,

Thanks for inviting me to the meeting this afternoon and keeping me in the loop with the Crestor labeling issue. We would concur with the idea of not accepting (b) (4) in place of "slow" as well based on the discussions about the clinical endpoints and study design.

Thanks,
Kanika

From: Simoneau, Margaret A
Sent: Wednesday, October 24, 2007 12:18 PM
To: Vij, Kanika
Subject: FW: NDA 21-366/S-010 Crestor

From: DeFeo, Pat A [mailto:pat.defeo@astrazeneca.com]
Sent: Tuesday, October 23, 2007 4:37 PM
To: Simoneau, Margaret A
Cc: Egan, Amy; Colman, Eric C; Sahlroot, Jon T
Subject: NDA 21-366/S-010 Crestor

Dear Ms. Simoneau,

We greatly appreciate the opportunity to talk with you and the other members of the review team yesterday regarding the addition of the Atherosclerosis data to the CRESTOR label. As discussed, AstraZeneca is forwarding an alternate suggestion for the graphical presentation of the METEOR data for inclusion in the Clinical Studies section of the label. We have also provided in the attached document some additional points which we respectfully request the FDA to consider in regards to the label.

<<Response to FDA_final draft.doc>>
Reference is made to 2 publications which were included in the Atherosclerosis sNDA CTD application. If need be, I can forward those articles to you as .pdf files. Please do not hesitate to contact me for anything further.

Thank you and best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Tuesday, October 23, 2007 4:37 PM
To: Simoneau, Margaret A
Cc: Egan, Amy; Colman, Eric C; Sahlroot, Jon T
Subject: NDA 21-366/S-010 Crestor
Attachments: Response; emfalert.txt

Dear Ms. Simoneau,

We greatly appreciate the opportunity to talk with you and the other members of the review team yesterday regarding the addition of the Atherosclerosis data to the CRESTOR label. As discussed, AstraZeneca is forwarding an alternate suggestion for the graphical presentation of the METEOR data for inclusion in the Clinical Studies section of the label. We have also provided in the attached document some additional points which we respectfully request the FDA to consider in regards to the label.

<<Response to FDA_final draft.doc>>
Reference is made to 2 publications which were included in the Atherosclerosis sNDA CTD application. If need be, I can forward those articles to you as .pdf files. Please do not hesitate to contact me for anything further.

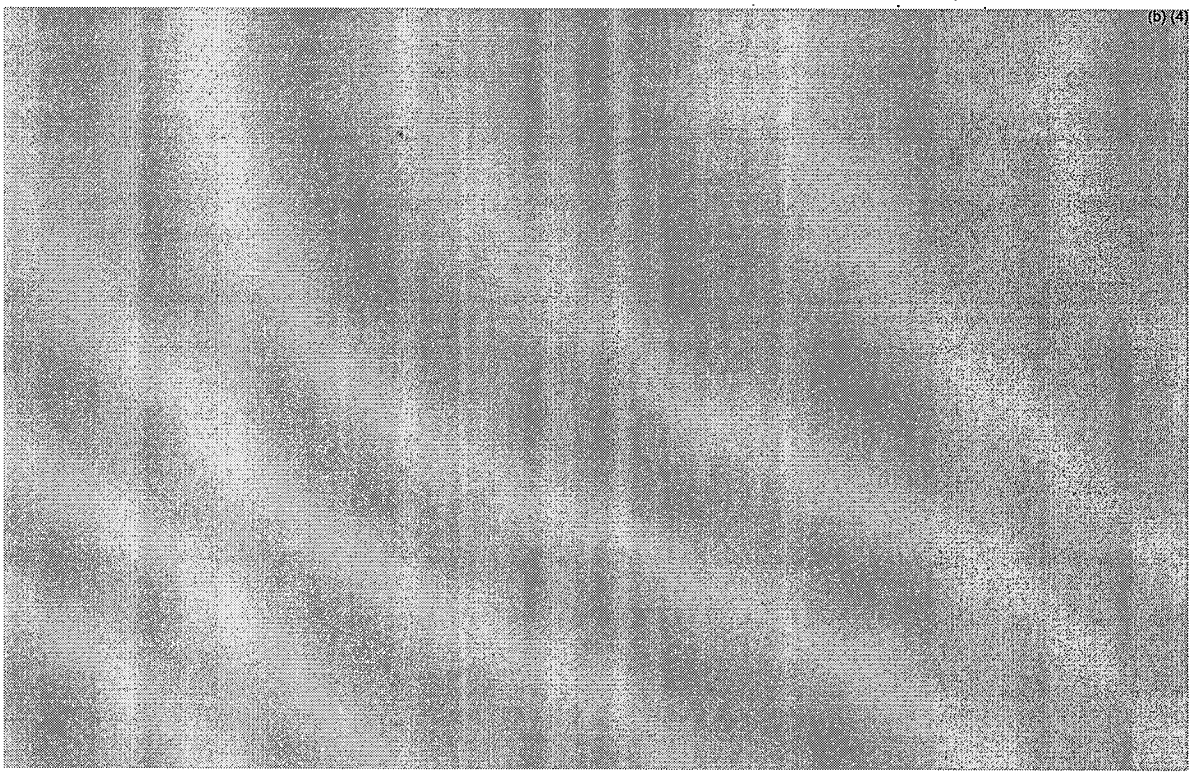
Thank you and best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

October 23, 2007 - Response to FDA regarding the CRESTOR Atherosclerosis label

Alternate figure for the METEOR Trial in the "Clinical Studies" section

AstraZeneca proposes the following graph and wording be added to section "14.5 Atherosclerosis" in section "14 Clinical Studies" of the CRESTOR label:



(b) (4)

We believe this graph addresses the concerns that the FDA expressed in our October 22, 2007 teleconference.

Significance of the word '(b) (4)' in the indication

During our teleconference on October 22, 2007, the Agency questioned the clinical relevance of the descriptor (b) (4) versus 'slow'. AstraZeneca would like to provide the following detailed information to address that question.

Data from previous studies have correlated changes in cIMT to CV risk, namely:

- The Rotterdam study (Bots, 1997) provides evidence that an increased common carotid IMT is associated with future cerebrovascular events. Stroke risk increased gradually with increasing IMT. The odds ratio for stroke per standard deviation increase (0.163 mm) was 1.41 (95% CI, 1.25 to 1.82). For myocardial infarction, an odds ratio of 1.43 (95% CI, 1.16 to 1.78) was found. When subjects with a previous myocardial infarction or stroke were excluded, odds ratios were 1.57 (95% CI, 1.27 to 1.94) for stroke and 1.51 (95% CI, 1.18 to 1.92) for myocardial infarction.
- The CLAS study (Hodis, 1998) demonstrated that for each 0.03-mm increase per year in carotid arterial intima-media thickness, the relative risk for non-fatal myocardial infarction or coronary death was 2.2 (95% CI, 1.4 to 3.6) and the relative risk for any coronary event was 3.1 (CI, 2.1 to 4.5) ($P < 0.001$). Absolute intima-media thickness was also related to risk for clinical coronary events ($P < 0.02$).

These data indicate a continuous relationship between cIMT and its change, and cardiovascular risk. In other words, an increase (or progression) in cIMT is associated with a higher risk. For a patient with an absence of disease progression (no change in cIMT), the risk would be lower than if the patient was still progressing, even at a reduced rate. This is important information for health care providers to understand. Slowing of progression does not equate to absence of progression. In the METEOR trial, for patients who had an absence of progression during the 2-year treatment period, progression of their atherosclerotic process was delayed. This may have a different impact on their CV risk as outlined above.

With this important distinction in mind, AstraZeneca respectfully requests that the FDA re-consider the inclusion of the phrase "to slow (b) (4) the progression of atherosclerosis..." in the Indications and Usage section of the CRESTOR label.

[redacted]Clinical Trial Section

AstraZeneca understands that the ASTEROID trial was an open label study that had no comparator group but wish to reiterate that there was blinding of reader assessments to the order (baseline and follow-up) for both the intravascular ultrasound (IVUS) and the quantitative coronary angiography (QCA) derived measures of coronary atherosclerosis that were used in these studies. Since the data for both the IVUS and QCA derived measures of atherosclerosis indicated lack of progression, we view ASTEROID as a trial that supports the findings in METEOR. It should be recognized that the mean change in percent diameter stenosis based on QCA in ASTEROID had a negative value, which is in contrast to the positive value observed in all previous statin trials that used QCA measurements. In addition, the information provided from ASTEROID is relevant to practicing physicians because it was conducted in patients with coronary artery disease. For these reasons, AstraZeneca proposes the addition of the sentence below as the last sentence in the Atherosclerosis section of the Clinical Studies section.

[redacted] (b) (4)

[redacted]

[redacted] APPEARS THIS WAY ON ORIGINAL

Simoneau, Margaret A

Subject:	NDA 21-366/S-010 Crestor/INDUSTRY Labeling T-con
Location:	CDER WO 3376 conf rm Bldg22
Start:	Mon 10/22/2007 10:00 AM
End:	Mon 10/22/2007 11:00 AM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Egan, Amy; Sahlroot, Jon T; Hoberman, David *
Resources:	CDER WO 3376 conf rm Bldg22

Simoneau, Margaret A

From: Lange, Dave [Dave.Lange@astrazeneca.com]
Sent: Friday, October 19, 2007 10:15 AM
To: Simoneau, Margaret A
Subject: RE: NDA 21-366/S-010 Crestor
Attachments: emfinfo.txt

Dear Margaret,

Thank you for the labeling comments below. As I mentioned in my voice message yesterday, I received your email and was able to open the attachment with no problems.

We look forward to discussing the basis for the Agency's recommendations at the teleconference on Monday. There are a number of specific topics that AstraZeneca would like to cover. In particular, we would like to explore FDA's positions relevant to 1) how the treatment effect of Crestor is characterized in the Indications and Usage section; 2) the inclusion of a figure as a method to present the METEOR results in an easily understandable way; and 3) the discussion of results described in the Clinical Studies section.

Feel free to call/email if have any questions or further information before the teleconference.

Kind regards.

David P. Lange
Associate Director, Global Regulatory Affairs
AstraZeneca R&D
Wilmington, DE
phone: 302.885.4516
(b) (6)

-----Original Message-----
From: Simoneau, Margaret A [mailto:margaret.simoneau@fda.hhs.gov]
Sent: Thursday, October 18, 2007 11:42 AM
To: Lange, Dave
Cc: Colman, Eric C; Egan, Amy; Sahlroot, Jon T
Subject: NDA 21-366/S-010 Crestor

Mr. Lange,

Attached to this email you will find our labeling comments regarding the atherosclerosis indication that will be discussed at a teleconference on Monday, October 22, 2007, at 10 AM. We will be discussing the PLR content and format in an additional meeting next week. If you have any questions, please feel free to call me.

Thank you.

<<CrestorS010label101807.doc>>

Margaret Simoneau, M.S., R.Ph.
FDA/CDER/DMEP
301-796-1295

Simoneau, Margaret A

From: Simoneau, Margaret A
Sent: Thursday, October 18, 2007 11:42 AM
To: 'Lange, Dave'
Cc: Colman, Eric C; Egan, Amy; Sahlroot, Jon T
Subject: NDA 21-366/S-010 Crestor

Attachments: CrestorS010label101807.doc

Mr. Lange,

Attached to this email you will find our labeling comments regarding the atherosclerosis indication that will be discussed at a teleconference on Monday, October 22, 2007, at 10 AM. We will be discussing the PLR content and format in an additional meeting next week. If you have any questions, please feel free to call me.

Thank you.



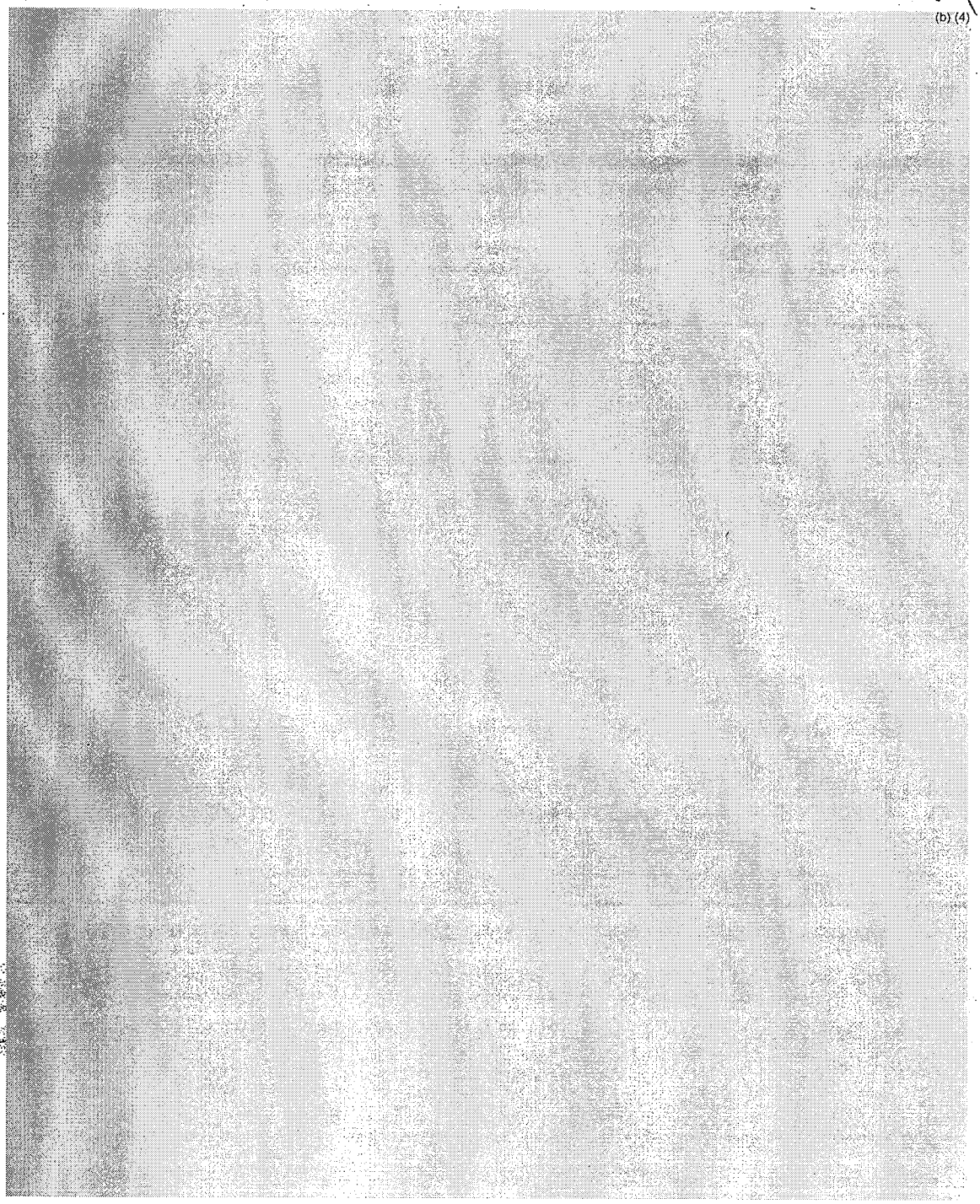
CrestorS010label10
1807.doc (32...

Margaret Simoneau, M.S., R.Ph.
FDA/CDER/DMEP
301-796-1295

Summary Page:

10/18

(b) (4)



Simoneau, Margaret A

From: Lange, Dave [Dave.Lange@astrazeneca.com]
Sent: Wednesday, October 17, 2007 4:30 PM
To: Simoneau, Margaret A
Subject: CRESTOR Atherosclerosis NDA 21-366/S-010
Attachments: emfinfo.txt

Dear Margaret,

I have included below a draft list of AstraZeneca participants in advance of our label discussion on Monday, October 22 – the final list may be modified slightly depending on the nature of the comments we receive from the Division.

Michael Cressman Exec Director, Clinical Research
Pat DeFeo Director, Regulatory Affairs
Dave Lange Assoc Director, Global Regulatory Affairs Jim Florentine
Mark Szewczak Director, Promotional Regulatory Affairs
Barry Traxler Principal Statistician
Robyn Tyler Assoc Director, Labeling

Also, I understood from Pat that you expected to send comments by the end of the day today; so I thought I'd ask if you had any information about how that work is progressing.

By the way, I've attached a delivery receipt to this message to confirm it has reached you – I had sent an initial message to your email address before Pat left to confirm I had the correct Entrust certificates, but I hadn't seen a response come back.

Feel free to call or email if you need any additional information or have questions.

Kind regards,
Dave

David P. Lange
Associate Director, Global Regulatory Affairs
AstraZeneca R&D
Wilmington, DE
office: 302.885.4516
(b) (6)
dave.lange@astrazeneca.com

Simoneau, Margaret A

Subject:	NDA 21-366/S-010 Crestor INTERNAL Labeling Meeting
Location:	CDER WO 3376 conf rm Bldg22
Start:	Mon 10/16/2006 2:00 PM
End:	Mon 10/16/2006 3:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Egan, Amy; Sahlroot, Jon T; Hoberman, David *
Resources:	CDER WO 3376 conf rm Bldg22

9/4/07 Robin (cell)

1. Defer from Oct 7 → 22 (WED Oct 18th)
2. PLR Crestor AR x table
   1. Viewer different
   2. New style sheet
   3. FDA editor view "White Space" + "lines through"

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Thursday, October 04, 2007 10:43 AM
To: Simoneau, Margaret A
Cc: Egan, Amy
Subject: CRESTOR contact and October 22 teleconference information
Attachments: emfalert.txt

Dear Margaret,

As you know, I will be out of the office for the weeks of October 8 and October 15, returning on October 22, 2007. I wanted to send you information on a contact for all matters related to CRESTOR during my absence. The contact will be Dave Lange, Associate Director, Regulatory Affairs. **Dave will be available via telephone at 302-885-4516 and is also equipped with secure e-mail: dave.lange@astrazeneca.com**

For the teleconference on Monday, October 22, I am including below ATT teleconference dial-in numbers and participant code:

Toll free:
Caller Paid:
Participant code: (b) (4)

I will be back in the office and present at the teleconference on the 22nd, and will input the Host Code. This dial-in can be used by multiple callers so if you are not all in one room, that will not be a problem. If you have any questions regarding the dial-in or participant code, please do not hesitate to contact Dave during my absence.

I would like to confirm that the time for the teleconference will be from 10:00am until 11:00am. Also, if possible, would you please provide a draft list of FDA staff that will be participating in the labeling teleconference? Dave will do the same for AstraZeneca staff.

If there is any additional information you should require or we can provide to you, please feel free to contact Dave. Additionally, if there is any information that you can provide to us to prepare for the upcoming teleconference or label discussion, it would be greatly appreciated.

Warm regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 26, 2007

TO: Margaret Simoneau, Regulatory Project Manager
Amy Egan, M.D., Clinical Reviewer
Division of Metabolism and Endocrinology Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Andrea Slavin, RN
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-366/SE#-010

APPLICANT: AstraZeneca Pharmaceuticals LP

DRUG: Crestor® (rosuvastatin calcium)

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of atherosclerosis

CONSULTATION REQUEST DATE: March 19, 2007

DIVISION ACTION GOAL DATE: October 22, 2007

PDUFA DATE: November 8, 2007

I. BACKGROUND:

Crestor (rosuvastatin calcium) is a member of the statin class of lipid-lowering compounds, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and reduce cholesterol synthesis. In addition to its effects on blood lipids, therapy with HMG-CoA reductase inhibitors has been shown to produce regression of atherosclerotic lesions. Crestor received initial FDA approval on 8/12/03. This supplement is for treatment of atherosclerosis.

The goals of the inspections were to assess adherence to FDA regulatory requirements, specifically, investigator oversight, protocol compliance, verification of primary efficacy endpoint data, adequacy of study records, protection of subjects' rights, safety, and welfare and to assess, if possible, a reason for the treatment difference between the 2 sites. The sites were selected by the medical reviewer based on protocol deviations and treatment effect. Site 101 (Dr. Crouse) had the largest treatment effect in a center of reasonable size. Site 108 (Dr. Hirsch) was the largest U.S. site and showed no apparent treatment effect.

The inspections audited protocol #4522IL/0088, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Phase III Study Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin 40 mg (METEOR)"

Summary Report of U.S. (and/or Foreign) Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
John Crouse, MD/101	Winston Salem, NC	4522IL/0088	7/24/07-8/9/07	9/18/07	NAI
*Alan Hirsch, MD/108	Minneapolis, MN	4522IL/0088	7/12/07-7/26/07	9/20/07	VAI

*assumed investigator responsibilities from Stephen P. Glasser, M.D.

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviation(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #4522IL/0088

1. John R. Crouse, M.D. (site 101)
   Wake Forest University Health Sciences
   Department of Internal Medicine, 3rd Floor
   Winston Salem, NC 27157-0001

a. What was inspected: 33 subjects were randomized; all subjects' records were audited for informed consent; 16 subjects' records were audited for data integrity and 8 subjects' records were audited for primary efficacy endpoint data.

b. Limitations of inspection: Carotid ultrasounds were performed at the clinical site; ultrasound images were sent to a core laboratory for measurement of intima media thickness.

c. General observations/commentary: No significant deviations from FDA regulations were observed.

d. Data from this site appear acceptable.

2. Alan T. Hirsch, M.D. (site 108)
1100 Washington Avenue, Suite 201
Epidemiology Clinical Research Center
Minneapolis, MN 55415

a. What was inspected: 65 subjects were randomized; all randomized subjects' records were audited for informed consent; 34 subjects' records were audited for data integrity, including primary efficacy endpoint data.

b. Limitations of inspection: Same as Dr. Crouse's site.

c. General observations/commentary: Significant findings: 2 subjects (#2112 and #2185) did not meet the inclusion criterion for Framingham risk score and 2 subjects (#2309 and #2465) did not have all adverse events reported. The following adverse events were recorded at the site, but were not listed in the sponsor's data listing: subject #2186 (lipoma), #2257 (elevated CK) and #2346 (knee pain).

At Dr. Hirsch's site, the FDA investigator observed that the sponsor had excluded several subjects from the per protocol population because the subjects had taken prohibited medications. These medications were not listed in the protocol as being prohibited (for example, vitamin E, Omega 3 and Balanced Ginseng). During the inspection, the sponsor was queried about this observation and responded that subjects who took prohibited medications or medications that could affect the outcome of the study would be excluded from the per protocol analysis. This could be thought to include any medication or dietary supplement that could affect lipids or lipoproteins whether or not they are listed by name in the prohibited medications list.

d. Data from this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As discussed above, 2 subjects at site 108 (Glasser/Hirsch) did not meet the inclusion criterion for Framingham risk score.

To assist with verification of IMT measurements, data from the core laboratory were sent to the clinical sites and the FDA investigator matched this data to the sponsor's data listing with no discrepancies observed at either site.

Overall, data from these 2 sites appear acceptable in support of this NDA supplement.

{See appended electronic signature page}

Andrea Slavin, RN
Consumer Safety Officer

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andrea Slavin
10/2/2007 04:54:31 PM
CSO

Constance Lewin
10/3/2007 08:11:48 AM
MEDICAL OFFICER

RECD
SEP 27 2007
CDER WHITE OAK DR

SE1-010 BL

Date: 27 September 2007

Mary Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-010
CRESTOR® (rosuvastatin calcium) Tablets
Response to July 12, 2007 and August 9 Review/Recommendations for the proposed labeling

ORIGINAL

Dear Dr. Parks:

Reference is made to NDA 21-366, CRESTOR® (rosuvastatin calcium) Tablets, submitted January 5, 2007 and to the review/recommendations memorandum dated July 12, 2007 for the proposed labeling. Further reference is made to the pre-arranged telephone conversation on August 9, 2007 with Margaret Simoneau, RHPM and Dr. Amy Egan, Medical Reviewer to discuss recommendations for the format of the proposed labeling to the new physician's labeling rule and the submission on August 22, 2007, which outlines AstraZeneca's understanding of the Agency's recommendations.

AstaZeneca is submitting an annotated, nonannoated, and SPL versions with comments to the Agency's August 9, 2007 proposed changes. Furthermore, each Agency request from the July 12, 2007 memorandum is noted below in bold followed by AstaZeneca's response.

General:

- **Please revise your highlights using the Sample Tool Illustrating the Format for Highlights and Contents located at http://www.fda.gov/cder/regulatory/physLabel/default.htm. In addition, inspect the example PLR labels on this web site carefully to correct your other format deficiencies throughout the FPI.**
- **There should be only one line of white space between the section headings (i.e., Dosage and Administration, etc.) and the end of the previous sections (e.g., Indications and Usage). Delete the other white space. In addition, delete the white space below these section headings.**

  The format of the SPL document that was submitted on January 5, 2007 was based on the FDA style sheet. AZ can only revise the content and not the format of the document. The white space does not appear when viewing the document in the FDA editor view.

- **Throughout the "Highlights of Prescribing Information" page, all sections including, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions Drug Interactions, and Use in Specific Populations have lines through the words.**

  The format of the SPL document that was submitted on January 5, 2007 was based on the FDA style sheet. When the document is viewed in the FDA editor view, the lines through the words do not appear. The FDA style sheet was recently updated to correct the "lines through the words", which appeared on the pdf version submitted on January 5, 2007. The update is reflected in the attached package insert.

Highlights of Prescribing Information:

Highlights of Prescribing Information should be bolded and the line after should be deleted.

The format of the SPL document that was submitted on January 5, 2007 was based on the FDA style sheet. AZ can only revise the content and not the format of the document.

The drug name, dosage form, route of administration and initial U.S. approval require bolding.

The format of the SPL document that was submitted on January 5, 2007 was based on the FDA style sheet. AZ can only revise the content and not the format of the document.

- **Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI.**

  [See 21 CFR 201.57(d)(6) and Implementation Guidance]

  The format and font size used for the SPL document that was submitted on January 5, 2007 was based on the FDA style sheet.

  The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

  A word version of the package insert has been included with this submission (8 point font) for visual verification that the highlights section is one-half page.

- **Add a Recent Major Changes section to Highlights. In addition, for recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]**

  Request has been incorporated into the attached package insert.

Simoneau, Margaret A

From: Hunt, Ian [Ian.Hunt@astrazeneca.com]
Sent: Monday, September 24, 2007 2:06 PM
To: Simoneau, Margaret A; Egan, Amy
Cc: DeFeo, Pat A
Subject: CRESTOR - secure email

Dear Margaret and Amy

I am the cardiovascular US Executive Director for Regulatory Affairs within AstraZeneca - Pat DeFeo (Regulatory Director for Crestor) is currently on leave and we wanted to send you a response regarding a question you had related to the Crestor atherosclerosis submission. Unfortunately I do not have secure email, however one of my colleagues, Jamie Huston, does and I will ask Jamie to send this to you on behalf of Pat.

You should receive the email from Jamie this afternoon - if you have any questions regarding the response, do not hesitate to call me (302 886 2586) alternatively, Pat will be back in the office tomorrow and I will ask her to follow up with you to ensure we have fully addressed questions.

Kind Regards

Ian Hunt
Executive Director
AstraZeneca Regulatory Affairs

Simoneau, Margaret A

From: Huston, Jamie [Jamie.Huston@astrazeneca.com]
Sent: Monday, September 24, 2007 2:20 PM
To: Egan, Amy; Simoneau, Margaret A
Cc: DeFeo, Pat A
Subject: (Crestor NDA 21-366) FDA Response to a Request
Attachments: Figure 2 - Crestor prescribing information final.doc; emfalert.txt

Dear Amy,

I am sending this response on behalf of Pat DeFeo, Regulatory Affairs Director, AstraZeneca and you should have received a prior email from Ian Hunt today giving you a contact number should you need it.

<<Figure 2 - Crestor prescribing information final.doc>>

Jamie Huston, MS
Regulatory Affairs, Cardiovascular
302.885.4466

2 Pages of Draft labeling have been Withheld as b4 (TS/CCI) immediately following this page

Simoneau, Margaret A

From: Lange, Dave [Dave.Lange@astrazeneca.com]
Sent: Wednesday, September 19, 2007 1:49 PM
To: Egan, Amy
Cc: Simoneau, Margaret A; DeFeo, Pat A
Subject: FW: 21-366 SE1
Attachments: emfinfo.txt

Dear Amy,

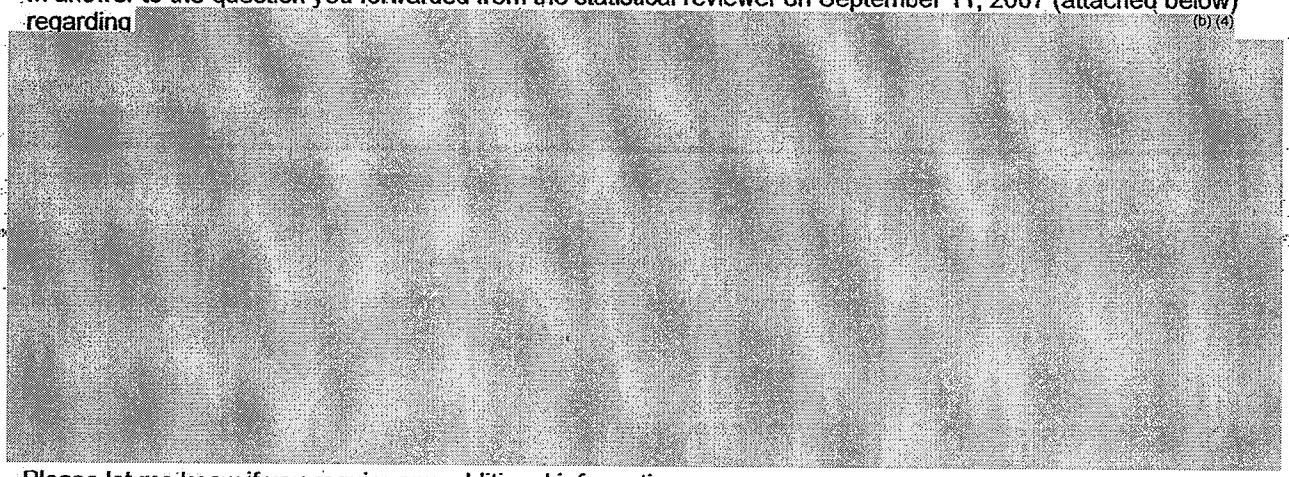
As requested, below is a copy of the answer to the stats question (from Sep 11).

Kind regards. - Dave
-----Original Message-----
From: DeFeo, Pat A
Sent: Friday, September 14, 2007 10:09 PM
To: Lange, Dave
Subject: FW: 21-366 SE1

-----Original Message-----
From: DeFeo, Pat A
Sent: Friday, September 14, 2007 9:27 PM
To: 'Egan, Amy'
Cc: Simoneau, Margaret A
Subject: RE: 21-366 SE1

Dear Amy,

In answer to the question you forwarded from the statistical reviewer on September 11, 2007 (attached below) regarding (b) (4)



Please let me know if you require any additional information.

Best regards,

Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR

AstraZeneca Pharmaceuticals LP
Chesapeake Building, C38-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

-----Original Message-----
From: Egan, Amy [mailto:Amy.Egan@fda.hhs.gov]
Sent: Tuesday, September 11, 2007 10:41 AM
To: DeFeo, Pat A
Cc: Simoneau, Margaret A
Subject: 21-366 SE1

Hi Pat -

Our statistical reviewer has a question regarding the figure (b) (4) that you are proposing be placed in the label. Specifically, he would like to know how the (b) (4) that are illustrated on the figure were derived.

Thanks.

Amy

Simoneau, Margaret A

From: Lange, Dave [Dave.Lange@astrazeneca.com]
Sent: Wednesday, September 19, 2007 1:44 PM
To: Egan, Amy
Cc: Simoneau, Margaret A
Subject: RE: 21-366 SE1
Attachments: emfinfo.txt

Amy,

I think I see what happened... there were two separate responses. The answer to the stats question (from Sep 11) about the (b)(4) on the figure in the PI was not included in the response to your requests of Aug 24, which was submitted to the NDA through the electronic gateway on Friday. I will forward a copy of the separate email response to the Sep 11 question under separate cover.

I hope this clears things up.
Kind regards. - Dave

-----Original Message-----
From: Egan, Amy [mailto:Amy.Egan@fda.hhs.gov]
Sent: Wednesday, September 19, 2007 1:22 PM
To: Lange, Dave
Subject: RE: 21-366 SE1

I do not see the answer to that specific question in the submission sent on Friday. If you could send it to me, I would greatly appreciate it.

Thanks.

Amy

From: Lange, Dave [mailto:Dave.Lange@astrazeneca.com]
Sent: Wednesday, September 19, 2007 1:17 PM
To: Egan, Amy
Subject: RE: 21-366 SE1

Hi Amy,
Yes – the response should have come through to you in an email from Pat late Friday evening (Sept 14). Would you like me to send a copy for your reference?
- Dave

-----Original Message-----
From: Egan, Amy [mailto:Amy.Egan@fda.hhs.gov]
Sent: Wednesday, September 19, 2007 12:01 PM
To: Lange, Dave
Subject: FW: 21-366 SE1

Dave -

I don't know if Pat passed this along to you or not, but we are still waiting for a response to

the question below.

Thanks.

Amy

From: Egan, Amy
Sent: Tuesday, September 11, 2007 10:41 AM
To: 'DeFeo, Pat A'
Cc: Simoneau, Margaret A
Subject: 21-366 SE1

Hi Pat -

Our statistical reviewer has a question regarding the (b) (4) that you are proposing be placed in the label. Specifically, he would like to know how the (b) (4) that are illustrated on the figure were derived.

Thanks.

Amy

AstraZeneca

RECEIVED

SEP 14 2007

CDER White Oak OR

Date: 14 September 2007

Mary Parks, MD, Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

21-010 BS

Re: NDA 21-366/S-010
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Additional Information / Analyses Relevant to the Primary Endpoint Analyses from the METEOR Study

Dear Dr. Parks:

On 08 January 2007, AstraZeneca Pharmaceuticals LP (AstraZeneca) submitted to the US Food and Drug Administration (FDA) an application for a new indication for CRESTOR® (rosuvastatin calcium) Tablets regarding atherosclerosis (NDA 21-366/S-010). On 24 August 2007, the FDA requested additional information / analyses relevant to the primary endpoint analyses in the METEOR study as follows:

- Please clarify the location in the NDA or submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population. Please comment on the discrepant results between the U.S. and Europe, specifically between the U.S. and the Netherlands and Finland.
- Please clarify the location in the NDA or submit an analysis of the inter-reader variability apparent in the METEOR trial.
- Please clarify the location in the NDA or submit an analysis of the variability in results introduced by the different scanners that were employed in the trial.
- Please perform the primary analysis using fixed effects for intercept, site, and time.
- Please perform an analysis of the annualized rate of change by baseline IMT.

This submission responds to that request.

This electronic submission has been scanned using Symantec AntiVirus, Version 9.0.5.1000 (Corporate Edition), with a virus definition file dated 12 September 2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manager, at (302) 885-7969.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

AM/PD

Enclosure

Desk Copy: Margaret Simoneau, W022, RM 3372 (Cover Letter Only)

Simoneau, Margaret A

From: Egan, Amy
nt: Tuesday, September 11, 2007 10:41 AM
: 'DeFeo, Pat A'
Cc: Simoneau, Margaret A
Subject: 21-366 SE1

Hi Pat -

Our statistical reviewer has a question regarding the figure (b)(4) that you are proposing be placed in the label. Specifically, he would like to know how the (b)(4) that are illustrated on the figure were derived.

Thanks.

Amy

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Friday, September 07, 2007 12:52 PM
To: Egan, Amy
Cc: Simoneau, Margaret A
Subject: RE: 21-366 SE1
Attachments: emfalert.txt

Dear Amy,

Our statisticians have provided the following answer in regards to your question in the e-mail below:

- Yes – unless specified otherwise, change from baseline in maximum cIMT expressed in mm/year refers to the change derived from the hierarchical mixed model.

Please don't hesitate to contact me should you have any additional questions.

Best regards,

Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

-----Original Message-----
From: Egan, Amy [mailto:Amy.Egan@fda.hhs.gov]
Sent: Wednesday, September 05, 2007 11:17 AM
To: DeFeo, Pat A
Cc: Simoneau, Margaret A
Subject: 21-366 SE1

Pat -

Our statistical reviewer has a question for the folks involved with this submission:

- Throughout the text of the submitted documents you refer to "change from baseline in maximum cIMT" in mm/year. He would like to clarify that this actually refers in all cases to the mm/year change derived from the hierarchical mixed model.

Thanks

Amy

Simoneau, Margaret A

From: Egan, Amy
Sent: Friday, August 24, 2007 8:57 AM
To: 'DeFeo, Pat A'
Cc: Simoneau, Margaret A
Subject: 21-366/S-010

Hi Pat -

I received the response to my 8/13/07 inquiry today. Thank you very much. I have a couple more requests for the folks involved with this supplement.

With respect to the METEOR trial:

- Please clarify the location in the NDA or submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population. Please comment on the discrepant results between the U.S. and Europe, specifically between the U.S. and the Netherlands and Finland.
- Please clarify the location in the NDA or submit an analysis of the inter-reader variability apparent in the METEOR trial.
- Please clarify the location in the NDA or submit an analysis of the variability in results introduced by the different scanners that were employed in the trial.
- Please perform the primary analysis using fixed effects for intercept, site, and time.
- Please perform an analysis of the annualized rate of change by baseline IMT.

Thanks.

Amy Egan

AstraZeneca

RECEIVED
AUG 22 2007
CDER White Oak DR

SE1-010 BL

Date: August 22, 2007

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-12666

ORIGINAL

RE: NDA 21-366/S-010
CRESTOR® (rosuvastatin calcium) Tablets
Response to recommendations for the proposed labeling format

Dear Dr. Parks:

Reference is made to NDA 21-366/S-010, CRESTOR® (rosuvastatin calcium) Tablets, submitted January 5, 2007. Additional reference is made to the pre-arranged telephone conversation on August 9, 2007 with Margaret Simoneau, RHPM and Dr. Amy Egan, Medical Reviewer to discuss recommendations for the format of the proposed labeling to the new physician's labeling rule. The Division verbally outlined recommendations to add and delete information from various sections of the highlights and the full prescribing information. AstraZeneca informed the Division that an annotated Word document would be submitted to confirm that all of the Division's comments and suggestions were captured during the telephone conversation. Accordingly, AstraZeneca is providing with this submission an annotated and nonannotated Word versions of the package insert. The package insert is also being provided in SPL format.

AstraZeneca is currently in the process of reviewing the Divisions' recommendations and will contact the division if necessary with any additional questions. Please confirm that all of the Division's comments and recommendations are reflected in the submission document

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.5.5001 (Corporate Edition), with a virus definition file dated August 19,2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

AstraZeneca

RECEIVED
AUG 2 2 2007
CDER White Oak DR

Date: 22 August 2007

Mary Parks, MD, Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

SE1-010 SM7

ORIGINAL

RE: NDA 21-366/S-010
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information Regarding Additional Analysis of Data from the METEOR Study

Dear Dr. Parks:

On 08 January 2007, AstraZeneca Pharmaceuticals LP (AstraZeneca) submitted to the US Food and Drug Administration (FDA) an application for a new indication for CRESTOR (rosuvastatin calcium) regarding atherosclerosis (NDA 21-366/S-010). On 13 August 2007, the FDA requested an additional analysis related to patients in the METEOR study as follows:

> *Please perform the same analysis of the primary endpoint, but exclude subjects who were concomitantly treated with any of the following medications: calcium channel blockers, beta-blockers, ACE inhibitors and/or angiotensin II receptor blockers.*

This submission responds to that request.

This electronic submission has been scanned using Symantec AntiVirus, Version 9.0.5.1000 (Corporate Edition), with a virus definition file dated 20 August 2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Wednesday, August 22, 2007 5:10 PM
To: Simoneau, Margaret A
Cc: Egan, Amy
Subject: eMC
Attachments: emfalert.txt

Hi Margaret,
Per our telephone conversation of yesterday, August 12, 2007 regarding NDA 21-366/S-010 and a reference within that supplement to eMC. I have been able to confirm that eMC refers to *electronic* Medicines Compendium which is the web-based source that we use for finding currently approved UK labels. The eMC provides electronic Summaries of Product Characteristics (SPCs) and Patient Information Leaflets (PILs). The web address for this site is http://emc..org.uk/medicines.

I hope this helps. Please let me know if you have any additional questions.
Best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

Simoneau, Margaret A

From: Egan, Amy
Sent: Monday, August 13, 2007 11:23 AM
To: 'pat.defeo@astrazeneca.com'
Cc: Simoneau, Margaret A
Subject: 21-366 S-10

Dear Pat -

Can the folks involved with Supplement 10 please perform the following additional analysis on the data from the METEOR study?

- Please perform the same analysis of the primary endpoint, but exclude subjects who were concomitantly treated with any of the following medications: calcium channel blockers, beta-blockers, ACE inhibitors and/or angiotensin II receptor blockers.

Thank you.

Amy Egan

Simoneau, Margaret A

From: Simoneau, Margaret A
Sent: Thursday, July 12, 2007 2:59 PM
To: 'DeFeo, Pat A'
Cc: Simoneau, Margaret A
Subject: NDA 21-366/S-010 PLR format labeling comments

Attachments: PLRCrestor010.doc

Ms. DeFeo,

Attached is a list of **format** revisions for your proposed labeling. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.



PLRCrestor010.doc
(61 KB)

Please feel free to call me with any questions or concerns.

Thank you,

Margaret

Please note new email address
Margaret.Simoneau@fda.hhs.gov

Division of Metabolism and Endocrinology Products

Application Number: 21-366/S-010

Name of Drug: Crestor (rosuvastatin calcium) Tablets

Applicant: AstraZeneca

Submission Date of Structure Product Labeling (SPL): January 5, 2007

Review/Recommendations

The following issues have been identified in your proposed labeling.

General:

- Please revise your highlights using the Sample Tool Illustrating the Format for Highlights and Contents located at http://www.fda.gov/cder/regulatory/physLabel/default.htm. In addition, inspect the example PLR labels on this web site carefully to correct your other format deficiencies throughout the FPI.

- There should be only one line of white space between the section headings (i.e., Dosage and Administration, etc.) and the end of the previous sections (e.g., Indications and Usage). Delete the other white space. In addition, delete the white space below these section headings.

- Throughout the "Highlights of Prescribing Information" page, all sections including, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions Drug Interactions, and Use in Specific Populations have lines through the words.

Highlights of Prescribing Information:

- Highlights of Prescribing Information should be bolded and the line after should be deleted.
- The drug name, dosage form, route of administration and initial U.S. approval require bolding.
- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
- Add a Recent Major Changes section to Highlights. In addition, for recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:
"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
- Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights. Also see the draft guidance at http://www.fda.gov/cder/guidance/7472dft.pdf." The pharmacologic class draft guidance was recently published.
- Under Indications and Usage, major limitations of use must be briefly noted.
- Under Contraindications, regarding hypersensitivity. List only known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.
- Delete the general company web site from the Adverse Reactions section statement. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]." AND "Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.
- Under Drug Interactions, requires bulleting and indentation.
- The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
- A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval. "12/2006" should be modified.
- A horizontal line must separate the Highlights, Contents, and FPI.
[See 21 CFR 201.57(d)(2)]

Full Prescribing Information:

General:

- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]"

- Delete the revision date at the end of labeling. The revision date in Highlights makes this redundant and unnecessary.

- All lines after the sections listed (i.e. Indication and Usage, Dosage and Administration, etc.) need to be deleted.
- Under Indications and Usage, bullet the indications instead of assigning each indication a subsection number. There is no reason to assign subsection numbers for cross referencing back to the Indications and Usage section since there is no additional text.
- Under Contraindications, each contradiction should be identified by its own subheading. Pregnancy Category X translates to a Contraindication.
- Under Use in Specific Populations, additional subsections should include patients with renal insufficiency and dosage in Asian patients.

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Wednesday, July 11, 2007 5:22 PM
To: Simoneau, Margaret A
Subject: NDA 21-366/S-010 - July 10, 2007 telephone request for information
Attachments: emfalert.txt

Dear Margaret:

In response to your telephone request of July 10, 2007, regarding NDA 21-366/S-010 for CRESTOR (rosuvastatin calcium), please see the information attached:

- Provide details of the location of the results of the mixed model (primary endpoint analysis) - **This table can be found on page 11181 of 11414 of the METEOR Clinical Study Report. (Module 5.5.3.1 Controlled Clinical Trials, D3562C00088: METEOR CSR, 12. Appendices, Table 12.2.12.1.1 "IMT Analysis Results from S-Plus".)**
- Provide the name of the data set - **IMTSITE.xpt** (located at ~/crt/datasets/4522IL0088/IMTSITE.xpt)

Please do not hesitate to contact me if these responses are unclear or should you require additional information.

Kind regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Tuesday, July 10, 2007 6:18 PM
To: Simoneau, Margaret A
Subject: July 10, 2007 telephone request
Attachments: emfalert.txt

Dear Margaret,

I spoke with Barry Traxler, our statistician, regarding the information you are seeking. Barry did need to contact our statistician in the UK, Mike Palmer, for the answers to your questions. Mike will be sending the information to Barry early in the morning (UK time) and therefore we should be able to forward if to you sometime tomorrow. Barry believes the details of the results of the mixed model do reside in one specific section, and there is only one dataset. Once we forward the section number and the name of the dataset to you, should you or the statistician on your side have any additional questions, we can set up a teleconference if needed.

Please feel free to contact me with anything additional.

Best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

AstraZeneca

RE

Date: 23 May 2007

MAY 2 3 2007

CDER

N-000 C

Mary Parks, MD, Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

ORIGINAL

Re: NDA 21-366/S-010
CRESTOR® (rosuvastatin calcium) Tablets
Notification of Clarification to a Previous Response Sent to the Division of Scientific Investigations Request for Site Specific Information

Dear Dr. Parks:

On 18 April 2007, the Division of Scientific Investigation (DSI) informed AstraZeneca Pharmaceuticals LP (AstraZeneca) for upcoming site inspections and requested information. On 26 April 2007, AstraZeneca responded to DSI. On 02 May 2007 AstraZeneca and DSI teleconferenced during which DSI requested clarification regarding information provided in the 26 April 2007 response. On 17 May 2007 AstraZeneca forwarded clarification to DSI of the previously submitted information. Attached, for your convenience, is a copy of the cover letter of that response.

This electronic submission has been scanned using Symantec AntiVirus, Version 9.0.5.1000 (Corporate Edition), with a virus definition file dated 21-May-2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manager, at (302) 885-7969.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

AM/PD
Enclosure

AstraZeneca

Date: 17 May 2007

Ms. Andrea Slavin, Consumer Safety Officer
Division of Scientific Investigations (HFD-46)
7520 Standish Place
Rockville, MD 20855

Re: NDA 21-366/S-010
CRESTOR (rosuvastatin calcium) Tablets
Clarification to a Previous Response Sent to the Division of Scientific Investigations
Request for Site Specific Information

Dear Ms. Slavin:

Please refer to the 26 April 2007 submission by AstraZeneca Pharmaceutical LP (AstraZeneca) in response to a request from the Division of Scientific Investigations (DSI) for information regarding NDA 21-366/S-010. Refer also to a telephone conversation on 02 May 2007 between DSI and AstraZeneca during which DSI requested clarification regarding information provided in the 26 April response.

During the 02 May 2007 telephone contact, DSI requested a description of information at study sites 101 and 108 that can be checked against the intima media thickness (IMT) measurement data submitted on 26 April 2007. In addition, DSI asked if demographic information can be found with the ultrasound scans.

In response to DSI's request, information located at the investigator sites for centres 101 and 108 includes the following:

- Source documentation of IMT measurements for study eligibility from ultrasound scans at Visit 2 and Visit 3;
- Source documentation of scans performed and records of IMT handling as outlined in the protocol (section 4.3.1).

In addition, while confirming the information above, AstraZeneca discovered that patient listings of IMT batch data submitted 26 April 2007 did not accurately account for IMT measurements at Visit 13 for a small number of patients at sites 101 and 108. Updated MS Word files for these listings are provided in the replacement CD-ROM attached to this response. To avoid confusion, please use this information to prepare for inspections as updated copies of the CD-ROM will not be available at the study sites.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

This submission is being provided electronically on CD-ROM. The media containing the electronic items of the submission have been scanned using Symantec AntiVirus, Version 9.0.5.1000 (Corporate Edition), with a virus definition file dated 15-May-2007. No viruses were detected, and AstraZeneca certifies that the media is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manager, at (302) 885-7969.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

PD/AM

Enclosure

Simoneau, Margaret A

From: Simoneau, Margaret A
Sent: Friday, April 27, 2007 11:20 AM
To: 'DeFeo, Pat A'
Cc: Egan, Amy
Subject: RE: Request for clarification of queries within the filing letter for NDA 21,366/S-010

Pat,

The following is in response to one of your voice mail questions this past week.

Would the Division please clarify if this information is requested for the METEOR primary investigators only, or for the primary investigators of all 3 studies included in the submission, METEOR, ASTEROID, and ORION?

Request is for all 3 studies.

Clarify the enrollment number at METEOR Site 457 in Essen, Germany. The dataset indicates 30 subjects were randomized at this site, while you state that 37 subjects were randomized at this site.

The correct number should be 30 and this is acceptable.

Thank you,

Margaret

From: DeFeo, Pat A [mailto:pat.defeo@astrazeneca.com]
Sent: Thursday, March 29, 2007 6:30 PM
To: Simoneau, Margaret A
Subject: Request for clarification of queries within the filing letter for NDA 21,366/S-010

Dear Margaret,

In reference to the filing letter for NDA 21-366/S-010 received by AstraZeneca Pharmaceuticals Inc. (AstraZeneca) on March 13, 2007, and to our telephone conversation of Thursday, March 22, 2006. We are currently working to supply responses to the two requests stated in the letter and would greatly appreciate further information prior to submitting an official response to the Division's requests.

The first request states:

"Submit the exact compensation received by the primary investigators."

Would the Division please clarify if this information is requested for the METEOR primary investigators only, or for the primary investigators of all 3 studies included in the submission, METEOR, ASTEROID, and ORION?

The next request states:

"Clarify the enrollment number at METEOR Site 457 in Essen, Germany. The dataset indicates 30 subjects were randomized at this site, while you state that 37 subjects were randomized at this site."

The correct number should be 30, however, AstraZeneca has been unable to locate where 37 subjects are mentioned either within the Study Report for METEOR or within the documents contained in the CTD. If the Division would like additional information on why 37 patients was stated, AstraZeneca would find it very helpful if the Division could describe where this number was found.

Additionally, AstraZeneca anticipates forwarding an official response to the MDS query shortly.

Please do not hesitate to contact me with any additional questions.

Kind regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

AstraZeneca

Date: 26 April 2007

Mary Parks, MD, Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Notification of the Division of Scientific Investigation's Intent for Inspection

Dear Dr. Parks:

On 18 April 2007, the Division of Scientific Investigation (DSI) informed AstraZeneca Pharmaceuticals LP (AstraZeneca) for upcoming site inspections and requested information. On 26 April 2007, AstraZeneca responded to DSI. Attached, for your convenience, is a copy of the cover letter of that response.

This electronic submission has been scanned using Symantec AntiVirus, Version 9.0.5.1000 (Corporate Edition), with a virus definition file dated 27-April-2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manager, at (302) 885-7969.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

AM/PD
Enclosure

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Simoneau, Margaret A

From: Simoneau, Margaret A
Sent: Wednesday, March 21, 2007 2:24 PM
To: Slavin, Andrea
Subject: FW: 21-366/S-010 Crestor

Attachments: METEOR trial treatment effect.doc

Hi Andrea,

Attached is additional information regarding the consult that was signed off in DFS yesterday. Further detail regarding the request can be found in the MO's filing memo located in DFS. If the sponsor does not need to be notified, that would be our preference. Please let me know if I can provide you any other information regarding this DSI inspection request.

Thank you.
Margaret
301 796-1295

From: Egan, Amy
Sent: Wednesday, March 21, 2007 12:11 PM
To: Simoneau, Margaret A
Cc: Colman, Eric C
Subject: 21-366 DSI

METEOR (Study D3562C00088) was a randomized, double-blind, placebo-controlled, parallel group study of 104 weeks duration using carotid intima media thickness to support an indication "to slow (b)(4) the progression of atherosclerosis in patients in whom lipid-lowering therapy is indicated." The primary objective was to assess the effects of rosuvastatin 40 mg on the change in the mean maximum IMT of the 12 vessel segments: the near and far walls of the CCA, the carotid bulb and the ICA segments for both right and left carotid arteries.

- METEOR Site 0101 in Winston-Salem, NC under Dr. John M. Crouse enrolled 33 subjects. There were 26 protocol deviations at this site, and this site had the largest treatment effect in a center of reasonable size. (See attachment)
- METEOR Site 0108 in Minneapolis, MN enrolled 65 subjects; it was the largest U.S. site. This site showed no apparent treatment effect. (See attachment)

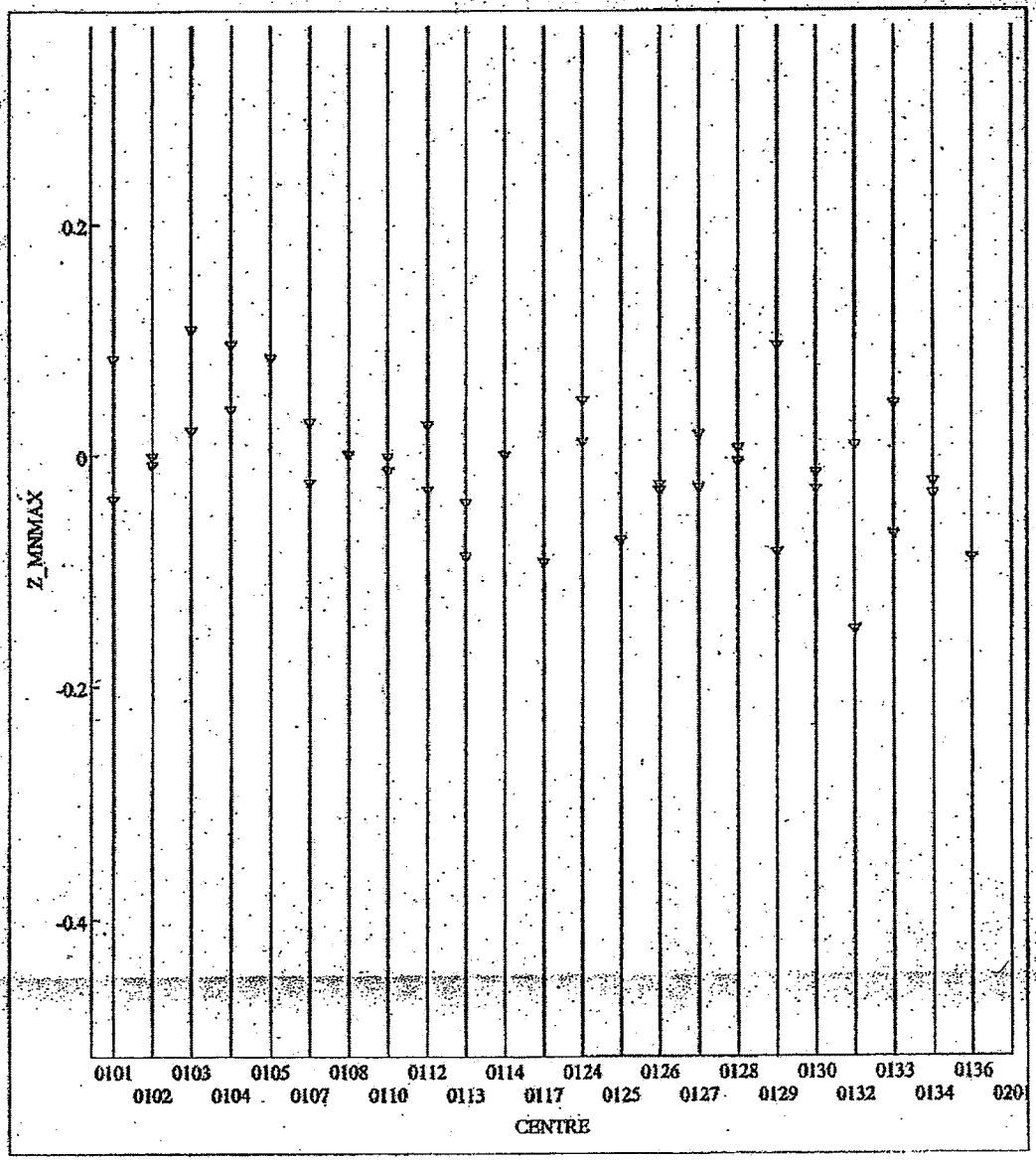
Sites 101 and 108 warrant DSI investigations to see if there are obvious reasons why these two sites report opposite results ("significant primary efficacy results pertinent to decision-making").

Site #	Investigator	Location	# Subjects Randomized	# Subjects Discontinued	# Subjects with Protocol Deviations/ Violations	# Subjects Not Randomized (Screen Failures/Investigator Discretion)
0101	John M. Crouse MD	Winston-Salem NC USA	33	8	26/1	100
0108	Stephen P. Glasser MD	Minneapolis MN USA	65	9	22/2	253



METEOR trial eatment effect....

Layer VISN: 13
Column REGION: 1



RANDTRT:
0
1

DSI CONSULT: Request for Clinical Inspections

Date: March 19, 2007

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: Eric Colman, M.D., Deputy Division Director, HFD-510
Division of Metabolism and Endocrinology Products

Subject: **Request for Clinical Site Inspections**
NDA 21-366/S-010
AstraZeneca Pharmaceuticals LP
Crestor (rosuvastatin calcium) Tablets

Protocol/Site Identification:

The following sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This efficacy supplemental NDA provides data for a new indication of Crestor for the treatment of atherosclerosis.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site 101 in Winston-Salem, NC, USA	Study D3562C00088 -METEOR	33/100 Randomized/Not Randomized	atherosclerosis
Site 108 in Minneapolis, MN USA	Study D3562C00088 -METEOR	65/253 Randomized/Not Randomized	atherosclerosis

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) September 1, 2007. We intend to issue an action letter on this application by (division action goal date) October 22, 2007. The PDUFA due date for this application is November 8, 2007.

Should you require any additional information, please contact Margaret Simoneau at (301) 796-1295.

Concurrence:

Amy Egan, MD, Medical Reviewer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
3/20/2007 02:14:57 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-366 Supplement # 010 Efficacy Supplement Type SE- 1

Proprietary Name: Crestor
Established Name: rosuvastatin calcium tablets
Strengths: 5, 10, 20 and 40mg

Applicant: IPR Pharmaceuticals, Inc
Agent for Applicant (if applicable): Astra Zeneca Pharmaceuticals LP

Date of Application: January 5, 2007
Date of Receipt: January 8, 2007
Date clock started after UN: NA
Date of Filing Meeting: February 21, 2007
Filing Date: March 9, 2007
Action Goal Date (optional): User Fee Goal Date: November 8, 2007

Indication(s) requested: atherosclerosis

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NDA 21-366 original

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance? (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?
   Gateway submission/Mod

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments: A Copy of Module 1 was submitted in paper on January 5, 2007

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,385

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) NA NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) NA NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐
- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? NA YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☒
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 16, 2007

NDA #: 21-366

DRUG NAMES: Crestor

APPLICANT: AstraZeneca

BACKGROUND: SE-1 for the indication of Crestor as therapy for the treatment of athersclerosis.

ATTENDEES: Drs. Colman and Egan, Todd Sahlroot, Joy Mele and Margaret Simoneau.

ASSIGNED REVIEWERS (including those not present at filing meeting): Sang Chung (DFS memo); Janice Brown (DFS review) and Karen Davis-Bruno (email response)

Discipline/Organization	Reviewer
Medical:	Egan, MD
Secondary Medical:	Colman, MD
Statistical:	Joy Mele
Pharmacology:	K.Davis-Bruno (NN)
Statistical Pharmacology:	NN
Chemistry:	Janice Brown
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Sang Chung (NN)
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	
DSI:	Yes
OPS:	NN
Regulatory Project Management:	M.Simoneau
Other Consults:	None at filing time

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS NA FILE ☐ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☐

PHARMACOLOGY/TOX N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☒ No filing issues have been identified. Ltr in DFS March 13, 2007 includes MDS Pharma Services information request

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Margaret Simoneau/3.16.07/
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

(a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES ☐ NO ☐

(***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
3/16/2007 03:14:48 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-366/S-010

AstraZeneca Pharmaceuticals LP
Attention: Patricia A. DeFeo, MS
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. DeFeo:

Please refer to your January 5, 2007, received January 8, 2007, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on March 9, 2007 in accordance with 21 CFR 314.101(a).

We request that you submit the following information:

- Submit the exact amount of compensation received by the primary investigators.
- Clarify the enrollment number at METEOR Site 457 in Essen, Germany. The dataset indicates 30 subjects were randomized at this site, while you state that 37 subjects were randomized at this site.

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We reference your February 27, 2007, response to our January 24, 2007, letter notifying the Agency that you submitted studies conducted by (b)(4) during the January 2000 through December 2004 time period for the original NDA. In view of these findings, we would like to know what steps you are taking to assure the accuracy of the data submitted in your original application and confirm the validity of (b)(4) analytical studies that were conducted and subsequently submitted to the Agency. With respect to those studies submitted in your original submission, we suggest that you do one of the following: (a) independent audit of the trials to verify the data; (b) re-assay samples if available and appropriate, or (c) repeat the studies. Please respond to this query within 6 weeks.

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
3/13/2007 02:10:08 PM
Eric Colman for Mary Parks

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366/S-010

PRIOR APPROVAL SUPPLEMENT

AstraZeneca Pharmaceuticals LP
US Agent for IPR Pharmaceuticals, Inc.
Attn: Patricia A. DeFeo, MS
Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. DeFeo:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Crestor® (rosuvastatin calcium) Tablets
NDA Number:	21-366
Supplement number:	S-010
Review Priority Class:	Standard (S)
Date of supplement:	January 5, 2007
Date of receipt:	January 8, 2007

This supplemental application proposes a new indication for the treatment of atherosclerosis.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 9, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 8, 2007.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
Attention: Document and Records Section
5901-B Ammendale Road
Beltsville, MD 20705-1266

Ui jt !jt !b!sf qsf t f oubjpo!pgbo!f rfduspojd!sf dpse!u bux bt !t jhof e!f rfduspojdbmz!boe
u jt !qbhf !jt !u f !n bojgf t ubjpo!pgu f !f rfduspojd!t jhobuvsf /

! 0t 0

Nbshbsf u! Tj npof bv
308031181 1: ; 59; 121 BN

Simoneau, Margaret A

From: Mele, Joy D
Sent: Monday, February 26, 2007 3:09 PM
To: Simoneau, Margaret A
Cc: Sahlroot, Jon T
Subject: meteor

Peggy -
I think the crestor files look OK - I am able to easily access them.
No issues to go to the sponsor --
Joy

3/1/07
Team Mtg
DSI - Site E
Krauss

Memo to File

NDA #:	21-366 SE1-010
Sponsor:	AstraZeneca
Drug:	Crestor (Rosuvastatin Calcium)
Submission Date:	January 5, 2007
Memo Date:	February 21, 2007
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Jim Wei, M.D., Ph.D. (Acting)
RE:	Filing Meeting

The submission is an efficacy supplement for a new indication and the proposed indication is to slow (b) (4) the progression of atherosclerosis. The dose range for the proposed indication is 5 to 40 mg once daily and it is the same as the approved one for hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb). There were no new data to be reviewed from clinical pharmacology perspectives.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sang Chung
2/21/2007 10:50:31 AM
BIOPHARMACEUTICS

Xiao-xiong Wei
2/21/2007 11:58:47 AM
BIOPHARMACEUTICS

Simoneau, Margaret A

Subject:	NDA 21-366/S-010 Crestor Filing Meeting (Gateway/EDR submission)
Location:	CDER WO 3376 conf rm Bldg22
Start:	Wed 2/21/2007 1:00 PM
End:	Wed 2/21/2007 2:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Egan, Amy; Sahlroot, Jon T; Chung, Sang; Brown, Janice
Resources:	CDER WO 3376 conf rm Bldg22

Simoneau, Margaret A

From: Chung, Sang
nt: Wednesday, February 21, 2007 9:03 AM
Simoneau, Margaret A
Subject: Declined: Updated: NDA 21-366/S-010 Crestor Filing Meeting (Gateway/EDR submission)

Hi Peggy,

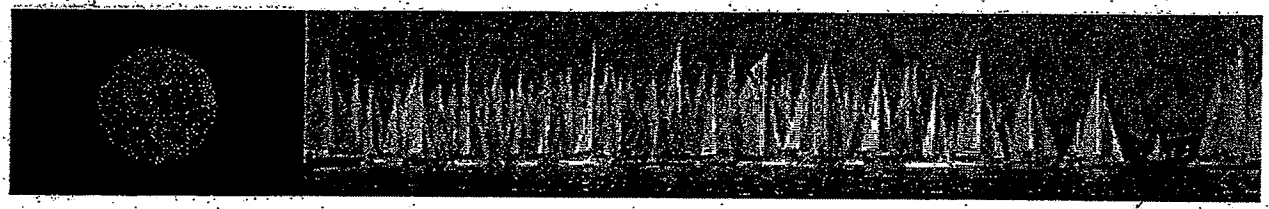
There is no new information to be reviewed in clinical pharmacology perspectives and thus I will not attend the filing meeting. I plan to have a memo in DFS as usual in this regard.

Thanks,

Sang

Simoneau, Margaret A

From: confirmations@mymeetings.com
Sent: Wednesday, February 21, 2007 8:22 AM
To: Simoneau, Margaret A
Subject: Conference Details (FEB 21, 2007--01:00 PM ET--Conf# (b) (4))



Welcome
Meeting Information
Audio Features
In-Conference Features
Participant Information

PLEASE DO NOT REPLY TO THIS E-MAIL.

Thank you for choosing FTS Conferencing for your upcoming meeting. To reschedule or cancel this reservation, visit us online. On this Web site,you can create reservations, invite participants, start Net Conferences, and view participant lists. For additional customer service, call us at 877-855-4797. Calls must be canceled at least 30 minutes prior to the start time to avoid cancellation fees.



For your convenience, we have included PARTICIPANT INFORMATION at the bottom of this e-mail for you to distribute. Meeting leaders are responsible for all charges associated with this conference, so please use discretion when giving out passcodes and other conference-related information.

MEETING INFORMATION

CONFIRMATION #:	(b) (4)
COMPANY:	FTS-HHS FDA CDER
LEADER:	MS MARGARET SIMONEAU
PHONE #:	1-301-827-6411
DAY OF CALL PHONE #:	1-301-827-6411
CRC:	
CONTACT:	MS MARGARET SIMONEAU
PHONE #:	1-301-827-6411

SERVICE LEVEL:	UNATTENDED
CALL ACCESS TYPE:	MEET ME
# OF LINES:	Total=4 Dialout=0 Meet Me=4 Meet Me Toll=0

DIAL-IN NUMBERS:

Country	Toll Numbers	Freephone/ Toll Free Number
USA		(b) (4)

Restrictions may exist when accessing freephone/toll free numbers using a mobile telephone.

PASSCODE: (b) (4)

CALL DATE:	FEB-21-2007 (Wednesday)
CALL TIME:	01:00 PM EASTERN TIME
DURATION:	1 hr

AUDIO FEATURES

Tones

IN-CONFERENCE FEATURES

All participants must use a touch-tone phone to participate in an Audio Conference. The following features are available for you to use on your phone during an active conference:

- Press *0 operator assistance (small fee may apply).
- Press *6 mute/unmute individual line.

The text below is the only information you should forward on to call participants. Please ensure that you provide all necessary information to participants in advance of the call.

PARTICIPANT INFORMATION

PARTICIPANT ACCESS INFORMATION

Please join MS MARGARET SIMONEAU on FEB-21-2007 (Wednesday) at 01:00 PM EASTERN TIME.
Access information is below.

AUDIO PARTICIPANT ACCESS

CALL DATE:	FEB-21-2007 (Wednesday)
CALL TIME:	01:00 PM EASTERN TIME
DURATION:	1 hr
LEADER:	MS MARGARET SIMONEAU

DIAL-IN NUMBERS:

Country	Toll Numbers	Freephone/ Toll Free Number
USA		(b) (4)

Restrictions may exist when accessing freephone/toll free numbers using a mobile telephone.

PASSCODE: (b) (4)

For security reasons, the passcode and the leader's name will be required to join your call.

IN-CONFERENCE FEATURES

The following features are available for you to use on your phone during an active conference:

- Press *0 operator assistance (small fee may apply).
- Press *6 mute/unmute individual line.

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
Sent: Wednesday, February 14, 2007 12:55 PM
To: Simoneau, Margaret A
Cc: Egan, Amy
Subject: RE: NDA 21-366/S-010 Information Request
Attachments: emfalert.txt

Dear Ms. Simoneau,

We are putting together the information you requested and will forward it shortly. Please note that the information is actually included in the dossier but due to a sorting error, the Principal Investigators at the sites listed below are mis-labeled or out of order within the Financial Disclosure document. The Principal Investigators are correctly listed in the respective study appendices. We will revise the Financial Disclosure document and send it with the appropriate changes.

We greatly apologize for any confusion this may have caused. Please do not hesitate to contact me with any additional questions.

Best regards,

Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CRESTOR
AstraZeneca Pharmaceuticals LP
Chesapeake Building, C3B-112
302-886-2050 (phone)
(b) (6)
302-886-2822 (fax)
pat.defeo@astrazeneca.com

-----Original Message-----
From: Simoneau, Margaret A [mailto:margaret.simoneau@fda.hhs.gov]
Sent: Monday, February 12, 2007 3:07 PM
To: DeFeo, Pat A
Cc: Egan, Amy
Subject: NDA 21-366/S-010 Information Request

Ms. DeFeo,

Please provide the following information for the efficacy supplement under review:

The names and the financial disclosure forms for the primary investigators at the following sites:

ASTEROID: Site 0084 in Montreal, Canada
Site 0101 in Paris, France

METEOR: Site 0457 in Essen, Germany
Site 0801 in Prague, Czech Republic

Thank you.

Margaret Simoneau, M.S., R.Ph.
FDA/CDER/DMEP
301-796-1295

Please note new email address
Margaret.Simoneau@fda.hhs.gov

Simoneau, Margaret A

To: Chung, Sang
Subject: RE: NDA 21-366/S-010 Crestor Filing Meeting (Gateway/EDR submission)

Perfect.

Thanks.

From: Chung, Sang
Sent: Thursday, January 11, 2007 9:14 AM
To: Simoneau, Margaret A
Cc: Wei, Xiaoxiong
Subject: Tentative: NDA 21-366/S-010 Crestor Filing Meeting (Gateway/EDR submission)
When: Wednesday, February 21, 2007 1:00 PM-2:00 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER WO 3376 conf rm Bldg22

Peggy,

I found no new labeling for clinical pharmacology perspectives so far, and I will write a memo to file if it is confirmed without attending the filing meeting.

Simoneau, Margaret A

From: Sahlroot, Jon T
Sent: Friday, January 12, 2007 10:47 AM
To: Simoneau, Margaret A
Cc: Colman, Eric C; Mele, Joy D
Subject: RE: EDR - NDA021366 from ASTRAZENECA PHARMS drug name CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

Peggy,

Joy is the stat reviewer.

Todd

-----Original Message-----

Simoneau, Margaret A

From: Davis Bruno, Karen L
Sent: Wednesday, January 10, 2007 10:20 AM
To: Simoneau, Margaret A
Subject: RE: EDR - NDA021366 from ASTRAZENECA PHARMS drug name CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

Attachments: FW: EDR - NDA021366 from ASTRAZENECA PHARMS drug name CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80



FW: EDR -
4021366 from AST[redacted]

[redacted] not needed (NN) for this efficacy supplement proposing a new clinical indication for athrosclerosis. No changes to our part of the label have been proposed.

Thanks,

Karen

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT IPR Pharmaceuticals, Inc.	DATE OF SUBMISSION 05 January 2007
TELEPHONE NO. *(Include Area Code)* (800) 456-3669	FACSIMILE (FAX) Number *(Include Area Code)* (302) 886-2822
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: P.O. Box 1967 Carolina, PR 00984-1967	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE AstraZeneca Pharmaceuticals LP Ian Hunt Executive Director, Regulatory Affairs 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355 (302) 886-2586 (302) 886-2822

RECEIVED
JAN – 8 2007
CDER White Oak DR 1

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-366

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* rosuvastatin calcium	PROPRIETARY NAME *(trade name)* IF ANY CRESTOR® (rosuvastatin calcium) tablets
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt	CODE NAME *(if any)* S4522, ZD4522

DOSAGE FORM: Tablets	STRENGTHS: 5mg, 10mg, 20mg, 40mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
To slow (b) (4) the progression of atherosclerosis.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☒ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☒ Prior Approval (PA)

REASON FOR SUBMISSION
Supplemental New Drug Application

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS: ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 56,385; NDA 21-366; DMFs (b) (4)

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
☒	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600; if applicable)
☒	16. Debarment certification (FD&C Act 306 (k) (1))
☐	17. Field copy certification (21 CFR 314.50 (l) (3))
☒	18. Use Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL/AGENT	TYPED NAME AND TITLE	DATE
Patricia.A.DeFeo	Ian Hunt Executive Director, Regulatory Affairs	

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	(302) 886-2586

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1226

Department of Health and Human Services
Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

AstraZeneca

ORIGINAL

Date: 05 January 2007

SE1-010 (L)
SUPPL NEW CORRESP

Mary Parks, M.D.
Division of Metabolism and Endocrinology Products (DMEP)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED
FEB 12 2007
CDER White Oak

RECEIVED
FEB 01 2007
CDER OSR

Re: NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Supplemental New Drug Application

Dear Dr. Parks:

In accordance with Section 50(b) of the Federal Food, Drug and Cosmetic Act and Section 314 of Title 21 CFR 314, AstraZeneca Pharmaceuticals LP (AstraZeneca) hereby submits this supplemental New Drug Application (sNDA 21-366) for the indication of CRESTOR® (rosuvastatin calcium) Tablets as therapy for the treatment of atherosclerosis. This submission is made on behalf of iPR Pharmaceuticals, Inc. A letter authorizing AstraZeneca to act on behalf of iPR Pharmaceuticals, Inc. is included.

Reference is made to pre-sNDA communications with the Agency and agreements on the content and format of the sNDA. These include a pre-sNDA meeting package and correspondences dated 05 October 2006, 24 October 2006, 20 November 2006 and 04 December 2006. Reference is also made to correspondences between AstraZeneca and the FDA on 14 January 2002 and 03 April 2002 in which the FDA stated that one positive pivotal trial could support an alternate indication.

This sNDA includes the results of one pivotal efficacy study, Study D3562C00088 (4522IL/0088, METEOR) and two additional studies D3562C00076 (4522IL/0076, ASTEROID) and D3560C00044 (4522IL/0044, ORION). The results of these studies support the use of CRESTOR in the treatment of atherosclerosis.

CRESTOR was approved for the treatment of Hypercholesterolemia (heterozygous familial and nonfamilial) and Mixed Dyslipedemia (Fredrickson Type IIa and IIb) on 12 August 2003 (original New Drug Application 21-366). As agreed by the Division in the pre-sNDA correspondence dated 20 November 2006, the Chemistry, Manufacturing and Controls (CMC) section (Module 3) and preclinical information (Module 4) are not applicable (N/A) to this application.

US Regulatory Affairs

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

All CRESTOR clinical studies utilized good clinical practices (GCP) in compliance with the Institutional Review Board (IRB) requirements in 21 CFR 56 and informed consent requirements in 21 CFR 50. All three clinical studies were performed under IND 56, 385.

Included in Module 1, AstraZeneca has requested a full waiver from Pediatric Use Information under 21 CFR 314.55(c)(2) as CRESTOR does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

In accordance with 21 CFR 314.50 (d)(1)(v), AstraZeneca certifies that a field copy of this sNDA is not applicable, as no new Chemistry, Manufacturing and Controls (CMC) information is included.

As required in 21 CFR 54.4, a certification (Form 3454) is enclosed regarding the financial interests and arrangements for all of the clinical investigators who contributed to the clinical studies submitted in this application. In addition, a certification statement is enclosed which states that AstraZeneca did not and will not use, in any capacity, the services of any person debarred under section 306(a) or (b).

Further, as required in Section 736(a)(1)(A)(i) of the Prescription Drug User Fee Act (PDUFA), iPR Pharmaceuticals, Inc., with AstraZeneca acting on its behalf, provided payment of $448,100.00 on 14 December 2006. This amount represents full payment of the application fee. The User Fee ID Number for sNDA 21-366 is PD3006915.

Also, please note, AstraZeneca is submitting the Prescribing Information (PI) in the new labeling format in accordance with the 30 June 2006 labeling rule entitled "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels."

This electronic submission has been scanned using Symantec AntiVirus, Version 9.0.5.1000 (Corporate Edition), with a virus definition file dated 02 January 2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

The format of this sNDA is consistent with 21 CFR 314.50 and with FDA guidelines for the preparation and submission of NDAs as described in the January, 1999 Guidance for Industry "Providing Regulatory Submission in Electronic Format-General Considerations".

As requested by the Division on 20 November 2006, AstraZeneca has provided a pool safety dataset for the three studies included in this submission, which can be found in Module 5.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manger at (302) 885-7969.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

PD/am

AstraZeneca

NDA NO. 21366 REF NO. 010
NDA SUPPL FOR SE1-010

Date: 05 January 2007

ORIGINAL

Mary Parks, M.D.
Division of Metabolism and Endocrinology Products (DMEP)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED
JAN - 8 2007
CDER White Oak DR 1

Re: NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Supplemental New Drug Application

Dear Dr. Parks:

In accordance with Section 50(b) of the Federal Food, Drug and Cosmetic Act and Section 314 of Title 21 CFR 314, AstraZeneca Pharmaceuticals LP (AstraZeneca) hereby submits this supplemental New Drug Application (sNDA 21-366) for the indication of CRESTOR® (rosuvastatin calcium) Tablets as therapy for the treatment of atherosclerosis. This submission is made on behalf of iPR Pharmaceuticals, Inc. A letter authorizing AstraZeneca to act on behalf of iPR Pharmaceuticals, Inc. is included.

Reference is made to pre-sNDA communications with the Agency and agreements on the content and format of the sNDA. These include a pre-sNDA meeting package and correspondences dated 05 October 2006, 24 October 2006, 20 November 2006 and 04 December 2006. Reference is also made to correspondences between AstraZeneca and the FDA on 14 January 2002 and 03 April 2002 in which the FDA stated that one positive pivotal trial could support an alternate indication.

This sNDA includes the results of one pivotal efficacy study, Study D3562C00088 (4522IL/0088, METEOR) and two additional studies D3562C00076 (4522IL/0076, ASTEROID) and D3560C00044 (4522IL/0044, ORION). The results of these studies support the use of CRESTOR in the treatment of atherosclerosis.

CRESTOR was approved for the treatment of Hypercholesterolemia (heterozygous familial and nonfamilial) and Mixed Dyslipedemia (Fredrickson Type IIa and IIb) on 12 August 2003 (original New Drug Application 21-366). As agreed by the Division in the pre-sNDA correspondence dated 20 November 2006, the Chemistry, Manufacturing and Controls (CMC) section (Module 3) and preclinical information (Module 4) are not applicable (N/A) to this application.

US Regulatory Affairs

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

All CRESTOR clinical studies utilized good clinical practices (GCP) in compliance with the Institutional Review Board (IRB) requirements in 21 CFR 56 and informed consent requirements in 21 CFR 50. All three clinical studies were performed under IND 56, 385.

Included in Module 1, AstraZeneca has requested a full waiver from Pediatric Use Information under 21 CFR 314.55(c)(2) as CRESTOR does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

In accordance with 21 CFR 314.50 (d)(1)(v), AstraZeneca certifies that a field copy of this sNDA is not applicable, as no new Chemistry, Manufacturing and Controls (CMC) information is included.

As required in 21 CFR 54.4, a certification (Form 3454) is enclosed regarding the financial interests and arrangements for all of the clinical investigators who contributed to the clinical studies submitted in this application. In addition, a certification statement is enclosed which states that AstraZeneca did not and will not use, in any capacity, the services of any person debarred under section 306(a) or (b).

Further, as required in Section 736(a)(1)(A)(i) of the Prescription Drug User Fee Act (PDUFA), iPR Pharmaceuticals, Inc., with AstraZeneca acting on its behalf, provided payment of $448,100.00 on 14 December 2006. This amount represents full payment of the application fee. The User Fee ID Number for sNDA 21-366 is PD3006915.

Also, please note, AstraZeneca is submitting the Prescribing Information (PI) in the new labeling format in accordance with the 30 June 2006 labeling rule entitled "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels."

This electronic submission has been scanned using Symantec AntiVirus, Version 9.0.5.1000 (Corporate Edition), with a virus definition file dated 02 January 2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

The format of this sNDA is consistent with 21 CFR 314.50 and with FDA guidelines for the preparation and submission of NDAs as described in the January, 1999 Guidance for Industry "Providing Regulatory Submission in Electronic Format-General Considerations".

As requested by the Division on 20 November 2006, AstraZeneca has provided a pool safety dataset for the three studies included in this submission, which can be found in Module 5.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manger at (302) 885-7969.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

PD/am

AstraZeneca

Date: DEC 1 4 2006

US Food and Drug Administration (360909)
Mellon Client Service Center
Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

RE: NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Prescription Drug User Fee Payment: User Fee I.D. No. PD3006915

Dear Madam/Sir:

In accordance with section 736 of the Federal Food, Drug and Cosmetic Act, AstraZeneca Pharmaceuticals LP (AstraZeneca) is providing a Prescription User Fee payment for a SNDA for the use of CRESTOR®.

The User Fee payment is made in the amount of $448,100.00 and represents the total SNDA application fee for fiscal year 2007. A copy of the User Fee Cover Sheet, Form FDA 3397, is enclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Angela Mikroulis, Regulatory Affairs Manager, at (302) 885-7969.

Sincerely,

Patricia A. DeFeo

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

PD/AM
Enclosure

Form FDA 3397 – User Fee Cover Sheet
User Fee Check No. PD3006915

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

ASTRAZENECA PHARMACEUTICALS LP
Patricia DeFeo
1800 CONCORD PIKE PO BOX 8355
WILMINGTON DE 198038355
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-366

2. TELEPHONE NUMBER

302-886 2050

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

CRESTOR Tablets (rosuvastatin calcium)

6. USER FEE I.D. NUMBER

PD3006915

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM -99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Patricia G. DeFeo	Regulatory Affairs Director	DEC 14 2006

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

$448,100.00

Form FDA 3397 (12/03)

Close Print Cover sheet

(b) (4)

18-DEC-2006	ASTRAZENECA PHARMA-CEUTICALS LP	3006915	N021366	448,100	CDER

(b) (4)

AstraZeneca

November 8, 2006

Dr. Mary Parks, M.D., Acting Division Director
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-12666

Direct Line (787) 957-4030
Fax Number (787) 957-1001

RE: Supplement for the Treatment of Arteriosclerosis, NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Authorization Letter

Dear Dr. Parks:

IPR Pharmaceuticals, Inc. hereby authorize AstraZeneca Pharmaceuticals LP (AstraZeneca) to act on its behalf, pursuant to 21 CFR 314.50 (a)(5), for submitting and executing all matters relating to NDA 21-366 for CRESTOR® (rosuvastatin calcium).

For and on behalf of

IPR Pharmaceuticals, Inc.,

Rubén Freyre
President and General Manager
Authorized Signatory

iPRPharmaceuticals, Inc.
A Part of AstraZeneca PLC

PO Box 1624
Canóvanas PR 00729-1624

Tel 787 876 1400
Fax 787 876 0980