CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 91226/S001

Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Sponsor: Mylan Pharmaceuticals Inc.

Approval Date: April 5, 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91226/S001

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	**X**
Labeling	
Labeling Review(s)	
Medical Review(s)	
Chemistry Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	**X**
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91226/S001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091226/S-001

Mylan Pharmaceuticals Inc.
Attn: Joseph J. Sobecki
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26505-4310

Dear Sir:

This is in reference to your supplemental new drug application dated June 15, 2012 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendments dated January 25, 2013 and March 1, 2013. The supplemental application, submitted as "Prior Approval Supplement", provides for:

-Change of the drug substance from (b) (4) to a crystalline form (trihydrate)

We have completed the review of this supplemental application and it is approved. We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Selfidentification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to selfidentify or pay facility fees are subject to being denied entry into the United States.

The material submitted is being retained in our files.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director Division of Chemistry III
Office of Generic Drugs
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/

VILAYAT A SAYEED
04/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91226/S001

OTHER ACTION LETTERS

Food and Drug Administration Silver Spring MD 20993

ANDA 091226/S-001

COMPLETE RESPONSE

Mylan Pharmaceuticals Inc.
Attention: Joseph Sobecki
Vice President, Regulatory Affairs
781 Chestnut Ridge Road, P.O. Box No. 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your supplemental new drug application dated June 15, 2012, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base).

Reference also made to your amendments dated November 27, 2012 and January 25, 2013.

The supplement, submitted as "Prior Approval Supplement," provides for a change in the Atorvastatin Calcium drug substance from (b) (4) form of drug substance (Atorvastatin Calcium USP) as approved in the ANDA, to a relatively more stable crystalline form (trihydrate), and consequential changes to the CMC controls.

We have completed the review of your sANDA and have determined that we cannot approve this sANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Please refer to the Quality deficiencies faxed by this agency on February 11, 2013.

BIOEQUIVALENCE

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified:

During an inspection conducted by the Office of Scientific Investigation (OSI) in (b) (4) for another application, at the analytical site, Mylan Laboratories Limited, Hyderabad, India, (formerly known as Matrix Laboratories Ltd.), the same site where your *in vivo* bioequivalence

(BE) study #24902/11-12 was conducted. The DBI is concerned that the following OSI finding may potentially impact the integrity of your study results.

(b) (4)

Please address the OSI finding above with respect to its impact on the BE study #24902/11-12 of your current application.

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a Minor AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION- *MINOR AMENDMENT*** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw this sANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit this sANDA. A resubmission response must fully address all the deficiencies listed. A partial reply will not be considered for review.

The material submitted is being retained in our files.

If you have any questions, call Robert Gaines, Regulatory Project Manager, at (240) 276-8495.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
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/

PAUL SCHWARTZ
02/22/2013
Signed for G. Geba

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91226/S001

CHEMISTRY REVIEWS

OFFICE OF GENERIC DRUGS

REVIEW OF SUPPLEMENT TO ABBREVIATED NEW DRUG APPLICATION

1. CHEMIST'S REVIEW NUMBER
Review #1

2. ANDA NUMBER
ANDA 91226/S-001

3. NAME AND ADDRESS OF APPLICANT
MYLAN PHARMACEUTICALS INC.
Attn: Joseph J Sobecki
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26505-4310

4. PURPOSE OF AMENDMENT/SUPPLEMENT
To provide for a change in the drug substance from (b) (4) to a crystalline form (trihydrate)

5. DATE(S) OF SUBMISSION(S)
6/15/2012 Original PAS Submission
1/25/2013 Gratuitous Amendment
3/1/2013 Tele Amendment

6. PHARMACOLOGICAL CATEGORY
Indicated in the prevention of cardiovascular disease and hypercholesterolemia

7. NAME OF DRUG
Atorvastatin Calcium Tablets

8. NONPROPRIETARY NAME
Atorvastatin Calcium Tablets

9. DOSAGE FORM
Tablets

10. POTENCY
10 mg, 20 mg, 40 mg and 80 mg

11. HOW DISPENSED
Oral

12. RELATED IND/NDA/DMF(s)
DMF 21477 for crystalline form of Atorvastatin Calcium

13. STERILIZATION
NA

14. LABELING
Per the labeling reviewer, per 21 CFR 314.70(d)(2)(ix), "a change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied…" is annual reportable.

15. ESTABLISHMENT INSPECTION
EES is not required as the firm provided cGMP certification.

16. BIOEQUIVALENCY STATUS
Pending review

17. COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
See review notes.

18. Packaging
N/A

19. STABILITY
See review notes.

20. REMARKS AND CONCLUSIONS
CMC Approvable

21. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt?

■ Yes or X☐ No. If no, explain reason(s) below:

The review is expedited per DARRTS document dated 12/3/2012.

Special Product Online Tracking (SPOT)?

☐ Yes or ■ No. If yes, complete a SPOT form.

22. REVIEWER AND DATE COMPLETED
3/13/2013

23. DMF CHECK LIST

DMF No.	DMF	Action Code	Result of Review	Date Review Completed
21477	II/ Mylan Pharmaceuticals Inc	1	Adequate with IR	March 12, 2013
	Comment			
	Comment			
	Comment			
	Comment			
	Comment			
	Comment			

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: (2) Type 1 DMF; (3) Reviewed previously and no relevant revision since last review; (4) Sufficient information in application; (5) Authority to reference not granted; (6) DMF not available; (7) Other (explain under "Comments").

Haitao Li		3/13/13
Reviewer	Signature	Date

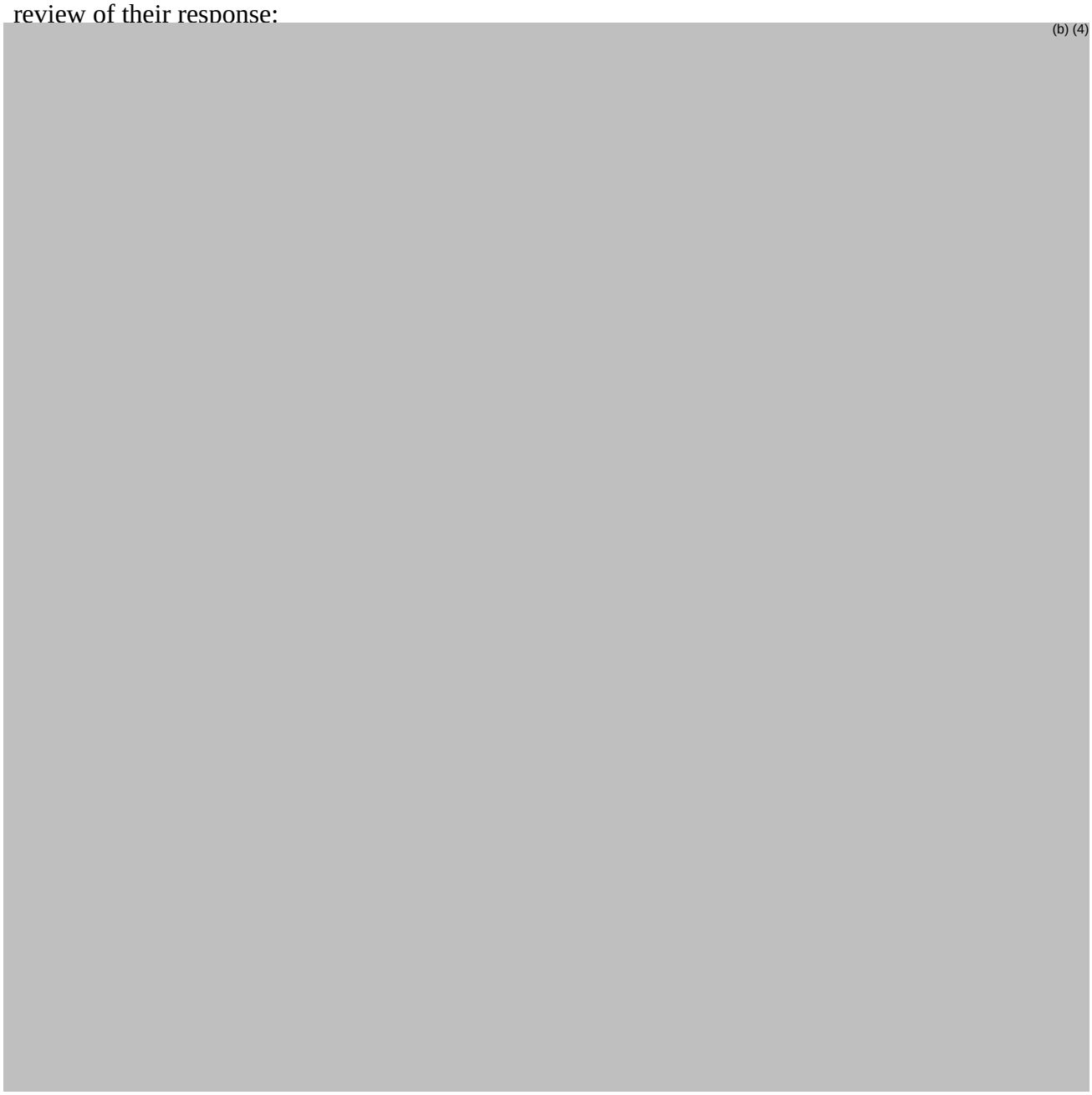
Review Notes

Applicant has submitted original supplement dated June 15, 2012 and a gratuitous amendment dated Jan 25, 2013. The contents of the gratuitous amendment are incorporated throughout the review at appropriate sections as they fit. The applicant has submitted a Tele Amendment dated 3/1/2013 in response to a Tele deficiency date 2/11/2013. These are reviewed in the order from the latest.

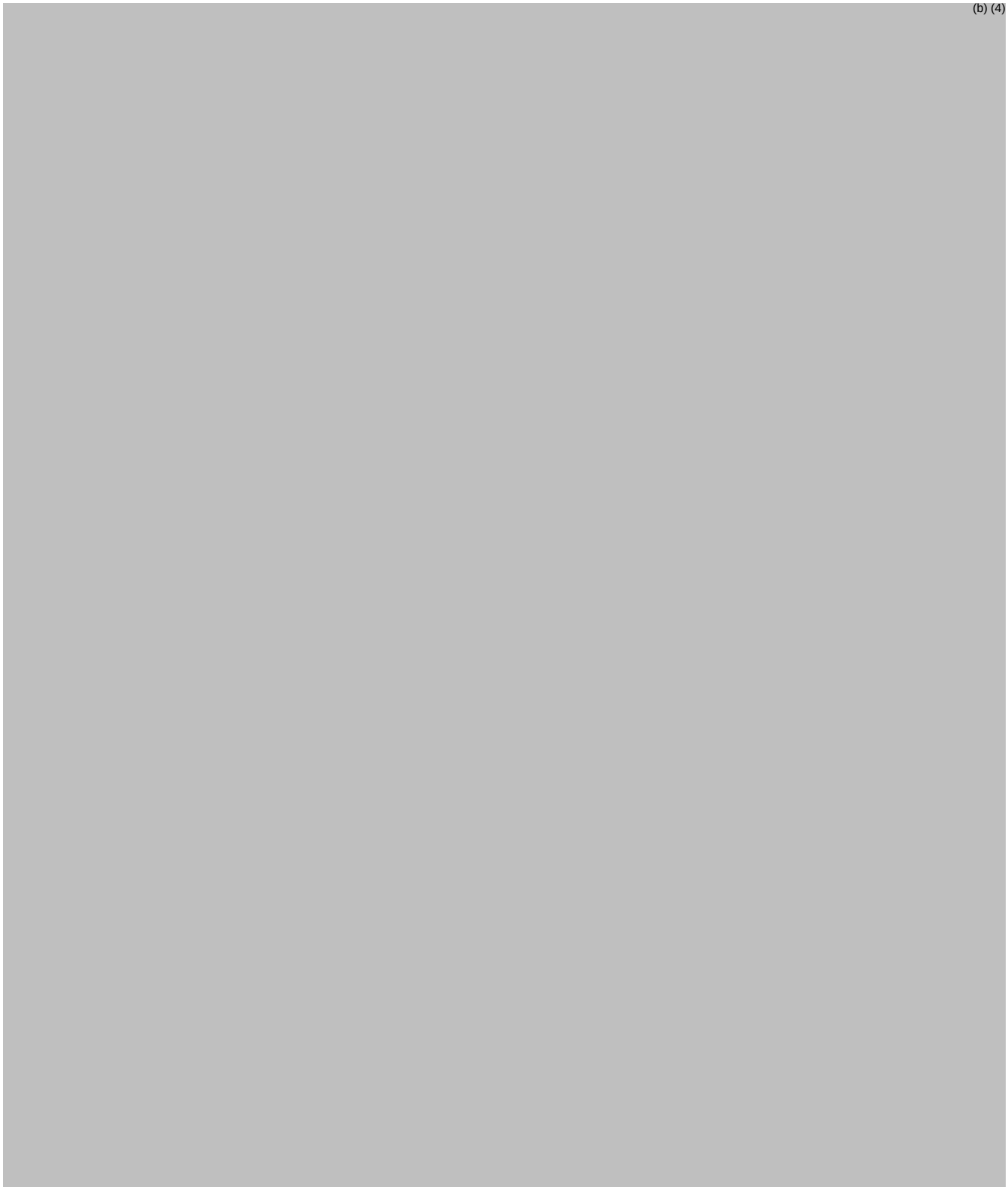
Review of Tele Amendment dated 3/1/2013:

The firm was cited telephone deficiencies from the review of original supplement; here is the review of their response:

(b) (4)



Following this page, 35 Pages Withheld in Full as (b)(4)



Reviewer's comment:
The information provided in this section is acceptable.

ANDA 091226/S001

MYLAN PHARMACEUTICALS INC.
Attn: Joseph J Sobecki
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26505-4310

Dear Sir:

This is in reference to your supplemental new drug application dated June 15, 2012 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendments dated January 25, 2013 and March 1, 2013.

The supplemental application, submitted as "Prior Approval Supplement", provides for:

-Change of the drug substance from (b) (4) to a crystalline form (trihydrate).

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

The material submitted is being retained in our files.

Sincerely yours,

{See appended electronic signature}
Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:
HFD-630/H.Li/3/20/2013
HFD-630/LNagavelli/3/21/2013
HFD-617/LASears/3/22/13

V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\PAS\91226_S001R1.doc

Type of Letter: Approvable

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/s/

HAITAO LI
04/04/2013

LEIGH A SEARS
04/04/2013

LAXMA R NAGAVELLI
04/04/2013

VILAYAT A SAYEED
04/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91226/S001

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091226/S001		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	EQ 10 mg, 20 mg, 40 mg and 80 mg base		
Applicant Name	Mylan Pharmaceuticals Inc.*		
Applicant Address	781 Chestnut Ridge Road, P.O.Box 4310 Morgantown, WV 26505		
US Agent Name and the mailing address	Joseph J. Sobecki, Vice President, Regulatory Affairs		
US agent's Telephone Number	304-599-2595 (extension 6429)		
US Agent's Fax Number	304-285-6407		
Original Supplement Submission Date(s)	06/18/2012 (proposal of changing API)		
Submission Date(s) of Supplement Amendment(s) Under Review	03/01/2013 (response to deficiency letter)		
First Generic (Yes or No)	No		
Reviewer	Qing Liu, PhD		
Study Number (s)	24902/11-12		
Study Type (s)	Fasting		
Strength (s)	EQ 80 mg base		
Clinical Site	Vimta Labs Ltd.		
Clinical Site Address	142, IDA, Phase II, Cherlapally, Hyderabad – 500 051, India		
Analytical Site	Mylan Laboratories Limited Clinical Research Centre		
Analytical Site Address	Saradhi Chambers, Plot No. 4-A Beside Poulomi Hospital, Rukminipuri, Dr. A.S. Rao Nagar Hyderabad 500062, India		
OSI Status	**ADEQUATE**		
OVERALL REVIEW RESULT	**ADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**YES/NO**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
402	Fasting	EQ 80 mg base	Adequate
402	Dissolution	EQ 20, 40, 80 mg base	Adequate

* Note: the current ANDA was originally submitted by Matrix Laboratories Limited India. Matrix was purchased by Mylan in May 2011.

1 EXECUTIVE SUMMARY

This is a post-approval supplement amendment review.

The original submission on 12/30/2008 contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, Atorvastatin Calcium Tablets, EQ 80 mg base, to the corresponding reference product, Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, EQ 80 mg base. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The firm's submission was found acceptable by Division of Bioequivalence I (DBI) (DARRTS: REV-BIOEQ-01(General Review) dated 09/02/2010 and 02/17/2011). The ANDA was approved by the Office of Generic Drugs on 05/29/2012.

In supplement 001 submitted on 06/18/2012, the firm proposed a change in the Atorvastatin Calcium drug substance from (b) (4) form (Atorvastatin Calcium USP) as approved previously to a relatively more stable crystalline form (trihydrate). Other than the active pharmaceutical ingredient (API), there is no additional change in the formulation. To support the proposal, the firm submitted a fasting BE study comparing the **changed** test product Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg. The fasting study was designed as a single-dose, two-way crossover study in healthy male subjects. The fasting study was found inadequate due to (b) (4) finding on the analytical site by the Office of Scientific Investigations (OSI) (DARRTS: REV-BIOEQ-01(General Review) dated 12/14/2012).

In the current amendment to the supplement submitted on 03/01/2013, the firm provides satisfactory response to the OSI finding.

The firm has conducted acceptable comparative dissolution testing between the pre-change and post-change test products of all strengths using the FDA-recommended dissolution method. The firm also used the dissolution specification of "NLT 80% (Q) in 15 minutes" as recommended by DBI previously.

The application is **adequate**.

2 TABLE OF CONTENTS

3 SUBMISSION CONTENT

3.1 Bioequivalence Deficiency Comment

During an inspection conducted by the Office of Scientific Investigation (OSI) in (b) (4) (b) (4) for another application, at the analytical site, Mylan Laboratories Limited, Hyderabad, India, (formerly known as Matrix Laboratories Ltd.), the same site where your *in vivo* bioequivalence (BE) study #24902/11-12 was conducted. The DBI is concerned that the following OSI finding may potentially impact the integrity of your study results.

(b) (4)

Please address the OSI finding above with respect to its impact on the BE study #24902/11-12 of your current application.

3.2 Firm's Response

Please note that the bioequivalence study #24902/11-12 referred to in the Agency's comment was conducted (May 22, 2012 - June 1, 2012) (b) (4) following the OSI findings (in (b) (4)) were submitted to the Agency and subsequently implemented at Mylan. We confirm that the data generated for study #24902/11-12 has complied with the criteria defined (b) (4) submitted to USFDA on the observations raised in (b) (4) DBI inspection. Additionally, Mylan has conducted a review of the data pertaining to study #24902/11-12 and confirms that there are no chromatograms with interfering peaks that would potentially impact the quantification of the analytes in the study.

3.3 Reviewer's Comment

By reviewing the 20% chromatograms submitted by the firm for fasting study #24902/11-12, the reviewer confirmed that there were no interfering peaks for the internal standard, Atorvastatin D5.

The firm's response is acceptable. The OSI finding (b) (4) not to have any impact on the study of the current ANDA.

3.4 Deficiency Comments

None

3.5 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (24902/11-12) conducted by Mylan Pharmaceuticals Inc. on its Atorvastatin Calcium Tablets, 80 mg, lot #1101983, with crystalline form API, comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, lot #V112208.

2. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals Inc. on its test product, Atorvastatin Calcium Tablets, 10 mg (lot #1101979), 20 mg (lot #1101980), 40 mg (lot #1101982) and 80 mg (lot #1101983), using crystalline form (trihydrate) of active pharmaceutical ingredient (API), is adequate.

3.6 Comments for Other OGD Disciplines

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091226/S001

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg base

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

We acknowledge that you will continue to conduct dissolution testing for your test product, Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg, and 80 mg base, using the following FDA-recommended dissolution method and specification:

Medium: 0.05 M Phosphate Buffer, pH 6.8
Volume: 900 mL
Temperature: 37°C ± 0.5°C
USP Apparatus: II (Paddle)
Rotational Speed: 75 rpm

The test product should meet the following specification:

NLT 80% (Q) of labeled amount of Atorvastatin in the dosage form is dissolved in **15 minutes**

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

3.7 Outcome Page

ANDA: 091226

Enter Review Productivity and Generate Report

Completed Assignment for 091226 ID: 19267

Reviewer: Liu, Qing **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Amendment: Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg base

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
19267	3/1/2013	Other (REGULAR)	OSI Inspection Review Report	1	1
				Total:	1

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/s/

QING LIU
03/13/2013

BING V LI
03/13/2013

HOAINHON N CARAMENICO
03/14/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/14/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091226/S001		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	EQ 10 mg, 20 mg, 40 mg and 80 mg base		
Applicant Name	Mylan Pharmaceuticals Inc.*		
Applicant Address	781 Chestnut Ridge Road, P.O.Box 4310 Morgantown, WV 26505		
US Agent Name and the mailing address	S. Wayne Talton, Vice President, Regulatory Affairs		
US agent's Telephone Number	304-599-2595		
US Agent's Fax Number	304-285-6407		
Original Submission Date(s)	12/30/2008 09/30/2009 (dissolution specification acknowledgement) 11/09/2010 (response to deficiency letter)		
Submission Date(s) of Supplement(s) Under Review	06/18/2012		
First Generic (Yes or No)	No		
Reviewer	Qing Liu, PhD		
Study Number (s)	24902/11-12		
Study Type (s)	Fasting		
Strength (s)	EQ 80 mg base		
Clinical Site	Vimta Labs Ltd.		
Clinical Site Address	142, IDA, Phase II, Cherlapally, Hyderabad – 500 051, India		
Analytical Site	Mylan Laboratories Limited Clinical Research Centre		
Analytical Site Address	Saradhi Chambers, Plot No. 4-A Beside Poulomi Hospital, Rukminipuri, Dr. A.S. Rao Nagar Hyderabad 500062, India		
OSI Status	**INADEQUATE**		
OVERALL REVIEW RESULT	**INADEQUATE (pending the firm's response to OSI findings)**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
402	Fasting	EQ 80 mg base	Inadequate
402	Dissolution	EQ 20, 40, 80 mg base	Adequate

* Note: the current ANDA was originally submitted by Matrix Laboratories Limited India. Matrix was purchased by Mylan in May 2011.

1 EXECUTIVE SUMMARY

This is a post-approval supplement review.

The original submission on 12/30/2008 contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, Atorvastatin Calcium Tablets, EQ 80 mg base, to the corresponding reference product, Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, EQ 80 mg base. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The firm's submission was found acceptable by Division of Bioequivalence I (DBI). (DARRTS: REV-BIOEQ-01(General Review) dated 09/02/2010 and 02/17/2011)

In the current supplement, the firm proposes a change in the Atorvastatin Calcium drug substance from (b) (4) form (Atorvastatin Calcium USP) as approved previously to a relatively more stable crystalline form (trihydrate). Other than the active pharmaceutical ingredient (API), there is no additional change in the formulation. To support the proposal, the firm submitted a fasting BE study comparing the **changed** test product Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg. The fasting study was designed as a single-dose, two-way crossover study in healthy male subjects. The fasting study is acceptable. The results are listed in the following table:

Atorvastatin Calcium Tablets Dose 1 x EQ 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 24902/11-12							
Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	407.50	66	401.18	66	1.02	94.79	108.84
AUC∞ (hr *ng/ml)	412.65	66	406.44	66	1.02	94.85	108.68
Cmax (ng/ml)	106.28	66	99.45	66	1.07	93.61	122.00
O-OH-Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	557.82	66	543.37	66	1.03	96.76	108.92
AUC∞ (hr *ng/ml)	564.33	66	550.47	66	1.03	96.74	108.64
Cmax (ng/ml)	87.38	66	80.9	66	1.08	96.86	120.46
P-OH-Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	76.16	66	70.07	66	0.98	94.75	108.84
AUC∞ (hr *ng/ml)	76.11	66	77.35	66	0.98	95.71	109.28
Cmax (ng/ml)	4.41	66	4.19	66	1.07	92.47	119.53

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolites, O-OH-Atorvastatin and P-OH-Atorvastatin were comparable. Therefore the metabolite data are supportive and the studies are acceptable.

The firm has conducted acceptable comparative dissolution testing between the pre-change and post-change test products of all strengths using the FDA-recommended dissolution method. The firm also used the dissolution specification of NLT 80% (Q) in 15 minutes as recommended by DBI previously.

Division of Scientific Investigations (OSI) inspection on the clinical site was completed (b) (4) The OSI inspection on the analytical site was completed on (b) (4) for ANDA 201790 (Ezetimibe Tablets) and NDA 022282 (Atazanavir Sulfate and Ritonavir Tablets). The outcome is (b) (4) for ANDA 201790 and (b) (4) for NDA 22282. The reviewer for ANDA 201790 found that the OSI findings are (b) (4) (DARRTS, ANDA 201790: (b) (4) (b) (4) The firm will be asked to (b) (4) findings of OSI for analytical site do not have significant impact on the outcome of the BE studies in the current application.

The application is inadequate pending firm's response to OSI findings.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1,2]

Test Product	Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg base
Reference Product	Lipitor® (atorvastatin calcium) Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg base (EQ 80 mg is designated as the RLD strength)
RLD Manufacturer	Pfizer Inc.
NDA No.	020702
RLD Approval Date	04/07/2000 (EQ 80 mg) 12/17/1996 (EQ 10 mg, 20 mg and 40 mg)
Indication	For prevention of cardiovascular disease.

3.2 PK/PD Information[3]

Bioavailability	LIPITOR® is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to LIPITOR® dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Plasma LIPITOR® concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.
Food Effect	Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether LIPITOR® is given with or without food.
Tmax	1 to 2 hrs
Metabolism	LIPITOR® is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of LIPITOR®. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of LIPITOR® metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of LIPITOR® in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.
Excretion	LIPITOR® and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Less than 2% of a dose of

[1] Electronic Orange Book, last assessed 08/27/2012
[2] http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=8a201c80-a51d-4c1c-963b-488c071908c0 (revised 03/20/12)
[3] http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=8a201c80-a51d-4c1c-963b-488c071908c0 (revised 03/20/12)

	LIPITOR® is recovered in urine following oral administration.
Half-life	Mean plasma elimination half-life of LIPITOR® in humans is approximately 14 hours, but the half-life of inhibitory activity for HMGCoA reductase is 20 to 30 hours due to the contribution of active metabolites.
Dosage and Administration	Recommended start dose: 10 mg or 20 mg once daily.
Maximum Daily Dose	80 mg
Drug Specific Issues (if any)	N/A

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ 80 mg base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%). For general information on this approach, please refer to the Individual Product Bioequivalence Recommendations Guidance on Progesterone Capsules.

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	5 EQ 80 mg base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Please see additional comments above.

Analytes to measure (in plasma/serum/blood):	Atorvastatin, and its active metabolites, ortho- and parahydroxylated Atorvastatin in plasma
Bioequivalence based on:	90% CI of Atorvastatin
Waiver request of in-vivo testing:	EQ.10 mg, 20 mg, and 40 mg Base based on (i) acceptable bioequivalence studies on the 80 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
Source of most recent recommendations:	http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082580.pdf (recommended May 2008, revised Oc. 2010)

Summary of OGD or DB History (for details, see Appendix 4.4):	Per electronic Orange Book, the following ANDAs have been approved as generic version of Lipitor®:

ANDA	Firm	Strength
090548	Apotex	EQ 10, 20, 40, 80 mg base
091650	Dr. Reddy	EQ 10, 20, 40, 80 mg base
091226	Mylan	EQ 10, 20, 40, 80 mg base
076477	Ranbaxy	EQ 10, 20, 40, 80 mg base
077575	Sandoz	EQ 10, 20, 40, 80 mg base
078773	Teva	EQ 10, 20, 40, 80 mg base

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	Yes	4
Waiver requests	Yes	3
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data		
Bioanalytical method validation report location: Bioanalytical method validation report, Attachment-5			
Analyte	**Atorvastatin**	**O-OH-Atorvastatin**	**P-OH-Atorvastatin**
Internal standard (IS)	Atorvastatin D5	Atorvastatin D5	Atorvastatin D5
Method description	Liquid-Liquid Extraction followed by LC/MS/MS analysis	Liquid-Liquid Extraction followed by LC/MS/MS analysis	Liquid-Liquid Extraction followed by LC/MS/MS analysis
Limit of quantitation	0.250 ng/mL	0.250 ng/mL	0.050 ng/mL
Average recovery of drug (%)	70.00% (LQC), 65.43% (M2QC) & 70.31% (HQC)	77.61% (LQC), 70.26% (M2QC) & 71.48% (HQC)	75.40% (LQC), 68.62% (M2QC) & 71.90% (HQC)
Average recovery of IS (%)	71.41%	71.41%	71.41%
Standard curve concentrations (units/mL)	0.250, 0.500, 5.010, 15.040, 50.130, 100.250, 150.380, 200.500, 250.630 ng/mL	0.250, 0.500, 2.480, 9.930, 29.780, 59.550, 84.360, 114.140, 148.880 ng/mL	0.050, 0.100, 0.500, 0.990, 1.990, 3.980, 5.960, 7.950, 9.940 ng/mL
QC concentrations (units/mL)	0.250 ng/mL (LLOQQC), 0.740 ng/mL (LQC), 24.560 ng/mL (M1QC), 78.600 ng/mL (M2QC), 176.850 ng/mL (HQC)	0.250 ng/mL (LLOQQC), 0.750 ng/mL (LQC), 19.900 ng/mL (M1QC), 49.750 ng/mL (M2QC), 104.480 ng/mL (HQC)	0.050 ng/mL (LLOQQC), 0.150 ng/mL (LQC), 1.490 ng/mL (M1QC), 3.480 ng/mL (M2QC), 7.160 ng/mL (HQC)
QC Intraday precision range (%)	1.44% to 6.07%	2.06% to 7.08%	1.67% to 7.26%
QC Intraday accuracy range (%)	83.12% to 109.56%	86.40% to 102.87%	96.42% to 107.40%
QC Interday precision range (%)	1.79 % to 7.72%	2.67% to 7.25%	4.25% to 12.72%
QC Interday accuracy range (%)	94.32% to 110.49%	93.20% to 102.71%	96.87% to 103.93%
Bench-top stability (hrs)	5 hrs	5 hrs	5 hrs
Stock stability (days)	Drug & IS - 74 days in dil-1 & 72 dil-2 days at 2-10°C ISTD- 74 days dil-1 & 68 dil-2 days at 2-10°C	Drug - 74 days in dil-1 & 72 dil-2 days at 2-10°C ISTD- 74 days dil-1 & 68 dil-2 days at 2-10°C	Drug - 74 days in dil-1 & 72 dil-2 days at 2-10°C ISTD- 74 days dil-1 & 68 dil-2 days at 2-10°C
Processed stability (hrs)	Auto Sampler about 46 hrs 20 min at 5°C Dry Extract 23 hrs at 2-10°C	Auto Sampler about 46 hrs 20 min at 5°C Dry Extract 23 hrs at 2-10°C	Auto Sampler about 46 hrs 20 min at 5°C Dry Extract 23 hrs at 2-10°C
Freeze-thaw stability (cycles)	4 Cycles	4 Cycles	4 Cycles
Long-term storage stability (days)	73 days@-20±5°C and -70±15°C	73 days@-20±5°C and -70±15°C	73 days@-20±5°C and -70±15°C
Dilution integrity	1/2 dilution – 1.88% (precision) 1/4 dilution – 11.28% (precision)	1/2 dilution – 2.84% (precision) 1/4 dilution – 11.78% (precision)	1/2 dilution – 4.78% (precision) 1/4 dilution – 11.22% (precision)
Selectivity	No interfering peaks were observed at the retention time of Drug and ISTD	No interfering peaks were observed at the retention time of Drug and ISTD	No interfering peaks were observed at the retention time of Drug and ISTD

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	Yes
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	Yes

Comments on the Pre-Study Method Validation:

The study samples contain Atorvastatin, O-OH-Atorvastatin and P-OH-Atorvastatin. The analytical method was validated by simultaneous analysis of these three components. Therefore, no interference study is needed.

The firm used the same method validation report as that in the original BE studies submitted on 12/30/2008.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Atorvastatin:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Parameters +/-SD (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T½ (hr)	Kel (hr-1)	
24902/11-12	To assess the single dose bioequivalence of Atorvastatin Calcium Tablets 80 mg (Mylan Laboratories Limited) and Lipitor® (Atorvastatin calcium) 80 mg Tablets Manufactured by: Pfizer Ireland Pharmaceuticals Dublin, Ireland and Distributed by: Parke-Davis, Division of Pfizer Inc NY, NY 10017 in healthy, adult, human study participants under fasting conditions and to monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Atorvastatin formulations under fasting conditions.	This was an open label, balanced, randomized two-treatment, two-period, two-sequence, two-way crossover bioequivalence study.	**Test** Atorvastatin Calcium Tablets 80 mg 1×80 mg, Oral Batch No.: 1101983	72 healthy male subjects admitted in to the study 66 subjects completed the study Male:66 Female:00 Mean age: 28.8 Years Range: 19 -43	124.516 ± 78.5880 (63.11)	1.25 (0.50-4.00) (66.83)	444.140 ± 193.7430 (43.62)	448.808 ± 194.9048 (43.43)	7.310 ± 2.8343 (38.77)	0.107 ± 0.0337 (31.58)	Tables 14.2.2-1 & 14.2.2-2
			Reference Lipitor® (Atorvastatin calcium) 80 mg Tablets 1×80 mg Tablets, Oral Batch No.:V112208		117.608 ± 79.5687 (67.66)	1.13 (0.50-5.00) (76.17)	447.243 ± 220.9566 (49.40)	451.865 ± 221.6273 (49.05)	7.047± 2.3413 (33.22)	0.108± 0.0320 (29.57)	

Ortho-Hydroxylated (O-OH) Atorvastatin:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Parameters +/-SD (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T½ (hr)	Kel (hr-1)	
24902 /11-12	To assess the single dose bioequivalence of Atorvastatin Calcium Tablets 80 mg (Mylan Laboratories Limited) and Lipitor® (Atorvastatin calcium) 80 mg Tablets Manufactured by: Pfizer Ireland Pharmaceuticals Dublin, Ireland and Distributed by: Parke-Davis, Division of Pfizer Inc NY, NY 10017 in healthy, adult, human study participants under fasting conditions and to monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Atorvastatin formulations under fasting conditions.	This was an open label, balanced, randomized two-treatment, two-period, two-sequence, two-way crossover bioequivalence study.	**Test** Atorvastatin Calcium Tablets 80 mg 1×80 mg, Oral Batch No.: 1101983	72 healthy male subjects admitted in to the study 66 subjects completed the study Male:66 Female:00 Mean age: 28.8 Years Range: 19 -43	100.688 ± 60.6818 (60.27)	1.51 (0.67-6.00) (59.10)	599.528 ± 240.6305 (40.14)	605.146 ± 241.6150 (39.93)	7.595 ± 2.0040 (26.38)	0.097 ± 0.0214 (22.20)	Tables 14.2.2-3 & 14.2.2-4;
			Reference Lipitor® (Atorvastatin calcium) 80 mg Tablets 1×80 mg Tablets, Oral Batch No.:V112208		94.964 ± 58.9767 (62.10)	1.75 (0.50-6.00) (58.39)	591.000 ± 250.4679 (42.38)	596.456 ± 249.9129 (41.90)	7.841 ± 2.1567 (27.50)	0.094 ± 0.0222 (23.55)	

Para-Hydroxylated (P-OH) Atorvastatin

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Parameters +/-SD (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T½ (hr)	Kel (hr-1)	
24902 /11-12	To assess the single dose bioequivalence of Atorvastatin Calcium Tablets 80 mg (Mylan Laboratories Limited) and Lipitor® (Atorvastatin calcium) 80 mg Tablets Manufactured by: Pfizer Ireland Pharmaceuticals Dublin, Ireland and Distributed by: Parke-Davis, Division of Pfizer Inc NY, NY 10017 in healthy, adult, human study participants under fasting conditions and to monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Atorvastatin formulations under fasting conditions.	This was an open label, balanced, randomized two-treatment, two-period, two-sequence, two-way crossover bioequivalence study.	**Test** Atorvastatin Calcium Tablets 80 mg 1×80 mg, Oral Batch No.: 1101983	72 healthy male subjects admitted in to the study 66 subjects completed the study Male:66 Female:00 Mean age: 28.8 Years Range: 19 - 43	5.374 ± 3.6707 (68.30)	4.50 (0.67-10.00) (57.32)	77.671 ± 35.6480 (45.90)	83.980 ± 39.2663 (46.76)	17.791 ± 4.3941 (24.70)	0.041 ± 0.0097 (23.43)	Tables 14.2.2-5 & 14.2.2-6;
			Reference Lipitor® (Atorvastatin calcium) 80 mg Tablets 1×80 mg Tablets, Oral Batch No.:V112208		5.155 ± 3.6386 (70.58)	5.00 (1.00-12.00) (55.80)	78.446 ± 38.9778 (49.69)	84.528 ± 41.1154 (48.64)	18.916 ± 5.7882 (30.60)	0.040 ± 0.0104 (26.20)	

Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).
The data of para hydroxylated (P-OH) atorvastatin was provided as supportive evidence of comparable therapeutic outcome.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Atorvastatin Calcium Tablets Dose 1 x EQ 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 24902/11-12							
Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	407.50	66	401.18	66	1.02	94.79	108.84
AUC∞ (hr *ng/ml)	412.65	66	406.44	66	1.02	94.85	108.68
Cmax (ng/ml)	106.28	66	99.45	66	1.07	93.61	122.00
O-OH-Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	557.82	66	543.37	66	1.03	96.76	108.92
AUC∞ (hr *ng/ml)	564.33	66	550.47	66	1.03	96.74	108.64
Cmax (ng/ml)	87.38	66	80.9	66	1.08	96.86	120.46
P-OH-Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	76.16	66	70.07	66	0.98	94.75	108.84
AUC∞ (hr *ng/ml)	76.11	66	77.35	66	0.98	95.71	109.28
Cmax (ng/ml)	4.41	66	4.19	66	1.07	92.47	119.53

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE?

Yes

Table 3. Reanalysis of Study Samples

ATORVASTATIN

Study No. 24902/11-12 Additional information in Appendix 16.5, Page # 45 of 109 to 55 of 109								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Unacceptable internal standard response	3	2	0.20	0.13	3	2	0.20	0.13
C: Instrument/Equipment malfunction	1	0	0.07	0.00	1	0	0.07	0.00
D: Sample concentration above upper limit of quantitation	11	9	0.73	0.59	11	9	0.73	0.59
Total	15	11	0.99	0.73	15	11	0.99	0.73

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."
Total assays 3029; Test product: 1513; Reference product: 1516

ORTHO HYDROXYLATED (O-OH) ATORVASTATIN

Study No. 24902/11-12 Additional information in Appendix 16.5, Page # 45 of 109 to 55 of 109								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Unacceptable internal standard response	3	2	0.20	0.13	3	2	0.20	0.13
C: instrument/Equipment malfunction	1	0	0.07	0.00	1	0	0.07	0.00
D: Sample concentration above upper limit of quantitation	35	26	2.31	1.72	35	26	2.31	1.72
Total	39	28	2.58	1.85	39	28	2.58	1.85

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."
Total assays: 3029; Test product: 1513; Reference product: 1516

PARA- HYDROXYLATED (P-OH) ATORVASTATIN

Study No. 24902/11-12 Additional information in Appendix 16.5, Page # 45 of 109 to 55 of 109								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Unacceptable internal standard response	3	1	0.20	0.07	3	1	0.20	0.07
C: instrument/Equipment malfunction	1	0	0.07	0.00	1	0	0.07	0.00
D: Sample concentration above upper limit of quantitation	30	28	1.98	1.85	30	28	1.98	1.85
Total	34	29	2.25	1.91	34	29	2.25	1.91

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Total assays: 3029; Test product: 1513; Reference product: 1516

Please provide detailed explanation for all repeats not related to analytical reasons.

1) The firm has provided 'Analyst' printouts for all study runs showing the internal standard (IS) peak areas for individual samples. The reviewer verified that all samples with IS peak areas more than 50% of the mean IS peak area of the calibration standards and quality control samples were correctly identified for repeats as unacceptable internal standard response repeats, per SOP CRCBL024-04 (Sample reanalysis and reporting of final concentration, effective date: 02/20/2012). The concentrations of these samples were also reported per firm's SOP.

2) The reviewer has verified that samples reanalyzed due to 'sample concentration above upper limit of quantitation' have been correctly identified. The concentrations of these samples were also reported per firm's SOP . The repeat values are all within 20% difference from the original values. The repeat values are all above upper limit of quantitation except the samples below for P-OH-Atorvastatin:

ID	Original (ng/mL)	Repeat (ng/mL)	% Difference (original-repeat)/original	Report (ng/mL)
(b) (6) PI, 2.5hrs	10.273	9.496	7.6%	9.496
PI, 4.0hrs	10.479	10	4.6%	10
, PII, 1.25hrs	10.285	9.762	5.1%	9.762

The upper limit of quantitation of P-OH-Atorvastatin is 10.126 ng/mL. Although the repeat values for the three samples above are below upper limit of quantitation, the repeat values are within 10% difference of the original values. Therefore, it is acceptable.

3) There is one sample (subject (b) (6) period II, 0.83 hrs) reanalyzed under code "instrument/equipment malfunction" for Atorvastatin, O-OH-Atorvastatin and P-OH-Atorvastatin. There are no initial values for this sample and the firm did not provide detail for instrument malfunction. By using the concentrations of this sample as missing and the repeat value in the PK analysis of Atorvastatin, O-OH-Atorvastatin and P-OH-Atorvastatin, the geometric mean ratios of Cmax, AUCT and AUCI are all within the acceptable range of 80% - 125%.

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CRCBL024-04	29/02/2012	Sample Reassay and Reporting of Final concentration

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria**: analytical and pharmacokinetic**	Yes
If not, list the criteria that you don't agree and provide additional comment below	N/A
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	
Did reviewer reanalyze study results?	No
Was the study outcome changed based on reviewer reanalysis?	N/A
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DB?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes

Comments from the Reviewer:

Acceptable

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	No
If a tablet, is the test product biostudy/exhibit batch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DB Dissolution Review	DARRTS: REV-BIOEQ-02(Dissolution Review) 06/16/2009
Submitted Method (USP, FDA, or Firm)	FDA
Recommended Method (details below) for the current ANDA	
Medium	0.05 M Phosphate Buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (paddle)
Rotation (rpm)	75 rpm
Specifications	NLT 80% (Q) in 15 minutes
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	Yes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Rapidly dissolving
If no, reason why F2 not calculated	
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

3.9 Deficiency Comments

During an inspection conducted by OSI in (b) (4) for another application, at the analytical Site, Mylan Laboratories Limited, Hyderabad, India, (previously called Matrix Laboratories Ltd.), the same site where the *in vivo* bioequivalence (BE) study #24902/11-12 was conducted, the following issue was observed:

(b) (4)

The firm will be asked to address the OSI finding above with respect to the impact on the BE study #24902/11-12 of the current application.

3.10 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (24902/11-12) conducted by Mylan Pharmaceuticals Inc. on its Atorvastatin Calcium Tablets, 80 mg, lot #1101983, with crystalline form API, comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, lot #V112208, inadequate due to the deficiency above.

2. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals Inc. on its test product, Atorvastatin Calcium Tablets, 10 mg (lot #1101979), 20 mg (lot #1101980), 40 mg (lot #1101982) and 80 mg (lot #1101983), using crystalline form (trihydrate) of active pharmaceutical ingredient (API), is adequate.

3.11 Comments for Other OGD Disciplines

None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	24902/11-12
Study Title	An open-label, randomized, single oral dose, two way crossover bioequivalence study of Atorvastatin Calcium Tablets 80 mg (Mylan Laboratories Limited) and Lipitor® (Atorvastatin calcium) 80 mg Tablets Manufactured by: Pfizer Ireland Pharmaceuticals Dublin, Ireland and Distributed by: Parke-Davis, Division of Pfizer Inc, NY, NY 10017 in 72 healthy, adult, human male and/ or female study participants under fasting conditions.
Study Type	☑In Vivo BE □ In Vitro BE □ Permeability □ Other (Specify)
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	 Location: Section 5.3.1.2 Location: Section 5.3.1.4, Attachment-5 Location: Section 5.3.1.4
Clinical Site **(Name, Address, Phone #, Fax #)**	Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, India. Tel: +91- 27264141 (ext-233) Fax: +91-40-27263657
Principal Clinical Investigator (Name, Email)	Dr. Sudershan Vishwanath, Email: jeevadaya@vimta.com
Dosing Dates	Period I: 08 May 2012 Period II: 18 May 2012
Analytical Site **(Name, Address, Phone #, Fax #)**	Mylan Laboratories Limited Clinical Research Centre, Saradhi Chambers, Plot No. 4-A, Beside Poulomi Hospital, Rukminipuri, Dr.A.S. Rao Nagar, Hyderabad 500062, India Tel# +91-40-30492903 Fax# +91-40-27138562
Analysis Dates	22 May 2012 to 01 June 2012
Principal Analytical Investigator (Name, Email)	Mr. Amarnath Jaiswal, Email: Amarnath.Jaiswal@mylan.in
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	25 days (From 08 May 2012 to 01 June 2012)

Table 6. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium	Lipitor® (Atorvastatin calcium)
Manufacturer	Manufactured By: Mylan Laboratories Limited, F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik-422113, Maharashtra, India.	Manufactured By: Pfizer Ireland Pharmaceuticals Dublin, Ireland Distributed by: Parke-Davis, Division of Pfizer Inc, NY, NY 10017
Batch/Lot No.	Batch No.: 1101983	Batch No.:V112208
Manufacture Date	Apr.2012	N/A
Expiration Date	(b) (4)	Nov.14
Strength	80mg	80mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	98.9 % *w/w*	100.1 % *w/w*
Content Uniformity (mean, %CV)	4.2	N/A
Dose Administered	1 x 80 mg	1 x 80 mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	N/A
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	Yes

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 72 Dosed: 72 (period I) 66 (period II) Completed: 66 Samples Analyzed: 66 Data Analyzed: 66
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	10 days
Randomization Scheme (Sequence of T and R)	TR: 1, 3, 4, 7, 8, 12, 13, 15, 18, 19, 21, 22, 25, 26, 29, 32, 35, 36, 39, 41, 42, 43, 45, 46, 51, 52, 54, 56, 58, 60, 61, 62, 65, 68, 71, 72. RT: 2, 5, 6, 9, 10, 11, 14, 16, 17, 20, 23, 24, 27, 28, 30, 31, 33, 34, 37, 38, 40, 44, 47, 48, 49, 50, 53, 55, 57, 59, 63, 64, 66, 67, 69, 70.
Blood Sampling Times	0, 0.16, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hrs after dose

Blood Volume Collected/Sample	6 mL per sample
Anticoagulant Used	K_3EDTA
Blood Sample Processing & Storage (include storage temperature)	After collection, the blood samples were placed in thermocol box containing ice packs or other cooling device. Once blood samples from all the study participants at each time point were available, they were centrifuged at 3800 rpm for 10 minutes at 10°C ± 2°C for separating the plasma. Centrifugation of all samples was done within 30 minutes after each sample drawn time point. All plasma samples were separated and were divided into two aliquots in properly labeled polypropylene tubes and immediately stored at -20°C or colder until completion of analysis. Plasma sample ready for analysis was sent to the bio-analytical facility (Mylan Laboratories Limited; Hyderabad) under frozen condition.
IRB Approval	04/23/2012
Informed Consent	04/23/2012
Length of Fasting	The subjects were fasted overnight for at least 10 hrs until 4 hrs post dose.
Length of Confinement	The subjects were checked into the clinical from at least 12 hrs prior to dosing and confined until at least 48 hrs after dosing.
Safety Monitoring	The safety assessments included monitoring of adverse events including adverse drug reactions, periodic physical examination, vital signs monitoring at regular predetermined intervals and as determined by Medical Investigator. Pre study 12-lead ECG, Chest X-ray, Urinalysis and Serology were conducted for screening of volunteers.

Was the study design used for the fasting BE study acceptable?	YES

4.1.1.2 Clinical Results

Study No.24902/11-12		
	Treatment Groups	
	Test Product N =66	Reference Product N =66
Age (Years)		
Mean ± SD	29.03 ± 6.054	29.03 ± 6.054
Range	19–43	19–43
Groups		
< 18	0 (0.0%)	0 (0.0%)
18 – 40	65 (98.49%)	65 (98.49%)
41 – 64	1 (1.51%)	1 (1.51%)
65 – 75	0 (0.0%)	0 (0.0%)
> 75	0 (0.0%)	0 (0.0%)
Sex		
Female	0 (0.0%)	0 (0.0%)
Male	66(100%)	66(100%)
Race		
Asian	66 (100%)	66 (100%)
Black	0 (0.0%)	0 (0.0%)
Caucasian	0 (0.0%)	0 (0.0%)
Hispanic	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)
BMI		
Mean ± SD	23..07 ± 1.619	23..07 ± 1.619
Range	20 – 25	20 – 25
Other Factors	Nil	Nil

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 24902/11-12				
Subject No.	**Reason for Dropout/Replacement**	**Period**	**Replaced**	**Replaced with**
(b) (6)	Participant had not presented himself for study participation on period II admission day due to his personal reasons.	II	No	Nil
	Participant had not presented himself for study participation on period II admission day due to his personal reasons.	II	No	Nil
	Participant had not presented himself for study participation on period II admission day due to his personal reasons.	II	No	Nil
	Participant had not presented himself for study participation on period II admission day due to his personal reasons.	II	No	Nil
	Participant withdrawn from the study due to detection of positive in urine tested for recent abuse of drugs prior to period II dosing.	II	No	Nil
	Participant had not presented himself for study participation on period II admission day due to his personal reasons.	II	No	Nil

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body system/Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasting Bioequivalence Study No.: 24902/11-12	
	Test (A) N=70	Reference (B) N=68
General disorders		
Fever	1(1.43%)	0 (0.00%)
Total	1(1.43%)	0 (0.00%)

Body system/Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasting Bioequivalence Study No.: 24902/11-12	
	Test (A) N=70	Reference (B) N=68
Incidence of Adverse Events during Post Study Evaluation		
Investigations		
Haemopoetic system		
^Eosinophil Count increased	-	1(1.43%)
^Blood sugar increased	-	1(1.43%)
^GGT increased	1(1.43%)	2(2.94%)
^AST increased	-	4 (5.88)
Total	1(1.43%)	8 (11.76)

During the entire duration of the study, 70 test treatments (A) and 68 reference treatments (B) were administered.
^Cannot be definitively associated to Treatment A or Treatment B because clinical chemistry laboratory evaluations were done only at screening and study exit

Subjects Experiencing Emesis (Include in eCTD)
None

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?
No

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?
N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.
Yes

Are there any safety concerns based on the adverse event profile?
No

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. 24902/11-12		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
72.0 hour Ambulatory blood sample was collected beyond the allowed time in period I due to late arrival of participants to the study facility.	(b) (6)	
72.0 hour Ambulatory blood sample was collected beyond the allowed time in period II due to late arrival of participants to the study facility.		
0.67 hour blood sample was collected 03 minutes late due to cannula block in period II		
Ambulatory blood sample was not collected in period I as the participant absent.		
Ambulatory blood sample was not collected in period II as the participant absent.		
Participant checked into the study facility late for period II admission.		

Reviewer's Comment:
There is some sampling time deviation. The firm used the scheduled sampling time for pharmacokinetic parameters calculation while the reviewer used actual sampling time for calculation. The firm and the reviewer showed similar results.

Did dropouts/adverse events/protocol deviations affect the study outcome?
No

Comments on Dropouts/Adverse Events/Protocol Deviations:

Acceptable

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Bioequivalence Study No. 24902/11-12									
Analyte Name: Atorvastatin									
Parameter	**Standard Curve Samples**								
Mean Concentration (ng/mL) (Nominal value)	**CS1**	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
	0.250	0.502	5.124	15.669	51.246	101.837	144.142	198.590	237.742
	0.251	0.501	5.011	15.034	50.113	100.226	150.340	200.453	250.566
Inter day Precision (%CV)	1.23	2.42	3.17	1.89	2.73	1.41	2.09	2.01	2.73
Inter day Accuracy (%Actual)	99.71	100.24	102.25	104.22	102.26	101.61	95.88	99.07	94.88
Linearity	0.9979								
Linearity Range (ng/mL)	0.251-250.566								
Sensitivity/LOQ (ng/mL)	0.251								
Parameter	**Quality Control Samples**								
Mean Concentration (ng/mL) (Nominal value)	**QC Low (ng/ml)**		**QC Medium (ng/ml)**		**QC Medium (ng/ml)**		**QC High (ng/ml)**		
	0.804		27.068		84.051		182.661		
	0.752		25.057		80.181		180.408		
Inter day Precision (%CV)	9.64		4.05		3.50		5.92		
Inter day Accuracy (%Actual)	106.97		108.03		104.83		101.25		

Bioequivalence Study No. 24902/11-12									
Analyte Name: O-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
Mean Concentration (ng/mL) (Nominal value)	**CS1**	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
	0.250	0.501	2.512	9.900	30.192	61.285	84.891	113.868	148.339
	0.250	0.500	2.500	10.001	30.004	60.008	85.011	115.015	150.020
Inter day Precision (%CV)	1.98	4.02	3.68	2.04	2.72	1.69	2.40	1.82	2.31
Inter day Accuracy (%Actual)	99.88	100.17	100.47	98.99	100.63	102.13	99.86	99.00	98.88
Linearity	0.9978								
Linearity Range (ng/mL)	0.250-150.020								
Sensitivity/LOQ (ng/mL)	0.250								

Parameter	**Quality Control Samples**			
Mean Concentration (ng/mL) (Nominal value)	**QC Low (ng/ml)**	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
	0.773	20.001	50.606	105.159
	0.750	20.003	50.007	105.014
Inter day Precision (%CV)	4.88	4.43	4.22	6.44
Inter day Accuracy (%Actual)	103.02	99.99	101.20	100.14

Bioequivalence Study No. 24902/11-12									
Analyte Name: P-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
Mean Concentration (ng/mL) (Nominal value)	**CS1**	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
	0.051	0.098	0.481	0.975	2.057	4.028	5.974	8.270	10.126
	0.050	0.100	0.501	1.001	2.002	4.005	6.007	8.009	10.011
Inter day Precision (%CV)	2.03	4.40	2.31	2.24	2.84	2.44	1.80	2.04	2.42
Inter day Accuracy (%Actual)	101.50	97.56	96.05	97.43	102.76	100.57	99.45	103.26	101.15
Linearity	0.9978								
Linearity Range (ng/mL)	0.050-10.011								
Sensitivity/LOQ (ng/mL)	0.050								

Parameter	**Quality Control Samples**			
Mean Concentration (ng/mL) (Nominal value)	**QC Low (ng/ml)**	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
	0.153	1.484	3.512	7.144
	0.150	1.503	3.507	7.215
Inter day Precision (%CV)	6.93	4.49	5.04	5.05
Inter day Accuracy (%Actual)	102.10	98.74	100.14	99.02

Number of Acceptable Runs	40
Number of Rejected Runs (Run ID, volume/page location)	3
If sample and QC diluted during study, specify all dilution factors	2 and 4 times
Was 100% of raw numerical data submitted?	Yes

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Agree

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (subjects #1-14)
Were the chromatograms submitted by the firm acceptable?	Yes

Table 126. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CRCBL024-04	29/02/2012	Sample Reassay and Reporting of Final concentration

Table 137. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A (no recalculation)
Does the reviewer agree with the outcome of the repeat assays?	Agree
If no, reason for disagreement	

Based on SOP No.CRCBL106, 304 samples were chosen to be extracted and injected to demonstrate reproducibility of the analytical methods for Atorvastatin, O-OH-Atorvastatin and P-OH-Atorvastatin as incurred samples. The SOP acceptance criteria was met, as at least 2/3 of the samples (302 out of 304 Atorvastatin samples; 301 out of 304 O-OH-Atorvastatin and 271 out of 304 P-OH-Atorvastatin samples) were reproducible (repeat results and original values within **20%** of each other).

Were Calibration and Quality Control for the Sample Analysis acceptable?

Yes

Summary/Conclusions, Study Assays:

Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Atorvastatin (N=66):

Fasting Bioequivalence Study, Study No.24902/11-12									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	444.140	43.62	173.60	1039.62	447.243	49.40	172.53	1147.70	0.99
AUC∞ (hr *ng/ml)	449.072	43.30	176.79	1051.12	452.107	48.96	179.95	1152.56	0.99
Cmax (ng/ml)	124.516	63.11	36.92	385.06	117.608	67.66	33.47	432.18	1.06
Tmax* (hr)	1.250	.	0.50	4.00	1.125	.	0.50	5.00	1.11
Kel (hr^{-1})	0.095	22.03	0.04	0.16	0.099	22.89	0.05	0.19	0.96
T1/2 (hr)	7.690	27.46	4.29	17.26	7.346	22.63	3.62	12.82	1.05

O-OH-Atorvastatin (N=66):

Fasting Bioequivalence Study, Study No.24902/11-12									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	599.528	40.14	242.87	1497.80	591.000	42.38	176.77	1454.58	1.01
AUC∞ (hr *ng/ml)	605.864	39.85	246.39	1504.84	597.177	41.85	187.87	1460.10	1.01
Cmax (ng/ml)	100.688	60.27	31.18	329.09	94.964	62.10	19.28	327.15	1.06
Tmax* (hr)	1.510	.	0.67	6.00	1.750	.	0.50	6.00	0.86
Kel (hr^{-1})	0.084	19.98	0.04	0.12	0.082	24.01	0.04	0.12	1.02
T1/2 (hr)	8.671	25.20	5.93	16.14	9.096	31.17	5.93	18.19	0.95

P-OH-Atorvastatin (N=66):

Fasting Bioequivalence Study, Study No.24902/11-12									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	77.671	45.90	35.58	202.83	78.446	49.69	25.47	197.01	0.99
AUC∞ (hr *ng/ml)	86.469	47.25	37.86	253.47	85.895	48.40	27.69	209.04	1.01
Cmax (ng/ml)	5.374	68.30	1.40	16.42	5.155	70.58	1.20	18.38	1.04
Tmax* (hr)	4.500	.	0.67	10.00	5.000	.	1.00	12.00	0.90
Kel (hr^{-1})	0.033	30.63	0.01	0.07	0.033	27.82	0.01	0.06	0.99
T1/2 (hr)	23.351	38.53	10.40	67.27	22.672	34.80	11.75	61.43	1.03

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated Atorvastatin (N=66):

Fasting Bioequivalence Study (Study No: 24902/11-12)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (ng*hr/mL)	407.4965	401.1833	101.57	94.79 – 108.84
$AUC_{0-\infty}$ (ng*hr/mL)	412.2595	406.0769	101.52	94.84 – 108.68
C_{max} (ng/mL)	106.2756	99.4502	106.86	93.61-122.00

Ortho-Hydroxylated (O-OH) Atorvastatin) (N=66)

Fasting Bioequivalence Study (Study No: 24902/11-12)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (ng*hr/mL)	557.8230	543.3663	102.66	96.76 - 108.92
$AUC_{0-\infty}$ (ng*hr/mL)	563.5344	549.6942	102.52	96.74 - 108.64
C_{max} (ng/mL)	87.3843	80.8964	108.02	96.86 - 120.46

Para-Hydroxylated (P-OH) Atorvastatin) (N=66):

Fasting Bioequivalence Study (Study No: 24902/11-12)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (ng*hr/mL)	71.1576	70.0737	101.55	94.75 - 108.84
$AUC_{0-\infty}$ (ng*hr/mL)	76.9901	75.9225	101.41	94.98 - 108.26
C_{max} (ng/mL)	4.4095	4.1943	105.13	92.47 - 119.53

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin Calcium Tablets Dose 1 x EQ 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 24902/11-12							
Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	407.50	66	401.18	66	1.02	94.79	108.84
AUC∞ (hr *ng/ml)	412.65	66	406.44	66	1.02	94.85	108.68
Cmax (ng/ml)	106.28	66	99.45	66	1.07	93.61	122.00
O-OH-Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	557.82	66	543.37	66	1.03	96.76	108.92
AUC∞ (hr *ng/ml)	564.33	66	550.47	66	1.03	96.74	108.64
Cmax (ng/ml)	87.38	66	80.9	66	1.08	96.86	120.46
P-OH-Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	76.16	66	70.07	66	0.98	94.75	108.84
AUC∞ (hr *ng/ml)	76.11	66	77.35	66	0.98	95.71	109.28
Cmax (ng/ml)	4.41	66	4.19	66	1.07	92.47	119.53

Table 17. Additional Study Information, Fasting Study No. 24902/11-12

Atorvastatin

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Reviewer's own calculation of PK parameters	
Root mean square error, AUC0-t	0.2378	
Root mean square error, AUC∞	0.2343	
Root mean square error, Cmax	0.4558	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	66	66
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax		
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	66	0.99	0.96	1.00
Reference	66	0.99	0.96	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

O-OH-Atorvastatin:

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Reviewer's own calculation of PK parameters	
Root mean square error, AUC0-t	0.2037	
Root mean square error, AUC∞	0.1996	
Root mean square error, Cmax	0.3752	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	66	66
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Agree	Agree
Indicate the number of subjects with the following:		

measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax		
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	66	0.99	0.97	1.00
Reference	66	0.99	0.94	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

P-OH-Atorvastatin:

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Reviewer's own calculation of PK parameters	
Root mean square error, AUC0-t	0.2386	
Root mean square error, AUC∞	0.2282	
Root mean square error, Cmax	0.4417	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	66	66
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax		
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	66	0.90	0.55	0.99
Reference	66	0.91	0.60	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	Please see comment below.			

The table below lists all the subjects with AUCt/AUCi ration less than 0.8:

Subject #	Treatment	AUCt/AUCi	Reason for AUCt/AUCi less than 0.8
(b) (6)	Test	0.55	unreliable determination of elimination phase
	Test	0.68	unreliable determination of elimination phase
	Test	0.78	unreliable determination of elimination phase
	Reference	0.76	unreliable determination of elimination phase
	Reference	0.77	unreliable determination of elimination phase
	Reference	0.60	unreliable determination of elimination phase
	Reference	0.77	unreliable determination of elimination phase

The concentration-time profiles for these subjects are as below:

(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

Since the AUCi/AUCt ratios for most of the subjects are greater than 0.8, the reviewer re-analyzed the data excluding subjects with AUCt/AUCi ratio less than 0.8 for Kel estimation of P-OH-Atorvastatin. The 90% CI of AUCi is still within the acceptable BE limit.

Was the fasting bioequivalence study acceptable?
Inadequate pending firm's response to OSI finding.

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

The Tmax is comparable between test and reference products.

Median Tmax (hrs)	Test	Reference
Atorvastatin	1.25	1.125
O-OH-Atorvastatin	1.5	1.75
P-OH-Atorvastatin	4.5	5

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin:

	Test (n=66)		Reference (n=66)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.16	0.88	281.60	0.70	314.63	1.25
0.33	23.48	123.36	20.17	153.70	1.16
0.50	58.32	100.80	49.39	112.29	1.18
0.67	67.63	91.58	64.71	91.09	1.05
0.83	70.81	89.71	74.20	91.72	0.95
1.00	72.28	86.25	75.44	87.18	0.96
1.25	82.65	91.43	76.88	90.56	1.07
1.50	76.44	78.05	71.16	79.36	1.07
2.00	65.59	60.77	65.95	67.36	0.99
2.50	53.56	54.38	58.15	65.86	0.92
3.00	49.54	78.88	50.24	62.14	0.99
4.00	42.37	65.91	42.80	71.92	0.99
5.00	32.87	59.71	34.19	65.30	0.96
6.00	24.96	50.81	25.45	57.51	0.98
8.00	18.07	46.51	18.01	55.56	1.00
10.00	12.58	47.35	12.85	52.87	0.98
12.00	8.02	52.17	8.15	54.22	0.98
16.00	4.27	52.88	4.40	58.47	0.97
24.00	1.44	56.43	1.51	63.33	0.95
36.00	0.70	59.32	0.73	73.48	0.97
48.00	0.17	138.41	0.15	161.54	1.08
72.00	0.01	549.37	0.01	565.37	0.98

O-OH-Atorvastatin:

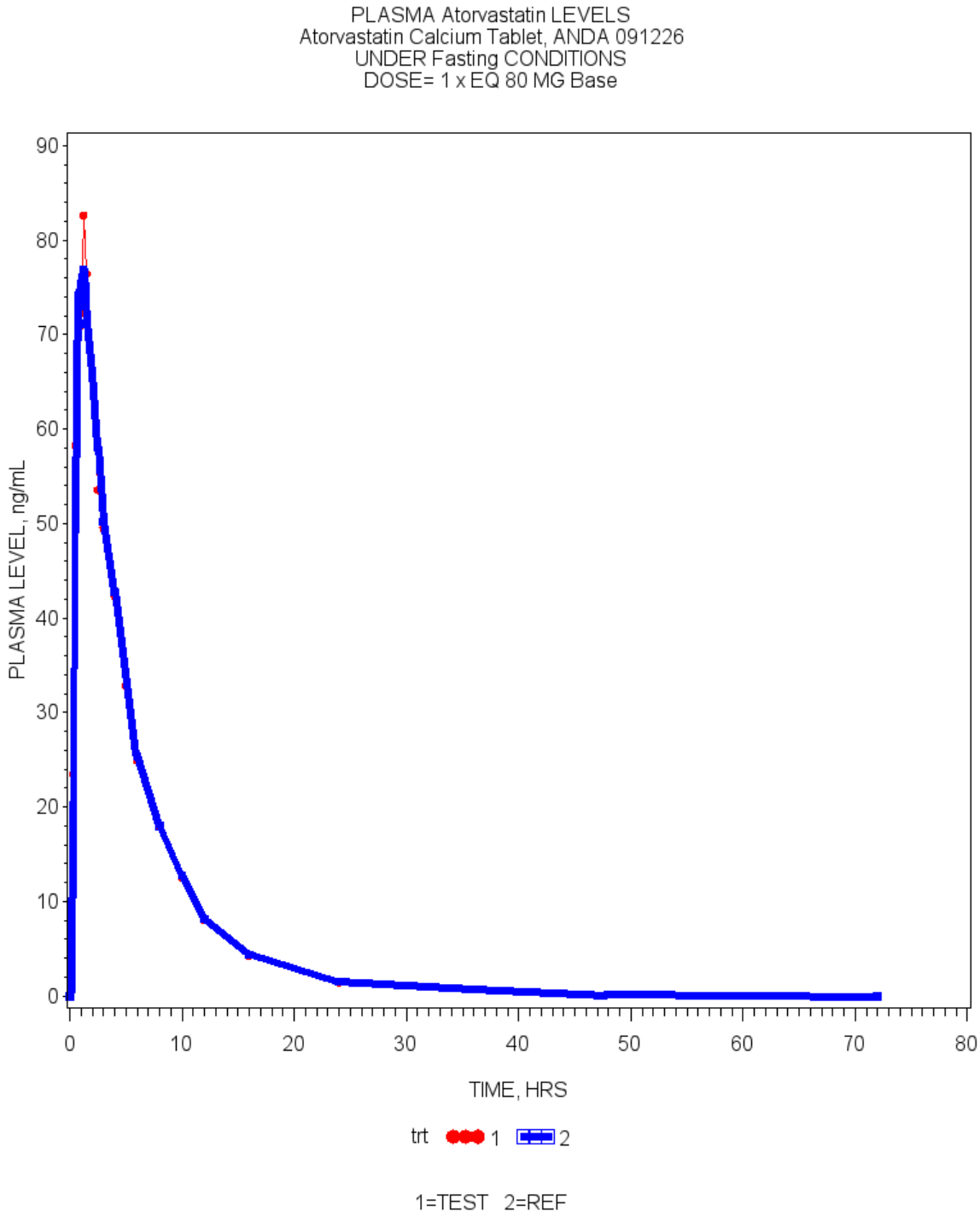
	Test (n=66)		Reference (n=66)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.16	0.04	383.23	0.05	451.12	0.84
0.33	5.23	179.68	4.19	189.63	1.25
0.50	25.77	133.47	18.97	124.75	1.36
0.67	43.05	111.40	36.12	94.51	1.19
0.83	53.20	96.29	51.67	88.20	1.03
1.00	60.06	92.33	60.73	88.38	0.99
1.25	71.12	82.50	68.06	84.08	1.04
1.50	74.55	82.45	68.57	73.52	1.09
2.00	72.65	66.57	69.84	61.81	1.04
2.50	64.57	57.84	66.08	59.77	0.98
3.00	60.90	58.99	61.21	54.64	0.99
4.00	54.11	44.39	54.78	57.29	0.99
5.00	44.50	42.86	44.74	48.96	0.99
6.00	37.36	42.18	36.86	44.98	1.01
8.00	30.21	39.81	29.29	43.74	1.03
10.00	21.82	39.94	21.67	42.57	1.01
12.00	15.50	43.81	15.28	39.72	1.01
16.00	8.50	49.09	8.33	44.76	1.02
24.00	2.80	46.35	2.80	43.80	1.00
36.00	1.50	44.76	1.49	57.29	1.01
48.00	0.45	66.03	0.44	70.49	1.02
72.00	0.04	288.27	0.07	195.81	0.57

P-OH-Atorvastatin:

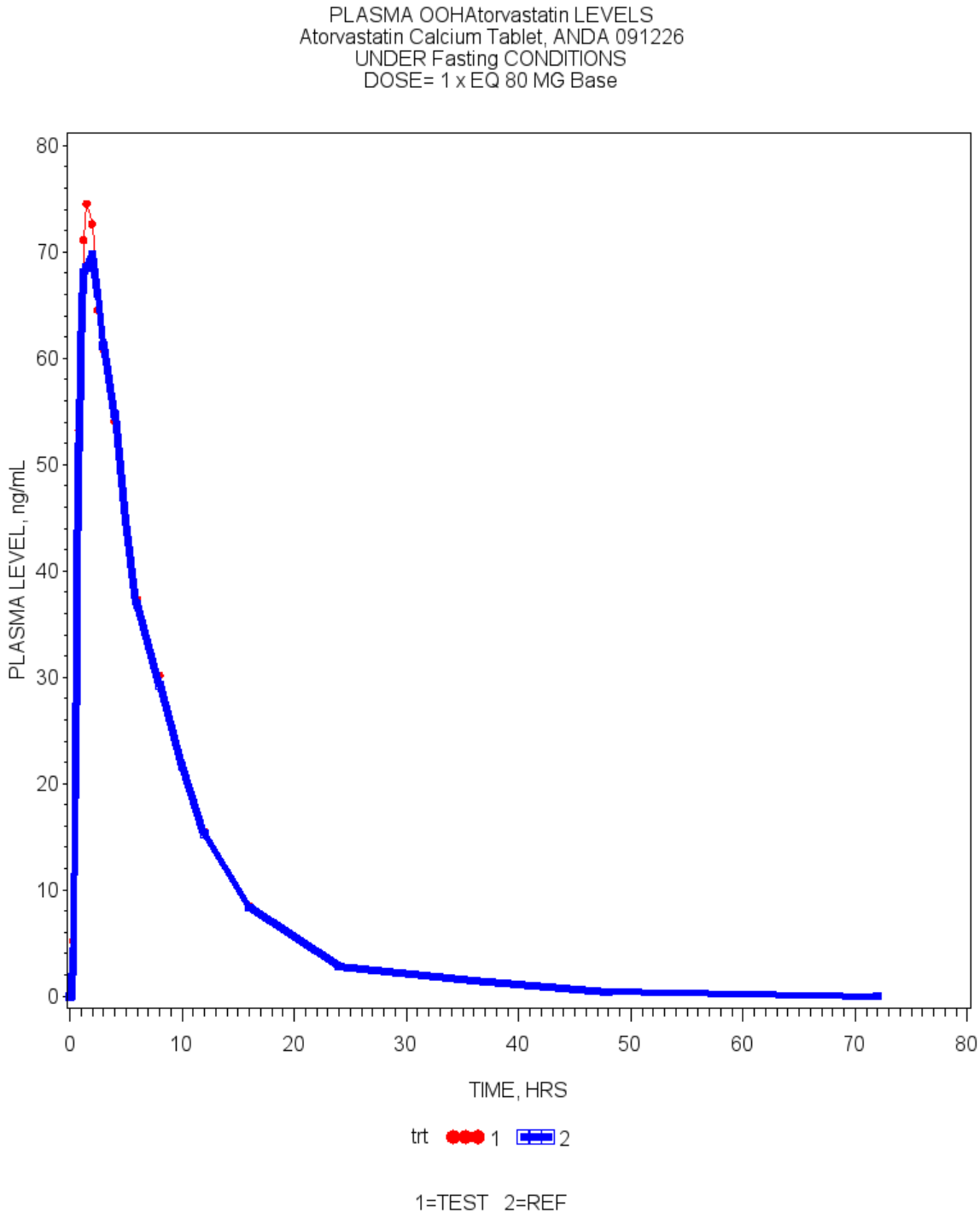
	Test (n=66)		Reference (n=66)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.16	0.00	570.17	0.00	570.81	1.00
0.33	0.28	291.80	0.19	238.50	1.42
0.50	1.06	206.30	0.71	155.99	1.50
0.67	1.47	156.87	1.16	120.49	1.27
0.83	1.74	140.61	1.64	128.87	1.06
1.00	1.97	136.86	1.90	127.79	1.04
1.25	2.54	129.50	2.33	134.41	1.09
1.50	2.77	123.20	2.56	124.67	1.08
2.00	3.09	99.91	3.05	98.99	1.02
2.50	3.22	82.53	3.39	94.24	0.95
3.00	3.56	86.60	3.53	85.91	1.01
4.00	3.87	70.11	3.89	77.66	1.00
5.00	3.76	67.97	3.91	72.54	0.96
6.00	3.44	62.70	3.44	63.90	1.00
8.00	3.67	50.43	3.57	55.65	1.03
10.00	3.25	47.25	3.26	54.61	1.00
12.00	2.45	45.37	2.54	52.56	0.97
16.00	1.77	46.07	1.78	48.58	1.00
24.00	0.90	50.01	0.93	52.31	0.97
36.00	0.62	45.01	0.62	44.51	1.01
48.00	0.35	63.19	0.34	54.03	1.02
72.00	0.20	57.00	0.20	57.21	1.00

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

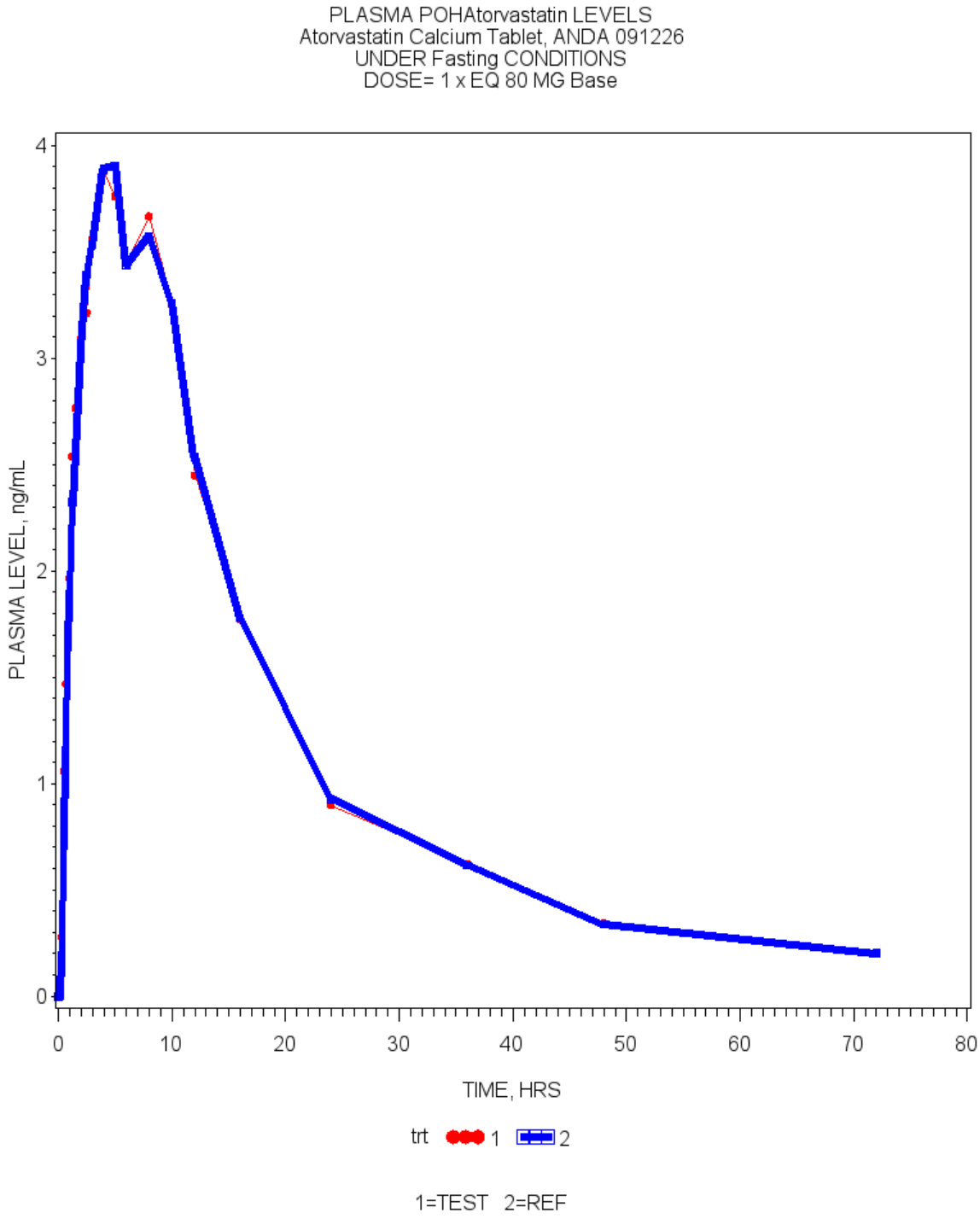
Atorvastatin:



O-OH-Atorvastatin:



P-OH-Atorvastatin:



4.2 Formulation Data

Pharmaceutical Function of Component, Formula and Quality Standards

Component	mg per tablet				
	10 mg	20 mg	40 mg	80 mg	% w/w
Active Ingredient					
Atorvastatin Calcium Trihydrate, USP [1,2]	(b) (4)				
Inactive Ingredients					
Colloidal Silicon Dioxide, NF	(b) (4)				
Sodium Carbonate Anhydrous, NF					
Microcrystalline Cellulose, NF	(b) (4)				
L-Arginine, USP					
Anhydrous Lactose, NF	(b) (4)				
Croscarmellose Sodium, NF	(b) (4)				
Hydroxypropyl Cellulose, NF	(b) (4)				
Magnesium Stearate, NF	(b) (4)				
	(b) (4)				

1 (b) (4)

2 (b) (4)

(b) (4)

(b) (4)

Reviewer's Comment:

The firm did not change the formulation except the API. The formulation of the test product has been found acceptable previously (DARRTS: REV-BIOEQ-01(General Review) dated 09/02/2010).

The RLD, Lipitor® Tablets, uses Atorvastatin Calcium Trihydrate, as proposed in the current supplement. (\\cdsnas\OGDS6\CONTROLS\2005-docs\05-1379.pdf)

4.3 Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02(Dissolution Review) dated 06/16/2009

Table 33. Dissolution Data

Dissolution Conditions	Apparatus:	USP-II (Paddle)
	Speed of Rotation:	75
	Medium:	6.8 pH Phosphate buffer
	Volume:	900 mL
	Temperature:	37 ± 0.5° C
Firm's Proposed Specifications	Complies with USP General Chapter <711> Not less than 80% (Q) of the labeled amount of Atorvastatin ($C_{66}H_{68}F_2N_4O_{10}$) is dissolved in 15 minutes	
Dissolution Testing Site (Name, Address)	Mylan Laboratories Limited, F-4 & F-12. Malegaon MIDC, Sinnar Nashik-422 113, Maharashtra, India.	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	Study Report Location
N/A	19-04-2012	Lipitor®(Atorvastatin Calcium) Tablets Lot: V112208 Expiry date: November 2014	80 mg Tablets	12	Mean	87	89	91	92	93	94	N/A
					Range	(b) (4)						
					%CV	3.6	2.7	2.5	1.7	1.4	1.6	
Pre-change	18-05-08	Atorvastatin Calcium Tablets Lot: 1004891 Mfg. Date: May 2008	80 mg Tablets	12	Mean	57	96	101	-	104	105	
					Range	(b) (4)						
					%CV	23.2	0.9	1.4	-	1.3	1.0	
Post-change	20/04/2012	Atorvastatin Calcium Tablets Lot: 1101983 Mfg. Date: April 2012	80 mg Tablets	12	Mean	41	76	97	100	100	101	
					Range	(b) (4)						
					%CV	15.9	9	2.6	1.2	1.1	1.1	
Pre-change	21-05-08	Atorvastatin Calcium Tablets Lot: 1004888 Mfg. Date: May 2008	10 mg Tablets	12	Mean	70	93	97	-	102	103	
					Range	(b) (4)						
					%CV	8.7	2.4	2.6	-	2.5	1.8	
Post-change	18/04/2012	Atorvastatin Calcium Tablets Lot: 1101979	10 mg Tablets	12	Mean	53	86	96	97	97	97	
					Range	(b) (4)						

		Mfg. Date: April 2012			%CV	14.9	3.8	1.3	1.8	1.6	1.6	
Pre-change	20-05-08	Atorvastatin Calcium Tablets Lot: 1004889 Mfg. Date: May 2008	20 mg Tablets	12	Mean	55	88	95	-	100	103	
					Range	(b) (4)						
					%CV	9.5	1.5	2.1	-	1.9	2.5	
Post-change	23/04/2012	Atorvastatin Calcium Tablets Lot: 1101980 Mfg. Date: April 2012	20 mg Tablets	12	Mean	43	79	96	98	99	99	
					Range	(b) (4)						
					%CV	17.4	7.4	1.9	1.8	2.1	2.2	
Pre-change	19-05-08	Atorvastatin Calcium Tablets Lot: 1004890 Mfg. Date: May 2008	40 mg Tablets	12	Mean	44	84	95	-	101	103	
					Range	(b) (4)						
					%CV	14.0	6.3	1.2	-	1.7	1.7	
Post-change	19/04/2012	Atorvastatin Calcium Tablets Lot: 1101982 Mfg. Date: April 2012	40 mg Tablets	12	Mean	35	68	92	98	99	99	
					Range	(b) (4)						
					%CV	8.8	7.9	3.2	1.2	1.2	0.9	

Reviewer's Comment:

1) The firm used the FDA-recommended method and proposed the dissolution specification of "NLT 80% (Q) in 15 minutes" as recommended by DBI.

2) The firm used the same analytical method for dissolution as submitted originally, which has been found acceptable by DBI.

3) The dissolution profiles for the pre-change and post-change products are comparable. The dissolution profiles for the post-change test product and RLD are listed in the following table. The dissolution data RLD are from the dissolution review of the original submission (DARRTS: REV-BIOEQ-02(Dissolution Review) dated 06/16/2009).

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	75
	Medium:	6.8 pH Phosphate buffer
	Volume:	900 mL
	Temperature:	37 ± 0.5° C
Firm's Proposed Specifications	Complies with USP General Chapter <711> Not less than 80% (Q) of the labeled amount of Atorvastatin ($C_{66}H_{68}F_2N_4O_{10}$) is dissolved in 15 minutes)	

Dissolution Testing Site (Name, Address)		Mylan Laboratories Limited, F-4 & F-12. Malegaon MIDC, Sinnar Nashik-422 113, Maharashtra, India.											
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
						5	**10**	**15**	**20**	**30**	**45**	
RLD	19-04-2012	Lipitor®(Atorvastatin Calcium) Tablets, Lot: V112208 Expiry date: November 2014	80 mg Tablets	12	Mean	87	89	91	92	93	94	N/A
					Range	(b) (4)						
					%CV	3.6	2.7	2.5	1.7	1.4	1.6	
Post-change	20/04/2012	Atorvastatin Calcium Tablets Lot: 1101983 Mfg. Date: April 2012	80 mg Tablets	12	Mean	41	76	97	100	100	101	
					Range	(b) (4)						
					%CV	15.9	9	2.6	1.2	1.1	1.1	
RLD	24/12/ 2008	LIPITOR® Tablets Batch # 13868V Exp date: Aug. 2011	10 mg Tablets	12	Mean	66	74	78	-	84	97	
					Range	(b) (4)						
					%CV	10.3	6.5	5.8	-	6.8	4.1	
Post-change	18/04/2012	Atorvastatin Calcium Tablets Lot: 1101979 Mfg. Date: April 2012	10 mg Tablets	12	Mean	53	86	96	97	97	97	
					Range	(b) (4)						
					%CV	14.9	3.8	1.3	1.8	1.6	1.6	
RLD	23/11/ 2008	LIPITOR® Tablets Batch # 0178017 Exp date: Dec 2009	20 mg Tablets	12	Mean	98	104	104	-	104	104	
					Range	(b) (4)						
					%CV	5.8	0.8	0.6	-	0.6	0.6	
Post-change	23/04/2012	Atorvastatin Calcium Tablets Lot: 1101980 Mfg. Date: April 2012	20 mg Tablets	12	Mean	43	79	96	98	99	99	
					Range	(b) (4)						
					%CV	17.4	7.4	1.9	1.8	2.1	2.2	
RLD	24/11/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 40 mg) Batch # 0117027 Exp date: Jan 2010	40 mg Tablets	12	Mean	96	102	103	-	103	101	
					Range	(b) (4)						
					%CV	8.1	0.5	0.7	-	0.5	3.7	
Post-change	19/04/2012	Atorvastatin Calcium Tablets Lot: 1101982 Mfg. Date: April 2012	40 mg Tablets	12	Mean	35	68	92	98	99	99	
					Range	(b) (4)						
					%CV	8.8	7.9	3.2	1.2	1.2	0.9	

Both the pre-change and post-change test product dissolved slower than the RLD for all strengths. However, the firm demonstrated in vivo BE of the 80 mg strength between the pre-change/post-change test and reference products *in vivo* two-way crossover studies. The BE study results for Atorvastatin calculated by the reviewers are summarized in the tables below:

Post-change test vs. RLD, fasting study

Atorvastatin Calcium Tablets Dose 1 x EQ 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 24902/11-12							
Atorvastatin							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	407.50	66	401.18	66	1.02	94.79	108.84
AUC∞ (hr *ng/ml)	412.65	66	406.44	66	1.02	94.85	108.68
Cmax (ng/ml)	106.28	66	99.45	66	1.07	93.61	122.00

Pre-change test vs. RLD, fasting study (DARRTS: REV-BIOEQ-01(General Review) dated 09/02/2010)

Atorvastatin Calcium Tablets Dose 1 x EQ 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 022-08					
Atorvastatin (N=67)					
Parameter (units)	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	325.18	308.06	1.06	99.01	112.53
AUC∞ (hr *ng/ml)	329.12	312.10	1.05	98.97	112.37
Cmax (ng/ml)	78.65	73.27	1.07	94.47	121.99

Pre-change test vs. RLD, fed study (DARRTS: REV-BIOEQ-01(General Review) dated 09/02/2010)

Atorvastatin Calcium Tablets Dose 1 x EQ 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 162-08					
Atorvastatin (N=56)					
Parameter (units)	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	249.53	262.50	0.95	88.92	101.62
AUC∞ (hr *ng/ml)	255.29	268.22	0.95	89.10	101.67
Cmax (ng/ml)	47.30	49.35	0.96	86.49	106.23

In addition, the median Tmax values for Atorvastatin of the test and RLD product, in the fasting and fed studies, did show some correlation "trend" between the observed difference in the dissolution profiles and the median Tmax values between the two products:

	Fasting 022-08	**Fed 162-08**	**Fasting 24902/11-12**
Pre-change Test	1.5	3.5	
RLD	1.0	3.25	1.125
Post-change Test			1.25

Possibly, this was the reason the firm conducted a BE study for its API change.

4) The post-change product meets the previously FDA-recommended specification of "NLT 80% (Q) in 15 minutes".

5) The dissolution testing is acceptable.

4.4 Detailed Regulatory History (If Applicable)

None

4.5 Consult Reviews

None

4.6 SAS Output

4.6.1 Fasting Study Data (Atorvastatin)

Fasting CONCENTRATION DATASET

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	(b) (6)	1	1	1	A	0	1.561	53.946	57.976	47.604	41.353	36.047	38.431	49.555	76.702	73.251	78.287	68.344	48.955
2		1	1	2	B	0	3.300	63.403	97.318	83.924	80.011	83.505	82.006	89.174	75.865	55.425	47.303	27.395	24.861
3		1	2	1	B	0	0.000	10.747	33.619	38.757	36.371	34.182	28.576	22.745	41.425	28.820	23.509	15.232	10.711
4		1	2	2	A	0	1.515	11.741	24.327	27.401	21.523	29.065	283.446	212.555	97.202	60.601	45.786	34.709	20.042
5		1	1	1	A	0	0.000	0.451	13.922	57.398	85.932	62.983	52.182	52.871	93.353	66.989	51.527	52.854	35.154
6		1	1	2	B	0	0.000	0.702	6.364	18.917	35.991	56.964	55.055	45.492	42.929	43.855	55.249	53.950	51.377
7		1	1	1	A	0	0.000	0.000	3.884	21.244	49.901	44.149	44.235	58.888	31.547	59.384	131.017	49.005	34.152
8		1	1	2	B	0	0.000	5.189	25.789	30.619	49.161	58.040	60.868	58.248	66.048	59.052	38.713	24.914	18.475
9		1	2	1	B	0	0.000	0.722	4.719	9.327	28.614	103.142	105.548	85.719	52.397	39.428	31.025	23.132	21.377
10		1	2	2	A	0	0.000	7.710	32.873	43.068	67.711	78.064	65.064	59.542	41.093	36.897	34.413	24.260	21.189
11		1	2	1	B	0	11.304	87.539	221.924	241.505	221.622	181.738	148.022	115.719	86.799	63.185	47.501	35.850	30.381
12		1	2	2	A	0	3.578	27.085	40.702	38.081	39.209	69.814	73.120	77.897	88.707	59.620	55.259	30.687	28.333
13		1	1	1	A	0	0.000	0.454	3.461	9.758	13.981	14.133	16.408	25.667	26.386	26.376	69.167	39.096	31.980
14		1	1	2	B	0	0.000	0.000	14.955	16.365	14.905	15.097	10.730	7.041	11.772	47.624	31.984	41.737	48.607
15		1	1	1	A	0	0.000	0.482	2.922	7.393	13.816	21.374	34.575	30.457	31.173	33.143	33.877	57.172	34.735
16		1	1	2	B	0	0.000	0.412	2.215	6.255	11.281	18.950	31.470	22.981	49.583	78.653	55.120	32.967	28.409
17		1	2	1	B	0	0.000	7.544	50.885	63.733	64.281	74.762	246.504	295.552	187.552	138.659	102.551	77.602	61.621
18		1	2	2	A	0	0.000	50.606	105.529	96.740	81.163	78.479	102.117	87.138	165.151	111.854	76.558	71.730	56.354
19		1	2	1	B	0	0.596	11.885	46.504	78.088	70.194	51.058	52.110	44.821	38.181	37.940	23.077	16.310	12.630
20		1	2	2	A	0	0.000	26.083	78.194	83.700	56.125	41.319	31.282	27.387	21.808	16.131	12.387	13.416	10.068
21		1	2	1	B	0	0.000	1.721	9.151	15.203	13.567	37.751	76.860	46.657	30.109	20.335	16.370	14.916	15.658
22		1	2	2	A	0	0.000	3.124	9.533	17.107	45.870	67.220	58.967	56.027	30.841	18.333	16.982	12.940	11.830
23		1	1	1	A	0	0.000	11.327	24.699	34.664	31.635	32.428	90.581	74.162	54.337	39.896	29.743	25.547	26.235

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
24	(b) (6)	1	1	2	B	0	0.394	22.574	62.775	57.391	37.879	34.544	36.225	33.560	22.617	23.457	20.684	18.186	21.362
25		1	1	1	A	0	0.000	58.650	159.726	126.472	94.615	70.265	54.544	43.062	29.132	19.539	16.136	11.661	11.670
26		1	1	2	B	0	0.265	15.782	64.795	64.392	57.465	46.310	31.743	28.823	20.891	16.690	13.612	10.318	10.134
27		1	2	1	B	0	0.000	13.774	26.573	30.391	53.656	84.487	96.889	70.487	69.551	64.814	69.277	58.127	48.391
28		1	2	2	A	0	0.000	3.471	6.989	14.561	75.931	119.561	96.281	76.595	58.223	49.964	35.229	26.601	24.784
29		1	1	1	A	0	0.000	6.693	25.613	42.399	34.686	32.030	26.679	30.028	17.860	13.596	11.352	12.861	13.951
30		1	1	2	B	0	0.000	0.887	3.650	5.237	9.937	23.896	28.772	21.836	18.124	14.734	9.750	49.167	31.364
31		1	2	1	B	0	8.645	99.153	99.202	69.993	45.776	35.861	25.703	28.441	27.474	24.749	22.273	19.026	18.374
32		1	2	2	A	0	5.956	65.511	109.757	79.954	53.032	42.169	33.572	31.406	26.142	26.744	21.698	17.331	17.210
33		1	2	1	B	0	0.000	2.177	20.696	28.396	20.460	24.187	21.973	34.996	78.005	47.887	80.262	107.090	74.946
34		1	2	2	A	0	0.000	17.078	70.949	69.189	57.522	63.305	74.686	86.667	94.356	91.446	86.415	116.050	64.634
35		1	1	1	A	0	0.000	0.427	3.794	11.883	25.780	33.515	36.921	23.829	17.943	18.674	30.195	30.336	15.095
36		1	1	2	B	0	0.000	0.755	18.164	43.086	44.616	70.253	58.032	56.206	37.079	36.079	27.768	17.179	12.224
37		1	1	1	A	0	7.266	115.722	143.305	141.322	223.458	234.381	244.433	183.200	105.602	87.372	73.999	51.664	47.161
38		1	1	2	B	0	10.619	42.442	43.090	118.796	198.093	212.813	147.895	99.251	74.536	44.719	47.488	30.703	21.867
39		1	2	1	B	0	0.000	10.281	31.879	37.239	43.075	38.325	49.955	42.993	45.915	43.185	30.606	24.943	20.456
40		1	2	2	A	0	1.777	45.683	133.239	136.525	117.621	105.391	89.496	88.695	73.497	68.068	49.089	34.582	29.705
41		1	1	1	A	0	0.000	16.463	72.508	87.202	157.755	226.132	311.300	279.890	142.404	100.869	69.872	37.425	19.415
42		1	1	2	B	0	0.481	40.523	82.350	101.165	90.079	82.031	68.213	52.635	35.759	25.843	29.869	15.996	9.599
43		1	1	1	A	0	0.000	1.337	7.093	6.560	4.900	3.577	2.730	6.947	12.941	13.609	10.154	42.370	19.284
44		1	1	2	B	0	0.000	22.191	43.161	39.041	28.554	23.005	18.549	16.913	13.217	9.323	10.867	8.955	10.053
45		1	2	1	B	0	0.313	33.889	114.950	119.145	106.684	76.585	67.623	61.948	66.646	106.752	128.915	130.141	104.207
46		1	2	2	A	0	0.000	6.357	33.899	48.213	79.194	94.365	97.837	103.873	98.679	98.119	97.137	135.775	111.590
47		1	2	1	B	0	0.000	6.459	101.994	85.165	80.178	85.062	77.408	76.740	68.668	53.908	45.158	34.866	29.168
48		1	2	2	A	0	0.000	0.435	6.853	33.676	55.243	63.247	66.547	59.096	50.014	39.726	36.550	30.345	24.613
49		1	1	1	A	0	0.411	49.021	226.843	286.864	190.836	168.891	146.895	128.730	99.384	74.781	69.584	43.672	37.642
50		1	1	2	B	0	0.000	1.157	12.526	30.393	39.951	45.775	48.030	67.601	86.923	75.199	61.755	54.262	44.651
51		1	1	1	A	0	0.000	0.319	6.627	51.406	58.344	53.207	52.127	57.391	69.986	70.842	46.740	37.219	26.272
52		1	1	2	B	0	0.000	2.410	44.755	94.944	85.727	65.832	62.642	60.755	53.763	30.073	28.392	20.263	18.909

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
53	(b) (6)	1	2	1	B	0	0.267	33.405	66.164	127.789	161.956	144.763	109.838	85.419	67.910	52.777	35.227	25.659	24.214
54		1	2	2	A	0	16.486	114.285	206.183	214.985	214.232	227.897	176.946	122.543	93.964	54.821	45.574	35.025	29.745
55		1	2	1	B	0	0.000	3.330	14.195	21.755	22.142	24.818	28.585	29.867	27.970	23.240	26.436	31.730	33.470
56		1	2	2	A	0	0.000	32.266	106.780	113.376	98.807	114.268	137.767	117.184	83.591	50.938	45.726	29.591	26.741
57		1	1	1	A	0	0.251	24.225	57.160	60.339	44.173	41.330	34.806	27.156	23.678	16.653	13.578	10.196	11.973
58		1	1	2	B	0	0.000	22.259	39.391	33.085	67.039	102.619	80.935	57.601	35.765	27.230	21.775	16.818	11.954
59		1	2	1	B	0	0.000	16.851	58.545	112.169	106.402	89.027	71.341	60.230	50.539	40.841	31.037	26.302	22.692
60		1	2	2	A	0	0.255	30.301	69.105	71.887	51.707	41.538	28.558	24.995	22.317	17.954	14.939	12.932	15.798
61		1	2	1	B	0	4.204	208.460	356.654	351.664	247.666	218.787	187.926	151.771	123.772	99.850	70.516	51.058	32.059
62		1	2	2	A	0	0.000	20.481	78.824	69.843	82.820	76.312	79.069	99.714	132.574	89.045	68.177	51.777	34.719
63		1	1	1	A	0	0.000	0.559	9.035	23.872	22.181	20.201	26.167	25.297	39.973	43.902	33.224	72.325	55.414
64		1	1	2	B	0	0.000	0.000	0.415	1.103	2.494	7.859	11.444	9.107	9.555	9.465	9.651	162.204	113.826
65		1	2	1	B	0	0.000	0.339	2.951	16.457	43.383	54.068	54.154	57.130	83.580	50.580	32.057	20.077	18.169
66		1	2	2	A	0	2.373	30.260	52.783	49.287	40.644	44.200	118.854	129.050	64.166	47.456	40.002	29.582	16.734
67		1	2	1	B	0	1.001	30.428	36.395	37.783	30.999	33.296	29.949	22.672	19.124	14.896	15.430	20.695	17.344
68		1	2	2	A	0	0.000	6.948	21.637	32.440	29.077	20.291	17.437	27.042	64.487	31.537	25.228	16.103	13.933
69		1	1	1	A	0	2.591	6.384	9.730	15.965	36.449	57.954	48.445	36.766	33.511	32.186	26.745	25.609	23.830
70		1	1	2	B	0	0.000	1.696	10.132	25.768	66.506	92.324	133.290	93.129	95.102	75.029	51.589	31.861	33.370
71		1	2	1	B	0	0.000	0.718	18.102	79.704	180.237	173.870	148.320	119.157	83.082	62.345	54.997	40.656	31.895
72		1	2	2	A	0	0.610	4.391	17.162	38.251	72.678	75.570	100.123	95.143	93.033	61.543	45.889	35.773	22.300
73		1	2	1	B	0	0.000	5.586	24.522	37.887	51.385	66.114	138.265	155.959	146.282	101.330	81.072	51.165	48.027
74		1	2	2	A	0	0.425	38.722	82.703	82.350	79.999	73.087	82.113	81.153	83.007	61.123	43.536	29.888	26.596
75		1	1	1	A	0	0.619	54.935	84.846	69.864	58.434	54.056	46.661	41.925	45.797	38.149	30.248	24.398	17.594
76		1	1	2	B	0	0.000	7.267	15.162	13.905	17.618	14.471	24.602	77.663	186.570	175.261	110.402	71.114	38.083
77		1	2	1	B	0	0.000	14.072	49.185	85.625	87.182	78.019	59.996	44.795	32.204	27.972	24.040	15.887	13.106
78		1	2	2	A	0	0.000	19.489	85.185	108.611	93.426	78.041	72.042	50.278	36.466	28.865	20.604	13.984	15.009
79		1	1	1	A	0	0.000	0.000	1.870	4.256	8.690	13.146	19.642	22.302	20.438	13.400	15.574	49.033	39.900
80		1	1	2	B	0	0.362	11.918	26.522	58.600	57.019	48.175	38.804	32.158	37.170	33.805	27.481	24.574	18.744
81		1	1	1	A	0	0.000	4.727	36.306	47.353	36.139	43.476	47.631	40.546	40.129	49.517	31.531	27.148	22.312

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
82	(b) (6)	1	1	2	B	0	0.000	17.590	115.887	136.415	133.680	120.324	95.960	89.397	57.502	39.832	27.065	20.932	15.280
83		1	2	1	B	0	0.545	7.437	10.108	23.092	39.468	63.017	65.683	65.520	96.917	74.231	68.314	48.151	43.501
84		1	2	2	A	0	0.000	2.185	10.796	10.360	8.955	9.278	29.521	73.377	34.121	75.103	48.909	35.041	29.059
85		1	1	1	A	0	0.000	42.319	119.660	115.008	111.984	108.417	86.094	77.818	146.248	111.660	100.387	77.999	60.808
86		1	1	2	B	0	0.000	37.608	127.480	165.646	137.934	118.435	111.647	112.070	142.336	126.860	101.372	86.550	80.468
87		1	1	1	A	0	0.515	51.455	107.047	72.509	51.121	37.445	40.983	47.760	32.436	24.411	19.616	19.184	17.286
88		1	1	2	B	0	0.000	13.790	40.747	68.805	85.039	82.998	89.036	88.684	72.409	49.897	42.210	42.456	33.011
89		1	2	1	B	0	0.000	0.000	1.634	9.247	23.333	36.055	52.931	58.480	63.530	144.027	119.813	86.676	57.777
90		1	2	2	A	0	0.000	1.917	13.004	37.497	73.687	59.037	57.398	45.899	34.564	39.559	35.743	27.243	24.653
91		1	2	1	B	0	0.000	13.171	54.241	74.416	98.711	90.109	104.653	93.252	88.165	73.934	71.970	43.756	32.670
92		1	2	2	A	0	0.000	1.642	15.681	24.877	33.439	83.132	100.158	82.413	69.669	70.562	57.538	45.637	47.912
93		1	2	1	B	0	0.881	31.124	43.317	35.366	33.997	35.569	29.456	43.758	32.455	22.204	18.094	16.833	15.717
94		1	2	2	A	0	0.000	0.475	27.009	36.955	24.943	16.453	24.125	39.591	70.439	46.768	28.290	22.643	21.839
95		1	1	1	A	0	0.000	28.993	79.182	289.244	385.058	350.472	292.246	235.059	162.583	117.428	86.032	75.014	68.905
96		1	1	2	B	0	0.000	6.968	64.946	197.479	432.184	420.826	345.146	280.284	191.718	142.476	115.219	100.314	82.227
97		1	1	1	A	0	0.000	5.249	40.341	47.804	76.984	140.312	201.700	175.469	102.843	78.667	69.072	48.189	33.296
98		1	1	2	B	0	0.434	39.893	59.216	60.081	52.657	56.427	66.924	100.659	155.320	84.924	58.297	43.649	42.527
99		1	2	1	B	0	1.006	26.527	73.195	88.549	60.611	40.274	30.182	23.747	18.256	15.354	14.484	12.188	11.635
100		1	2	2	A	0	0.000	0.938	7.842	11.188	9.843	9.382	9.506	8.716	8.385	8.734	7.713	128.862	69.853
101		1	1	1	A	0	5.322	41.347	42.041	32.053	25.429	22.488	37.801	34.455	67.195	66.860	49.718	70.015	46.366
102		1	1	2	B	0	0.000	40.696	62.767	84.649	100.564	95.758	83.524	157.295	116.357	67.862	78.739	43.414	36.189
103		1	2	1	B	0	0.000	1.580	6.267	10.259	12.546	18.734	35.874	89.966	102.194	83.480	75.197	64.244	54.519
104		1	2	2	A	0	0.300	48.924	235.370	192.902	136.026	95.209	87.868	61.684	51.321	41.223	37.650	29.004	24.092
105		1	1	1	A	0	0.312	38.332	79.133	72.383	66.903	71.104	63.304	55.788	45.767	36.595	34.686	28.281	24.420
106		1	1	2	B	0	0.000	40.162	134.973	108.374	82.221	63.203	51.770	49.123	44.880	40.400	38.246	28.869	26.171
107		1	2	1	B	0	0.000	1.356	11.723	68.602	131.263	98.462	68.354	61.642	57.458	41.968	55.917	30.540	23.738
108		1	2	2	A	0	0.000	25.184	77.418	68.133	54.959	42.657	32.563	33.580	36.850	25.100	25.538	14.840	15.389
109		1	1	1	A	0	4.862	136.307	236.580	208.136	203.556	197.003	165.690	136.070	96.311	65.713	51.634	35.097	19.629
110		1	1	2	B	0	0.252	50.762	63.633	62.141	64.999	64.243	61.525	60.833	52.177	41.713	33.240	24.634	19.983

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
111	(b) (6)	1	1	1	A	0	0.000	1.342	6.547	20.171	20.970	17.217	17.683	12.024	16.247	11.513	15.797	96.591	59.007
112		1	1	2	B	0	0.000	2.743	12.047	23.633	34.428	32.560	37.471	55.732	57.687	91.707	78.303	44.977	41.673
113		1	1	1	A	0	0.922	60.993	110.722	102.917	83.593	88.929	79.528	68.676	48.314	43.308	36.788	30.850	30.799
114		1	1	2	B	0	0.000	26.314	57.701	57.572	40.781	31.593	26.700	26.797	24.215	20.581	20.030	44.889	37.859
115		1	2	1	B	0	0.000	1.380	9.866	36.618	39.704	27.688	21.934	20.954	16.481	13.739	14.511	11.991	11.601
116		1	2	2	A	0	0.000	0.000	3.418	4.695	6.010	7.566	6.786	105.320	99.466	79.417	65.674	76.113	58.370
117		1	1	1	A	0	0.000	10.093	11.773	14.822	23.902	30.639	34.811	26.129	22.648	66.338	268.932	67.763	59.835
118		1	1	2	B	0	1.188	26.654	38.910	36.293	122.874	240.977	401.072	236.172	145.083	93.082	92.094	47.763	40.641
119		1	2	1	B	0	0.000	4.089	24.739	31.491	57.874	85.665	84.762	63.063	43.438	32.998	31.845	17.838	20.160
120		1	2	2	A	0	0.000	12.103	86.494	122.252	120.898	90.096	73.919	67.308	52.565	37.757	28.915	19.616	22.720
121		1	2	1	B	0	0.286	17.754	31.841	40.879	37.538	32.810	26.189	32.654	58.632	120.307	99.971	99.703	45.986
122		1	2	2	A	0	0.000	5.894	25.129	17.964	22.131	35.629	367.004	277.216	136.899	75.201	53.250	30.237	21.877
123		1	1	1	A	0	0.000	6.119	30.609	112.869	112.036	96.356	63.735	85.430	116.500	69.030	59.022	40.754	40.709
124		1	1	2	B	0	0.000	8.522	61.531	113.975	112.163	87.160	90.007	59.218	60.455	69.341	71.772	40.370	35.455
125		1	2	1	B	0	0.000	11.718	73.313	104.755	113.059	88.646	72.409	66.558	99.660	144.184	109.034	110.605	82.786
126		1	2	2	A	0	0.000	23.768	59.585	84.049	82.190	68.078	68.184	79.455	71.032	123.004	147.073	104.792	88.048
127		1	2	1	B	0	0.000	0.610	4.453	16.524	18.948	17.434	8.915	13.781	10.997	26.465	45.786	49.210	29.077
128		1	2	2	A	0	0.000	4.598	30.746	45.257	48.521	50.025	45.086	40.082	46.489	31.288	23.528	17.073	15.991
129		1	1	1	A	0	0.000	5.549	7.789	13.660	23.292	69.160	69.942	58.702	87.996	83.472	56.275	39.583	32.869
130		1	1	2	B	0	0.000	35.905	65.727	50.984	38.746	29.897	22.720	27.375	35.200	62.776	57.845	53.975	36.670
131		1	1	1	A	0	0.000	25.528	60.758	82.822	120.506	108.093	138.308	164.485	140.749	93.328	72.085	45.274	40.756
132		1	1	2	B	0	0.000	6.534	6.906	34.369	81.526	87.539	134.503	135.559	108.601	88.828	85.617	57.330	42.470

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
1	28.282	15.859	9.352	6.788	2.803	0.722	0.360	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
2	17.018	10.642	8.949	5.023	2.305	0.663	0.359	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
3	9.695	7.142	6.292	3.826	2.034	0.745	0.453	0.000	0.000	18	21	0	0.16	0.35	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
4	18.589	11.724	8.730	4.908	2.558	0.979	0.547	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
5	28.046	16.945	12.723	6.927	3.820	1.132	0.495	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
6	33.649	18.172	13.242	7.692	3.218	1.275	0.495	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
7	19.942	12.182	7.183	4.704	2.376	0.802	0.447	0.000	0.000	18	21	0	0.16	0.33	0.52	0.67	0.83	1	1.25	1.50	2.00	2.50	3
8	18.114	13.454	8.584	7.247	3.249	0.995	0.568	0.000	0.000	18	21	0	0.18	0.36	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
9	18.978	13.669	10.121	6.003	3.894	1.269	0.606	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
10	15.877	11.211	8.343	5.317	3.420	0.888	0.368	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
11	28.487	16.484	11.788	7.409	3.770	1.015	0.534	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.02	2.50	3
12	20.730	14.638	9.143	6.034	3.262	0.970	0.390	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
13	25.767	17.062	10.850	6.669	2.701	0.961	0.368	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
14	28.060	16.466	9.773	7.592	2.956	1.187	0.477	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
15	25.525	18.623	13.931	7.609	4.112	1.862	0.820	0.343	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
16	19.873	14.519	12.057	8.300	4.655	2.061	0.849	0.419	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
17	47.816	36.279	28.586	15.813	9.533	2.807	1.545	0.580	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
18	56.562	41.164	28.095	17.330	10.562	3.577	1.774	0.740	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
19	10.888	8.810	8.873	4.522	2.843	1.011	0.609	0.281	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
20	8.195	6.503	7.619	3.712	2.513	0.965	0.619	0.353	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
21	11.894	9.030	5.469	4.654	2.196	0.975	0.427	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
22	11.139	11.307	6.438	4.617	2.276	0.817	0.487	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
23	17.617	15.221	12.239	7.979	6.122	1.378	0.966	0.338	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
24	16.021	15.178	13.046	7.149	4.098	1.243	0.702	0.000	0.000	18	21	0	0.19	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
25	12.649	10.733	8.745	6.500	3.723	1.133	0.714	0.286	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
26	8.856	8.280	7.151	5.219	2.664	1.109	0.818	0.359	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
27	36.134	29.515	19.711	17.275	10.247	4.490	2.211	0.837	0.330	20	23	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
28	18.874	18.411	11.561	8.361	4.770	1.703	1.305	0.534	0.254	20	23	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
29	13.622	10.315	10.130	7.382	4.194	1.502	0.827	0.289	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
30	20.753	15.191	12.782	8.781	4.828	1.570	0.895	0.272	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
31	21.438	13.967	7.899	4.572	2.274	1.037	0.520	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
32	14.902	12.438	7.722	4.658	2.517	1.071	0.481	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
33	49.047	35.441	26.401	15.727	8.104	4.699	1.246	0.562	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
34	42.009	30.804	18.038	13.404	6.085	2.567	1.071	0.339	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
35	11.964	8.499	6.389	4.338	2.160	0.670	0.401	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
36	10.102	6.240	4.634	3.481	2.155	0.803	0.324	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
37	39.081	29.096	20.754	20.072	11.689	3.460	1.120	0.400	.	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
38	18.396	16.295	11.297	9.631	4.223	2.134	0.969	0.392	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
39	16.014	13.374	10.764	6.977	4.154	1.481	0.786	0.315	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
40	19.289	17.327	11.989	8.217	3.453	1.447	0.591	0.252	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
41	15.186	11.326	4.868	3.629	3.005	0.815	0.335	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
42	7.093	6.720	4.756	2.451	1.875	0.381	0.000	0.000	0.000	17	20	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
43	17.921	11.882	9.238	6.295	3.660	1.142	0.817	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
44	8.620	12.582	6.336	4.470	2.959	1.038	0.620	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
45	70.837	53.279	32.681	19.964	12.715	3.815	1.753	0.734	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
46	69.015	51.269	35.469	25.876	13.427	4.428	2.172	0.918	0.000	19	22	0	0.16	0.33	0.50	0.72	0.83	1	1.25	1.50	2.00	2.50	3
47	21.842	13.006	12.463	7.146	3.341	0.946	0.373	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
48	18.013	13.585	12.755	8.425	4.609	1.540	0.667	0.299	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
49	37.116	23.829	16.419	9.063	4.771	1.269	0.600	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
50	38.838	24.850	20.337	9.012	4.781	1.546	0.539	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
51	20.884	18.276	10.343	7.773	3.613	1.518	0.692	0.291	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.52	2.00	2.50	3
52	13.180	10.041	9.286	6.512	5.623	1.399	0.656	0.327	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
53	22.028	11.403	7.424	5.051	2.472	0.621	0.312	0.000	.	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
54	34.776	18.624	11.111	6.764	2.752	0.687	0.364	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
55	25.817	11.552	7.977	4.528	2.407	0.954	0.372	0.000	0.000	18	21	0	0.16	0.33	0.52	0.67	0.83	1	1.25	1.50	2.00	2.50	3
56	17.747	12.964	8.103	4.642	2.300	0.618	0.275	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
57	9.870	8.417	5.160	3.240	1.443	0.515	0.000	0.000	0.000	17	20	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
58	10.095	6.244	4.565	2.860	1.209	0.306	0.000	0.000	0.000	17	20	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
59	17.445	11.688	8.448	5.123	2.881	0.640	0.280	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
60	11.861	11.050	7.532	3.548	2.637	0.674	0.298	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
61	23.525	12.958	10.028	5.490	2.252	1.098	0.388	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
62	28.447	18.925	13.812	6.108	4.680	1.731	0.765	0.263	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
63	51.861	27.768	16.929	8.389	4.427	1.965	0.647	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
64	70.795	37.292	22.921	12.637	5.749	2.931	0.475	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
65	13.147	8.907	10.554	5.888	3.144	1.170	0.596	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
66	9.510	6.956	6.415	4.181	2.130	0.594	0.343	0.000	0.000	18	21	0	0.19	0.33	0.50	0.67	0.83	1	1.25	1.52	2.00	2.50	3
67	13.115	9.458	6.814	4.611	2.306	0.682	0.550	0.000	0.000	18	21	0	0.16	0.36	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
68	10.429	10.694	6.844	4.253	2.281	0.467	0.331	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
69	21.375	17.145	12.775	7.479	5.131	2.058	0.876	0.313	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
70	20.626	15.940	12.309	7.187	5.908	1.686	0.956	0.260	0.000	19	22	0	0.19	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
71	27.301	19.954	12.031	9.080	4.430	1.587	0.712	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
72	25.607	15.778	10.791	9.703	5.129	2.013	0.905	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
73	33.616	21.429	12.267	7.955	3.775	1.014	0.474	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
74	18.631	16.448	12.580	7.535	4.516	1.352	0.865	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
75	15.065	12.682	8.245	4.721	2.762	1.624	0.745	0.332	0.000	19	22	0	0.16	0.36	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
76	21.130	17.408	10.987	5.206	3.792	1.262	0.337	0.000	0.000	18	21	0	0.18	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
77	8.944	5.924	3.934	2.352	1.442	0.475	0.000	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
78	11.681	10.277	5.585	3.316	1.554	0.455	0.310	0.000	0.000	18	21	0	0.18	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
79	25.714	17.974	11.917	7.635	4.242	1.447	0.594	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
80	19.243	18.159	10.144	7.274	3.926	1.113	0.609	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
81	14.748	11.710	7.789	4.687	2.243	1.003	0.404	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
82	13.101	10.328	6.980	5.747	2.624	0.965	0.432	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
83	31.886	20.872	15.424	10.541	5.301	1.449	0.687	0.402	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.52	3
84	25.726	18.619	10.928	8.699	3.803	0.856	1.046	0.319	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
85	53.982	35.479	22.230	17.404	8.344	3.177	1.786	0.790	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
86	63.222	44.403	33.756	28.276	13.529	4.051	2.409	1.060	0.259	20	23	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
87	17.754	31.841	12.710	8.583	4.988	1.737	0.818	0.286	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
88	22.911	23.095	16.786	9.608	4.313	1.356	0.803	0.298	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
89	40.745	24.747	15.591	9.396	4.139	1.312	0.668	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
90	17.883	16.595	14.149	8.587	4.093	1.323	0.675	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
91	21.098	10.667	11.102	7.465	3.855	1.419	0.506	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
92	31.020	19.937	14.246	10.978	5.163	1.867	0.516	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
93	16.215	11.415	11.064	7.639	5.503	1.787	1.102	0.347	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
94	24.298	25.531	23.904	13.828	6.969	2.533	1.985	0.710	0.297	20	23	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
95	39.384	26.173	18.865	10.379	6.124	2.225	1.058	0.494	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
96	54.752	34.766	21.632	13.635	7.132	2.214	1.044	0.412	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
97	30.502	24.398	23.916	13.817	6.463	2.370	1.064	0.375	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
98	33.809	34.261	20.951	11.508	5.360	2.392	1.259	0.407	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
99	9.795	11.450	7.901	5.700	3.359	1.206	0.617	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
100	38.894	23.859	14.121	7.381	3.868	1.252	0.669	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
101	36.893	21.792	15.315	7.278	3.154	1.503	0.643	0.256	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
102	28.842	15.296	9.486	6.845	4.355	1.487	0.473	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
103	45.251	33.691	26.462	16.170	9.636	3.548	1.894	0.690	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
104	22.708	18.768	18.854	10.883	5.820	2.103	0.858	0.302	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
105	22.243	12.175	8.492	5.809	2.607	1.115	0.641	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
106	23.248	19.265	9.822	8.425	3.228	1.351	0.743	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
107	18.957	12.974	9.118	5.953	2.605	0.739	0.474	0.000	0.000	18	21	0	0.16	0.35	0.50	0.67	0.85	1	1.25	1.50	2.00	2.50	3
108	15.265	9.417	8.465	6.813	4.648	1.019	0.675	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
109	14.389	12.868	8.458	4.155	1.797	0.721	0.000	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
110	16.578	16.640	10.752	6.652	3.210	1.032	0.503	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
111	37.572	20.523	12.069	8.979	4.441	1.075	0.605	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
112	30.557	19.254	14.169	9.666	4.086	0.993	0.703	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
113	24.743	20.823	14.587	8.876	4.459	1.637	0.684	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
114	40.161	25.114	14.310	10.880	5.660	2.508	0.731	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
115	10.509	8.402	6.182	5.954	3.262	1.024	0.423	0.000	.	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
116	34.430	16.951	11.612	6.560	2.704	0.812	0.274	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
117	36.857	28.582	17.292	8.870	4.894	1.214	0.625	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
118	26.193	23.649	16.837	9.227	4.075	1.266	0.659	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
119	14.802	11.368	7.988	5.892	2.380	0.769	0.427	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
120	19.770	15.809	8.511	5.926	2.728	0.607	0.343	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
121	25.771	15.478	7.902	5.045	2.286	0.698	0.264	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
122	17.815	10.965	6.364	4.139	2.111	0.588	0.274	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
123	29.567	19.537	12.701	8.471	5.211	1.421	1.002	0.436	.	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
124	39.130	34.243	14.795	9.708	9.822	1.873	2.919	0.411	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
125	44.977	25.242	21.657	11.432	5.924	2.020	0.785	0.299	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
126	49.702	31.306	14.230	12.709	6.595	2.760	0.936	0.390	.	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
127	21.103	11.326	9.858	4.572	3.064	0.776	0.331	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
128	12.320	7.377	7.394	4.009	2.785	0.746	0.370	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
129	23.269	19.250	24.233	8.930	4.531	1.191	0.586	0.000	.	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
130	22.755	14.305	23.795	7.294	2.841	1.038	0.473	0.000	0.000	18	21	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
131	36.331	26.402	21.741	14.252	7.273	2.550	1.068	0.429	.	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3
132	34.823	29.570	19.776	12.884	8.348	2.933	1.221	0.553	0.000	19	22	0	0.16	0.33	0.50	0.67	0.83	1	1.25	1.50	2.00	2.50	3

Obs	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	trt
1	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.90	1
2	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.63	2
3	4	5.00	6	8.00	10.00	12.02	16	24.00	36	48	72.00	2
4	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.75	1
5	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.57	1
6	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.52	2
7	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.25	1
8	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.08	2
9	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.18	2
10	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.62	1
11	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.27	2
12	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.60	1
13	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	74.10	1
14	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.07	2
15	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.65	1
16	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.55	2
17	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.13	2
18	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.92	1
19	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.53	2
20	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.45	1
21	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.40	2
22	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.42	1
23	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.98	1
24	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.78	2
25	4	5.00	6	8.00	10.00	12.03	16	24.00	36	48	71.90	1
26	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.87	2
27	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.65	2
28	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.62	1
29	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.10	1
30	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.83	2
31	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.37	2
32	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	1
33	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.78	2
34	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.75	1
35	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.70	1
36	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.22	2

Obs	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	trt
37	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	1
38	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.73	2
39	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	74.93	2
40	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	74.60	1
41	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.55	1
42	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.38	2
43	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.63	1
44	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.40	2
45	4	5.00	6	8.02	10.00	12.00	16	24.00	36	48	72.63	2
46	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.08	1
47	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.50	2
48	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.08	1
49	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.17	1
50	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.95	2
51	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.22	1
52	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.43	2
53	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	2
54	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.40	1
55	4	5.00	6	8.03	10.00	12.00	16	24.00	36	48	71.38	2
56	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.43	1
57	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.68	1
58	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.57	2
59	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.67	2
60	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.52	1
61	4	5.00	6	8.00	10.02	12.00	16	24.00	36	48	73.83	2
62	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.67	1
63	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.43	1
64	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.43	2
65	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.47	2
66	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.82	1
67	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.17	2
68	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.30	1
69	4	5.02	6	8.00	10.00	12.00	16	24.00	36	48	71.40	1
70	4	5.00	6	8.03	10.00	12.00	16	24.00	36	48	71.93	2
71	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.87	2
72	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.58	1
73	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.97	2

Obs	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	trt
74	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.17	1
75	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.35	1
76	4	5.00	6	8.00	10.00	12.00	16	24.02	36	48	73.08	2
77	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.70	2
78	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.43	1
79	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.67	1
80	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.63	2
81	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.07	1
82	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	2
83	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.22	2
84	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.78	1
85	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.63	1
86	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.52	2
87	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.97	1
88	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.53	2
89	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.98	2
90	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.60	1
91	4	5.00	6	8.02	10.00	12.03	16	24.00	36	48	71.63	2
92	4	5.00	6	8.03	10.00	12.00	16	24.00	36	48	71.45	1
93	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.98	2
94	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.45	1
95	4	5.00	6	8.00	10.00	12.02	16	24.00	36	48	71.87	1
96	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.73	2
97	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.77	1
98	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.42	2
99	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.53	2
100	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.68	1
101	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.43	1
102	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.10	2
103	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.45	2
104	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.38	1
105	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.27	1
106	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.52	2
107	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.68	2
108	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.73	1
109	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.97	1
110	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.62	2

Obs	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	trt
111	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.65	1
112	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.20	2
113	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.28	1
114	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.15	2
115	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	2
116	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.30	1
117	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.53	1
118	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.53	2
119	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.70	2
120	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.32	1
121	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.87	2
122	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.52	1
123	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	1
124	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	75.07	2
125	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.27	2
126	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	1
127	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	73.03	2
128	4	5.00	6	8.00	10.00	12.02	16	24.00	36	48	72.98	1
129	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	1
130	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	71.38	2
131	4	5.00	6	8.00	10.00	12.00	16	24.00	36	48	72.00	1
132	4	5.00	6	8.00	10.02	12.00	16	24.00	36	48	73.93	2

4.6.2 Fasting Study Output (Atorvastatin)

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	66	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 36 37 38 39 40 41 42 44 45 46 47 48 49 52 54 55 56 57 58 59 60 61 62 63 65 66 67 68 69 70 71 72
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	132
Number of Observations Used	132

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	67	21.63494304	0.32290960	5.71	<.0001
Error	64	3.62034860	0.05656795		
Corrected Total	131	25.25529165			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.856650	3.962533	0.237840	6.002225

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.06823965	0.06823965	1.21	0.2762
sub(seq)	64	21.55850175	0.33685159	5.95	<.0001
per	1	0.00015635	0.00015635	0.00	0.9582
trt	1	0.00804528	0.00804528	0.14	0.7073

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.06823965	0.06823965	1.21	0.2762
sub(seq)	64	21.55850175	0.33685159	5.95	<.0001
per	1	0.00015635	0.00015635	0.00	0.9582
trt	1	0.00804528	0.00804528	0.14	0.7073

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.06823965	0.06823965	0.20	0.6542

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01561398	0.04140266	0.38	0.7073

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	67	21.21065725	0.31657697	5.77	<.0001
Error	64	3.51267534	0.05488555		
Corrected Total	131	24.72333259			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.857921	3.894859	0.234277	6.015022

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.06712265	0.06712265	1.22	0.2729
sub(seq)	64	21.13585179	0.33024768	6.02	<.0001
per	1	0.00010656	0.00010656	0.00	0.9650
trt	1	0.00757625	0.00757625	0.14	0.7115

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.06712265	0.06712265	1.22	0.2729
sub(seq)	64	21.13585179	0.33024768	6.02	<.0001
per	1	0.00010656	0.00010656	0.00	0.9650
trt	1	0.00757625	0.00757625	0.14	0.7115

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.06712265	0.06712265	0.20	0.6536

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01515200	0.04078233	0.37	0.7115

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	67	26.93613537	0.40203187	1.93	0.0043
Error	64	13.29912109	0.20779877		
Corrected Total	131	40.23525646			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.669466	9.839513	0.455850	4.632846

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01184412	0.01184412	0.06	0.8121
sub(seq)	64	26.68515118	0.41695549	2.01	0.0030
per	1	0.09373827	0.09373827	0.45	0.5042
trt	1	0.14540179	0.14540179	0.70	0.4060

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01184412	0.01184412	0.06	0.8121
sub(seq)	64	26.68515118	0.41695549	2.01	0.0030
per	1	0.09373827	0.09373827	0.45	0.5042
trt	1	0.14540179	0.14540179	0.70	0.4060

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01184412	0.01184412	0.03	0.8667

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.06637857	0.07935321	0.84	0.4060

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.99
2		1	0.99
3		1	0.99
4		1	0.99
5		1	0.99
6		1	0.99
7		1	0.99
8		1	0.99
9		1	0.99
10		1	0.97
11		1	0.98
12		1	0.99
13		1	0.99
14		1	0.98
15		1	0.98
16		1	0.98
17		1	0.99
18		1	0.98
19		1	1.00
20		1	0.99
21		1	0.99
22		1	0.96
23		1	0.99
24		1	0.99
25		1	0.99
26		1	0.99
27		1	0.99
28		1	0.99
29		1	0.98
30		1	0.99
31		1	0.99
32		1	0.99
33		1	0.99
34		1	0.99
35		1	0.99
36		1	0.98
37		1	0.98
38		1	0.98
39		1	0.99

Obs	sub	trt	AUCRATIO
40	(b) (6)	1	0.98
41		1	0.99
42		1	0.99
43		1	0.99
44		1	0.99
45		1	0.98
46		1	0.99
47		1	0.99
48		1	0.99
49		1	0.99
50		1	0.98
51		1	0.99
52		1	0.99
53		1	0.98
54		1	0.98
55		1	0.99
56		1	0.99
57		1	0.99
58		1	1.00
59		1	0.99
60		1	0.99
61		1	1.00
62		1	0.99
63		1	0.99
64		1	0.98
65		1	0.99
66		1	0.99
67		2	0.99
68		2	0.97
69		2	0.99
70		2	0.98
71		2	0.98
72		2	0.99
73		2	0.99
74		2	0.98
75		2	0.99
76		2	0.98
77		2	0.98
78		2	0.97
79		2	0.97

Obs	sub	trt	AUCRATIO
80	(b) (6)	2	0.99
81		2	0.99
82		2	0.98
83		2	0.99
84		2	0.99
85		2	0.99
86		2	0.99
87		2	0.99
88		2	0.96
89		2	0.99
90		2	0.99
91		2	0.99
92		2	0.99
93		2	0.99
94		2	0.99
95		2	0.99
96		2	0.99
97		2	0.99
98		2	0.99
99		2	0.98
100		2	0.97
101		2	0.99
102		2	0.99
103		2	0.99
104		2	0.99
105		2	0.98
106		2	0.98
107		2	0.99
108		2	0.99
109		2	1.00
110		2	0.99
111		2	0.99
112		2	0.99
113		2	0.99
114		2	1.00
115		2	0.99
116		2	0.97
117		2	0.99
118		2	0.99
119		2	0.98

Obs	sub	trt	AUCRATIO
120	(b) (6)	2	0.99
121		2	0.99
122		2	0.99
123		2	0.98
124		2	0.98
125		2	0.99
126		2	0.99
127		2	1.00
128		2	0.99
129		2	1.00
130		2	0.99
131		2	0.99
132		2	0.99

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.20	1.20	0.80	6.00	1.11	0.90
	2	2.30	2.27	6.84	0.63	1.02	0.98
	1	1.06	1.06	1.64	2.00	1.01	0.99
	1	1.19	1.18	1.98	1.50	0.93	1.07
	2	0.90	0.89	0.74	0.80	1.17	0.85
	2	0.67	0.67	0.37	2.99	1.04	0.96
	1	1.01	1.01	1.42	0.60	1.06	0.94
	1	1.00	1.00	0.73	1.60	1.02	0.98
	2	0.90	0.90	0.56	1.33	0.97	1.03
	2	0.79	0.80	1.07	1.00	0.85	1.18
	2	1.05	1.05	0.87	0.80	0.96	1.04
	1	1.30	1.28	1.44	2.50	0.84	1.19
	1	1.42	1.40	2.47	1.00	1.29	0.78
	2	0.62	0.62	1.23	0.80	0.74	1.35
	1	0.77	0.77	0.86	0.17	0.94	1.07
	2	0.96	0.96	1.11	1.00	1.06	0.94
	2	1.03	1.02	1.08	1.00	1.02	0.98
	1	0.89	0.90	0.53	1.25	0.99	1.01
	1	1.72	1.71	1.15	1.25	1.41	0.71
	2	1.52	1.51	2.73	0.54	1.05	0.95
	1	2.56	2.55	3.08	1.87	0.61	1.63
	1	1.25	1.25	0.98	8.00	1.02	0.98
	2	1.02	1.03	1.04	1.00	0.94	1.06
	2	0.87	0.87	0.65	2.50	0.68	1.47
	1	1.32	1.32	3.30	0.34	0.97	1.03
	1	1.20	1.19	0.75	3.73	0.91	1.10

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.49	1.49	1.41	1.20	1.03	0.97
	2	1.61	1.60	4.12	0.25	1.15	0.87
	1	0.79	0.79	0.59	0.67	0.85	1.18
	2	0.64	0.64	0.64	1.00	0.87	1.14
	2	0.76	0.76	0.37	4.00	0.83	1.20
	1	0.74	0.74	0.45	1.00	0.79	1.26
	2	1.09	1.08	1.54	0.76	1.11	0.90
	2	1.06	1.05	1.71	2.99	1.24	0.81
	1	0.71	0.71	0.43	0.80	0.94	1.07
	2	0.84	0.85	0.56	1.51	0.93	1.07
	2	0.73	0.74	0.53	1.33	0.78	1.28
	1	0.55	0.56	0.45	0.25	0.57	1.77
	2	1.19	1.19	1.25	0.81	0.72	1.38
	1	0.99	0.99	0.84	5.97	1.02	0.98
	1	0.78	0.78	0.36	3.73	0.94	1.06
	2	0.73	0.73	0.77	1.25	0.85	1.18
	1	0.79	0.80	0.88	2.99	1.18	0.85
	1	0.77	0.77	1.20	0.40	1.10	0.91
	2	0.56	0.57	0.51	0.33	0.97	1.03
	2	1.05	1.05	0.96	1.00	1.13	0.89
	2	1.56	1.56	1.61	1.33	0.57	1.75
	1	0.84	0.85	0.89	1.00	0.89	1.12
	1	1.06	1.06	1.30	0.63	1.11	0.90
	2	1.88	1.85	1.46	5.97	1.07	0.93
	1	0.87	0.87	0.45	2.67	0.69	1.45
	2	0.75	0.74	2.30	0.25	1.15	0.87
	1	0.87	0.87	0.59	1.00	0.92	1.09
	2	0.75	0.76	0.59	0.59	0.98	1.02
	1	1.56	1.55	3.64	0.60	1.34	0.75
	1	0.87	0.87	1.05	1.60	1.05	0.95
	1	1.08	1.08	1.92	1.00	0.95	1.05
	2	2.65	2.61	2.65	1.81	1.17	0.85
	1	0.85	0.85	0.67	2.40	1.04	0.96
	2	1.22	1.22	1.43	0.67	1.12	0.89
	2	1.06	1.06	3.05	0.50	0.93	1.07
	1	0.86	0.87	1.02	2.99	0.85	1.17
	2	1.02	1.02	1.02	1.20	0.97	1.03
	2	0.88	0.89	1.02	0.25	0.91	1.10
	1	1.14	1.14	1.34	4.00	1.04	0.96
	1	1.04	1.04	1.21	1.00	1.04	0.96

4.7 Additional Attachments

None

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 091226/S001

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg base

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified:

During an inspection conducted by the Office of Scientific Investigation (OSI) in (b) (4) (b) (4) for another application, at the analytical site, Mylan Laboratories Limited, Hyderabad, India, (formerly known as Matrix Laboratories Ltd.), the same site where your *in vivo* bioequivalence (BE) study #24902/11-12 was conducted. The DBI is concerned that the following OSI finding may potentially impact the integrity of your study results.

(b) (4)

Please address the OSI finding above with respect to its impact on the BE study #24902/11-12 of your current application.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 091226

Enter Review Productivity and Generate Report

Completed Assignment for 091226 ID: 18607

Reviewer: Liu, Qing **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Supplement: Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
18607	6/18/2012	Bioequivalence Study (REGULAR)	Fasting Study	1	1
18607	6/18/2012	Other (REGULAR)	Dissolution-Based Waiver	1	1
18607	6/18/2012	Other (REGULAR)	Dissolution-Based Waiver	1	1
18607	6/18/2012	Other (REGULAR)	Dissolution-Based Waiver	1	1
				Total:	4

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

/s/

QING LIU
12/13/2012

BING V LI
12/13/2012

HOAINHON N CARAMENICO
12/14/2012

DALE P CONNER
12/14/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91226/S001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

TELEPHONE AMENDMENT FAX

ANDA 091226/ S-001

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: MYLAN PHARMACEUTICALS INC.
ATTN: Joseph J Sobecki

TEL: (304) 599-2595
FAX: (304) 285-6407

FROM: Haitao Li, PhD

FDA CONTACT PHONE: 240-276-8462

Dear Sir:

This facsimile is in reference to your supplemental new drug application dated June 15, 2012 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendment dated January 25, 2013.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" with in ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Leigh Ann Sears at 240-276-8453. Please submit documentation by fax to the attention of Haitao Li at 240-276-8747. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091226/S-001
APPLICANT: MYLAN PHARMACEUTICALS INC.
DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

The deficiencies presented below represent telephone deficiencies.

A. Deficiencies:

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

/s/

HAITAO LI
02/11/2013

LAXMA R NAGAVELLI
02/11/2013

VILAYAT A SAYEED
02/11/2013

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 091226/S-001
DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

APPLICANT: Mylan Pharmaceuticals Inc.
DATE OF SUBMISSION:11/27/12

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,& MaPP 5240.3). At least one of the criteria must be met to receive Expedited Review Status:

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - Relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).
   e) MaPP 5240.3 conditions.

RECOMMENDATIONS:

DISCIPLINE	STATUS		SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒	Deny☐	RG 11/30/12
Chemistry Team Leader (sign as needed)	Grant☐	Deny☐	
Micro Team Leader (sign as needed)	Grant☐	Deny☐	
Labeling Team Leader (sign as needed)	Grant☐	Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐	Deny☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☒	Deny☐	RLW/RG for 11/30/12

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: Team 34
a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS DATE 11/30/12
Paste Email Copy Below:

From: West, Robert L
Sent: Friday, November 30, 2012 2:36 PM
To: Gaines, Robert
Subject: RE: ANDA 091624 - Atorvastatin Tablets - Kremers --ANDA 91-226s/001 Mylan
Yes.

Bob

From: Gaines, Robert
Sent: Friday, November 30, 2012 2:35 PM
To: West, Robert L; Greenberg, Harvey A; Sears, Leigh Ann
Cc: Rickman, William P
Subject: RE: --ANDA 91-226s/001 Mylan
Last question: Do we categorize it as drug shortage expedite? I'm asking because the points difference is significant.

Thanks

Bob

From: West, Robert L
Sent: Friday, November 30, 2012 2:34 PM
To: Greenberg, Harvey A; Gaines, Robert; Sears, Leigh Ann
Cc: Rickman, William P
Subject: RE: --ANDA 91-226s/001 Mylan
Absolutely. Bob - Please do the paperwork for both and forward to me early next week. Repeat for any other Atorvastatin ANDAs or supplements discovered by Harvey.

Bob

From: Greenberg, Harvey A
Sent: Friday, November 30, 2012 2:30 PM
To: West, Robert L; Gaines, Robert; Sears, Leigh Ann
Cc: Rickman, William P
Subject: RE: --ANDA 91-226s/001 Mylan
Hello everyone,
Couple things, this is going to be a very big recall and does have the potential of a large shortage which we really do not want or need at this time. In addition, again Ranbaxy gives generics a bad name. I believe we need to expedite the pending ANDA 91-624 by Kremer Urban to prevent the potential shortage. Plus I have another firm requesting an expedite of their supplemental application 91-226/s-001 by Mylan to provide a bigger supply. Plus I believe we will have more companies requesting help. So at this time--Bob West do you concur that we expedite the current ANDA 91-624 and ANDA 91-226/S-001--Thanks Harvey

From: West, Robert L
Sent: Friday, November 30, 2012 12:20 PM
To: Gaines, Robert; Sears, Leigh Ann
Cc: Greenberg, Harvey A; Rickman, William P

Subject: FW: ANDA 091624 - Atorvastatin Tablets - Kremers -
Bob:

I'm forwarding this message to you for follow up. I'll be out of the office next week. I've also included Harvey on this message for potential drug shortage input.

Thanks,

Bob

From: Kurt.Zimmer@ucb.com [mailto:Kurt.Zimmer@ucb.com]
Sent: Friday, November 30, 2012 8:51 AM
To: West, Robert L
Subject: ANDA 091624
Good morning Bob,

I have left a couple messages for Bob Gaines but have not heard back to date and I believe he works from home on Fridays. I realize it has only been a few days since the initial message, but as you can imagine, this is extremely high on the Kremers Urban priority list. The content of the messages were to inquire about an approximate review/approval timeline and confirmation of expedited review for ANDA 091624, Atorvastatin Calcium Tablets.

A brief background, Kremers Urban (KU) submitted electronically November 21 the responses to the Complete Response letter. KU was notified the DMF holder, (b) (4) (b) (4) responded November 27 to a deficiency they had received.

As a result of the recent Ranbaxy recall, Kremers Urban believes a shortage of product will occur as early as end of business today, as Ranbaxy has approximately (b) (4) of the market share. If there is any additional information and/or review timeline you can provide, it would be greatly appreciated. If you have any questions, my contact information is below. Thank you for your time.

Best regards,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.
1101 C Ave West
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12/03/2012