

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-366/S-016

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**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)

Rosuvastatin calcium

STRENGTH(S)

5mg, 10mg, 20mg, and 40mg

DOSAGE FORM

Tablet

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.

GENERAL

a. United States Patent Number

7,030,152

b. Issue Date of Patent

4/18/2006

c. Expiration Date of Patent

4/2/2018

d. Name of Patent Owner

The Brigham and Women's Hospital, Inc.

Address (of Patent Owner)

101 Huntington Avenue, 4th Floor

City/State

Boston, MA

ZIP Code

02215

FAX Number (if available)

Telephone Number

(617) 954-9382

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

19803

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

If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) 1, 2, 3, 4, 5, 6 Does (Do) the patent claim(s) 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.) In adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization) and related references throughout the Label including , but not limited to 1 INDICATIONS AND USAGE; 2 DOSAGE AND ADMINISTRATION; 3 DOSAGE FORMS AND STRENGTHS; 4 CONTRAINDICATIONS; 5 WARNINGS AND PRECAUTIONS; 6 ADVERSE REACTIONS; 7 DRUG INTERACTIONS; 8 USE IN SPECIFIC POPULATIONS; 10 OVERDOSAGE; 11 DESCRIPTION; 12 CLINICAL PHARMACOLOGY; 13 NONCLINICAL TOXICOLOGY; 14 CLINICAL STUDIES; 16 HOW SUPPLIED/STORAGE AND HANDLING; and 17 PATIENT COUNSELING INFORMATION.

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

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



3/23/09

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

Glenn M. Engelmann, Vice President, Policy, Legal & Scientific Affairs & General Counsel

Address

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19803

Telephone Number

(302) 886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

glenn.engelmann@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 20 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.

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. Sending 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 April 2007) 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://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.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 (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 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.

**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)
Rosuvastatin calcium

STRENGTH(S)
5mg, 10mg, 20mg, and 40mg

DOSAGE FORM
Tablet

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.

GENERAL

a. United States Patent Number RE 37,314	b. Issue Date of Patent 08/07/2001	c. Expiration Date of Patent 01/8/2016
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 19803	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? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		
If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

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.
****PLEASE NOTE:** Regarding response to 2.2 through 2.4, certain claims of this patent 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 submitted for listing on that basis.

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) 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 manufacture, use, or sale of the drug product. Yes

6. 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



3/23/09

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

Glenn Engelmann, Vice President, Policy, Legal & Scientific Affairs & General Counsel

Address

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19803

Telephone Number

(302) 886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

glenn.engelmann@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 20 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.

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. Sending 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 April 2007) 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://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.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 (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 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.

**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)

Rosuvastatin calcium

STRENGTH(S)

5mg, 10mg, 20mg, and 40mg

DOSAGE FORM

Tablet

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.

GENERAL

a. United States Patent Number

6,316,460

b. Issue Date of Patent

11/13/2001

c. Expiration Date of Patent

8/04/2020

d. Name of Patent Owner

AstraZeneca AB

Address (of Patent Owner)

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)

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

19803

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

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)

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

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) 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 a manufacture, use, or sale of the drug product. Yes

6. 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



3/23/09

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

Glenn M. Engelmann, Vice President, Policy, Legal & Scientific Affairs & General Counsel

Address

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19803

Telephone Number

(302) 886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

glenn.engelmann@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 20 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.

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. Sending 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 April 2007) 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://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.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 (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 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.

EXCLUSIVITY SUMMARY

NDA # 21-366

SUPPL # 016

HFD # 510

Trade Name Crestor

Generic Name Rosuvastatin calcium tablets

Applicant Name AstraZeneca Pharmaceuticals, US agent for IPR Pharmaceuticals

Approval Date, If Known February 8, 2010

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?

No

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 D3560L00030 [4522US/0011], Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)

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"):

Study D3560L00030 [4522US/0011], Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)

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:
AZ Pharmaceuticals LP, the agent and subsidiary of
AZ UK Limited, is the sponsor

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

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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: January 2, 2010

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICA LS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

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

/s/

MARGARET A SIMONEAU
02/16/2010

ERIC C COLMAN
02/16/2010

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).


Michael Cressman, DO, Executive Medical Director

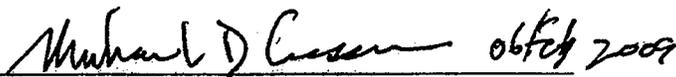
(b) Essential to Approval

(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.


Michael Cressman, DO, Executive Medical Director

(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) provides safety and efficacy data regarding the use of CRESTOR® (rosuvastatin calcium) Tablets for the prevention of cardiovascular events in adults 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 AstraZeneca UK Limited, 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 was 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 REPORT



December 22, 2009 11:30:57 AM

Selection Criteria:

Appl Type Number: NDA 21366
Submission Type(s): SUPPL;16
Sort Order: Appl Type No

<Reports start from Page 2>

Organization: DMEP **Product Name:** CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80
Appl Type No: NDA 21366 **Applicant:** IPR PHARMACEUTICALS INC
Submission Type #: SUPPL - 16 **Submission Status:** PENDING

FDA Received Date: 4/8/2009 **Dosage Form:** TABLET (IMMED./COMP. RELEASE), FILM COATED
Orphan: N **Subm Date:** 4/8/2009 **Goal Due Date:** 2/8/2010 **Submission Classification/ Supplement Category Level:** Two INDICATION **Submission Indication:**

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
443	WAIVED	FULL	0	16	NECESSARY STUDIES ARE NOT FEASIBLE	THE INDICATION IS FOR AN ADULT RELATED CONDITION.	

Organization: DMEP **Product Name:** CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80
Appl Type No: NDA 21366 **Applicant:** IPR PHARMACEUTICALS INC
Submission Type #: SUPPL - 17 **Submission Status:** APPROVED

FDA Received Date	Dosage Form	Orphan	Subm Date	Goal Due Date	Submission Classification/ Supplement Category Level	Submission Indication
4/16/2009	TABLET (IMMED./COMP. RELEASE), FILM COATED	N	10/15/2009	10/16/2009	Two PAT POPUL	TREATMENT OF HEFH IN AGES 10 TO 17 YEARS

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
366	COMPLETED	YEARS	10	17	STUDIES COMPLETED		
366	WAIVED	YEARS	0	9	NECESSARY STUDIES ARE NOT FEASIBLE	TOO FEW CHILDREN (BETWEEN 0-8 YRS OF AGE) WITH DISEASE/CONDITION TO STUDY	

Simoneau, Margaret A

From: Stowe, Ginneh D.
Sent: Wednesday, February 03, 2010 10:05 AM
To: Simoneau, Margaret A
Cc: Greeley, George
Subject: Crestor Full Waiver- PeRC Discussion
Importance: High

Hi Margaret,

We are running ahead of schedule today and the PeRC discussed Crestor earlier than planned. The PeRC members reviewed and agreed with the waiver and don't have any follow up questions. George Greeley will be sending you an email so that you have documentation of the PeRC's recommendations.

Thanks,
Ginneh

Ginneh D. Stowe, MS
Public Health Analyst, Regulatory Affairs Team
Pediatric and Maternal Health Staff
Office of New Drugs
FDA-Center for Drug Evaluation and Research
White Oak Complex
Building #22 , Room 6481
Office: 301-796-4049
Fax: 301-796-9855
Email: Ginneh.Stowe@fda.hhs.gov

2/3/2010

Pediatric Research and Equity Act Waivers

IND/NDA/BLA #: 21-366 Supplement Type: SE-1

Supplement Number: 016

Product name and active ingredient/dosage form: Crestor/ rosuvastatin calcium/ tablet

Sponsor: AstraZeneca Pharmaceuticals LP; US Agent for IPR Pharmaceuticals, Inc.

Indications(s): Primary Prevention of Cardiovascular Disease

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures

1. Pediatric age group to be waived. 0-17 years of age
2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**): "a"
 - a. Studies are impossible or highly impractical. This is because the indication is for an adult-related condition.
 - b. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. Suggested language includes, "FDA has not required pediatric studies in ages ___ to ___ because (state the safety or effectiveness reason)."
 - c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - d. Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this report submitted by the Sponsor will be publicly posted.

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration	Cancer:
Alzheimer's disease	Basal cell
Amyotrophic lateral sclerosis	Bladder
Atherosclerotic cardiovascular disease	Breast
Benign prostatic hypertrophy	Cervical
Chronic Obstructive Pulmonary Disease	Colorectal
Erectile Dysfunction	Endometrial
Infertility	Gastric
Menopausal and perimenopausal disorders	Hairy cell leukemia
Organic amnesic syndrome (not caused by alcohol or other psychoactive substances)	Lung (small & non-small cell)
Osteoarthritis	Multiple myeloma
Parkinson's disease	Oropharynx (squamous cell)
Postmenopausal Osteoporosis	Ovarian (non-germ cell)
Vascular dementia/ Vascular cognitive disorder/impairment	Pancreatic
	Prostate
	Renal cell
	Uterine

Simoneau, Margaret A

From: Stowe, Ginneh D.
Sent: Thursday, January 28, 2010 5:10 PM
To: Simoneau, Margaret A; Jamison, Janet; Snyder, Kristen; McKee, Amy; Waxman, Ian; Compton, Kimberly
Cc: Greeley, George; Cross Jr, Frank H
Subject: PeRC BPCA/PREA Subcommittees Meeting on 2/3/2010-ROOM 1419 BLDG 22
Importance: High

All,

Below is the agenda for next weeks' PeRC meeting scheduled for Wednesday, February 3rd. We ask that each Division arrive at least **ten** minutes prior to the start time listed for your product. The meeting invites have been sent as this meeting will occur in conference room 1419 in building 22.

BPCA
9:00 (b) (4) - Written Request

PREA
10:00 (b) (4) - Partial Waiver/Deferral/Plan/Extrapolation
Crestor- Full Waiver

Review division staff are not being requested to attend PeRC for the **Crestor** waiver application. If staff are still inclined to do so the discussion for the waiver can occur anytime as filler between applications starting at or around 9:30 that morning. The call-in number for the meeting is 866-815-7591 and the pass code 239100.

Thanks,
Ginneh

Ginneh D. Stowe, MS
Public Health Analyst, Regulatory Affairs Team
Pediatric and Maternal Health Staff
Office of New Drugs
FDA-Center for Drug Evaluation and Research
White Oak Complex
Building #22 , Room 6481
Office: 301-796-4049
Fax: 301-796-9855
Email: Ginneh.Stowe@fda.hhs.gov

Be there at 10:15 am

Simoneau, Margaret A

From: Stowe, Ginneh D.
Sent: Thursday, December 31, 2009 12:18 PM
To: Fortney, Russell; Simoneau, Margaret A; Fahnbulleh, Frances; Johnson, Tamara; Adams-King, Janice
Cc: Greeley, George
Subject: PeRC BPCA/PREA Subcommittees Meeting on 1/6/2010-ROOM 1419 BLDG 22
Importance: High

All,

Below is the agenda for next weeks' PeRC meeting scheduled for Wednesday, January 6th. We ask that each Division arrive at least **ten** minutes prior to the start time listed for your product. The meeting invites have been sent as this meeting will occur in conference room 1419 in building 22.

BPCA

9:00 (b) (4) - Written Request

PREA

10:00 (b) (4) - Partial Waiver/Deferral/Plan/Appropriately Labeled

10:30 (b) (4) - Partial Waiver/Appropriately Labeled

10:40 Crestor- Full Waiver

Review division staff are not being requested to attend PeRC for the **Crestor** waiver application. If staff are still inclined to do so the discussion for the waiver can occur anytime as filler between applications starting at or around 9:30 that morning. The call-in number for the meeting is 866-815-7591 and the pass code 239100.

Thanks,
Ginneh

Ginneh D. Stowe, MS
Public Health Analyst, Regulatory Affairs Team
Pediatric and Maternal Health Staff
Office of New Drugs
FDA-Center for Drug Evaluation and Research
White Oak Complex
Building #22 , Room 6481
Office: 301-796-4049
Fax: 301-796-9855
Email: Ginneh.Stowe@fda.hhs.gov

1/4/2010

1.3.3 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 Supplemental New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

A handwritten signature in cursive script, reading "Anthony F. Rogers 3/25/09", is written over a horizontal line.

Anthony F. Rogers, Vice President
Regulatory Affairs
AstraZeneca



1.3.4 Financial Certification and Disclosure

Drug Substance: Rosuvastatin calcium

Date: 2 April 2009

1.3.4 Financial Certification and Disclosure

No Participation Report

This submission / 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

1.3.4 Financial Certification and Disclosure
Drug Substance: Rosuvastatin calcium
Date: 2 April 2009

	PAGE
TITLE PAGE	1
1. NO PARTICIPATION REPORT	3

1.3.4 Financial Certification and Disclosure
Drug Substance: Rosuvastatin calcium
Date: 2 April 2009

1. NO PARTICIPATION REPORT

The attached report identifies investigators who did not participate in the study (e.g., did not screen and/or enroll patients), therefore, financial disclosure was not obtained. These investigators were listed on a Form FDA 1572 at one time.

Drug ID: Crestor

Study No.: [REDACTED]

Report Date: April 2, 2009

Investigators' Reply to Request for Disclosure No Participation

Name	Investigator Type/Center No.	Facility/Department	Address	Comments
------	------------------------------	---------------------	---------	----------

Site was not initiated as per email from study team 5/5/08.

Site was not initiated as per email from study team 5/5/08.

Site was not initiated as per email from study team 5/5/08.

Listed in [REDACTED] database as a study coordinator, not on 1572 as per email from study team 10/28/08.

Site was not initiated as per email from study team 5/5/08.

Site was not initiated as per email from study team 5/5/08.

(b) (6)

Site was not initiated as per email from study team 5/5/08.

Site was not initiated as per email from study team 5/5/08.

Site was not initiated as per email from study team 5/5/08.

PI was adding for referrals. Never participated in study as per memo from the study team.

PI was adding for referrals. Never participated in study as per memo from the study team.

PI was adding for referrals. Never participated in

Drug RESTOR
Study (b) (6)
Report Date: May 1, 2009

Investigators' Reply to Request for Disclosure
No Disclosable Financial Interest

Centre No.	Name	Inv. Type	Centre Address	Country	Subjects Screened	Subjects Randomized	Subjects Not Randomized	Subjects Completed	Major Violations	Major Deviations
------------	------	-----------	----------------	---------	-------------------	---------------------	-------------------------	--------------------	------------------	------------------



(b) (6)

Centre No.	Name	Inv. Type	Centre Address	Country	Subjects Screened	Subjects Randomized	Subjects Not Randomized	Subjects Completed	Major Violations	Major Deviations
------------	------	-----------	----------------	---------	-------------------	---------------------	-------------------------	--------------------	------------------	------------------



(b) (6)

Drug **RESTOR**
Study **(b) (6)**
Report Date: May 1, 2009

Investigators' Reply to Request for Disclosure
No Disclosable Financial Interest

Centre No.	Name	Inv. Type	Centre Address	Country	Subjects Screened	Subjects Randomized	Subjects Not Randomized	Subjects Completed	Major Violations	Major Deviations
------------	------	-----------	----------------	---------	-------------------	---------------------	-------------------------	--------------------	------------------	------------------



(b) (6)

(b) (6)





Date: 11 May 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA SUPPL AMENDMENT

ORIGINAL

MAY 11 2009

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Additional Financial Disclosure
Information for JUPITER sNDA

SEI-016-C

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to communication on 25 March 2009 between Ms. Margaret Simoneau, FDA project manager, and AstraZeneca Pharmaceuticals LP (AstraZeneca) requesting that the following additional information be included in the financial disclosure reports for the JUPITER sNDA submission:

“Include in tabular format financial disclosure information on all investigators. The tables should list all investigators (e.g., one for those who have financial information to disclose and one for those who do not). The tables should also include site (including country), number of patients screened, number of patients enrolled, number of protocol violations (major and other), number of protocol deviations, number of patients who completed the trial, and for the table with financials, the amount of money received and in what form (speaker's fees/cash/stock, etc.).”

This submission includes:

- A completed and signed Form FDA 356h
- The requested additional financial disclosure information in Module 1.3.4 Financial Certification and Disclosure

Additionally, AstraZeneca is informing the Division that the following investigator information was inadvertently included in the “ no participation report”. The information has been moved to the “no disclosable interest report” since the investigators participated in the study (e.g., screened patients). Financial Disclosure had been obtained for these investigators.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Centre No.	Name	Inv Type (b) (6)	Address	Country
[Redacted Content]				

Centre No.	Name	Inv Type	Address	Country
(b) (6)				

Also, the following investigator was included in Appendix 12.1.4.1 List of staff at investigational site(s) of the JUPITER Study [(b) (4)] Clinical Report located in Module 5.3.5.1., but was inadvertently omitted from the “no disclosable interest report”. The investigator participated in the study (e.g., screened and enrolled patients) and financial disclosure had been obtained for this investigator.

Centre No.	Name	Inv Type	Address	Country
(b) (6)				

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 10-May-2009, rev. 3. 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-

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

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. Paula R. Clark, Regulatory Affairs Director, at (302) 885-1492.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PRC



TRANSMITTED BY FACSIMILE

Wanda Hill
Director, Promotional Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike P.O. Box 15437
Wilmington, DE 19850-5437

RE: NDA #21-366
CRESTOR® (rosuvastatin calcium) Tablets
MACMIS #18245

Dear Ms. Hill:

This letter responds to AstraZeneca Pharmaceuticals LP's (AstraZeneca) February 3, 2010, request to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for advisory comments regarding a proposed press release for CRESTOR® (rosuvastatin calcium) Tablets (Crestor).

DDMAC, in consultation with the Division of Metabolic and Endocrine Drug Products (DMEP), has reviewed the proposed press release for Crestor and offers the following comments, which should be applied to this proposed piece and all future promotional materials that contain the same or similar claims and representations for Crestor.

These comments are tentative because they are based on the draft product labeling submitted with the proposed press release. The proposed press release, as well as future promotional materials, should be updated to reflect the final approved product labeling (PI) for Crestor.

Given the requested turnaround time, our comments are based on the assumption that the data provided in the proposed press release are accurate and complete.

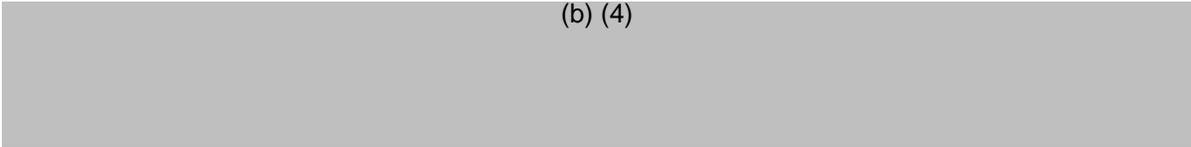
General

We note that the proposed press release states "Please see accompanying full Prescribing Information." We remind you that the approved product labeling (PI) must accompany all promotional labeling.

Broadening of Indication

The proposed press release presents the claims:

(b) (4)



(b) (4)

These claims are misleading because they suggest that Crestor has been approved to treat a broader range of patients or conditions than has been demonstrated by substantial evidence. **Specifically the Indications and Usage section of the draft PI states, "In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age \geq 50 years old in men and \geq 60 years old in women, hsCRP \geq 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to: reduce the risk of stroke; reduce the risk of myocardial infarction; reduce the risk of arterial revascularization procedures" (emphasis added).** We note that the full indication is presented on the first page of the proposed press release; however, this does not mitigate the overall misleading impression.

In addition, page two of the proposed press release claims, (b) (4)
(b) (4)

(b) (4) " This claim is misleading because it broadens the indication for Crestor by suggesting that all individuals require Crestor therapy and that Crestor will prevent a heart attack or stroke in every individual, when such is not the case. We recommend that this claim be deleted.

Omission of Material Fact

Promotional materials are false or misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the proposed press release misleadingly omits the following information from the draft PI:

(b) (4)

-
-
-
-

(b) (4)

-
-

We recommend revising the proposed press release to include this important information in conjunction with the claims of efficacy and safety regarding the JUPITER trial.

Minimization of Risk Information

Promotional materials are misleading if they fail to present risk information with a prominence and readability reasonably comparable to the presentation of efficacy claims. The proposed press release presents numerous efficacy claims for Crestor prominently throughout the first two pages of the proposed press release. In contrast, the risk information is only initially discussed on page two of the proposed press release. We recommend that you revise the proposed press release to present the risks associated with Crestor with a prominence and readability reasonably comparable to the efficacy claims, taking into account all techniques apt to achieve emphasis.

Page two of the proposed press release claims, (b) (4)

(b) (4) (b) (4)
" This claim is misleading because it minimizes the risks associated with Crestor by suggesting that the adverse reactions reported by patients in the JUPITER trial did not differ in any way from what had been previously observed in the clinical trials for Crestor. Specifically, the Adverse Reactions section of the draft PI states, " (b) (4)
(b) (4)

(b) (4) " We recommend that this claim be revised or deleted. We note that page three of the proposed press release states, " (b) (4)
(b) (4)

(b) (4) " however this does not correct this misleading presentation.

Page two of the proposed press release also claims, " (b) (4)

(b) (4) " This claim is misleading because it minimizes the risks of Crestor by failing to include the incidence rates for the most commonly reported adverse events for Crestor and placebo, from the JUPITER study. We recommend that you include the incidence rates for Crestor and placebo for completeness and consistency with the PI.

Lack of Contextual Information

Page one of the proposed press release claims, " (b) (4)

(b) (4) (b) (4)
(b) (4) " This claim is misleading because it lacks important contextual information from

the draft PI. Specifically, the Clinical Studies section of the draft PI states, “ (b) (4)
(b) (4)

(b) (4) (emphasis added). We recommend this presentation be revised to incorporate this important contextual information.

Page two of the proposed press release presents a general description of the JUPITER study under the header “ABOUT JUPITER” (emphasis original). This description is misleading because it lacks important contextual information from the Clinical Studies section of the draft PI regarding the studied population and the baseline values for the study endpoints. For example, the Clinical Studies section of the draft PI describes the age, percentage of patients with different risk factors, as well as median baseline LDL-C and hs-CRP levels for the individuals included in the JUPITER study. We recommend revising the proposed press release to include this important contextual information.

Misleading Claims

Page one of the proposed press release claims:

- (b) (4)
-

The totality of this presentation is misleading because it suggests that Crestor has been demonstrated to reduce the risk of fatal MIs and fatal strokes, when this has not been demonstrated by substantial evidence. Specifically, the Clinical Studies section of the draft PI states, “ (b) (4)
(b) (4)

We recommend that this presentation be revised or deleted to correct this misleading impression.

If you have any questions or comments, please contact me by facsimile at (301) 847-8444 or write to me at The 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.

Wanda Hill
AstraZeneca Pharmaceuticals LP
NDA #21-366/MACMIS #18245

Page 5

Please refer to MACMIS #18245 in addition to the NDA number in all future correspondence relating to this particular matter. DDMAC reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	ORIG-1	IPR PHARMACEUTICA LS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

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

/s/

SAMUEL M SKARIAH
02/05/2010



Date: 21 January 2010

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Tables of number and percentage of
subjects discontinuing study medication due to AEs, by SOC and preferred term

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 11 January 2010. The Division requested the following information:

1. Please provide the location of the Table that lists the preferred terms for adverse events that led to study medication discontinuation (not study withdrawal of participation as in Table 11.3.5.1.2.1). If it has not been submitted, please do so.
2. Please provide an analysis of the adverse events for the all the subjects that discontinued medication due to an adverse event. According to Table 11.1.1.8.2.4.1, pg 1865 in the CSR there were 584 subjects in the RSV group and 553 in the placebo group that discontinued study medication due to an adverse event. The Table previously provided in an email on 11 January 2010 included only 486 and 477 subjects in the RSV and placebo groups, respectively. Please submit a revised table with the subjects referred to in Pg 1865 in the CSR with the SOC and preferred terms.

Responses to FDA Request No. 1 and No. 2 were sent to the Division via email on 11 January 2010 and 20 January 2010, respectively.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of responses to FDA request for information are included in Module 5.3.5.1

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 20-January-2010. 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PAD

AstraZeneca



Date: 19 January 2010

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Sequence 0069

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009 and the telephone communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 12 January 2010. Reference is also made to Sequence 0068 submitted to the Division on 15 January 2010. The Environmental Concentrations of Rosuvastatin response document, dated 15 January 2010 was inadvertently omitted from Module 1.12.14 in Sequence 0068. AstraZeneca is hereby submitting the response document for Sequence 0068 under Sequence 0069. The cover letter included in Sequence 0068 and the response document included in this submission were sent via email to Ms. Margaret Simoneau and Dr. Janice Brown, FDA Chemistry Team Leader on 15 January 2010.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the response document for Sequence 0068

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 18-January-2010. 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

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PAD



Date: 15 January 2010

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Additional Data to Support Categorical
Exclusion included in the JUPITER sNDA (S-016)

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009 and the telephone communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 12 January 2010. Reference is also made to the 4 December 2009 response provided to the Division with regard to data to support the Categorical Environmental Exclusion included in the JUPITER sNDA and the CRESTOR NDA Annual Report submitted on 8 December 2009. During the teleconference, the Division requested the following information:

- Please provide an accurate projection of the expected use of CRESTOR based on the JUPITER indication. In addition, please include the sales forecast numbers (XX number of patients) used to calculate the data to support the Categorical Exclusion statement from the 4 December response and recalculate the Categorical exclusion calculations to reflect the current amount (based on the 2009 CRESTOR NDA Annual Report Distribution Data) plus the amount of use based on the projected forecast.

Notes to the Reviewer

At the request of the FDA a recalculation of the forecast for CRESTOR was performed. A new environmental concentrations document has been generated to reflect the forecast recalculation and is included in Module 1.12.14. The slight increase in the Expected Introduction Concentration (EIC) reflects the addition of samples to the sales data.

It should also be noted that in the 4 December 2009 response document a 7-year projection rather than a 5-year projection was performed for the forecast. While the maximum quantity of CRESTOR ((b) (4)) was estimated to be produced in the year 2015, it was erroneously assigned to the year 2013 in the document. The recalculation included in the 15 January 2010 response document, included in this submission, is based on the maximum quantity of

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

CRESTOR ((b) (4)) estimated to be produced in the year 2015 plus the addition of the CRESTOR unit samples ((b) (4)) derived from the Distribution Data included in the 2009 CRESTOR NDA Annual Report. Thus, the total maximum quantity of CRESTOR estimated to be produced in the year 2015 which as been used to calculate the EIC in the 15 January 2010 response document is (b) (4)

The expected total number of patients to be treated with CRESTOR which was used to calculate the EIC in the 4 December 2009 response and the 15 January 2010 document, included in this submission, is (b) (4) for CRESTOR treated patients plus (b) (4) Certriad treated patients).

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the response for FDA request for information is included in Module 1.12.14 Environmental Analysis

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 31-December-2009. 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD



Date: 11 January 2010

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Additional Questions regarding the
Efficacy and Safety Data

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 5 January 2010. The Division requested the following information:

1. Of the people with 1 risk factor (defined as age unadjusted) and in subjects with 0 risk factors (defined as age plus HDL 60 or greater) what were the adverse events frequency overall and by SOC, and the specific neuropsychiatric adverse events in Table 11.3.6.1.1.7B, and incidence of investigator reported diabetes.
2. Of the 18 subjects with confusional state, please provide in tabular format for each subject, the date of the confusional state onset, date when rosuvastatin was stopped, if RSV was stopped during the confusion AE, date when it was restarted or if it was not restarted please state as such. If RSV was not stopped during the confusion AE, please include this information as well. Also please provide any additional neuropsychiatric adverse events within the 4 weeks prior to the confusion AE and anytime after.
3. Please provide the CEC adjudication forms that provide the rationale for the adjudicated CV deaths with the cause of death deemed due to "other" as being cardiovascular in nature.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of responses to FDA request for information are included in Module 5.3.5.1

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 31-December-2009. 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD



Date: 21 December 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366
CRESTOR[®] (rosuvastatin calcium) Tablets
Re: General Correspondence - JUPITER sNDA (S-016)

Dear Dr. Parks:

AstraZeneca Pharmaceuticals LP (AstraZeneca) appreciated the discussion of sNDA 21-366/S-016 for CRESTOR at the Endocrinologic and Metabolic Advisory Committee (EMDAC) Meeting on 15 December 2009, and the Division's thorough review of the application. We have drawn on the committee's insights to inform revisions to our proposed changes to the CRESTOR label, and append these for the Division's consideration.

In summary, AstraZeneca received the following guidance from the advisory committee meeting:

1. The committee agreed with a significant majority that the benefits outweighed the risks in the overall JUPITER study population.
2. The committee concurred with AstraZeneca's position that the analysis of risks and benefits in JUPITER supported the use of rosuvastatin for cardiovascular risk prevention in individuals (b) (4)
[REDACTED]
3. hsCRP was recognized as useful as JUPITER's enrichment strategy, but the committee did not recommend that it be used for cardiovascular risk assessment of all patients. The committee was in agreement that a global risk assessment based on cardiovascular risk factors was appropriate. Use of hsCRP was seen as useful for some patients as part of global risk assessment.
4. There was a mild effect on glycemic control in JUPITER (0.1% mean increase in Hb_{A1C}), resulting in a higher percentage of participants with investigator-reported diabetes in the rosuvastatin group compared to placebo, although the benefits of treatment clearly outweighed the risks in those at risk for investigator-reported diabetes. The committee agreed with the FDA reviewer that the mild effect on glycemic control appeared to be a class effect of statin therapy.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

5. Total mortality was an important finding in JUPITER. There was no formal multiplicity adjustment for this endpoint. However, the endpoint reached nominal statistical significance and was a likely consequence of reduction in myocardial infarctions and strokes without an increase in non-cardiovascular mortality.

AstraZeneca proposes to address this guidance by incorporating a more (b) (4)
(b) (4)

Given the committee's overall position, hsCRP is included in the list of risk markers to be utilized in global risk assessment. Reference is also made to the response to FDA's request for information (submitted 30 October 2009) in which the benefit in subjects with hsCRP < 2 on one of the pre-randomization visits is presented.

The committee did not address clinical endpoints in JUPITER in detail, although consistent benefit across all components of the primary endpoint was noted by several panel members. In the attached revision, the primary endpoint is presented according to its definition of "major cardiovascular events", followed by the pre-specified list of the individual components.

Given the conclusions regarding the glycemic findings, AstraZeneca will await the Agency's guidance on the anticipated class labeling for statins. In the interim, AstraZeneca proposes to include the increased Hb_{A1C} observation in Section 6.1 (ADVERSE REACTIONS, Clinical Studies Experience) of the US Prescribing Information (PI).

Additionally, based on the learnings taken away from the 15 December EMDAC, AstraZeneca proposes the following US PI indication language for the JUPITER data:

1.6 Prevention of Cardiovascular Disease

In adult patients at (b) (4) risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.

AstraZeneca would greatly appreciate the opportunity to discuss this proposal with the Division and looks forward to doing so. Therefore, AstraZeneca proposes meeting with the Division via teleconference during the week of 11 January 2009 to discuss this proposal. We look forward with anticipation to your response.

This submission includes:

- A completed and signed Form FDA 356h

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 21-December-2009. 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 Margaret G. Melville, M.S., Executive Director, Regulatory Affairs, at (302) 886-2118.

Sincerely,

Patricia A. DeFeo, M.S.
Regulatory Affairs Director, CRESTOR
Telephone: (302) 886-2050
Fax: (302) 886-2822

PAD/mgm

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do **NOT** send this page with the letter.

Application #(s):	sNDA 21-366/S-016
DSI Electronic Archive:	sNDA 21-366/S-016
FEL/CFN:	3007759163
Field Classification:	VAI
Headquarter's Classification:	VAI (Voluntary Action Indicated-no response requested)
If headquarters classification is different from field classification, please explain why:	N/A
Deficiencies Noted:	<input checked="" type="checkbox"/> failure to adhere to protocol (05) <input checked="" type="checkbox"/> inadequate and inaccurate records (06)
Deficiency Code(s):	05, 06
Drafted by and dates:	SL: 12/09/09
Reviewed by and dates:	TPS: 12/16/09
Reviewed by and dates:	
Meeting dates:	
Finalized:	SL: 12/17/09
Filename:	O:\Leibenhaut\Rosuvastatin 21-366\Sarmiento VAI letter.doc
Case Closed :	Yes. This is a foreign inspection; the EIR is released through DSI to the clinical investigator.
DFS Key Words:	DSI Staff Letters – Clinical Investigator Program
CC:	<u>Reviewer when entering in DARRTS, cc the following:</u> Review Division/MO/Mary Roberts Review Division/PM/ Margaret Simoneau DSI/Branch Chief/Tejashri Purohit-Sheth DSI/GCP Reviewer/Susan Leibenhaut DSI/GCP Branch CST/Joseph Peacock/Kimberly Gifford DSI/Database PM/Dana Walters/Christina Thompson HFR-SW250 /Field Investigator/ Kelly Moore HFC-134/Rebecca Hackett/Tania Mercado <u>CST place paper copy in File</u> DSI Doc. Rm. GCP #13081

CST enter into DSI Electronic Archive #
NDA #21-366/S-016

**DSI note to Review
Division**

This inspection was performed as a routine data audit for NDA#21-366/S-016. At this site, 2,446 subjects were screened, and 322 subjects were randomized.

An audit of 45 subjects' records was conducted in depth. All sites were blinded to lipid levels and C-reactive protein levels during the study, including during screening. Sites received a report stating whether a subject was eligible, but did not receive the actual laboratory values.

Inspection revealed the regulatory violation that the second half of exclusion criterion #3, "CHD risk equivalent as defined by NCEP ATP III" was not determined for any subject. The site was unable to follow the protocol because there was a systemic procedural issue in the trial. The sites were told that the (b) (4) Central Laboratory would calculate this value when, in fact, the laboratory was not determining this value. Therefore, subjects with "CHD risk equivalent as defined by NCEP ATP III" could be enrolled in the trial. In discussions with the sponsor, it appeared that this occurred in all sites in the trial. This clinical trial conduct issue was communicated by DSI to the review division on October 1, 2009 in an e-mail and a telecon.

Additional regulatory violations cited on the Form FDA 483 were that "clinically significant" urinalyses for Subjects 1450 and 1052 were not reported to the sponsor as adverse events. No other instances of under reporting of adverse events were detected, and the primary endpoint data were verified.

Dr. Sarmiento adequately responded to the inspectional findings in a letter dated October 14, 2009. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication, with the caveat that the review division should consider the impact of the systemic issue noted in the utilization of Exclusion Criterion #3 in their evaluation of study outcome.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



Date: 11 December 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

SDN 346
RECEIVED

DEC 11 2009

COER WITH 11/11/09

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information received via e-mail on 4 December 2009

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an e-mail request for information from the Division of Metabolism and Endocrinology Products (DMEP) to AstraZeneca Pharmaceuticals LP (AstraZeneca) dated 4 December 2009. The Division requested the following information:

- In your final briefing document Subject 50020367 is reported as dying of duodenal ulcer. However in the regulatory response document of 18 August 2009 the subject is listed as did not die in Table 2 and Page 95 and in the draft briefing document in Table 24. Please clarify the discrepancy.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the response for FDA request for information is included in Module 5.3.5.1.

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 8-December-2009 r41. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

AstraZeneca 

RECEIVED

DEC 11 2009

CDER White Oak DR 1

SD# 0347

Date: 11 December 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information Received via e-mail on 7 December 2009

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an e-mail request for information from the Division of Metabolism and Endocrinology Products (DMEP) to AstraZeneca Pharmaceuticals LP (AstraZeneca) dated 7 December 2009. The Division requested the following information:

- Please clarify the differences between Table 28 in the final briefing document and the Tables 37, 38, and 39 in the CSR? In particular what is the definition of a treatment-emergent AE as opposed to an adverse events reported during the randomized treatment phase.
- Please supply the location of the reference table in the CSR which created Table 28 in the final briefing document.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the response for FDA request for information is included in Module 5.3.5.1.

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 8-December-2009r41. 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



Date: 10 December 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Ré: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information received via e-mail on 8 December 2009

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an e-mail request for information from the Division of Metabolism and Endocrinology Products (DMEP) to AstraZeneca Pharmaceuticals LP (AstraZeneca) dated 8 December 2009. The Division requested the following information:

- In table 2.25 of the original submission, the incidence of neoplasms benign, malignant, and unspecified any adverse event is 300 (7.2%) for rosuvastatin treated subjects with an LDL-c <50 mg/dL. Please explain the discrepancy between Table 2.25 and Table 37 in your briefing document.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the response for FDA request for information is included in Module 5.3.5.1.

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 9-December-2009r41. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

Dear Dr. Parks:

R. Parks, M.D.
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Beltsville, MD 20705-1266

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Regulatory
Affairs
Director

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. Omaira Meléndez Nesbit, PharmD, Associate Director, Regulatory Affairs, at (302) 886-2762.

Sincerely,

Patricia A. DeFeo, MS
Regulatory Affairs Director
Telephone: (302) 886-2050
Fax: (302) 886-2822

Patricia A. DeFeo, MS
Regulatory Affairs Director

PAD/giw

Regulatory Affairs
Director
AstraZeneca
Regulatory Affairs
Director

Please direct
any questions
to me

Patricia A. DeFeo, MS
Regulatory Affairs Director

Regulatory Affairs
Director

AstraZeneca
Regulatory Affairs
Director

Regulatory Affairs
Director

AstraZeneca
Regulatory Affairs
Director

Regulatory Affairs
Director

AstraZeneca
Regulatory Affairs
Director

Regulatory Affairs
Director



RECEIVED

DEC - 9 2009

CDER White Oak DR 1

SD# 344

Date: 9 December 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information Received via e-mail on 2 December 2009

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an e-mail request for information from the Division of Metabolism and Endocrinology Products (DMEP) to AstraZeneca Pharmaceuticals LP (AstraZeneca) dated 2 December 2009. The Division requested the following information:

- Provide the values of the HR and confidence intervals for Figures 11.2.2.1.2.1 through 39 (starting Page 2975 of CSR) with the p-value for interaction term.
- Clarify that the three secondary composite endpoints (CV death/MI/stroke, fatal/nonfatal mi, fatal/nonfatal stroke) were time to first event analyses.
- Provide the number of fatal MI that contributed to the fatal MI/non-fatal MI analysis.
- Provide the number of fatal strokes that contributed to the fatal stroke/non-fatal stroke analysis.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the response for FDA request for information is included in Module 5.3.5.1.

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 7-December-2009. 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



RECEIVED

DEC - 4 2009

CDER White Oak DR 1

SD#0342

Date: 4 December 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Data to Support Categorical Exclusion
included in the JUPITER sNDA (S-016)

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to telephone communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 30 November 2009. The Division requested the following information:

- Data to support the Categorical Exclusion included in the CRESTOR NDA 21-366/S-016 (JUPITER) submission

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the response for FDA request for information is included in Module 1.12.14 Environmental Analysis

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 3-December-2009. 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

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD



Date: 01 December 2009

Paul Tran, RPh.
Advisors and Consultants Staff, HFD-021
Office of Executive Programs
5600 Fishers Lane (Bldg. 5630 Rm.1086)
Rockville, MD 20857-0001

Re: FDA/CDER December 15, 2009 Endocrinologic and Metabolic Drugs Advisory
Committee CDER meeting materials – comments attached

Dear Dr. Tran:

AstraZeneca has reviewed the FDA Briefing Book (BB), forwarded on 24 November 2009, for the 15 December 2009 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting to discuss CRESTOR and the JUPITER application. From our reading of the FDA's draft BB, it appears there are many points of agreement between our analyses, however we have included some minor comments for FDA's consideration. I have attached a spreadsheet identifying these comments and included suggestions for revising the text where appropriate. We do not believe any of the comments warrants discussion with CDER however we would be happy to address any questions that might arise regarding them.

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 do not hesitate to contact me, or in my absence, Ms. Margaret Melville, Executive Director Regulatory Affairs, at (302) 886-2118.

Sincerely,

A handwritten signature in cursive script that reads "Patricia A. DeFeo".

Patricia A. DeFeo, M.S.
Regulatory Affairs Director, CRESTOR
Telephone: (302) 886-2050
Fax: (302) 886-2822

OMN/PAD

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Table 1 Comments on Clinical Briefing Document sent by the Agency on 24 November 2009

Page	Section/ Paragraph/ Table	Comment	Suggested change
35	last bullet	There was no evidence of a differential effect between Framingham risk groups. Table 16 on page 29 of the Agency's briefing book has a p value of 0.945.	
38	Deaths	Not all deaths were adjudicated by the Clinical Events Committee (CEC); only deaths with available documentation were adjudicated.	Suggest revising sentence to "All deaths for which documentation was available and that occurred during the randomized treatment phase of JUPITER were adjudicated by the Clinical Events Committee as either cardiovascular or non-cardiovascular."
44	1 st paragraph; preceding Table 29	This section discusses non-fatal psychiatric SAEs but has no sub-heading separating it from information in the previous section on GI SAEs.	Suggest adding a sub-heading to differentiate the non-fatal psychiatric SAEs from the non-fatal GI SAEs.
63	paragraph under Table 50	3 rd sentence states that "Two subjects were not on study medication..." According to Table 51, this number should be 4.	Suggest revising sentence to "Four subjects were not on study medication at the time and others had concurrent medical conditions and/or medications ongoing at the time of the event."

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do **NOT** send this page with the letter.

Application #(s):	sNDA 21-366/S-016
DSI Electronic Archive	sNDA 21-366/S-016
FEI/CFN:	3007759136
Field Classification:	VAI
Headquarter's Classification:	VAI (Voluntary Action Indicated-no response requested)
If headquarters classification is different from field classification, please explain why:	N/A
Deficiencies Noted:	<input checked="" type="checkbox"/> failure to adhere to protocol (05) <input checked="" type="checkbox"/> inadequate and inaccurate records (06)
Deficiency Code(s):	05, 06
Drafted by and dates:	SL: 11/30/09
Reviewed by and dates:	TPS: 11/30/09
Reviewed by and dates:	
Meeting dates:	
Finalized:	SL: 11/30/09
Filename:	O:\Leibenhaut\Rosuvastatin 21-366\Cervantes VAI letter.doc
Case Closed :	Yes. This is a foreign inspection; the EIR is released through DSI to the clinical investigator.
DFS Key Words:	DSI Staff Letters – Clinical Investigator Program
CC:	<u>Reviewer when entering in DARRTS, cc the following:</u> Review Division/MO/Mary Roberts Review Division/PM/ Margaret Simoneau DSI/Branch Chief/Tejashri Purohit-Sheth DSI/GCP Reviewer/Susan Leibenhaut DSI/GCP Branch CST/Joseph Peacock/Kimberly Gifford DSI/Database PM/Dana Walters/Christina Thompson HFR-CE4530 /Field Investigator/ Hugh McClure III HFC-134/Rebecca Hackett/Tania Mercado <u>CST place paper copy in File</u> DSI Doc. Rm. GCP #13080

CST enter into DSI Electronic Archive #

NDA #21-366/S-016

**DSI note to Review
Division**

This inspection was performed as a routine data audit for NDA#21-366/S-016. At this site, 1,257 subjects were screened, 280 subjects were randomized, and 268 subjects completed the study. An audit of 76 subjects' records was conducted.

For this protocol, all sites were blinded to lipid levels and C-reactive protein levels during the study, including during screening. Sites received a report stating whether a subject was eligible, but did not receive the actual laboratory values. The primary endpoint data were verifiable. At the end of the inspection, a Form FDA 483 was issued to the clinical investigator. Inspection revealed the following regulatory violations:

1. In preparation for the FDA audit, Dr. Cervantes realized that he had not initialed and dated the laboratory reports, so he backdated the reports to correct his oversight. This was detected by the sponsor in preparation for FDA audit and was reported by the sponsor to FDA. The FDA audit found that, in the case of at least 86 laboratory reports, the date of review indicated by Dr. Cervantes was actually prior to the date that the report was faxed to the site. FDA inspection did not find any evidence that actual clinical trial data was falsified or altered. This appears to represent utilization of incorrect recordkeeping practices, and was emphasized to Dr. Cervantes at the end of the inspection. Dr. Cervantes responded in his letter received by October 9, 2009 that he acknowledged his error in inappropriate correction to study documents and that would not do this again and he would engage in GCP training.
2. A total of 13 adverse events (AEs) were not reported to the sponsor:
 - a. Subject 0685 reported muscle cramping at visit 4.
 - b. Subject 1190 had SGPT 164 at visit 5.
 - c. Subject 0160 was diagnosed with Diabetes Mellitus at the final study visit.
 - d. Other AEs not reported included colitis, anemia, cutaneous lesion on abdomen, depression, and five subjects with urosepsis.
3. Not all subjects met eligibility criteria. For example, Subject 0420 did not have a C-reactive protein (CRP) of > 2. Clinical investigators were blinded to lipid and CRP values during the study including screening phase and the laboratory made the eligibility determination. The original report of March 17, 2006 indicated that the subject was eligible, but the corrected report of April 18, 2006 stated that the subject was not eligible. This violation is appropriately noted in the NDA Listing 12.2.2.1 "Subjects with Protocol Deviations and/or Violations."

4. Test article was not dispensed to subjects accurately according to procedures. Subjects 0685, 0550, and 0187 were not supplied with the correct bottle numbers. The bottles supplied had the same test article and dose to which they were randomized, so study outcome is unlikely to be affected.

Dr. Cervantes adequately responded to the inspectional findings in a letter received by FDA on October 1, 2009. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. See also comments above concerning the eligibility criterion #3. The review division may wish to take into account the above unreported AEs in the determination of safety outcome.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do **NOT** send this page with the letter.

Application #(s):	sNDA 21-366/S-016
DSI Electronic Archive	sNDA 21-366/S-016
FEI/CFN:	3005346345
Field Classification:	VAI
Headquarter's Classification:	VAI (Voluntary Action Indicated-no response requested)
If headquarters classification is different from field classification, please explain why:	N/A
Deficiencies Noted:	<input checked="" type="checkbox"/> inadequate informed consent form (03) <input checked="" type="checkbox"/> failure to adhere to protocol (05)
Deficiency Code(s):	03, 05
Drafted by and dates:	SL: 11/17/09
Reviewed by and dates:	TPS: 11/19/09
Reviewed by and dates:	
Meeting dates:	
Finalized:	SL: 11/30/09
Filename:	O:\Leibenhaut\Rosuvastatin 21-366\Robinson VAI letter.doc
Case Closed :	Yes. This is a foreign inspection; the EIR is released through DSI to the clinical investigator.
DFS Key Words:	DSI Staff Letters – Clinical Investigator Program
CC:	<u>Reviewer when entering in DARRTS, cc the following:</u> Review Division/MO/Mary Roberts Review Division/PM/ Margaret Simoneau DSI/Branch Chief/Tejashri Purohit-Sheth DSI/GCP Reviewer/Susan Leibenhaut DSI/GCP Branch CST/Joseph Peacock/Kimberly Gifford DSI/Database PM/Dana Walters/Christina Thompson HFR-SW250 /Field Investigator/ Kelly Moore HFC-134/Rebecca Hackett/Tania Mercado <u>CST place paper copy in File</u> DSI Doc. Rm. GCP #13082

CST enter into DSI Electronic Archive #

NDA #21-366/S-016

**DSI note to Review
Division**

This inspection was performed as a routine data audit for NDA#21-366/S-016. At this site, 2,182 subjects were screened, 348 subjects were randomized, nine subjects died, and nineteen subjects withdrew from the study.

An audit of 59 subjects' records was conducted in depth. All sites were blinded to lipid levels and C-reactive protein levels during the study, including during screening. Sites received a report stating whether a subject was eligible, but did not receive the actual laboratory values.

Inspection revealed the regulatory violation that the second half of exclusion criterion #3, "CHD risk equivalent as defined by NCEP ATP III" was not determined for any subject. The site was unable to follow the protocol because there was a systemic procedural issue in the trial. The sites were told that the (b) (4) Central Laboratory would calculate this value when, in fact, the laboratory was not determining this value. Therefore, subjects with "CHD risk equivalent as defined by NCEP ATP III" could be enrolled in the trial. In discussions with the sponsor, it appeared that this occurred in all sites in the trial. This clinical trial conduct issue was communicated by DSI to the review division on October 1, 2009 in an e-mail and a telecon.

Dr. Robinson adequately responded to the inspectional findings in a letter dated October 10, 2009. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication, with the caveat that the review division should consider the impact of the systemic issue noted in the utilization of Exclusion Criterion #3 in their evaluation of study outcome.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

AstraZeneca 

RECEIVED

NOV 23 2009

CDER White Oak DR 1

SD#0341

Date: 23 November 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Additional Questions regarding the
Efficacy and Safety Data

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 10 and 13 November 2009. The Division requested the following information:

10 November 2009

1. In Table 1 of the regulatory response document dated 10 September 2009, please define the "randomized population". The ITT population would include 17802 subjects and the safety population would include 17733 subjects (rosuva 8869, placebo 8864). Please also define the "randomized population" referred to in Table 3 and Table 4 of the regulatory response document dated 21 August 2009.
2. If a subject in the rosuvastatin group had a MCE event and blinded study therapy was discontinued, did they then restart rosuvastatin?
3. In retrieving vital status on subjects that had withdrawn from the study, did the company count a subject as in the total mortality analysis if they died after their projected Final visit? What percentage of study subjects had vital status at study close?

13 November 2009

1. The number of all fatal MI and fatal strokes and sudden deaths and heart failure that comprise the first event of cardiovascular deaths (35 rosuvastatin and 44 placebo) in

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

tabular format below and in similar fashion for the 29 and 37 cardiovascular deaths that contributed to the primary composite endpoint.

	Rosuvastatin	Placebo
Cardiovascular Death	35	44
Fatal MI		
Fatal stroke		
Heart failure		
Sudden death		

This submission includes:

- A completed and signed Form FDA 35
- A separate copy of responses for each FOIA request for information (10 and 13 November 2009) is included in Module 3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 20-November-2009, rev. 5. No viruses were detected, and AstraZeneca certifies that this 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira M. Lóndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: November 19, 2009

TO: Margaret Simoneau, Regulatory Project Manager
Mary Roberts, M.D., Medical Officer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-366/S-016

APPLICANT: AstraZeneca Pharmaceuticals, US Agent for IPR Pharmaceuticals, Inc.

DRUG: Crestor (rosuvastatin calcium) tablets

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: For prevention of major cardiovascular events (mortality, stroke, myocardial infarction, unstable angina, or arterial revascularization) in adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated "high sensitivity assay C-reactive protein" (hsCRP) level, age, hypertension, low "high density lipoprotein cholesterol (HDL-C)" level, smoking, or a family history of premature coronary heart disease.

CONSULTATION REQUEST DATE: June 15, 2009

DIVISION ACTION GOAL DATE: February 8, 2010

PDUFA DATE: February 8, 2010

I. BACKGROUND:

IPR Pharmaceuticals, Inc. has submitted NDA 21-366/S-016 for Rosuvastatin (Crestor) for a new indication of prevention of major cardiovascular events (mortality, stroke, myocardial infarction, unstable angina, or arterial revascularization) in adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated "high sensitivity assay C-reactive protein" (hsCRP) level, age, hypertension, low "high density lipoprotein cholesterol (HDL-C)" level, smoking, or a family history of premature coronary heart disease.

Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for the clinical trial conducted for approval. The efficacy result of the study is important in making a regulatory decision with regard to drug approval. The sites were selected based on enrollment of large numbers of study subjects.

The protocol inspected was Study D3560L0 0030 (4522US/ 0011), entitled "A Randomized, Double-Blind, Placebo Controlled, Multicenter, Phase 3 Study of Rosuvastatin (Crestor) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL-Cholesterol and Elevated Levels of C-Reactive Protein."

II. RESULTS (by Site):

Name of Clinical Investigator (CI) and Location	Protocol #/ # of Subjects enrolled	Inspection Dates	Final Classification
CI #1 Jose Luis Cervantes, M.D. Hospital Angeles del Pedregal Periferico Sur #3697-Suite 1050 Col. Heroes de Padierna Mexico City, C.P. 10700, Mexico	Study D3560L0 0030 (4522US/ 0011/ 280 subjects	September 7 to 11, 2009	VAI
CI #2 Rex Sarmiento, M.D. Synexus Midlands Birmingham Research Park Vincent Drive, Egbaston Birmingham, B15 2SQ United Kingdom	Study D3560L0 0030 (4522US/ 0011/ 322 subjects	September 21 to 25, 2009	Pending (Preliminary classification VAI)
CI #2 John S. Robinson, M.D. Synexus Manchester Clinical Research Centre, William House Manchester Science Park, Lloyd Street North Manchester M15 6SX, United Kingdom	Study D3560L0 0030 (4522US/ 0011/ 348 subjects	September 14 to 18, 2009	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

1. Jose Luis Cervantes, M.D.
Hospital Angeles del Pedregal, Periferico Sur #3697-Suite 1050
Col. Heroes de Padierna, Mexico City, C.P. 10700, Mexico
 - a. **What was inspected:** At this site, 1,257 subjects were screened, 280 subjects were randomized, and 268 subjects completed the study. An audit of 76 subjects' records was conducted.
 - b. **General observations/commentary:** All sites were blinded to lipid levels and C-reactive protein levels during the study, including during screening. Sites received a report stating whether a subject was eligible, but did not receive the actual laboratory values. The primary endpoint data were verifiable. At the end of the inspection, a Form FDA 483 was issued to the clinical investigator. Inspection revealed the following regulatory violations:
 1. In preparation for the FDA audit, Dr. Cervantes realized that he had not initialed and dated the laboratory reports, so he backdated the reports to correct his oversight. This was detected by the sponsor in preparation for FDA audit and was reported by the sponsor to FDA. The FDA audit found that, in the case of at least 86 laboratory reports, the date of review indicated by Dr. Cervantes was actually prior to the date that the report was faxed to the site. FDA inspection did not find any evidence that actual clinical trial data was falsified or altered. This appears to represent utilization of incorrect recordkeeping practices, and was emphasized to Dr. Cervantes at the end of the inspection. Dr. Cervantes responded in his letter received by October 9, 2009 that he acknowledged his error in inappropriate correction to study documents and that would not do this again and he would engage in GCP training.
 2. A total of 13 adverse events (AEs) were not reported to the sponsor:
 - a. Subject 0685 reported muscle cramping at visit 4.
 - b. Subject 1190 had SGPT 164 at visit 5.
 - c. Subject 0160 was diagnosed with Diabetes Mellitus at the final study visit.
 - d. Other AEs not reported included colitis, anemia, cutaneous lesion on abdomen, depression, and five subjects with urosepsis.
 3. Not all subjects met eligibility criteria. For example, Subject 0420 did not have a C-reactive protein (CRP) of > 2. Clinical investigators were blinded to lipid and CRP values during the study including screening phase and the laboratory made the eligibility determination. The original report of March 17, 2006 indicated that the subject was eligible, but the corrected report of April 18, 2006 stated that the subject was not eligible. This violation is appropriately noted in the NDA Listing 12.2.2.1 "Subjects with Protocol Deviations and/or Violations."

4. Test article was not dispensed to subjects accurately according to procedures. Subjects 0685, 0550, and 0187 were not supplied with the correct bottle numbers. The bottles supplied had the same test article and dose to which they were randomized, so study outcome is unlikely to be affected.
 - c. **Assessment of data integrity:** Dr. Cervantes adequately responded to the inspectional findings in a letter received by FDA on October 1, 2009. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. See also comments below concerning the eligibility criterion #3. The review division may wish to take into account the above unreported AEs in the determination of safety outcome.
2. Rex Sarmiento, M.D.
Synexus Midlands, Birmingham Research Park
Vincent Drive, Egbaston, Birmingham, B15 2SQ, United Kingdom

Note: Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** A total of 2,446 subjects were screened and 322 subjects were enrolled and randomized into this study. Forty-five subject records were reviewed in depth.
- b. **General observations/commentary:** As noted above, all sites were blinded to lipid levels and C-reactive protein levels during the study, including during screening. Sites received a report stating whether a subject was eligible, but did not receive the actual laboratory values. There was no under reporting of adverse events and the primary endpoint data were verifiable. A Form FDA 483 was issued because the investigation was not conducted in accordance with the investigational plan. Specifically, the FDA audit revealed that the second half of the protocol exclusion criterion #3, "CHD risk equivalent as defined by NCEP ATP III" was not determined for any subject. The site was unable to follow the protocol because there was a systemic procedural issue in the trial. The sites were told that the ^{(b) (4)} Central Laboratory would calculate this value when, in fact, the laboratory was not determining this value. Therefore, subjects with "CHD risk equivalent as defined by NCEP ATP III" could be enrolled in the trial. In discussions with the sponsor, it appeared that this occurred at all sites in the trial. This clinical trial conduct issue was communicated by DSI to the review division on October 1, 2009 in an e-mail and a telecon.

- c. **Assessment of data integrity:** As discussed above, the audit found systemic clinical trial conduct issues concerning lack of determination of eligibility concerning the second half of exclusion criterion #3. Other than this one item, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. John S. Robinson, M.D.
Synexus Manchester Clinical Research Centre, William House
Manchester Science Park, Lloyd Street North
Manchester M15 6SX, United Kingdom

- a. **What was inspected:** A total of 2,182 subjects were screened and 348 subjects were randomized. Nineteen subjects withdrew from the study and nine subjects died. Forty-five subject records were reviewed in depth.
- b. **General observations/commentary:** As noted above, all sites were blinded to lipid levels and C-reactive protein levels during the study, including during screening. Sites received a report stating whether a subject was eligible, but did not receive the actual laboratory values. There was no under reporting of adverse events and the primary endpoint data were verifiable. A Form FDA 483 was issued because the investigation was not conducted in accordance with the investigational plan. Specifically, the FDA audit revealed that the second half of the protocol exclusion criterion #3, "CHD risk equivalent as defined by NCEP ATP III" was not determined for any subject. The site was unable to follow the protocol because there was a systemic procedural issue in the trial. The sites were told that the ^{(b) (4)} Central Laboratory would calculate this value when, in fact, the laboratory was not determining this value. Therefore, subjects with "CHD risk equivalent as defined by NCEP ATP III" could be enrolled in the trial. In discussions with the sponsor, it appeared that this occurred at all sites in the trial. This clinical trial conduct issue was communicated by DSI to the review division on October 1, 2009 in an e-mail and a telecon.
- c. **Assessment of data integrity:** As discussed above, the audit found systemic clinical trial conduct issues concerning lack of determination of eligibility concerning the second half of exclusion criterion #3. Other than this one item, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this study. In general, the study appeared to be conducted appropriately and the data is considered reliable. However, as discussed above, audits of the above sites were able to validate the primary endpoint and determine that there was no under reporting of significant adverse events. However, the audit found a systemic clinical trial conduct issue, in that the second half of the protocol exclusion criterion #3, "CHD risk equivalent as defined by NCEP ATP III" was not determined for any subject in the clinical trial. The review division will need to evaluate the impact of the systemic issue of not using exclusion criterion #3 for eligibility determination in their evaluation of study outcome.

The inspection of Dr. Cervantes found additional violations as noted above. The review division may wish to take into account the above unreported AEs in the determination of safety outcome. Although a number of regulatory violations were noted, it is unlikely that they significantly affect overall data reliability from these sites. The data from all sites appear acceptable in support of the proposed indication.

The final classification for the inspection of Dr. Sarmiento is pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for these inspections.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICA LS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

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

/s/

SUSAN LEIBENHAUT
11/19/2009

TEJASHRI S PUROHIT-SHETH
11/19/2009



Date: 13 November 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Additional Safety Data

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 3 November 2009. The Division requested the following information:

1. Provide the source documents, verbatim terms, and narratives of the rosuvastatin and placebo treated subjects who experienced the AE of confusional state.
2. Incorporate the following preferred terms depression, anxiety, and insomnia into Table 11.3.6.1.1.7A and resubmit.
3. Provide further information regarding subject 7651-0133 in regards to follow up of the CK of 11,404 at the final visit and information if muscle symptoms were present and what his creatinine and urine values were.
4. Provide information regarding subjects who had a clinically significant increase from baseline in urine protein or urine blood that did not resolve.
5. Provide additional information as to what the category of "other" represents in the reasons for discontinuing study medication.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of responses to FDA request for information are included in Module 5.3.5.1

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 12-November-2009, rev. 5. 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PAD

AstraZeneca 

RECEIVED

OCT 30 2009

CDER White Oak DR 1

SD#0334

Date: 30 October 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: sNDA Data-related Questions

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 15 and 28 October 2009. The Division requested the following information:

1. Please refer to Table 12.1.9.1.4.2, Page 684 regarding the analysis of <2 and ≥ 2 risk factors. These are subjects ($n=4279$) that only have age as a risk factor (numbers match Table 14 in the CSR) and the HR is 0.91 and there is a significant treatment interaction term of 0.034. Please explain the difference in numbers of people with ATP risk factors from the Ridker 2008 NEJM which has 6375 subjects with no risk factors other than age with a HR of 0.63 and no significant treatment interaction.
2. Were the subjects with protocol violations such as a CRP <2 mg/L included in the efficacy and safety analyses?
3. How was hypertension defined in the JUPITER trial?
4. What is the exact definition of who was defined as "hypertensive" at baseline. It would be the definition of who was coded as "1" for the variable "b_ht".

This submission includes:

- A completed and signed Form FDA 356h
- A copy of responses to FDA request for information are included in Module 5.3.5.1

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR[®] (rosuvastatin calcium) Tablets

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 29-October-2009, rev. 5. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

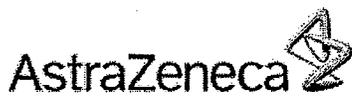
This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD



Date: 19 October 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
General Correspondence: AstraZeneca's response to Form FDA 483 issued to
JUPITER Study Sites 5007, John S. Robinson, MD (Manchester UK) and 5001, Rex
Sarmiento, MD (Birmingham, UK)

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009 and the clinical study D3560L00030 (4522US/0011) entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of Rosuvastatin (CRESTOR) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL-Cholesterol and Elevated Levels of C-Reactive Protein" (also referred to as JUPITER).

Reference is also made to the FDA Inspections, which were conducted by FDA investigators, Ms. Kelly D. Moore, Ms. Patricia M. Beers Block and Dr. Susan Leibenhaut, for the following JUPITER Study sites:

1. **Site 5007, John S. Robinson, MD (Manchester, UK)**
 - FDA inspection occurred Monday, 14 September 2009 through Friday, 18 September 2009
 - Form FDA 483 Inspectional Observations Report was issued by the FDA investigators to Principal Investigator, Dr. John S. Robinson, on 18 September 2009
2. **Site 5001, Rex Sarmiento, MD (Birmingham, UK)**
 - FDA inspection occurred Monday, 21 September 2009 through Friday, 25 September 2009
 - Form FDA 483 Inspectional Observations Report was issued by the FDA investigators to Principal Investigator, Dr. Rex Sarmiento, on 25 September 2009

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

The purpose of this submission is to provide the Division with additional background information pertaining to the Investigators' responses to Observation 1 (item 1) identified in the Form FDA 483:

- The clinical investigator did not have documentation to verify that the exclusion criterion #3 (CHD risk equivalent as defined NCEP ATP III) was met prior to enrolling subjects into the JUPITER study 4522US/0011, version 6.

Please note that AstraZeneca has sent Dr. Susan Leibenhaut a copy of Dr. John S. Robinson response's via email and mail correspondence on Friday, 9 October 2009. A copy of responses from Dr. Rex Sarmiento were sent directly to Dr. Leibenhaut from clinical site 5001 located in Birmingham, UK.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of AstraZeneca's response to Form FDA 483 issued to JUPITER Study Sites 5007, John S. Robinson, MD and 5001, Rex Sarmiento, MD, which is located in Module 1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 18-October-2009, rev. 20. 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.

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PAD

AstraZeneca 

RECEIVED

OCT 13 2009

CDER White Oak DR 1

SD#0335

Date: 13 October 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Hepatic-related Lab Assessments

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 23 September 2009. The Division requested the following information:

1. Report whether there were any Hy's Law cases in the trial.
2. In tabular format, provide the n/% of patients with ALT and/or AST >3x, >5x, and >10x, by treatment group.
3. In tabular format, provide alkaline phosphatase and TB associated with ALT/AST >3x.
4. Provide case report forms/hospital records/pathology reports on the cases of hepatic failure.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of responses to FDA request for information relating to Hepatic lab assessments are included in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 12-October-2009, rev. 40. 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-

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD



Date: 2 October 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

OCT 02 2009

CDER White Oak DR

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Measure Effect of change in hsCRP
(baseline to one year) on Cardiovascular Risk (CV death and non-fatal MI) and
contribution of CRP to Cardiovascular Risk

SDN334

10/1/09

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to email communications between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 2 and 10 September 2009 and to teleconferences held on 11 and 28 September 2009. The Division requested the following information:

clinical

From your primary prevention cardiovascular trial data, please provide the following Information/analyses:

1. To measure the effect of change in hsCRP (baseline to one year) on cardiovascular risk (CV death and non-fatal MI), please perform a logistic regression in your drug-treated group adding change in LDL (baseline to one year) to the model.
2. To measure the contribution of CRP to cardiovascular risk, please perform a logistic regression in your placebo group adding baseline Framingham Risk Score, baseline CRP, and baseline LDL to the model.
3. Please calculate the number and percent of patients whose Framingham risk score would be modified to a higher risk category if CRP were added to the Framingham covariables and present them in tabular format as below:

Model without CRP	Model with CRP				Reclassified into New Risk Category	
	0%-5%	5%-10%	10%-20%	≥20%	Lower	Higher
0% to <5%						
5% to <10%						
10% to <20%						
≥20%						

Notes to the Reviewer

The FDA request for information with regard to the primary prevention cardiovascular trial data detailed above is the original request received from the Agency on 02 September in an email and updated via email on 10 September 2009. As agreed with the Division in a 28 September 2009 teleconference, a response to the first 2 items is included in this submission. Response to the 3rd item has not been included as the Division requested on 01 October 2009 that the request be withdrawn.

This submission includes:

- A completed and signed Form FDA 356h
- Analyses on the effect of change in hsCRP (baseline to one year) on cardiovascular risk (CV death and non-fatal MI) and contribution of CRP to cardiovascular risk are included in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 2-October-2009, rev. 2. 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.

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD



Date: 14 September 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

SEP 14 2009

SDN 331

CDER White Oak DR1

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Sequence 0046

Dear Dr. Parks:

ORIGINAL

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to Sequence 0046 submitted to the Division on 11 September 2009. The incorrect cover letter and FDA form 356h were included with the submission, however the correct response document dated, 11 September 2009, was included in Module 5.3.5.1. Ms. Margaret Simoneau was informed via email of the error by Ms. Patricia A DeFeo on Friday, 11 September 2009. AstraZeneca is hereby resubmitting the correct cover letter and FDA form 356h for Sequence 0046 under Sequence 0047.

This submission includes:

- A completed and signed Form FDA 356h
- A copy of the correct cover letter for Sequence 0046

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 13-September-2009, rev. 4. 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.

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD

AstraZeneca



RECEIVED

SEP 11 2009

SDN 829

CDER White Oak DM

ORIGINAL

Date: 11 September 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: JUPITER Clinical Study Report -
Definition of "Completer" and Treatment Emergent Cognitive Adverse Events

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 3 September 2009. The Division requested the following information:

- 1) Please define a completer. Would someone who discontinued study drug but continued with follow-up visits until study close be considered a completer? Is someone who had a MCE and later withdrew from study a completer? Is there a difference between final endpoint ascertainment and being a completer?
- 2) Please incorporate the following preferred terms into Table 11.3.6.1.1.7 and resubmit. Memory impairment, amnesic disorder, global amnesia, amnesia, and disturbance in attention.

This submission includes:

- A completed and signed Form FDA 356h
- A definition of completer and the revised Table 11.3.6.1.1.7 with the requested cognitive terms, which is located in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 8-September-2009, rev. 18. 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

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD

AstraZeneca

Date: 11 September 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Amundale Road
Beltsville, Md 20705-1266

RECEIVED

SDN 336

Re: NDA 21-366-S-016

SEP 11 2009

CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information SUPPLEMENT Clinical Study Report -
Definition of "Completer" and Treatment Emergent Cognitive Adverse Events

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 3 September 2009. The Division requested the following information:

- 1) Please define a completer. Would someone who discontinued study drug but continued with follow-up visits until study close be considered a completer? Is someone who had a MCE and later withdrew from study a completer? Is there a difference between final endpoint ascertainment and being a completer?
- 2) Please incorporate the following preferred terms into Table 11.3.6.1.1.7 and resubmit. Memory impairment, amnesic disorder, global amnesia, amnesia, and disturbance in attention.

This submission includes:

- A completed and signed Form FDA 356h
- A definition of completer and the revised Table 11.3.6.1.1.7 with the requested cognitive terms, which is located in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 8-September-2009, rev. 18. 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

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1100 North 17th Street, Wilmington, DE 19803-8355



Date: 11 September 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: JUPITER Clinical Study Report - CV
deaths, AE deaths, Total mortality and JUPITER Diabetes-related Adverse Events

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 10 September 2009. The Division requested the following information:

- 1) Please explain why the adjudicated CV deaths plus AE deaths do not equal the total mortality numbers.

	Rosuva	Placebo
Total mortality	198	247
Adj CV death	35	44
AE deaths	141	179

- 2) Please give the breakdown of JUPITER diabetes related AEs in both treatment groups and include in the MH Forest Plot, as was done for the METEOR, CORONA, and AURORA trials.

This submission includes:

- A completed and signed Form FDA 356h
- An explanation of why the adjudicated CV deaths plus AE deaths do not equal the total mortality numbers and JUPITER diabetes-related AEs, which are located in Module 5.3.5.1

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR[®] (rosuvastatin calcium) Tablets

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 10-September-2009, rev. 2. 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PAD

Simoneau, Margaret A

From: DeFeo, Pat A [pat.defeo@astrazeneca.com]
nt: Friday, September 11, 2009 4:11 PM
Simoneau, Margaret A
subject: Questions AstraZeneca would like to explore with the Division re: NDA 21-366/S-016 (JUPITER)

Dear Margaret,

During our telephone call of Tuesday, September 8, 2009, we discussed forwarding questions that AstraZeneca (AZ) would like to discuss with the Division regarding the JUPITER sNDA (21-366/S-016). This was re-iterated in a follow-up telephone call of Thursday, September 10, 2009. Below please find a list of questions that AZ is interested in pursuing:

Regarding the Advisory Committee Meeting (ACM):

- * JUPITER results are very robust and we believe support labeling for CV risk reduction. Can you tell us why an ACM is needed?
- * What issues will be raised for the advisors? AZ is asking in order to partner with FDA to help address the issues and support a successful review and ACM.

Proposed Indication

- * Does the Agency have comments on the proposed indication?
- * AZ proposed this indication to reconcile the study results with the current evidence and practical considerations for clinical use of statin therapy in cardiovascular disease prevention. Does the Agency have comments on describing the appropriate population in the indication?
- * What is the Agency's view on the inclusion of hsCRP within the proposed indication?
- * AZ attempted to follow the Agency's precedent in including the endpoint components in the indication. What is the Agency's view on the proposed way of including the primary composite endpoint?

Other

- * AZ has received from FDA a number of questions pertaining to Diabetes Mellitus (DM). Has AZ sufficiently addressed your concerns and are there any remaining issues with regard to DM that FDA would like to further discuss?
- * Does the Agency agree with AZ's conclusions on DM, based on the entirety of CRESTOR data as described in the submission?
- * Is it the Agency's opinion that the JUPITER observations are consistent with other statin studies?
- * Are there any other concerns that the FDA would like to share with the sponsor at this time, recognizing that the review is ongoing?
- * We would like the opportunity to further partner with FDA in preparation for the Advisory Committee Meeting (for example, sharing our briefing book and presentation slides with the Agency) and as additional review issues arise. Would the Agency be open to additional discussions?
- * Would the Agency be prepared to share with AZ who will be invited to participate in the ACM (e.g. Cardio-Renal Committee members, DSARM)?

AstraZeneca is hoping to have the opportunity to discuss these questions in a teleconference with the Division in the very near future. We believe this would be of great benefit to both the Agency and the sponsor in identifying and addressing issues on which we are aligned.

Please feel free to contact me to discuss the possibility and timing for a teleconference, or if you should have another need to do so.

Thank you,
> Pat

Patricia A. DeFeo, MS
> US Regulatory Affairs Director, CRESTOR
> AstraZeneca Pharmaceuticals LP
> Chesapeake Building, C3B-112



Date: 1 September 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

SDN 328

SEP 02 2009

ORIGINAL

CDER White Oak DR1

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: JUPITER Clinical Study Report - Table of
Subjects on Concomitant Therapy

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 17 August 2009. The Division requested that AstraZeneca submit a table of subjects on concomitant therapy using the following categories (see below) by treatment group and overall, or to provide the location for this table if it has already been submitted. The table should include the number of subjects (and percentage of total subjects) in each concomitant drug therapy group.

Concomitant drug therapy categories

Metformin only
Sulfonylureas only
Metformin + sulfonylureas only
Insulin only
Insulin +metformin
Insulin+metformin +sulfonylureas
Other
Diet only

Antiplatelet medications (not including aspirin)
Aspirin
ACE inhibitors
Beta blockers
Nitrates
Calcium channel blockers
Thiazide diuretics

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Loop diuretics
Fibrates
Angiotensin II receptor antagonists
Alpha blockers
Potassium sparing diuretics
Cardiac glycosides
Statins (other than CRESTOR)

This submission includes:

- A completed and signed Form FDA 356h
- A Table of Subjects on Concomitant Drug Therapy Grouped by Categories, which is located in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 31-August-2009, rev. 18. 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 Patricia A. DeFeo, MS, Regulatory Affairs Director, at (302) 886-2050.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PAD



Date: 24 August 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Analysis Supporting JUPITER CSR, page
111, Section 9.1.2.2 Diabetes Mellitus Information

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to the teleconference between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 8 July 2009 in which Drs. Mary Roberts and Amy Egan requested AstraZeneca to provide:

- 1) The analysis used to support the following statement included in the JUPITER CSR, page 111, Section 9.1.2.2 Diabetes Mellitus: "Although the number of investigator-reported diabetes cases was higher among rosuvastatin versus placebo treated subjects in JUPITER, there was no statistical difference in diabetes reported as an AE in the 2 previously reported long-term, placebo controlled studies of rosuvastatin (METEOR [AstraZeneca Clinical Study Report D3562C00088, November 2006] and CORONA [AstraZeneca Clinical Study Report D3562C00098, April 2008]) that were conducted by AstraZeneca."
- 2) The exclusion criteria relating to diabetes, fasting glucose for the CORONA AND METEOR studies.

In addition, based on discussions with Dr. Mary Roberts on 27 July 2009, AstraZeneca is including in this response data from another placebo-controlled double blind, non-IND study of patients with end stage renal disease receiving dialysis (Study D3562C00096, AURORA) The clinical study report is included in Module 5.3.5.4 for reference only.

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

This submission includes:

- The Analysis Supporting JUPITER CSR, page 111, Section 9.1.2.2 Diabetes Mellitus Information, which is located in Module 5.3.5.1
- A completed and signed Form FDA 356h

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 23-August-2009, rev. 3. 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 Mr. Ian Hunt, Executive Director, Regulatory Affairs, at (302) 886-2586.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/IH



Date: 20 August 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Source Documents for all GI Deaths

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to an email communication between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 12 August 2009. The Division requested source documents for all the GI deaths that occurred in the JUPITER study. Specifically, the Division requested all autopsy reports, hospital discharge reports, and Emergency Department notes.

This submission includes:

- A completed and signed Form FDA 356h
- Source documents for all GI deaths, which are located in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 19-August-2009, rev. 34. 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

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Mr. Ian Hunt, Executive Director, Regulatory Affairs, at (302) 886-2586.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ IH

RECEIVED

AUG - 5 2009

CDER White Oak DR 1

SD# 0322

AstraZeneca 

Date: 5 August 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Additional Lipid Variables/Datasets for
JUPITER sNDA

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to the teleconference between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 27 July 2009 in which Drs. David Hoberman, Mary Roberts and Amy Egan had questions pertaining to the JUPITER efficacy datasets submitted 1 May 2009. As a result of the discussions, Dr. Hoberman requested AstraZeneca to provide:

- The identical efficacy datasets, submitted to the Division on 1 May 2009, with the three additional variables appended to the dataset (e.g., HDL, APO_B, APO_{A1}) and only including baseline and 1-year measurements.

Notes to the Reviewer

The efficacy dataset submitted to the Division on 1 May 2009 will be replaced with the dataset included in this submission.

This submission includes:

- A completed and signed Form FDA 356h
- The revised efficacy electronic datasets, which are located in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 4-August-2009, rev. 3. 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

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR[®] (rosuvastatin calcium) Tablets

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 Mr. Ian Hunt, Executive Director, Regulatory Affairs, at (302) 886-2586.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/IH

AstraZeneca 

Date: 31 July 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Amundale Road
Beltsville, MD 20705-1266

RECEIVED

JUL 31 2009

SDN 320

IGIN

Re: NDA 21-366/S-016 **CDER White Oak DR1**
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: efficacy data clarifications for JUPITER sNDA

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to the teleconference between AstraZeneca Pharmaceuticals LP (AstraZeneca) and the Division on 8 July 2009 in which the medical reviewers were seeking clarification regarding information contained in the efficacy tables and eNarratives. As a result of the discussions, Drs. Mary Roberts and Amy Egan requested AstraZeneca to provide:

- 1) Analyses of major cardiac events plus deaths due to any cause, including events with the "IDA" (Insufficient Data to Adjudicate) code.
- 2) Clarification of the days from stopping randomized treatment in table 11.3.3.2.3 as there were various negative numbers identified in the table.

Drs. Roberts and Egan also requested AstraZeneca to provide:

- 3) The analysis used to support the following statement included in the JUPITER CSR, page 111, Section 9.1.2.2 Diabetes Mellitus: "Although the number of investigator-reported diabetes cases was higher among rosuvastatin versus placebo treated subjects in JUPITER, there was no statistical difference in diabetes reported as an AE in the 2 previously reported long-term, placebo controlled studies of rosuvastatin (METEOR [AstraZeneca Clinical Study Report D3562C00088, November 2006] and CORONA [AstraZeneca Clinical Study Report D3562C00098, April 2008]) that were conducted by AstraZeneca."
- 4) The exclusion criteria relating to diabetes, fasting glucose for the CORONA AND METEOR studies.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

This submission will only include:

- The responses to clarification regarding information contained in the efficacy tables and eNarratives (Items 1 and 2 as described above), which are located in Module 5.3.5.1
- A completed and signed Form FDA 356h

The analysis used to support the statement included in the JUPITER CSR, page 111, Section 9.1.2.2 Diabetes Mellitus and the exclusion criteria relating to diabetes, fasting glucose for the CORONA AND METEOR studies (Items 3 and 4 described above) will be submitted in a separate response and will be provided to the Division shortly. In addition, based on discussions with Dr. Mary Roberts on 27 July 2009, AstraZeneca will be including in the response for Items 3 and 4, data from another placebo-controlled double blind, non-IND study of patients with end stage renal disease receiving dialysis (Study D3562C00096, AURORA) and the clinical study report will be included for reference only.

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 30-July-2009, rev. 7. 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 Mr. Ian Hunt, Executive Director, Regulatory Affairs, at (302) 886-2586.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ IH



Date: 01 July 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA SUPPL AMENDMENT

RECEIVED

JUL 01 2009

CDER WASHINGTON

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Information for JUPITER sNDA

Dear Dr. Parks:

SEI-016-BM

ORIGINAL

Reference is made to NDA 21-366 and the JUPITER sNDA (S-016) submitted on 7 April 2009 by AstraZeneca Pharmaceuticals LP (AstraZeneca). Reference is also made to emails received from the division on 22 and 24 June 2009. In these emails the division requested additional information about the endpoint adjudication process in the JUPITER study. AstraZeneca was also asked to clarify some of the variable names and definitions used in the analysis.

This submission includes:

- A completed and signed Form FDA 356h
- The requested information and associated table, located in Module 1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.5.5001 (Corporate Edition), with a virus definition file dated 30 June 2009, rev. 2. 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.

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

Please direct any questions or requests for additional information to me, or in my absence, to Ms. Sally A Walsh, Associate Director, Regulatory Affairs, at (302) 556-8194.

Sincerely,

Mr. Ian Hunt
Executive Director, Regulatory Affairs
Telephone: (302) 886-2586
Fax: (302) 886-2822

SAW/giw

DSI CONSULT: Request for Clinical Inspections

Date: June 10, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Susan Leibenhaut, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Mary Parks, M.D., Division Director, Division of Metabolism and Endocrinology
Drug Products (DMEP)
Eric Colman, M.D., Deputy Director/Team Leader, DMEP

From: Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, DMEP

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA 21-366/S-016
Applicant/ AstraZeneca Pharmaceuticals, US Agent for IPR Pharmaceuticals, Inc.
Drug Proprietary Name: Crestor (rosuvastatin calcium) tablets
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard
Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

In adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:¹

- reduce the risk of total mortality
- reduce the risk of cardiovascular death
- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization
- reduce the risk of unstable angina

PDUFA:

Action Goal Date: February 8, 2010

Inspection Summary Goal Date: December 1, 2009

Note: Supplement is scheduled for presentation at the Metabolic Drugs Advisory Committee (EMDAC) on Tuesday, December 15, 2009

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
7153 Hospital Angeles del Pedregal Periferico Sur #3697-1050 Col. Heroes de Padierna C.P. 10700 Mexico	(Study D3560L0 0030 [4522US/0011])	280	In adults for the prevention of cardiovascular events in subjects with an increased risk of cardiovascular disease based on the presence of cardiovascular risk markers.
5001 Birmingham Clinical Research Center Vincent Drive Birmingham Research Park Birmingham Egbaston B15 2SQ UK	Same	322	Same
5007 Manchester Clinical Research Centre Lloyd Street North 1 st Floor, Williams House, Manchester Science Park Manchester M15 6SX UK	Same	348	Same

III. Site Selection/Rationale

Domestic Inspections: N/A

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: Inspection sites were chosen based on enrollment of large numbers of study subjects.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (not applicable)

Should you require any additional information, please contact Margaret Simoneau at 301-796-1295 or Mary Roberts, M.D. at 301-796-4088.

Concurrence:

Eric Colman, M.D.	Medical Team Leader
Mary Roberts, M.D.	Medical Reviewer
Mary Parks, M.D.	Division Director

**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
6/15/2009 03:33:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-366/S-016

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

Dear Ms. Clark:

Please refer to your April 8, 2009, received April 8, 2009, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets. This supplemental application proposes new information to be added to the Crestor package insert, based on the results of the study entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (Crestor) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)".

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 7, 2009, in accordance with 21 CFR 314.101(a).

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.

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
6/1/2009 08:18:05 AM
Eric Colman for Mary Parks

AstraZeneca 

Date: 21 May 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

NDA SUPPL AMENDMENT

MAY 21 2009

SA-016-BS

CDER White Oak DR1

Re: NDA 21-366/S-016
CRESTOR® (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Statistical Information for JUPITER
sNDA

ORIGINAL

Dear Dr. Parks:

Reference is made to NDA 21-366 and the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to the teleconference between AstraZeneca and the Division on 17 April 2009 regarding statistical questions. In the teleconference, AstraZeneca was asked to provide a more complete explanation of what was meant, and the reasoning behind, the statement, "...there was no difference in diabetes-free survival..." located in the second paragraph on page 97 of the JUPITER Clinical Study Report in Module 5.3.5.1 (see below for complete paragraph).

"Investigator-reported diabetes mellitus was more frequent in the subjects assigned to rosuvastatin (251/8901, 2.8%) compared with placebo (205/8901, 2.3%). An analysis censoring subjects who died in the absence of reported diabetes gave an HR of 1.27 (95% CI 1.05, 1.53; p=0.015)(see Tables 11.3.6.1.2.7 and 11.3.6.1.2.8, see Figure 11.3.6.1.2.9 for the Kaplan-Meier plot); however, there was no difference in diabetes-free survival in the rosuvastatin treatment group compared to the placebo treatment group (HR 1.02; 95% CI 0.89, 1.16; p=0.817) (see Table 11.2.1.36.2)."

The purpose of this submission is to provide clarification of the analysis of increase in diabetes corrected for survival effects included in the JUPITER sNDA, as follows:

Rosuvastatin had an overall survival advantage compared to placebo and death represents a competing risk. Hence, simple censoring deaths is therefore problematic as we know the event (death) is informative. One way to deal with this is to create a composite endpoint that includes total mortality. This approach is commonplace in other areas like Oncology where death is frequently an informative competing risk. This composite endpoint of time to a first event of either a diagnosis of diabetes, or death is what we are referring to as "diabetes-free survival" in the JUPITER Clinical Study Report i.e. it is the length of time patients are alive

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

and free from a diagnosis of diabetes. It is this composite endpoint that showed no difference between the two groups.

This submission includes:

- A completed and signed Form FDA 356h

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 20-May-2009, rev. 3. 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. Paula R. Clark, Regulatory Affairs Director, at (302) 885-1492.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PRC



Date: 11 May 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Amendment to a Pending Application: Update to Errata in the JUPITER Clinical
Study Report

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009 for the use in adults for the prevention of cardiovascular events in subjects with an increased risk of cardiovascular disease based on the presence of cardiovascular risk markers.

In accordance with 21 CFR 314.60, AstraZeneca Pharmaceuticals LP (AstraZeneca) is hereby submitting an amendment to the above referenced application. This amendment contains an Errata to Appendix 12.1.4.1 List of staff at investigational site(s) of the JUPITER Study [D3560L00030 (4522US/0011)] Clinical Report located in Module 5.3.5.1. This Errata, Edition 2, dated 7 May 2009, replaces the existing Errata, Edition 1, dated 31 March 2009. Please note that this change does not have an impact on the interpretation of the data and therefore, AstraZeneca does not consider this to be a significant amendment.

Appendix 12.1.4.1 was updated to include the following investigator names:

Country	Centre	Name	Role Code	Qualifications	Address
Canada	4025	Rakesh Bhargava	PI	MD	Heart Care Research Medical Sciences Building 372 King Street West Oshawa, ON L1J 2J9

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Country	Centre	Name	Role Code	Qualifications	Address
Canada	4025	(b) (6)	Sub-I	MD	Heart Care Research Medical Sciences Building 372 King Street West Oshawa, ON L1J 2J9
Canada	4055	David Bewick	PI	MD	Saint John Medical Clinic 299 Metcalf Street Saint John, NB E2K 4P8

This submission includes:

- A completed and signed Form FDA 356h
- JUPITER Study [D3560L00030 (4522US/0011)] Clinical Report Errata, Edition 2, dated 7 May 2009

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 10-May-2009, rev. 3. 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. Paula R. Clark, Regulatory Affairs Director, at (302) 885-1492.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/ PRC



RECEIVED

MAY 01 2009

CDER White Oak DR 1

Date: 1 May 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

SUPPLEMENT AMENDMENT

Re: NDA 21-366/S-016
CRESTOR[®] (rosuvastatin calcium) Tablets
Response to FDA Request for Information: Variables/Datasets for JUPITER sNDA

SEA-016 (BS)

Dear Dr. Parks:

Reference is made to the JUPITER sNDA (S-016) submitted on 7 April 2009. Reference is also made to the teleconference between AstraZeneca and the Division on 17 April 2009 regarding statistical questions. Specifically, as the basis for the teleconference, the statistician, Dr. Hoberman had questions regarding the electronic data sets and locations of all variables to allow review of the submission. As a result of the discussions, Dr. Hoberman requested AstraZeneca to provide:

- single analysis dataset for the primary and secondary endpoints referenced in pages 7 and 10 of the SAP
- LDL-C and CRP values at different time points (absolute values)
- variables and flags for the primary analysis
- detailed description of analysis of increase in diabetes corrected for survival effects (more details of statistical analyses and methods)

This submission includes:

- A completed and signed Form FDA 356h
- The requested electronic variables and datasets, which are located in Module 5.3.5.1

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 30-April-2009, rev. 18. 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,

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

NDA 21-366/S-016: CRESTOR® (rosuvastatin calcium) Tablets

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. Paula R. Clark, Regulatory Affairs Director, at (302) 885-1492.

Sincerely,

Omaira Meléndez Nesbit, PharmD
Associate Director, Regulatory Affairs
Telephone: (302) 886-2762
Fax: (302) 886-2822

OMN/PRC



NDA 21-366/S-016

PRIOR APPROVAL SUPPLEMENT

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

Dear Ms. Clark:

We have received your supplemental new 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-016
Review Priority Classification: Standard (S)
Date of supplement: April 8, 2009
Date of receipt: April 8, 2009

This supplemental application proposes new information to be added to the Crestor package insert, based on the results of the study entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (Crestor) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)".

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 June 7, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 8, 2010.

We refer to your request for a priority review for this supplement. Upon careful consideration of your application, we have concluded that this application should receive a standard review.

The basis for your request for a priority review includes: 1) evidence of increased effectiveness in the prevention of CV events in subjects with LDL-C levels ≤ 130 and hsCRP levels ≥ 2.0 , and 2) evidence of safety and effectiveness in a new subpopulation (women, non-Caucasians, and subjects with "normal-to-low" LDL levels and "high" hsCRP levels).

The Manual of Policies and Procedures for Review Classification Policy states that a priority review may be granted if the sponsor provides evidence that the drug product has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: **(1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products** (approved, if approval is required), including *nondrug* products or therapies. Significant improvement is illustrated by the following examples: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation.

DMEP response to criterion #1: Satisfactory alternative therapy to rosuvastatin exists. Eighty mg of atorvastatin reduces LDL levels to a similar degree as 20 mg of rosuvastatin. Statins other than rosuvastatin also reduce hsCRP levels. Significant reductions in LDL and hsCRP can be achieved, for example, with coadministration of a statin with ezetimibe.

DMEP response to criterion #2: Strictly speaking, you have not demonstrated significant improvement compared to a marketed product because the JUPITER trial did not include an active-comparator arm (e.g., a marketed statin). Furthermore, the cardiovascular risk reductions reported in the JUPITER trial may overestimate the true treatment effects, as the trial was stopped early.

For these reasons, together with the facts that the results of the JUPITER trial have been published in a high-profile medical journal and rosuvastatin is readily available to healthcare prescribers and patients, your supplement will receive a standard review.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 21-366/S-016

Page 3

If you have 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

**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
4/22/2009 01:22:37 PM
Eric Colman for Mary Parks

Simoneau, Margaret A

From: Davis Bruno, Karen L
Sent: Wednesday, April 08, 2009 11:36 AM
Subject: Simoneau, Margaret A
RE: Successfully Processed eCTD: nda021366 in COMIS
Attachments: FW: Successfully Processed eCTD: nda021366 in COMIS



FW: Successfully
Processed eCT...

No pharm/tox assignment needed this is a clinical efficacy suppl.



S-016

Date: 7 April 2009

Mary Parks, M.D., Division Director
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

Re: NDA 21-366
CRESTOR[®] (rosuvastatin calcium) Tablets
Supplemental New Drug Application: Efficacy - JUPITER Study and Request for Priority Review

Dear Dr. Parks:

In accordance with Section 505(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) to NDA 21-366 to provide safety and efficacy information on the use of CRESTOR[®] (rosuvastatin calcium) Tablets in adults for the prevention of cardiovascular events in subjects with an increased risk of cardiovascular disease based on the presence of cardiovascular risk markers. This application is made on behalf of iPR Pharmaceuticals, Inc. The letter authorizing AstraZeneca to serve as agent for iPR Pharmaceuticals, Inc. is included in Module 1.4.1. 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 11 July 2008, 19 August 2008, 18 September 2008, 6 October 2008 and 14 October 2008. For your convenience, a document summarizing the interactions between the FDA and AstraZeneca for this submission is located in Module 1.2 (Relevant FDA interactions). A copy of FDA responses to a 45-day Special Protocol Assessment and FDA responses (1 of 2 and 2 of 2) to questions included in the pre-sNDA meeting package are also included in Module 1.2.

This sNDA is based primarily on results of one single pivotal study, (Study D3560L00030 [4522US/0011]), entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (CRESTOR[®]) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)". The clinical study report which supports the proposed indication is provided in Module 5.3.5.1 of this application. The proposed US prescribing information to support this efficacy supplement is provided in Module 1.14.1.2. A Pediatric Waiver Request for the proposed indication was previously submitted on 25 February 2009 to IND 56,385 (Serial No. 0704) and is included for your reference in Module 1.9.1.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

The pivotal clinical trial was carried out at 1438 multi-centers in 26 countries under IND 56,385 and conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation /Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics. A certification statement is included in Module 1.3.3, 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) of the Food, Drug and Cosmetic Act. In addition, in accordance with 21 CFR 54.4, certifications are included in Module 1.3.4 regarding the financial interests and arrangements for all of the clinical investigators who contributed to the JUPITER study:

- Form FDA 3454 Certification (No disclosable information)
- Form FDA 3455 Disclosure (Disclosure information)
- Form FDA 3454 Certification (Due diligence)

A non-participant report has been included in Module 1.3.4 to identify investigators who were listed on the Form FDA 1572 at one time but did not participate in the study.

Request for Consideration of Priority Review

Background

AstraZeneca conducted a large, placebo-controlled, double-blind clinical endpoint study called the “Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (the JUPITER study),” to assess the long-term safety and cardiovascular risk reducing efficacy of CRESTOR® (rosuvastatin calcium) in 17802 adult subjects (8901 to each treatment group). The efficacy of rosuvastatin calcium treatment was assessed using a composite endpoint of major cardiovascular events (cardiovascular death, myocardial infarction, stroke, unstable angina, or arterial revascularization). In order to add to the data from prior studies and address important medical questions, the JUPITER study identified a subject population with low to normal serum concentrations of Low-Density Lipoprotein Cholesterol (LDL-C), no clinical evidence of pre-existing cardiovascular (CV) disease, but considered to have an increased CV disease risk based on age (≥ 50 years for men; ≥ 60 years for women) as a CV risk factor and a high sensitivity assay C-Reactive Protein (hsCRP) level that was ≥ 2.0 mg/L. Although most of the JUPITER study subjects had multiple risk factors for CV disease, they did not qualify for cholesterol-lowering treatment based on ATP III guidelines (Expert Panel [NCEP] 2001).

Executive Summary

CRESTOR® (rosuvastatin calcium) Tablets, if approved in adults for the prevention of cardiovascular events in subjects with an increased risk of cardiovascular disease, would be a significant improvement in the prevention of cardiovascular events, for the following reasons:

- 1) In the JUPITER study, a large reduction in the risk of major CV events (44%) and a statistically significant reduction in total mortality (20%) accompanied the marked reduction in LDL-C that occurred during rosuvastatin calcium treatment.
- 2) These observations are of particular importance from a public health perspective, since many subjects at increased risk of CV disease do not receive lipid lowering drug treatment based on current NCEP ATP III guidelines. However, these individuals were identified to be at increased risk and benefited from rosuvastatin calcium therapy in the JUPITER study.
- 3) The study enrolled an exceptionally large number of women and non-Caucasian individuals, thereby adding important data for these subpopulations.

Therefore, AstraZeneca is requesting that the current sNDA be considered for priority review.

The justification for the priority review is summarized for the following two categories, according to FDA guidance:

1. *Evidence of increased effectiveness in the treatment, prevention, or diagnosis of disease*

The AstraZeneca clinical development program for rosuvastatin calcium included a large number of controlled clinical trials that included over 50000 study subjects worldwide. The program included a large number of studies to assess the lipid altering effects of rosuvastatin calcium as well as studies to assess the effects of rosuvastatin calcium on progression of atherosclerosis. Treatment with rosuvastatin calcium has been shown to induce dose-related reductions in LDL-C levels in subjects with hypercholesterolemia (Jones et al 2003). The reductions are in the 40-55% range when rosuvastatin calcium is administered in its usually recommended dose range. They are accompanied by significant increases in High-Density Lipoprotein Cholesterol (HDL-C). Rosuvastatin calcium has also been shown to reduce progression of atherosclerosis among asymptomatic individuals with subclinical atherosclerosis and induce regression of atherosclerosis in subjects with established coronary artery disease (Crouse et al 2007, Nissen et al 2006).

Taken together, these findings strongly suggested that rosuvastatin calcium would be capable of reducing the risk of major CV disease events to a greater extent than previously documented with statin therapy. The JUPITER study provided clear evidence of this treatment benefit. The principal results of the JUPITER study were that subjects who received rosuvastatin calcium (20 mg once daily) had a statistically significant 44% ($p < 0.0001$) reduction in major CV events (cardiovascular death, myocardial infarction, stroke, unstable angina and arterial revascularization) and a statistically significant 20% reduction in total mortality ($p = 0.02$) when compared to placebo. Additional analyses in the study showed that rosuvastatin calcium therapy resulted in 54% reduction in risk of fatal or nonfatal myocardial infarction, 48% reduction in fatal or non-fatal stroke ($p < 0.001$) and 48% in the combined endpoint of CV death, myocardial infarction and stroke ($p = 0.002$). The reduction in total mortality had not been previously documented with statin therapy for subjects without known

pre-existing CV disease. Both CV event reduction and LDL-C reduction in JUPITER were greater than observed in prior statin outcomes studies. This finding is particularly noteworthy in view of the fact that JUPITER subjects had LDL-C <130 mg/dL (3.36 mmol/L) at baseline, and did not qualify for statin therapy under current guidelines.

2. *Evidence of safety and effectiveness of a new subpopulation*

The JUPITER study included 6801 women and 5119 non-Caucasian subjects, providing important information in subpopulations under-represented in other statin outcomes studies (Heart Protection Study Collaborative Group 2002, Downs et al 1998, The Scandinavian Simvastatin Survival Study Group 1994, Sacks et al 1996). Statistically significant and clinically meaningful reductions in the risk of major CV events with rosuvastatin calcium were observed in a wide range of subgroups regardless of gender, age, ethnicity, hypertension, family history of premature coronary disease, pre-diabetes, smoking status, geographic region, or baseline lipoprotein or hsCRP levels. Further, the study demonstrated safety and tolerability of rosuvastatin calcium and resulting low on-treatment LDL-C levels (median 55 mg/dL).

Finally, the JUPITER study included a patient population that according to current clinical guidelines does not qualify for statin treatment. There is a large unmet medical need in this population of patients at increased risk of major CV events who may account for up to 50% of all such events, resulting in a significant burden on these individuals, families and society. The JUPITER study results provide important information for clinicians, who make therapeutic decisions for patients at increased risk of CV events.

Additional Reviewer's Guide

This application does not include any new information regarding the Chemistry, Manufacturing and Controls (Module 3). A Categorical Environmental Analysis Exclusion request is included in Module 1.12.14. CRESTOR is currently commercially available in tablet strengths of 5 mg, 10 mg, 20 mg, and 40 mg. Therefore, 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 information is included. In addition, this application does not include any new information regarding non-clinical data (Module 4) for CRESTOR.

The METEOR and CORONA clinical study reports are included in Module 5.3.5.4 for reference only. Both clinical study reports were previously submitted to the Agency:

- METEOR (NDA 21-366; 5 January 2007; Supplement 010)
- CORONA (IND 56,385; 12 January 2009; Serial No. 0700)

The Periodic Safety Update Report (07 November 2007 to 06 November 2008), referenced in the Summary of Clinical Safety, was also previously submitted to NDA 21-366 (22 December 2008; eCTD sequence 0016) and is included in Module 5.3.6.

As required by Section 736 of the Federal Food, Drug and Cosmetic Act, the Prescription Drug User Fee in the amount of \$623,600.00 (User Fee Check No. 1500215824) was delivered to the FDA in care of Wachovia Bank, Charlotte, NC on 20 February 2009. The User Fee ID No. for this application is PD3009113. A copy of the submission is included in Module 1.1.3.

The format of this sNDA is being submitted in eCTD format and 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".

The case report form (CRF) domain is provided as a single data set and includes raw data; e.g., the concomitant medications data set, the Adverse Event (AE) data set, and analysis data sets. The analysis data sets includes raw, analysis, and derived variables, and contains data variables (raw or derived) from a combination of several raw data sets. The analysis data sets contain all relevant variables necessary for generating analysis reports. All laboratory data were collected electronically and have no CRF pages. Therefore, data is provided as individual data sets. Corresponding analysis data sets are also provided.

Imaged CRFs are provided for any subjects who have died or had an AE leading to withdrawal from the study. Annotated case report forms are provided. Paper CRFs were designed and used in the study to capture protocol-required data in the database used by the clinical research organization (CRO).

The Agency responded in a written correspondence, dated 6 October 2008, that AstraZeneca's proposal for how CRFs would be presented (as noted above) in the sNDA sounded acceptable and further noted that imaged CRFs should be provided for any patient who died or discontinued drug treatment due to an AE or who experienced a serious AE or who withdrew consent.

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.7.7000 (Corporate Edition), with a virus definition file dated 1-April-2009, rev. 3. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

A signed, completed Form FDA 3674, Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C., § 282(j)) is provided as discussed in the April 2008 *Draft Guidance for Sponsors, Industry, Researchers, Investigators and Food and Drug Administration Staff: Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007*.

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,

NDA 21-366: CRESTOR® (rosuvastatin calcium) Tablets

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 Omaira Meléndez Nesbit, PharmD, Associate Director, Regulatory Affairs, at (302) 886-2762.

Sincerely,

Paula R. Clark
Regulatory Affairs Director
Telephone: (302) 885-1492
Fax: (302) 886-2822

OMN/ PRC



1.2 Relevant Food and Drug Administration Interactions

Drug Substance: Rosuvastatin calcium

Date: 1 April 2009

1.2 Relevant Food and Drug Administration Interactions

CRESTOR[®] (rosuvastatin calcium) for the Prevention of Cardiovascular Events in Adults

This submission /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

	PAGE
TITLE PAGE	1
TABLE OF CONTENTS	2
1. RELEVANT FDA INTERACTIONS	3

1. RELEVANT FDA INTERACTIONS

Date	Interaction
10 September 2002	AstraZeneca Pharmaceuticals LP (AstraZeneca) requests an End of Phase II meeting to discuss a clinical outcome trial entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of Rosuvastatin (Crestor®) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL-Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER Study)". AstraZeneca also submits with the request a Briefing Information Package with questions to the Food and Drug Administration (FDA) regarding the design and conduct of the proposed study program; indications that would be sought upon program completion and the regulatory management of the program. (IND 56,385; Serial No. 0343)
24 September 2002	FDA responds to AstraZeneca's meeting request, dated 10 September 2002, to discuss the development of a primary prevention of coronary events indication for CRESTOR® (rosuvastatin calcium) tablets, stating the meeting was premature at this time. FDA suggests that AstraZeneca refer to the "Special Protocol Assessment" draft Guidance for Industry to determine whether the referenced protocol qualifies for a 45-day review. If the protocol qualifies for special assessment, then AstraZeneca could submit specific questions, as described in the Guidance, and the FDA would respond in writing within 45 days.
04 October 2002	AstraZeneca requests a 45-day Special Protocol Assessment, along with a briefing package containing questions for the Division to consider in the review of the proposed protocol entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (CRESTOR®) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)" (Trial No. D3560L00030 [4522US0011]), in support of a primary prevention of coronary events indication for CRESTOR® (rosuvastatin calcium) tablets. (IND 56,385; Serial No. 0348)
20 November 2002	FDA provides written responses to the 45-day Special Protocol Assessment Request submitted on 4 October 2002.

Date	Interaction
29 January 2003	<p>AstraZeneca submits Protocol Amendment No. 1 for the JUPITER study incorporating changes based on the Division's response to the 45-day Special Protocol Assessment Request (IND 56,385; Serial No. 0367). The following changes were made prior to start of subject recruitment:</p> <p>Eligibility:</p> <ul style="list-style-type: none">• Changed Triglyceride inclusion criterion from <600 mg/dL (6.8 mmol/L) to <500 mg/dL (5.6 mmol/L)• Added "or CHD risk equivalent" to exclusion for prior cardiovascular event <p>Endpoints:</p> <ul style="list-style-type: none">• Added venous thromboembolic events and bone fractures as secondary endpoints• Added health economic evaluation• Laboratory evaluation: added urinalysis at follow up visits and creatinine, CK at final visit
14 February 2003	<p>AstraZeneca and FDA teleconference to discuss the JUPITER Protocol Amendment No. 1 dated 29 January 2003. The FDA discusses the additional secondary endpoints in the study, (venous thromboembolic events and the incidence of bone fractures), and wants assurance that AstraZeneca does not plan to include these endpoints in the target indication which was agreed in the Special Protocol Assessment. AstraZeneca responds that the additional secondary endpoints were for hypothesis generation, and not intended for label indication.</p>
27 May 2003	<p>AstraZeneca submits Protocol Amendment No. 2 for the JUPITER study (IND 56,385; Serial No. 0395). The following changes were made after start of subject recruitment:</p> <ul style="list-style-type: none">• Recruitment: Added Canadian centers• Eligibility: Added exclusion for creatinine >2.0 mg/dL (177 µmol/L)

Date	Interaction
22 November 2004	<p>AstraZeneca submits Protocol Amendment No. 3 for the JUPITER study (IND 56,385; Serial No. 0490). The following changes were made after start of subject recruitment:</p> <p>Recruitment:</p> <ul style="list-style-type: none">• Added centers outside United States and Canada (Latin America, Europe, Middle East)• Added optional screening consent• Added telephone contact between clinic visits
05 October 2005	<p>AstraZeneca submits Protocol Amendment No. 4 for the JUPITER study (IND 56,385; Serial No. 0533). The following changes were made after start of subject recruitment:</p> <p>Eligibility:</p> <ul style="list-style-type: none">• Lowered eligible age from 55 to 50 years for men and from 65 to 60 years for women• Added unstable angina to exclusion for prior cardiovascular event Analysis: added subgroup analysis for age-at-entry ≥ 55 (for men) or 65 (for women) vs. younger subjects <p>Recruitment:</p> <ul style="list-style-type: none">• Extended recruitment period for subjects until August 2007• Added additional countries
27 October 2005	<p>FDA project manager communicates to AstraZeneca that the Protocol Amendment for the JUPITER study submitted on 5 October 2005 would not be handled per 45-day Special Protocol Assessment rules (although the original protocol was). AstraZeneca should not expect an official response to the amendment. However, the FDA project manager reviewed the online notes made by the Medical Reviewer stating that the study could proceed as amended. The FDA Project Manager did not see any notes from the Statistical Reviewer but agreed to follow-up with any feedback.</p>
31 October 2005	<p>FDA project manager communicates to AstraZeneca that the Statistical Reviewer had reviewed the Medical Reviewer's notes, and stated that there were no statistical issues regarding the Protocol Amendment for the JUPITER study submitted on 5 October 2005.</p>

Date	Interaction
09 May 2007	<p>AstraZeneca submits an Administrative Change for the JUPITER study (IND 56,385; Serial No. 0606). The current administrative changes affect the following protocol sections:</p> <ul style="list-style-type: none">• Section 3.1 Overall Study Design and Flow Chart (page 21 paragraph 6 and page 25, paragraph 2)• Section 3.1 Study Flow Chart Figure 1 and Study Plan Table 4• Section 3.3.4.2 Voluntary Discontinuation by a Subject• Section 6.1 Determination of Sample Size
04 June 2008	<p>AstraZeneca informs the FDA project manager about an FDA meeting to discuss the interim results of the JUPITER trial arranged by upper level management of both AstraZeneca and FDA. The meeting is scheduled for Wednesday, 23 July 2008, from 3:00 pm to 4:30 pm. AstraZeneca wants to confirm that the meeting date and time was acceptable to the AstraZeneca team. A list of potential AstraZeneca attendees was also included.</p>
20 June 2008	<p>AstraZeneca communicates with the FDA project manager that AstraZeneca intends to forward a pre-sNDA briefing document in the next several weeks with information on the content and format of the planned JUPITER efficacy supplement. AstraZeneca would also be requesting a face-to-face meeting with the Agency to discuss topics related to both the operational aspects of this sNDA submission as well as a more theoretical discussion on the labeling possibilities. The meeting requested in the pre-sNDA briefing document submission was not intended to be in lieu of the planned meeting between upper level management of both AstraZeneca and FDA that was scheduled for 23 July 2008.</p>
23 June 2008	<p>AstraZeneca informs the FDA project manager that the meeting originally scheduled for 23 July 2008 is postponed until late October/early November 2008 following the JUPITER database lock and just prior to AHA.</p>
24 June 2008	<p>FDA project manager communicates to AstraZeneca that, although there were differences between the two meetings (upper level management and pre-sNDA meetings), the FDA project manager could not guarantee that a face-to-face pre-sNDA meeting may occur. A teleconference would more likely be possible. Once the Division reviews the briefing package and the questions, a decision as to the utility of a pre-sNDA meeting would be assessed.</p>

Date	Interaction
11 July 2008	AstraZeneca submits a pre-sNDA Briefing Document with information related to the product/development plan for an indication for CRESTOR® (rosuvastatin calcium) Tablets for the prevention of cardiovascular events. The document includes a brief outline of the JUPITER clinical program with specific questions included within each section of the briefing document and details of the proposed sNDA. The sNDA will be submitted 1 st quarter 2009 and will be provided electronically in a Common Technical Document (CTD) format. In addition, AstraZeneca requests a formal face-to-face (Type B) meeting with the Division for early to mid-September 2008 to discuss the proposed application. (IND 56,385; Serial No. 0681)
19 August 2008	FDA denies AstraZeneca's request for a Type B Meeting, dated 11 July 2008, to discuss the JUPITER study and references that a second meeting is unnecessary. FDA notes that the forthcoming 27 October 2008 meeting will discuss the same proposed future efficacy supplement and once the FDA reviews the briefing document, written responses to our questions will be provided.
04 September 2008	FDA requests the Statistical Analysis Plan (SAP) for the JUPITER study based on statistical questions included in the JUPITER pre-sNDA Briefing Document submitted on 11 July 2008. AstraZeneca submits to the FDA project manager via email the SAP and notes that the SAP has just been finalized but it has not yet fully published; meaning that, although bookmarks appear, it has not yet been hyper-linked. An official correspondence submitting the SAP to the Division would follow shortly.
18 September 2008	AstraZeneca submits a Statistical Analysis Plan for the JUPITER study. (IND 56,385; Serial No. 0688)
26 September 2008	AstraZeneca communicates to FDA that background materials will be submitted to the Division for the upcoming meeting on Monday, 27 October 2008 between upper level management from AstraZeneca and FDA to discuss the JUPITER study. The background information will also include the AstraZeneca attendees. AstraZeneca requests that the FDA project manager forward the names of the FDA attendees in advance of the meeting. AstraZeneca also asks when FDA responses to the pre-sNDA briefing document are expected.

Date	Interaction
01 October 2008	FDA project manager communicates to AstraZeneca the FDA attendees for the 27 October 2008 meeting, scheduled from 10:30 am to 12:00 noon. The FDA project manager explains that several Medical Officers from the Lipid team have been invited because some of the work may be redistributed and it is currently uncertain who will be assigned to the JUPITER efficacy supplement. AstraZeneca asks whether a pediatric waiver request for this supplement may be submitted in advance of the efficacy supplement. The FDA project manager advises to submit with the sNDA submission and a response will be included in the 74-day filing letter for the sNDA.
01 October 2008	AstraZeneca requests clarification around the patient population for the JUPITER label and guidance from the Division. FDA project manager recommends that AstraZeneca draft a document with specific issues and clear concerns and send it via email. The FDA project manager would follow-up with the Medical Review Team Leader to check if he agrees with an informal teleconference.
06 October 2008	FDA provides responses to questions included in the pre-sNDA Briefing Document, submitted on 11 July 2008, for the JUPITER sNDA submission.
08 October 2008	AstraZeneca seeks guidance from the Agency regarding its approach to a JUPITER labeling issue and appreciates the chance for a brief discussion via teleconference with appropriate Division representatives to help clarify this issue. Although AstraZeneca will be in attendance at a meeting with the FDA on 27 October 2008, AstraZeneca understands that the purpose of that meeting is to inform FDA of the JUPITER results and not to discuss the sNDA filing. Further, AstraZeneca fully understands that the Agency cannot provide detailed comments on any proposed labeling until the sNDA has been reviewed. AstraZeneca does, however, seek general guidance on the appropriate approach to developing the sNDA package and proposed label. AstraZeneca fully appreciates the time constraints of Division personnel and would be happy to meet with them at their convenience, whether it be in the next few weeks or any time following the meeting on the 27 th of October.
09 October 2008	FDA responds to AstraZeneca's request for general guidance on the appropriate approach to developing the sNDA package and proposed label by stating that it is premature for the Division to engage in a discussion about how best to describe the population for whom rosuvastatin is indicated to reduce the risk for MACE. FDA further notes that they will need to at least review the data superficially and give some thought to AstraZeneca's comment about how the totality of the statin data might apply to rosuvastatin.

Date	Interaction
14 October 2008	FDA provides responses to statistical questions included in the pre-sNDA Briefing Document, submitted on 11 July 2008, for the JUPITER sNDA submission.
20 October 2008	FDA confirms the time and location of the face-to-face meeting on Monday, 27 October 2008 to discuss the JUPITER study results and AstraZeneca confirms the list of AstraZeneca attendees.
26 October 2008	AstraZeneca confirms additional AstraZeneca attendees for the meeting on Monday, 27 October 2008.
29 October 2008	FDA project manager communicates with AstraZeneca and asks whether any issues needed to be addressed with respect to chemistry in the upcoming JUPITER sNDA submission (expected 2Q09), specifically with the Environmental Assessment (EA). Following the meeting on Monday, 27 October 2008, there was some thought by FDA that the CRESTOR population might be broadened, which could trigger greatly increased drug use. If this happens, the FDA project manager wanted to ensure that CRESTOR was covered by the current EA or that AstraZeneca provides a Categorical Exclusion (CE). The FDA project manager wanted to make sure AstraZeneca was prepared to address this so that AstraZeneca would not encounter difficulties once the application was submitted. AstraZeneca explained that the original EA had been over-estimated, that CRESTOR distribution had not nearly reached the numbers used in that estimate, and that AstraZeneca should be eligible to submit a CE. AstraZeneca would check with the appropriate AstraZeneca contacts and confirm to FDA that this was correct.
07 November 2008	AstraZeneca provides FDA via email the final JUPITER study results press release, dated 9 November 2008, as agreed at the 27 October 2008 meeting with the Agency. The FDA was reminded that this information is under embargo until 9 November 2008 at 8 AM CT.

Date	Interaction
13 January 2009	AstraZeneca communicates to the FDA project manager that a supplemental New Drug Application for the JUPITER study will be filed in early April 2009. AstraZeneca also asks if there was any information on whether there might be an Advisory Committee Meeting regarding the JUPITER application. The FDA project manager states that the question is asked at the internal FDA filing meeting following an efficacy submission and, at the very least, that information would be included in the 74-day filing letter. The FDA project manager contacted the FDA Medical Review Team Leader regarding any thoughts on an Advisory Committee Meeting for the JUPITER indication and there were “no plans at this point” to request a meeting. The FDA project manager reminds AstraZeneca that this could change at any point but re-iterated that there were currently no plans for an Advisory Committee Meeting.
26 January 2009	The FDA project manager requests the date when the final JUPITER protocol was submitted. AstraZeneca responds that the last amendment (#5) was submitted to the FDA on 5 October 2005 (Serial No. 0533). This amendment included a full protocol. An administrative change document (dealing with over recruitment and other administrative items) was submitted on 9 May 2007 (Serial No. 0606). However, a protocol was not included with this submission as these were considered minor changes not affecting conduct of the trial.
04 February 2009	FDA requests a description of the criteria used to diagnose the 1 case of rhabdomyolysis in the JUPITER trial.
05 February 2009	AstraZeneca responds that the criteria used to diagnose the 1 case of rhabdomyolysis in the JUPITER trial was the AHA/ACC/NHLBI definition of rhabdomyolysis. In addition, hospital notes provided by the treating physician were also provided. (http://www.nhlbi.nih.gov/guidelines/cholesterol/statins.pdf)
25 February 2009	AstraZeneca requests a full waiver of the requirement to conduct CRESTOR® studies in pediatric patients to support a proposed indication for the prevention of cardiovascular events in adults with an increased risk of cardiovascular disease. A justification for requesting this waiver is provided in the request. (IND 56,385, Serial No. 0704)

1.2 Relevant FDA Interactions
Drug Substance: Rosuvastatin calcium
Date: 1 April 2009

Date	Interaction
16 March 2009	FDA project manager communicates to AstraZeneca that the Request for a Full Pediatric Waiver submitted by AstraZeneca on 25 February 2009 would not be reviewed until the JUPITER sNDA submission was submitted. The FDA project manager explains that there is a 3-step process for PREA. First, the Request goes thru PREA when FDA receives the actual efficacy supplement. Then, closer the end of the review cycle of the JUPITER sNDA submission, the request is either granted or denied and the Sponsor is notified. The FDA project manager suggests that AstraZeneca includes the cover letter from the Pediatric Waiver Request with the JUPITER sNDA under Module 1.



1.4.4 Cross reference to other applications

Drug Substance: Rosuvastatin calcium

Date: 23 March 2009

1.4.4 Cross reference to other applications

CRESTOR[®] (rosuvastatin calcium) for the Prevention of Cardiovascular Events in Adults

This submission / 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

	PAGE
TITLE PAGE	1
TABLE OF CONTENTS	2
1. CROSS REFERENCE TO OTHER APPLICATIONS	3

LIST OF TABLES

Table 1	Cross reference to other applications.....	4
---------	--	---

1.4.4 Cross reference to other applications
Drug Substance: Rosuvastatin calcium
Date: 23 March 2009

1. CROSS REFERENCE TO OTHER APPLICATIONS

AstraZeneca Pharmaceuticals LP (AstraZeneca) holds an IND and NDA for the formulation of CRESTOR[®] (rosuvastatin calcium) tablets shown in Table 1.

1.4.4 Cross reference to other applications
 Drug Substance: Rosuvastatin calcium
 Date: 23 March 2009

Table 1 Cross reference to other applications

Application No.	Established Name (Proper name, USP/USAN name)	Proprietary Name (Trade name)	Strength/Dosage Form	Route	Indication	Submission Date	Approval Date
IND 56,385	rosuvastatin calcium	CRESTOR®	5, 10, 20, 40 mg / Tablets	Oral Administration	Hypercholesterolemia (heterozygous familial and nonfamilial) and Mixed Dyslipedemia (Fredrickson Type IIa and IIb)	July 10, 1998	Not applicable
NDA 21-366	rosuvastatin calcium	CRESTOR®	5, 10, 20, 40 mg / Tablets	Oral Administration	Hypercholesterolemia (heterozygous familial and nonfamilial) and Mixed Dyslipedemia (Fredrickson Type IIa and IIb)	June 26, 2001	August 12, 2003
NDA 21-366 / S-010	rosuvastatin calcium	CRESTOR®	5, 10, 20, 40 mg / Tablets	Oral Administration	Slow the Progression of Atherosclerosis	January 5, 2007	November 8, 2007

1.4.4 Cross reference to other applications
 Drug Substance: Rosuvastatin calcium
 Date: 23 March 2009

Table 1 Cross reference to other applications

Application No.	Established Name (Proper name, USP/USAN name)	Proprietary Name (Trade name)	Strength/Dosage Form	Route	Indication	Submission Date	Approval Date
NDA 21-366 / S-013	rosuvastatin calcium	CRESTOR®	5, 10, 20, 40 mg / Tablets	Oral Administration	Primary Dysbetalipoproteinemia (Fredrickson Type III Hyperlipoproteinemia)	January 10, 2008	November 6, 2008

(b) (4)



Date: 20 February 2009

Food and Drug Administration
C/O Wachovia Bank
Lockbox 70963
1525 West WT Harris Boulevard, Room NC 0810
Charlotte, NC 28262

RE: NDA 21-366
CRESTOR[®] (rosuvastatin calcium) Tablets
Prescription Drug User Fee Payment: User Fee I.D. No. PD3009113

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 \$623,600.00 and represents the total sNDA application fee for fiscal year 2009. 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 Omaira Meléndez Nesbit, PharmD, Associate Director, Regulatory Affairs, at (302) 886-2762.

Sincerely,

A handwritten signature in black ink, appearing to read "Paula R. Clark".

Paula R. Clark
Regulatory Affairs Director
Telephone: (302) 885-1492
Fax: (302) 886-2822

OMN

Enclosure

Form FDA 3397 – User Fee Cover Sheet
User Fee Check No. 1500215824

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.		
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 Paula Clark 1800 CONCORD PIKE PO BOX 8355 WILMINGTON DE 198038355 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-366
2. TELEPHONE NUMBER		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> 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: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME CRESTOR Tablets (rosuvastatin calcium)		6. USER FEE I.D. NUMBER PD3009113
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.		
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)		
<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A		
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 738(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act		<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes 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 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 DIRECTOR, REG. AFFAIRS	DATE Feb. 19, 2009
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$623,600.00		
Form FDA 3397 (03/07)		

Close Print Cover sheet



January 23, 2009

Mary Parks, M.D., Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Direct Line **Fax Number**
(787) 957-4030 (787) 957-1001

RE: NDA 21-366, Supplement for the Prevention of Cardiovascular Events in
Adults
CRESTOR[®] (rosuvastatin calcium) Tablets
Authorization Letter.

Dear Dr. Parks:

iPR Pharmaceuticals, Inc. hereby authorizes 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) tablets.

For and on behalf of

iPR Pharmaceuticals, Inc.,

A handwritten signature in black ink, appearing to read "Ajayi".

Dapo Ajayi
President and General Manager
Authorized Signatory

iPRPharmaceuticals, Inc.
A Part of AstraZeneca PLC

PO Box 1624 **Tel** 787 876 1400
Canóvanas PR 00729-1624 **Fax** 787 876 0980

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21366

SUPPL-16

IPR
PHARMACEUTICA
LS INC

CRESTOR(ROSUVASTATIN
CALCIUM)10/20/40/80

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

/s/

NIKOO N MANOCHEHRI-KALANTARI
02/24/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,385

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) tablets.

We also refer to your submission dated July 11, 2008, serial No. 0681, requesting information regarding a future efficacy supplement for your clinical trial entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (CRESTOR®) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)."

Additional reference is made to your submission dated September 18, 2008, serial No. 0688, regarding the Statistical Analysis Plan. We have the following statistical review comments.

1. The plan to analyze three secondary variables (CV death, nonfatal MI or stroke; MI and stroke) sequentially to address multiplicity is acceptable but not necessary given that these variables are all components of the primary outcome and thereby the results of these variables are expected to be correlated with the results for the primary outcome. The alpha level applied to these endpoints should be one that accounts for the two looks (approximately 0.047).
2. Please perform an analysis including primary efficacy events collected after March 30, 2008.
3. The proposed sensitivity analyses described in Section 4 of the statistical analysis plan appear to be acceptable for assessing the impact of dropouts on the results;

although these analyses will need to be considered more carefully in the context of the magnitude of the dropout rate.

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**

Linked Applications

Sponsor Name

Drug Name

IND 56385

ASTRAZENECA
PHARMACEUTICALS LP

CRESTOR (ROSUVASTATIN CALCIUM)

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

/s/

ERIC C COLMAN

10/14/2008

Eric Colman for Mary Parks



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,385

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) tablets.

We also refer to your submission dated July 11, 2008, serial No. 0681, requesting information regarding a future efficacy supplement for your clinical trial entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (CRESTOR®) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)."

Additional reference is made to your September 18, 2008, submission to include the Statistical Analysis Plan (SAP). We have completed the review of your July 11, 2008 briefing document and have the following responses to your questions. However, these answers were developed without consideration of the September 18, 2008 SAP. If we have any comments based on review of the SAP, they will be forwarded in a separate document.

Question 1: Does the Agency agree with AstraZeneca's proposal that the JUPITER trial can be used to support an indication for CRESTOR to reduce the risk of developing protocol-specified major cardiovascular events in patients at risk for cardiovascular disease?

Agency's response: The Division agrees that a single pivotal trial is sufficient to support the submission of the sNDA. Approval and wording of an indication will be determined following review of the NDA.

Question 2: Does the Agency agree with AstraZeneca's proposal for handling Type I error in the analyses of the primary endpoint and the named secondary endpoints as outlined below?

Statistical analysis of the primary endpoint will be based on the proportional hazards model using the intention-to-treat (ITT) population. The primary analysis of time to a major cardiovascular event (MCE) will be unadjusted Cox regression, comparing treatments, using the likelihood ratio test. Efficacy analyses will be based on all randomized subjects. Follow-up for subjects continued after an event, and there will be an analysis of each component of the composite MCE to the time of the specific event. Analyses of the primary endpoint and components will be based on adjudicated events. For efficacy analyses, subjects' follow-up time will be the time from randomization to their last contact with assessment of endpoints or date of withdrawal from the study or 30 March 2008, whichever occurs first. The cut-off date for efficacy analyses is 30 March 2008. Cardiovascular events occurring after 30 March 2008 will be reported as serious adverse events.

As discussed in section 2.4, the study stopped early. The alpha that will be reported for the primary analysis will come from the approximate O'Brien-Fleming alpha-spending function that is referenced in the protocol. Nominal p-values will be reported for secondary analyses. The statistical analysis plan introduces and defines secondary endpoints, to be tested in sequence as a control for multiplicity. These would be tested at $\alpha=0.05$, as long as results are statistically significant.

To support the robustness of the primary endpoint, additional analyses will be performed. The sequence of testing after the primary analysis is:

- 1. CV death or nonfatal stroke or nonfatal MI*
- 2. Fatal or nonfatal MI*
- 3. Fatal or nonfatal stroke*

The first composite endpoint comprises 3 of the 5 components of the primary endpoint, and it is based on adjudicated events. The second and third endpoints are based on adjudicated and unadjudicated events.

Agency's response: The Division cannot adequately address this question until the Statistical Analysis Plan for JUPITER has been reviewed.

Question 3: Does the Agency agree with AstraZeneca's proposal for handling withdrawn subjects in the statistical analyses as outlined below?

There are a large number of withdrawn subjects in JUPITER for a variety of reasons (eg unfavourable mass media reports about CRESTOR, trial fatigue, participants refusing transfer from clinics closing due to investigator death, Hurricane Katrina). Due to Health Insurance Portability and Accountability Act (HIPAA) requirements and similar privacy requirements in other countries, follow up represents more of a challenge than with prior statin studies. In the submission documents, there will be a description of baseline characteristics by treatment group of the withdrawn subjects, as well as reasons for withdrawal. As previously mentioned, the

primary statistical analyses will include follow-up information from withdrawn subjects up to the date of withdrawal, and up to the date of the last outcomes ascertainment for all other subjects.

Agency's response:

The Division cannot adequately address this question until the Statistical Analysis Plan for JUPITER has been reviewed.

Question 4: Would the Agency agree to engage in a non-binding, medically-based discussion regarding the impact of JUPITER on the labeling of rosuvastatin?

Pending successful completion of JUPITER, AstraZeneca anticipates proposing changes to the following sections of the CRESTOR prescribing information (PI):

- *Section 1 - INDICATIONS AND USAGE*
- *Section 14 - CLINICAL STUDIES*

Appropriate text will be added to these sections of the CRESTOR label, as well as other sections as applicable, according to the results of the JUPITER study. Because of the size and complexity of the JUPITER study, AstraZeneca wishes to engage the Agency in discussions regarding presentation of the study results and their impact on the potential labelling text for this new CRESTOR indication.

Agency's response: The Division denies the request for a preliminary discussion regarding CRESTOR labeling before the sNDA has been submitted and reviewed. The sponsor is required to submit the full labeling proposal with the sNDA.

Question 5: Does the Agency agree with AstraZeneca's proposal for the submission of electronic subject safety narratives and case report forms as described below?

Electronic narratives (eNarratives) were generated programmatically for JUPITER from the database and include safety-related subject information. They will be contained in the JUPITER clinical study report (CSR) located in Module 5, Section 5.3.5.1 of the Common Technical Document (CTD). Electronic narratives will be provided in the CSR for all subjects who died or had an AE leading to withdrawal from the study. Case Report Forms (CRFs) will be provided for all subjects for whom eNarratives are generated, as identified above.

Additionally, brief summaries of any cases of particular interest may be presented in the text of the CSR as appropriate. These summaries may include data in addition to those found in eNarratives, such as laboratory data from a non-core laboratory.

Agency's response: Electronic narratives and CRFs should also be provided for all subjects who experienced a nonfatal treatment-emergent serious AE or AE of special interest including but not limited to: muscle events (myopathy, elevated CK, myalgia), hepatic, and renal events.

Question 6: Does the FDA agree with this organization and content of the CTD?

The planned application includes efficacy and safety data from 1 pivotal clinical study (JUPITER, Study 4522US/0011). The data will be reported and discussed in a CSR to be included in Module 5, Section 5.3.5.1 of the CTD. The synopsis of the CSR will be located in Module 2, Section 2.7.6 of the CTD.

Because there is only a single pivotal study and no pooling of data is necessary, no independent Integrated Summary of Efficacy (ISE) or Integrated Summary of Safety (ISS) will be provided in Section 5.3.5.3 of the CTD. However, summaries of clinical efficacy and safety derived from results of the JUPITER study will be provided in Section 2.7.3 and Section 2.7.4 of the CTD, respectively.

Summarization and critical discussions of the study design, safety and efficacy results, postmarketing safety review, as well as Risk/Benefit assessment and dosing recommendations, will be provided in a more extensive Clinical Overview document in Module 2, Section 2.5 of the CTD.

The most recent periodic safety update report (PSUR) at the time of completion of the submission will be provided in Module 5 of the CTD.

There are no new CMC or non-clinical data that will be included in this submission. This will be noted in the appropriate sections of the CTD.

Agency's response: Yes, the Division acknowledges that no integrated summary of efficacy or safety, CMC, or non-clinical data will be provided.

Question 7: Does the Agency agree that the contents of the proposed submission are sufficient for filing of a new indication for rosuvastatin?

Agency's response: It appears that the submission outlined will meet the requirements for filing. Approval for an indication will be determined following review of the efficacy supplement.

Question 8: Does the Agency agree with this electronic format described below?

The case report form (CRF) domain will be provided as a single data set and will include raw data; e.g., the concomitant medications data set, the AE data set, and analysis data sets. The analysis data sets will include raw, analysis, and derived variables, and may contain data variables (raw or derived) from a combination of several raw data sets. The analysis data sets will contain all relevant variables necessary for generating analysis reports.

As some laboratory data were collected electronically and have no CRF pages, those data will be provided as individual data sets. Corresponding analysis data sets will also be provided.

Imaged CRFs will be provided for any patients who died or had an AE leading to withdrawal from the study.

Annotated case report forms will be provided. Paper CRFs were designed and used in the study to capture protocol required data in the database used by the clinical research organization (CRO).

Agency's response: In general, your proposal sounds acceptable. You are referred to the document "Study Data Specifications" available at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm> for specific questions regarding dataset submissions for your eCTD.

Imaged case report forms should be provided for any patient who died or discontinued drug treatment due to an AE or who experienced a serious AE or who withdrew consent.

Question 9: Does the Agency agree with plan described below for the provision of safety updates in this submission?

All trials in support of this submission will be completed and no studies will be ongoing at the time of the submission. Therefore, no additional follow-up safety updates (eg, 4-month safety update, pre-approval safety update) in support of this submission will be provided.

Agency's response: The Division will review the data submitted at the time of filing. If during the course of its review, the Division finds that additional clinical information would facilitate the review process, it reserves the right to request such information.

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

Linked Applications

Sponsor Name

Drug Name

IND 56385

ASTRAZENECA
PHARMACEUTICALS LP

CRESTOR (ROSUVASTATIN CALCIUM)

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

/s/

ERIC C COLMAN

10/06/2008

Eric Colman for Mary Parks



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 56,385

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets.

We also refer to your submission dated July 11, 2008, serial No. 0681, requesting a meeting to discuss your trial entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (CRESTOR®) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)". We have considered your request and concluded that a second meeting is unnecessary. We note that the forthcoming October 27, 2008 meeting will discuss the same proposed future efficacy supplement. In addition, once we have reviewed your briefing document, we will provide written responses to your questions.

If you have any questions, please call me at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

IND 56385

ASTRAZENECA
PHARMACEUTICALS LP

CRESTOR (ROSUVASTATIN CALCIUM)

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

/s/

MARGARET A SIMONEAU
08/19/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

2002/542

Crestor

IND 56,385

IND 56,385

AstraZeneca Pharmaceuticals LP
Attention: Mark S. Eliason, M.Sc.
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, Delaware 19850-8355

RECEIVED

NOV 25 2002

DRUG AFFAIRS

Dear Mr. Eliason:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets.

We also refer to your October 4, 2002, request, serial number 348, for a special clinical protocol assessment, received October 7, 2002. The protocol is entitled "A Randomized, Double-blind, Placebo-Controlled, Multicenter, Phase 3b Study of Rosuvastatin 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL-C and Elevated Levels of C-reactive protein (JUPITER).

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions:

2.1) Choice of Population

2.1.1) Does the Agency agree that this is an appropriate population to study in this trial for the proposed indication?

Division Response:

It is the Agency's position that subjects in this study be patients who would not currently be recommended to receive statin therapy, since it is unethical to withhold therapy from such patients in a placebo-controlled trial of 3 to 4 years duration. Therefore, patients should not have CHD or CHD risk equivalents, such as diabetes or multiple risk factors that confer a 10-year risk of CHD >20% as defined in the current NCEP guidelines. Similarly patients should not have triglycerides ≥ 500 mg/dL as such patients should be treated as per the NCEP guidelines.

You need to redefine escape criteria for patients who during the course of the trial develop elevations in LDL-cholesterol ($\geq 130\text{mg/dL}$) or in triglycerides ($\geq 500\text{mg/dL}$), so that these patients may be placed on appropriate therapy.

2.2) Choice of Endpoints

2.2.1) Does the Agency agree that the proposed primary endpoint would support the target indication as noted below?

Division Response:

It is the Agency's policy not to agree to proposed labeling before the review of the study data is completed.

The primary endpoint (e.g., first occurrence of a major cardiovascular event after randomization) will need to be statistically significant and sufficiently robust to merit a labeling claim.

Assuming the results for the primary efficacy assessment favor drug treatment, the individual components (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization procedures) would need to be evaluated as secondary or tertiary endpoints to determine their contribution to the overall efficacy findings.

2.2.2) Does the Agency agree that [REDACTED] (b) (4)

[REDACTED] (b) (4)

Division Response:

It is the Agency's policy not to agree to proposed labeling before the review of the study data is completed.

It is not clear from a mechanistic point of view how [REDACTED] (b) (4) [REDACTED] (b) (4) The study you are proposing is designed to evaluate the cardiovascular benefits of treating cholesterol in a specific patient population. Any data from such a trial which may suggest [REDACTED] (b) (4) [REDACTED] would be considered hypothesis-generating and require further validation in appropriately designed studies.

2.2.3) Does the Agency agree that the proposed procedures for classifying events, as described in Section 2.5 are adequate?

See response to section 2.5.

2.3) Single Trial

2.3.1) Does the Agency agree that a successful single trial, powered as described above, could support the target indication, provided that the primary endpoint is met?

Division Response:

A single trial, if it is statistically significant and shows a sufficiently robust response, would be acceptable.

Comments related to the target indication were already discussed in the response to question 2.2.1.

2.4) Duration of Trial

2.4.1) Does the Agency agree that a trial of this planned duration will support the indication?

Division Response:

It is not the position of the Agency to predict the trial duration that is required to get statistically significant results.

The Agency will review the trial results independent of the trial duration.

2.5) Request for waiver from reporting endpoint serious adverse drug events (SAEs) as expedited reports.

2.5.1) Does the Agency agree with AstraZeneca's proposals for handling SAEs that are also endpoints proposed in the trial?

Division Response:

All primary endpoints need not be reported on an ongoing basis.

Other SAEs such as rhabdomyolysis and renal failure, for example, should be reported on an ongoing basis.

In addition, we have the following comments:

1. According to Section 4.4.2.4 of the protocol, the IDMB will review unblinded SAE's and clinical endpoints every six months and give a report to the Steering Committee. This 6-monthly report should not be shared with the Steering Committee for reasons clearly delineated in a draft FDA guidance on IDMB's (See Section 4.2.2 of the Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees at <http://www.fda.gov/cber/gdlns/clindatmon.htm>). Blinded data should only be shared with the steering committee when a decision to terminate the trial is recommended or when the trial is complete (see Data Monitoring Committees in Clinical Trials by Ellenberg, Fleming and DeMets).

2. In addition to a stopping rule for superiority of Crestor over placebo, you should also consider setting a stopping rule for futility. That is, if the data shows the null hypothesis could not be rejected with continued follow-up, the trial could be stopped early for lack of a treatment effect.
3. While this study may identify a population of subjects with high CRP levels who would benefit from therapy with rosuvastatin, this does not identify CRP as a validated surrogate for risk of cardiovascular disease and specific target of therapy. Several clinical studies have shown that a variety of statins are capable of lowering CRP levels but the clinical benefits of lowering CRP have not been established. It is unlikely that the results of JUPITER will support labeling for CRP as a goal of statin therapy.
4. It is recommended that subjects have urinalysis measurements included in the initial screening and at each of the follow up visits.
5. It is recommended that escape criteria are defined for subjects who develop hyperlipidemia, LDL \geq 130 mg/dL (depending on 10 year CHD risk as per NCEP guidelines) or triglycerides \geq 500mg/dL, during the course of the trial.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our draft "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
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/

David Orloff
11/20/02 11:04:40 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 21366 BLA #	NDA Supplement # 016 BLA STN #	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: Crestor Established/Proper Name: rosuvastatin calcium Dosage Form: tablets		Applicant: AstraZeneca Pharmaceuticals LP, Agent for IPR Agent for Applicant (if applicable):
RPM: M. Simoneau		Division: DMEP
<p>NDA's: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 8, 2010</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes, date
<p>❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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 notice of certification?

Yes No

(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)?

Yes No

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 the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(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.

- (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)?

Yes No

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).

<p>(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?</p> <p>(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 within the 45-day period).</p> <p><i>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).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) February 8, 2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	January 29, 2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	April 7, 2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	6.17.2009
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>January 6 and February 3, 2010</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> 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 (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	included
❖ Internal memoranda, telecons, etc.	

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 12/4/09

❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	Not applicable NA
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	sNDA meeting (advice ltr)
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	December 15, 2009
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Eric Colman, M.D. (Deputy Division Director)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Amy Egan, MD
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	Mary Roberts, MD
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	In MO review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested included

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None David Hoberman
Clinical Pharmacology <input checked="" type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None
Nonclinical <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None Janice Brown
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	January 8 and 19, 2010
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

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 ADRA.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21366

SUPPL-16

IPR
PHARMACEUTICA
LS INC

CRESTOR(ROSUVASTATIN
CALCIUM)10/20/40/80

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

/s/

MARGARET A SIMONEAU
02/16/2010