CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-540

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION I

NDA 21540 Submission Date: October 9, 2003
N-000-(BB)

CADUET™ (Amlodipine besylate/Atorvastatin calcium) Tablets
Pfizer, Inc.

Type of Submission: Dissolution Data Analysis Methodology for Biowaiver

Background:

The sponsor submitted a proposal for the analysis of dissolution data of amlodipine besylate and atorvastatin calcium from fixed combination tablet (CADUET™) of the two drugs.
In a teleconference on October 31st, 2001 it was conveyed to the sponsor that dissolution studies on the two dose strengths (5/10 and 10/80 mg) are required. Bracketing approach in which the highest-dose and lowest-dose combinations are tested for bioequivalence against the individual components was also discussed on August 19th 1999.
According to the suggestions from the Agency, the sponsor submitted the dissolution data from the fixed combination tablets and proposed an alternative method for evaluating the dissolution data since one of the active ingredients in CADUET, atorvastatin calcium, is not amenable to low pH media and would demonstrate incomplete dissolution and variable results. Since atorvastatin demonstrated solubility limited dissolution for the higher dose strengths, data for atorvastatin calcium from CADUET tablets will be provided for all eight strengths in pH 4.5 and pH 1.2 media and compared to that of the commercial Lipitor tablets instead of comparison with highest strength of the CADUET tablet in the same media. The proposal was based on prior information about the individual components and approval was sought from the agency for the proposal discussed in Appendix I.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation-I (OCPB/DPEI) has reviewed the information provided and considers the approach acceptable.

Venkatesh Atul Bhattaram, Ph.D
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marrroum, Ph.D._____

CC list: HFD-110: NDA 21540; HFD-860: (Mehta, Sahajwalla);

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APPENDIX –I

Amlodipine: Amlodipine is a member of the 1,4-dihydropyridine structural class of calcium channel blockers, and is approved for use in hypertension, chronic stable angina, and confirmed or suspected vasospastic angina. The besylate salt of amlodipine is marketed as Norvasc® in the US (NDA 19-787) at doses of 5 and 10 mg once daily (QD), with a 2.5-mg starting dose available for small, fragile, or elderly individuals or for patients with hepatic insufficiency.

Atorvastatin: Atorvastatin, a synthetic inhibitor of 3-hydroxy-3-methylglutary-coenzyme A (HMG CoA) reductase, is approved for use as an adjunct to diet to reduce elevated cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, and triglycerides and to increase high-density lipoprotein cholesterol in patients with primary hypercholesterolemia, mixed dyslipidemia, and homozygous familial hypercholesterolemia. The calcium salt of atorvastatin is marketed as Lipitor® in the United States (NDA-20-702) at doses of 10, 20, 40 and 80 mg QD.

The sponsor has developed a tablet dosage form containing combinations of the two active ingredients, amlodipine besylate and atorvastatin. Fixed combination tablets have been developed for oral administration in the following 8 respective dose combinations: 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, 10/80 mg amlodipine/atorvastatin, respectively. The intent is to offer fixed dose combinations of all commonly used amlodipine and atorvastatin QD dosing options currently available for the 2 drugs individually.

Formulation Issues

Amlodipine besylate/Atorvastatin calcium tablets will be provided as film coated tablets in 8 dose strength combinations of 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg amlodipine/atorvastatin, respectively.

Combinations of atorvastatin with 5 mg amlodipine will be film coated white and combinations of atorvastatin with 10 mg amlodipine will be film coated blue.

The development effort for the formulation and process development was conducted with the intent of providing commercially viable multidose combinations of amlodipine besylate and atorvastatin calcium in tablet dosage form, minimizing tablet weight to assure patient acceptance, and to establish bioequivalence to commercial Norvasc and Lipitor tablets.

Minor changes were necessary to the commercial products:

1. Lipitor is manufactured using [redacted] s. For a fixed dose combination tablet, atorvastatin calcium is [redacted] using a [redacted]
2. The [redacted] in the fixed dose combination tablet is greater than in Lipitor to produce acceptable tablet weight.
3. [redacted] in the fixed dose combination tablet due to potential incompatibility with the [redacted] in amlodipine besylate. This ingredient is replaced with pregelatinized starch.
4. [redacted] used in Norvasc is not used in the fixed dose combination tablet.
5. The [redacted] used in Norvasc is replaced with croscarmellose sodium in the fixed dose combination product.
6. The fixed combination tablet contains colloidal silicon dioxide. This excipient is not used in commercial Norvasc and Lipitor.

Dissolution

A single dissolution method for amlodipine besylate/atorvastatin calcium tablets was developed by the sponsor by selecting a dissolution medium appropriate for monitoring both active ingredients simultaneously. Previous knowledge of Norvasc and Lipitor dissolution methodologies were applied. Dissolution studies were performed for the batches of fixed dose combination tablets used in pivotal studies at pH 1.2, 4.5 and 6.8. The data are shown in Appendix II.

Amlodipine

1. Active moiety is basic in nature
2. Dissolution
   USP 2(Paddles) at 75 rpm
   Medium: 500 mL 0.01M hydrochloric acid
   Acceptance Criteria: Q= [redacted] after 30 min (according to USP)

Atorvastatin

1. Low solubility below pH 4.6 (pKa=4.6)
2. [redacted]
3. Dissolution
   USP II (paddles) at 75 rpm
   Medium: 900 mL pH 6.8 phosphate buffer
   Acceptance criteria: Q= [redacted] after 15 min

Pivotal Bioequivalence Studies

The studies demonstrated the proposed commercial fixed dose combination tablets are bioequivalent to coadministered commercial Norvasc and Lipitor tablets at highest (10/80 mg) and lowest (5/10 mg) strength.

Issues

The sponsor indicated that one of the active ingredients in CADUET, atorvastatin calcium, is not amenable to low pH media and would demonstrate incomplete and variable results in dissolution. The sponsor collected the data at pH 1.2 and 4.5 and the results are shown in Appendix II. As expected, atorvastatin calcium is not well behaved at low pH across all dose strengths due to chemical instability and poor solubility. This causes different dosage strengths to plateau at different levels. Hence, the sponsor is requesting endorsement of an alternate approach for analysis of atorvastatin data to support a biowaiver.

Sponsor Proposal

The sponsor proposed the following methodology for analysis:

1. Because amlodipine is readily soluble across the physiological pH range, data for amlodipine besylate will be provided for all eight strengths in pH 4.5 and pH 1.2 media and compared to the 10/80 mg lot used in the bioequivalence study. Profile similarity will be evaluated using the f2 metric as appropriate, or by other analyses consistent with FDA guidance documents.
2. Because atorvastatin demonstrates solubility limited dissolution for the higher dose strengths, data for atorvastatin calcium from CADUET tablets will be provided for all eight strengths in pH 4.5 and pH 1.2 media and compared to that of commercial Lipitor tablets instead of comparison with highest strength of the CADUET tablet in the same media. Profile similarity will be evaluated using the f2 metric as appropriate, or by other analysis consistent with FDA guidance documents.

Amlodipine Comparisons			
Strength	Test	Reference	Comparison
5-mg	Caduet 5/10 BEQ lot	Norvasc 5-mg	BEQ Study A3841010
5-mg	Caduet 5/20	Caduet 10/80 BEQ lot	Dissolution Profile Similarity
5-mg	Caduet 5/40	Caduet 10/80 BEQ lot	Dissolution Profile Similarity
5-mg	Caduet 5/80	Caduet 10/80 BEQ lot	Dissolution Profile Similarity
10-mg	Caduet 10/10	Caduet 10/80 BEQ lot	Dissolution Profile Similarity
10-mg	Caduet 10/20	Caduet 10/80 BEQ lot	Dissolution Profile Similarity
10-mg	Caduet 10/40	Caduet 10/80 BEQ lot	Dissolution Profile Similarity
10-mg	Caduet 10/80 BEQ lot	Norvasc 10-mg	BEQ Study A3841009
Atorvastatin Comparisons			
10-mg	Caduet 5/10 BEQ lot	Lipitor 10-mg	BEQ Study A3841010
10-mg	Caduet 10/10	Lipitor 10-mg	Dissolution Profile Similarity
20-mg	Caduet 5/20	Lipitor 20-mg	Dissolution Profile Similarity
20-mg	Caduet 10/20	Lipitor 20-mg	Dissolution Profile Similarity
40-mg	Caduet 5/40	Lipitor 40-mg	Dissolution Profile Similarity
40-mg	Caduet 10/40	Lipitor 40-mg	Dissolution Profile Similarity
80-mg	Caduet 5/80	Lipitor 80-mg	Dissolution Profile Similarity
80-mg	Caduet 10/80 BEQ lot	Lipitor 80-mg	BEQ Study A3841009

FDA Response

Yes, the approach is acceptable due to the fact that

1. Bioequivalence for amlodipine besylate and atorvastatin calcium has been demonstrated for the highest (10/80 mg) and lowest (5/10 mg) combination tablet inspite of differences in ingredients in the individual tablets and combination tablet.
2. The acceptable dissolution profile of both ingredients in the compendial media for dissolution (pH 6.8).

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/s/

Atul Bhattaram
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BIOPHARMACEUTICS

Patrick Marroum
11/7/03 12:27:09 PM
BIOPHARMACEUTICS

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION-I

NDA 21-540	
Submission Date	March 31, 2003 August 7, 2003 October 9, 2003 November 5, 2003 November 12, 2003
Drug Name	CADUET™ (Amlodipine besylate/ Atorvastatin Calcium)
Tablet Strengths	Tablets (5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, 10/80 mg)
Sponsor	Pfizer
OCPB Reviewer	Venkatesh Atul Bhattaram Ph.D
OCPB Team Leader	Patrick Marroum, Ph.D

Executive Summary/OCPB Summary

Pfizer, Inc is proposing a combination tablet (CADUET®) for amlodipine besylate and atorvastatin calcium. The various strengths to be marketed are 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg of amlodipine/atorvastatin. The developmental program of CADUET included:

- A multi- national, prospective, randomized, double- blind, multi-center, placebo- controlled study to evaluate the efficacy and safety of a fixed combination therapy of amlodipine and atorvastatin in the treatment of concurrent hypertension and hyperlipidemia (The RESPOND Trial).
- Pharmacokinetic interaction study of amlodipine and atorvastatin in healthy subjects.
- Bioequivalence study at highest (10/80 mg) and lowest (5/10 mg) strengths of CADUET in healthy subjects.
- Food effect study.
- Dissolution study of the CADUET formulation at pH 1.2, 4.5 and 6.8.

Based on the submitted information, no significant pharmacokinetic and pharmacodynamic interactions were observed. The formulations were bioequivalent at the highest and lowest strengths. Administration of the combination tablets (10/80 mg) with a high fat meal decreased C_{max} and $AUC_{0-\infty}$ by 32 and 11% respectively which is not clinically significant. Biowaiver for six intermediate strengths (5/20, 5/40, 5/80, 10/10, 10/20, 10/40 mg) was granted based on the dissolution data at pH 1.2, 4.5 and 6.8.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information provided in the NDA 21-540. The requested biowaiver for six intermediate strengths (5/20, 5/40, 5/80, 10/10, 10/20, 10/40 mg) of CADUET is granted.

The sponsor is requested to:

1. Change the proposed dissolution for both ingredients according to FDA recommendation as follows:

Condition	FDA Recommendation
Dissolution Media	: pH 6.8
Volume	: 900 ml
USP 2 Paddle	
Paddle Speed	:75 rpm
Specifications	: Q= [redacted] in 15 minutes

Venkatesh Atul Bhattaram, Ph.D
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marrroum, Ph.D._____

Clinical Pharmacology and Biopharmaceutics briefing was held on December 17, 2003. The attendees were Dr Mehul Mehta, Dr Patrick Marroum and Dr Venkatesh Atul Bhattaram.

CC list: HFD-110: NDA 21540; HFD-860: (Mehta, Sahajwalla);

Question Based Review

Regulatory History

1. What is the current approved indication for amlodipine besylate and atorvastatin calcium?

Amlodipine is a 1,4-dihydropyridine calcium channel blocker approved for use in the treatment of hypertension/angina.

Atorvastatin, a synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, is approved for use as adjunct in diet for dyslipidemia.

2. What is the current approved dose for amlodipine and atorvastatin?

The besylate salt of amlodipine is marketed as Norvasc® (NDA 19-787) in the United States at doses of 5 and 10 mg once daily. Small, fragile or elderly individuals or patients with hepatic impairment may be started on amlodipine 2.5 mg QD for hypertension, and this dose may be used when adding Norvasc to other antihypertensive therapy.

The calcium salt of atorvastatin is marketed as Lipitor® in the US (NDA 20-702) at doses of 10, 20, 40 and 80 mg QD.

Biopharmaceutics

1. Was an adequate link established between the clinical and to be marketed formulations of CADUET?

Yes.

The sponsor submitted data from two pivotal bioequivalence studies in which formulations containing highest (10/80 mg) and lowest (5/10 mg) combination strengths of amlodipine and atorvastatin were used.

The clinical trial formulation is identical to the marketed formulation except in the film coating (a SUPAC Level 1 Change) that is not expected to impact on formulation quality and performance.

2. What is the basis for the justification of biowaiver for intermediate strengths?

The sponsor proposes to market 8 different strengths of amlodipine and atorvastatin as combination tablets. The biowaiver was granted for 6 intermediate strengths based on the following reasons:

- Bioequivalence has been demonstrated for individual components at highest (10/80 mg) and lowest (5/10 mg) strengths.
- Similarity of dissolution profiles at pH 1.2, 4.5 and 6.8 for most strengths or differences that of such magnitude did not result in bioavailability differences.

3. Is there an effect of food on the bioavailability of amlodipine and atorvastatin from CADUET tablets?

   Administration of amlodipine (10 mg)/Atorvastatin (80 mg) combination tablets with a high fat meal had no effect on the pharmacokinetic profile of amlodipine. The mean atorvastatin Tmax was delayed by 1 hour and the mean Cmax was decreased by 32%. There was a 11% decrease in the extent of absorption but the 90% confidence interval (CI) was well in the range of 80-125%. The effect of food is not clinically significant.

4. Are the sponsor proposed dissolution medium and specifications acceptable?

   Yes, with minor modification.The sponsor proposes the following dissolution media for CADUET tablets.

Dissolution Media	: pH 6.8
Volume	: 900 ml
USP 2 Paddle	
Paddle Speed	:75 rpm
Acceptance Criterion: Q=	

The OCPB recommendations are to change the acceptance criterion of Q= for both amlodipine and atrovastatin to 15 minutes since dissolution is achieved for both ingredients at pH 6.8 from CADUET tablets.

Exposure-Response (PK-PD)

1. Is there any pharmacokinetic interaction when amlodipine and atorvastatin are coadministered?

   No. There is no significant pharmacokinetic interaction when amlodipine and atorvastatin are coadministered at the lowest (5/10 mg) and highest (10/80 mg) strength in healthy volunteers as seen in Figure 1.

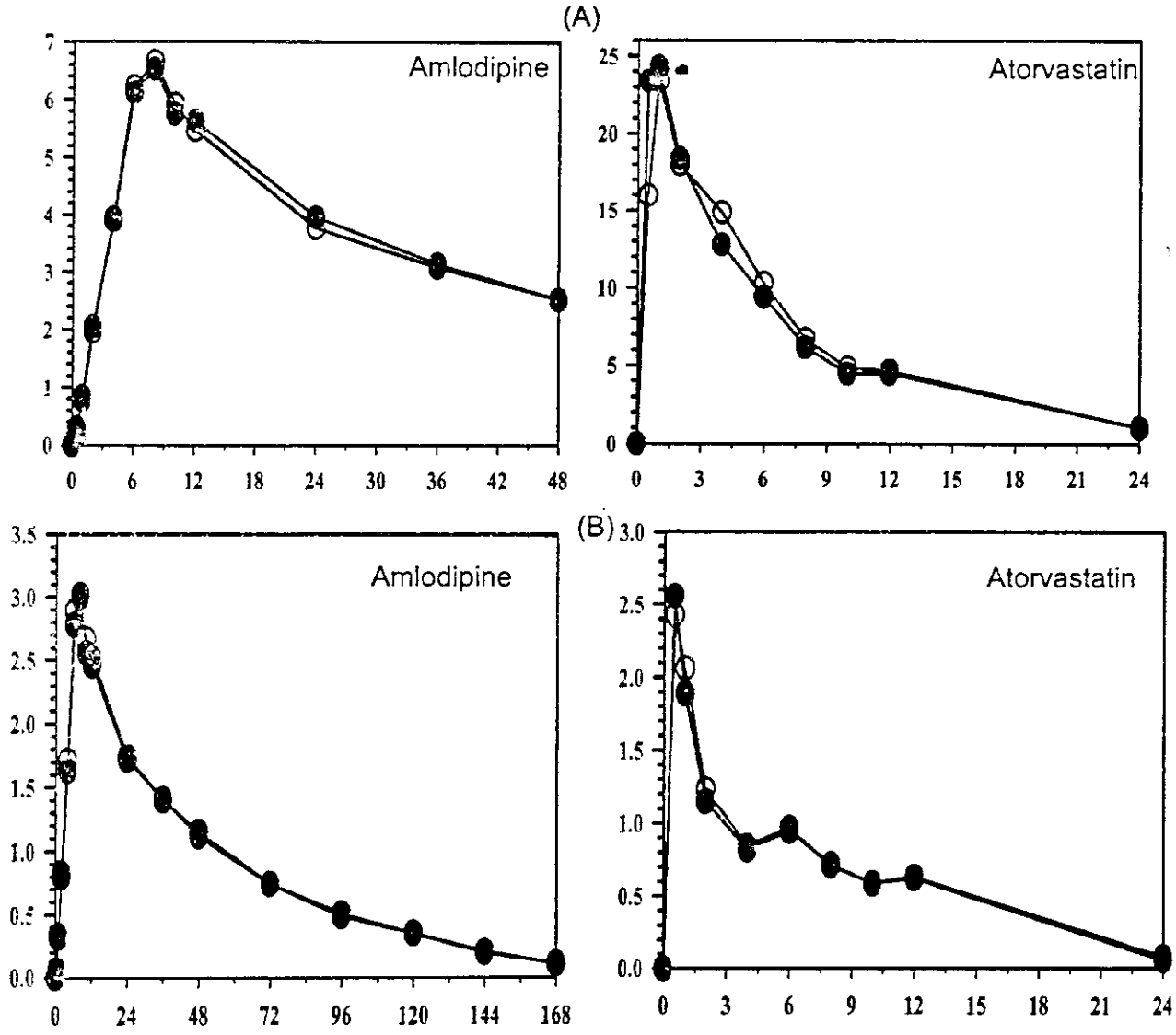

Figure 1. Plasma concentration-time profile of amlodipine and atorvastatin in pharmacokinetic interaction study. The labels A and B refer to the formulations containing combination of 5/10 and 10/80 mg of amlodpine/atorvastatin.

2. Is there any pharmacodynamic interaction between amlodipine and atorvastatin when coadministered?

No. There is no pharmacodynamic interaction between amlodipine and atorvastatin when coadministered. This was confirmed by the sponsor using fixed combinations of amlodipine and atorvastatin in clinical trials in the target population. Figure 2 below shows that the reductions in low density lipoprotein (LDL-C) when atorvastatin 10, 20, 40 or 80 mg was administered concurrently with any amlodpine dose were similar to the reductions seen when atorvastatin was administered alone. Figure 3 show that the reductions in systolic blood pressure when amlodipine 5 or 10 mg was administered concurrently with any atorvastatin doses were similar to the reductions seen when 5 or 10 mg amlodipine was administered alone.

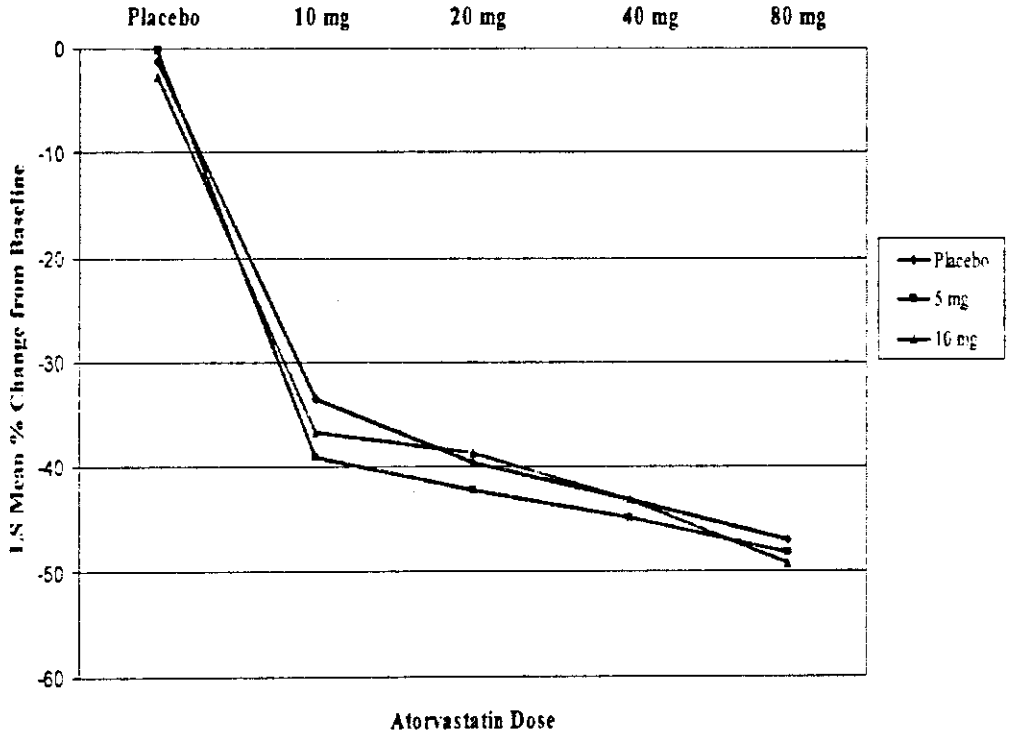

Figure 2. Effect of amlodipine (Placebo, 5 and 10 mg) on atrovastatin dose response curve--LDL-C.

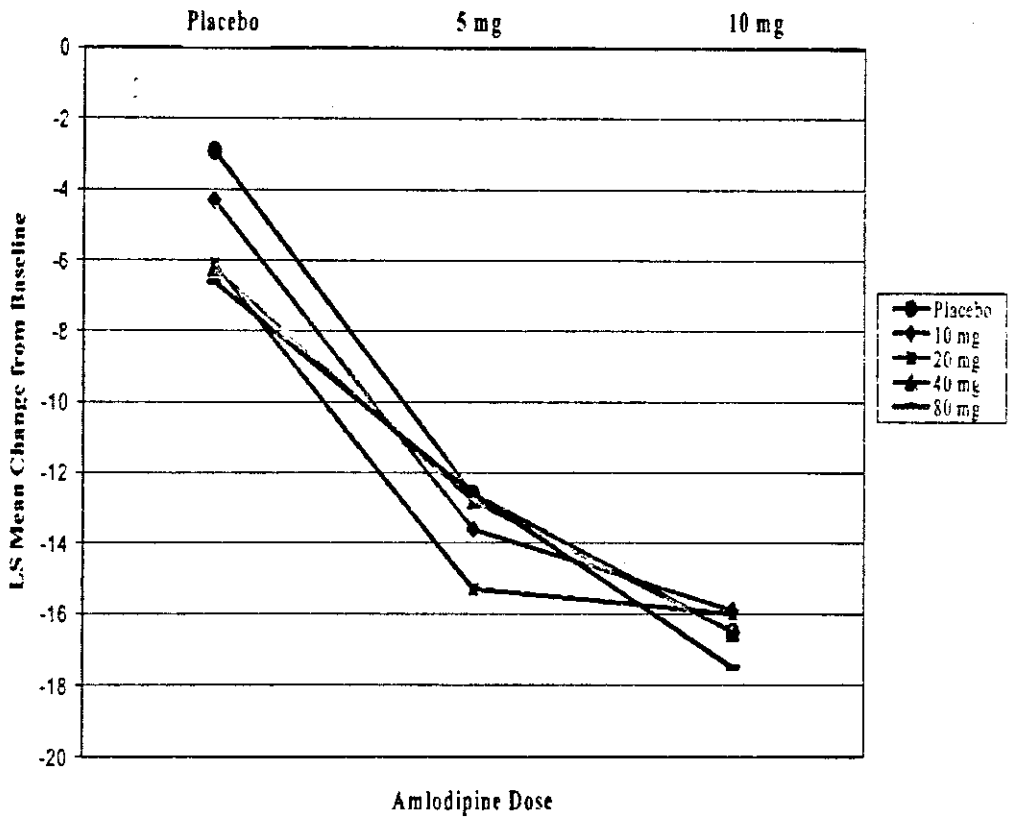

Figure 3. Effect of atorvastatin (Placebo, 10, 20, 40 and 80 mg) on amlodipine dose response curve—Systolic BP.

3. Is the proposed label by the sponsor for CADUET acceptable?

Yes. The proposed label by the sponsor is acceptable from biopharmaceutics perspective.

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Draft Labeling
(not releasable,

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Individual Study Reviews

Amlodipine-Atorvastatin Interaction

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Protocol No. A 0531029- Phase I Open Study to Evaluate a Drug Interaction Between Atorvastatin and Amlodipine

STUDY INVESTIGATORS AND Center(s):

[redacted]

Objective

To determine a potential interaction between atorvastatin and amlodipine.

Formulation

Amlodipine (10 mg) + Atorvastatin (2x40 mg).

Amlodipine (Norvasc) 10-mg tablet, Lot 0QP025A-G1.

Atorvastatin (Lipitor) 2x40-mg tablet, Lot 0082020-G1.

Study Design

The sponsor conducted a randomized, open-label, three-treatment crossover study with a 14-day washout period between treatments. The study was conducted in 24 healthy subjects. Amlodipine 10 mg and atorvastatin 80 mg (2x40 mg tablets) were administered as follows:

	Day 1	Day 15	Day 29
Group 1	Amlodipine 10 mg	Atorvastatin 80 mg	Amlodipine 10 mg + Atorvastatin 80 mg
Group 2	Atorvastatin 80 mg	Amlodipine 10 mg + Atorvastatin 80 mg	Amlodipine 10 mg
Group 3	Amlodipine 10 mg + Atorvastatin 80 mg	Amlodipine 10 mg	Atorvastatin 80 mg
Group 4	Amlodipine 10 mg	Amlodipine 10 mg + Atorvastatin 80 mg	Atorvastatin 80 mg
Group 5	Atorvastatin 80 mg	Amlodipine 10 mg	Amlodipine 10 mg + Atorvastatin 80 mg
Group 6	Amlodipine 10 mg + Atorvastatin 80 mg	Atorvastatin 80 mg	Amlodipine 10 mg

Dosage Administration

Subjects were dosed on Days 1, 15 and 29 at approximately 0800 after a fast of at least 8 hours. Subjects received single oral doses of 10 mg amlodipine, 80 mg atorvastatin or 10 mg amlodipine + 80 mg atorvastatin according to a randomization schedule.

Evaluations

The schedule of observations and evaluations is shown in Appendix-I. Plasma samples were collected for pharmacokinetic analysis of amlodipine, atorvastatin and its two metabolites at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168 and 192 hours after each dose and pharmacokinetic parameters were estimated using standard noncompartmental methods. Safety issues such as vital signs, clinical laboratory assessments, and adverse events (AEs) were evaluated.

Pharmacokinetic and Statistical Methods

Standard noncompartmental analysis was performed. The C_{max} and AUC values were log-transformed and 90% confidence intervals were calculated for the ratios of the treatment means. If the confidence intervals were contained entirely in the 80% to 125% range then the absence of interaction was concluded. Secondary parameters included in the analysis were λ_z, $t_{1/2}$ and t_{max} as well as untransformed C_{max} and AUC. Log-transformed AUC_{inf}, AUC_t and C_{max} and untransformed T_{max} and $t_{1/2}$ were analyzed separately by means of analysis of variance (ANOVA) with sequence, period and treatment as fixed effects and subject as a random effect.

Analytical Methods

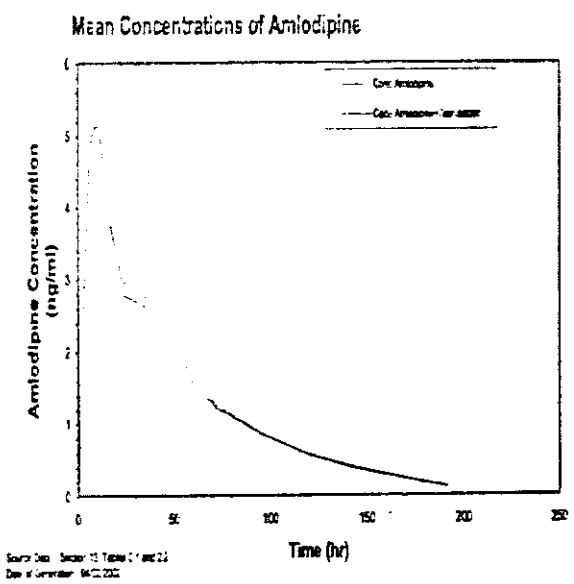
Plasma concentrations of amlodipine and atorvastatin were determined using validated assay methods using ——— and LC/MS/MS method respectively.

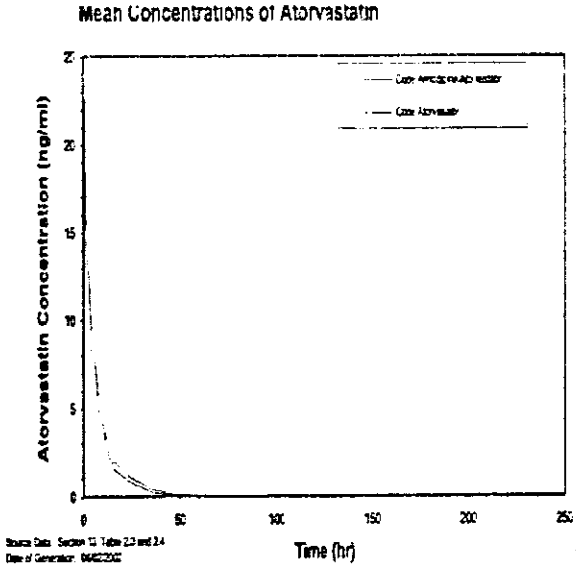
Amlodipine: The intra and inter-assay precision results (RSD) calculated from QC samples were [redacted] at all concentrations. The mean intra-assay and inter-assay accuracy values (RE) calculated from QC samples ranged from [redacted] The range of the calibration curve was from [redacted] The limit of quantification was [redacted]

Atorvastatin and Metabolites: The intra- assay and inter- assay precision (RSD) results calculated from QC samples were [redacted] for all analytes at all concentrations. The mean intra- assay and inter- assay accuracy values (RE) calculated from QC samples ranged from [redacted] for all analytes at all concentrations. The range of the calibration curve of all the analytes was from [redacted] The limit of quantitation was [redacted]

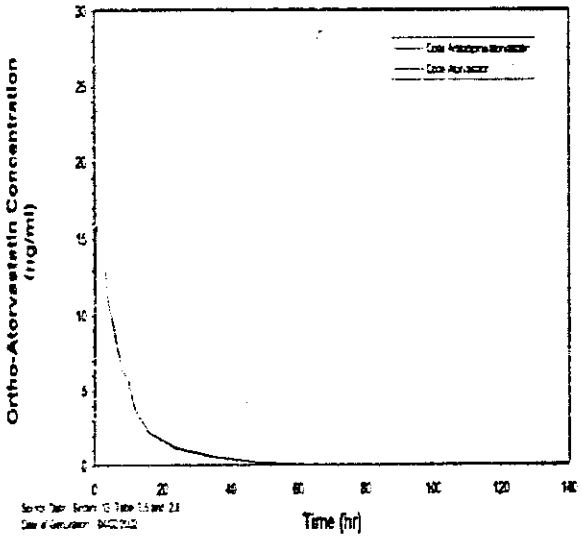
Results

The mean plasma concentration-time profiles of amlodipine, atorvastatin, para-atorvastatin and ortho-atrovastatin are shown below.

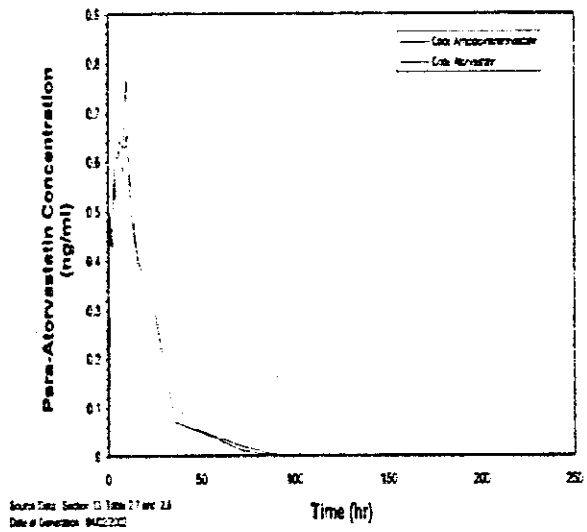




Mean Concentrations of Ortho-Atorvastatin



Mean Concentrations of Para-Atorvastatin



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The mean pharmacokinetic parameter values are shown in Table 1 with ratios and confidence intervals.

Discussion

Coadministration of single dose 10 mg atorvastatin did not affect the single dose pharmacokinetics of 80 mg amlodipine. The atorvastatin AUC_{inf} was increased on average 18% following coadministration of amlodipine. Atorvastatin C_{max} was not affected. Coadministration of amlodipine did not affect the AUC of ortho-atorvastatin metabolite, however, C_{max} decreased by 30% compared with the administration of atorvastatin alone. The pharmacokinetics of para-atorvastatin were similar in the presence and absence of amlodipine.

Conclusion

The data obtained in this study indicates that the interaction between 10 mg amlodipine and 80 mg atorvastatin is not clinically significant.

Table 1. Mean Pharmacokinetic Parameters of Amlodipine, Atorvastatin and Ortho-Atorvastatin. In the table below "A" refers to the parameter estimate when amlodipine and atorvastatin are not administered together, while "B" refers to the parameter estimate when amlodipine and atorvastatin are administered together.

Analyte	AUC_{inf} (ng.hr/ml)		C_{max} (ng/ml)		T_{max} (hr)		$T_{1/2}$ (hr)	
	A	B	A	B	A	B	A	B
Amlodipine	274 (95.3)	268 (99.1)	5.57 (1.65)	5.51(1.67)	9.17(1.76)	9.17(2.20)	39.6(7.27)	40.6(7.69)
90%CI	97 (91-104)		99 (93-106)		-0.06 (-0.84-0.72h)		1.17 (-0.63-2.98h)	
Atorvastatin	126 (72.3)	145 (73.3)	23.8 (15.6)	20.9 (13.4)	1.32 (0.69)	1.48 (0.71)	7.40 (2.69)	8.1 (3.62)
90%CI	118 (109-127)		91 (80-10.3)		0.15 (-0.15-0.46 h)		0.72 (0.15-1.28h)	
Ortho-atorvastatin	164 (54.8)	153 (31.5)	28.3 (13.2)	19.5 (8.9)	1.3 (0.7)	1.7 (1.2)	8.9 (2.2)	9.7 (4.1)
90%CI	93 (86-100)		70 (61-79)		0.39 (-0-0.78h)		0.86 (-0.11-1.82h)	

Study Procedures

Study Day	Screening	1[a]									2		3	4	5	6	7	8	Final Eval[b]
Hours Following Dosing		0	0.5	1	2	4	6	8	10	12	24	36	48	72	96	120	144	168	
History[c]	X	X[d,e]																	
Physical Exam	X																		X
Clinical Laboratory Tests	X[f]																		X
Electrocardiogram	X																		
Urine Pregnancy Test (Females Only)		X[d]																	
Serum Pregnancy Test (Females Only)	X																	X[g]	
Dosing		X																	
Pharmacokinetic Blood Samples		X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Monitoring		X[d]			X					X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs (BP HR)	X	X[d]			X					X									
Concomitant Medicines Questions		X[d]									X	X	X	X	X	X	X	X	X
Confined to the Clinic		X	----------							X									

[a] Days 1 to 8 occurred in both Study Periods I and II. Days 1 to 8 of Period II are Days 15 to 22 in the data listings.

[b] Within 48 hours of the collection of the final, Study Period II. pharmacokinetic blood sample

[c] Medical, prior medication, alcohol and tobacco use histories

[d] Prior to dosing

[e] Changes since Screening. Study Period I only

[f] Included urine drug screen

[g] Following collection of the final, Study Period II. pharmacokinetic sample

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Protocol No. A 3841007- A Comparative Bioavailability Study of Amlodipine (10mg)/Atorvastatin (80 mg) Combination Tablet Following Single Dose Under Fed and Fasted Conditions

STUDY INVESTIGATORS AND SITES: Bramson CR
Pfizer Research Clinic
2800 Plymouth Road
Ann Arbor, MI 48105

Objective

To evaluate the effect of a high-fat meal on the bioavailability of amlodipine (10 mg)/atorvastatin (80 mg) combination tablet following a single-dose administration under fed and fasted conditions.

Formulation

Amlodipine (10 mg)/atorvastatin (80 mg) combination tablet, Lot CG 0341201, Formulation 15927-10.

Study Design

The sponsor conducted an open-label, single-dose, randomized, 2-way crossover study with a 14-day washout period between doses conducted in 40 healthy subjects. On Day 1 of each study period, subjects received a single dose of medication under fed or fasted conditions as follows:

	Period 1 (Day 1)	Period 2 (Day 1)
Group 1	Fasted	Fed
Group 2	Fed	Fasted

Dosage Administration

Fasted (Reference): Subjects fasted overnight for at least 10 hours before administration of an amlodipine (10 mg)/ atorvastatin (80 mg) combination tablet with 240 mL of water. They continued to fast for 4 hours after dosing.

Fed (Test): A standardized meal (2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, 2 slices of toast with 2 pats of butter, and 8 oz of whole milk) was given 30 minutes before dosing and completely consumed over 30 minutes with administration of a CADUET (10/80 mg) combination tablet with 240 mL of water immediately after the meal. No food was allowed for 4 hours after the dose.

Evaluations

The schedule of observations and evaluations is shown in Appendix I. Plasma samples were collected for amlodipine and atorvastatin pharmacokinetic analysis at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after each dose and pharmacokinetic parameters were estimated using standard noncompartmental methods. Safety issues such as vital signs, clinical laboratory assessments, and adverse events (AEs) were evaluated.

Pharmacokinetic and Statistical Methods

Standard noncompartmental analysis was performed using WinNonlin Pro Version 2.1. The C_{max} and AUC values were log-transformed and 90% confidence intervals were calculated for the ratios of the treatment means. If the confidence intervals were contained entirely in the 80% to 125% range then the absence of food effect was concluded. Secondary parameters included in the analysis were λ_z, $t_{1/2}$ and t_{max} as well as untransformed C_{max} and AUC. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, group, subject within sequence and group, period and treatment effects.

Analytical Methods

Plasma concentrations of amlodipine and atorvastatin were determined using validated assay methods using [redacted] and LC/MS/MS method respectively. The assay performance of the methods is shown below:

Analyte	Analytical Range		Quality Control	
	Lower Limit (LLOQ, ng/mL)	Upper Limit (ULOQ, ng/mL)	Precision (%CV)	Accuracy (%RE)
Amlodipine	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]

Results

The mean plasma amlodipine and atorvastatin concentration-time profiles are shown in Figure 1.

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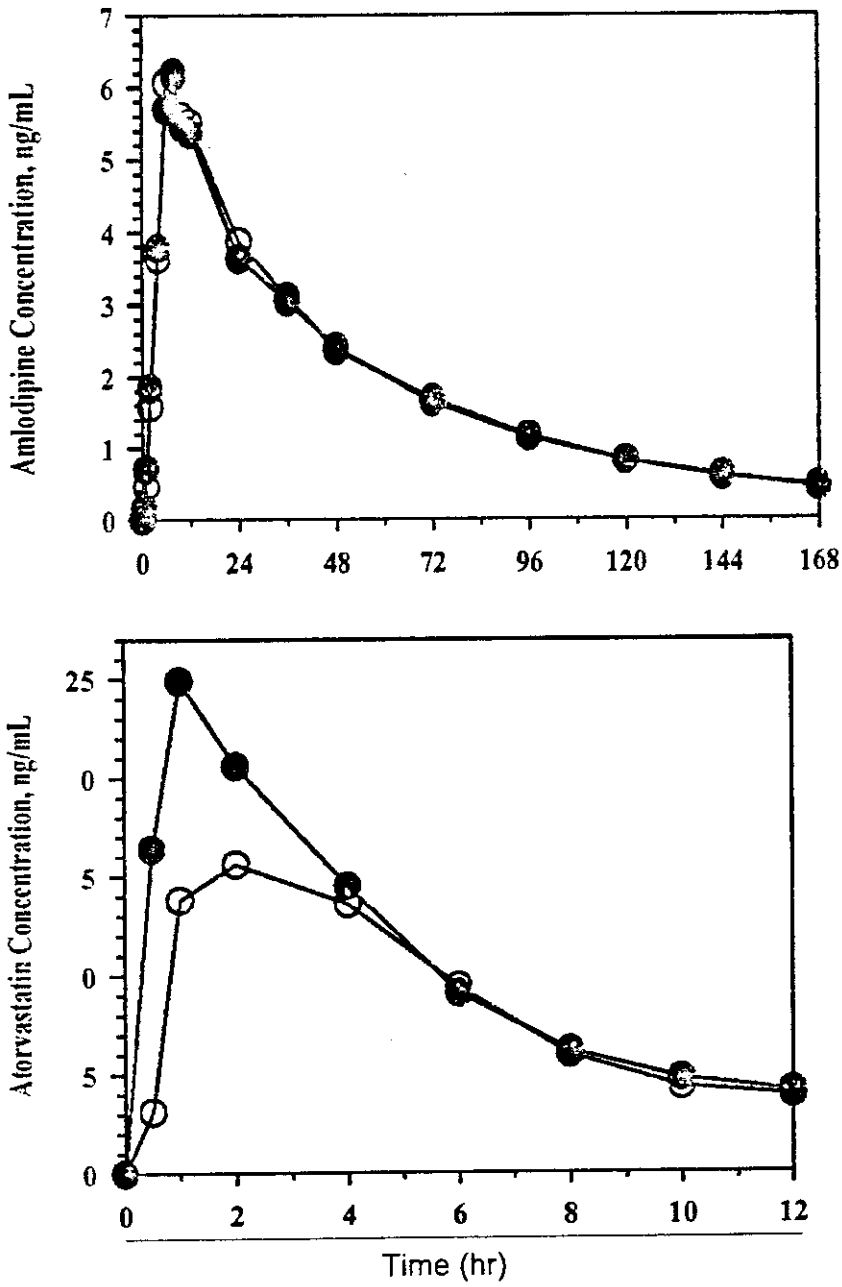

Figure 1. Mean amlodipine plasma concentration-time profiles of amlodipine and atorvastatin following administration of CADUET (10/80 mg) Combination Tablets to Subjects Under Fasting Conditions (Filled Circles) and With a High-Fat Meal (Open Circles) (Study A3841007)

The mean pharmacokinetic parameter values along with ratios and confidence intervals are shown below.

Atorvastatin

Parameter	Least-Squares Mean Values		Ratio (%)	90% Confidence Interval
	Fasting (Reference)	With a High-Fat Meal (Test)		
Cmax*, ng/mL	29.5	20.1	68.1	59.5 to 78.7
tmax, hr	1.38	2.53	183	Not Applicable
AUC(0-tlqc)*, ng·hr/mL	157	136	86.6	81.0 to 92.5
AUC(0-∞)*, ng·hr/mL	167	148	88.6	83.4 to 94.9
t½, hr	14.9	19.4	130	102.2 to 158.3

Amiodipine

Parameter	Least-Squares Mean Values		Ratio (%)	90% Confidence Interval
	Fasting (Reference)	With a High-Fat Meal (Test)		
Cmax*, ng/mL	6.14	6.43	105	98.8 to 111.0
tmax, hr	8.15	7.80	95.7	Not Applicable
AUC(0-tlqc)*, ng·hr/mL	298	306	103	98.6 to 107.0
AUC(0-∞)*, ng·hr/mL	336	340	101	97.4 to 105.3
t½, hr	51.7	51.4	99.4	92.6 to 106.3

Discussion

Administration of amlodipine (10 mg)/Atorvastatin (80 mg) combination tablets with a high fat meal had no effect on the pharmacokinetic profile of amlodipine. The 90% CI for the ratio of treatment geometric mean amlodipine C_{max} and $AUC_{0-\infty}$ values were both within 80% and 125% range indicating absence of an effect of high fat meal. Administration of the combination tablets with a high-fat meal delayed the mean atorvastatin t_{max} value approximately 1 hour and decreased the mean C_{max} value nearly 32%. The 90% CI for the ratio of the geometric mean atorvastatin C_{max} values was outside of the 80 to 125% range indicating an effect of a high fat meal on atorvastatin C_{max} values. There was a 11% decrease in the extent of atorvastatin absorption but the 90%CI was well in the range of 80 to 125%.

Overall, the food effect findings were similar to those observed in similar studies with amlodipine (Norvasc®) and atorvastatin (Lipitor®).

Conclusion

Administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high fat meal has no effect on amlodipine pharmacokinetic profiles. Administration of these tablets with food decreased the rate and extent of atorvastatin absorption by 32% and 11%, respectively, as assessed by C_{max} and $AUC_{(0-\infty)}$. The effect of food is not clinically significant and hence, CADUET tablets can be administered without regard to food.

Study Procedures

Study Day	Screening	1[a]									2		3	4	5	6	7	8	Final Eval[b]
Hours following dosing		0	0.5	1	2	4	6	8	10	12	24	36	48	72	96	120	144	168	
History[c]	X	X[d,e]																	
Physical Exam	X																		X
Clinical Laboratory Tests	X[f]																		X
Electrocardiogram	X																		
Urine Pregnancy Test (females only)		X[d]																	
Serum Pregnancy Test (females only)	X																	X[g]	
Dosing		X																	
Pharmacokinetic Blood Samples		X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Monitoring		X[d]			X					X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs (BP HR)	X	X[e]			X					X									
Concomitant Medicines Questions		X[d]									X	X	X	X	X	X	X	X	X
Confined to the clinic		X	----------							X									

[a] Days 1 to 8 occur in both Study Periods 1 and 2. Days 1 to 8 of Period 2 are Days 15 to 22 in the data listings.
[b] Within 48 hours of the collection of the final, Study Period 2, pharmacokinetic blood sample
[c] Medical, prior medication, alcohol and tobacco use histories
[d] Prior to dosing
[e] Changes since Screening, Study Period 1 only
[f] Included urine drug screen
[g] Following collection of the final, Study Period 2, pharmacokinetic sample

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Bioequivalence Study (Amlodipine 5mg/Atorvastatin 10 mg)

Protocol No. A 3841010- A Single Dose Bioequivalence Study Comparing a 5-mg Amlodipine/10-mg Atorvastatin Combination Tablet to Coadministration of 5-mg Amlodipine and 10-mg Atorvastatin Tablets.

STUDY INVESTIGATORS AND Center(s): Bramson CR
Pfizer Research Clinic
2800 Plymouth Road
Ann Arbor, MI 48105

Objective

To evaluate whether 1 amlodipine (5-mg)/atorvastatin (10-mg) combination tablet is bioequivalent to coadministration of one 5-mg amlodipine (Norvasc®) tablet and one 10-mg atorvastatin (Lipitor®) tablet.

Formulation

Amlodipine (5 mg)/atorvastatin (10 mg) combination tablet, Lot CG 0251201, Formulation 15927-11. Lot size: [redacted] Production batch size [redacted]
Amlodipine (Norvasc) 5-mg tablet, Lot 1QL272A.
Atorvastatin (Lipitor) 10-mg tablet, Lot 0070399.

Study Design

The sponsor conducted an open-label, single-dose, randomized, 2-way crossover study with a 14-day washout period between doses in 62 healthy subjects. On Day 1 of each study period, subjects received a single dose of medication following an overnight fast.

	Period I	Period II
Group 1	Combination[a]	Coadministration[b]
Group 2	Coadministration[b]	Combination[a]

[a] Combination (Test): Administration of one amlodipine (5 mg)/atorvastatin (10 mg) combination tablet

[b] Coadministration (Reference): Coadministration of one 5-mg amlodipine (Norvasc) and one 10-mg atorvastatin (Lipitor) tablet

On Day1 of Study Period 1 or 2, the subjects received 1 amlodipine (5-mg)/atorvastatin (10- mg) combination tablet or coadministration of one 5-mg amlodipine and one 10-mg atorvastatin tablet. Subjects were required to fast for at least 8 h before each drug administration. The two doses were separated by a washout period of at least 14 days.

Evaluations

The schedule of observations and evaluations is shown in Appendix-1. Plasma samples were collected for amlodipine and atorvastatin pharmacokinetic analysis at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after each dose and pharmacokinetic parameters were estimated using standard noncompartmental methods. Safety issues such as vital signs, clinical laboratory assessments, and adverse events (AEs) were evaluated.

Pharmacokinetic and Statistical Methods

Standard noncompartmental analysis was performed using WinNonlin Pro Version 2.1. The C_{max} and AUC values were log-transformed and 90% confidence intervals were calculated for the ratios of the treatment means. Bioequivalence would be concluded if the 90% confidence interval for the treatment ratios of the geometric means of C_{max} and AUC values for both amlodipine and atorvastatin were entirely within the bioequivalence limit of 80% to 125%.

Secondary parameters included in the analysis were λ_z, $t_{1/2}$ and t_{max} as well as untransformed C_{max} and AUC. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, group, subject within sequence and group, period and treatment effects.

Analytical Methods

Plasma concentrations of amlodipine and atorvastatin were determined using validated assay methods using [redacted] and LC/MS/MS method respectively. The assay performance of the methods is shown below:

Analyte	Analytical Range		Quality Control	
	Lower Limit (LLOQ, ng/mL)	Upper Limit (ULOQ, ng/mL)	Precision (%CV)	Accuracy (%RE)
Amlodipine				
Atorvastatin				

Results

The mean plasma concentration-time profiles of amlodipine and atorvastatin are shown in Figure 1.

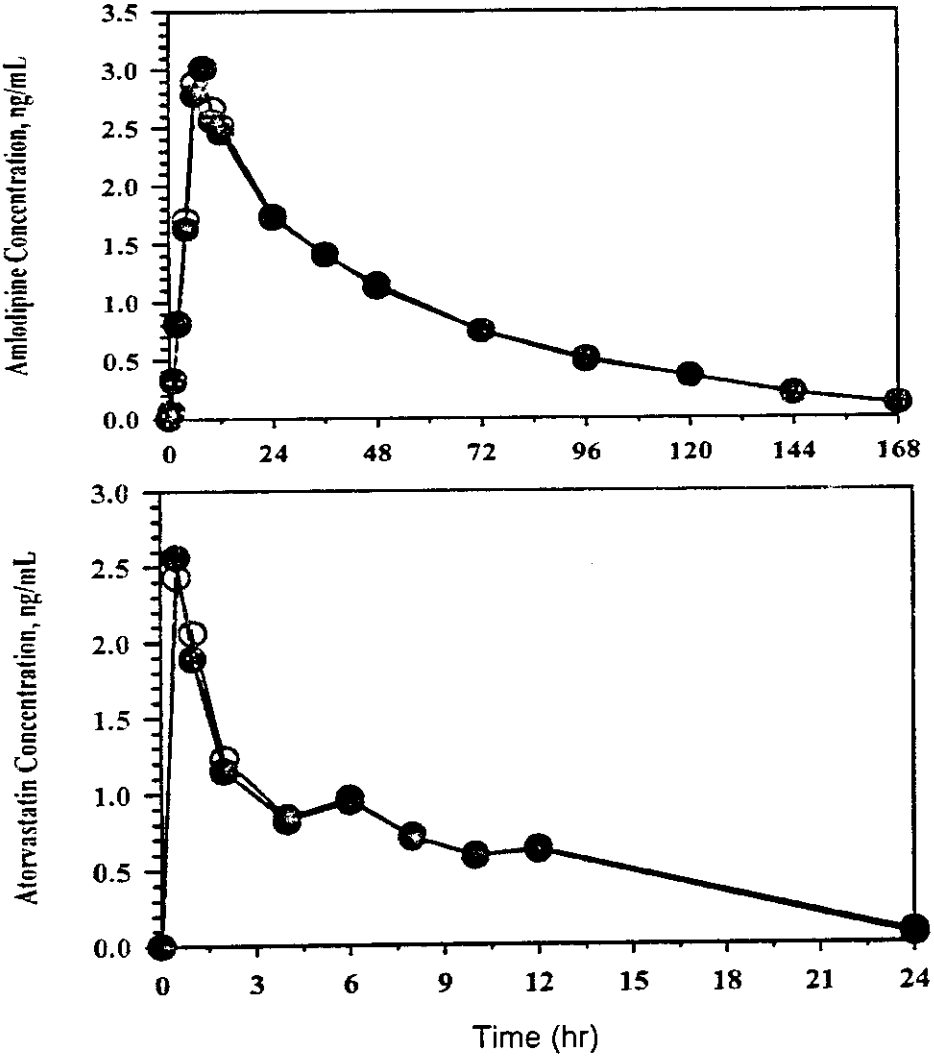

Figure 1. Mean plasma concentration-time profiles of amlodipine and atorvastatin following administration of single CADUET (5/10 mg) combination tablets (Open circles) and single 5 mg amlodipine, 10 mg atrovastatin tablets (Filled circles).

The mean pharmacokinetic parameter values along with ratios and confidence intervals.are shown below:

Amlodipine

Parameter	Least-Squares Mean Values: Co-administered Tablets (Reference)	Least-Squares Mean Values: Combination Tablet (Test)	Ratio (%)	90% Confidence Interval
N	63	63		
Cmax*, ng/mL	2.94	3.04	103	99.6 to 107.7
tmax, hr	7.67	7.80	102	Not Applicable
AUC(0-tlqc)*, ng·hr/mL	130	133	102	99.1 to 105.5
AUC(0-∞)*, ng·hr/mL	147	151	103	98.9 to 105.4
t½, hr	45.1	44.9	99.6	94.5 to 104.6

Atorvastatin

Parameter	Least-Squares Mean Values: Co-administered Tablets (Reference)	Least-Squares Mean Values: Combination Tablet (Test)	Ratio (%)	90% Confidence Interval
N	63	63		
Cmax*, ng/mL	2.43	2.40	98.8	88.3 to 110.6
tmax, hr	0.807	0.791	98.0	Not Applicable
AUC(0-tlqc)*, ng·hr/mL	10.5	11.5	110	103.2 to 116.1
AUC(0-∞)*, ng·hr/mL	15.6	16.2	104	96.4 to 111.8
t½, hr	7.60	7.30	96.1	78.1 to 114.0

Discussion

Based on $AUC_{(0-\infty)}$ values, the extent of amlodipine and atorvastatin absorption following administration of combination tablets was similar to that observed for coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets. There was no significant change in the t_{max} and C_{max} of amlodipine and atorvastatin.

Conclusion

The 5-mg amlodipine/10-mg atorvastatin combination tablet formulation is bioequivalent to coadministration of marketed 5-mg amlodipine and 10-mg atorvastatin tablets.

APPENDIX-I Study Procedures

Study Day	Screening	1[a]									2	3	4	5	6	7	8	Final Eval[b]
Hours Following Dosing		0	0.5	1	2	4	6	8	10	12	24	36	48	72	96	120	144	168	
History[c]	X	X[d,e]																	
Physical Exam	X																		X
Clinical Laboratory Tests	X[f]																		X
Electrocardiogram	X																		
Urine Pregnancy Test (Females Only)		X[d]																	
Serum Pregnancy Test (Females Only)	X																	X[g]	
Dosing		X																	
Pharmacokinetic Blood Samples		X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Monitoring		X[d]			X					X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs (BP HR)	X	X[d]			X					X									
Concomitant Medicines Questions		X[d]									X	X	X	X	X	X	X	X	X
Confined to the Clinic		X	———							X									

[a] Days 1 to 8 occurred in both Study Periods I and II. Days 1 to 8 of Period II are Days 15 to 22 in the data listings.

[b] Within 48 hours of the collection of the final, Study Period II, pharmacokinetic blood sample

[c] Medical, prior medication, alcohol, and tobacco use histories

[d] Prior to dosing

[e] Changes since Screening, Study Period I only

[f] Included urine drug screen

[g] Following collection of the final, Study Period II, pharmacokinetic sample

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Bioequivalence Study (Amlodipine 10mg/Atorvastatin 80 mg)

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Protocol No. A 3841009- A Single Dose Bioequivalence Study Comparing a 10-mg Amlodipine/80-mg Atorvastatin Combination Tablet to Coadministration of 10-mg Amlodipine and 80-mg Atorvastatin Tablets.

STUDY INVESTIGATORS AND Center(s): Bramson CR
Pfizer Research Clinic
2800 Plymouth Road
Ann Arbor, MI 48105

Objective

To evaluate whether 1 amlodipine (10-mg)/atorvastatin (80-mg) combination tablet is bioequivalent to coadministration of one 10-mg amlodipine (Norvasc®) tablet and one 80-mg atorvastatin (Lipitor®) tablet.

Formulation:

Amlodipine (10 mg)/atorvastatin (80 mg) combination tablet, Lot CG 0341201, Formulation 15927-10. Lot size: [redacted] Production batch size: [redacted]

Amlodipine (Norvasc®) 10-mg tablet, Lot 1QL278A.

Atorvastatin (Lipitor®) 80-mg tablet, Lot 00972V.

Study Design

The sponsor conducted an open-label, single-dose, randomized, 2-way crossover study with a 14-day washout period between doses in 62 healthy subjects. On Day 1 of each study period, subjects received a single dose of medication following an overnight fast.

	Period I	Period II
Group 1	Combination[a]	Coadministration[b]
Group 2	Coadministration[b]	Combination[a]

[a] Combination (Test): Administration of 1 amlodipine (10-mg)/atorvastatin (80-mg) combination tablet

[b] Coadministration (Reference): Coadministration of one 10-mg amlodipine (Norvasc) and one 80-mg atorvastatin (Lipitor) tablet

Dosage Administration

On Day1 of Study Period 1 or 2, the subjects received 1 amlodipine (10-mg)/atorvastatin (80- mg) combination tablet or coadministration of one 10-mg amlodipine and one 80-mg atorvastatin tablet. Subjects were required to fast for at least 8 h before each drug administration. The two doses were separated by a washout period of at least 14 days.

Evaluations

The schedule of observations and evaluations is shown in Appendix-I. Plasma samples were collected for amlodipine and atorvastatin pharmacokinetic analysis at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after each dose and pharmacokinetic parameters were estimated using standard noncompartmental methods. Safety issues such as vital signs, clinical laboratory assessments, and adverse events (AEs) were evaluated.

Pharmacokinetic and Statistical Methods

Standard noncompartmental analysis was performed using WinNonlin Pro Version 2.1. The C_{max} and AUC values were log-transformed and 90% confidence intervals were calculated for the ratios of the treatment means.

Bioequivalence would be concluded if the 90% confidence interval for the treatment ratios of the geometric means of C_{max} and AUC values for both amlodipine and atorvastatin were entirely within the bioequivalence limit of 80% to 125%. Secondary parameters included in the analysis were λ_z, $t_{1/2}$ and t_{max} as well as untransformed C_{max} and AUC. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, group, subject within sequence and group, period and treatment effects.

Analytical Methods

Plasma concentrations of amlodipine and atorvastatin were determined using validated assay methods using [redacted] and LC/MS/MS method respectively. The assay performance of the methods is shown below:

Analyte	Analytical Range		Quality Control	
	Lower Limit (LLOQ, ng/mL)	Upper Limit (ULOQ, ng/mL)	Precision (%CV)	Accuracy (%RE)
Amlodipine	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]

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Results

The mean plasma amlodipine and atorvastatin concentration-time profiles are shown in Figure 1.

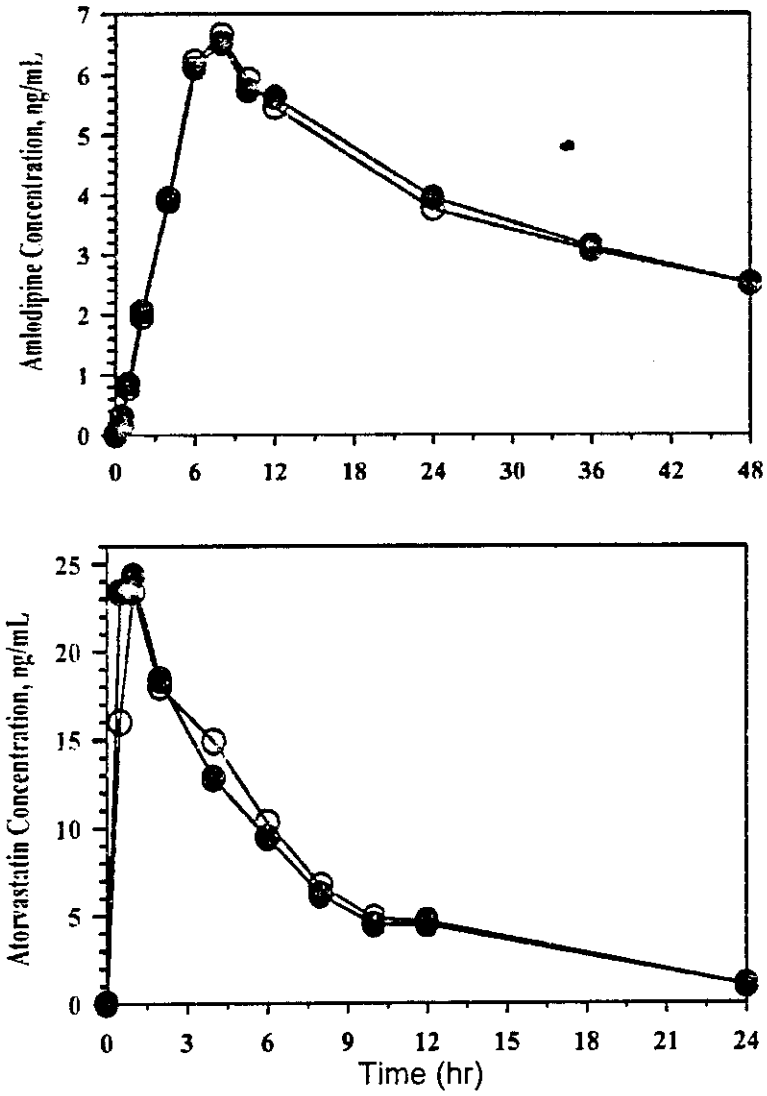

Figure 1-. Mean amlodipine plasma concentration-time profiles following administration of amlodipine (10-mg)/atorvastatin (80-mg) combination tablets (Open Circles) and coadministration of 10-mg amlodipine and 80-mg atorvastatin tablets (Filled Circles).

The mean pharmacokinetic parameter values along with ratios and confidence intervals are shown below

Atorvastatin :

Parameter	Least-Squares Mean Values		Ratio (%)	90% Confidence Interval
	Coadministration (Reference)	Combination Tablets (Test)		
Cmax*, ng/mL	27.1	25.5	94.1	84.6 to 104.4
tmax, hr	1.54	0.893	58.0	Not Applicable
AUC(0-tlqc)*, ng·hr/mL	149	157	105.4	98.5 to 111.5
AUC(0-∞)*, ng·hr/mL	156	163	104.5	98.8 to 110.8
t½, hr	9.34	9.10	97.4	84.6 to 110.3

* Geometric mean

Amlodipine

Parameter	Least-Squares Mean Values		Ratio (%)	90% Confidence Interval
	Co-administration (Reference)	Combination Tablets (Test)		
Cmax*, ng/mL	6.58	6.63	100.8	97.6 to 103.9
tmax, hr	8.07	7.61	94.3	Not Applicable
AUC(0-tlqc)*, ng·hr/mL	307	307	100	97.4 to 102.7
AUC(0-∞)*, ng·hr/mL	336	336	100	97.2 to 102.9
t½, hr	46.9	45.8	97.7	93.2 to 102.1

* Geometric mean

Discussion

Based on $AUC_{(0-\infty)}$ values, the extent of amlodipine and atorvastatin absorption following administration of combination tablets was similar to that observed for coadministration of 10-mg amlodipine and 80-mg atorvastatin tablets. There was no significant change in the t_{max}, C_{max} and $t_{1/2}$ of amlodipine and atorvastatin.

Conclusion

The 10-mg amlodipine/80-mg atorvastatin combination tablet formulation is bioequivalent to coadministration of marketed 10-mg amlodipine and 80-mg atorvastatin tablets.

APPENDIX – I Study Procedures

Study Day	Screening	1[a]									2		3	4	5	6	7	8	Final Eval[b]
Hours Following Dosing		0	0.5	1	2	4	6	8	10	12	24	36	48	72	96	120	144	168	
History[c]	X	X[d,e]																	
Physical Exam	X																		X
Clinical Laboratory Tests	X[f]																		X
Electrocardiogram	X																		
Urine Pregnancy Test (Females Only)		X[d]																	
Serum Pregnancy Test (Females Only)	X																	X[g]	
Dosing		X																	
Pharmacokinetic Blood Samples		X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Monitoring		X[e]			X					X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs (BP HR)	X	X[d]			X					X									X
Concomitant Medicines Questions		X[d]									X	X	X	X	X	X	X	X	X
Confined to the Clinic		X	----------							X									

[a] Days 1 to 8 occurred in both Study Periods 1 and 2. Days 1 to 8 of Period 2 are Days 15 to 22 in the data listings.

[b] Within 48 hours of the collection of the final, Study Period 2, pharmacokinetic blood sample

[c] Medical, prior medication, alcohol and tobacco use histories

[d] Prior to dosing

[e] Changes since Screening, Study Period 1 only

[f] Included urine drug screen

[g] Following collection of the final, Study Period 2, pharmacokinetic sample

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

26 pages

(E)

New Drug Application and Filing Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21540	Brand Name	CADUET
OCPB Division (I, II, III)	DPE 1	Generic Name	Amlodipine Besylate / Atrovastatin Calcium tablets
Medical Division	HFD-110	Drug Class	
OCPB Reviewer	Venkatesh Atul Bhattaram	Indication(s)	
OCPB Team Leader	Patrick Marroum	Dosage Form	Combination product; tablets containing 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg of amlodipine and atorvastatin respectively.
		Dosing Regimen	QD
Date of Submission	31 March 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Pfizer Pharmaceuticals Group
PDUFA Due Date		Priority Classification	
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	11		Only 5 studies need to be reviewed.
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
Biopharmaceutics				
Bioequivalence (Pilot studies)	X	6		
Pivotal Bioequivalence studies -				

Crossover:		2		
Drug-drug interaction studies:	X	2		
Food-drug interaction studies:	X	1		
Dissolution:	X	Summary Data Only		Sponsor asked to submit all raw data and also data from three pH ranges for biowaiver.
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
Total Number of Studies		11		2- Pivotal Bioequivalence studies, 1 pivotal food effect study, 1 pivotal drug interaction study, 1 supportive drug interaction study, 3- bioequivalence studies (prototype tablets), 3- bioequivalence studies (Protoype [redacted] tablets (UK))

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Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	???	Dissolution data needed for biowaiver.
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-540 HFD-110 (McDonaldZ). HFD-860 (MehtaM, SahajwallaC, MarroumP, BhattaramA).
CDR Central Document Room

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

/s/

Atul Bhattaram
12/17/03 02:21:10 PM
BIOPHARMACEUTICS

Patrick Marroum
12/17/03 02:24:05 PM
BIOPHARMACEUTICS

(F)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE