CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-540

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
HFD 110

Medical Review of NDA

Reviewer:	**A.O.Williams, M.D.**
NDA #:	21-540
Drug:	CADUET
Chemical Names:	Amlodipine besylate and Atorvastatin calcium
Sponsor:	Pfizer Pharmaceuticals Group
Proposed indication:	[redacted]

Pharmacologic type:

- Amlodipine = 1,4-dihydropyridine calcium channel blocker
- Atorvastatin = Synthetic inhibitor of 3-hydroxy-3-methyl glutaryl-coenzyme A reductase.

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Medical Review Completed:	December 5, 2003

128 Pages, 84 Tables, 9 Figures, 10 Appendices

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Financial Disclosure

The US Food and Drug Administration Financial Disclosure by Clinical Investigator regulation requires sponsors to obtain financial information from investigators participating in covered clinical studies; each principal investigator and sub-investigator is required and did provide financial disclosure information; and updated Pfizer with any relevant changes to their financial information throughout the course of the clinical studies and will do so for up to one year after its completion.

1.0 Executive Summary

This New Drug Application (NDA) seeks approval to market 8 amlodipine-atorvastatin fixed-dose combination tablets as either initial or substitution therapy for the indication of (

. The rationale for this drug development is based on the universally accepted independent risk factors in pathogenesis of cardiovascular pathology and events in populations with hypertension and dyslipidemia.

This NDA provides data from a single prospective study that compares a single pill, fixed dose, o.d. combination regimen (CADUET) versus a concurrent 2-pill regimen (AMLODIPINE AND ATORVASTATIN). The preference for a single pill makes CADUET a very useful drug for therapy of 2 common conditions with increasing frequency in the aging population if approved.

Hyperlipidemia and hypertension are both major independent risk factors for the development of premature cardiovascular disease. Several studies have also indicated that the presence of either condition predisposes an individual to developing the other. Thus, the two diseases commonly coexist. Because of published favorable outcomes associated with effective treatment of either condition, professional organizations in both the United States and Canada that provide recommendations regarding the treatment of hyperlipidemia and hypertension continue to advocate standard therapeutic targets that need to be achieved when treating each condition if optimal reduction of cardiovascular risks is to be achieved. Furthermore, when both risk factors coexist, the professional organizations have recommended a more aggressive approach to the treatment of either condition. Several placebo-controlled, randomized, double blind studies have demonstrated that atorvastatin and amlodipine are safe and effective therapies for hyperlipidemia and hypertension respectively. And since the use of either agent is not a contraindication to the use of the other, except in hepatically impaired patients, this study aims to explore the dual use of atorvastatin and amlodipine in the clinical setting of coexisting hyperlipidemia and hypertension.

The sponsor refers to the same two independent risk factors for Coronary Heart Disease, that have been implicated in the inevitable pathological substrate in the coronary arteries, namely, atheroma that leads to coronary atherogenesis and atherosclerosis. Functionally, these coronary artery changes may be clinically silent or become symptomatic giving rise, for example, to angina and/or ischemic heart disease. The differences in coronary artery structure and function therefore assumes some importance and raises questions when a claim for angina arises in the absence of a clinical study as in this NDA. This will be discussed later.

INTRODUCTION

1.1 AMLODIPINE

Amlodipine is a member of the 1,4- dihydropyridine structural class of calcium channel blockers, and is approved for use in the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina, herein collectively termed hypertension/ angina. The besylate salt of amlodipine is approved under NDA 19-787 in 1992, and marketed as Norvasc in the United States (US) at doses of 5 and 10 mg once daily (QD).

ATORVASTATIN

The calcium salt of atorvastatin was approved in 1996 and marketed as Lipitor in the US under NDA 20- 702 at doses of 10, 20, 40, and 80 mg QD.

Atorvastatin, a synthetic inhibitor of 3- hydroxy- 3- methylglutaryl-coenzyme A reductase, is approved for use as an adjunct to diet to reduce elevated total cholesterol (TC), low- density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C), in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; as an adjunct to diet for the treatment of patients with elevated TG; for the treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet; and to reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid- lowering treatments or if such treatments are unavailable; these various lipid disorders are herein collectively termed dyslipidemia

1.2 Post-marketing experience

Both amlodipine and atorvastatin, when used separately, have proven efficacy and safety profiles since market launch. Exposure to amlodipine and atorvastatin, over time, amounts to 100.6 million and 44.5 million patient-years, respectively. Furthermore, postmarketing adverse event data for those patients taking amlodipine and atorvastatin concurrently are comparable to post marketing adverse event data reported for the individual compounds. Collectively there is adequate evidence of safety data for the combination and the individual components.

2.0 Clinical Development-CADUET

The clinical development program for CADUET is summarized in Tables 1-5 and Appendix 4. Some studies have been completed, some are either still ongoing or not completed (Table 1). This review evaluates in detail two completed, controlled clinical studies, AVALON and RESPOND (Table 2), to show whether both amlodipine and atorvastatin, when used either separately or in combination, as CADUET, have proven efficacy, tolerability and acceptable safety profiles (Tables 3-5). The total number of patients enrolled in all the studies (3,976 as of April 4, 2003) is in Appendix 7 including the ongoing studies.

Table 1: Clinical Development Program for CADUET

Table 1. Amlodipine/Atorvastatin Clinical Studies Ongoing as of 04 April 2003

Study ID	Objective	Study Design	Test Treatment (mg QD); Duration	Subjects
Ongoing Efficacy and Safety Studies: Caduet™ Clinical Development Program				
AVALON (A384100)	Evaluate ability of amlodipine, atorvastatin, and amlodipine + atorvastatin to treat patients to evidence-based blood pressure and lipid level goals	• Double-Blind, Randomized, Parallel-Arm • Single-Blind • Open-Label Dose-Titration • Open-Label Extension	• Placebo + Placebo, Amlo 5 + Placebo, and Placebo + Ator 10 versus Amlo 5 + Ator 10; 8 weeks, then • Amlo 5 + Ator 10; 8 weeks for all patients, then • Amlo + Ator titrated to BP and LDL-C goals; 12 weeks	Patients with comorbid hypertension and hyperlipidemia
RESPOND (A384003)	Evaluate blood pressure and lipid-lowering efficacy of amlodipine, atorvastatin, and amlodipine + atorvastatin in factorial dose combinations	• Double-Blind, Randomized, Parallel-Arm • Open-Label Extension	• Fifteen treatments comprising all possible combinations of Amlo placebo, 5, or 10 and Ator placebo, 10, 20, 40, or 80; 8 weeks	Patients with comorbid hypertension and hyperlipidemia
GEMINI (A384012)	Evaluate ability of amlodipine atorvastatin combination tablets to treat patients to evidence-based blood pressure and lipid level goals	• Open-Label Dose-Titration • Open-Label Extension	• Amlo Ator combination tablets in QD dose combinations appropriate to patients' baseline blood pressure and lipid levels, with doses titrated to BP and LDL-C goals as necessary; 14 weeks	Patients with comorbid hypertension and hyperlipidemia
Ongoing Efficacy and Safety Studies: Amlodipine Clinical Development Program				
MARGAUX (A055100)	Evaluate effect of amlodipine + atorvastatin on endothelium-mediated brachial artery vasodilation	• Double-Blind, Randomized, Parallel-Arm, Dose-Titration	• Amlo 5 or 10 (titrated to maximum dose at which BP <90/60 mm Hg) + Ator 10 or 80 (titrated to 1.3 mmol/L <LDL-C <2.6 mmol/L) versus Placebo + Ator 10 or 80 (titrated to 1.3 mmol/L <LDL-C <2.6 mmol/L); 12 months	CAD patients with LDL-C ≥3.2 mmol/L and TG <4.5 mmol/L
DUAAL (A055103)	Evaluate effect of amlodipine, atorvastatin, and amlodipine + atorvastatin on exercise tolerance	• Double-Blind, Randomized, Parallel-Arm	• Amlo 5 + Placebo and Placebo + Ator 10 versus Amlo 5 + Ator 10; 4 weeks, then Amlo 10 + Placebo & Placebo + Ator 80 versus Amlo 10 + Ator 80; 22 weeks	CAD patients with stable angina pectoris and TC ≥5.2 mmol/L

QD = Once daily; Amlo = Amlodipine; Ator = Atorvastatin; BP = Blood pressure; LDL-C = Low-density lipoprotein cholesterol; CAD = Coronary artery disease; TG = Triglycerides; TC = Total cholesterol.

Table 2: Clinical Development Program-Efficacy and Safety Studies

Type of Study Study ID	Objective	Study Design	Test Treatment mg Duration Route	Subjects Number	StudyStatus Type of Report

Type of Study Study ID	Objective	Study Design	Test Treatment mg Duration Route	Subjects Number	StudyStatus Type of Report
Efficacy and Safety Studies, CADUET AVALON (A3841001) Evaluate the ability of amlodipine, atorvastatin, and amlodipine +atorvastatin to treat patients to evidence-based blood pressure and lipid level targets.		Randomized, Parallel-Arm, placebo controlled followed by open label Dose titration	Picbo+Picbo, Amlo5 + Picbo&Picbo+Ator10vsAmlo5+Ator10 8 weeks QD oral then Amlo5 +Ator 10 8 weeks QD oral then Amlo and Ator titrated to BP and LDL-C Targets: 12 weeks QD oral	Patients with comorbid hypertension/ hyperlipidemia : Target 1000	Completed
RESPOND Evaluate blood pressure and lipid lowering efficacy of amlodipine atorvastatin and amlodipine +atorvastatin in factorial dose combinations.		Randomized, Parallel-Arm, placebo controlled	Fifteen treatments: all possible combinations of amlo, placebo, 5,10 and Ator placebo, 10 – 80. 8 weeks QD oral	Patients with comorbid hypertension/ hyperlipidemia : Target 1500	Completed

Table 3: Clinical Development Program-Ongoing

Type of Study Study ID	Objective	Study Design	Test Treatment mg Duration Route	Subjects Number	Study Report
Efficacy and Safety Studies, CADUET MARGAUX Evaluate effect of amlodipine +atorvastatin on endothelium mediated brachial artery vasodilatation		Randomized, Parallel-Arm, placebo controlled	Amlo5 or 10 (titrated to max dose with BP>90/60mmHg) +Ator10 or 80 (titrated to 1.3nmol/L <LDL-C<2.6nmol/L) vs Picbo + Ator 10 or 80 (titrated to 1.3nmol/L <LDL-C<2.6nmol/L): 12 months QD oral	CAD patients with LDL-C>3.2nmol/L and TG<4.5nmol/L Target 150	None
DUAAL Evaluate effect of amlodipine, atorvastatin and amlodipine+atorvastatin on exercise tolerance		Randomized. Parallel-Arm, placebo controlled	Amlo 5+Picbo&Picbo+Ator 10 vs Amlo5 + Ator 10 4weeks QD oral then Amlo10 +Picbo & Picbo+Ator80 vs Amlo10+Ator80 22 weeks QD oral	CAD patients with stable angina pectoris and TC > 5.2nmol/L Target 360	None

2.1 Scope of Clinical Review

The reviewer analyzed data from 2 completed, double blind, controlled studies and one open label extension of one of the double blind trials.

- AVALON, ACCESS and RESPOND clinical trials (Tables 1, 4 and 5 above).
- Data from two ongoing outcome studies, MARGAUX AND DUUAL, are incomplete and have not been reviewed (Table 3).
- Safety data from an open label study (GEMINI) attempted to demonstrate the clinical utility of the combination treatment from approximately 250 study sites in the US with about 1,000 subjects. The safety data from this ongoing study has been included in the submitted 4-month safety update otherwise data from this study have not been reviewed.
- The 4-month safety update that was submitted containing serious adverse events, deaths, and medical discontinuations from the ongoing studies.

In addition to the clinical trials the reviewer will evaluate safety data from the following additional studies in Tables 4 and 5.

- Evaluation of two pivotal bioequivalence studies for 5mg amlodipine/10mg atorvastatin and 10mg amlodipine/80 mg atorvastatin.
- Evaluation of *seven supportive bioequivalence studies.

- Evaluation of two pharmacokinetic interaction studies, and
- One pharmacodynamic study (ACCESS).

Table 4: Clinical Development Program-Bioequivalence and Bioavailability Studies

Type of Study Study ID	Dual Therapy Formulation Objective	Study Design	Test Treatment mg Duration Route	Subjects Number	StudyStatus Type of Report
Pivotal Bioequivalence Studies A3841009:Bioequivalence vs marketed Norvasc 5mg+Lipitor 10mg		Crossover	Amlo/Ator10/80 Single oral dose	Healthy volunteers 62/62	Complete Full
A3841010: Bioequivalence vs marketed Norvasc 10mg+Lipitor 80mg		Crossover	Amlo/Ator5/10 Single oral dose	Healthy volunteers 64/62	Complete Full
Pivotal Food Effect Study A3841007: Bioequivalence fed vs fasting		Crossover	Amlo/Ator10/80 Single oral dose	Healthy volunteers 40/40	Complete Full
Bioequivalence Studies Prototype Tablets 1038-001: Comparative bioavailability vs Norvasc 5mg + Lipitor 10mg		Crossover	Amlo/Ator5/10 Single oral dose	Healthy volunteers 36/35	Complete Full
1038-002: Comparative bioavailability vs Norvasc 10mg + Lipitor 40mg		Crossover	Amlo/Ator10/40 Single oral dose	Healthy volunteers 36/36	Complete Full
1038-003 Comparative bioavailability vs Norvasc 10mg + Lipitor 2X40mg		Crossover	Amlo/Ator10/80 Single oral dose	Healthy volunteers 36/36	Complete Full
Bioequivalence Studies : Prototype Tablets (UK)			Amlo/Ator5/10 Single oral dose	Healthy volunteers 40/38	Complete Full
A2581029:Compare single dose PK vs Istin 5mg +Lipitor 10mg		Crossover	Amlo/Ator10/80 Single oral dose	Healthy volunteers 40/40	Complete Full
A2581030 Compare single dose PK vs Istin 10mg +Lipitor 2X40mg		Crossover	Amlo/Ator10/40 Single oral dose	Healthy volunteers 38/38	Complete Full
A2581032 Compare single dose PK vs Istin 10mg +Lipitor 40mg		Crossover			

Table 5: Clinical Development Program-PK and PD interaction Studies

Type of Study Study ID	Dual Therapy Formulation Objective	Study Design	Test Treatment mg., Duration, Route	Subjects Number	StudyStatus Type of Report
Pharmacokinetic Interaction Studies A0581029: Evaluate PK of Amlo10mg and Ator 80mg on one another.		Crossover	Amlo10 +Ator 80 vs Amloand Ator 80 single oral dose	Healthy volunteers 27/25	Complete Full
053-019:Evaluate PK effect of Amlo 10mg QD on HMGRI activity of Ator 80mg QD		Crossover	Amlo10+Ator 80 vsPlcbo+Ator80:8 days QD oral	Healthy volunteers 16/16	Complete Full
Pharmacodynamic Interactions ACCESS (981-176) Evaluate lipid-lowering efficacy of atorvastatin vs other HMGRIs		Randomized, Parallel-arm, Active control	Atorvastatin 10 vs Fluvastatin 20 Lovastatin 20 Pravastatin 10 Simvastatin 10 54 weeks QD oral	Patients with hyperlipidemia 3916/3785	Complete Full
Evaluate effect of amlodipine on lipid-lowering efficacy of atorvastatin		Parallel-Arm, Active control	Amlo+Ator vs Ator only	Patients with hyperlipidemia who took atorvastatin 1958/1888	Complete Addendum

Sources of Materials used for review

- The data, protocols, study reports, case report forms were supplied in electronic format and volumes in hard copy.
- SBA for Norvasc in 1992
- NDA 19,787 for Amlodipine.

Meetings with Agency

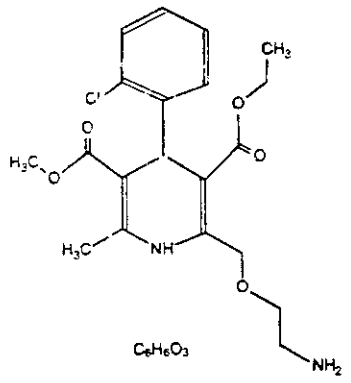
- The Agency requested the sponsor to justify adequacy of the only ongoing study, AVALON, that administered the 5mg amlodipine and 10mg atorvastatin, in support of a claim of "no pharmacodynamic interaction" for all the 8 to-be-marketed CADUET doses.
- Since it was unlikely that data from AVALON will provide compelling evidence to show lack of interaction between the two components, the Agency requested an additional clinical study that will provide sufficient evidence for all doses to be marketed as this will be critical for approval.
- The sponsor agreed with the Agency that there would be a need for additional clinical efficacy study to be included in the NDA submission.
- To complement the AVALON study, an additional trial, RESPOND, addressed the issue of PD interactions using the 8 fixed-dose combinations to be marketed.
- RESPOND was a double-blind, placebo-controlled, 3X5 matrix, factorial design study in 1,660 subjects covering the full dose ranges of amlodipine, atorvastatin and their combinations.
- ACCESS study is the open label extension of AVALON that provided additional safety data.
- The Agency requested the sponsor to include the

*The results of bioequivalence and pharmacokinetic interaction studies demonstrated that CADUET can be prescribed in the same manner as amlodipine or atorvastatin, to be taken at any time of day with or without food, with no clinically significant variation expected in drug concentration or exposure (See Biopharm review).

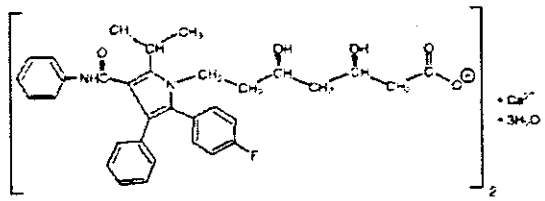
Background

The chemical structures of amlodipine and atorvastatin are in Figure 1 below.

Figure 1: Chemical structures of Amlodipine and Atorvastatin



Amlodipine



Atorvastatin

2.2 Indication
The proposed indication for CADUET is for the treatment [redacted]

[redacted]

Reviewer's comments on Indication
No data are submitted by the sponsor in this NDA to justify a claim for co-morbid angina with or without dyslipidemia, using combination tablet in any of the studies. No patients with co-morbid hypertension/angina and dyslipidemia were studied even though amlodipine has been approved for angina. The sponsor makes references to evidence for efficacy presented in the approved NDAs for Norvasc and Lipitor and to the worldwide clinical utility of amlodipine and atorvastatin and also to the data derived from AVALON. These are inadequate in the opinion of the reviewer to justify this claim now. [redacted]

or. Even though the Summary Basis of Approval (SBA) for Norvasc in 1992 (40–45 patients per group in 2 pivotal studies (Nos. 335 and 102 of NDA 19-787) indicated that amlodipine does not affect lipid levels adversely in hypertension/angina patients it cannot be assumed that CADUET has been shown to be effective in patients with angina. It could not be argued that elevated lipid levels cause angina per se and that elevated lipid levels initiate or adversely affect the symptoms of angina, Therefore an extrapolation from the SBA and other sources for this indication will be untenable.

Recommendation
The label submitted includes a claim for "anti-hypertensive/antianginal action of CADUET". Based on available data reviewed and published reports, the [redacted] should not be approved and should be deleted from the proposed label (See Section 10.2).

3.0 AVALON (Study A3841001)
The AVALON Study consists of four phases and one sub-study. The first phase has been completed and its report forms the basis of this review.

- The study began on 28 February 2001 and ended on November 29, 2002.
- The study was conducted at 147 sites in the United States and Canada.

The first phase was an 8-week, randomized, double blind, placebo-controlled evaluation of the efficacy of treatment with atorvastatin 10 mg and amlodipine 5 mg QD in subjects with comorbid hyperlipidemia and hypertension.

- The second phase was an 8-week study during which all subjects received single-blind treatment with atorvastatin 10mg + amlodipine 5mg.
- The third phase was a 12-week open label during which subjects could be titrated to the maximum allowed daily doses of atorvastatin 40 mg and amlodipine 10 mg in order to reach an LDL-C level of <100mg/dL and JNC recommended blood pressure goals.
- The fourth phase was a 64-week open label extension during which subjects could be titrated to the maximum allowed doses at atorvastatin and amlodipine as described above.
- The sub-study was an arterial compliance that was conducted over the entire study at those centers that possessed equipment for measuring arterial compliance.

In general, during the open-label treatment periods, all patients received first amlodipine 5 mg QD and atorvastatin 10 mg QD (weeks 9 through 16) and then amlodipine and atorvastatin at doses titrated to JNC and NCEP goals (weeks 17 through 28). The open label treatment ended in January 2003.

The results of the second, third, and fourth study phases, which evaluated the long-term efficacy and safety of combined treatment with atorvastatin and amlodipine in this patient population, as well as those of an arterial compliance sub-study, are not reviewed here. With the exception of

safety data, the results of these three ongoing study phases do not contribute directly to the approval of CADUET.

3.1 AVALON (Study A3841001)

The AVALON study was a randomized double-blind, placebo-controlled, superiority study designed to show that one fixed combined dose of CADUET, 5mg amlodipine and 10 mg atorvastatin was superior to 5mg amlodipine and 10 mg atorvastatin given separately to patients with hypertension and dyslipidemia. The sponsor claimed that these two dose levels were the lowest for each component and most prescribed in the US. However, a lower dose of amlodipine, 2.5 mg, that showed efficacy in patients with hypertension had been approved under NDA 19-787.

Data from AVALON alone was considered by the Agency to be inadequate for NDA approval because it lacked a dose response component, it did not represent the 8 fixed-dose combinations to-be marketed and also did not evaluate safety of these other dose levels to-be marketed. Furthermore the AVALON study did not adequately evaluate pharmacodynamic interactions of the other fixed dose combinations.

The efficacy endpoints for AVALON were prespecified in the protocol as therapeutic goals in the guidance of professional organizations, hitherto not officially approved or endorsed by the Agency. While similar goals have been used, in principle, for other drugs, they are not usually adopted in preference to pharmacodynamic data. The pharmacodynamic data provided will be used for evaluation of efficacy and safety. In addition to the therapeutic goals that have been prespecified as primary endpoints could only be supportive to the RESPOND trial.

AVALON is a multicenter, 8-week, randomized, double blind, placebo-controlled evaluation of the blood pressure- and LDL-C- lowering efficacy of concurrent amlodipine + atorvastatin in patients with comorbid hypertension and dyslipidemia. Efficacy is evaluated primarily in terms of percentages of patients who reached goals specified, respectively, by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) and the National Cholesterol Education Program (NCEP).

During the initial 8-week treatment period of AVALON, patients were randomized to receive in double-blind, double-dummy fashion either placebo, amlodipine 5 mg QD, atorvastatin 10 mg QD, or amlodipine 5 mg QD and atorvastatin 10 mg QD (Table 6).

Table 6: 8-week study and extension phase for additional 12/28 weeks-AVALON

Type of Study Study ID	Objective	Study Design	Test Treatment mg Duration Route	Subjects Number	StudyStatus Type of Report
Efficacy and Safety Studies, CADUET AVALON (A3841001)	Evaluate the ability of amlodipine, atorvastatin, and amlodipine +atorvastatin to treat patients to evidence-based blood pressure and lipid level targets.	Randomized, Parallel-Arm, placebo-controlled followed by open label dose titration forup to 28 weeks.	Plcbo+Plcbo, Amlo5 + Plcbo & Plcbo+Ator10vs Amlo5+Ator10 8 weeks QD oral then Amlo5 +Ator 10 8 weeks QD oral then Amlo and Ator titrated to BP and LDL-C Targets: 12 weeks QD oral	Patients with comorbid hypertensio n / hyperli pidemia: Target 1,000	Completed

3.2 STUDY DESIGN OF DOUBLE-BLIND PHASE - AVALON

This was an 8-week, multi-center, randomized, double blind, and double dummy, placebo-controlled study composed of the following

(1) A screening visit;

(2) A taper/ washout (if required) of lipid-lowering and antihypertensive medications lasting 6 weeks and 3 weeks, respectively;
(3) A two- to three-visit run- in/ qualification period during which baseline efficacy assessments were performed;
(4) Randomization of eligible subjects in 1: 1: 1: 1 ratio to double-blind, double-dummy treatment with atorvastatin 10 mg + amlodipine 5 mg, atorvastatin 10 mg, amlodipine 5 mg, or placebo;
(5) Four on-treatment visits that occurred at two-week intervals during which efficacy and safety assessments were performed.
(6) The doses were fixed in this phase of the study and the treatment groups are referred to in this review as combination, atorvastatin, amlodipine, and placebo treatment groups.

3.3 PRIMARY OBJECTIVE - AVALON

- The primary objective of the double- blind phase of the AVALON study was to determine whether co-administration of atorvastatin 10 mg and amlodipine 5 mg QD is superior to amlodipine 5 mg QD in the treatment of hyperlipidemia and superior to atorvastatin 10 mg QD in the treatment of hypertension.

3.4 SECONDARY OBJECTIVES –AVALON

- To compare the safety profile of 8 weeks of double-blind treatment with atorvastatin 10 mg and amlodipine 5 mg with that of atorvastatin 10 mg and that of amlodipine 5 mg.

- To determine whether atorvastatin 10 mg QD when co-administered with amlodipine 5 mg QD modifies the blood pressure lowering efficacy of amlodipine 5 mg QD, and whether amlodipine 5 mg QD when co-administered with atorvastatin 10 mg QD modifies the LDL-C lowering efficacy of atorvastatin 10 mg QD.

- Although not specified in the protocol, the sponsor evaluated pharmacodynamic interactions between atorvastatin 10 mg and amlodipine 5 mg when administered in combination that would reduce the effect size of either component.

- For statistical evaluation, the analysis plan specified that between-group differences in the least square mean percent change from baseline in LDL-C and least square mean change from baseline in systolic and diastolic blood pressure be described by 95% confidence intervals.

3.5 The drug supply is in Table 7 below.

Table 7: Drug supply- AVALON

Drug	Lot number
Atorvastatin 10 mg Formulation no 134298A-63A2	CG0050102 CG0290700
Atorvastatin 10 mg matching placebo Formulation 134298A-75PA1	CX1411101
Amlodipine 5mg Formulation QC1654	N8077-G1 N8160-G1
Amlodipine 5mg matching placebo tablets: Formulation QC1655	N8076-G1 N8159-G1

TREATMENT – AVALON STUDY

Subjects were given two tablets of double-blind study medication once daily at 8 am ± 2 hours throughout the 8-week treatment period. The treatments were:

Atorvastatin 10 mg + amlodipine 5 mg atorvastatin 10 mg + placebo (matching amlodipine 5 mg) amlodipine 5 mg + placebo (matching atorvastatin 10 mg) placebo (matching atorvastatin 10 mg) + placebo (matching amlodipine 5 mg)

The atorvastatin 10 mg QD dosage is the lowest in the approved dose range whereas 2.5 mg amlodipine is the lowest effective dose for amlodipine. The approved dose range for amlodipine is 2.5-10 mg QD.

DIAGNOSES AND CRITERIA FOR INCLUSION OF SUBJECTS

3.6 Inclusion Criteria

- Males and non-childbearing females, age 18 to 75 years,
- Women of childbearing potential had to be using adequate contraceptive measures to prevent pregnancy; and a negative pregnancy test.
- Provide written informed consent,
- Subjects with a diagnosis of both hyperlipidemia and hypertension who at two or three run-in visits seven to 14 days apart met all the inclusion criteria listed in one of the three categories of risk for CHD in Table 8.

At screening all eligible subjects will be classified as follows in order to determine enrollment inclusion criteria.

Table 8: Inclusion Criteria for Risk categories for CHD

	Group I	Group II	Group III
Fasting LDL-C	161-250mg/dL (4.1 – 6.5 mmol/L)	131 – 250 mg/dL (3.4 – 6.5 mmol/L)	101 – 250 mg/dL (2.6 – 6.5 mmol/L)
Blood Pressure	Systolic, 140–179 mm Hg and/or Diastolic 90 – 109 mmHg	Systolic, 140–179mm Hg and/or Diastolic 90– 109 mmHg	Systolic, 130–159 mm Hg and/or Diastolic 85 – 99 mmHg
Additional CV risk factors	0	>1 excluding CHD and DM	CHD, DM, or other atherosclerotic disease

Average of measurements collected at 2 or 3 pre-randomization visits occurring 7-14 days apart. CHD = Coronary Heart Disease, DM = Diabetes Mellitus, BP = Blood Pressure; CV = Cardiovascular.

Additional risk factors for Group II included the following:

- Age of > 45 years if male and >55 years if female
- A history of premature coronary heart disease in a first-degree relative. If male premature coronary heart disease would have to occur before age 55 and if female before age 65.
- A current smoker
- HDL-Cholesterol of <40mg/dL (1.0 mmol/L). An HDL-cholesterol of <60 mg/dL (.6 mmol/L) was considered a negative risk factor. In such cases the patient was required to have 2 additional risk factors.

The risk categories were based on the NCEP ATP III guidelines for the treatment of high blood cholesterol and the JNC VI guidelines for the treatment and prevention of high blood pressure. These guidelines continue to change as reflected in some parts of this NDA. Subjects with a history of myocardial or cerebral infarction or other serious cardiovascular diseases were excluded. It is not clear whether patients with vasospastic angina and/or chronic stable angina were specifically excluded since patients with MI were excluded.

3.7 Exclusion criteria

Subjects presenting with any of the following were not included in the study:

- Pregnant or lactating women.
- Participation in any other studies involving investigational or marketed products within one month prior to entry into the study.
- Prior or concurrent treatment for hyperlipidemia and hypertension not meeting the specified criteria in Table 8.
- Subjects with prior myocardial infarction within 6 months, coronary artery bypass or intra-coronary interventions within 3 months.

- Subjects with cardiac arrhythmias (including second or third degree AV block, sick sinus syndrome, atrial fibrillation, atrial flutter or any arrhythmias requiring medications), or an accessory bypass track (e. g., Wolff Parkinson White or Lown Ganong Levine syndromes)
- Subjects with secondary hyperlipidemia of any etiology, such as nephrotic syndrome, hypothyroidism, or Cushing's syndrome.
- Subjects with prior atherosclerotic brain infarction, stroke or transient ischemic attack (TIA) within 3 months of the screening visit.
- Subjects with Type 1 Diabetes Mellitus. Subjects with Type 2 Diabetes Mellitus who do not require insulin may be enrolled if screen Hb-A1C <9.0% and no proteinuria greater than trace on urine dipstick examination.
- Subjects with secondary hypertension of any etiology such as renal disease, pheochromocytoma, or Cushing's disease.
- Exclusionary laboratory values.
- History of intolerance/ hypersensitivity to the HMG Co- A Reductase inhibitors and/ or dihydropyridine calcium channel blockers, or to drugs with similar chemicals.
- Any condition, which in the Investigator's judgment might result in increased risk to the subject or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.

- GROUP I – subjects with hypertension and hyperlipidemia as defined in Table 8, with no other cardiovascular risk factors.
- GROUP II – subjects with hypertension and hyperlipidemia as in Table 8 with at least one additional cardiovascular risk factor, excluding CHD and diabetes mellitus (DM).
- GROUP III – subjects with hypertension and hyperlipidemia as defined in Table 8 with CHD, DM or other atherosclerotic disease as defined in Appendix I.

3.8 ASSESSMENTS FOR EFFICACY

The efficacy evaluations were based on serum lipid levels (fasting) and seated blood pressure measurements obtained at 8 am ± 2 hours at each of the two (or three) run-in qualification (baseline) visits and at the end of 8 weeks of double-blind treatment and, for blood pressure only, at the end of 2, 4, and 6 weeks of double-blind treatment (Table 9).

Blood pressure was measured on the same arm throughout the study; following a five-minute seated rest period, three seated readings were to be obtained at two-minute intervals.

Table 9: Schedule of efficacy assessments - AVALON

	SCRN	Wk - 2	Wk - 1	Wk-0	Randomiz	Wk 2	Wk 4	Wk 6	Wk 8
Serum Lipids (fasting)									
Tot cholesterol		X	X	X					X
Triglycerides		X	X	X					X
HDL-C		X	X	X					X
LDL-C		X	X	X					X
VLDL-C		X	X	X					X
HDL/LDL ratio		X	X	X					X
Apolipoprotein B					X				X
Vital signs									
BP, Systolic, Diastolic		X	X	X		X	X	X	X
Global risk factors	X	x	x	x					x

3.9 STATISTICS: Efficacy evaluation - AVALON

The primary, intent-to-treat (ITT) efficacy population included all subjects who took at least one dose of assigned treatment during the double-blind phase of the study and had at least one

efficacy assessment during this phase. In all analyses reported in this review, subjects in Groups I, II, and III were combined.

The baseline value was defined as the average of all measurements taken during the run-in phase. Endpoint was defined as the last non-missing, post-baseline observation carried forward (LOCF) for each subject during the double- blind phase.

Efficacy parameters were

- The percentage of subjects who reached NCEP LDL-C therapeutic goals at endpoint,
- The percentage of subjects who reached JNC blood pressure, and
- Changes from baseline to endpoint in systolic and diastolic blood pressure.

Categorical data were analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test for general association with Groups I, II, and III as strata. Continuous data were analyzed using the appropriate contrast from a 2 X 2 factorial analysis of covariance (ANCOVA) model with terms for atorvastatin, amlodipine, atorvastatin-by-amlodipine interaction, and baseline measurement (the covariate). The tests were two-sided with a significance level of = 0.05 and no adjustments for multiple comparisons. Ninety-five percent confidence intervals around between-treatment differences in least square mean percent changes and least square mean changes from baseline to endpoint were also reported.

3.10 Safety evaluation - AVALON

Safety was assessed at each visit through the collection of observed and reported adverse events and heart rate measurements (Table 10).

The safety population included subjects who took at least one dose of study medication and had at least one post-randomization safety measurement. The incidences of treatment-emergent adverse events (AEs) were summarized descriptively. A treatment-emergent AE was defined as an adverse event that began or worsened in severity from the first day double- blind study drug was administered up through the last dose of double-blind study medication.

Table 10: Schedule of safety assessments - AVALON

	SCRN	Wk - 2	Wk - 1	wk-0	Wk 2	Wk 4	Wk 6	Wk 8	ET
Adverse events									X
Clinical laboratory tests									
Hematology	X								X
Blood Chemistry	X								X
Urinalysis	X								X
B-HCG preg test	X								X
Vital signs									
Heart rate	X	X	X	X	X	X	X	X	X
ECG									X
Physical examination	X								X

ET=Early Termination event

4.0 RESULTS - AVALON

4.1 Subject disposition and demographics

Patient disposition, demographics, discontinuations, primary and other efficacy results of interest, and an adverse event summary from the 8-week double-blind phase only are presented in Tables 30-32.

Table 11 below summarizes disposition of subjects in each treatment group.

Table 11: Disposition of Patients - AVALON

Number (%) of subjects	COMBINATION 207	ATORVASTATIN 200	AMLODIPINE 201	PLACEBO 239
Screened 1505				
Assigned to Study Treatment- 848 Treated Completed Discontinued	207 191(92.3) 16(7.7)	200 185(92.5) 15(7.5)	201 187(93.0) 14(7.1)	239 216(90.4) 23(9.6)
Analyzed for Efficacy:				
Arterial Compliance	162 (78.3)	143 (71.5)	142 (70.6)	172 (72.0)
Intent-to-Treat	205 (99.0)	199 (995)	199 (99.0)	238 (99.6)
Analyzed for Safety: Adverse events	207(100.0)	200(100.0)	201(100.0)	239(100.0)

Source Data Section 13, Table 5.

A total of 847 subjects took at least one dose of study medication (207 combination, 200 atorvastatin, 201 amlodipine, and 239 placebo). Similar proportions of treated subjects in the combination (16/207, 7.7%), atorvastatin (15/200, 7.5%), and amlodipine (14/201, 7.1%), treatment groups discontinued from the study. The discontinuation rate was slightly higher in the placebo treatment group (23/ 239, 9.6%) compared to the combination group 16/207 (7.7%)(Table 11). The number of patients and reasons for discontinuations due to adverse safety experiences are similar in all groups (Tables 12 and 13). The only patient who died was in the placebo group (Tables 13 and 57).

Table 12: Discontinuations due to most common safety adverse safety experiences - AVALON

Number (%) of subjects	COMBINATION 207(%)	ATORVASTATIN 200(%)	AMLODIPINE 201(%)	PLACEBO 239 n(%)
Subjects who discontinued due to an adverse safety experience	6(2.9)	5(2.5)	3(1.5)	9(3.8)
Subjects who discontinued due to >1 adverse safety experience				
Severe	1(<1.0)	3(1.5)	0	6(2.5)
Serious	0	1(<1.0)	0	3(1.3)
Adverse safety experiences leading to the discontinuation of >1 subject in a group				
Asthenia	1	0	0	2(<1.0)
Headache	0	0	0	2(<1.0)
Muscular hypertonia	0	2(1.0)	0	0
Myalgia	2(<1.0)	0	0	1(<1.0)
Palpitations	1(<1.0)	2(1.0)	0	0
Peripheral edema	2(<1.0)	0	1(<1.0)	0

Table 13: Reasons for discontinuations-AVALON

Number (%) of subjects	COMBINATION 207	ATORVASTATIN 200	AMLODIPINE 201	PLACEBO 239
Discontinuations Patient Died Related to Study Drug Adverse event Lack of efficacy	0 5(2.4) 4(1.9) 1(0.5)	0 3(1.5) 3(1.5) 0	0 3(1.5) 2(1.0) 1(0.5)	1(0.4) 8(3.3) 5(2.1) 3(1.3)
Not related to Drug Adverse event Laboratory abnormality	11(5.3) 2(1.0) 0	12(6.0) 2(1.0) 0	11(5.5) 0 1(0.5)	14(5.9) 4(1.7) 0

Other	5(2.4)	5(2.5)	2(1.0)	0
Subject defaulted	4(1.9)	5(2.5)	8(4.0)	10(4.2)
Total	16(7.7)	15(7.5)	14(7.0)	23(9.6)

4.2 Demographics

As can be seen in Tables 14 and 15 that summarize demographic and baseline characteristics of subjects by treatment group, the four treatment groups were generally similar and reasonably balanced. In each treatment group, the majority of subjects were male (combination, 65.2%; each group), and from 45 to 64 years of age (combination, 60.7%; atorvastatin, 74.5%; amlodipine, 66.2%; placebo, 71.5%), with a mean age in each group of approximately 55 years. The mean weight and height of males were similar across treatment groups (approximately 95 kg and 177 cm, respectively), as were the mean weight and height of females (approximately 82 kg and 162 cm, respectively). The majority of subjects were included in the Group II risk category (Table 8), and the proportions of such subjects in each treatment group were similar (combination, 74.9%; atorvastatin, 80.0%; amlodipine, 71.1%; placebo, 79.1%).

Table 14: Demographics of randomized patients with comorbid hypertension/dyslipidemia

	COMBINATION			ATORVASTATIN		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
No.Subjects	**135**	**72**	**207**	**111**	**89**	**200**
Age (years)						
18-44	17(12.6)	7(9.7)	24(11.6)	21(18.0)	3(3.4)	23(11.5)
45-64	97(71.9)	41(56.9)	138(66.7)	76(68.5)	73(82.0)	149(74.5)
>65	21(15.6)	24(33.3)	45(21.7)	15(13.5)	13(14.6)	28(14.0)
Mean	54.3	58.0	55.6	52.9	67.9	55.1
SD	9.6	9.9	9.9	10.2	7.1	9.3
Range	27.76	30.74	27.75	23.74	41.75	23.75
Race:						
Whites	114(84.4)	59(81.9)	173(83.6)	91(82.0)	76(85.4)	167(83.5)
Black	13(9.6)	11(15.3)	24(11.6)	12(10.8)	10(11.2)	22(11.0)
Asian	5(3.7)	1(1.4)	6(2.9)	1(0.9)	1(1.1)	2(1.0)
Other	3(2.2)	1(1.4)	4(1.9)	7(6.3)	2(2.2)	9(4.5)
Weight(kg)						
Mean	95.0	81.4		96.1	83.4	
SD	17.2	17.2		18.1	17.4	
Range	59.0-158	54.0-143		70.0-156	44.0-126	
N	135(100)	72(100.0)		110(99.1)	89(100)	
Height (cm)						
Mean	177.3	161.4		177.0	163.5	
SD	5.9	6.2		7.1	6.6	
Range	163.0-193.	149.0-179		159.0-193	146-180	
N	135(100)	72(100.0)		111(100.0)	89(100)	
Group Classification						
I	7(5.2)	7(9.7)	14(6.8)	6(5.4)	5(5.6)	11(5.5)
II	109(80.7)	46(63.9)	155(74.9)	87(78.4)	73(82.0)	160(80.0)
III	19(14.1)	19(26.4)	38(18.4)	18(16.2)	11(12.4)	29(14.5)

Source Data Section 13 Table 6

Table 15: Patient Demographics and Baseline characteristics- AVALON

	Placebo N=239	**Amlodipine N=201**	**Atorvastatin N=200**	**Amlo + Ator N=207**
Sex (n) %				
• Male	151(63.2)	117(58.2)	111(55.5)	135(56.2)
• Female	88(36.8)	84(41.8)	89(44.5)	72(34.8)
Race (n)%				

	Placebo N=239	Amlodipine N=201	Atorvastatin N=200	Amlo + Ator N=207
• White	193(80.8)	169(84.1)	167(83.5)	173(83.6)
• Black	27(11.3)	18(9.0)	22(11.0)	24(11.6)
• Asian	3(1.3)	4(2.0)	2(1.0)	6(2.9)
• Other	16(6.7)	10(5.0)	9(4.5)	4(1.9)
Age, years				
• Mean	55.3	56.2	55.1	55.6
• SD	9.2	10.3	9.3	9.9
• Range	28-75	31-76	23-75	27-75
Group classification(n)%				
• Group I	9(3.8)	18(9.0)	11(5.5)	14(6.8)
• Group II	189(79.1)	143(71.1)	160(80.0)	155(74.9)
• Group III	41(17.2)	40(19.9)	29(14.5)	38(18.4)

Source data Section 13 Table 1

Duration of Exposure to drugs was for 8 weeks in the majority of patients.
The most common concomitant medications by categories are summarized in Table 16.

4.3 Concomitant Medications

Table 16: Most Common Concomitant Medication by categories-AVALON

	Combination	Atorvastatin	Amlodipine	Placebo
N	207 n(%)	200 n(%)	201 n(%)	239 n(%)
Subjects who took >1 antihypertensive and Lipid lowering medication	75(36.2)	66(33.0)	85(42.3)	91(38.1)
Subjects who took >1 medication by BNF drug treatment category				
β-blockers	32(15.5)	30(15.0)	34(16.9)	35(14.6)
Diuretics	29(14.0)	26(13.0)	31(15.4)	28(11.7)
Antihypertensives	23(11.1)	28(14.0)	29(14.4)	37(15.5)
Drugs for hyperlipidemia	21(10.1)	20(10.0)	28(13.9)	26(10.9)
Subjects who took >1 medication by BNF drug treatment category				
Drugs used in Rheumatic diseases and gout	82(39.6)	78(39.0)	65(32.3)	97(40.6)
Vitamins	64(30.9)	54(27.0)	63(31.3)	62(25.9)
Analgesics	31(15.0)	32(16.0)	18(9.0)	44(18.4)
Sex Hormones	26(12.6)	30(15.0)	18(9.0)	19(7.9)
Ulcer healing drugs GI	21(10.1)	15(7.5)	18(9.0)	15(6.3)
Minerals and trace elements	20(9.7)	28(14.0)	24(11.9)	23(9.6)
Drugs used in allergic diseases	20(9.7)	23(11.5)	13(6.5)	24(10.0)
Antidepressant drugs	13(6.3)	22(11.0)	12(6.0)	24(10.0)

4.5 Primary Efficacy Results

Similar proportions of subjects in each treatment group were included in the ITT efficacy analysis (combination, 205/ 207, 99.0%; atorvastatin, 199/ 200, 99.5%; amlodipine, 199/ 201, 99.0%; placebo, 238/ 239, 99.6%).

The primary efficacy results showed that the percentage of combination-treated subjects (82.1%) who reached their NCEP LDL-C goals was significantly greater ($p < 0.001$) than that of subjects treated with amlodipine alone (12.4%), and that the percentage of combination-treated subjects (51.0%) who reached their JNC blood pressure goals was significantly greater ($p < 0.001$) than

that of subjects treated with atorvastatin alone (32.3%) (Table 17). These results indicate that combination treatment with atorvastatin 10 mg and amlodipine 5 mg was statistically significantly more effective than amlodipine alone in lowering LDL-C levels and also statistically significantly more effective than atorvastatin alone in lowering blood pressure levels in these patients with comorbid hyperlipidemia and hypertension at the end of 8 weeks exposure.

In effect, at the end of the 8-week double-blind treatment period of AVALON, a greater percentage of amlodipine + atorvastatin patients achieved JNC blood pressure goals (51.0%) versus atorvastatin-only patients (32.3%), and a greater percentage of amlodipine + atorvastatin patients achieved NCEP LDL- C goals (82.1%) versus amlodipine- only patients (12. 4%): both of these treatment differences were statistically significant (p< 0.001 for each) (Table17).

In addition, 45.5% of amlodipine + atorvastatin patients achieved both JNC and NCEP goals during double- blind treatment; this percentage was significantly greater than the percentages of either amlodipine- only or atorvastatin- only patients who reached both JNC and NCEP goals (8.3% and 28.6% respectively; p <0.001 for each) (Table 17).

Primary Efficacy Conclusion

The sponsor therefore achieved their primary efficacy endpoint using prespecified evidenced based goals..

Table 17: Patients who reached NCEP and JNC goals-All Risk Groups

Parameter	Combination	Atorvastatin	Amlodipine	Placebo	Combination versus Atorvastatin 95% CI p-value	Combination versus Amlodipine 95%CI p-value
NCEP GOAL N n (%)	201 165(82.1)	193 151(78.2)	193 24(12.4)	229 15(6.6)	-4.02,11.72;**0.225**	62.60,76.71;**<0.001**
JNC GOAL N n(%)	204 104 (51)	198 64 (32.3)	198 107 (54)	236 70 (29.7)	9.20,28.12;**<0.001**	-12.8,6.70; **0.520**
BOTH NCEP /JNC GOALS N n(%)	200 91(45.5%)	192 55 (28.6)	192 16 (8.3)	227 8 (3.5)	7.45,26.26;**<0.001**	29.23,45.10;**<0.001**

Endpoint is defined as the last non-missing observation during double-blind phase N= No of patients assessed for therapeutic goals. P values for the Cochran mantel Haenszel 2 sided chi square test for general association with groups I II and III.

The achievement of evidence-based goals in the AVALON is not consistent with the gold standard for approval of combination medications. In accordance with FDA guidelines regarding fixed-dose combination medications, the sponsor must demonstrate that the therapeutic effect of the combination is greater than the therapeutic effect of a matching dose of either of the two components taken alone. For a combination of 2 drugs to treat 2 separate conditions as in this NDA, this requirement can be met by showing either that the combination is bioequivalent to a matching dose of either of the 2 components drugs taken alone and/or that the therapeutic effect of each component drug is retained when the 2 drugs are taken in combination. The following studies on interaction between the two drugs and the retention of therapeutic efficacy of the 2 drugs taken in combination were performed. The first study is to show the effect of atorvastatin on the blood pressure lowering efficacy of amlodipine and the second study is to show the effect of amlodipine on the LDL-C lowering efficacy of atorvastatin.

4.6 Effect of Atorvastatin on the Blood Pressure Lowering Efficacy of Amlodipine

In the combination and amlodipine treatment groups, the least square mean changes from baseline to endpoint in systolic blood pressure were –12.7 and –14.3 mmHg, respectively, and, in diastolic blood pressure, -8.2 and –8.9 mmHg, respectively (Tables 18 and 19). These reductions were consistent with those reported in Amlodipine Studies 102 and 335, the two pivotal dose-ranging studies included in the original Amlodipine NDA #19- 787.

The differences between the two groups were neither clinically meaningful nor statistically significant for both systolic (95% CI, -0.44, 3.83; **p= 0.120**) and diastolic (95% CI, -0.57, 2.05; **p= 0.268**) blood pressure (Tables 18 and 19). There was also no significant difference between the percentages of combination-treated subjects (51%) and amlodipine-treated subjects (54%) who reached their JNC blood pressure goals (95% CI, -12.8, 6.70; p= 0.520). Taken together, the results provide no statistically significant evidence that atorvastatin 10 mg QD modified the blood pressure lowering efficacy of amlodipine 5 mg QD when the two treatments were taken in combination by patients with comorbid hypertension and hyperlipidemia. This provides evidence of lack of interaction between the two drugs and the retention of efficacy of amlodipine to lower systolic and diastolic blood pressure (Table 18).

Table 18: Change from baseline to endpoint-Systolic Blood Pressure in patients receiving CADUET -

Parameter Systolic BP	Combin -ation	Atorvas tatin	Amlodipi ne	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo	Amlo Vs Placebo
Baseline N	204	198	198	236				
Mean	146.7	147.0	147.5	146.7				
S.D.	12.3	10.8	10.0	10.8				
Endpoint N	204	198	198	236				
Mean	134.1	141.0	133.1	141.4				
S.D.	13.9	14.1	11.1	15.8				
Change N	204	198	198	236				
L.S. Mean	-12.7	-5.9	-14.3	-5.4				
S.E.	0.8	0.8	0.8	0.7				
95% C.I.	-14.2	-7.5	-15.9	-6.9				
	-11.2	-4.4	-12.8	-4.0				
P-value					<0.001	*0.120	0.631	<0.001
95% CI					-0.05,-4.581	-0.44,3.83	-2.57,1.561	-11.0,-6.85

N= number of patients with both baseline and endpoint measurements

Table 19: Change from baseline to endpoint -Diastolic Blood Pressure in patients receiving CADUET

Parameter Diastolic BP	Combin a-tion	Atorvas tatin	Amlodipi ne	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo	Amlo Vs Placebo
Baseline N	204	198	198	236				
Mean	92.1	91.4	92.6	92.4				
S.D.	7.2	7.8	6.9	6.2				
Endpoint N	204	198	198	236				
Mean	83.9	87.4	83.6	89.1				
S.D.	8.8	9.4	8.6	9.2				
Change N	204	198	198	236				
L.S. Mean	-8.2	-4.2	-8.9	-3.3				
S.E.	0.5	0.5	0.5	0.4				
P-value					<0.001	*0.268	0.190	<0.001
95% CI					-5.35,-2.72	-0.57,2.05	-2.12,0.42	-4.94,-1.58

4.7 Effect of Amlodipine on the LDL-C Lowering Efficacy of Atorvastatin

Table 20 shows that the least square mean percent changes from baseline to endpoint in LDL-C in subjects in the combination and atorvastatin treatment groups were -37.2% and -33.9%, respectively. The statistically significant difference seen in the present study between the combined therapy and atorvastatin 10 mg alone in reducing LDL-C, (95% CI, -5.77, -0.93; **p= 0.007**), is considered by this reviewer to be unexpected and indicates that the efficacy of atorvastatin is reduced. Contrary to what the sponsor stated, these results are not consistent with those four Pfizer-sponsored studies of atorvastatin 10 mg in patients with hyperlipidemia that are reported in the current Lipitor product label. In those four studies, atorvastatin 10 mg reduced LDL-C levels by 35- 39% but this was in the absence of amlodipine. A suggestion of modification

by amlodipine is evident from the statistically significant difference (p=0.007) between the lipid lowering capacity of atorvastatin in the combination. However, there was no statistically significant difference between the percentages of combination-treated subjects (82.1%) and atorvastatin- treated subjects (78.2%) who reached their NCEP LDL-C therapeutic goals (95% CI, -4.02, 11.72; p= 0.225). The apparent discord between the Pharmacodynamic data and the prespecified goals suggest a lack of superiority of combination therapy in respect of Atorvastatin's LDL-C lowering efficacy whereas going by percentages of patients who reached prespecified goals Caduet appeared effective. This reviewer does not believe that by having larger numbers of patients reach prespecified goals invariably confers superiority when the PD data suggests an element of interaction. However, this FDA requirement has not been met by this study at this dose level although the prespecified efficacy endpoint for this study had been achieved (Tables 17 and 20).

Table 20: % change from baseline to endpoint LDL-C in patients receiving CADUET

Parameter LDL Cholesterol	Combination	Atorvastatin	Amlodipine	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo
Baseline N	201	193	193	229			
Mean	164.0	162.2	164.2	163.7			
S.D.	24.8	24.6	26.1	25.0			
Endpoint N	201	193	193	229			
Mean	102.6	107.2	160.3	163.7			
S.D.	21.3	23.8	28.7	31.0			
Change N	201	193	193	229			
L.S. Mean	-37.2	-33.9	-1.8	0.2			
S.E.	0.9	0.9	0.9	0.8			
95% C.I.	-38.9	-35.6	-3.5	-1.3			
	-35.5	-32.1	-0.3	1.8			
P-value					*0.007	<0.001	<0.001
95% CI					-5.77,-0.93	-37.8,-33.0	-36.5,-31.8

4.8 Effect of Amlodipine on the Efficacy of Atorvastatin in Reducing Lipid Levels Other than LDL- C

Between- group differences in the least square mean percent changes from baseline in other lipid parameters revealed a pattern similar to that observed in the analyses of least square mean percent changes in LDL-C described above (Tables 21-26). There were statistically significantly greater least square mean percent changes from baseline in the combination treatment group compared with the atorvastatin treatment group for total cholesterol (combination, -27.7; atorvastatin, -24.4; 95% CI, -5.02, -1.45; p< 0.001), HDL/ LDL ratio (combination, +72.0; atorvastatin, +61.8; 95% CI, 4.86, 15.61; p< 0.001), and apolipoprotein B (combination, -30.7; atorvastatin, -27.9; 95% CI, -4.99, -0.60; p= 0.013), and a trend toward greater mean percent changes in the combination treatment group versus the atorvastatin treatment group for triglycerides (combination, -23.0; atorvastatin, -17.2; 95% CI, -12.0, 0.57; p= 0.075), HDL- C (combination, +5.0; atorvastatin, +4.1; 95% CI, -1.93, 3.68; p= 0.542), and VLDL (combination, -22.4; atorvastatin, -17.3; 95% CI, -11.2, 0.98; p= 0.101) (Table 25). As with the LDL-C data, these results are consistent with those of four Pfizer-sponsored studies of atorvastatin 10 mg in patients with hyperlipidemia that are reported in the current Lipitor product label. In the four studies, atorvastatin 10 mg reduced total cholesterol levels by 25-29%, triglycerides by 17- 23 %, and apolipoprotein B by 27- 34%, and increased HDL levels by 6-7%. Thus, the differences observed in the present study between the combined therapy and amlodipine 5 mg alone in their respective effects on lipid parameters other than LDL- C were not considered clinically meaningful by the sponsor but considered noteworthy by this reviewer in respect of Triglycerides and Apolipoprotein.

Table 21: % change from baseline to endpoint - Total Cholesterol- in patients receiving CADUET

Parameter/ Statistics Total Cholesterol		Combination	Atorvastatin	Amlodipine	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo
Total Cholesterol mg/dL Baseline	N	201	193	193	229			
	Mean	247.4	248.5	246.4	248.5			
	S.D.	30.1	32.0	33.3	31.8			
Endpoint	N	201	193	193	229			
	Mean	178.6	187.3	240.5	245.8			
	S.D.	28.1	30.2	34.3	36.9			
%Change	N	201	193	193	229			
	Mean	-27.7	-24.4	-2.1	-0.9			
	S.E.	0.6	0.6	0.6	0.6			
	95% C.I.	-26.9	-25.7	-3.4	-2.6			
		-26.4	-23.2	-0.8	0.3			
P-value						<0.001	<0.001	<0.001
95% CI						-5.02,-1.45	-27.4, -23.8	-25.3,-21.8

Table 22: % change from Baseline to endpoint - Tryglycerides- in patients receiving CADUET

Parameter/ Statistics: Triglycerides		Combination	Atorvastatin	Amlodipine	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo
Triglycen-des mg/dL Baseline	N	201	193	193	229			
	Mean	180.5	185.0	169.3	188.5			
	S.D.	90.6	94.7	79.0	94.0			
Endpoint	N	201	193	193	229			
	Mean	134.2	147.3	161.4	180.2			
	S.D.	74.5	92.3	88.5	98.6			
%Change	N	201	193	193	229			
	LS Mean	-23.0	-17.2	-2.3	-0.1			
	S.E.	2.2	2.3	2.3	2.1			
	95% C.I.	-27.4	-21.7	-6.8	-4.2			
		-18.6	-12.7	2.2	4.0			
P-value						0.075	<0.001	<0.001
95% CI						-12.0,0.57	-27.0,-14.4	-23.3,-11.1

Table 23: % change from baseline to endpoint- HDL-C in patients receiving CADUET

Parameter/ Statistics Total Cholesterol		Combination	Atorvastatin	Amlodipine	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo
Total Cholesterol mg/dL Baseline	N	201	193	193	229			
	Mean	47.4	49.5	48.3	46.8			
	S.D.	12.9	13.7	12.2	10.6			
Endpoint	N	201	193	193	229			
	Mean	49.3	51.0	48.0	46.8			
	S.D.	13.3	14.8	12.9	11.8			
%Change LS Mean	N	201	193	193	229			
	Mean	5.0	4.1	0.0	0.2			
	S.E.	1.0	1.0	1.0	0.9			
P-value						<0.542	<0.001	<0.005

95% CI						-1.93,3.68	2.14,7.75	1.20,6.66

Table 24: % change from baseline to endpoint - HDL/LDL Ratio in patients receiving CADUET

Parameter/ Statistics HDL/LDL Ratio		Combination	Atorvastatin	Amlodipine	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo
Total Cholesterol mg/dL Baseline	N	196	188	188	216			
	Mean	0.3	0.3	0.3	0.3			
	S.D.	0.1	0.1	0.1	0.1			
Endpoint	N	196	188	188	216			
	Mean	0.5	0.5	0.3	0.3			
	S.D.	0.2	0.2	0.1	0.1			
%Change LS Mean	N	196	188	188	216			
	Mean	72.0	61.8	2.7	1.0			
	S.E.	1.9	2.0	2.0	1.0			
P-value						<0.542	<0.001	<0.005
95% CI						-1.93,3.68	2.14,7.75	1.20,6.66

Table 25: % change from baseline to endpoint - VLDL- in patients receiving CADUET

Parameter/ Statistics VLDL		Combination	Atorvastatin	Amlodipine	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo
Total Cholesterol mg/dL Baseline	N	198	190	188	217			
	Mean	35.0	35.6	32.3	35.3			
	S.D.	16.5	16.8	12.9	16.3			
Endpoint	N	198	190	188	217			
	Mean	26.3	28.2	30.5	33.4			
	S.D.	14.4	15.2	13.5	15.8			
%Change LS Mean	N	198	193	188	217			
	Mean	-22.4	-17.3	-3.1	-0.8			
	S.E.	2.2	2.2	2.2	2.1			
P-value						0.101	<0.001	<0.001
95% CI						-11.2,0.98	-25.4,-13.2	-22.4,-10.6

Table 26: % change from baseline to endpoint-Apolipoprotein B- in patients receiving CADUET

Parameter/ Statistics Apolipoprotein B		Combination	Atorvastatin	Amlodipine	Placebo	Combina Vs Atorva	Combina Vs Amlodip	Atorvas Vs Placebo
Total Cholesterol mg/dL Baseline	N	189	183	185	210			
	Mean	132.7	132.4	131.6	134.4			
	S.D.	21.2	23.0	22.0	21.8			
Endpoint	N	189	183	185	210			
	Mean	91.6	95.3	128.8	132.1			
	S.D.	17.1	20	21.8	23.3			
%Change LS Mean	N	189	183	185	210			
	Mean	-30.7	-27.9	-1.7	-1.7			
	S.E.	0.8	0.8	0.7	0.7			
P-value						0.013	<0.001	<0.001
95% CI						-4.99, -0.60	-31.2,-26.8	-29.0,-24.7

4.9 Subgroup Analysis for Age and sex - AVALON

Subgroup analyses for Systolic blood pressure and LDL-C by age and sex are presented in Tables 27 and 28. There are no significant changes for both parameters by age and sex.

Table 27: Systolic Blood Pressure and LDL-C by Age and Sex - AVALON

	Placebo		Amlodipine		Atorvastatin		Amlo + Atorvastatin	
Parameter	N	LS Mean Change	N	LS Mean Change	N	LS Mean Change	N	LS Mean Change
SBP								
Male	**149**	-5.30	**117**	-12.39	**110**	-4.7	**132**	-11.30
Female	**87**	-5.60	**81**	-17.23	**88**	-7.59	**72**	-15.04
<65yrs	**196**	-5.41	**157**	-13.32	**170**	-6.01	**160**	-13.07
≥65yrs	**40**	-5.47	**41**	-18.45	**28**	-5.16	**44**	-11.31
	N	LS Mean Change	N	LS Mean Change	N	LS Mean Change	N	LS Mean Change
LDL-C								
Male	**143**	-0.52	**114**	-1.12	**107**	-33.04	**129**	-37.97
Female	**86**	1.49	**79**	-2.78	**86**	-34.94	**72**	-35.90
<65yrs	**192**	0.11	**153**	-1.50	**166**	-33.70	**158**	-37.15
≥65yrs	**37**	1.04	**40**	-2.97	**27**	-35.18	**43**	-37.51

SBP=Systolic Blood Pressure

Subgroup analysis: Age - AVALON

Table 28 shows patients over 65 who reached NCEP and JNC goals from the four treatment groups. More than 75% over the age of 65 reached their evidence-based NCEP goal during the double blind period of study and about 41% reached their JNC goal suggesting that age did not affect the efficacy of the combination drug. Table 29 shows the number and percent of patients by gender who reached NCEP and JNC goals from the four treatment groups. No differences are seen between the genders.

Table 28: Patients who reached NCEP and JNC goals >65 years at endpoint - AVALON

Gender	Combination		Atorvastatin		Amlodipine		Placebo	
NCEP GOAL N / (%)	33/43	(76.7)	24/27	(88.9)	4/4	(10)	0/37	(0)
JNC GOAL N / (%)	18/44	(40.9)	3/28	(10.7)	23/41	(56.1)	10/40	(25)

Table 29: Patients who reached NCEP and JNC goals at endpoint by gender - AVALON

Gender	Combination		Atorvastatin		Amlodipine		Placebo	
	Males	Females	Males	Females	Males	Females	Males	Females
NCEP GOAL N n (%)	110/129 (85.3)	55/72 (76.4)	84/107 (78.5)	67/86 (77.9)	15/114 (13.2)	9/79 (11.4)	10/143 (7.0)	5/86 (5.8)
JNC GOAL N n(%)	68/132 (51.5)	36/72 (50.0)	30/110 (27.8)	34/88 (38.6)	57/117 (48.7)	50/81 (81.3)	42/149 (28.2)	28/87 (32.2)

Endpoint is defined as the last non-missing observation during double-blind phase N= No of patients assessed for therapeutic goals

5.0 Safety results - AVALON

All treated subjects were included in the safety evaluation

Treatment emergent adverse events and serious adverse events are summarized in Tables 30-32. The proportions of subjects who had at least 1 treatment emergent AE were generally similar across all 4 treatment groups (combination, 50.2%; atorvastatin, who discontinued due to at least 1 treatment- emergent AE (combination, 2.9%; atorvastatin, 2.5%; amlodipine. 2.0%; placebo, 4.6%). The incidences of treatment emergent AEs by body system were also generally similar across treatment groups. These results are summarized in Tables 30 and 31 below.

Table 30: Treatment Emergent Adverse Events occurring in at least 2% of patients in the combination treatment group-AVALON

Body System	Combination	Atorvastatin	Amlodipine	Placebo
N	207 n(%)	200 n(%)	201 n(%)	239 n(%)
Body as a whole				
Accidental injury	8(3.9)	5(2.5)	3(1.5)	6(2.5)
Asthenia	7(3.4)	8(4.0)	6(3.0)	11(4.6)
Headache	14(6.8)	20(10.0)	14(7.0)	24(10.0)
Pain	5(2.4)	4(2.0)	5(2.5)	5(2.1)
Digestive				
Flatulence	5(2.4)	6(3.0)	3(1.5)	6(2.5)
Metabolic and Nutritional				
Peripheral edema	11(5.3)	1(0.5)	11(5.5)	5(2.1)
Musculoskeletal				
Myalgia	10(4.8)	5(2.5)	5(2.5)	5(2.1)
Respiratory				
Respiratory tract Infection	15(7.2)	12(6.0)	17(8.5)	17(7.11)
Sinusitis	6(2.9)	2(1.0)	2(1.0)	2(0.8)

Table 31: Treatment Emergent Adverse Events by Body system - AVALON

Panel 5.—Treatment-Emergent Adverse Events by Body System, Safety-Evaluable Subjects

Parameter / statistic	Combination (N=207)		Atorvastatin (N=200)		Amlodipine (N=201)		Placebo (N=239)	
Subjects with ≥1 TEAE / (n, %)	104	(50.2)	104	(52.0)	102	(50.7)	125	(52.3)
Subjects who discontinued due to ≥1 TEAE / (n, %)	6	(2.9)	5	(2.5)	4	(2.0)	11	(4.6)
Subjects with TEAEs by body system / (n, %)								
Body as a whole	46	(22.2)	51	(25.5)	42	(20.9)	58	(24.3)
Respiratory	25	(12.1)	22	(11.0)	28	(13.9)	37	(15.5)
Digestive	24	(11.6)	27	(13.5)	22	(10.9)	34	(14.2)
Musculoskeletal	22	(10.6)	16	(8.0)	19	(9.5)	20	(8.4)
Skin and appendages	14	(6.8)	7	(3.5)	8	(4.0)	10	(4.2)
Metabolic and nutritional	12	(5.8)	2	(1.0)	12	(6.0)	13	(5.4)
Nervous	12	(5.8)	22	(11.0)	21	(10.4)	35	(14.6)
Special senses	6	(2.9)	1	(0.5)	5	(2.5)	4	(1.7)
Urogenital	5	(2.4)	5	(2.5)	13	(6.5)	4	(1.7)
Cardiovascular	4	(1.9)	6	(3.0)	10	(5.0)	10	(4.2)
Hemic and lymphatic	0		1	(0.5)	3	(1.5)	3	(1.3)

TEAE indicates treatment-emergent adverse event

N = No. of subjects in the safety population; n (%) = number (percentage) of subjects with a treatment-emergent AE.

Source: Table 6.1.1.2

5.1 Serious Adverse events

A total of 12 patients experienced serious adverse events that began during the double-blind treatment period of AVALON (Study A3841001), including the one death described below. Numbers of patients with serious adverse events were similar across treatment groups, and no serious adverse events involved either the musculoskeletal system or liver function at this dose level. None of the serious adverse events experienced by these 12 patients were considered by any of the investigators to be related to study medication. Five of these were related to the cardiovascular system. These events are presented in table 32 below. They are considered unrelated to the study drug.

Table 32: Serious Adverse events – ITT - AVALON

Treatment group / Patient ID	Serious Adverse event
Combination therapy	
1055-0694	Small bowel obstruction
1106-1327	Melanoma
Atorvastatin	
1048-0589	Vestibular neuronitis
1154-2019	Viral meningitis
Amlodipine	
1033-0435	Vasovagal reaction
1060-0743	Gastroesophageal reflux disease
Placebo	
1098-1197	Spondylolisthesis
1121-1563	Accidental fall
1116-1524	Unstable angina
1135-1824	Unsepcified cardiovascular event
1098-1198	Myocardial infarction and coronary artery stenosis
1043-1237	Atrial fibrillation and pulmonary embolus

5.2 Deaths

Deaths and Serious Adverse Events

Investigator terms for serious adverse events during the AVALON (Study A3841001) double-blind treatment period were mapped to preferred terms using COSTART.

One death was reported during the double- blind treatment period of AVALON (Study A3841001): Patient 1135- 1824, a 55- year- old white male, died on Day 50 of treatment with double- blind placebo due to an unspecified cardiovascular event. In the opinion of the investigator, the cause of the unspecified cardiovascular event was atherosclerotic cardiovascular disease, and was not related to study medication (See medical narratives in Appendix 2) (Table 57).

5.3 Global Risk Factor scores-AVALON

The global risk scores in the four treatment groups are presented in Table 33 for males and females. The baseline scores ranged from 7.2 to 7.6 for males and 10.4 to 11.1 for females and at end point they were 4.0 and 7.4 for combination treated males and females, respectively. Using these scores, at endpoint combination treated males and females had statistically significant decreases in their global risk scores compared to atorvastatin- and amlodipine only treated patients ($p<0.005$) suggesting greater efficacy in lowering these scores in this patient population.

Table 33: Changes in Global risk factor scores from baseline to endpoint - AVALON

	Placebo	Amlo	Ator	Combinatio	Combination	
					Vs Amlo	Vs Ator
Global Risk scores for males						
N	142	114	107	128		
Mean at BL	7.6	7.5	7.2	7.2		
Mean EP	7.1	6.6	4.9	4.0		
Ls Mean ch	-0.5	-0.9	-2.3	-3.3		
P value					**<0.001**	**<0.001**

	Placebo	Amlo	Ator	Combinatio	Combination	
Global Risk scores for females						
N	85	77	85	72		
Mean at BL	10.4	10.5	10.6	11.1		
Mean at EP	9.6	8.5	7.8	7.4		
Ls Mean ch	-0.8	-2.0	-2.8	-3.7		
P value					<0.001	<0.005

BL=Baseline; EP=Endpoint

5.4 Summary and Conclusions - AVALON

The primary efficacy results indicate that in patients with comorbid hyperlipidemia and hypertension, combined treatment with atorvastatin 10 mg and amlodipine 5 mg was statistically significantly more effective than amlodipine alone in lowering subjects' LDL- C levels to their NCEP goals, and highly statistically significantly more effective than atorvastatin alone in lowering subjects' blood pressure levels to their JNC therapeutic goals. These results are supported by a secondary analysis that showed that the combined treatment was statistically significantly more effective than either atorvastatin alone or amlodipine alone in therapeutic targets.

- Although the primary objective of AVALON as a superiority trial was achieved there were no clinical outcome data to support the prespecified therapeutic NCEP and JNC goals other than the significant decrease in global risk scores among patients treated with combination drug.
- The majority of the patients were in the group II risk factor and the data had not been analyzed for superiority by individual risk group.
- PD effects were demonstrated even though they were not prespecified in the protocol.
- Both short long term safety data are acceptable with the exception of liver function tests that show some dose related increased trend of SGPT and alkaline phosphatase with the combination drug compared with placebo ($p<0.0001$)(See Table in RESPOND). The significance of this observation in the absence of clinically overt liver disease is not clear but suggestive of some sub-clinical drug-related hepatopathy. The sponsor is not aware of this finding with the combination but elevated SGPT has been observed with amlodipine in the approved NDA 19,787.The lack of statistically significant elevation of SGOT with Combination compared to placebo supports the hypothesis that hepatotoxicity pattern is specific for individual drugs.
- No data and no patients with angina were specifically recruited into any of the studies.
- The selection of a single dose used for this study did not reflect the range of doses to be marketed and therefore lacked a dose ranging quality.
- The results of these studies lend support to the RESPOND study by showing lack of interaction between the two components of the drug and that the combined drug is superior to the individual components.

Secondary analyses of blood pressure parameters provided no statistically significant evidence that atorvastatin 10 mg QD modified the blood pressure lowering efficacy of amlodipine 5 mg QD when the two treatments were taken in combination by patients with comorbid hypertension and hyperlipidemia. In both treatment groups, these reductions in systolic and diastolic blood pressure were consistent with those reported in former Amlodipine Studies 102 and 335, the two relatively small pivotal dose-ranging studies in the original Amlodipine NDA #19- 787.

Amlodipine 5 mg QD when combined with atorvastatin 10 mg resulted in statistically significantly greater reductions in LDL-C than treatment with atorvastatin 10 mg alone. A similar pattern was observed in analyses of some other lipid parameters. In both treatment groups, the changes in LDL- C and other lipid parameters were consistent with those reported in the current Lipitor product label. And the between-group differences were small and may not be clinically meaningful.

All these taken together, the data support the conclusion that combined treatment with atorvastatin 10 mg and amlodipine 5 mg is effective in treating patients with co-morbid hyperlipidemia and hypertension.

6.0 RESPOND Trial- Factorial Design

Introduction

Hypertension and hyperlipidemia are modifiable CVD risk factors that frequently exist concurrently but may also occur consecutively. Recent estimates put the numbers of US hypertensive and hyperlipidemic patients at about 50 million each, and about 40% of patients who have one of these conditions also have the other. A consistent feature of published recommendations on effective coronary heart disease (CHD) risk reduction, such as the NCEP ATP III and JNC VI guidelines, has been the treatment of high blood pressure and elevated LDL-C to evidence-based goals. However, hypertension and hyperlipidemia remain poorly controlled worldwide partly because of their asymptomatic nature.

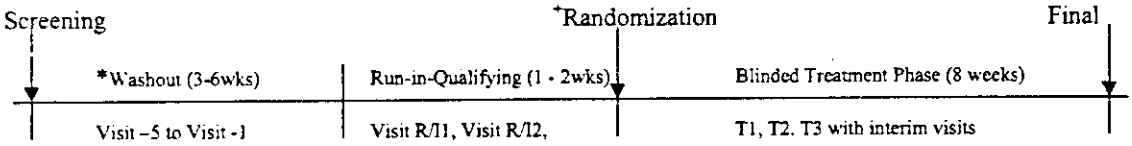
The RESPOND trial is considered pivotal for this NDA. The results of this eight-week evaluation of the efficacy and safety of amlodipine in combination with atorvastatin in patients seek to address the control of comorbid hypertension and hyperlipidemia using a factorial design.

6.1 Study Design - RESPOND

The RESPOND trial was a multi-national, prospective, randomized, double-blind, placebo-controlled study consisting of a screening visit, a taper/washout, a run-in/qualification period, an eight-week double- blind treatment phase (Figure 1), and a 60-week, open- label extension, which is ongoing. The 8 week study that is completed is reviewed here (Table 36).

At the screening visit, eligible patients were preliminarily assigned to one of three groups (Groups I, II, III) on the basis of their risk for developing coronary heart disease (CHD) (Table 34). The patients then underwent a taper/washout (if required) of antihypertensive and lipid- lowering medications lasting at least three weeks and six weeks, respectively. During the two- to- three visit run-in/qualification period, baseline efficacy assessments were performed. Subjects at this point could be reassigned to another cardiovascular (CV) risk group depending on their baseline HDL-C levels. Subjects who met CV group- specific blood pressure and LDL-C criteria based on the run- in measurements, as well as all other study entry criteria, were randomized to treatment with one of the 15 possible combinations of amlodipine (0 mg, 5 mg, 10 mg) and atorvastatin (0 mg, 10 mg, 20 mg, 40 mg, 80 mg), where 0 mg denotes placebo Tables 35,36,38. Table 39 shows the a balanced duration of the disease in the four treatment groups prior to drug exposure on day 1. The study design is presented in Figure 1 below.

Figure 2: RESPOND TRIAL



*** Washout if necessary *Randomization to one of 15 possible dual therapy combination arms with matching placebo.**

During the first phase of the study, 1660 subjects were randomly assigned to treatment with one of the 15 possible combinations of amlodipine (0 mg, 5 mg, 10 mg) and atorvastatin (0 mg, 10 mg, 20 mg, 40 mg, 80 mg). There were slightly more males than females, and over 90% of subjects were White. The mean age was 58 years, and the average subject was overweight based on his or her BMI. All subjects had comorbid hypertension and hyperlipidemia, and the vast majority (97%) had one or more additional CV risk factors or had CHD or a CHD risk equivalent.

Subjects returned to the study site for a minimum of two visits for collection of efficacy and safety assessments, the first occurring one week following randomization and the second, after eight weeks of double- blind treatment. Subjects who completed the double- blind phase or who discontinued the study due to insufficient clinical response after at least four weeks of double-blind treatment were eligible to enter the 60- week extension.

Table 34: Cardiovascular Risk factors required for stratification and initial assignment- Gps I, II III

Group I	Group II.	Group III
Hypertension and Hyperlipidemia only	Hypertension and Hyperlipidemia only and > 1 of the following: • ≥45 years if male • ≥55years if female • family history of premature CHD • current smoker • HDL-C<40mg/dL	Hypertension and Hyperlipidemia and CHD, diabetes mellitus or other atherosclerotic disease

About 48% of subjects assigned to Group III had either a CHD or a CHD risk equivalent that should militate against any form of analysis for prevention of risk related outcomes in the global risk factor analyses. The rationale for the use of the dual therapy is to aggressively control elevated high blood pressure and elevated LDL-C before the development of CHD, atherosclerosis or their clinical sequelae. The inclusion of this group in the efficacy study should not alter the primary efficacy study conclusions as specified in the protocol but it might affect some secondary efficacy conclusions if the Group III patients are not excluded from, for example, the global risk factor analyses. There was a striking paucity (<2%) of pure Group I patients who were in fact the ideal target population for this combination.

The 15 treatment groups are summarized in table 35 below.

Table 35: Double blind treatment groups - RESPOND

Treatments	ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
Amlodipine 0mg	0+0 mg	0+10 mg	0+20 mg	0+40 mg	0+80 mg
Amlodipine 5mg	5+0 mg	5+10 mg	5+20 mg	5+40 mg	5+80mg
Amlodipine10mg	10+0 mg	10+10mg	10+20 mg	10+40 mg	10+80 mg
0 mg denotes placebo. ATO = Atorvastatin					

Double-blind Treatments

The treatments included ATO 0 mg ATO 10 mg ATO 20 mg ATO 40 mg ATO 80 mg AML 0 mg 0+ 0 mg 0+ 10 mg 0+ 20 mg 0+ 40 mg 0+ 80 mg AML 5 mg 5+ 0 mg 5+ 10 mg 5+ 20 mg 5+ 40 mg 5+ 80 mg AML 10 mg 10+ 0 mg 10+ 10 mg 10+ 20 mg 10+ 40 mg 10+ 80 mg 0 mg denotes placebo; AML, amlodipine; ATO, atorvastatin.

Table 36: Completed phase of study - RESPOND TRIAL

Type of Study Study ID	Objective	Study Design	Test Treatment mg Duration Route	Subjects Number	StudyStatus Type of Report
RESPOND	Evaluate blood pressure and lipid lowering efficacy of amlodipine atorvastatin and amlodipine +atorvastatin in factorial dose combinations.	Randomized, Parallel-Arm, placebo controlled	Fifteen treatments: all possible combinations of amlo, placebo, 5,10 and Ator placebo, 10 – 80. 8 weeks QD oral	Patients with comorbid hypertension/ hyperlipidemia : Target 1500	Completed

6.2 Study objectives - RESPOND

The primary objective of the double-blind phase of this study was to determine whether co-administration of eight different dosage combinations of amlodipine and atorvastatin (5+ 10 mg, 5+ 20 mg, 5+ 40 mg, 5+ 80 mg, 10+ 10 mg, 10+ 20 mg, 10+ 40 mg, 10+ 80 mg) are superior to the respective amiodipine dosages alone (5 mg, 10 mg) in reducing LDL- C and superior to the respective atorvastatin dosages alone (10 mg, 20 mg, 40 mg, 80 mg) in reducing systolic blood pressure.

Inclusion Criteria

Diagnoses and Criteria for Inclusion of Subjects: Subjects were men and women from 18 to 75 years of age with both hyperlipidemia and hypertension.

Exclusion Criteria

Patients with a history of myocardial or cerebral infarction within 6 and 3 months respectively were excluded. Other patients with a history of serious cardiovascular diseases were also excluded.

The drug supply for the trial is in Table 37 below.

Table 37: Drug supply – RESPOND TRIAL

Drug	Lot number
Amlodipine besylate 5mg	ED-O-366-901 FID G00595AA-K ED-O-309-801 FID-G00596AA-J
Amlodipine besylate 10 mg	ED-O-387-901 FID G00596AA-K ED-O-310-801 FID-G00596AA-H
Atorvastatin 10mg	960350-3000081-Gi FID 960350
Atorvastatin 40 mg	961293-3002101-G1 FID961293
Placebo matching atorvastatin 10 and 40	961073-3000081-GI, FID 961073 CX0980901-G1 FID WL 134,298A-76P A3 CX0960901-G1 FID WL 134,298A-76P A3
Placebo matching amlodipine 5 and 10 mg	ED-O-008-101 FID G00699AA

Table 38: Cardiovascular Risk group-specific LDL-C and Blood pressure criteria - RESPOND

	Group I	Group II	Group III
Fasting LDL-C	190-250mg/dL (4.9-6.5mmol/L)	160-250mg/dL (4.1-6.5mmol/L)	130-250mg/dL (3.4-6.5mmol/L)
Blood Pressure	Systolic, 140-179 mmHg and/ or Diastolic, 90-109 mmHg	Systolic,140-179 mmHg and /or Diastolic,90-109 mmHg	Systolic,130-159 mmHg and/ or Diastolic, 85-99 mmHg

Table 39: Duration (years) from first diagnosis to Day 1 of study drug

	Amlplb+ atoplb	Aml5+ atoplb	Aml10+ atoplb	Amlplb+ ato10	Aml5mg+ ato10
N	**111**	**110**	**111**	**111**	**111**
Primary diagnosis Hypertension Number of subjects Duration since first diagnosis Mean Range Unspecified	111 9.5 0.1-39.1 0	110 8.3 0.1-41.9 0	111 7.1 0.0-31.7 1	111 8.7 0.1-43.5 0	111 8.8 0.1-47.9 0
Primary diagnosis Hyperlipidemia Number of subjects Duration since first diagnosis Mean Range Unspecified	111 5.4 0.0-31.5 0	110 5.0 0.1-22.5 0	111 4.5 0.0-22.8 2	111 5.0 0.1-20.9 0	111 4.6 0.1-19.0 0

6.3 Efficacy evaluation - RESPOND

Primary efficacy parameters were the percent change from baseline to endpoint in LDL-C and the change from baseline to endpoint in systolic blood pressure. Secondary efficacy parameters included the percent changes from baseline to endpoint in total cholesterol, HDL- C, triglycerides, HDL- C/ LDL- C ratio, VLDL- C, apolipoprotein B; changes from baseline to endpoint in diastolic blood pressure, pulse pressure, and global risk factor scores; and the percentages of subjects who reached their therapeutic goals for LDL- C, blood pressure, as well as for both LDL-C and blood pressure at endpoint.

The baseline value for all lipid parameters (except apolipoprotein B), which was the value collected at the randomization visit) and all blood pressure parameters was defined as the average of all measurements taken during the run- in phase. The baseline value for global risk factor scores was based on factors collected at screening (age, gender, and diabetes status) and during the run-in period (LDL-C, HDL-C, systolic and diastolic blood pressure). Endpoint was defined as the last non-missing, post-baseline values carried forward (LOCF) for each subject during the eight- week double- blind phase.

6.4 Safety evaluation

Adverse events and profile

Safety was assessed at each visit through the collection of observed and reported adverse events and heart rate measurements. Laboratory safety tests, a physical examination, and ECGs were performed at a pre- treatment visit and at the final visit.

The following databases were reviewed for safety:

- 11 Phase 1 PK studies (435 subjects)
- AVALON and RESPOND (207 and 885 patients, respectively. Duration of exposure)
- GEMINI (975 patients), MARGAUX, DUAAL, AND ARISg
- Post marketing adverse event reports for patients taking concurrent amlodipine and atorvastatin (57.6 million patient years); 3,050 non-clinical study cases in Pfizer's safety database; ALLHAT, IDNT, PREVENT
- 4-month safety update up to July 31 2003. Open label extension AVALON (292 PATIENTS; RESPOND 213 PATIENTS; GEMINI 975 patients)

There were no data for studies on patients with angina and no safety data were reviewed for this indication.

A treatment-emergent AE was defined as an AE that began or worsened in severity from the first day double- blind study drug was administered up through the last dose of double- blind study medication. The incidences of clinical laboratory test abnormalities and the median changes from baseline to endpoint in clinical laboratory parameters were presented. Median changes from baseline to endpoint in heart rate were also presented. In addition, case information on subjects who had serious adverse events or who died during the double-blind phase of the study or within 30 days of the last dose of double- blind study drug was recorded. The incidences and frequencies of treatment-emergent adverse events (AEs) and serious adverse events are summarized in Tables 54-57.

Discontinuation

The most common safety-related reasons for discontinuation from the study in the combination treatment groups were the adverse events peripheral edema and headache, but these events led to the discontinuation of combination- treated subjects no more frequently than they did among subjects treated with either amlodipine alone or atorvastatin alone. Only one subject (no. 3137), who was randomized to amlodipine 5 mg and atorvastatin 80 mg, discontinued due to laboratory abnormalities (SGPT values of 111 U/ L and 115 U/ L and SGOT values of 61 U/ L and 48 U/ L on Days 29 and 36 of treatment, respectively)(Tables 42-44)

Protocol Deviations

Deviations from the protocol were classified within the following categories: patient not withdrawn from study as required by the protocol, adverse event reporting, inclusion and exclusion criteria, informed consent, prohibited concomitant medications, procedures and tests not followed in accordance with the protocol, study visit outside of the visit window, study drug administration. The proportions of subjects were similar across the 15 treatment groups. None of the deviations affected study conclusions.

In December 2002, the study sites were instructed to screen only patients who did require a washout so that any patients who were screened that month would have the opportunity to complete the double-blind phase of the study by March 2003. However, some sites had already screened patients who required a six- week washout. These sites were instructed to allow these patients to undergo an abbreviated washout period, but the patients were still required to undergo the run- in phase to determine if they satisfied all other study entry criteria. This deviation did not alter the study conclusions, and in any case would appear to reduce the magnitude of the effect of the study treatment(s) on blood pressure and/ or LDL- C.

Statistics

6.5 Statistical Methods: Analysis populations

The primary, intent-to-treat (ITT) efficacy population included all subjects who took at least one dose of assigned treatment during the double- blind phase of the study and had at least one post-baseline efficacy assessment (either blood pressure or lipids) during this phase. The safety population included subjects who took at least one dose of study medication and had at least one post- baseline safety measurement.

Categorical data were analyzed using the Cochran-Mantel-Haenszel (CMH) test for general association with Groups I, II, and III as strata. Continuous data were analyzed using the appropriate comparisons from a 3 x 5 factorial analysis of covariance (ANCOVA) model with terms for atorvastatin, amlodipine, atorvastatin- by- amlodipine interaction, and baseline measurement (the covariate). The tests were two-sided with a significance level of =0.05; no adjustments for multiple comparisons were made. Ninety-five percent confidence intervals around between- treatment differences were also reported.

RESULTS

6.6 Subject disposition and Demographics - RESPOND

The disposition of the subjects is presented in Table 40. Within the population of all treated subjects, there were slightly more males than females and over 90% of subjects were White. The mean age was 58 years, and the average subject was overweight based on his or her BMI (Table 41). All subjects had comorbid hypertension and hyperlipidemia. Approximately 49% of all subjects had one or more additional CV risk factors (ie, they were Group II subjects), and approximately 48% of all subjects had CHD or a CHD risk equivalent (ie, they were Group III subjects) (Table 34). The distribution by age, sex, and other ethnic races are graphically presented in Figures 3-5. A relatively high proportion of Hispanic speaking people is notable.

Table 40: Subject disposition - RESPOND

Subject Disposition

Status parameter		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Treated (N)	111	111	111	111	110
	Completed (n,%)	102 (91.9)	99 (89.2)	103 (92.8)	96 (86.5)	96 (87.3)
	Discontinued (n,%)	9 (8.1)	12 (10.8)	8 (7.2)	15 (13.5)	14 (12.7)
	ITT analysis (n,%)	111(100.0)	111(100.0)	111(100.0)	111(100.0)	110(100.0)
	Safety analysis (n,%)	111(100.0)	111(100.0)	111(100.0)	111(100.0)	110(100.0)
AML 5 mg	Treated (N)	110	111	111	110	111
	Completed (n,%)	104 (94.5)	102 (91.9)	106 (95.5)	101 (91.8)	105 (94.6)
	Discontinued (n,%)	6 (5.5)	9 (8.1)	5 (4.5)	9 (8.2)	6 (5.4)
	ITT analysis (n,%)	110(100.0)	110 (99.1)	111(100.0)	109 (99.1)	111(100.0)
	Safety analysis (n,%)	110(100.0)	111(100.0)	111(100.0)	110(100.0)	111(100.0)
AML 10 mg	Treated (N)	111	110	110	111	111
	Completed (n,%)	100 (90.1)	101 (91.8)	99 (90.0)	103 (92.8)	100 (90.1)
	Discontinued (n,%)	11 (9.9)	9 (8.2)	11 (10.0)	8 (7.2)	11 (9.9)
	ITT analysis (n,%)	109 (98.2)	108 (98.2)	110(100.0)	111(100.0)	111(100.0)
	Safety analysis (n,%)	111(100.0)	110(100.0)	110(100.0)	111(100.0)	111(100.0)

Subject no. 2610 was randomized to combined treatment with amlodipine 10 mg and atorvastatin 80 mg but received treatment with amlodipine 5 mg and atorvastatin 0 mg. In all analyses, the subject's data were included in the treatment group to which the subject was randomized.

6.70 Demographics

Table 41: Demographics - RESPOND

Panel 9. Demographic and Baseline Characteristics. All Treated Subjects

	All Treatment Groups		
Parameter / unit (statistic)	Male	Female	Total
No. of randomized subjects (N)	884 (53.3)	776 (46.7)	1660 (100.0)
Age (yrs)			
18-44 (n [%])	84 (9.5)	33 (4.3)	117 (7.0)
45-64 (n [%])	593 (67.1)	490 (63.1)	1083 (65.2)
≥65 (n [%])	207 (23.4)	253 (32.6)	460 (27.7)
Mean (SD)	56.8 (9.5)	59.9 (8.4)	58.3 (9.1)
Race (n [%])			
White	827 (93.6)	705 (90.9)	1532 (92.3)
Black	24 (2.7)	24 (3.1)	48 (2.9)
Asian	16 (1.8)	19 (2.4)	35 (2.1)
Other	17 (1.9)	28 (3.6)	45 (2.7)
BMI (kg/m^2)			
Mean (SD)	28.4 (4.2)	29.3 (5.3)	N/A
Range	14.0-63.0	18.0-56.0	N/A
Duration 1° diagnoses (yrs) (mean, range)			
Hypertension	N/A	N/A	8.5 0.0-52.5
Hyperlipidemia	N/A	N/A	5.0 0.0-36.1
Efficacy parameters (mean [SD])			
LDL-C (mg/dL)	N/A	N/A	182.0 (25.5)
Systolic blood pressure (mmHg)	N/A	N/A	148.4 (9.5)
Concurrent history of:			
Diabetes mellitus (n [%])	N/A	N/A	244 (14.7)
Ischemic heart disease (n [%])	N/A	N/A	470 (28.3)
CV risk group assignment [1] (n [%])			
Group I	15 (1.7)	37 (4.8)	52 (3.1)
Group II	396 (44.8)	413 (53.2)	809 (48.7)
Group III	473 (53.5)	326 (42.0)	799 (48.1)

[1] See Panel 1 of this study report for CV risk group criteria.

Source: Tables 2.1.2, 2.2.2, 2.3; datasets

Figure 3: Sex distribution - RESPOND

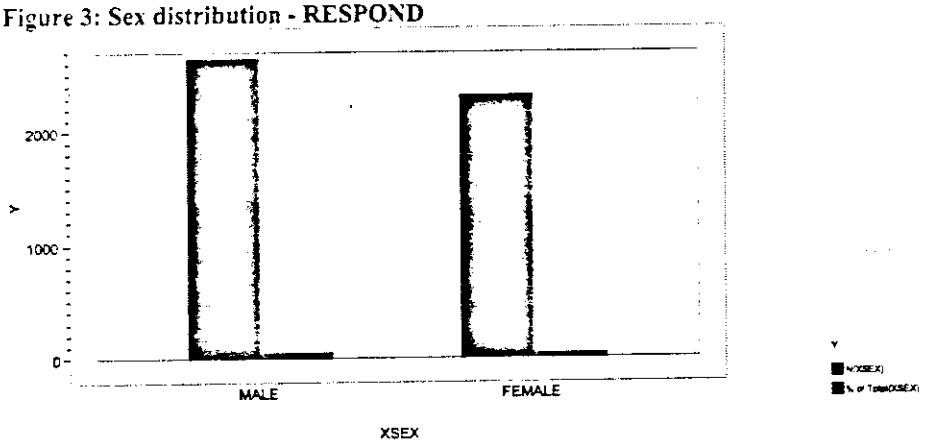


Figure 4: Showing age distribution-RESPOND Study

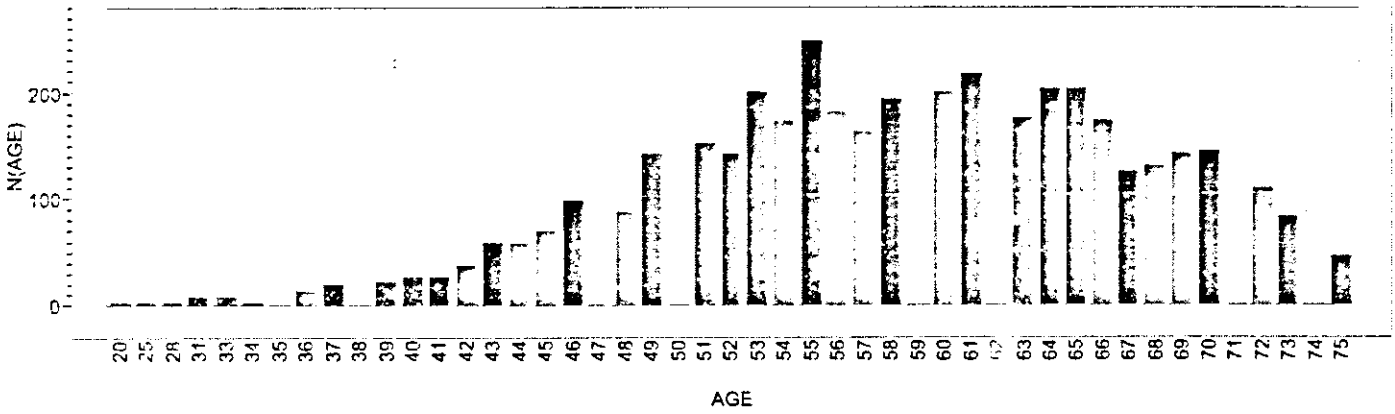
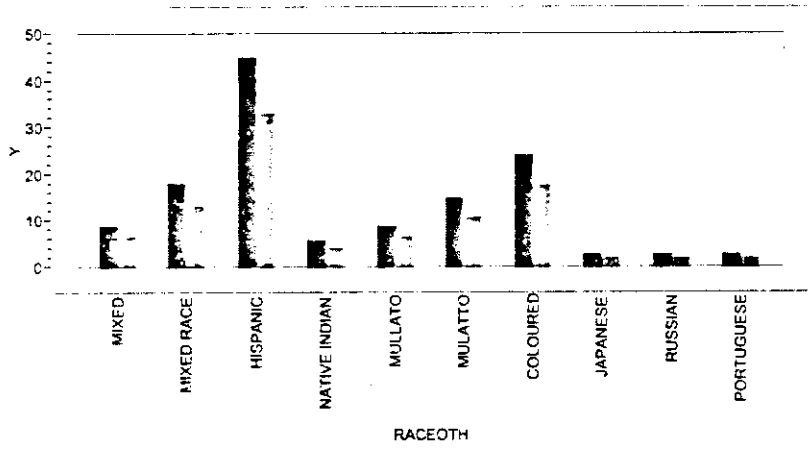


Figure 5: Showing distribution of other races in RESPOND study



6.71 Discontinuations due to adverse events - RESPOND

The reasons for discontinuation from the study are in Table 42. The overall rates of discontinuation due to adverse events were low across treatment groups (Table 43). Rates of discontinuation due to AEs appeared to be slightly higher in subjects treated with amlodipine 10 mg than in subjects treated with amlodipine 5 mg or amlodipine placebo. However, the rates of discontinuation due AEs were affected but not unduly affected by increases in atorvastatin dosage.

The most common safety-related reasons for discontinuation from the study in the combination treatment groups were the adverse events peripheral edema and headache, but these events led to the discontinuation of subjects in the combination treatment groups no more frequently than they did among subjects treated with either amlodipine alone or atorvastatin alone. Only one

subject (no. 3137), who was randomized to amlodipine 5 mg and atorvastatin 80 mg, discontinued due to laboratory abnormalities (SGPT values of 111 U/ L and 115 U/ L and SGOT values of 61 U/ L and 48 U/ L on Days 29 and 36 of treatment, respectively).

Table 42 : Reasons for discontinuation from RESPOND

Panel 11. Subjects who Discontinued from the Study

No. (%) of subjects who discontinued due to:		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Any reason	9 (8.1)	12 (10.8)	8 (7.2)	15 (13.5)	14 (12.7)
	Death	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
	Adverse event[1]	5 (4.5)	8 (7.2)	1 (0.9)	6 (5.4)	3 (2.7)
	Lack of efficacy	4 (3.6)	2 (1.8)	1 (0.9)	2 (1.8)	3 (2.7)
	Defaulted[2]	0 (0.0)	0 (0.0)	3 (2.7)	4 (3.6)	4 (3.6)
	Other[3]	0 (0.0)	2 (1.8)	2 (1.8)	3 (2.7)	3 (2.7)
AML 5 mg	Any reason	6 (5.5)	9 (8.1)	5 (4.5)	9 (8.2)	6 (5.4)
	Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse event[1]	3 (2.7)	5 (4.5)	2 (1.8)	7 (6.4)	5 (4.5)
	Lack of efficacy	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
	Defaulted[2]	1 (0.9)	0 (0.0)	2 (1.8)	1 (0.9)	1 (0.9)
	Other[3]	2 (1.8)	3 (2.7)	1 (0.9)	1 (0.9)	0 (0.0)
AML 10 mg	Any reason	11 (9.9)	9 (8.2)	11 (10.0)	8 (7.2)	11 (9.9)
	Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse event[1]	9 (8.1)	7 (6.4)	10 (9.1)	5 (4.5)	9 (8.1)
	Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
	Defaulted[2]	1 (0.9)	2 (1.8)	0 (0.0)	2 (1.8)	1 (0.9)
	Other[3]	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)

[1] Includes subjects who discontinued from the study during the double-blind phase due to any adverse event, laboratory abnormality, or objective test abnormality, regardless of suspected causal relationship to treatment or prior history of the event.

[2] Includes subjects who during the double-blind phase were lost to follow-up or were unwilling to participate further in the study.

[3] Includes subjects who during the double-blind phase were determined to have not met the study entry criteria, who deviated from the protocol, or who discontinued for any other reason.

Source: Table 4.1

Adverse events associated with discontinuation of greater than 1% of subjects in any combination treatment group and the frequencies of discontinuations are summarized in Table 44. Vital signs (heart rate and blood pressure) from baseline to final observation are summarized in Table 45.

Table 43: Frequencies of discontinuations due to adverse events - RESPOND

Panel 12. Overview of Discontinuations from the Study due to Adverse Events[1]

No. (%) of subjects who discontinued due to:		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Any AE	5 (4.5)	8 (7.2)	1 (0.9)	6 (5.4)	3 (2.7)
	Severe AEs	0 (0.0)	2 (1.8)	0 (0.0)	2 (1.8)	0 (0.0)
	Serious AEs	0 (0.0)	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)
	Death	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
AML 5 mg	Any AE	3 (2.7)	5 (4.5)	2 (1.8)	7 (6.4)	5 (4.5)
	Severe AEs	2 (1.8)	1 (0.9)	0 (0.0)	3 (2.7)	3 (2.7)
	Serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
	Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AML 10 mg	Any AE	9 (8.1)	7 (6.4)	10 (9.1)	5 (4.5)	9 (8.1)
	Severe AEs	3 (2.7)	2 (1.8)	5 (4.5)	1 (0.9)	4 (3.6)
	Serious AEs	0 (0.0)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
	Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[1] Includes adverse events, laboratory abnormalities, and other objective test abnormalities, regardless of suspected causal relationship to treatment or prior history of the event, that led to discontinuation of a subject during the double-blind phase of the study.

NOTE: This panel reports the number of subjects who discontinued due to an AE during the double-blind phase of the study. In Section 8.1.1.5, which reports data from Pfizer's early alert safety database, subjects with SAEs that began during the double-blind phase or within 30 days after the last dose of double-blind study medication are reported. As a consequence, one additional subject is reported to have withdrawn due to a SAE in Section 8.1.2 than in this section.

Source: Tables 4.2.1 and 4.2.3; Listing 13

Table 44: Adverse events associated with discontinuations of >1% of subjects in any combination treatment - RESPOND.

Panel 13. Adverse Events[1] Associated with Discontinuation of >1% of Subjects in Any Combination Treatment Group

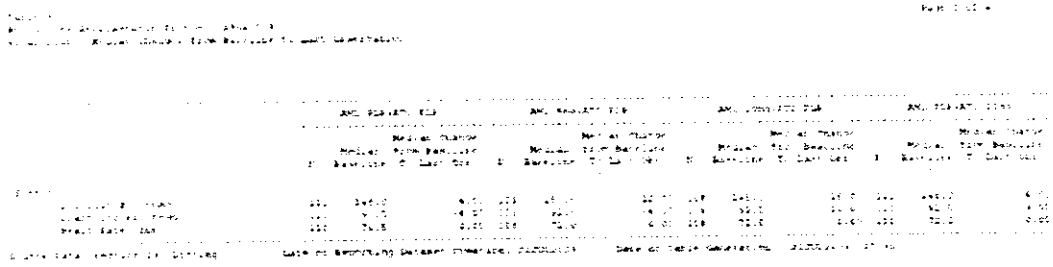
No. (%) of subjects who discontinued due to:		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Headache	1 (0.9)	1 (0.9)	0 (0.0)	3 (2.7)	0 (0.0)
	Peripheral edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Myalgia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	1 (0.9)
	Palpitation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Dizziness	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
	Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
	Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
	Vasodilatation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
AML 5 mg	Headache	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)
	Peripheral edema	2 (1.8)	1 (0.9)	0 (0.0)	3 (2.7)	0 (0.0)
	Myalgia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)
	Palpitation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Dizziness	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
	Abdominal pain	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.8)
	Nausea	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.8)
	Vasodilatation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AML 10 mg	Headache	1 (0.9)	2 (1.8)	4 (3.6)	1 (0.9)	3 (2.7)
	Peripheral edema	5 (4.5)	2 (1.8)	3 (2.7)	1 (0.9)	3 (2.7)
	Myalgia	1 (0.9)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
	Palpitation	1 (0.9)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Dizziness	2 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)
	Abdominal pain	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	2 (1.8)
	Nausea	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	1 (0.9)
	Vasodilatation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)

[1] Includes any AE, laboratory abnormality, or objective test abnormality, regardless of suspected causal relationship to treatment or prior history of the experience that led to discontinuation of a subject during the double-blind phase. AEs are reported using COSTART preferred terms.

Source: Tables 4.2.1 and 4.2.3

Vital signs – RESPOND

Table 45: Vital Signs - RESPOND



7.0 Efficacy - RESPOND

Primary efficacy parameters are the percent change from baseline to endpoint in LDL-C and change from baseline to endpoint in systolic blood pressure. The clinical rationale for the primary comparisons is that the dual therapy should be better than the amlodipine for the treatment of hyperlipidemia and be better than the atorvastatin for the treatment of hypertension. To demonstrate superiority of different dose combinations of atorvastatin and amlodipine over amlodipine only treatment in reducing LDL-C, eight comparisons were made (Table 47).

7.1 Efficacy Results: Primary efficacy results

LDL-C

In evaluating efficacy of the combination treatments in reducing LDL- C, the appropriate comparisons from a 3 x 5 factorial ANCOVA model were specified, and were made utilizing a step-down approach with closed testing procedures. The results show that

(1) atorvastatin overall ($p< 0.001$), as well as

(2) each active atorvastatin dosage combined across amlodipine doses (80 mg, $p< 0.001$; 40 mg, $p< 0.001$, 20 mg, $p< 0.001$, 10 mg, $p< 0.001$), had a statistically significant treatment effect on LDL- C.

Furthermore the eight comparisons show that the least square mean percent changes from baseline in LDL- C in each of the eight combination treatment groups was significantly greater ($p< 0.001$ for all comparisons) than that in the corresponding amlodipine- alone treatment group. Results of this last set of 8 comparisons are shown below in Table 46.

Table 46: Primary Efficacy analysis- RESPOND-Combined treatments in reducing LDL-C

Primary Efficacy Analysis: Efficacy of the Combined Treatments in Reducing LDL-C

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	LS mean % change /	-1.2	-33.5	-39.5	-43.1	-47.0
AML 5 mg	LS mean % change /	-0.1	-39.0	-42.2	-44.9	-48.2
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-38.9	-42.2	-44.8	-48.2
	95% CI		-42.9, -34.9	-46.2, -38.2	-48.8, -40.8	-52.2, -44.2
AML 10 mg	LS mean % change /	-2.6	-36.6	-38.6	-43.2	-49.2
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-34.0	-36.0	-40.6	-46.6
	95% CI		-38.1, -30.0	-40.0, -32.0	-44.6, -36.7	-50.6, -42.6

Data were analyzed using the appropriate comparisons from a 3x5 factorial ANCOVA model. Comparisons described above were between each individual combination treatment group and the corresponding amlodipine treatment group.

7.2 Effect of combination drug on Systolic Blood Pressure

Similar to the analyses described above, analyses evaluating the efficacy of the combination treatments in reducing systolic blood pressure utilized the appropriate comparisons from a 3 x 5 factorial ANCOVA model and a step-down approach with closed testing procedures. The results showed that (1) amlodipine overall ($p< 0.001$), as well as (2) each active amlodipine dosage combined across all atorvastatin doses (10 mg, $p< 0.001$; 5 mg, $p< 0.001$), had a statistically significant treatment effect on systolic blood pressure. Results of eight comparisons showed that there were significantly greater least square mean changes from baseline in systolic blood pressure in each of the eight combination treatment groups ($p< 0.001$ for all comparisons) compared with the corresponding atorvastatin-alone treatment group. Results of this final set of eight comparisons are shown below in Table 47.

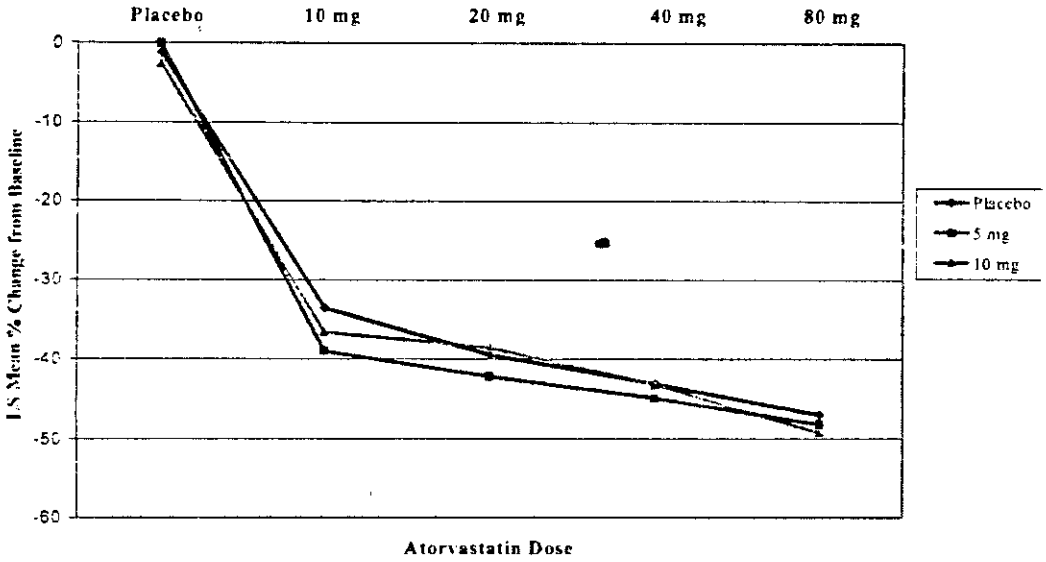
Table 47: Primary Efficacy analysis- RESPOND-Combined treatments in reducing SBP

Primary Efficacy Analysis: Efficacy of the Combined Treatments in Reducing Systolic Blood Pressure (mmHg)

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	LS mean change /	-2.9	-4.3	-6.1	-6.2	-6.6
AML 5 mg	LS mean change /	-12.6	-13.6	-15.3	-12.8	-12.6
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-9.3	-9.2	-6.6	-6.0
	95% CI		-12.3, -6.3	-12.2, -6.2	-9.7, -3.6	-9.0, -3.0
AML 10 mg	LS mean change /	-16.5	-15.9	-16.0	-16.5	-17.5
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-11.6	-9.9	-10.3	-11.0
	95% CI		-14.6, -8.5	-12.9, -6.8	-13.3, -7.2	-14.0, -7.9

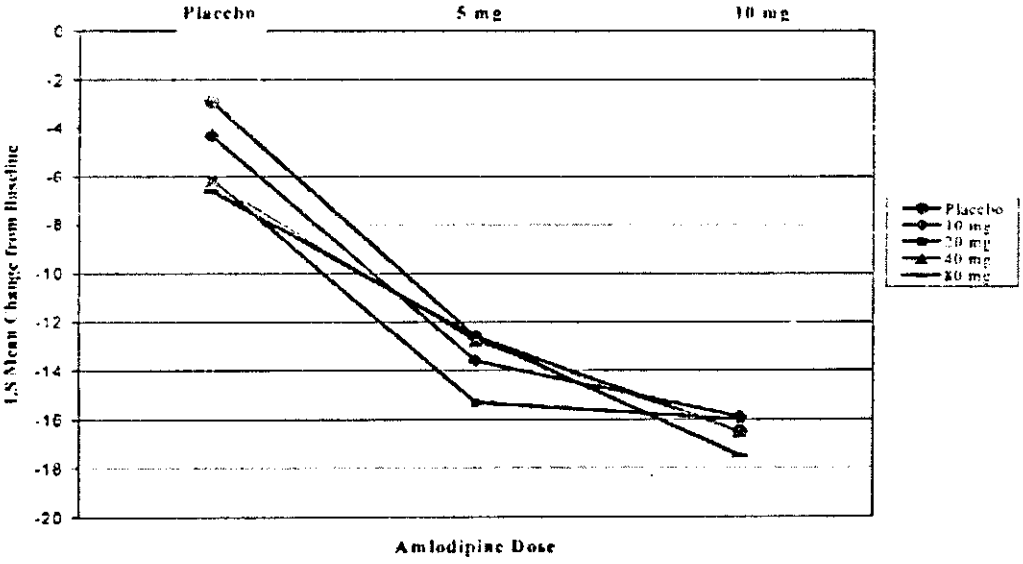
Data were analyzed using the appropriate comparisons from a 3x5 factorial ANCOVA model. In this analysis, comparisons were made between each individual combination treatment group and the corresponding atorvastatin treatment group.

Figure 6 :Effect of amlodipine on atorvastatin dose response curve - LDL-C



Source: Table 5.1.2

Figure 7: Effect of Atorvastatin on Amlodipine Dose Response curve-Systolic BP



Source: Table 5.2.2

7.21 Primary efficacy conclusion - RESPOND

The primary efficacy results demonstrated that concurrent treatment with each of the eight active amlodipine and atorvastatin dosage combinations was significantly more effective than

amlodipine alone in lowering subjects' LDL-C levels, and significantly more effective than atorvastatin alone in lowering subjects' systolic blood pressure.

These data demonstrate that each of the eight-fixed dose combinations of amlodipine and atorvastatin was superior to amlodipine alone in reducing LDL- C and superior to atorvastatin alone in lowering systolic blood pressure. All eight fixed- dose combination treatments were therefore highly effective in the concurrent treatment of hypertension and hyperlipidemia. It is conceivable that ——— amlodipine combined dose may also b e superior to the individual component in lowering LDL-C.

7.3 Secondary efficacy analyses - RESPOND

In analyses evaluating whether amlodipine modifies the LDL-C lowering efficacy of atorvastatin, the appropriate, specified comparisons from a 3 x 5 factorial ANCOVA model were made. For two of the comparisons, the least square mean percent changes from baseline in LDL- C for (1) amlodipine 10 mg combined over all atorvastatin doses and (2) amlodipine 5 mg combined over all atorvastatin doses were compared to those in the groups of subjects treated with active atorvastatin alone. In the remaining comparisons, (3) each of the eight amlodipine and atorvastatin dose combination groups was compared with the group receiving the corresponding amlodipine dose alone. Results are shown below in Table 48.

Table 48: Effect of amlodipine on LDL-C lowering efficacy of Atorvastatin

Effect of Amlodipine on the LDL-C–Lowering Efficacy of Atorvastatin

Parameter / Analysis		ATO 10 mg, ATO 20 mg, ATO 40 mg, and ATO 80 mg combined			
AML 0 mg	LS mean % change /	-40.8			
AML 5 mg	LS mean % change /	-43.6			
	P-value	0.006			
	LS mean difference	-2.8			
	95% CI	-4.8, -0.8			
AML 10 mg	LS mean % change /	-41.9			
	P-value	0.250			
	LS mean difference	-1.2			
	95% CI	-3.2, 0.8			
Parameter / Analysis		ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	LS mean % change /	-33.5	-39.5	-43.1	-47.0
AML 5 mg	LS mean % change /	-39.0	-42.2	-44.9	-48.2
	P-value	0.007	0.172	0.372	0.547
	LS mean difference	-5.5	-2.8	-1.8	-1.2
	95% CI	-9.5, -1.5	-6.7, 1.2	-5.8, 2.2	-5.2, 2.8
AML 10 mg	LS mean % change /	-36.6	-38.6	-43.2	-49.2
	P-value	0.126	0.674	0.927	0.280
	LS mean difference	-3.2	0.9	-0.2	-2.2
	95% CI	-7.2, 0.9	-3.1, 4.9	-4.2, 3.8	-6.2, 1.8

Data were analyzed using the appropriate comparisons from a 3x5 factorial ANCOVA model. In this analysis, the appropriate comparisons were between combined or individual amlodipine + atorvastatin treatments and the appropriate combined or individual atorvastatin treatments.

Results of the comparison described in (1) above and presented in table 48 show that the effect on LDL- C of amlodipine 10 mg combined across active atorvastatin dosages was not significantly different from that of the active atorvastatin dosages alone (p= 0.250). This indicates that amlodipine 10 mg when administered in combination with the active atorvastatin dosages did not alter the LDL- C lowering efficacy of atorvastatin. The comparison described in (2) above reveals that there was a significant difference (p= 0.006) in the reductions in LDL-C between amlodipine 5 mg combined across all active atorvastatin dosages and the active atorvastatin doses alone. This indicates that amlodipine 5 mg when administered in combination with the active atorvastatin dosages did significantly alter the LDL- C lowering efficacy of atorvastatin. In

addition, the least square mean percent change from baseline in LDL- C observed when amlodipine 5 mg was added to atorvastatin 10 mg (- 39.0%) was significantly greater (p= 0.007) than that seen when atorvastatin 10 mg was administered alone (- 33.5%) (Table 46). None of the other comparisons described in (3) above reveals a significant treatment effect for either amlodpine 5 mg or amlodipine 10 mg. The data demonstrate that, with the exception of the 5/10 combination, there was no modification of atorvastatin's effect on LDL- C when the drug was taken in combination with amlodipine. ***Taken together, these results provide statistically significant evidence that atorvastatin 10 mg QD modified the blood pressure-lowering effect of concurrent amlodipine 5 mg QD in patients with comorbid hypertension and hyperlipidemia.***

7.4 Effect of combination drug on Systolic and Diastolic Blood Pressure- RESPOND

Results of the comparisons described in (1) and (2) above and presented in the panel show that there was no significant difference between the groups in the least square mean changes from baseline in systolic blood pressure (p= 0.746 and p= 0.490, respectively) (Table 47). This indicates that when co-administered with amlodipine, neither the "high" atorvastatin dosages nor the "low" atorvastatin dosages altered the systolic blood pressure lowering efficacy of amlodipine. Results of the remaining eight comparisons described in (3) above show that the effect on systolic blood pressure observed when any of the active atorvastatin dosages was co-administered with amlodipine 5 mg or 10 mg was no different from that observed when the corresponding amlodipine dosage was administered alone. The data thus provide no evidence that atorvastatin modified amlodipine's effect on systolic blood pressure when the two drugs were taken in combination. In contrast, there was significant modification of the diastolic blood pressure when any of the atorvastatin dosages was co-administered with amlodipine 5mg or 10mg (Table 48). Analyses evaluating the effect of atorvastatin on the systolic blood pressure lowering efficacy of amlodipine consisted of the appropriate comparisons from a 3 x 5 factorial ANCOVA model. For two of the comparisons, the least square mean changes in systolic blood pressure for (1) the "high" atorvastatin doses (ie, 80 mg or 40 mg) combined over both amlodipine doses and (2) the "low" atorvastatin doses (ie, 20 mg or 10 mg) combined over both amlodipine doses were compared to those in the groups treated with amlodipine alone. In the remaining eight comparisons, each of the eight amlodipine and atorvastatin dose combination groups was compared with the group receiving the corresponding atorvastatin dose alone. The rationale for combining 5 and 10 mg amlodipine against atorvastatin that showed lack of effect on systolic blood pressure and not for diastolic blood pressure is not clear to the reviewer (Tables 49 -50).

Table 49: Effect of Atorvastatin on the systolic blood pressure lowering efficacy of amlodipine

Effect of Atorvastatin on the Systolic Blood Pressure–Lowering Efficacy of Amlodipine (mmHg)

Parameter / Analysis		ATO 0 mg	ATO 10 mg and 20 mg combined		ATO 40 mg and 80 mg combined	
AML 5 mg and 10 mg	LS mean change / P-value LS mean difference 95% CI	-14.4	-15.2 0.490 -0.7 -2.5, 1.2		-14.8 0.746 -0.3 -2.2, 1.5	
Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 5 mg	LS mean change / P-value LS mean difference 95% CI	-12.6	-13.6 0.522 -1.0 -4.0, 2.0	-15.3 0.081 -2.7 -5.7, 0.3	-12.8 0.892 -0.2 -3.2, 2.8	-12.6 0.972 0.1 -3.0, 3.1
AML 10 mg	LS mean change / P-value LS mean difference 95% CI	-16.5	-15.9 0.705 0.6 -2.5, 3.6	-16.0 0.761 0.5 -2.6, 3.5	-16.5 0.995 0.0 -3.0, 3.0	-17.5 0.485 -1.1 -4.1, 1.9

Data were analyzed using the appropriate comparisons from a 3×5 factorial ANCOVA model. In this analysis, the appropriate comparisons were between combined or individual amlodipine + atorvastatin treatments and the appropriate combined or individual amlodipine treatments.

Table 50 Effect of Atorvastatin on the diastolic blood pressure lowering efficacy of amlodipine (mmHg)

Panel 20. Secondary Efficacy Analysis: Efficacy of the Combined Treatments in Reducing Diastolic Blood Pressure (mmHg)

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	LS mean change /	-3.3	-3.9	-3.8	-3.1	-4.3
AML 5 mg	LS mean change /	-7.6	-8.2	-9.4	-7.7	-8.5
	P-value		<0.001	<0.001	0.005	<0.001
	LS mean difference		-4.3	-5.6	-2.6	-4.4
	95% CI		-6.1, -2.5	-7.4, -3.8	-4.2, -0.8	-6.2, -2.6
AML 10 mg	LS mean change /	-10.4	-8.9	-10.5	-9.8	-11.0
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-5.0	-6.7	-4.7	-6.8
	95% CI		-6.8, -3.2	-8.5, -4.9	-6.5, -2.9	-8.6, -5.0

Data were analyzed using the appropriate comparisons from a 3x5 factorial ANCOVA model. For the results presented above, the appropriate comparisons were between each individual combination treatment group and the corresponding atorvastatin treatment group. See Panel 6, in Section 5.7.2.3.3, *Statistical Analysis of Efficacy Parameters*, above, for details.

Source: Table 5.2.2

Secondary analyses of changes in other lipid and systolic blood pressure parameters yielded results almost similar to the primary efficacy results described above. All eight combination treatments were shown to be significantly more effective than amlodipine alone in reducing total cholesterol, VLDL- C, triglycerides, (Table 51) and apolipoprotein B as well as in raising the HDL-C/ LDL- C ratio (but not HDL- C), and significantly more effective than atorvastatin in reducing diastolic blood pressure (Table 50).

Table 51: Efficacy of combined treatments in reducing Total Cholesterol and Triglycerides but not HDL-C

Panel 19. Secondary Efficacy Analyses: Efficacy of the Combined Treatments in Reducing HDL-C, Total Cholesterol, and Triglycerides

HDL-C						
Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	LS mean % change /	1.3	5.4	5.0	3.4	2.7
AML 5 mg	LS mean % change /	3.3	5.7	5.9	3.5	6.6
	P-value		0.263	0.225	0.914	0.125
	LS mean difference		2.5	2.7	0.2	3.4
	95% CI		-1.8, 6.8	-1.6, 6.9	-4.1, 4.5	-0.9, 7.6
AML 10 mg	LS mean % change /	4.1	6.0	6.7	4.5	5.3
	P-value		0.394	0.247	0.847	0.592
	LS mean difference		1.9	2.5	0.4	1.2
	95% CI		-2.5, 6.2	-1.8, 6.9	-3.9, 4.7	-3.1, 5.5
Total Cholesterol						
Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	LS mean % change /	-0.1	-24.0	-29.4	-32.6	-35.6
AML 5 mg	LS mean % change /	0.7	-28.2	-31.0	-33.6	-36.2
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-28.9	-31.6	-34.3	-36.8
	95% CI		-32.1, -25.7	-34.8, -28.5	-37.5, -31.1	-40.0, -33.7
AML 10 mg	LS mean % change /	-2.4	-27.1	-28.5	-32.5	-37.3
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-24.7	-26.1	-30.1	-34.9
	95% CI		-27.9, -21.5	-29.3, -23.0	-33.3, -26.9	-38.1, -31.8
Triglycerides						
Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	LS mean % change /	8.5	-10.7	-21.4	-24.7	-27.4
AML 5 mg	LS mean % change /	4.4	-19.8	-22.7	-24.5	-26.3
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-24.3	-27.2	-28.9	-30.8
	95% CI		-32.1, -16.4	-35.0, -19.3	-36.8, -21.0	-38.6, -22.9
AML 10 mg	LS mean % change /	-4.4	-18.6	-22.2	-21.3	-33.4
	P-value		<0.001	<0.001	<0.001	<0.001
	LS mean difference		-14.2	-17.9	-16.9	-29.0
	95% CI		-22.1, -6.2	-25.7, -10.0	-24.7, -9.1	-36.9, -21.2

Data were analyzed using the appropriate comparisons from a 3x5 factorial ANCOVA model. For the results presented above, the appropriate comparisons were between each individual combination treatment group and the corresponding amlodipine treatment group. See Panel 6, in Section 5.7.2.3.3, *Statistical Analysis of Efficacy Parameters*, above, for details.

Source: Table 5.1.2

7.5 Efficacy Conclusions - RESPOND

The primary efficacy results confirm that in patients with comorbid hyperlipidemia and hypertension, combined treatment with each of the eight active amlodipine and atorvastatin dosage combinations was significantly more effective than amlodipine alone in lowering subjects' LDL- C levels, and significantly more effective than atorvastatin alone in lowering subjects' systolic blood pressure.

The main secondary objective was to determine whether amlodipine when co- administered with atorvastatin modifies the LDL- C lowering efficacy of atorvastatin, and whether atorvastatin when co- administered with amlodipine modifies the systolic blood pressure lowering efficacy of amlodipine. Analyses of changes in LDL- C demonstrate that there was no overall modification of atorvastatin's effect on LDL- C when the drug was taken in combination with amlodipine. There was an isolated, statistically significant increase in the LDL- C lowering efficacy when amlodipine 5 mg was combined with atorvastatin 10 mg. This was consistent with results obtained in the AVALON study at the same doses, amlodipine 5 mg in combination with atorvastatin 10 mg. The magnitude of this effect according to the sponsor was sufficiently small to be considered of no clinical relevance. This conclusion cannot be justified in the absence of outcome studies. The results from the Respond Trial show that amlodipine 5 mg and 10 mg had no significant effect on LDL- C when administered in combination with any of the other atorvastatin doses. Analyses of changes in systolic blood pressure provide no evidence that atorvastatin modified the systolic blood pressure -lowering efficacy of amlodipine when the treatments were taken once daily in combination by the patients in this study.

Additional secondary analyses show that all eight combination treatments were significantly more effective than amlodipine alone in reducing total cholesterol, VLDL- C, triglycerides, and apolipoprotein B as well as in raising the HDL- C/ LDL- C ratio (but not HDL-C), and significantly more effective than atorvastatin in reducing diastolic blood pressure.

7.6 Prior Drug Treatment for subjects

Medications excluding antihypertensives or lipid- lowering agents that were taken prior to study entry are summarized by treatment group and BNF drug treatment category in Table 52. The table shows that subjects most commonly took medications in the following BNF drug treatment categories: drugs used in rheumatic diseases and gout (including primarily anti- inflammatory analgesics), analgesics (including primarily analgesics used for mild to moderate pain), drugs used in diabetes (including primarily oral antidiabetic drugs), and vasodilators (including primarily vasodilators used in angina pectoris). The treatment groups were similar with respect to the proportions of subjects taking individual prior medications.

During the period of up to six months prior to study entry, approximately one- third of subjects had not been treated with any antihypertensive or lipid-lowering agents. The remaining two- thirds of subjects reported having taken at least one medication to treat their hypertension and/ or hyperlipidemia.

Table 52: Prior treatment for hypertension and hyperlipidemia for subjects on combination

Panel 10. Prior Drug Treatments [1] for Hypertension and Hyperlipidemia for Subjects in Any Combination Treatment Group

No. (%) of subjects who took:		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	AHT *and/or* lipid-lowering drugs	75 (67.6)	82 (73.9)	73 (65.8)	78 (70.3)	76 (69.1)
	Antihypertensive drugs [2]	54 (48.6)	60 (54.1)	55 (49.5)	58 (52.3)	55 (50.0)
	Beta-adrenoceptor blocking drugs [3]	28 (25.2)	23 (20.7)	23 (20.7)	17 (15.3)	19 (17.3)
	Diuretics [4]	17 (15.3)	22 (19.8)	15 (13.5)	17 (15.3)	15 (13.6)
	Lipid-lowering drugs [5]	42 (37.8)	41 (36.9)	29 (26.1)	38 (34.2)	36 (32.7)
AML 5 mg	AHT *and/or* lipid-lowering drugs	76 (69.1)	77 (69.4)	73 (65.8)	75 (68.2)	73 (65.8)
	Antihypertensive drugs [2]	55 (50.0)	56 (50.5)	50 (45.0)	55 (50.0)	52 (46.8)
	Beta-adrenoceptor blocking drugs [3]	26 (23.6)	24 (21.6)	22 (19.8)	20 (18.2)	26 (23.4)
	Diuretics [4]	17 (15.5)	15 (13.5)	26 (23.4)	15 (13.6)	12 (10.8)
	Lipid-lowering drugs [5]	29 (26.4)	37 (33.3)	37 (33.3)	33 (30.0)	36 (32.4)
AML 10 mg	AHT *and/or* lipid-lowering drugs	76 (68.5)	78 (70.9)	69 (62.7)	72 (64.9)	78 (70.3)
	Antihypertensive drugs [2]	54 (48.6)	56 (50.9)	49 (44.5)	54 (48.6)	56 (50.5)
	Beta-adrenoceptor blocking drugs [3]	24 (21.6)	24 (21.8)	27 (24.5)	29 (26.1)	24 (21.6)
	Diuretics [4]	18 (16.2)	18 (16.4)	16 (14.5)	11 (9.9)	16 (14.4)
	Lipid-lowering drugs [5]	33 (29.7)	34 (30.9)	31 (28.2)	31 (27.9)	31 (27.9)

[1] Drug treatments reported by the investigator were summarized above using British National Formulary terms.

[2] Primarily angiotensin-converting enzyme inhibitors, calcium-channel blocking drugs, antiotensin II receptor antagonists, and antihypertensive diuretic combinations.

[3] Primarily betablocking drugs, single agents.

[4] Including primarily thiazides and related diuretics, potassium-sparing diuretics, and loop diuretics.

[5] Primarily HMG-CoA reductase inhibitors.

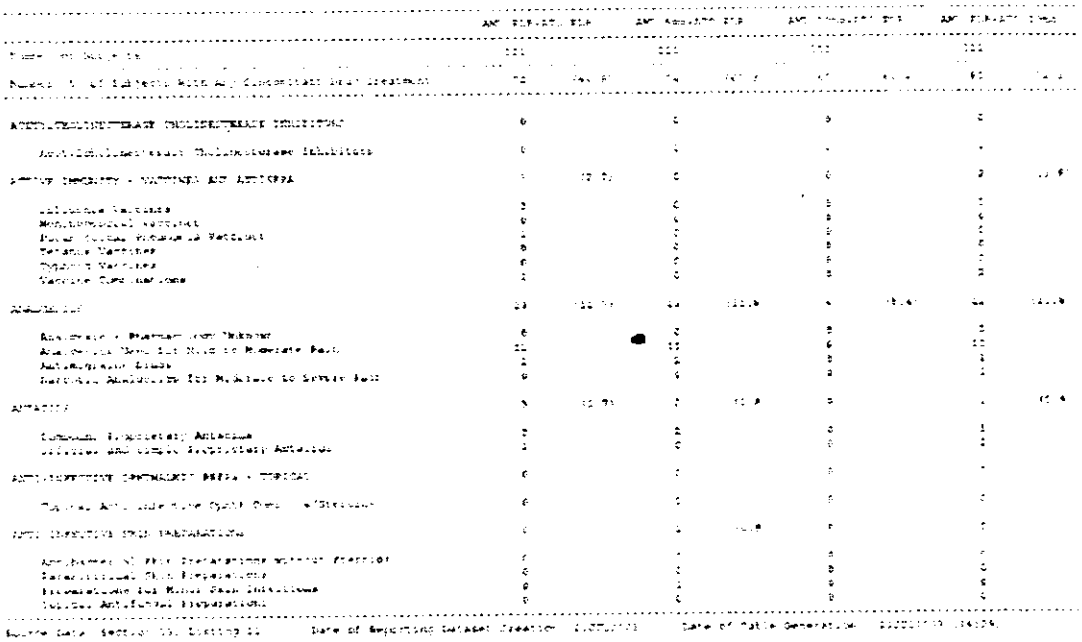
Drug treatments reported by the investigator were coded using British National Formulary (BNF) terms.

Source: Table 2.4.1

7.7 Concomitant Medication

Concomitant medications are summarized in Table 53. The most commonly taken concomitant medications, as well as the proportions of subjects taking those medications, were very similar to the prior medications listed in Table 52.

Table 53: Concomitant Medication - RESPOND



8.0 SAFETY- RESPOND

8.1Clinical Safety: RESPOND

The majority of treatment emergent AEs (all causalities) reported in this study were mild or moderate in severity (Tables 54 - 59). The treatment emergent AEs that occurred in at least 1% of all combination- treated subjects and with an incidence of at least two times placebo were peripheral edema (2.7% vs 9.9%), abdominal pain (0.0% vs 2.3%), GGT increased (0.0% vs 1.8%), SGPT increased (0.0% vs 1.7%), alkaline phosphatase increased (0.0% vs 1.1%), and hyperglycemia (0.0% vs 1.1%). The incidences of these events in combination- treated subjects were similar to either those in subjects treated with amlodipine alone or those in subjects treated with atorvastatin alone. It is notable that the incidences of the myalgia were low, and were similar across treatment groups. In patients with hypertension, the incidence of headache was lower in combination-treated subjects than n subjects treated with placebo.

Table 54: Frequencies of Treatment Emergent Adverse events - RESPOND

Panel 21. Summary of Treatment Emergent AEs (All Causalities)

Parameter		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	No. of TEAEs	82	66	80	73	78
	No. (%) subjects with:					
	TEAEs	43 (38.7)	39 (35.1)	40 (36.0)	38 (34.2)	41 (37.3)
	Severe TEAEs	2 (1.8)	2 (1.8)	3 (2.7)	3 (2.7)	2 (1.8)
	Serious TEAEs	1 (0.9)	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
AML 5 mg	No. of TEAEs	65	76	74	73	107
	No. (%) subjects with:					
	TEAEs	35 (31.8)	39 (35.1)	45 (40.5)	41 (37.3)	50 (45.0)
	Severe TEAEs	4 (3.6)	2 (1.8)	2 (1.8)	5 (4.5)	4 (3.6)
	Serious TEAEs	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)
AML 10mg	No. of TEAEs	92	83	105	119	106
	No. (%) subjects with:					
	TEAEs	53 (47.7)	46 (41.8)	55 (50.0)	52 (46.8)	46 (41.4)
	Severe TEAEs	4 (3.6)	2 (1.8)	6 (5.5)	5 (4.5)	6 (5.4)
	Serious TEAEs	1 (0.9)	1 (0.9)	2 (1.8)	4 (3.6)	2 (1.8)

TEAE indicates treatment emergent adverse event.

NOTE: Only TEAEs that began or worsened in severity from the first to the last day of double-blind study treatment are included in this panel. In Section 8.1.2, which reports data from Pfizer's early alert safety database, all SAEs that began during the double-blind phase or within 30 days of the last dose of double-blind study medication are reported. As a result, seven additional subjects with SAEs are reported in Section 8.1.2 than above.

Source: Table 6.1.1

Table 55: Treatment emergent adverse events affecting the digestive system-RESPOND

Panel 24. Digestive TEAEs (All Causalities) in ≥2% of Subjects in Any Combination Treatment Group

Incidences of AEs by body system / COSTART preferred term		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	**Digestive /**	**10 (9.0)**	**11 (9.9)**	**11 (9.9)**	**8 (7.2)**	**9 (8.2)**
	Constipation	1 (0.9)	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)
	Diarrhea	2 (1.8)	3 (2.7)	0 (0.0)	1 (0.9)	1 (0.9)
	GGT increased	0 (0.0)	0 (0.0)	2 (1.8)	1 (0.9)	3 (2.7)
AML 5 mg	**Digestive /**	**7 (6.4)**	**8 (7.2)**	**8 (7.2)**	**10 (9.1)**	**10 (9.0)**
	Constipation	1 (0.9)	1 (0.9)	1 (0.9)	0 (0.0)	2 (1.8)
	Diarrhea	0 (0.0)	2 (1.8)	3 (2.7)	2 (1.8)	2 (1.8)
	GGT increased	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	3 (2.7)
AML 10 mg	**Digestive /**	**9 (8.1)**	**9 (8.2)**	**7 (6.4)**	**12 (10.8)**	**13 (11.7)**
	Constipation	2 (1.8)	3 (2.7)	1 (0.9)	4 (3.6)	3 (2.7)
	Diarrhea	2 (1.8)	2 (1.8)	2 (1.8)	1 (0.9)	3 (2.7)
	GGT increased	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.8)	7 (6.3)

TEAE indicates treatment emergent adverse event.

Source: Table 6.1.3

Tables 54 and 55: Treatment emergent adverse events affecting the body as a whole or the cardiovascular system-RESPOND

Panel 22. Body as a Whole TEAEs (All Causalities) in ≥2% of Subjects in Any Combination Treatment Group

Incidences of AEs by body system / COSTART preferred term		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	**Body as a whole /**	**16 (14.4)**	**13 (11.7)**	**17 (15.3)**	**18 (16.2)**	**21 (19.1)**
	Abdominal pain	0 (0.0)	1 (0.9)	2 (1.8)	2 (1.8)	5 (4.5)
	Accidental injury	0 (0.0)	2 (1.8)	2 (1.8)	1 (0.9)	3 (2.7)
	Asthenia	3 (2.7)	1 (0.9)	4 (3.6)	3 (2.7)	0 (0.0)
	Back pain	1 (0.9)	0 (0.0)	3 (2.7)	2 (1.8)	0 (0.0)
	Flu syndrome	1 (0.9)	3 (2.7)	1 (0.9)	1 (0.9)	3 (2.7)
	Headache	11 (9.9)	5 (4.5)	7 (6.3)	11 (9.9)	11 (10.0)
AML 5 mg	**Body as a Whole /**	**12 (10.9)**	**18 (16.2)**	**15 (13.5)**	**12 (10.9)**	**22 (19.8)**
	Abdominal pain	0 (0.0)	2 (1.8)	1 (0.9)	0 (0.0)	6 (5.4)
	Accidental injury	4 (3.6)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Asthenia	1 (0.9)	1 (0.9)	3 (2.7)	2 (1.8)	5 (4.5)
	Back pain	1 (0.9)	2 (1.8)	0 (0.0)	4 (3.6)	2 (1.8)
	Flu syndrome	0 (0.0)	1 (0.9)	3 (2.7)	1 (0.9)	2 (1.8)
	Headache	3 (2.7)	6 (5.4)	6 (5.4)	3 (2.7)	7 (6.3)
AML 10 mg	**Body as a Whole /**	**16 (14.4)**	**16 (14.5)**	**20 (18.2)**	**20 (18.0)**	**14 (12.6)**
	Abdominal pain	2 (1.8)	2 (1.8)	4 (3.6)	2 (1.8)	3 (2.7)
	Accidental injury	2 (1.8)	1 (0.9)	1 (0.9)	0 (0.0)	3 (2.7)
	Asthenia	3 (2.7)	0 (0.0)	3 (2.7)	3 (2.7)	2 (1.8)
	Back pain	3 (2.7)	2 (1.8)	2 (1.8)	2 (1.8)	1 (0.9)
	Flu syndrome	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
	Headache	8 (7.2)	5 (4.5)	8 (7.3)	6 (5.4)	6 (5.4)

TEAE indicates treatment emergent adverse event.

Source: Table 6.1.3

As can be seen in Panel 22, none of the AEs listed above occurred in combination-treated subjects any more frequently than they occurred in subjects treated with either amlodipine alone or atorvastatin alone.

Panel 23. Cardiovascular TEAEs (All Causalities) in ≥2% of Subjects in Any Combination Treatment Group

Incidences of AEs by body system / COSTART preferred term		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	**Cardiovascular /**	**8 (7.2)**	**7 (6.3)**	**7 (6.3)**	**5 (4.5)**	**7 (6.4)**
	Palpitation	2 (1.8)	0 (0.0)	3 (2.7)	1 (0.9)	0 (0.0)
	Tachycardia	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	1 (0.9)
	Vasodilatation	3 (2.7)	0 (0.0)	1 (0.9)	0 (0.0)	2 (1.8)
AML 5 mg	**Cardiovascular /**	**4 (3.6)**	**8 (7.2)**	**6 (5.4)**	**5 (4.5)**	**9 (8.1)**
	Palpitation	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.8)
	Tachycardia	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Vasodilatation	0 (0.0)	3 (2.7)	1 (0.9)	1 (0.9)	3 (2.7)
AML 10 mg	**Cardiovascular /**	**12 (10.8)**	**7 (6.4)**	**11 (10.0)**	**9 (8.1)**	**12 (10.8)**
	Palpitation	3 (2.7)	4 (3.6)	4 (3.6)	2 (1.8)	4 (3.6)
	Tachycardia	0 (0.0)	0 (0.0)	2 (1.8)	4 (3.6)	0 (0.0)
	Vasodilatation	2 (1.8)	2 (1.8)	2 (1.8)	2 (1.8)	4 (3.6)

TEAE indicates treatment emergent adverse event.

The majority of serious adverse events reported in this study were hospitalizations due to events that in the investigator's opinion were related to intercurrent illnesses, and unrelated to the study treatment. Only one serious adverse event was considered related to treatment: postural hypotension, in a 53- year- old male subject randomized to amlodipine 5 mg and atorvastatin 20 mg. was considered to be related to treatment with amlodipine. Thus, none of the SAEs reported

in this study were considered to be related to concurrent treatment with amlodipine and atorvastatin (Table 56).

Table 56: Serious adverse events -RESPOND

Panel 34 Serious Adverse Events

Treatment group / Patient ID / case number	Event term(s)	Relationship to study treatment [1]	Action Taken with Respect to Study Drug; Outcome
AML 0 mg + ATO 0 mg / 1008-2939 / 2002022387 1011-3069 / 2002063854	Arthralgia Progression of vertigo	Not related Not related	Discontinued; recovered No action [2]; recovered
AML 5 mg + ATO 0 mg / 1257-3055 / 2003011936	Cough; gastroenteritis; heart disorder	Not related	No action [2]; recovered
AML 10 mg + ATO 0 mg / 1015-2628 / 2003000417	Acute back pain	Not related	No action; recovered
AML 0 mg + ATO 10 mg / 1203-2232 / 2003005594 1240-2163 / 2003002314 1206-2888 / 2002065623	Liver tumors; ischemic stroke; pancreatic cancer; cardiovascular failure Hemoptysis; rectorrhagia; diarrhea; increased PT Embolism pulmonary	Not related Not related Not related	No action [2]; death No action; recovered Discontinued; recovered
AML 0 mg + ATO 20 mg / 1220-12204490 / 2003002384	Sudden cardiac death	Not related	No action; death
AML 0 mg + ATO 40 mg / 1226-00[illegible] / 2003015528	Chest pain; musculoskeletal; noncardiac	Not related	Discontinued; recovered
AML 0 mg + ATO 80 mg / 1219-00383542 / 2003002387	Acute MI; paroxysmal atrial fibrillation; pulmonary thromboembolism; pulmonary edema	Not related	No action; death
AML 5 mg + ATO 10 / 1069-0518 / 2002061337 1062-1273 / 2003010874 1125-3955 / 2003024983	Thyroid nodule Worsening atherosclerosis Right inguinal hernia	Not related Not related Not related	No action [2]; recovered Discontinued; recovered No action; recovered
AML 5 mg + ATO 20 / 1144-1640 / 2002061203	Atypical chest pain; postural hypotension	Related to AML; not related to ATO	Multiple challenge; rechallenge; interruption; recovered
AML 5 mg + ATO 40 mg / 1048-2878 / 2003013089	Myocardial infarction	Not related	No action; recovered
AML 5 mg + ATO 80 mg / 0007-1894 / 2003014523	Rib fracture; paraesthesia left arm; laceration of forehead; bruises; hit by car	Not related	No action [2]; unknown
AML 10 mg + ATO 10 mg / 1041-0151 / 2002065125	Ischemic colitis	Not related	Discontinued; recovered
AML 10 mg + ATO 20 mg / 1017-2753 / 2002058391 1085-3022 / 2002055155	Hematuria; urinary hesitancy; kidney stone Myocardial infarction	Not related Not related	No action; recovered Discontinued; recovered
AML 10 mg + ATO 40 mg / 1086-1486 / 2002065731 1311-1446 / 2003021175 1278-4298 / 2003006044 1219-4552 / 2003009255	Syncopal episode; urinary sepsis Worsening coronary artery disease Epidermoid carcinoma Pneumonia	Not related Not related Not related Not related	Multiple challenge; rechallenge; interruption; recovered No action; recovered Discontinued; not recovered No action; recovered
AML 10 mg + ATO 80 mg / 1088-0019 / 2002067607 1251-0481 / 2002067241	Joint disorder Worsening ureteropelvic junction obstruction; diverticulitis	Not related Not related	No action; recovered Discontinued; recovered

[1] In the judgment of the investigator [2] Event either began or met criteria for "seriousness" as defined in Section 5.5.2 of this report within 30 days after the last dose of double-blind study medication was taken.

NOTE: In this panel, which reports data from Pfizer's early alert safety database, all SAEs that began during the double-blind phase or within 30 days after the last dose of double-blind study medication are reported. In contrast, Section 8.1.1 reports only treatment emergent AEs that began or worsened in severity from the first to the last day of double-blind study treatment. As a consequence, seven additional subjects are reported to have had a SAE here than in Section 8.1.1.

Source: Tables 6.4 and 6.5

8.2 Deaths

Table 57 summarizes case information for subjects who died during the CADUET program including double-blind phase of the study or who had serious adverse events during the double-blind phase that were considered to be the cause of the subject's subsequent death. According to these criteria, three deaths were reported for the double- blind phase of the study. All three subjects (subject nos. 2232, 4542, and 4490) were treated with atorvastatin alone. None of the deaths were due to events considered to be causally related to the study treatment. These cases are summarized along with all serious adverse events in Serious Adverse Event Narratives in Appendix 2, for details on each of the three deaths.

Table 57 :Deaths in the CADUET program at 4 month safety update

Table 3. Deaths in Amlodipine/Atorvastatin Clinical Trials Ongoing as of 04 April 2003

Study ID Treatment Period	Patient ID	Sex	Age (years)	Race	Treatment (mg QD)	Serious Adverse Event
AVALON (A3841001)						
Double-Blind	490301 1135-1824	Male	55	White	Placebo	Unspecified cardiovascular event*
Single-Blind	035613 1096-1171*	Male	57	Asian	Amlo 5 + Ator 10	Acute myocardial infarction*; Pulmonary edema; Arrhythmia ventricular
RESPOND (A3841003)						
Double-Blind	1203-2232	Male	57	White	Blinded*	Liver tumors; Pancreatic cancer*; Ischemic stroke*; Cardiovascular failure*
	1220-4490	Male	64	White	Blinded	Sudden cardiac death*
	1219-90384542	Male	70	White	Blinded	Acute myocardial infarction*; Pulmonary edema; Paroxysmal atrial fibrillation; Pulmonary artery thromboembolism*
GEMINI (A3841012)						
Open-Label Extension	1158-3043	Male	74	White	Caduet 5/40	Atrial fibrillation; Worsening mitral valve prolapse; Heart blockages; Multi-organ failure*

* Cause of death

QD = Once daily; Amlo = amlodipine; Ator = atorvastatin; Blinded = amlodipine 5 or 10 mg QD or matching placebo plus atorvastatin 10, 20, 40, or 80 mg QD or matching placebo; Caduet = amlodipine/atorvastatin combination tablet

† This death was reported previously in the Caduet New Drug Application (NDA 21-450).

‡ Liver tumors and pancreatic cancer were discovered in follow-up to symptoms reported at the final clinic visit of the RESPOND double-blind phase; the patient did not enter the RESPOND open-label extension. The patient died 22 days after taking his final dose of double-blind study medication and 4 days after the onset of ischemic stroke and cardiovascular failure (see medical narrative in Appendix C).

8.3 Serious Adverse Events

A total of 25 subjects (including the three subjects described above who died) had SAEs that began in the double- blind phase of this study or within 30 days after the last dose of double-blind study medication was taken.

8.4 Vital Signs: Heart Rate and Blood Pressure

Median changes from baseline to last observation in heart rate show no changes. Median changes from baseline heart rate were 0.00 bpm in all 15 treatment groups.

8.5 Electrocardiogram

ECG data collected during the double- blind phase of the study did not reveal any unusual or unexpected changes in subjects' ECGs.

8.6 Laboratory Safety: RESPOND

Abnormal laboratory findings are in Tables 58 – 68. The source of Tables 58 to 63 is from the sponsor and the source of tables 64 to 68 is from the medical reviewer with statistical collaboration by Dr Jasmine Choi for calculation of p values in the tables. The sponsors table 59 uses the acronym WNL (Within normal limits) that the reviewer considers to be inadequate for evaluation of changes of liver enzymes after drug exposure. The reviewer's comments are in Section 8.7.

Table 58: Liver function tests abnormalities – RESPOND TRIAL

Panel 35. Incidences of LFT Abnormalities without Regard to Baseline that Occurred in ≥2% of Subjects in a Combination Treatment Group

Laboratory Abnormality		Criteria	ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	SGOT (AST) (IU/L)	> 3.0x ULN	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)
	SGPT (ALT) (IU/L)	> 3.0x ULN	1 (1)	0 (0)	1 (1)	1 (1)	1 (1)
	GGT	> 3.0x ULN	2 (2)	3 (3)	2 (2)	3 (3)	3 (3)
AML 5 mg	SGOT (AST) (IU/L)	> 3.0x ULN	1 (1)	0 (0)	0 (0)	0 (0)	3 (3)
	SGPT (ALT) (IU/L)	> 3.0x ULN	2 (2)	0 (0)	0 (0)	0 (0)	4 (4)
	GGT	> 3.0x ULN	1 (1)	4 (4)	1 (1)	4 (4)	7 (7)
AML 10 mg	SGOT (AST) (IU/L)	> 3.0x ULN	0 (0)	1 (1)	0 (0)	2 (2)	0 (0)
	SGPT (ALT) (IU/L)	> 3.0x ULN	0 (0)	2 (2)	2 (2)	1 (1)	3 (3)
	GGT	> 3.0x ULN	2 (2)	1 (1)	5 (5)	3 (3)	8 (7)

Source Table 7.3

Table 59: Liver function tests and CK abnormalities - RESPOND

Panel 14. LFT and CK Data for Subjects who Discontinued due to Muscle Pain-Related AEs, Peripheral Edema, or LFT Abnormalities

Study Treatment / randomization no.	Severity of AE(s) leading to withdrawal	Duration of AE (days)	SGOT (U/L) (Normal range, 9-34)[1]		SGPT (U/L) (Normal range, 6-34)[1]		CK (U/L) (Normal rng, 18-169)[1]	
			Pre-treatment	On-treatment	Pre-treatment	On-treatment	Pre-treatment	On-treatment
Subjects discontinuing due to muscle pain-related AEs								
AML 10 mg 0769	Sev. Myalgia	Days 26-40	WNL	WNL	WNL	WNL	WNL	223H
ATO 20 mg[2] 4258	Mod. Myalgia	Day 21	WNL	WNL	WNL	WNL	WNL	WNL
ATO 40 mg 0924	Mod. Myalgia	Days 44-47	WNL	None rptd	WNL	None rptd	WNL	None rptd
ATO 80 mg[3] 6318	Mod. Myalgia	Days 14-19	WNL	WNL	WNL	WNL	WNL	WNL
AML 5 mg + ATO 20 mg 2806	Sev. Myalgia	Days 33-46	WNL	36H	WNL	WNL	587H	667H
AML 5 mg + ATO 80 mg[3] 4930	Mod. Myalgia	Days 2-9	WNL	54H	WNL	62H	WNL	316H
AML 10 mg + ATO 20 mg 0825	Sev. Myalgia	Days 36-37	39H	WNL	56H	48H	871H	506H
AML 10 mg + ATO 20 mg 2690	Mod. Myalgia	Days 12-45	WNL	None rptd	WNL	None rptd	WNL	None rptd
AML 5 mg + ATO 40 mg[3] 0136	Mild back pain, arthralgia	Days 29-52	WNL	WNL	WNL	WNL	WNL	WNL
AML 10 mg + ATO 80 mg 4367	Mod. back pain	Days 2-6	WNL	WNL	WNL	WNL	WNL	WNL
Subjects discontinuing due to peripheral edema								
AML 5 mg[3] 2578	Severe	Days 4-6	WNL	None rptd	WNL	None rptd	WNL	None rptd
2599	Severe	Days 13-20	WNL	WNL	WNL	WNL	WNL	WNL
AML 10 mg 1849	Severe	Days 14-18	WNL	None rptd	WNL	None rptd	WNL	None rptd
4986	Mild	Days 10-23	WNL	WNL	46H	38H	WNL	WNL
0769	Severe	Days 34-40	WNL	WNL	WNL	WNL	WNL	223H
2190	Moderate	Days 15-22	46H	62H	44H	WNL	WNL	1316H
5852	Moderate	Days 18-29	WNL	WNL	WNL	25H	WNL	WNL
AML 5 mg + ATO 10 mg 2195	Moderate	Days 9-35	WNL	WNL	None rptd	WNL	WNL	WNL
AML 5 mg + ATO 40 mg 2686	Severe	Day 20	WNL	WNL	48H	45H	202H	557H
2663	Moderate	Days 22-61	WNL	WNL	WNL	38H	WNL	WNL
3755	Moderate	Days 9-15	WNL	None rptd	WNL	None rptd	WNL	None rptd
AML 10 mg + ATO 10 mg 5144	Moderate	Days 3-5	WNL	WNL	WNL	WNL	WNL	WNL
4971	Moderate	Days 22-36	WNL	None rptd	WNL	None rptd	WNL	None rptd
AML 10 mg + ATO 20 mg 4676	Moderate	Days 4-12	WNL	WNL	WNL	WNL	WNL	WNL
2146	Severe	Days 16-26	WNL	WNL	WNL	46H	WNL	WNL
5930	Moderate	Days 17-29	WNL	WNL	WNL	WNL	WNL	WNL
AML 10 mg + ATO 40 mg 2730	Moderate	Days 15-23	WNL	WNL	WNL	WNL	WNL	WNL
AML 10 mg + ATO 80 mg 2665	Severe	Days 9-24	WNL	WNL	WNL	WNL	WNL	WNL
4387	Severe	Days 8-9	WNL	None rptd	WNL	None rptd	WNL	None rptd
0612	Moderate	Days 29-65	WNL	WNL	WNL	WNL	WNL	WNL
Subjects discontinuing due to LFT abnormalities								
AML 5 mg + ATO 80 mg[3] 3137	Sev. SGPT↑, Mod. SGOT↑	Days 29-57	WNL	61H, 48H	WNL	111H, 115H	WNL	WNL

[1] Normal range for a small proportion of subjects was 11-36 U/L for SGOT; 6-43, 6-35, and 6-32 U/L for SGPT; and 18-198 U/L for CPK

WNL indicates within normal limits

Source: Tables 4.2.1 and 4.2.3; Section 13, Listing 16

Table 60Creatinine Kinase Abnormalities in patients > 2% on combination drug
Table 61: Renal function tests abnormalities >1% - RESPOND
Table 62: Clinical Chemistry abnormalities > 2% - RESPOND

Panel 36. Incidences of Creatine Kinase Abnormalities without Regard to Baseline that Occurred in ≥2% of Subjects in a Combination Treatment Group

Laboratory Abnormality		Criteria	ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Creatine Kinase (U/L)	> 2.0x ULN	1 (1)	1 (1)	1 (1)	0 (0)	2 (2)
AML 5 mg	Creatine Kinase (U/L)	> 2.0x ULN	5 (5)	5 (5)	1 (1)	3 (3)	3 (3)
AML10 mg	Creatine Kinase (U/L)	> 2.0x ULN	3 (3)	3 (3)	4 (4)	1 (1)	2 (2)

Source: Table 7.3

The incidences of CPK abnormalities do not reveal any apparent drug- or dose-related patterns.

Panel 37. Incidences of Renal Function Test Abnormalities without Regard to Baseline that Occurred in ≥2% of Subjects in a Combination Treatment Group

Laboratory Abnormality		Criteria	ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Creatinine (mg/dL)	> 1.3x ULN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Uric Acid (mg/dL)	> 1.2x ULN	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
AML 5 mg	Creatinine (mg/dL)	> 1.3x ULN	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
	Uric Acid (mg/dL)	> 1.2x ULN	1 (1)	2 (2)	1 (1)	0 (0)	1 (1)
AML 10 mg	Creatinine (mg/dL)	> 1.3x ULN	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)
	Uric Acid (mg/dL)	> 1.2x ULN	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Table 7.3

The incidences of renal function test abnormalities were low, and there were no apparent drug- or dose-related patterns across treatment groups.

Panel 38. Incidences of Other Clinical Chemistry Abnormalities without Regard to Baseline that Occurred in ≥2% of Subjects in a Combination Treatment Group

Laboratory Abnormality		Criteria	ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Potassium (MEQ/L)	< 0.9x LLN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Glucose (fasting) (mg/dL)	> 1.5x ULN	2 (2)	7 (7)	2 (2)	5 (5)	5 (5)
AML 5 mg	Potassium (MEQ/L)	< 0.9x LLN	0 (0)	0 (0)	1 (1)	0 (0)	2 (2)
	Glucose (fasting) (mg/dL)	> 1.5x ULN	4 (4)	3 (3)	6 (6)	5 (5)	6 (6)
AML 10 mg	Potassium (MEQ/L)	< 0.9x LLN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Glucose (fasting) (mg/dL)	> 1.5x ULN	0 (0)	8 (8)	5 (5)	3 (3)	2 (2)

Source: Table 7.3

Table 63: Urinary abnormalities in >2% of patients in combination therapy

Panel 39. Incidences of Urinalysis Laboratory Abnormalities without Regard to Baseline that Occurred in ≥2% of Subjects in a Combination Treatment Group

Laboratory Abnormality		Criteria	ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Urinalysis						
	Gravity	>1.030	1 (4)	1 (4)	0 (0)	3 (10)	3 (9)
	Urine RBC (HPF)	>= 6	2 (9)	1 (4)	3 (13)	1 (4)	0 (0)
	Urine WBC (HPF)	>= 6	4 (17)	2 (8)	3 (13)	4 (14)	0 (0)
AML 5 mg	Urinalysis						
	Gravity	>1.030	2 (7)	1 (4)	0 (0)	2 (7)	4 (11)
	Urine RBC (HPF)	>= 6	0 (0)	1 (4)	2 (8)	0 (0)	4 (11)
	Urine WBC (HPF)	>= 6	3 (11)	1 (4)	4 (15)	5 (19)	2 (6)
AML 10 mg	Urinalysis						
	Gravity	>1.030	0 (0)	0 (0)	1 (3)	1 (5)	2 (9)
	Urine RBC (HPF)	>= 6	0 (0)	1 (4)	1 (3)	0 (0)	0 (0)
	Urine WBC (HPF)	>= 6	1 (4)	4 (15)	2 (7)	1 (5)	1 (4)

Source: Table 7.3

There were no apparent drug- or dose-related patterns across treatment groups in the laboratory test abnormalities summarized above.

8.7 Hepatic enzyme changes- Source Reviewer in collaboration with Dr J. Choi.

Both amlodipine and atorvastatin therapies have been associated with elevated hepatic enzymes of varying degrees. Atorvastatin for example is contraindicated in the hepatic impaired patient. The combination of the two drugs therefore requires careful evaluation of hepatic enzymes. This is particularly important as the dose level of atorvastatin in the combination tablet reaches 80 mg. The sponsor acknowledges that only one patient randomized to 5/80 was discontinued due to elevated hepatic enzymes and table 56 submitted by the sponsor lists the number of patients/events (76 total) with elevated hepatic enzymes in the RESPOND trial. The reviewer has evaluated the changes in mean values from baseline to final values of SGPT, SGOT, GGT and alkaline phosphatase from the four treatment groups. Although the guideline for hepatotoxicity usually requires LFT values to be > 3 times the upper limit of normal, there are no guidelines for mean changes that may be 2 or 3 times higher than the baseline with or without clinically evident liver disease. Because of the potential for hepatotoxicity by either of the drugs, the reviewer has evaluated the differences in mean changes of SGPT from baseline to endpoints in patients with low dose combination 5/10 and 5/20 versus high dose 10/40 and 10/80 and 5/40 and 5/80. There is a statistically significant difference between the two groups (males and females) suggesting that the higher doses are associated with higher levels of SGPT compared to the lower doses (p=0.0002). These differences are also evident in the sexes with the females having higher values compared to males. The differences range from 2 to 3+ fold increases between these groups. Assuming that the baseline value is the normal, the final values in excess of 3X the normal limit may have merit to consider a trend towards hepatotoxicity. This aspect of validating hepatotoxicity was not reflected in the brown book that was written in 1975 by DHEW. Less severe changes were seen for SGOT, GGT, and alkaline phosphatase when the baseline mean values were compared with the final values. However the differences were statistically significant at p<0.001 depending on the dose levels. Without exception all comparisons of low doses versus high doses showed statistical significance for SGPT, SGOT, GGT and Alkaline phosphatase. Furthermore all comparisons between placebo with or without one therapy, amlodipine or atiorvastatin, versus combination therapy showed statistical significance for SGPT (p<0.0001), SGOT (p=0.0008) GGT (p=0.01) and alkaline phosphatase (p=0.0001) (Tables 62, 63 and 64). While there is no corresponding hyperbilirubinemia, urobilinuria, or clinical jaundice, a reflection of hepatic reserve, nevertheless these findings are considered to be important and may be safety issues in patients exposed to the higher dose levels of the combination therapy. The label should reflect these potential hepatic safety issues as they constitute manifestations of subclinical liver injury, both hepatocellular and hepatobiliary. Females tend to be more susceptible than men are. The statistical help from statistician, Dr Jasmine Choi, is hereby acknowledged for analyses of the liver function tests.

Liver function tests:

Table 64: Comparison of mean changes from baseline to final values of liver enzymes between combination and amlodipine and atorvastatin

Parameter-Liver Enzymes	Amlodipine 5 and 10 mg combined	Atorvastatin 10,20,40,80mg combined	Combination all 8 fixed doses	Aml v combin ation	Ator v combin ation
GGT	2.30 (15.45)	12.84(67.79)	9.24(38.61)	0.002	0.7316
SGOT	0.94 (7.04)	3.16(19.44)	3.61(15.23)	0.0005	0.2305
SGPT	1.06(11.69)	6.03(18.29)	7.28(21.69)	<0.0001	0.1143
Alk. Phos.	3.91(10.65)	12.16(66.58)	11.84(23.04)	<0.0001	0.0020
Total Bilirubin	-0.01(1.32)	0.30(4.38)	0.27(4.19)	0.0012	0.2655

Table 65: Comparison of mean changes from baseline to final values of liver enzymes between low dose combination and high dose combination

Parameter-Liver Enzymes	Caduet 5 and 10 mg and 5 and 20 combined	Caduet 10/40 and 10/80 combined	p-value
GGT	2.30 (15.45)	12.84(67.79)	0.0016
SGOT	0.94 (7.04)	3.16(19.44)	0.0044
SGPT	1.06(11.69)	6.03(18.29)	0.0002
Alk Phos.	3.91(10.65)	12.16(66.58)	<0.0001

Table 66: Tests of Liver function - Change in Mean values from Baseline to Final values in patients receiving either low or high doses of CADUET - Respond trial

	Low Dose Caduet – 5/10; 5/20		High Dose Caduet –5/40; 5/80; 10/40; 10/80	
	N	Mean ± (SD)	N	Mean ± (SD) p-value
SGPT				
Male and Female	210	4.21 (12.01)	418	9.91(27.25)**<0.0002**
Males	109	5.04(14.00)	241	9.61(20.43)
Females	101	3.32(9.40)	177	10.32(134.49)
	Placebo + one therapy(AML5/10 or 10/20/40/80 ATOR)		**Combination Therapy CADUET (All doses)**	
	N	Mean ± (SD)	N	Mean ± (SD) p-value
SGPT				
Male and Female	743	3.87(15.91)	832	7.28(21.69)**<0.0001**
Female	367	4.00(18.50)	365	6.78(25.78)
Male	376	3.75(21.91)	467	7.67(17.96)
SGOT				
Male and Female	733	2.26(16.40)	819	3.61(15.23) **0.0008**
Female	364	2.36(21.77)	356	3.36(16.86)
Male	369	2.16(8.23)	463	3.81(13.86)
GGT				
Male and Female	747	8.81(54.12)	842	9.24(38.61) **0.01**
Female	370	10.62(60.14)	370	9.43(45.82)
Male	377	7.04(47.49)	472	9.09(31.88)
Alkaline Phosphatase				
Male and Female	747	8.57(50.78)	842	11.84(23.04) **0.0001**
Female	370	10.86(69.70)	370	13.07(31.08)
Male	377	6.32(18.35)	472	10.88(13.75)

Only one subject (no. 3137), who was randomized to amlodipine 5 mg and atorvastatin 80 mg, discontinued due to laboratory abnormalities (SGPT values of 111 U/ L and 115 U/ L and SGOT values of 61 U/ L and 48 U/ L on Days 29 and 36 of treatment, respectively).

Only one subject (no. 3137), who was randomized to amlodipine 5 mg and atorvastatin 80 mg, discontinued due to laboratory abnormalities (SGPT values of 111 U/ L and 115 U/ L and SGOT values of 61 U/ L and 48 U/ L on Days 29 and 36 of treatment, respectively).

Table 67: Tests of Liver function: Change in Mean values from Baseline to Final values-Respond trial - Comparisons of different dosages of CADUET against placebo and individual components.

LFTs: Change in Mean values	**Low Dose Combination vs Placebo Aml 5/10; 5/20Ato vs Aml 0/0 Ator**	**High Dose Combination vs Placebo Aml 10/40; 10/80 vs Aml 0/0 Ator**	**Low Dose Combination vs High Dose Combination Aml 5/10; 5/20 vs Aml 10/40, 10/80**
SGPT- Mean values N for combination (211) N for placebo (107) pvalue	4.21±12.01 0.98±11.1 **0.0001**	9.97±23.6 0.98±11.1 **<0.0001**	4.21±12.01 (low dose) 9.97±23.6(high dose) **0.0017**
Alk. Phos N for combination (211) N for placebo (107) pvalue	6.07±11.85 3.75±10.26 **0.0152**	17.44±24.30 3.75±10.26 **<0.0001**	6.07±11.85(low dose) 17.44±24.30(high dose) **<0.0001**
SGOT N for combination (211) N for placebo (107) p-value	1.60(6.37) 1.34(16.69) **0.0215**	4.80(13.42) 1.34(16.69) **<0.0001**	1.60(6.37) 4.80(13.42) **0.004**
GGT N for combination (211) N for placebo (107) p-value	3.01(18.72) 6.02(40.36) **0.2978**	15.08 (49.25) 6.02(40.36) **0.006**	3.07(18.72) 15.08(49.25) **0.0008**

Table 68: Tests of Liver function: Change in Mean values from Baseline to Final values-continued

LFTs: Change in Mean values	**All 8 dose Combination vs Placebo Aml 5/10- 10/80 Ato Vs Aml 0/0 Ator**		
SGPT- Mean values N for combination (832) N for placebo (107) pvalue	7.28±21.69 0.98±11.12 **<0.0001**		
Alk. Phos N for combination (842) N for placebo (107) p-value	11.85±23.04 3.75±10.26 **<0.0001**		
SGOT N for combination (211) N for placebo (107) p-value	3.61(15.23) 1.34(16.69) **0.0006**		
GGT N for combination (211) N for placebo (107) p-value	9.24(38.61) 6.03(40.36) **0.008**		

Adverse events-RESPOND-Summary
The majority of treatment emergent AEs (all causalities) reported in this study was mild or moderate in severity. The treatment emergent AEs that occurred in at least 1% of all combination-treated subjects (N= 885) and with an incidence of at least two times placebo were peripheral edema (2.7% vs 9.9%), abdominal pain (0.0% vs 2.3%), GGT increased (0.0% vs 1.8%), SGPT increased (0.0% vs 1.7%), alkaline phosphatase increased (0.0% vs 1.1%), and hyperglycemia (0.0% vs 1.1%). The incidences of these events in combination- treated subjects were similar to either those in subjects treated with amlodipine alone or those in subjects treated with atorvastatin alone. It is notable that the incidence of myalgia in combination- treated subjects was low (1.6%), and similar to those in the other treatment groups. As may be expected in these patients with hypertension, the incidence of headache was lower in combination- treated subjects than in subjects treated with placebo.

The majority of serious adverse events (SAEs) reported in this study were hospitalizations due to events that in the investigator's opinion were related to intercurrent illnesses, and unrelated to the study treatment. Only one SAE was considered related to treatment: postural hypotension, in a 53- year- old male subject randomized to amlodipine 5 mg and atorvastatin 20 mg (subject no. 1640), was considered to be related to treatment with amlodipine. Thus, none of the SAEs reported in this study were considered to be related to concurrent treatment with amlodipine and atorvastatin.

There were no unusual or unexpected laboratory test or ECG abnormalities reported in subjects treated with concurrent amlodipine and atorvastatin.

Conclusions: The results from the eight- week double- blind phase of this study support the conclusion that treatment with each of the eight dosage combinations of amlodipine (5 mg, 10 mg) and atorvastatin (10 mg, 20 mg, 40 mg, 80 mg) is safe and effective in the treatment of patients with comorbid hypertension and hyperlipidemia. Further, the data demonstrate that there was no overall modification of atorvastatin's effect on LDL-C when the drug was taken in combination with amlodipine, and provide no evidence that atorvastatin modifies the systolic blood pressure lowering efficacy of amlodipine when the treatments were taken in combination.

5.8 Global Risk scores-RESPOND
Results of secondary analyses evaluating the efficacy of the combination treatments in reducing subjects' Framingham CHD global risk factor scores are presented in Table 5.3.2. The risk scores are based on subjects' gender, age, LDL-C, HDL-C, systolic and diastolic blood pressure, smoking status, and the presence of diabetes, and they are used to provide an estimate of a subject's risk for developing CHD. As a consequence, ITT subjects in Groups I and II only are included in the analyses; subjects in Group III were excluded because, according to the group-specific criteria, they had either CHD or a CHD risk equivalent at study entry.

The results demonstrate that atorvastatin overall ($p< 0.001$), as well as each active atorvastatin dosage combined across amlodipine doses (80 mg, $p< 0.001$; 40 mg, $p< 0.001$, 20 mg, $p< 0.001$, 10 mg, $p< 0.001$), had a statistically significant treatment effect on subjects' global risk factor scores. In addition, the least square mean changes from baseline in global risk factor scores in all of the eight combination treatment groups were highly statistically significantly greater ($p< 0.001$ for all comparisons) than that in the corresponding amlodipine- alone treatment group. Similarly, amlodipine overall ($p< 0.001$), as well as each active amlodipine dosage combined across atorvastatin doses (10 mg, $p< 0.001$; 5 mg, $p< 0.001$), had a significant treatment effect on subjects' scores. In addition, the least square mean changes in the scores in all of the combination treatment groups ($p< 0.022$) except the 10+ 10 mg group ($p< 0.108$) were significantly greater than that in the corresponding atorvastatin- alone treatment group. Taken together, these results indicate each of the combination treatments (except for the 10+ 10 mg group) was significantly more effective in reducing subjects' global risk factor scores than either amlodipine alone or atorvastatin alone.

Results of analyses evaluating the efficacy of the combination treatments in reducing subjects' Framingham CHD global risk factor scores are presented for males and females separately and showed significant reductions. The scores are gender-specific.) These results were generally consistent with the results for males and females combined described above in the AVALON study.

Results of analyses evaluating whether there was an association between the ability of subjects treated concurrently with amlodipine and atorvastatin to reach their NCEP therapeutic goals and their ability to reach their JNC therapeutic goals show significant association. Similarly the same analysis using EAS and WHO- ISH therapeutic goals for LDL- C and blood pressure respectively showed significant association. As expected, the results showed that there was a statistically significant association between combination- treated subjects' ability to reach both their NCEP and JNC therapeutic goals (p= 0.002), as well as between subjects' ability to reach both their EAS and WHO- ISH therapeutic goals (p= 0.045).

8.9Efficacy of combined treatment on reducing Global risk factor scores

Analyses evaluating the efficacy of the combination treatments in reducing the patients Framingham CHD global risk factor scores, which provide an estimate of a patient's risk for developing CHD, show that the combination treatments were significantly more effective compared to amlodipine alone and to atorvastatin alone in reducing the patients scores. The risk scores are based on gender, age, lipid levels (LDL-C, HDL-C), systolic and diastolic blood pressure, presence of diabetes, and smoking status. These scores provide an estimate of a subject's risk for developing CHD. However in the RESPOND study about half of the patients in Groups II and III already have features of CHD. Analyses of these scores therefore have limited value in predicting risk for developing CHD. In the AVALON study there was a demonstrable decrease in their global risk scores for combined treated patients compared to atorvastatin and amlodipine treated patients ($p<0.005$). This suggests that combination was significantly more effective than either atorvastatin alone or amlodipine alone in reducing the risk scores of patients with hypertension and hyperlipidemia. This suggestion will require to be validated by outcome studies.

In summary, the data support the conclusion that concurrent, once- daily treatment with amlodipine (5 mg or 10 mg) and atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg) for up to eight weeks was highly effective in these subjects with comorbid hypertension and hyperlipidemia, the majority of whom also had at least one additional CV risk factor or CHD (or a CHD risk equivalent).

8.10 Safety summary and conclusions

The safety results from the double-blind phase of this study support the conclusion that combined treatment with amlodipine 5 mg or 10 mg QD and atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg QD for up to eight weeks was safe and well tolerated by these subjects with comorbid hypertension and hyperlipidemia.

The most common safety- related reasons for discontinuation from the study in the combination treatment groups were the adverse events peripheral edema and headache, but these events led to the discontinuation of combination- treated subjects no more frequently than they did among subjects treated with either amlodipine alone or atorvastatin alone. Only one subject (no. 3137), who was randomized to amlodipine 5 mg and atorvastatin 80 mg, discontinued due to laboratory abnormalities (SGPT values of 111 U/ L and 115 U/ L and SGOT values of 61 U/ L and 48 U/ L on Days 29 and 36 of treatment, respectively).

The majority of treatment emergent AEs (all causalities) reported in this study were mild or moderate in severity. The treatment emergent AEs that occurred in at least 1% of all combination-treated subjects and with an incidence of at least two times placebo were peripheral edema (2.7% vs 9.9%), abdominal pain (0.0% vs 2.3%), GGT increased (0.0% vs 1.8%), SGPT

increased (0.0% vs 1.7%), alkaline phosphatase increased (0.0% vs 1.1%), and hyperglycemia (0.0% vs 1.1%). The incidences of these events in combination- treated subjects were similar to either those in subjects treated with amlodipine alone or those in subjects treated with atorvastatin alone. It is notable that the incidences of myalgia were low, and were similar across treatment groups. As may be expected in these patients with hypertension, the incidence of headache was lower in combination- treated subjects than in subjects treated with amlodipine placebo.

The majority of SAEs reported in this study were hospitalizations due to events that in the investigator's opinion were related to intercurrent illnesses, and unrelated to the study treatment. Only one SAE was considered related to treatment: postural hypotension, in a 53- year- old male treatment with amlodipine. Thus, none of the SAEs reported in this study were considered to be related to concurrent treatment with amlodipine and atorvastatin.

The safety results from the double- blind phase of this study support the conclusion that combined treatment with amlodipine 5 mg or 10 mg QD and atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg QD for up to eight weeks was safe and well tolerated by these subjects with comorbid hypertension and hyperlipidemia.

The most common safety- related reasons for discontinuation from the study in the combination treatment groups were the adverse events peripheral edema and headache, but these events led to the discontinuation of combination- treated subjects no more frequently than they did among subjects treated with either amlodipine alone or atorvastatin alone. Only one subject (no. 3137), who was randomized to amlodipine 5 mg and atorvastatin 80 mg, discontinued due to laboratory abnormalities (SGPT values of 111 U/ L and 115 U/ L and SGOT values of 61 U/ L and 48 U/ L on Days 29 and 36 of treatment, respectively).

The majority of treatment emergent AEs (all causalities) reported in this study were mild or moderate in severity. The treatment emergent AEs that occurred in at least 1% of all combination-treated subjects and with an incidence of at least two times placebo were peripheral edema (2.7% vs 9.9%), abdominal pain (0.0% vs 2.3%), GGT increased (0.0% vs 1.8%), SGPT increased (0.0% vs 1.7%), alkaline phosphatase increased (0.0% vs 1.1%), and hyperglycemia (0.0% vs 1.1%). The incidences of these events in combination- treated subjects were similar to either those in subjects treated with amlodipine alone or those in subjects treated with atorvastatin alone. It is notable that the incidences of myalgia were low, and were similar across treatment groups. As may be expected in these patients with hypertension, the incidence of headache was lower in combination- treated subjects than in subjects treated with amlodipine placebo.

In addition, significantly higher percentages of subjects treated with amlodipine and atorvastatin reached their therapeutic LDL- C goals, their therapeutic blood pressure goals, as well as both LDL- C and blood pressure goals than subjects treated with either amlodipine alone or atorvastatin alone.

In summary, the data support the conclusion that concurrent, once- daily treatment with amlodipine (5 mg or 10 mg) and atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg) for up to eight weeks was relatively safe and effective in these subjects with comorbid hypertension and hyperlipidemia, the majority of whom had at least one additional CV risk factor or CHD (or a CHD risk equivalent).

8.11 Study summary and conclusions

In this first phase of the study, 1660 subjects were randomly assigned to treatment with one of the 15 possible combinations of amlodipine (0 mg, 5 mg, 10 mg) and atorvastatin (0 mg, 10 mg, 20 mg, 40 mg, 80 mg). There were slightly more males than females, and over 90% of subjects were White. The mean age was 58 years, and the average subject was overweight based on his

or her BMI. All subjects had comorbid hypertension and hyperlipidemia, and the vast majority (97%) had one or more additional CV risk factors or had CHD or a CHD risk equivalent.

The primary efficacy results demonstrated that concurrent treatment with each of the eight active amlodipine and atorvastatin dosage combinations was highly significantly more effective than amlodipine alone in lowering subjects' LDL- C levels, and highly significantly more effective than atorvastatin alone in lowering subjects' systolic blood pressure.

Secondary analyses of changes in LDL- C demonstrate that there was no overall modification of atorvastatin's effect on LDL- C when the drug was taken in combination with amlodipine in this patient population. There was a statistically significant increase in the LDL- C lowering efficacy when amlodipine 5 mg was combined with atorvastatin 10 mg. This was consistent with results obtained in the AVALON study at the same doses 34, amlodipine 5 mg in combination with atorvastatin 10 mg. Importantly in both studies, the magnitude of this effect was sufficiently small to be considered of no clinical relevance. Further, results from the present study show that amlodipine 5 mg and 10 mg had no significant effect on LDL- C when administered in combination with any of the other atorvastatin doses. Analyses of changes in systolic blood pressure provide no evidence that atorvastatin modified the systolic blood pressure lowering efficacy of amlodipine when the treatments were taken once daily in combination by the patients in this study.

The sponsor has not provided any data from studies to support a claim for anti-anginal effects but wishes to derive this claim from the mechanism of action of amlodipine that relaxes smooth muscle. The smooth muscle relaxation in turn predisposes to dilatation of peripheral arteries, reduction of peripheral vascular resistance, blood pressure and myocardial oxygen demand. Extrapolation of these pathophysiological features of amlodipine will presumably form the basis of a claim of clinical benefit: relief of exertional angina, predominantly by decreasing cardiac load at a given level of exercise without any alteration of the rate-pressure product at end-point. In the absence of data, this is a rather tenuous link for a clinical benefit claim because there is no evidence that amlodipine improves blood supply to ischemic myocardium. Although the ALLHAT study showed that amlodipine reduced the combined incidence of fatal CHD and non-fatal MI in a cohort of high-risk hypertensive patients, it does not provide compelling evidence for anti-anginal efficacy.

8.12 Integrated summary of safety

The following sources have provided sufficient data for a comprehensive review safety. The sources include the following clinical studies and databases:

- AVALON-------8 weeks
- ACCESS---------12/28 weeks
- RESPOND-------8 weeks
- OPEN LABEL EXTENSION OF RESPOND TRIAL -uncompleted
- MARGAUX----Uncompleted
- DUAL---uncompleted
- GEMINI---uncompleted
- 4- MONTH SAFETY UPDATE
- POSTMARKETING EXPERIENCE OF 2 INDIVIDUAL COMPONENTS SINCE MARKET LAUNCH
- 7 BIOEQUIVALENCE STUDIES

The tables on safety in the different studies in this review will not be repeated here. Some of these studies have extension phases that are still ongoing. However there are adequate numbers of patients exposed to the drugs for reasonable periods of time to allow a development of safety profiles of the combination product. There is no evidence on the safety that the frequency or severity of the adverse events is worse with the combination drug compared to the individual components. Furthermore no unexpected events have been reported with the combination

product. In summary, from the available safety data reviewed it can be concluded that combined treatment with amlodipine 5 mg or 10 mg QD and atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg QD is safe and well tolerated by patients with either hypertension or dyslipidemia and also from the relatively limited numbers, so far, of patients with comorbid hypertension and hyperlipidemia. Apart from the well known adverse events for the individual components no other adverse have been reported with the combination drug. The only noteworthy safety issue is increased liver enzymes that is suggestive of a ? subclinical drug- related hepatopathy. This has been reflected in the label in addition to the other common treatment emergent adverse events.
From this review it would appear that atorvastatin is responsible for the significant change in SGOT, SGPT and GGT whereas amlodipine is responsible for the significant change in alkaline phosphatase. The reassuring aspects of these findings are 1) that there is no significant change in total bilirubin and there are no data in the FDA Medwatch database to indicate any hepatic signal with patients taking both drugs concurrently. However it must be realized that less than less than 6% of hepatic adverse events are reported in postmarketing period in France and about 10% or less of hepatic adverse events are reported in the US. The sponsor has adequately addressed this safety issue of potential hepatic adverse events in the label.

[redacted]

8.13 4-month safety update

Deaths and serious adverse events reported in this 120- Day Safety Update were similar to those that would be expected in a population of patients with comorbid hypertension/ angina and dyslipidemia. The increase in total number of serious adverse event cases reported in this Safety Update for all ongoing studies (110 cases; 04 April 2003 cutoff) relative to the Caduet NDA (17 cases; 15 July 2002 cutoff) is consistent with the substantial increase in patient exposure (5- 10 fold) represented by this Safety update. Out of these 110 cases, only 1 patient experienced a serious adverse event that was considered related to study medication (postural hypotension); neither of the 2 serious adverse events that coded to the MedDRA preferred term myalgia were related to study medication; and there were no cases of myopathy, rhabdomyolysis, or abnormalities in ALT or AST reported as serious adverse events. For the double- blind treatment period of AVALON (Study A3841001), numbers of serious adverse events in amlodipine + atorvastatin patients were similar to those in patients randomized to amlodipine monotherapy, atorvastatin monotherapy, or placebo, and no serious adverse events were considered related to study medication. Therefore, this 120- Day Safety Update presents no findings or conclusions that differ significantly from those reported in [redacted] which indicated that the safety profile of Caduet is similar to the safety profiles of amlodipine and atorvastatin taken separately.

Only 1 serious adverse event reported in an ongoing clinical study was considered related to study medication: Patient 1144- 1640, a 53- year- old male (race unspecified) in RESPOND (Study A3841003), experienced (MedDRA preferred terms) atypical chest pain on Day 21 and postural hypotension on Day 23 of treatment with blinded therapy; the investigator considered the atypical chest pain unrelated to study medication and the postural hypotension related to amlodipine (but not atorvastatin) taken as study medication (see medical narrative in Appendix C). In addition, there was 1 serious adverse event for which the relationship to study medication is unknown: Patient 0791- 082, a 47- year- old white male in MARGAUX (Study A0531006), experienced a syncopal episode on Day 113 of treatment with blinded therapy; the investigator did not report causality for this serious adverse event (see medical narrative in Appendix C).

Serious adverse events that coded to the MedDRA preferred event term myalgia were reported for 2 patients in ongoing clinical studies; there were no serious adverse events that coded to MedDRA preferred terms for myopathy or rhabdomyolysis. Neither of the 2 myalgia serious adverse events were considered related to study medication, and no creatine kinase laboratory values were included in ARISg reports for either of these 2 patients (see medical narratives in Appendix 2)

Patient 1153- 1043, a 62- year- old white female in GEMINI (Study A3841012), began to experience chest muscle pain (investigator term) on Day 41 of treatment with Caduet 5/ 10 mg QD, after attending a football game, and was hospitalized the next day. A stress test indicated possible coronary artery disease, but cardiac catheterization revealed normal results; the condition was diagnosed as chest muscle pain and was considered by the investigator to be likely due to muscle strain and not related to study medication. The patient was considered recovered on Day 42 of treatment and was discharged home on the next day, and study medication was still being administered at last report.

Patient 1205- 5205, a 63- year- old white male in GEMINI (Study A3841012), was hospitalized with chest muscle pain (investigator term) on Day 4 of treatment with Caduet 5/ 10 mg QD. Electrocardiogram was normal, and unspecified tests were negative for myocardial ischemia; the chest muscle pain was considered by the investigator to be related to sternal wires from coronary artery bypass graft surgery 6 years previous and not related to study medication. The patient was considered recovered on Day 5 of treatment and was discharged home on the same day, and study medication was still being administered at last report.

There were no serious adverse events reported in any ongoing clinical study that coded to MedDRA preferred event terms indicating abnormal or increased levels of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST).

Deaths and Serious Adverse Events
Investigator reports of serious adverse events in ongoing studies are recorded in ARISg on a case- by- case basis; as a result, a single patient may be represented by multiple cases, and each case may represent multiple serious adverse events that occur at approximately the same time. Cumulative listings and summaries of serious adverse events recorded in ARISg up to the 04 April 2003 cutoff date (Appendix B) include deaths together with other (nonfatal) serious adverse events, and include serious adverse events from the double- blind treatment period of AVALON (Study A3841001) together with those from ongoing studies. Medical narratives for deaths and serious adverse events in ongoing studies are provided in Appendix C.

For the Summary of Clinical Safety submitted as part of [redacted], investigator terms for serious adverse events were mapped to preferred terms using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). However, for this 120- Day Safety Update, investigator terms for serious adverse events in ARISg were mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Since this 120- Day Safety Update is cumulative, cases reported in [redacted] appear here also, but adverse event preferred terms might differ. Other case information may differ as well, since new information for these cases (eg, unblinded treatment assignments) may have been received after the 15 July 2002 cutoff date for [redacted]

8.14 RECOMMENDATIONS

AVALON: Primary Efficacy Conclusion

The sponsor achieved their primary efficacy endpoint using prespecified evidenced based goals.. The primary efficacy results indicate that in patients with comorbid hyperlipidemia and hypertension, combined treatment with atorvastatin 10 mg and amlodipine 5 mg was statistically significantly more effective than amlodipine alone in lowering subjects' LDL- C levels to their NCEP goals, and highly statistically significantly more effective than atorvastatin alone in lowering subjects' blood pressure levels to their JNC therapeutic goals. These results are supported by a secondary analysis that showed that the combined treatment was statistically significantly more effective than either atorvastatin alone or amlodipine alone in therapeutic targets.

Secondary analyses of blood pressure parameters provided no statistically significant evidence that atorvastatin 10 mg QD modified the blood pressure lowering efficacy of amlodipine 5 mg QD when the two treatments were taken in combination by patients with comorbid hypertension and hyperlipidemia. In both treatment groups, these reductions in systolic and diastolic blood pressure

were consistent with those reported in former Amlodipine Studies 102 and 335, the two relatively small pivotal dose-ranging studies in the original Amlodipine NDA #19- 787.

Amlodipine 5 mg QD when combined with atorvastatin 10 mg resulted in statistically significantly greater reductions in LDL-C than treatment with atorvastatin 10 mg alone. A similar pattern was observed in analyses of some other lipid parameters. In both treatment groups, the changes in LDL- C and other lipid parameters were consistent with those reported in the current Lipitor product label. And the between-group differences were small and may not be clinically meaningful.

RESPOND

The primary efficacy results confirm that in patients with comorbid hyperlipidemia and hypertension, combined treatment with each of the eight active amlodipine and atorvastatin dosage combinations was significantly more effective than amlodipine alone in lowering subjects' LDL- C levels, and significantly more effective than atorvastatin alone in lowering subjects' systolic blood pressure

These data demonstrate that each of the eight-fixed dose combinations of amlodipine and atorvastatin was superior to amlodipine alone in reducing LDL- C and superior to atorvastatin alone in lowering systolic blood pressure. All eight fixed- dose combination treatments were therefore highly effective in the concurrent treatment of hypertension and hyperlipidemia

Secondary analyses of changes in other lipid and systolic blood pressure parameters yielded results almost similar to the primary efficacy results described above. All eight combination treatments were shown to be significantly more effective than amlodipine alone in reducing total cholesterol, VLDL- C, triglycerides, (Table 51) and apolipoprotein B as well as in raising the HDL-C/ LDL- C ratio (but not HDL- C), and significantly more effective than atorvastatin in reducing diastolic blood pressure (Table 48).
Results of the comparison described in (1) above and presented in table 48 show that the effect on LDL- C of amlodipine 10 mg combined across active atorvastatin dosages was not significantly different from that of the active atorvastatin dosages alone (p= 0.250). This indicates that amlodipine 10 mg when administered in combination with the active atorvastatin dosages did not alter the LDL- C lowering efficacy of atorvastatin. The comparison described in (2) above reveals that there was a significant difference (p= 0.006) in the reductions in LDL-C between amlodipine 5 mg combined across all active atorvastatin dosages and the active atorvastatin doses alone. This indicates that amlodipine 5 mg when administered in combination with the active atorvastatin dosages did significantly alter the LDL- C lowering efficacy of atorvastatin. In addition, the least square mean percent change from baseline in LDL- C observed when amlodipine 5 mg was added to atorvastatin 10 mg (- 39.0%) was significantly greater (p= 0.007) than that seen when atorvastatin 10 mg was administered alone (- 33.5%) (Table 46). None of the other comparisons described in (3) above reveals a significant treatment effect for either amlodpine 5 mg or amlodipine 10 mg. The data demonstrate that, with the exception of the 5/10 combination, there was no modification of atorvastatin's effect on LDL- C when the drug was taken in combination with amlodipine. ***Taken together, these results provide statistically significant evidence that atorvastatin 10 mg QD modified the blood pressure-lowering effect of concurrent amlodipine 5 mg QD in patients with comorbid hypertension and hyperlipidemia.***

Safety Conclusions: The results from the eight- week double- blind phase of this study support the conclusion that treatment with each of the eight dosage combinations of amlodipine (5 mg, 10 mg) and atorvastatin (10 mg, 20 mg, 40 mg, 80 mg) is safe and effective in the treatment of

patients with comorbid hypertension and hyperlipidemia. Further, the data demonstrate that there was no overall modification of atorvastatin's effect on LDL-C when the drug was taken in combination with amlodipine, and provide no evidence that atorvastatin modifies the systolic blood pressure lowering efficacy of amlodipine when the treatments were taken in combination.

Biopharm results relevant to dosage and administration
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 decreases the rate and extent of atorvastatin absorption by 32% and 11%, respectively, as assessed by Cmax and AUC(0-).

Administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal had no effect on amlodipine pharmacokinetic profiles. The 90% confidence intervals for the ratios of treatment geometric mean amlodipine Cmax and AUC (0-∞) values were both within the 80% to 125% range indicating absence of an effect of a high-fat meal and establishing equivalence of treatments. This result is the same as the finding that food has no effect on the bioavailability of Norvasc® (product labeling).

Recommendations
The reviewer recommends that the drug CADUET be approved subject to
1) [redacted]

[redacted]

9.0 ONGOING CLINICAL STUDIES

Drug Exposure

As of the 04 April 2003 cutoff date, the 5 ongoing clinical studies described in Table 1 represented a total enrollment of approximately 3976 patients (See appendix). This total includes approximately 2010 patients known to have taken either Caduet or amiodipine + atorvastatin (any dose) as study medication at least once; these 2010 patients comprise the total number patients who entered the single- blind treatment period of AVALON (Study A3841001) or the open- label dose- titration period of GEMINI (Study A3841012), plus 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006). Treatment assignments remained effectively blinded as of 04 April 2003 for approximately 1901 patients, comprising the total number of patients who entered the double- blind treatment period of either RESPOND (Study A3841003), MARGAUX (Study A0531006), or DUAAL (Study A0531031), less 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and less 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

Although total patient exposure could not be determined for ongoing studies, it can be inferred from study designs and enrollment figures (Table 1 and Table 2, respectively) that this Safety Update (04 April 2003 cutoff) represents a substantial increase in total patient exposure to Caduet/ concurrent amlodipine + atorvastatin (5- 10 fold) relative to the Caduet NDA (15 July 2002 cutoff).

. Deaths

As of the cutoff date for this 120- Day Safety Update (04 April 2003), a total of 6 deaths had been reported in ongoing clinical studies (Table 3). All 6 deaths reported during ongoing clinical studies were due to cardiovascular adverse events, and none were considered by the investigator to be related to study medication (see medical narratives in Appendix C).

Serious Adverse Events

As of the cutoff date for the Caduet NDA (15 July 2002), ARISg contained 17 cases reporting serious adverse events in ongoing clinical studies for a total of 16 patients (1 patient had 2 cases). Eleven of these patients were in AVALON (Study A3841001), 4 were in MARGAUX (Study A0531006), and 1 was in DUAAL (Study A0531031). When summarized by COSTART body system and preferred term, serious adverse events were related to the cardiovascular system for 10 of these patients, including 6 patients with myocardial infarction, 2 with angina, and 1 each with atrial fibrillation, syncopal episode, and vasovagal reaction; serious adverse events for the remaining 6 patients were acute cholecystitis, breast and lung cancer (together in a single patient), diabetes mellitus, spermatocele, vestibular neuronitis, and progression of gastroesophageal reflux disease.

As of the cutoff date for this 120- Day Safety Update (04 April 2003), ARISg contained 110 cases reporting serious adverse events in ongoing clinical studies for a total of 105 patients (5 patients had 2 cases each), including 70 cases in which the study medication was known to be either Caduet or concurrent amlodipine + atorvastatin and 30 cases in which treatment assignments remained blinded (Table 4). When summarized by MedDRA system organ class for patients who took either Caduet or amlodipine + atorvastatin, serious adverse events were most commonly cardiac disorders (24 cases), with gastrointestinal disorders (14 cases), nervous system disorders (8 cases), and neoplasms (8 cases) next most common.

When summarized by MedDRA preferred event terms for amlodipine + atorvastatin patients (Table 5), the most common serious adverse events were atrial fibrillation (7 patients), myocardial infarction (5 patients), acute myocardial infarction (3 patients), syncope (3 patients), and congestive cardiac failure aggravated (3 patients). No other serious adverse event was reported for more than 2 amlodipine + atorvastatin patients.

Table 5. Serious Adverse Events Reported in ≥2 Cases During Amlodipine + Atorvastatin Treatment, by MedDRA Preferred Event Term

	AVALON DB			AVALON DB + AVALON SB – GEMINI[a]	RESPOND + MARGAUX – DUAAL
System Organ Class MedDRA Preferred Event Term	Placebo N = 239[b]	Amlo N = 201[b]	Ator N = 200[b]	Amlo + Ator N = 2010[c]	Blinded N = 1901[d]
Atrial Fibrillation	1	0	0	7	1
Myocardial Infarction	1	0	0	5	3
Acute Myocardial Infarction	0	0	0	3	2
Syncope	0	0	0	3	1
Congestive Cardiac Failure Aggravated	0	0	0	3	0
Angina Pectoris	0	0	0	2	3
Chest Pain	0	0	0	2	3
Pulmonary Edema NOS	0	0	0	2	1
Pneumonia NOS	0	0	0	2	1
Coronary Artery Disease NOS	0	0	0	2	0
Myalgia	0	0	0	2	0
Fall	1	0	0	2	0
Sick Sinus Syndrome	0	0	0	2	0
Ventricular Tachycardia	0	0	0	2	0
Lung Cancer Stage Unspecified	0	0	0	2	0
Joint Disorder NOS	0	0	0	2	0
TOTAL EVENTS REPORTED	8	2	2	101	51

DB = Double-blind period; SB = Single-blind period, Amlo = Amlodipine (any dose); Ator = Atorvastatin (any dose); NOS = Not otherwise specified.

[a] Includes serious adverse events for 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

[b] N = Number of patients who took at least 1 dose of the indicated study medication during the AVALON double-blind treatment period (Study A3841001).

[c] N = Number of patients who took at least 1 dose of either concurrent amlodipine + atorvastatin or Caduet (amlodipine/atorvastatin combination tablet) during the single-blind treatment period of AVALON (Study A2841001) or the open-label dose-titration period of GEMINI (Study A3841012), plus 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

[d] N = Number of patients randomized to blinded study medication (placebo, amlodipine, atorvastatin, or amlodipine + atorvastatin) in RESPOND (Study A3841003), MARGAUX (Study A0531006), and DUAAL (Study A0531031), less 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and less 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

Table 8. Serious Adverse Events: AVALON (Study A3841001)
Double-Blind Treatment Period

Treatment Patient ID	Sex	Age (years)	Race	Serious Adverse Event
Placebo				
1043-1237	M	68	White	Atrial fibrillation; Pulmonary embolus
1098-1197	M	52	White	Spondylolisthesis
1098-1198	M	63	White	Myocardial infarction; Coronary artery stenosis
1116-1524	M	56	White	Unstable angina
1121-1563	M	50	White	Accidental fall
1135-1824	M	55	White	Unspecified cardiovascular event[a]
Amlo 5 mg QD				
1033-0435	M	53	Black	Vasovagal reaction
1060-0743	F	40	White	Gastroesophageal reflux disease
Ator 10 mg QD				
1048-0589	F	54	White	Vestibular neuronitis
1154-2019	M	51	White	Viral meningitis
Amlo 5 mg QD + Ator 10 mg QD				
1056-0694	M	62	White	Small bowel obstruction
1106-1327	M	60	White	Melanoma

Amlo = Amlodipine; Ator = Atorvastatin; QD = Once Daily; M = Male; F = Female.
[a] This patient died due to this serious adverse event.

10.0 ACCESS STUDY
Introduction

AMLODIPINE

- Amlodipine is a member of the 1,4- dihydropyridine structural class of calcium channel blockers, and is approved for use in the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina, herein collectively termed hypertension/ angina. The besylate salt of amlodipine is approved under NDA 19-787 in 1992, and marketed as Norvasc in the United States (US) at doses of 5 and 10 mg once daily (QD).

ATORVASTATIN

- The calcium salt of atorvastatin was approved in 1996 and marketed as Lipitor in the US under NDA 20- 702 at doses of 10, 20, 40, and 80 mg QD.
- Atorvastatin, a synthetic inhibitor of 3- hydroxy- 3- methylglutaryl-coenzyme A reductase, is approved for use as an adjunct to diet to reduce elevated total cholesterol (TC), low- density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C), in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; as an adjunct to diet for the treatment of patients with elevated TG; for the treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet; and to reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments or if such treatments are unavailable; these various lipid disorders are herein collectively termed dyslipidemia

- Hypertension and dyslipidemia are largely asymptomatic conditions that are modifiable CHD and stroke risk factors that coexist not infrequently and are inadequately controlled globally including the US. The control of comorbid hypertension and dyslipidemia is evidently of great benefit in the prevention of hypertension and stroke.

The AVALON protocol is being amended in order to offer subjects the option of participating in an open- label extension phase of study for a duration of 64 weeks (approximately 15 months). In addition, subjects will be offered a single tablet formulation of atorvastatin/ amlodipine to replace the individual tablets of each of these medications that were administered in the open- label phase of the original protocol. Subjects will continue with the single pill formulation for a period of one year.

The rationale for protocol amendment 2 involved the expansion of the populations under study to include patients who will not be subjected to arterial compliance measurements. These patients will be enrolled at additional study centers that do not possess the equipment for measuring arterial wall compliance and are referred to as Non-AWC Centers throughout this amendment.

This amendment also provided for closer adherence to the therapeutic strategies outlined in the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III treatment guidelines (not yet published when Amendment 1 was finalized). Thus, subjects with Diabetes Mellitus are considered members of GROUP III (as opposed to GROUP II) in keeping with the ATP III declaration that diabetic patients have a risk for future cardiovascular events equivalent to that of subjects with known coronary heart disease. Additionally, in compliance with the latest guidelines, an HDL-cholesterol level of less than 40mg/ dL (1. 0 mmol/ L) is also considered an additional risk factor for premature coronary heart disease which is higher than the level of 35 mg/ dL (0.9 mmol/ L) used in previous versions of the protocol.

Finally, this amendment incorporated administrative changes, establishes greater consistency between other dual therapy clinical trials and this study, and further clarifies the statistical methodology for the primary and secondary efficacy evaluations.

From the statistical and reporting prospective, extension phase of the AVALON will be considered as a separate study.

9.1 Access: Study Design:
This is a North American, multi- center, randomized, double- blind, placebo-controlled and open-label evaluation of the safety and efficacy of dual therapy with atorvastatin and amlodipine when compared to either therapy alone in the treatment of subjects with simultaneous hyperlipidemia and hypertension (The AVALON study). This will be assessed in three different subject populations as characterized at the time of screening. GROUP I will include subjects with hypertension and hyperlipidemia only. GROUP II will include subjects with hypertension and hyperlipidemia plus one additional cardiovascular risk factor excluding known coronary heart disease (CHD) and diabetes mellitus (DM). GROUP III will include subjects with hypertension and hyperlipidemia and CHD, DM or other atherosclerotic diseases.

9.2 Secondary Objective(s) AVALON and ACCESS

- To evaluate efficacy of the dual therapy of atorvastatin 10mg + amlodipine 5mg. To demonstrate that the dual therapy is superior to the amlodipine 5mg in the treatment of hyperlipidemia and superior to the atorvastatin 10mg in the treatment of hypertension. The evaluation of efficacy will be based on the comparisons of percentages of subjects reaching their NCEP and JNC therapeutic targets.

- To provide statistical assessment of the possible synergistic effect of the dual therapy in reducing systolic blood pressure. To demonstrate additional beneficial effect of atorvastatin, when added to amlodipine, by comparing changes in systolic blood pressure after eight weeks of double- blind treatment between dual therapy and amlodipine 5 mg treatment groups.

- To provide comparative evaluation of efficacy of the dual therapy by assessing percentages of subjects reaching both NCEP and JNC goals, changes in lipid parameters, blood pressure parameters, and global risk factor scores after 8 weeks of double- blind treatment.

- To assess efficacy of the long- term (up to 28 weeks) dual therapy as measured by percentage of subjects achieving NCEP therapeutic targets, percentage of subjects achieving an LDL-C of 100mg/ dL (2.6 mmol/ L) or less, percentage of subjects reaching JNC goals, changes in lipid parameters, blood pressure parameters and global risk factor scores.

- To assess efficacy of the 12-week open-label dual therapy with titration of atorvastatin and amlodipine doses to reach LDL-C and blood pressure therapeutic targets.

- To assess effect of atorvastatin on the blood pressure parameters by comparing changes after 8 weeks of double-blind treatment between atorvastatin 10mg and placebo treatment groups.

- To provide comparative evaluation of the safety profile of 8 weeks of the dual therapy with atorvastatin 10mg + amlodipine 5mg versus atorvastatin 10mg treatment and versus amlodipine 5 mg treatment.

- To evaluate long- term (up to 28 weeks) safety of dual therapy with atorvastatin and amlodipine.

Efficacy Measures: Fasting serum lipids: Total cholesterol, LDL- cholesterol, HDL- cholesterol and total triglycerides. Seated blood pressures. (all centers) Proximal and distal arterial compliance. (selected AWC centers only)

Physician and Patient Satisfaction Survey assessing the acceptability of the single tablet formulation as compared to the multiple tablet dosage of combination therapy with atorvastatin and amlodipine will be utilized in the Extension Study.

Safety: Safety laboratory assessment, blood pressure assessment and evaluation of adverse events will serve as the basis for safety surveillance during the study.

Decision Points: Statistical methods: Interim analysis:

Up to 1000 subjects will be randomized. A statistical rationale for the number of subjects in the study and the statistical methods is provided in the protocol.

This was a multicenter, open label, randomized, parallel-arm Phase 3B study in the atorvastatin clinical development program that evaluated the lipid lowering efficacy of atorvastatin and other statins over 54 weeks in patients who met NCEP criteria for the initiation of lipid-lowering therapy. Patients were randomly assigned in 4:1:1:1:1 ratio to what at the time were approved starting doses of atorvastatin (10mg QD), fluvastatin (20mg QD), lovastatin (20 mg QD), pravastatin (10mg QD) simvastatin (10mg QD) for the first 6 weeks of the study, and doses were doubled at 6 week intervals for patients who had not yet achieved LDL-C goals, up to maximum doses of atorvastatin 80 mg QD, fluvastatin 80 mg QD, lovastatin 80 mg QD, pravastatin 40 mg QD, or simvastatin 40 mg QD. At week 6, a significantly greater percentage of ACCESS patients had achieved LDL-C goals on the initial atorvastatin dose (52.8%) than on the initial doses of any of the other statins (15.1% for simvastatin, 24.4% for lovastatin, 37.4% for pravastatin, and 38.3% for fluvastatin).

Patients with hypertension or angina were not excluded from ACCESS, and routine monitoring of concurrent medication use indicated that among the 1958 patients who took atorvastatin during the study there were 232 patients who took prescription amlodipine concurrently and 1726 patients who did not (Table 66).

Table 69: Demographics and Baseline characteristics: Patients who took Atorvastatin during ACCESS (Study 981-176)

	Amlodipine + Atorvastatin* N=232	Atorvastatin only** N=1726
Sex Male Female	 137 (59.1) 95 (40.9)	 1063 (61.6) 663 (38.4)
Race White Black Asian Others	 198 (85.3) 22 (9.5) 4 (1.7) 8 (3.4)	 1527 (88.5) 116 (6.7) 20 (1.2) 63 (3.7)
Age, years N Mean,SE	 232 64.2,0.6	 1726 60.9,0.3
Body Mass N Mean,SE	 221 29.1,0.4	 1638 28.7,0.1
Risk Factors <2 Risk factors >2 Risk factors	 3 (1.3) 30 (12.9)	 243 (14.1) 366 (21.2)

CHD or PVD	199 (85.8)	1117 (64.7)
Type of Hyperlipidemia		
Primary Hyper-cholesterolemia	145 (62.5)	1046 (60.6)
Mixed Dyslipidemia	87 (37.5)	680 (39.4)

*Patients who took amlodipine at any dose for any duration concurrently with atorvastatin.
**Patients who took atorvastatin but had no record of concurrent use of amlodipine.
PVD = Peripheral Vascular disease; CHD = Coronary Heart Disease.

In a post-hoc analysis of ACCESS data, changes in blood pressure and lipid levels were evaluated separately for amlodipine + atorvastatin patients and atorvastatin-only patients: Results of this post hoc analysis are in Tables 67-70 below. It is however noteworthy that hypertension was not an entry criterion in ACCESS and this study was not double blinded and placebo controlled. Therefore data from ACCESS are not comparable to AVALON for efficacy or for retention of therapeutic effects but data for safety are additional for the evaluation.

Table 70: Mean BP values of patients who took atorvastatin during ACCESS Study (981-176)

	Amlodipine + Atorvastatin* N=232			**Atorvastatin only** N=1726**		
	n	Mean	SE	n	Mean	SE
Systolic Blood Pressure, mmHg						
Week 0	224	137.0	(1.26)	1672	131.2	0.43
Week 6	225	137.5	(1.36)	1672	130.9	0.43
Week 54	194	136.1	(1.26)	1502	131.4	0.44
Diastolic Blood Pressure, mmHg						
Week 0	224	78.8	(0.64)	1672	78.5	0.24
Week 6	225	78.8	(0.71)	1672	78.2	0.24
Week 54	194	77.4	(0.69)	1502	78.0	0.24

*Patients who took amlodipine at any dose for any duration concurrently with atorvastatin.
**Patients who took atorvastatin but had no record of concurrent use of amlodipine.

Table 71: Mean percent change in lipid levels from baseline to end of treatment SBA for Norvasc (1992) – 16 clinical trials.

	Amlodipine N=1024	**Placebo N=771**
Total cholesterol		
Baseline	235.3	234.6
Treatment	234.2	233.5
% change	-0.5	-0.5
Triglycerides		
Baseline	166.3	172.4
Treatment	158.5	163.7
%Change	-4.7	-5.0

There was no effect on blood pressure among those who took Atorvastatin –Lipitor suggesting that there is no modification of blood pressure on concurrent or concomitant use of both drugs. This evidence is consistent with the findings in AVALON and RESPOND trials.

Table 72: Mean change in blood pressure (mmHg) from baseline to end of treatment: Atorvastatin (2.5 mg –80 mg QD; 4-52 wks)/all completed studies (Lipitor NDA 20-702).

	Placebo N=110	Atorvastatin N=2502	Other statins N=742
Systolic BP, mean (SE)			
Baseline	121.5 (1.4)	125.4 (0.3)	126.8 (0.6)
Treatment	125.1 (1.5)	126.0 (0.3)	128.1 (0.6)
Change	3.71. (1.5)	0.6(0.3)	1.3 (0.6)
Diastolic BP, mean (SE)			
Baseline	77.7 (0.9)	77.4 (0.2)	77.7 (0.3)
Treatment	79.2 (0.9)	77.6 (0.2)	78.0 (0.3)
Change	1.6 (0.9)	0.2 (0.2)	0.3 (0.3)

Table 73: Mean percent change in lipid levels from baseline to end of treatment Atorvastatin 10 mg QD patients of Fredrickson Type IIa or IIb - NDA Lipitor NDA 20-702

	Hypertensive Patients* N=510	Normotensive Patients** N=975
Change in Lipid levels, mean (SE)		
LDL-C	-37 (1)	-35 (<1)
Apo B	-29 (1)	-28 (<1)
TC	-27 (<1)	-26 (<1)
TG	-18 (1)	-17 (1)
VLDL-C	-21 (1)	-20 (1)
HDL-C	6 (1)	7 (<1)
VLDL-C/HDL-C	-32 (1)	-32 (<1)
Non-HDL/HDL-C	-37 (1)	-37 (<1)

*Patients who used anti-hypertensive medications concurrently with atorvastatin
**Patients who did not use anti-hypertensive medications concurrently with atorvastatin.

Drug Exposure-ACCESS

Table 74: Summary of mean Exposure in days by treatment group and course of Titration

	Norvasc			Not Norvasc		
Treatment	N	*Exposure	Avg Dose	N	*Exposure	Avg Dose
Atorvastatin			23.2			20.3
10mg	232	180.9		1726	212.7	
20mg	126	146.0		760	163.1	
40mg	74	161.9		400	169.6	
80mg	35	207.5		180	232.6	
All Controls			37.6			37.4
10mg	112	124.1		851	125.1	
20mg	171	105.3		1501	110.5	
40mg	129	164.5		1103	166.5	
80mg	59	258.5		492	253.4	

*Mean Exposure in days

10.1 Summary and Conclusions – Clinical review - ACCESS Study

- This NDA provides data from a single prospective study that compares a single pill, fixed dose, o.d. combination regimen (CADUET) versus a concurrent 2-pill regimen (AMLODIPINE AND ATORVASTATIN).

Rationale for Atorvastatin use in the combination

- A separate study, ACCESS, showed that atorvastatin showed the highest efficacy for lowering LDL-C among all the 5 statins in the study.

- At Week 54/ Endpoint, the atorvastatin group displayed the greatest mean percent reduction (42.1%) in LDL-C from baseline. Overall, the differences in mean percent change between the atorvastatin group and the other 4 treatment groups were somewhat smaller than those seen at Week 6 because of the forced titration design and the greater number of titrations occurring in the other groups. A treatment comparison of adjusted mean difference showed that the differences in mean percent change in LDL-C levels between the atorvastatin group and the other 4 treatment groups were statistically significant (- 6.2 for the simvastatin group, -6.5 for the lovarstatin group, -13.1 for the fluvastatin group, and -14.1 for the pravastatin group, p= 0.0001 for all 4 comparisons).

- Mean increases in HDL-C were similar across treatment groups, ranging from 4.7% in the atorvastatin group to 6.0% in the pravastatin group. A treatment comparison of adjusted mean difference indicated that the differences in mean percent change in HDL- C between atorvastatin and the four other treatment groups were not statistically significant.

- The mean percent reductions in LDL-C/HDL-C ratios from baseline to endpoint ranged from 31.1% in the pravastatin group to 44.1% in the atorvastatin group. A treatment comparison of adjusted mean difference showed that the differences in mean percent change in LDL-C/HDL-C ratios between the atorvastatin group and the other four treatment groups were statistically significant (- 5.5 for the simvastatin group, -6.1 for the lovastatin group, -12.3 for the fluvastatin group, and -13.0 for the pravastatin group, p= 0.0001 for all 4 comparisons).

- Among all treatment groups, the atorvastatin group achieved the greatest mean percent reduction (19.3%) in TG levels. A treatment comparison of adjusted mean difference indicated that the differences in mean percent change in triglyceride levels between the atorvastatin group and the other four treatment groups were statistically significant (- 6.3 for the simvastatin group, -7.5 for the lovastatin group, -9.7 for the pravastatin group, and -12.1 for the fluvastatin group, p= 0.0001 for all 4 comparisons).

- The mean percent reductions in TC levels from baseline to Week 54/ Endpoint ranged from 19.9% in the pravastatin group to 30.8% in the atorvastatin group. A treatment comparison of adjusted mean difference indicated that the differences in mean percent change in TC levels between the atorvastatin group and the other four treatment groups were statistically significant (- 5.4 for the simvastatin group, -5.4 for the lovastatin group, -10.6 for the fluvastatin group, and -10.9 for the pravastatin group, p=0.0001 for all comparisons).

- The mean percent reductions in Apo B levels from baseline to Week 54/ Endpoint ranged from 18.7% in the pravastatin group to 31.9% in the atorvastatin group. A treatment comparison of adjusted mean difference indicated that the differences in mean percent change in Apo B levels between the atorvastatin group and the other four treatment groups were statistically significant (- 6.2 for the simvastatin group, -6.5 for the lovastatin group, -12.8 fluvastatin group, and -13.0 for the pravastatin group, p= 0.0001 for all 4 comparisons).

10.2 Label

The following constitutes preliminary views of the reviewer as the final clean copy of the label has just been received. There are three main issues to be addressed. The first is the question of the cl

[redacted]

This reviewer will add more comments on the label as this was only received a few days ago.

Biopharmaceutics
Three clinical biopharmaceutical studies using tablets containing amlodipine and atorvastatin in fixed combination are considered pivotal for this NDA (A 3841009, 3841010, and 3841007). Two of these used crossover designs and compared 10/80 mg combination tablets for bioequivalence versus Norvasc and Lipitor tablets taken together in matching doses. The third also used a crossover design to compare 10/80mg combination tablets taken under fed versus fasting conditions to evaluate food effects. The data from these studies are briefly reviewed below in Section 11.0. Biopharm review will deal with this section of the NDA in greater detail.

11.0 Bioequivalence studies
A3841009
10-mg Amlodipine/80-mg Atorvastatin Combination Tablet to Coadministration of 10-mg Amlodipine and 80-mg Atorvastatin Tablets (Protocol A3841009)
Study Center(s): Pfizer Research Clinic, 2800 Plymouth Road, Ann Arbor, MI 48105
Publication (reference): None Study Period:11 Mar 2002 to 06 Jun 2002
Objective(s): 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.
Methodology: This was an open-label, single-dose, randomized, 2-way crossover study in healthy subjects with a minimum 14-day washout period between doses.
Number of Subjects: Sixty-two subjects entered the study and received both the test and reference doses in a random sequence.
Diagnosis and Main Criteria for Inclusion: Male or female subjects, 18 to 64 years of age. Females were not of childbearing potential or were practicing contraception. Subjects were in good health as determined by a medical history, physical examination, electrocardiogram (ECG) and clinical laboratory tests, with body mass index (BMI) between 18 to 30 kg/m 2 , inclusive.
Test Product, Dose and Mode of Administration, Batch Number: Amlodipine (10 mg)/atorvastatin (80 mg) combination tablet, Lot CG 0341201, Formulation 15927-10
Administration: Oral
Duration of Treatment: Single dose
Results of PK data for studies A3841009
Table 75: PK data for bioequivalence of amlodipine /atorvastatin 10/80mg and 5/10 mg

Study ID, Combination		Least-Squares Mean Values		Ratio	90% CI
Assay Drug	Parameter	Reference	Test	(%)	(%)
A3841009, Amlodipine/Atorvastatin 10/80 mg					
Amlodipine	n	62	62		
	Cmax, ng/mL	6.58	6.63	100.8	97.6 to 103.9
	tmax, hr	8.07	7.61	94.3	N/A
	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
Atorvastatin	n	62	62		
	Cmax, ng/mL	27.1	25.5	94.1	84.6 to 104.4
	tmax, hr	1.54	0.893	58.0	N/A
	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
A3841010, Amlodipine/Atorvastatin 5/10 mg					
Amlodipine	n	63	63		
	Cmax, ng/mL	2.94	3.04	103	99.6 to 107.7
	tmax, hr	7.67	7.80	102	N/A
	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	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	N/A
	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

Test = Combination tablet. Reference = Norvasc® and Lipitor® tablets taken together in doses matching the respective combination tablet. Ratio = Ratio of treatment mean values (100% x test/reference); 90% CI = 90% confidence interval estimate for the ratio of treatment mean values; n = numbers of subjects who provided pharmacokinetic data; Cmax = Maximum plasma concentration (geometric mean); tmax = Time to Cmax; AUC(0-tlqc) = Area under plasma concentration-time profile from zero to time for last quantifiable concentration (geometric mean); AUC(0-∞) = area under plasma concentration-time profile from zero to infinity (geometric mean); t½ = terminal half-life; N/A = Not applicable.

Safety: Vital signs, physical examination results, clinical laboratory assessments, and adverse events (AEs) were evaluated.

Pharmacokinetics: Plasma concentrations of amlodipine and atorvastatin were measured by validated methods and pharmacokinetic parameters were estimated using standard noncompartmental methods.

Statistical Methods:

Safety: Descriptive statistics were used to summarize adverse events.

Pharmacokinetics: Log-transformed Cmax and AUC were the primary parameters used in the evaluation of bioequivalence. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, group, subject within sequence and group, period, and treatment effects. Results from the ANOVA were used to calculate 90% confidence intervals for the ratios (test/reference) of least-squares treatment mean values, where coadministration of 10-

mg amlodipine and 80-mg atorvastatin tablets was the reference treatment. Bioequivalence would be concluded if the 90% confidence interval for the treatment ratios of geometric means of Cmax and AUC values for both amlodipine and atorvastatin were entirely within the bioequivalence limit of 80% to 125%.

SUMMARY – CONCLUSIONS

Subject Characteristics and Disposition: Sixty-two subjects (29 male, 33 female) entered and completed the study. The mean (range) age was 39.5 (20-64) years and the mean (range) weight was 76.3 (51.1-105.6) kg.

Safety Results: There were no deaths or other serious adverse events. A total of 211 treatment-emergent adverse events were reported by 52 of the 62 subjects. One treatment-associated. Adverse events occurred with the greatest frequency in the body as a whole and the nervous system. The most frequently reported adverse events were **headache** (43 subjects, treatment-associated in 36 subjects) and **somnolence** (12 subjects, treatment-associated in 7 subjects). Treatment-associated adverse events experienced by more than single subjects were: Asthenia (6 subjects), urinary frequency (5 subjects), dizziness (3 subjects), and anorexia, nausea, and pain (2 subjects each).

A 3841010
This is bioequivalence versus marketed Norvasc 5 mg and Lipitor 10 mg.

Title of Study: 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 (Protocol A3841010)

Investigators: Bramson CR

Study Center(s): Pfizer Research Clinic, 2800 Plymouth Road, Ann Arbor, MI 48105

Publication (reference): None

Studied Period: 16 Jan 2002 to 21 Mar 2002 Phase of Development: 1

Objective(s): To evaluate whether an 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

Methodology: This was an open-label, single-dose, randomized, 2-way crossover study in healthy subjects with a minimum 14-day washout period between doses.

Number of Subjects: Sixty-four subjects entered the study and 62 subjects received both the test and reference doses in a random sequence. Two subjects withdrew after receiving only 1 of the 2 treatments.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, 18 to 64 years of age. Females were not of childbearing potential or were practicing contraception. Subjects were in good health as determined by a medical history, physical examination, electrocardiogram (ECG) and clinical laboratory tests, with Body Mass Index (BMI) between 18 and 30 kg/m 2 , inclusive.

Test Product, Dose and Mode of Administration, Batch Number: Amlodipine (5 mg)/atorvastatin (10 mg) combination tablet, Lot CG 0251201, Formulation 15927-11

Administration: Oral

Duration of Treatment: Single dose
Atorvastatin (Lipitor) (10 mg) tablet, Lot CG 0070399

Administration: Oral

Criteria for Evaluation:

Safety: Vital signs, physical examination results, clinical laboratory assessments, and adverse events (AEs) were evaluated.

Pharmacokinetics: Plasma concentrations of amlodipine and atorvastatin were measured by validated methods, and pharmacokinetic parameters were estimated using standard noncompartmental methods.

Statistical Methods:

Safety: Descriptive statistics were used to summarize adverse events.

Pharmacokinetics: Log-transformed Cmax and AUC were the primary parameters used in the evaluation of bioequivalence. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, group, subject within sequence and group, period, and treatment effects. Sequence as well as group effects were assessed using the subject within sequence and group mean square from ANOVA as the error term.

Results from the ANOVA were used to calculate 90% confidence intervals for the ratios (test/reference) of least-squares treatment mean values, where coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets was the reference treatment. Bioequivalence would be concluded if the 90% confidence interval for the treatment ratios of geometric means of Cmax and AUC values for both amlodipine and atorvastatin were entirely within the bioequivalence limit of 80% to 125%.

SUMMARY – CONCLUSIONS

Subject Characteristics and Disposition: Sixty-four subjects (17 male, 47 female) entered the study and 62 subjects completed it. Two subjects withdrew due to adverse events. The mean (range) age was 38.9 (19-61) years and the mean (range) weight was 72.8 (53.9-100.7) kg. 72.8 (53.9-100.7) kg.

Protocol (Page 4)

Summary of Amlodipine Pharmacokinetic Parameter Values Following Coadministration of 5-mg Amlodipine and 10-mg Atorvastatin Tablets (Reference) and 5-mg Amlodipine/10-mg Atorvastatin Combination Tablets (Test) (Study A3841010)

Parameter	Least-Squares Mean Values		Ratio (%)	90% Confidence Interval
	Coadministered Tablets (Reference)	Combination Tablet (Test)		
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

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Cmax = Maximum plasma concentration. Geometric mean.

tmax = Time to Cmax.

AUC(0-tlqc) = Area under plasma concentration-time profile from time zero to the time for the last quantifiable concentration (lqc): Geometric mean.

AUC(0-∞) = Area under plasma concentration-time profile from time zero to infinity: Geometric mean.

t½ = Terminal half-life.

Based on tmax, Cmax, and AUC(0-) values, rate and extent of amlodipine absorption following administration of 5-mg amlodipine/10-mg atorvastatin combination tablets were similar to that observed for coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets.
Mean amlodipine Cmax and AUC(0-) values following administration of 5-mg amlodipine/10-mg atorvastatin combination tablets were both 3% higher than those for coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets. The 90% confidence intervals for the ratios of treatment mean Cmax and AUC(0-) values, based on log-transformation, were within the 80% to 125% bioequivalence range.

Atorvastatin: Atorvastatin pharmacokinetic parameters values following coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets (Reference) and 5-mg amlodipine/10-mg atorvastatin combination tablets (Test) were analyzed.

Safety Results: There were no deaths or other serious adverse events. Two subjects withdrew due to adverse events that were considered to be unrelated to the study drug. A total of 215 treatment-emergent adverse events were reported by 56 of the 64 subjects. Ninety-one adverse events reported by 35 subjects were considered to be treatment- associated. Adverse events occurred with the greatest frequency in the body as a whole and the nervous system. The most frequently reported adverse events were **headache** (40 subjects, treatment-associated in 25 subjects), **somnolence** (18 subjects, treatment- associated in 13 subjects), pain (12 subjects, treatment-associated in 2 subjects), and **dizziness** (9 subjects, all treatment-associated). The following treatment-associated adverse events were experienced by 2 subjects each: Asthenia, back pain, menstrual disorder, nausea, and rash. Other treatment-associated adverse events occurred in single subjects.

Pharmacokinetic Results:

Amlodipine: Amlodipine pharmacokinetic parameters values following coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets (Reference) and 5-mg amlodipine/10-mg atorvastatin combination tablets (Test) are summarized in Table

Table 76: Summary of atorvastatin PK values following coadministration of 5mg amlodipine and 10mg of reference 10mg Atorvastatin combination

Summary of Atorvastatin Pharmacokinetic Parameter Values Following Coadministration of 5-mg Amlodipine and 10-mg Atorvastatin Tablets (Reference) and 5-mg Amlodipine/10-mg Atorvastatin Combination Tablets (Test) (Study A3841010)

Parameter	Least-Squares Mean Values		Ratio (%)	90% Confidence Interval
	Coadministered Tablets (Reference)	Combination Tablet (Test)		
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
$t_{1/2}$, hr	7.60	7.30	96.1	78.1 to 114.0

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Cmax = Maximum plasma concentration: Geometric mean.

tmax = Time to Cmax.

AUC(0-tlqc) = Area under plasma concentration-time profile from time zero to the time for the last quantifiable concentration (lqc): Geometric mean.

AUC(0-∞) = Area under plasma concentration-time profile from time zero to infinity: Geometric mean.

$t_{1/2}$ = Terminal half-life.

Based on tmax, Cmax, and AUC(0-∞) values, rate and extent of atorvastatin absorption following administration of 5-mg amlodipine/10-mg atorvastatin combination tablets were similar to that observed for coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets. Mean atorvastatin Cmax and AUC(0-∞) values following administration of 5-mg amlodipine/10-mg atorvastatin combination tablets were approximately 2% lower than and nearly identical to, respectively, those for coadministration of 5-mg amlodipine and 10-mg atorvastatin tablets. The 90% confidence intervals for the ratios of treatment Cmax and AUC(0-∞) values, based on log-transformed values, were within the 80% to 125% bioequivalence range.

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

A3841007
Fed versus Fasted

Title of Study: A Comparative Bioavailability Study of Amlodipine (10 mg)/ Atorvastatin (80 mg) Combination Tablet Following a Single Dose Under Fed and Fasted Conditions

Investigators: Bramson CR

Study Center(s): Pfizer Research Clinic, 2800 Plymouth Road, Ann Arbor, MI 48105

Publication (reference): None

Studied Period: 08 Mar 2002 to 30 Apr 2002 Phase of Development: 1

Objective(s): 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

Methodology: This was an open-label, single-dose, randomized, 2-way crossover study in healthy subjects with a minimum 14-day washout period between doses.

Number of Subjects: Forty subjects entered the study and received the dose under both fasted and fed conditions in a random sequence. One subject withdrew before the end of the study.

Diagnosis and Main Criteria for Inclusion: Healthy male or female subjects between the ages of 18 and 64 inclusive. Females were not of childbearing potential or were practicing contraception. Subjects were in good health as determined by a medical history, physical examination, electrocardiogram (ECG) and clinical laboratory tests, with Body Mass Index (BMI) between 18 and 30 kg/m 2 , inclusive.

Test Product, Dose and Mode of Administration, Batch Number: Amlodipine (10 mg)/atorvastatin (80 mg) combination tablet, Lot CG 0341201, Formulation 15927-10

Administration: Orally after high-fat meal

Duration of Treatment: Single dose

Administration: Orally after 10- hour fast

Criteria for Evaluation:

Safety: Vital signs, clinical laboratory assessments, and adverse events (AEs) were evaluated.

Pharmacokinetics: Plasma concentrations of amlodipine and atorvastatin were measured by validated methods and pharmacokinetic parameters were estimated using standard noncompartmental methods.

Statistical Methods:

Safety: Descriptive statistics were used to summarize adverse events.

Pharmacokinetics: Results from ANOVA of log- transformed Cmax and AUC values were used to calculate 90% confidence intervals for the ratios of treatment means. Absence of a food effect would be concluded if the 90% confidence intervals for the treatment ratios of geometric means of Cmax and AUC values for both amlodipine and atorvastatin were entirely within the 80% to 125% range. Confidence intervals for secondary parameters were used as supportive data.

SUMMARY – CONCLUSIONS

Subject Characteristics and Disposition: Forty subjects (25 male, 15 female) entered the study and 39 completed it. One subject withdrew for reasons unrelated to the study drug. The mean (range) age was 36.1 (20- 60) years and the mean (range) weight was 79.8 (56.2- 110.3) kg.

Safety Results: There were no deaths or other serious adverse events. There were no withdrawals due to adverse events. A total of 88 treatment- emergent adverse events were reported by 35 of the 40 subjects. Thirty- seven adverse events reported by 22 subjects were considered to be treatment- associated. Adverse events occurred with the greatest frequency in the body as a whole and the digestive and nervous systems. The most frequently reported adverse events were **headache** (23 subjects, treatment-associated in 19 subjects), **somnolence** (5 subjects, treatment-associated in 3 subjects), and back pain, infection, and pain (5 subjects each, treatment-associated in 0 subjects each). The only other treatment-associated adverse event experienced by more than 1 subject was nausea, experienced by 2 subjects.

3.1. Study Design

This was 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.

Table 77: Study design of single dose fed or fasted -A3841007- study

Table 1. Study Design (Study A3841007)

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

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 amlodipine (10 mg)/ atorvastatin (80 mg) combination tablet with 240 mL of water immediately after the meal. No food was allowed for 4 hours after the dose.

3.2. Protocol Amendments and Addenda

There were no protocol amendments or addenda.
Pharmacokinetic Results:

Amlodipine: Amlodipine pharmacokinetic parameter values following administration of single amlodipine (10 mg)/atorvastatin (80 mg) combination tablets to subjects under fasting conditions and fed a high-fat meal are summarized in the following table.

Summary (N = 40) of Amlodipine Pharmacokinetic Parameter Values Following Administration of Single Amlodipine (10 mg)/Atorvastatin (80 mg) Combination Tablets to Subjects Under Fasting Conditions (Reference) and With a High-Fat Meal (Test) (Study A3841007) Least-Squares Mean Values

Parameter Fasting (Reference) With a High-Fat Meal (Test) Ratio (%) 90% Confidence Interval 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 Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean. Cmax = Maximum plasma concentration: Geometric mean. tmax = Time to Cmax. AUC(0-tlqc) = Area under plasma concentration-time profile from time zero to the time for the last quantifiable concentration (lqc): Geometric mean. AUC(0-) = Area under plasma concentration-time profile from time zero to infinity: Geometric mean . t½ = Terminal half-life.

Based on tmax, Cmax and AUC(0-) values, rate and extent of amlodipine absorption following administration of 10mg amlodipine/80 mg atorvastatin combination tablets with a high-fat meal were similar to those observed in subjects under fasting conditions. Mean amlodipine Cmax and AUC(0-) values following administration of combination tablets with food were 5% and 1% higher, respectively, than those under fasting conditions. The 90% confidence intervals for the ratios of treatment geometric mean Cmax and AUC(0-) values were within the 80% to 125% range.

Atorvastatin: Atorvastatin pharmacokinetic parameter values following administration of single amlodipine (10 mg)/atorvastatin (80 mg) combination tablets to subjects under fasting conditions and fed a high-fat meal are summarized in the following table.

Summary (N = 40) of Atorvastatin Pharmacokinetic Parameter Values Following Administration of Single Amlodipine (10 mg)/Atorvastatin (80 mg) Combination Tablets to Subjects Under Fasting Conditions (Reference) and With a High-Fat Meal (Test) (Study A3841007) Least-Squares Mean Values

Parameter Fasting (Reference) With a High-Fat Meal (Test) Ratio (%) 90% Confidence Interval 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 Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean. Cmax = Maximum plasma concentration: Geometric mean. tmax = Time to Cmax. AUC(0-tlqc) = Area under plasma concentration-time profile from time zero to the time for the last quantifiable concentration (lqc): Geometric mean. AUC(0-) = Area under plasma concentration-time profile from time zero to infinity: Geometric mean. t½ = Terminal half-life.

Based on tmax and Cmax values, rate of atorvastatin absorption following administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal was slower than that observed under fasting conditions. The mean tmax value with food was approximately 1 hour longer than that under fasting conditions. The mean atorvastatin Cmax value following administration of combination tablets with food was 32% lower than that under fasting conditions. The 90% confidence interval for the ratio of treatment geometric mean Cmax values was outside of the 80% to 125% range.

Based on AUC(0-) values, extent of atorvastatin absorption following administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal was similar to that observed under fasting conditions. The mean atorvastatin AUC(0-) value following administration of combination tablets with food was approximately 11% lower than that under fasting conditions. The 90% confidence interval for the ratio of treatment geometric mean AUC(0-) values was within the 80% to 125% range.

Discussion: The amlodipine (10 mg)/atorvastatin (80 mg) combination tablet formulation was well-tolerated by healthy volunteers whether administered with food or fasting.

Administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal had no effect on amlodipine pharmacokinetic profiles. The 90% confidence intervals for the ratios of treatment geometric mean amlodipine Cmax and AUC(0-) values were both within the 80% to 125% range indicating absence of an effect of a high-fat meal and establishing equivalence of treatments. This result is the same as the finding that food has no effect on the bioavailability of Norvasc® (product labeling).

Administration of combination tablets with a high-fat meal delayed the mean atorvastatin tmax value approximately 1 hour and decreased the mean Cmax value nearly 32%. The 90% confidence interval for the ratio of geometric mean atorvastatin Cmax values was outside of the 80% to 125% range indicating an effect of a high-fat meal on atorvastatin Cmax values. The 90% confidence interval for the ratio of geometric mean atorvastatin AUC(0-) values, on the other hand, was within the 80% to 125% range indicating absence of a food effect on the extent of atorvastatin absorption. The results are similar to the food effect on the rate (25%) and extent (9%) of absorption, as assessed by Cmax and AUC for Lipitor® (product labeling).

Conclusion(s): **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 decreases the rate and extent of atorvastatin absorption by 32% and 11%, respectively, as assessed by Cmax and AUC(0-).**

This was 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 (Table 1).

Table 1. Study Design (Study A3841007) Period 1 (Day 1) Period 2 (Day 1) Group 1 Fasted Fed Group 2 Fed Fasted

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 amlodipine (10 mg)/ atorvastatin (80 mg) combination tablet with 240 mL of water immediately after the meal. No food was allowed for 4 hours after the dose.

3.2. Protocol Amendments and Addenda

There were no protocol amendments or addenda.

3.3. Subject Selection

3.3.1. Inclusion Criteria

Subjects of any race who met the following criteria were eligible to participate in the study.

· Age: 18 to 64 years (inclusive).
Gender: Males and females. Females were to be either not of childbearing potential (surgically sterilized or at least 2 years postmenopausal; not breastfeeding) or practicing successful contraception for at least 3 months prior to entry into the study with 1 of the following methods: (a) oral or transdermal contraceptives; (b) intrauterine device; (c) implanted contraceptive (such as

[redacted]); (d) diaphragm; (e) sexual partner using condom or surgically sterilized; or (f) sexually inactive. Females of childbearing potential were instructed to avoid pregnancy during study participation;

In good health as determined by a detailed medical history, full physical examination (including blood pressure and pulse rate measurement), 12-lead electrocardiogram (ECG) and clinical laboratory tests;

Body Mass Index (BMI) between 18 to 30 kg/m 2 , inclusive;

Laboratory Parameters: White blood cell (WBC) count, absolute neutrophil count, hemoglobin, and hematocrit within the laboratory reference range. Albumin not less than the lower limit of the reference range. Blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and total bilirubin not greater than the upper limit of the reference range. If total bilirubin was greater than the upper limit of the reference range under fasted conditions, the test could be repeated under fed conditions. These values for the following tests:

Urine drug screen —negative;
Serum pregnancy test (female subjects) —negative;
All other laboratory parameters were not to be clinically significantly abnormal as judged by the investigator;
Willing and able to provide written informed consent;
Willing and able to be confined to the Clinical Research Unit as required by the protocol; and
Willing to refrain from illegal drug use for the duration of the study.
Exclusion Criteria
Subjects could not participate in the study if any of the following conditions existed:
Any condition possibly affecting drug absorption, eg, gastrectomy;
Evidence or history of clinically significant allergic (except for untreated, asymptomatic, seasonal allergies at time of dosing), hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurologic disease;
History of significant adverse reaction to HMG-CoA reductase inhibitors or calcium channel blockers;
History of drug or alcohol dependence or drug allergies with a history of regular alcohol consumption defined as exceeding 7 drinks/week for women or 14 drinks/week for men (1 drink = 5 oz of wine, or 12 oz of beer, or 1.5 oz of hard liquor) within 6 months of screening;
Donation of blood or blood components for at least 4 weeks prior to the start of the study and during the study;
If female, pregnancy or lactation;
Sitting blood pressure at screening or predose below 100/60 mm Hg on at least 2 evaluations.
Use of any medication not considered acceptable by the clinical investigators within 28 days or 5 half-life values (whichever was longer) prior to the first dose of study medication;
Positive urinary drug screen;
Screening 12-lead ECG demonstrating at least 1 of the following: heart rate >100 bpm, QRS 120 msec, QTc >430 msec (male), QTc >450 msec (female), or PR >220 msec;
Consumption of grapefruit juice within 7 days prior to the first dose of study medication; or
Use of St John's Wort within 14 days prior to the first dose of study medication.
. Guidelines for Subject Withdrawal

Subjects were free to withdraw from the study at any time at their own discretion. The protocol specified conditions of AST/ ALT, alkaline phosphatase, and total bilirubin elevations at which the investigator would consider a subject for withdrawal, and at which a subject would be withdrawn from the study. Female subjects were to be withdrawn from the study in the case of a positive serum or urine pregnancy test. The final evaluation required by the protocol was to be performed at the time of study discontinuation. The investigator was to record the reason for study discontinuation, provide or arrange for appropriate follow- up (if required) for such subjects, and

document the course of the subject's condition. Subjects who withdrew from the study could be replaced by a substitute who would repeat the entire study.

Study Treatment

Treatments Administered

Forty subjects received both of the 2 regimens: Administration of 1 amlodipine (10 mg)/ atorvastatin (80 mg) combination tablet under fasted or fed conditions, on Day 1 of Study Period 1 or 2 according to a randomization schedule provided by the PGRD Biometircs Department. The 2 doses were separated by a washout period of at least 14 days. One subject did not complete Period 2.

Subjects were required to report to the Clinical Research Unit at approximately 0700 hours following an overnight fast of at least 10 hours. Subjects under fasting condition continued fasting for 4 hours after dosing. For subjects under fed condition, the standardized meal was given 30 minutes prior to dosing and was consumed completely over 30 minutes with administration of amlodipine (10 mg)/ atorvastatin (80 mg) combination tablet with 240 mL of water immediately after the meal. Water could be consumed freely during the fasting periods except for 1 hour before and 1 hour after study drug administration.

Medication was administered at 0800 hours (1 hour) with 240 mL of tepid water. Subjects swallowed the tablets intact. Subjects were required to stay in the Clinical Research Unit for at least 12 hours after dosing.

A meal, which was the same in both study periods, was provided approximately 4 hours after dosing. Soft drinks without caffeine or fruit juices (except grapefruit juice) could be consumed freely beginning after this meal. Dinner was provided approximately 9 to 10 hours after dosing and an evening snack was permitted up until 2200 hours. While confined to the clinic, the total daily nutritional composition was to be approximately 50% carbohydrate, 35% fat, and 15% protein.

During each study period, subjects were to abstain from alcohol and from caffeine- or xanthine-containing products for 24 hours prior to the start of dosing until collection of the period's 72-hour pharmacokinetic sample.

Subjects were required to fast from all food and drink (except water) at least 4 hours prior to any laboratory safety evaluations and to abstain from any increase in physical activity level during the study periods.

Identity of Study Treatments

Open-label amlodipine (10 mg)/atorvastatin (80 mg) combination tablets (Lot CG 0341201, Formulation 15927-10) were supplied by the study sponsor, PGRD. A detailed set of study medication storage, dispensing, and administration instructions was provided with the initial shipment of study medication.
Method of Assigning Subjects to Treatment Groups

A computer-generated randomization schedule was be used to assign subjects to the treatment sequences. Details of subject assignment are contained in the Global Investigational Drug Information and Management System (GIDIAMS) documentation maintained by the Ann Arbor Pharmacy Operations Department. Randomization codes are provided in Appendix C.1.
. Selection of Dose for the Study

The amlodipine (10 mg)/atorvastatin (80 mg) combination tablet is the highest dose strength among 8 combinations Pfizer is developing based on currently marketed strengths of amlodipine and atorvastatin.

STUDY SUBJECTS

Disposition of Subjects

Forty subjects entered the study and 39 completed it. One subject withdrew on Day 19 (Day 5 of Period 2) for reasons unrelated to the study drug.

Table 78: Comparison of 10/80 combination tabletsadministered with a high meal test and fasting

Table 2. Summary of Statistical Evaluations for Amlodipine Parameter Values Comparing 10/80 Combination Tablets Administered with a High-Fat Meal (TEST) and Fasting (REF): Protocol A3841007

	LEAST SQUARES Mean Values		Difference	
Parameter	REF	TEST	(% REF)	90% Confidence Intervals
Cmax	6.40	6.75	5.5%	97.8% to 113.2%
tmax	8.15	7.80	-4.3%	88.7% to 102.7%
AUCtime	310	319	2.9%	98.7% to 107.1%
AUCinf	354	358	1.1%	97.1% to 105.2%
HL	51.7	51.4	-0.6%	92.6% to 106.3%

Difference = Difference between Reference and Test treatment LEAST SQUARES mean values.

90% Confidence Interval = Confidence interval based on two one-sided test for the difference between REF and TEST LEAST SQUARES mean values expressed as a percentage of REF.

Table 79: Amlodipine PK parameter values following coadministration of single amlodipine 10mg and 80 mg atorvastatin fastring and with a high fat meal.

Table 10. Summary (N = 40) of Amlodipine Pharmacokinetic Parameter Values Following Administration of Single Amlodipine (10 mg)/Atorvastatin (80 mg) Combination Tablets to Subjects Under Fasting Conditions (Reference) and With a High-Fat Meal (Test) (Study A3841007)

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 106.5

* Geometric mean

Parameters are described in Table 5.

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Protocol Deviations

Several subjects had Screening clinical laboratory values (Section 9.3.11) slightly the ranges specified in Section 3.3.1, Inclusion Criteria. These minor variances were considered by the Investigator to be unimportant in the context of the study and these subjects were allowed to enter the study.

A total of 88 treatment-emergent adverse events were reported by 35 of the 40 subjects. Thirty-seven adverse events reported by 22 subjects were considered to be treatment- associated. During administration of the amlodipine/atorvastatin combination tablet under fed conditions, 33 treatment-emergent adverse events were reported by 22 of the 40 subjects. Twelve of these, reported by 11 subjects, were considered to be treatment- associated. During administration of the amlodipine/atorvastatin combination tablet under fasted conditions 55 treatment-emergent adverse events were reported by 30 of the 40 subjects. Twenty-five of these, reported by 17 subjects, were considered to be treatment-associated.

There were no adverse events of severe intensity, withdrawals due to adverse events, deaths, or serious adverse events .

Adverse events occurred with the greatest frequency in the body as a whole and the digestive and nervous systems. The most frequently reported adverse events were **headache** (23 subjects, treatment-associated in 19 subjects), **somnolence** (5 subjects, treatment-associated in 3 subjects), and back pain, infection, and pain (5 subjects each, treatment-associated in 0 subjects each). The only other treatment-associated adverse event experienced by more than 1 subject was nausea, experienced by 2 subjects. Log transformed data table on page 88 for 10/80 fed and fasting.

Table 80: Summary of Adverse events by body system A 3841007

Table 8. Summary of TESS Adverse Events by Body System (Study A3841007)
(Number [%] of Subjects)

Body System[a] Adverse Event	1 × 10-mg Amlodipine/80-mg Atorvastatin Combination Tablet, Fed (N = 40)	1 × 10-mg Amlodipine/80-mg Atorvastatin Combination Tablet, Fasted (N = 40)	Total 10 mg Amlodipine/80 mg Atorvastatin (N = 40)
Body as a Whole	19 (47.5)	25 (62.5)	30 (75.0)
Headache	14 (35.0)	17 (42.5)	23 (57.5)
Back Pain	1 (2.5)	4 (10.0)	5 (12.5)
Infection	3 (7.5)	4 (10.0)	5 (12.5)
Pain	1 (2.5)	4 (10.0)	5 (12.5)
Accidental Injury	2 (5.0)	1 (2.5)	3 (7.5)
Abdominal Pain	1 (2.5)	0 (0.0)	1 (2.5)
Asthenia	1 (2.5)	0 (0.0)	1 (2.5)
Chills	0 (0.0)	1 (2.5)	1 (2.5)
Neck Pain	0 (0.0)	1 (2.5)	1 (2.5)
Digestive System	3 (7.5)	4 (10.0)	7 (17.5)
Dyspepsia	2 (5.0)	1 (2.5)	3 (7.5)
Nausea	0 (0.0)	2 (5.0)	2 (5.0)
Diarrhea	0 (0.0)	1 (2.5)	1 (2.5)
Dry Mouth	1 (2.5)	0 (0.0)	1 (2.5)
Vomiting	0 (0.0)	1 (2.5)	1 (2.5)
Nervous System	3 (7.5)	4 (10.0)	6 (15.0)
Somnolence	1 (2.5)	4 (10.0)	5 (12.5)
Dizziness	1 (2.5)	0 (0.0)	1 (2.5)
Insomnia	1 (2.5)	0 (0.0)	1 (2.5)
Respiratory System	2 (5.0)	2 (5.0)	4 (10.0)
Pharyngitis	2 (5.0)	1 (2.5)	3 (7.5)
Rhinitis	0 (0.0)	1 (2.5)	1 (2.5)
Sinusitis	0 (0.0)	1 (2.5)	1 (2.5)
Musculoskeletal System	1 (2.5)	1 (2.5)	2 (5.0)
Myalgia	1 (2.5)	1 (2.5)	2 (5.0)
Skin and Appendages	0 (0.0)	2 (5.0)	2 (5.0)
Rash	0 (0.0)	2 (5.0)	2 (5.0)
Cardiovascular System	0 (0.0)	1 (2.5)	1 (2.5)
Migraine	0 (0.0)	1 (2.5)	1 (2.5)
Special Senses	0 (0.0)	1 (2.5)	1 (2.5)
Ear Pain	0 (0.0)	1 (2.5)	1 (2.5)

[a] Total for a given body system may be less than the combined number of subjects reporting individual AEs because an individual subject may have more than one AE in a body system

5.1.1.4. Deaths No deaths occurred during this study.
5.1.1.5. Serious Adverse Events No serious adverse events occurred during this study.
5.1.1.6. Withdrawals Due to Adverse Events No withdrawals due to adverse events occurred during this study.

Table 81Summary of Adverse events by body system (A3841007)

Table 9. Summary of TESS Associated[a] Adverse Events by Body System (Study A3841007) (Number [%] of Subjects)

Body System[b] Adverse Event	1 × 10-mg Amlodipine/80-mg Atorvastatin Combination Tablet, Fed (N = 40)	1 × 10-mg Amlodipine/80-mg Atorvastatin Combination Tablet, Fasted (N = 40)	Total 10 mg Amlodipine/80 mg Atorvastatin (N = 40)
Body as a Whole	9 (22.5)	15 (37.5)	19 (47.5)
Headache	9 (22.5)	15 (37.5)	19 (47.5)
Asthenia	1 (2.5)	0 (0.0)	1 (2.5)
Chills	0 (0.0)	1 (2.5)	1 (2.5)
Nervous System	2 (5.0)	2 (5.0)	4 (10.0)
Somnolence	1 (2.5)	2 (5.0)	3 (7.5)
Dizziness	1 (2.5)	0 (0.0)	1 (2.5)
Digestive System	0 (0.0)	2 (5.0)	2 (5.0)
Nausea	0 (0.0)	2 (5.0)	2 (5.0)
Vomiting	0 (0.0)	1 (2.5)	1 (2.5)

[a] Considered by the investigator to be related to treatment

[b] Total for a given body system may be less than the combined number of subjects reporting individual AEs because an individual subject may have more than one AE in a body system.

Table 82: Summary of statistical analysis of amlodipine PK parameter values (A3841007)

Table 1. Summary of Statistical Analysis of Amlodipine Pharmacokinetic Parameter Values: Protocol A3841007

Parameter	p-Value Period	Sequence[a]	Group[a]	Treatment	RMSE[b]
LnCmax	0.236	0.0374*	0.412	0.189	0.154
LnAUC(0-∞)	0.508	0.0716	0.631	0.592	0.103
LnAUC(0-tlqc)	0.155	0.0660	0.764	0.280	0.108
tmax	0.0622	0.589	0.748	0.308	1.51
λz	0.0696	0.708	0.588	0.542	0.00205
t½	0.0736	0.476	0.568	0.897	9.38
Cmax	0.269	0.0226*	0.370	0.242	1.31
AUC(0-∞)	0.654	0.0674	0.627	0.645	38.1
AUC(0-tlqc)	0.218	0.0651	0.802	0.286	34.7

[a] = Derived from Subject (Sequence*Group) error term

[b] = Root Mean Square Error derived from Mean Square Error

[c] = Statistical significance determined to be inconsequential

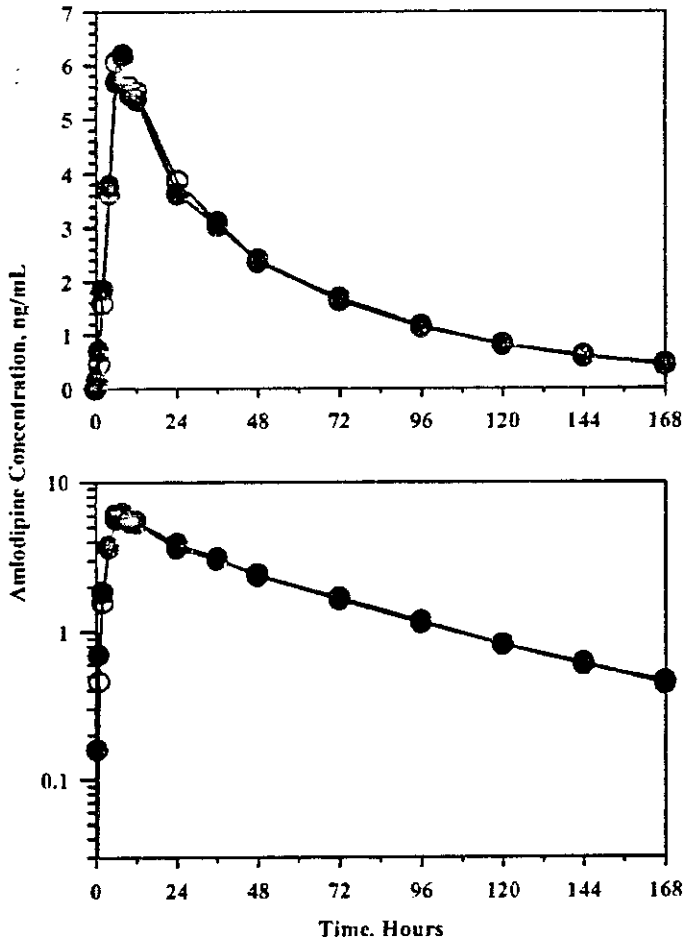


Figure 1. Mean Amlodipine Plasma Concentration-Time Profiles Following Administration of Single Amlodipine (10 mg)/Atorvastatin (80 mg) Combination Tablets to Subjects Under Fasting Conditions (Filled Circles) and With a High-Fat Meal (Open Circles) (Study A3841007)

Upper and lower panels are linear and semi-logarithmic plots, respectively.

Table 83Log transformed value differences comparing 10/80 combination with a high fat meal and fasting

Table 3 Summary of Statistical Evaluations for Amlodipine Log Transformed Parameter Value Differences Comparing 10/80 Combination Tablets Administered with a High-Fat Meal (TEST) and Fasting (REF): Protocol A3841007

	LEAST SQUARES Mean Values		Difference	
Parameter	REF	TEST	(% REF)	90% Confidence Intervals
Cmax	6.14	6.43	4.7%	98.8% to 111.0%
AUCtime	298	306	2.7%	98.6% to 107.0%
AUCinf	336	340	1.2%	97.4% to 105.3%

Mean values are antilogs of log transformed LEAST SQUARES values
Difference = Difference between reference and Test treatment LEAST SQUARES mean values.
90% Confidence Interval = Confidence interval based on two one-sided test for the difference between REF and TEST LEAST SQUARES mean values expressed as a percentage of REF.

A 3841007

Figure 8: Mean plasma atorvastatin equivalent concentrations vs Time following co administration with and without 10 mg amlodipine

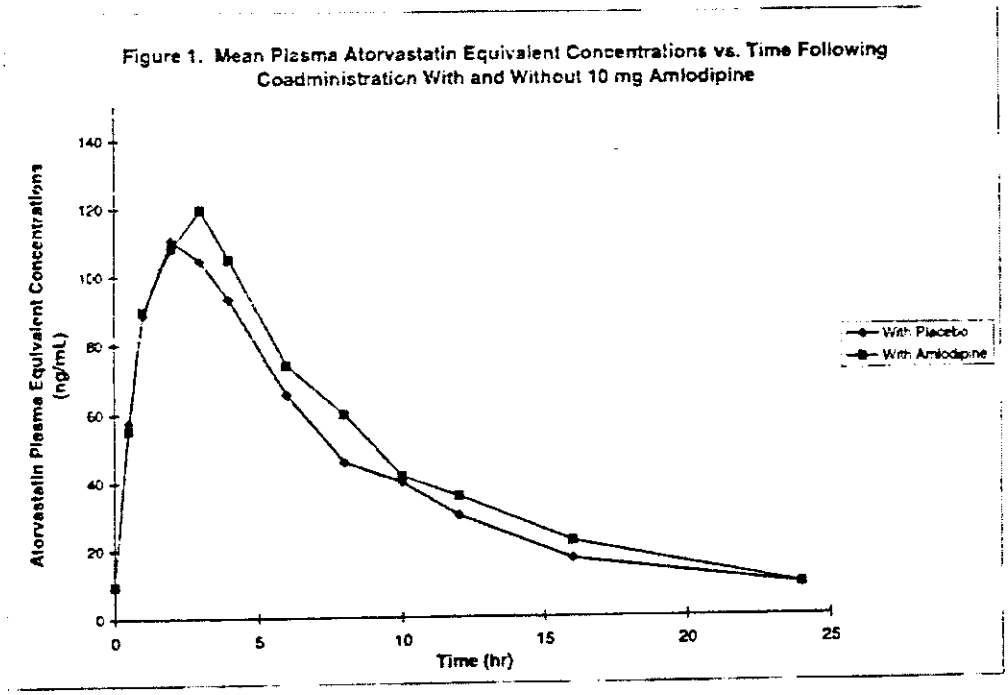


Figure 9: Mean atorvastatin plasma concentration-time profiles following single amlodipine 10/80 mg combined under fasting and high fat meal

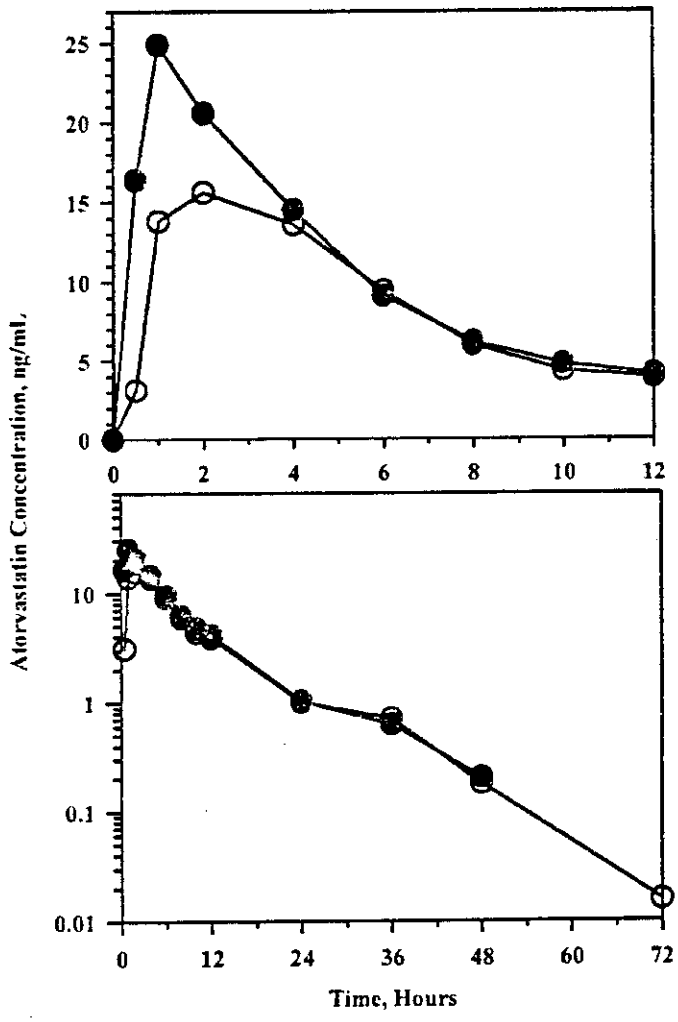


Figure 3. Mean Atorvastatin Plasma Concentration-Time Profiles Following Administration of Single Amlodipine (10 mg)/Atorvastatin (80 mg) Combination Tablets to Subjects Under Fasting Conditions (Filled Circles) and With a High-Fat Meal (Open Circles) (Study A3841007)

Upper and lower panels are linear and semi-logarithmic plots, respectively. Time scale on lower panel expanded to illustrate t½.

Table 84 Atorvastatin PK values following administration of single 10/80 combination under fasting and high fat meal.

Table 11. Summary (N = 40) of Atorvastatin Pharmacokinetic Parameter Values Following Administration of Single Amlodipine (10 mg)/Atorvastatin (80 mg) Combination Tablets to Subjects Under Fasting Conditions (Reference) and With a High-Fat Meal (Test) (Study A3841007)

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
$T_{1/2}$, hr	14.9	19.4	130	102.2 to 158.3

* Geometric mean

Parameters are described in Table 5.

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test reference) of treatment mean values, expressed as a percentage of the reference mean.

DISCUSSION

The amlodipine (10 mg)/atorvastatin (80 mg) combination tablet formulation was well-tolerated by healthy volunteers whether administered fasting or with a high-fat meal.

Administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal had no effect on amlodipine pharmacokinetic profiles. The 90% confidence intervals for the ratio of treatment geometric mean amlodipine Cmax and AUC(0-) values were both within the 80% to 125% range indicating absence of an effect of a high-fat meal and establishing equivalence of treatments. This result is the same as the finding that food has no effect on the bioavailability of Norvasc.

Administration of combination tablets with a high-fat meal delayed the mean atorvastatin tmax value approximately 1 hour and decreased the mean Cmax value nearly 32%. The 90% confidence interval for the ratio of geometric mean atorvastatin Cmax values was outside of the 80% to 125% range indicating an effect of a high-fat meal on atorvastatin Cmax values. The 90% confidence interval for the ratio of treatment geometric mean atorvastatin AUC(0-) values, on the other hand, was within the 80% to 125% range indicating absence of a food effect on the extent of atorvastatin absorption. The results are similar to the food effect on the rate (25%) and extent (9%) of absorption, as assessed by Cmax and AUC for 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 decreases the rate and extent of atorvastatin absorption by 32% and 11%, respectively, as assessed by Cmax and AUC(0-).

Cmax value following administration of combination tablets with food was 32% lower than that under fasting conditions. The 90% confidence interval for the ratio of treatment geometric mean Cmax values was outside of the 80% to 125% range.

Based on AUC (0-∞) values, extent of atorvastatin absorption following administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal was similar to that observed under fasting conditions. The mean atorvastatin AUC (0-∞) value following administration of combination tablets with food was approximately 11% lower than that under fasting conditions. The 90% confidence interval for the ratio of treatment geometric mean AUC (0-∞) values was within the 80% to 125% range.

Discussion: The amlodipine (10 mg)/atorvastatin (80 mg) combination tablet formulation was well-tolerated by healthy volunteers whether administered with food or fasting.

Administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal had no effect on amlodipine pharmacokinetic profiles. The 90% confidence intervals for the ratios of treatment geometric mean amlodipine Cmax and AUC (0-∞) values were both within the 80% to 125% range indicating absence of an effect of a high-fat meal and establishing equivalence of treatments. This result is the same as the finding that food has no effect on the bioavailability of Norvasc® (product labeling).

Administration of combination tablets with a high-fat meal delayed the mean atorvastatin tmax value approximately 1 hour and decreased the mean Cmax value nearly 32%. The 90% confidence interval for the ratio of geometric mean atorvastatin Cmax values was outside of the 80% to 125% range indicating an effect of a high-fat meal on atorvastatin Cmax values. The 90% confidence interval for the ratio of geometric mean atorvastatin AUC(0-) values, on the other hand, was within the 80% to 125% range indicating absence of a food effect on the extent of atorvastatin absorption. The results are similar to the food effect on the rate (25%) and extent (9%) of absorption, as assessed by Cmax and AUC for Lipitor® (product labeling).

Conclusion(s): Administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal has no effect on amlodipine Mean Cmax value following administration of combination tablets with food was 32% lower than that under fasting conditions. The 90% confidence interval for the ratio of treatment geometric mean Cmax values was outside of the 80% to 125% range.

Based on AUC(0-∞) values, extent of atorvastatin absorption following administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal was similar to that observed under fasting conditions. The mean atorvastatin AUC(0-∞) value following administration of combination tablets with food was approximately 11% lower than that under fasting conditions. The 90% confidence interval for the ratio of treatment geometric mean AUC(0-) values was within the 80% to 125% range.

Discussion: The amlodipine (10 mg)/atorvastatin (80 mg) combination tablet formulation was well-tolerated by healthy volunteers whether administered with food or fasting.

Administration of amlodipine (10 mg)/atorvastatin (80 mg) combination tablets with a high-fat meal had no effect on amlodipine pharmacokinetic profiles. The 90% confidence intervals for the ratios of treatment geometric mean amlodipine Cmax and AUC(0-∞) values were both within the 80% to 125% range indicating absence of an effect of a high-fat meal and establishing equivalence of treatments. This result is the same as the finding that food has no effect on the bioavailability of Norvasc® (product labeling).

Administration of combination tablets with a high-fat meal delayed the mean atorvastatin tmax value approximately 1 hour and decreased the mean Cmax value nearly 32%. The 90% confidence interval for the ratio of geometric mean atorvastatin Cmax values was outside of the 80% to 125% range indicating an effect of a high-fat meal on atorvastatin Cmax values. The 90%

confidence interval for the ratio of geometric mean atorvastatin AUC(0-∞) values, on the other hand, was within the 80% to 125% range indicating absence of a food effect on the extent of atorvastatin absorption. The results are similar to the food effect on the rate (25%) and extent (9%) of absorption, as assessed by Cmax and AUC for Lipitor® (product labeling).

Conclusion(s): 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 decreases the rate and extent of atorvastatin absorption by 32% and 11%, respectively, as assessed by Cmax and AUC(0-∞).

Results of pivotal bioequivalence studies comparing 5/ 10- mg and 10/ 80- mg combination tablets versus Norvasc and Lipitor tablets taken together in matching doses are summarized below and results of a pivotal study comparing bioavailability of the 10/ 80- mg combination tablet under fed versus fasted conditions are also summarized below Results of comparative bioavailability studies using prototype formulations are summarized below and details of these studies are in Biopharm review.

In Study A3841007, the 10/80-mg combination tablet taken under fed conditions (immediately after a high-fat breakfast) was bioequivalent for amlodipine relative to the same tablet taken under fasting conditions (after the first 10 hours of a 14-hour fast); 90% confidence intervals for test (fed)/reference (fasting) ratios of geometric mean amlodipine Cmax and AUC fell within bioequivalence limits of 80% to 125%, indicating no significant effect of food on the bioavailability of amlodipine (Table 3). This result is consistent with the finding of no food effect on amlodipine bioavailability described in the Norvasc package insert.

For atorvastatin, taking the 10/80-mg combination tablet under fed conditions reduced the rate of absorption and overall exposure relative to the same tablet taken under fasting conditions, but only the reduction in rate of absorption was statistically significant: geometric mean atorvastatin Cmax and AUC(0-∞) were 32% and 11% lower, respectively, but only the Cmax reduction resulted in a 90% confidence interval for test/reference ratio (60% to 79%) that fell outside bioequivalence limits (80% to 125%). These food effects are comparable to the respective 25% (statistically significant) and 9% (not statistically significant) reductions in atorvastatin Cmax and AUC(0-∞) that result when Lipitor is taken with food, as indicated in the Lipitor package insert. For Lipitor, these food effects on atorvastatin Cmax and AUC(0-∞) did not reduce lipid-lowering efficacy and were therefore not clinically significant.

Table 3. Pharmacokinetic Analysis: Pivotal Food-Effect Study A3841007

Study ID, Combination		Least-Squares Mean Values		Ratio	90% CI
Assay Drug	Parameter	Reference	Test	(%)	(%)
A3841007, Amlodipine/Atorvastatin 10/80 mg					
Amlodipine	n	40	40		
	Cmax, ng/mL	6.14	6.43	105	98.8 to 111.0
	tmax, hr	8.15	7.80	95.7	N/A
	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
Atorvastatin	n	40	40		
	Cmax, ng/mL	29.5	20.1	68.1	59.5 to 78.7
	tmax, hr	1.38	2.53	183	N/A
	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

Reference = Combination tablet taken under fasting conditions; Test = Combination tablet taken under fed conditions; Ratio = Ratio of treatment mean values (100% x test/reference); 90% CI = 90% confidence interval estimate for the ratio of treatment mean values; n = numbers of subjects who provided pharmacokinetic data; Cmax = Maximum plasma concentration (geometric mean); tmax = Time to Cmax; AUC(0-tlqc) = Area under plasma concentration-time profile from zero to time for last quantifiable concentration (geometric mean); AUC(0-∞) = area under plasma concentration-time profile from zero to infinity (geometric mean); t½ = terminal half-life; N/A = Not applicable.

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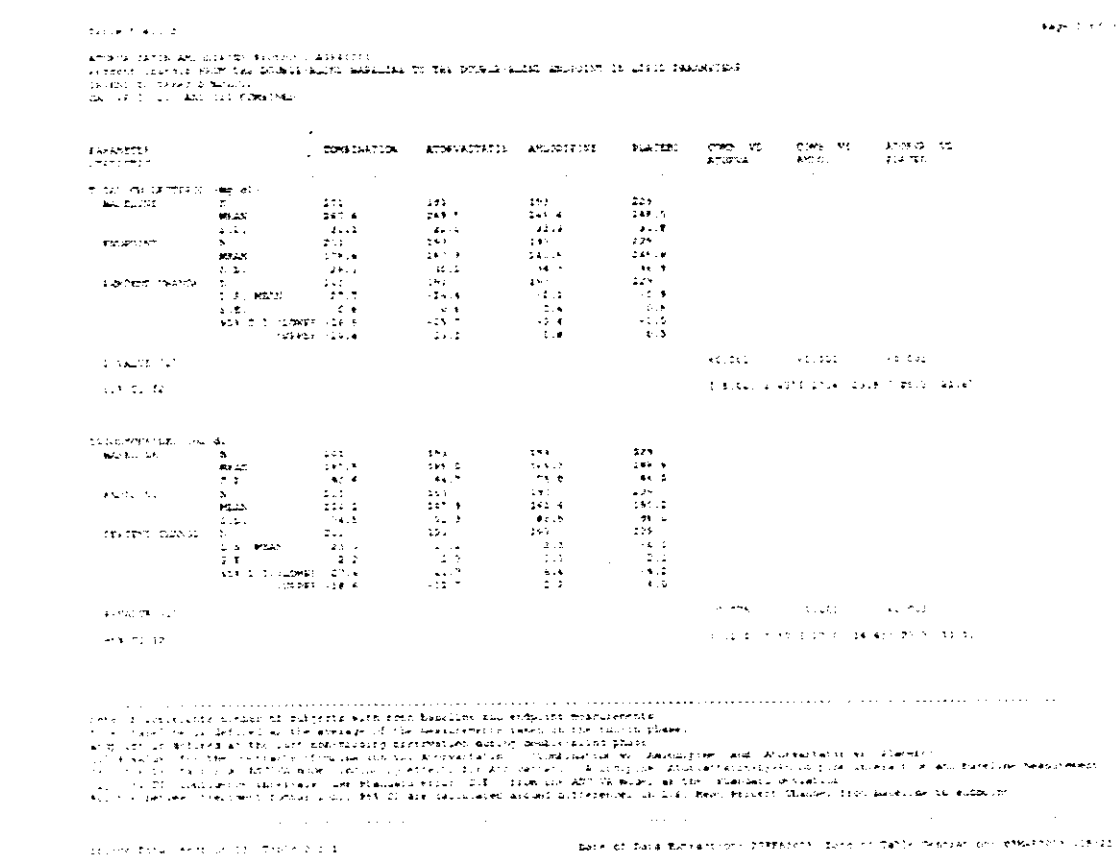

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13.0 Appendix

Appendix 1 : Listing of Protocol Amendments to NDA 21540

1.1 Amended Protocol 3 08-Nov-2002

1.2 Amended Protocol 2 17-May-2002

1.3 Amended Protocol 1 29-Oct-2001

1.4 Global Protocol 01-Oct-2001

1.5 Canadian Amended Protocol 5 13-Dec-2002 - IRB Services Amendment 5a 18-Feb-2003 (Global Amendment 3 08-Nov-2002)

1.6 Canadian Amended Protocol 5 13-Dec-2002 (Global Amendment 3 08-Nov-2002)

1.7 Canadian Amended Protocol 4 23-Jul-2002

1.8 Canadian Amended Protocol 3 18-Jun-2002

1.9 Canadian Amended Protocol 2 11-Dec-2001

1.10 Finland Protocol Amendment 1 3-May-2002

1.11 Ireland Protocol Amendment 1 12-Aug-2002

1.12 UK Protocol Amendment 1 31-Jan-2002

Appendix 2: Narratives for serious adverse events and deaths- CADUET Program

Subject ID: 1069- 0518 AER Case No.: 2002061337

This 68- year- old White male received double- blind, double- dummy amlodipine 5 mg and atorvastatin 10 mg once daily from 11 Jul 2002 to 05 Sep 2002 (57 days).

On [redacted] during the end- of- study physical, the subject's enlarged thyroid gland was palpated. An ultrasound of the thyroid was performed on [redacted] and it revealed multiple nodules in the right lobe, each measuring approximately 1 cm in size. The left lobe also had a multinodular appearance with two discrete nodes, one approximately 2 cm and the other approximately 3 cm. A radionuclide scan was suggested, and on [redacted] a thyroid uptake and scan was performed and revealed at least two to three cold nodules in the left lobe and one cold nodule in the right upper pole. There were no hot nodules. The total iodine uptake was normal. A fine needle biopsy of the nodules was performed on [redacted] Pathology results

revealed thyroid carcinoma. The subject was hospitalized, and on [redacted] a thyroidectomy was performed, revealing that the thyroid nodule was not cancerous.

No action was taken with the study medication in response to the serious adverse event thyroid nodule, a post- therapy event. In the investigator's judgment, the cause of the thyroid nodule was unknown, but not related to the study medication.

Medical problems present at study entry included benign prostatic hypertrophy, erectile dysfunction, gastroesophageal reflux disease, and seasonal allergies. Past medical history included benign schwannoma of the right carotid artery bifurcation.

Concomitant medications included acetylsalicylic acid, lansoprazole, tamsulosin hydrochloride, cetirizine hydrochloride, rofecoxib, and hydrochlorothiazide.

Subject ID: 1085- 0122 AER Case No.: 2002055155

This 51- year- old white male received double- blind, double- dummy amlodipine 10 mg and atorvastatin 20 mg once daily from 19 Jul 2002 to 27 Aug 2002 (48 days).

The subject experienced angina from 24 Aug 2002 (Day 37 of treatment) to 27 Aug 2002, and on [redacted] was admitted to the hospital with left arm pain, left chin pain, nausea, vomiting and diaphoresis. On [redacted] an electrocardiogram revealed myocardial infarction; troponin I was 208 (units and normal range unspecified), and creatine phosphokinase- MB was 2300 U/ L (normal range unspecified). The subject was treated with 50 mg of tissue plasminogen activator, and a cardiac catheterization on [redacted] revealed an occluded obtuse margin (OM) at a branch of the dominant

circumflex coronary artery and a 70% occluded right coronary artery. The OM was opened and a stent was placed. The subject was considered recovered on [redacted], and was discharged from the hospital.

Study medication was permanently discontinued on [redacted] due to myocardial infarction.

According to the investigator the serious adverse event, myocardial infarction, represented a complication of the disease under investigation and was unrelated to the study medication. The angina, left arm pain, left chin pain, nausea, vomiting, and diaphoresis were considered nonserious symptoms of myocardial infarction.
Medical problems present at study entry included smoking.

The only concomitant medication reported was salbutamol.

Subject ID: 1041- 0151 AER Case No.: 2002065125

This 73- year- old white male with a history of hypothyroidism, rectal bleeding, and hemorrhoids received double- blind, double- dummy amlodipine 10 mg and atorvastatin 10 mg once daily from 30 Sep 2002 to 30 Oct 2002 (31 days).

The subject experienced abdominal pain on 27 Oct 2002 (Day 28 of treatment) and diarrhea on 30 Oct 2002, and was admitted to the hospital on [redacted] Computed tomography of the abdomen on [redacted] was essentially negative but revealed a dilated colon, especially on the right side, with no sign of acute disease. Blood cultures [redacted], and [redacted] were negative, but red blood cell count, hematocrit, hemoglobin, lymphocytes and neutrophils on [redacted] were abnormal and the subject was diagnosed with

ischemic colitis. The ischemic colitis was considered resolved on [redacted], and the following day, [redacted] the subject was discharged home with medications (oral metronidazole and ciprofloxacin).

Study medication was permanently discontinued on 30 Oct 2002 in response to the event.

According to the investigator the serious adverse event, ischemic colitis, most likely represented an intercurrent illness and was unrelated to the study medication; the abdominal pain on 27 Oct 2002 was considered a nonserious symptom of ischemic colitis. The diarrhea on 30 Oct 2002 and the abnormal blood cell counts and values for hematocrit and hemoglobin while the subject was hospitalized were also considered not serious.

Medical problems present at study entry included headaches, benign prostatic hypertrophy, and hearing loss.

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No concomitant medications were reported at the onset of ischemic colitis; while hospitalized the subject was treated with cefotetan, intravenous fluids, metronidazole, and ciproflaxacin.

Subject ID: 1251- 0481 AER Case No.: 2002067241

This 42- year- old white female with a history of kidney stone, cholecystectomy, and appendicitis received double- blind, double- dummy amlodipine 10 mg and atorvastatin 80 mg once daily from 15 Oct 2002 to 24 Oct 2002 (10 days).

The subject experienced left kidney pain on 24 Oct 2002 (Day 10 of treatment) and nausea and abdominal pain on 25 Oct 2002. On [redacted] computed tomography revealed an obstruction of the uteropelvic junction that (UPJ) that had progressed since Apr 2000 and was now moderately severe; the same computed tomography also revealed descending and sigmoid colon diverticulitis. The subject was hospitalized for surgery on [redacted] that included kidney cyst removal to treat the worsening UPJ obstruction and partial colon resection to treat diverticulitis; both conditions were considered resolved after surgery. It was not reported whether or when the subject was discharged from the hospital.

Study medication was permanently discontinued on 24 Oct 2002 due to the worsening UPJ obstruction and diverticulitis.

According to the investigator, the cause of the serious adverse event worsening UPJ obstruction was the subject's history of UPJ obstruction, and the cause of the serious adverse event diverticulitis was unknown; both events were considered unrelated to the study medication. The left kidney pain was considered a nonserious symptom of worsening UPJ obstruction, and the nausea and abdominal pain were considered nonserious symptoms of diverticulitis. The kidney cyst was also considered nonserious.

Medical problems present at study entry included UPJ obstruction and sinusitis.

The only concomitant medication reported was levofloxacin

Subject ID: 1088- 0019 AER Case No.: 2002067807

This 70- year- old white female with a history of angina, myocardial infarction, arthritis (including bilateral knee replacement), hysterectomy, and venous leg vein stripping received double- blind, double- dummy amlodipine 10 mg and atorvastatin 80 mg once daily from 09 Jul 2002 to 04 Sep 2002 (58 days).

In Jul 2002 (exact date/ study day of treatment unknown) the subject experienced left knee swelling and increased left knee pain with clicking. X- ray revealed lucency along the tibia, fracture in the cement line, and windshield wiping of the stem indicating a loose tibial component. On [redacted] the subject had a needle aspiration to remove fluid from

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the left knee; cytology revealed no evidence of infection, and the subject's symptoms improved. In Sep 2002 (exact date unknown) the subject experienced increasing discomfort in her left knee that was later diagnosed as failed total left knee replacement. On [redacted] the subject was admitted to hospital for a revision of the left knee arthroplasty. The subject's post- operative recovery was uneventful and she was discharged from the hospital on 28 Sep 2002. The subject continued physical therapy after discharge and was considered recovered on 07 Nov 2002 when she could walk without a cane.

No action was taken with respect to study drug in response to this event. The subject went on to complete the study and took her last dose of study medication on 04 Sep 2002; on 06 Sep 2002 the subject was started on commercial amlodipine by her physician.

According to the investigator the cause of the serious adverse event, joint disorder, was failed left total knee replacement arthroplasty unrelated to the study medication. The left knee swelling, increased left knee pain, and clicking during Jul 2002 were considered signs of the failed left knee replacement and were not considered serious, as were the lucency along the tibia, fracture in the cement line, and windshield wiping of the stem indicating a loose tibial component, as observed by X- ray. The left knee fluid removal [redacted] was also considered nonserious.

Medical problems present at study entry included hiatal hernia, hypothyroidism, migraine headaches (with nausea and vomiting), allergies, osteoporosis, arthritis (cervical discs), neuropathy (feet), and bladder spasms.

Concomitant medications included levothyroxine sodium, tolterodine l- tartrate, estrogens conjugated, gabapentin, esomeprazole, ibuprofen, pyridoxine hydrochloride, tocopherol, ascorbic acid, multivitamins, and calcium.

Subject ID: 1017- 2733 AER Case No.: 2002058391

This 45- year- old Asian male received double- blind, double- dummy amlodipine 10 mg and atorvastatin 20 mg once daily beginning on 14 Sep 2002 to 12 Nov 2002.

On [redacted] (Day [redacted] of treatment) the subject experienced hematuria and urinary hesitancy and was admitted to hospital for investigation. Pelvic and abdominal ultrasound [redacted] showed a mass lesion (kidney stone) protruding into the left side of the bladder just superior to the level of the prostate. During cystoscopy performed [redacted] the kidney stone present in the bladder was crushed, and the remnants of the kidney stone were subsequently passed. There was some inflammatory reaction around the kidney stone, but no tumors were visible. The subject was considered recovered on [redacted], and was discharged from the hospital the same day.

No action was taken with study medication in response to this adverse event.

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According to the investigator the serious adverse events, hematuria, urinary hesitancy, and kidney stone, represented an intercurrent illness other than the disease under study and were unrelated to the study medication.

Medical problems present at study entry included drug allergy (paracetamol) and ischemic heart disease.

Concomitant medications included acetylsalicylic acid, and the subject received oral ciprofloxacin from 23 Sep 2002 to 27 Sep 2002.

Subject ID: 1144- 1640 AER Case No.: 2002061203

This 53- year- old male (race unspecified) with a history of atypical malaise and atypical angina pectoris received double- blind, double- dummy amlodipine 5 mg and atorvastatin 20 mg once daily beginning on 26 Aug 2002 to 22 Oct 2002.

On [redacted] (Day [redacted] of treatment) the subject was hospitalized for atypical chest pain, from which he recovered the same day. On [redacted] the subject, while still hospitalized, experienced a single episode of postural hypotension, from which he recovered the same day but which led to prolongation of hospitalization until [redacted]. Examinations performed during hospitalization were normal: ECG without modification; no elevated cardiac enzymes for 3 days; stress test clinically and electrically negative at 120 watt; and stress cardiac echography with no sign of myocardial ischemia. The atypical chest pain was considered resolved on 15 Sep 2002, and the postural hypotension was considered resolved on 17 Sep 2002.

Study medications were temporarily discontinued due to these adverse events (date unknown), and postural hypotension did not recur when blinded study medications were reintroduced (date unknown); the subject continued in the study with no further change to study medication regimen.

According to the investigator the serious adverse event atypical chest pain was most likely related to stress and depression and not related to study medication. The subject was known to have experienced atypical malaise and atypical thoracic pain in the context of previous stress and depression. The investigator considered the serious adverse event postural hypotension to be related to amlodipine taken as study medication.

Medical problems present at study entry included gastritis and depression.

Concomitant medications included fluoxetine, lysine acetylsalicylate, glyceryl trinitrate, paracetamol, omeprazole, alprazolam, zolpidem, and etifoxine.

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Subject ID: 1086- 1400 AER Case No.: 2002065731

This 74- year- old white male with a history of myocardial infarction, angioplasty with stent, and coronary artery bypass graft received double- blind, double- dummy amlodipine 10 mg and atorvastatin, 40 mg once daily from 04 Nov 2002 to 30 Dec 2002 (57 days).

On [redacted] (Day [redacted] of treatment) the subject experienced fever and chills and subsequently had a syncopal episode resulting in a fall. The subject was admitted to the hospital and diagnosed with urinary sepsis, bladder infection, and syncopal episode. The syncopal episode resolved on 05 Nov 2002 and the urinary sepsis resolved on 07 Nov 2002; it was not reported whether or when the subject was discharged from the hospital.

No action was taken with study medication in response to these adverse events.

According to the investigator the cause of the serious adverse event urinary sepsis was other illness, bacterial (nonserious). The syncopal episode and bladder infection were considered, respectively, serious and nonserious symptoms of urinary sepsis; the fever, chills, and fall were

also considered nonserious. The urinary sepsis was considered by the investigator to be unrelated to study medication.

Medical problems present at study entry included diabetes, arthritis (shoulder), leg cramps, leg weakness, diabetic neuropathy, lower back pain, recent prostate surgery, Achilles tendonitis, depression, gastritis, urethral dilation, and mild Alzheimer's disease.

Concomitant medications included glipizide, metformin, rosiglitazone maleate, fluoxetine hydrochloride, valdecoxib, acetylsalicylic acid, donepezil hydrochloride, quinidine sulfate, ranitidine hydrochloride, esomeprazole, multivitamins, calcium citrate, folic acid, ubidecarenone, serenoa repens, pycnogenol, ginkgo tree leaf extract, cortisone, terbinafine hydrochloride, tolterodine l- tartrate, and insulin glargine.

Subject ID: 1275- 4298 AER Case No.: 2003000044

This 47- year- old female (race unspecified) received double- blind, double- dummy amlodipine 10 mg and atorvastatin 40 mg once daily from 27 Nov 2002 to 01 Jan 2003 (35 days).

The subject consulted a dentist for mouth pain (date unknown) and was referred to a surgeon for biopsy; on [redacted] (Day [redacted] of treatment) biopsy revealed epidermoid carcinoma. The subject was hospitalized on [redacted] for removal of the endobuccal epidermoid carcinoma (tumor of buccal floor, gradeT2N0). Removal was complete, and no further treatment was introduced; the subject was not yet considered recovered at the time of the last report.

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Study medication was permanently discontinued on 02 Jan 2003 in response to the epidermoid carcinoma of buccal cavity.

According to the investigator the serious adverse event, epidermoid carcinoma, most likely represented an intercurrent illness and was not related to the study medication.

Medical problems present at study entry included type II diabetes.

Concomitant medications included levonorgestrel, ethylestradiol, metformin and eugynon.

Subject ID: 1009- 2878 AER Case No.: 2003001099

This 53- year- old white female received double- blind, double- dummy amlodipine 5 mg and atorvastatin 40 mg once daily from 02 Dec 2002 to 04 Jan 2003 (33 days).

On [redacted] (Day [redacted] of treatment) the subject experienced retrosternal pain, dyspnea, sweating, and malaise and went to emergency room; electrocardiogram (ECG) and enzymes (unspecified) were normal. On [redacted] the subject presented with dyspnea and malaise again and was hospitalized for acute inferior wall myocardial infarction; ECG and LDH (469 U/ L, normal is <480) were normal and aspartate aminotransferase (220 U/ L, normal range 10- 39 U/ L), creatine phosphokinase (1991 U/ L, normal range 26- 189 U/ L), and creatine phosphokinase-MB (260 U/ L, normal is <25 U/ L) were high. Coronary angiography detected 100% obstruction in the right coronary artery, and the subject underwent coronary angioplasty with stent implantation. The subject was discharged from hospital on [redacted] and was considered recovered that same day.

The subject was not discontinued from the study in response to this adverse event. However, the last dose of study medication was taken on 04 Jan 2003, and the subject was noncompliant with study medication regimen thereafter.

According to the investigator the serious adverse event, myocardial infarction, most likely represented intercurrent coronary disease and was unrelated to study medication. The retrosternal pain, dyspnea, sweating, and malaise were not considered serious.

Medical problems present at study entry included coronary artery disease and systemic arterial hypertension.

No concomitant medications were reported.

Subject ID: 1219- 4532 AER Case No.: 2003009253

This 61- year- old white male with a history of acute myocardial infarction received double- blind, double- dummy amlodipine 10 mg and atorvastatin 40 mg once daily from 13 Jan 2003 to 10 Mar 2003 (57 days).

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Beginning on 24 Feb 2003 (Day 43 of treatment), the subject experienced cough, weakness, excess perspiration, shortness of breath, and mild pyrexia. On [redacted] an X- ray of the lungs revealed inflammatory infiltration of the back and lateral regions of the right lung; the subject was hospitalized on [redacted] with a diagnosis of pneumonia (lower lobe right lung). An X- ray on [redacted] showed no inflammation in the lungs; the subject was considered recovered on [redacted] and was discharged from the hospital the same day.

No action was taken with study medication in response to this adverse event, and the subject completed the study per protocol; the last dose of study medication was taken on 10 Mar 2003.

According to the investigator the serious adverse event, pneumonia, most likely represented an intercurrent illness (bacterial infection), and was not related to the study medication.

Medical problems present at study entry included coronary artery disease. Past medical history included acute MI.

While hospitalized from [redacted] to [redacted] the subject received gentamicin intramuscularly, aminophylline and furosemide intravenously, and acetylsalicylic acid orally. No other concomitant medications were reported. Subject ID: 1311- 1446 AER Case No.: 2003021175

This 62- year- old white male with a history of myocardial infarction and constipation received double- blind, double- dummy amlodipine 10 mg and atorvastatin 40 mg once daily from 21 Jan 2003 to 18 Mar 2003 (57 days).

On 18 Mar 2003, the subject experienced nonserious shortness of breath and visited his cardiologist. On [redacted], he was admitted to the hospital to undergo an angiogram and stent replacement. The subject was subsequently diagnosed with worsening coronary artery disease. The EKG and cardiac enzyme results (CK- MB 18.0, range 0.0- 7.0; creatine kinase 327 U/ L, normal value <170 U/ L on 21 Mar 2003 were considered by the investigator to be nonserious events. The subject was discharged from the hospital on [redacted], and the investigator considered the event to be resolved that day.

No action was taken with regard to study medication in response to the event of worsening coronary artery disease. However, the subject has stopped taking the study drug on 18 Mar 2003 and did not enter the extension phase of the study.

According to the investigator the serious adverse event of worsening coronary artery disease most likely represented an intercurrent illness (history of coronary artery disease), and was not related to the study medication.

Medical problems present at study entry included coronary artery disease, hypothyroidism, and benign prostatic hypertrophy.

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The only concomitant medication reported was levothyroxine sodium.

Subject ID: 0007- 1894 AER Case No.: 2003014523

This 64- year- old white female with a history of angina, arrhythmia, cholecystitis, and vertigo received double- blind, double- dummy amlodipine 5 mg and atorvastatin 80 mg once daily from 17 Dec 2002 to 16 Feb 2003 (62 days).

On [redacted] days after the last dose of study drug , the subject was hit by a car and hospitalized the same day with rib fractures, paresthesia of the left arm, lacerations of the forehead, and bruises. The subject was discharged from the hospital on [redacted] , and was scheduled to enter a neurological rehabilitation center on [redacted] The dates of resolution of these adverse events were unknown at the time of the last report.

The subject had completed the course of study medication at the time of the events.

In the opinion of the investigator, the serious adverse events of rib fractures, paresthesia of the left arm, lacerations of the forehead, and bruises were the result of a motor vehicle accident and not related to the study medication.

Medical problems present at study entry included congestive heart failure (CHF).

There were no concomitant medications reported.

Subject ID: 1125- 3955 AER Case No.: 2003024983

This 57- year- old white male with a history of bronchitis, hepatitis A, sinusitis, and wrist fracture received double- blind, double- dummy amlodipine 5 mg and atorvastatin 10 mg once daily starting 02 Jan 2003. The blinded therapy was completed on 27 Feb 2003, and the subject continued with open- label therapy from that day.

On 05 Feb 2003 (Day 35), the subject developed a right inguinal hernia that was diagnosed during a scheduled study visit on 28 Feb 2003 (Day 58). The subject was hospitalized on [redacted] and underwent an operation on [redacted] . He was discharged from the hospital on [redacted] , and the serious adverse event of right inguinal hernia was considered resolved on that date.

No action was taken with regard to study medication in response to the event of right inguinal hernia.

In the opinion of the investigator, the serious adverse event of right inguinal hernia most likely represented an intercurrent illness (abdominal integument weakness) and was not related to the study medication.

Medical problems present at study entry included osteoarthritis and heartburn.

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This 72- year- old white female with a history of chest infection, depression, and hysterectomy received double- blind, double- dummy amlodipine 5 mg once daily from 22 Oct 2002 to 16 Dec 2002 (56 days).

On [redacted], the subject began coughing up dark colored sputum and was hospitalized that day. Gastroenteritis and hypertensive heart disease were diagnosed, and low potassium levels (no values given) were detected. The subject was prescribed bendroflumethazide, atenolol, and potassium salts and discharged from hospital. The serious adverse event of cough was considered resolved on 06 Jan 2003. The event of serious adverse gastroenterisitis resolved but no date was provided in the report, and the serious adverse event of hypertensive heart disease was ongoing as of the last report.

The subject had completed the course of study medication at the time of onset of the events.

The serious adverse events of cough, gastroenteritis, and hypertensive heart disease were considered to represent intercurrent illnesses and were not related to the study medication.

Amlodipine / Atorvastatin Protocol A3841003 12 of 19 Medical problems present at study entry included increased gamma glutamyl transferase levels (no values given). Concomitant medications included bendroflumethazide, atenolol, clarithromycin, trifluoperazine, acetominophen, topical miconazole, topical clotrimazole, paracetamol, and unspecified antihypertensives.

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ATORVASTATIN TREATMENT GROUPS

Subject ID: 1296- 4888 AER Case No.: 2002067633

This 64- year- old white male received double- blind, double- dummy atorvastatin 10 mg once daily from 30 Oct 2002 to 14 Nov 2002 (16 days).

On 02 Nov 2002 the subject had a mild automobile accident, suffering bruised ribs (contusion of right costae) as a consequence. During the following week the subject complained of chest pain on the right side, breathlessness, anorexia, and weight loss. The subject was hospitalized on [redacted], diagnosed with multiple pulmonary emboli, and treated with unspecified anticoagulants. The subject was discharged from the hospital on [redacted] and considered recovered on 22 Nov 2002.

Study medication was permanently discontinued on [redacted] due to the pulmonary embolism.

According to the investigator the serious adverse event, pulmonary embolism, was possibly caused by probable deep venous thrombosis (right) proceeding from the automobile accident, and was unrelated to the study medication; however, no evidence of deep venous thrombosis was reported. The automobile accident, bruised ribs (contusion of right costae), chest pain on the right side, breathlessness, anorexia, weight loss, and probable deep venous thrombosis were not considered serious.

Medical problems present at study entry included hypothyroidism and hay fever.

Concomitant medications included levothyroxine.

Subject ID: 1240- 2163 AER Case No.: 2003002314

The only concomitant medication reported was ranitidine.

Subject ID: 1062- 1373 AER Case No.: 2003010874

This 66- year- old white male with a history of prostatectomy, tobacco use, and a family history of myocardial infarction received double- blind, double- dummy amlodipine 5 mg and atorvastatin 10 mg once daily from 17 Jan 2003 until 11 Feb 2003 (26 days).

On 06 Feb 2003 (Day 21), the subject underwent an exercise stress test and during the test experienced chest pain that was considered to be non- serious. An angiogram performed on [redacted] revealed 85% stenosis in 3 vessels. [redacted] the subject was admitted to the hospital for the serious adverse event of worsening atherosclerosis, and on [redacted]) underwent a 5- vessel coronary artery bypass graft (CABG). The serious adverse event was considered resolved on 17 Feb 2003.

In response to the instructions of the treating physician for the atherosclerosis, the subject withdrew from the study and discontinued the study medication on 11 Feb 2003.

In the opinion of the investigator, the serious adverse event of worsening atherosclerosis most likely represented the intercurrent illness of coronary artery disease and was not related to the study medication.

Medical problems present at study entry included type 2 diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease (mild emphysema), and atherosclerosis.

Concomitant medications reported were pioglitazone and acetylsalicylic acid. 01000002610687\ 1.0 \

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AMLODIPINE TREATMENT GROUPS

Subject ID: 1015- 2628 AER Case No.: 2003000417

This 54- year- old white female took double- blind, double- dummy amlodipine 10 mg once daily from 27 Nov 2002 to 21 Jan 2003.

On [redacted] of treatment) the subject was hospitalized for 3 days with acute back pain possibly related to a motor vehicle accident in Sep 2001; daily physiotherapy was prescribed. The subject was considered recovered and discharged from the hospital on [redacted]

No action was taken with respect to study medication in response to this event.

According to the investigator the serious adverse event, acute back pain, most likely was due to a previous motor vehicle accident and was unrelated to the study medication.

Medical problems present at study entry included asthma and smoking.

Concomitant medications included salbutamol, ipratropium bromide, and paracetamol; acute back pain was treated (started 06 Jan 2003, stop date not specified) with tenoxicam, paracetamol/ dextropropoxyphene napsylate and ketorolac tromethamine.

Subject ID: 1257- 4684 AER Case No.: 2003001906

This 60- year- old white male smoker with a history of possible tuberculosis received double-blind, double- dummy atorvastatin 10 mg once daily from 20 Dec 2002 to 26 Dec 2002 (7 days).

On [redacted] the subject was hospitalized due to hemoptysis and epistaxis; a previous episode of epistaxis was also reported to have occurred (date/ study day of treatment unspecified), from which the subject was considered recovered on [redacted] when a nasal obturation was removed. During hospitalization from [redacted] bronchoscopy (exact date unspecified) detected remains of blood; a second bronchoscopy (exact date unspecified) was normal, with no site of bleeding detected. Thoracic computed tomography (Jan 2003, exact date unspecified) revealed lymphadenopathy compatible with tuberculosis during childhood. Arterial blood tests (Jan 2003, exact dates unspecified) showed pH of 7.43, carbon dioxide of 43 mm Hg, arterial oxygen tension of 85 mm Hg, bicarbonate of 28 meq/ L, coproculture of negative, hematologic

and chemical (including transaminases and transferrin) of normal, and oxygen saturation of 93% (normal ranges for all blood tests were unspecified). During hospitalization the subject also experienced rectorrhagia, diarrhea, (onset [redacted]) and an increased prothrombin time of 66 (units unspecified). The subject was considered recovered from hemoptysis and discharged from the hospital on [redacted] and was considered recovered from rectorrhagia, diarrhea, and increased prothrombin time on an unspecified date in Jan 2003.

The subject permanently discontinued study medication on [redacted] . due to epitaxis.

According to the investigator the serious adverse event, hemoptysis, was caused by probable chronic obstructive pulmonary disease. The causes of the serious adverse events of rectorrhagia, diarrhea, and increased prothrombin time were not specified; nor was the cause of the epitaxis, which was considered nonserious. None of these adverse events were considered related to study medication.

Medical problems present at study entry included smoking.

No concomitant medications were reported during the double- blind treatment period. While hospitalized, the subject received vitamin K (to increase prothrombin time), unspecified antibiotics, unspecified treatment to avoid cough, and oxygen therapy. Prescribed treatment on discharge from the hospital was candesartan, doxazoxin, and fitometadione (vitamin K). The subject was also told to avoid smoking.

Subject ID: 1220- 4490 AER Case No.: 2003002384

This 64- year- old white male received double- blind, double- dummy atorvastatin 20 mg once daily from 06 Nov 2002 to [redacted] .

On [redacted]) the subject collapsed and died suddenly in the street after physical exercise (walking); death was confirmed after passers- by brought him to a nearby pharmacy.

The last dose of study medication before sudden cardiac death was taken on [redacted]

According to the investigator the serious adverse event, sudden cardiac death, most likely resulted from ischemic heart disease and angina functional class II, and was unrelated to the study medication.

Medical problems present at study entry included ischemic heart disease, arterial hypertension, hyperlipidemia, exertional angina, diabetes type II, atherosclerosis of aorta, aortic stenosis (1st

degree), aortic insufficiency (1st degree), vertebral osteochondrosis, adenoma of prostate, urolithiasis, and stage I obesity.

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Concomitant medications included acetylsalicylic acid, metformin, glimepiride, and menthyl valerate.

Subject ID: 1219- 4542 AER Case No.: 2003002387

This 70- year- old white male with a history of acute myocardial infarction (AMI) received double-blind, double- dummy atorvastatin 80 mg once daily from 05 Dec 2002 to 24 Jan 2003 (51 days).

On 19 Jan 2003 (Day 46 of treatment) the subject developed prolonged chest pain, shortness of breath, and pulmonary edema. The subject was hospitalized on [redacted] with AMI, and was considered recovered from pulmonary edema on the same day; electrocardiogram showed sinus rhythm, tachycardia, and acute period of anterior myocardial infarction. On [redacted] the subject experienced paroxysmal atrial fibrillation, from which he recovered the same day, followed by another AMI and elevated creatine kinase (391.3 U/ L); electrocardiogram showed additional ST segment elevation. On [redacted] creatine kinase was also elevated (178 U/ L, normal = 24 U/ L), and the subject experienced pulmonary artery thromboembolism. The subject died on [redacted]

Study medication was permanently discontinued on 24 Jan 2003 in response to the AMI that occurred on 19 Jan 2003.

In the investigator's opinion death was due to the serious adverse events AMI and pulmonary artery thromboembolism. These serious adverse events, together with the serious adverse events pulmonary edema and paroxysmal atrial fibrillation, most likely represented an intercurrent illness and were unrelated to the study medication. The chest pain and shortness of breath were subsumed under the serious adverse event AMI.

Medical problems present at study entry included coronary artery disease and angina.

No concomitant medications were reported.

Subject ID: 1203- 2232 AER Case No.: 2003005594

This 57- year- old white male with a history of acute myocardial infarction (AMI) and brain concussion received double- blind, double- dummy atorvastatin 10 mg once daily from 03 Dec 2002 to 28 Jan 2003 (57 days).

On 26 Jan 2003, the subject complained of discomfort in the right hypochondrium, and during a physical exam on 28 Jan 2003 experienced pain on palpation in that region. Laboratory results revealed elevated liver enzyme levels, elevated WBC count, and a low albumin level (see table below, normal ranges not provided for all tests). On 29 Jan 2003, the subject reported an aversion to food, worsening appetite, and weight loss. On 04 Feb 2003, the subject experienced pain on palpation of the right hypochondrium.

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Laboratory tests again revealed abnormal liver enzyme levels. In the opinion of the investigator this represented a worsening of chronic cholecystitis. Ultrasound examinations on [redacted] and [redacted] revealed numerous round formations in the liver. The subject refused hospitalization at that time. On [redacted] the subject was hospitalized following complaints of

pain on the right side of the head, vomiting, and falling down. A CT scan performed that day revealed an ischemic stroke involving the right medial cerebral artery. On 17 Feb 2003, the subject vomited coffee- ground material and experienced decreasing blood pressure. Esphagogastroduodenoscopy revealed an acute bleeding ulcer of the middle third of the stomach. On [redacted], the subject's cardiovascular condition worsened and he died due to acute respiratory and cardiovascular failure.

Laboratory test [redacted] Alkaline phosphatase (range: not provided) 397 -

SGOT (range: 0- 40 U/ L) 58 U/ L 72.9 U/ L

SGPT (range: 0- 40 U/ L) 67 U/ l 54.5 U/ L

GGT (range: not provided) 923 U/ L -

WBC (range: 3.5- 10x10 3 /mm 3) 13.76x10 3 /mm 3 8x10 3 /mm 3

Albumin (range: not provided) 42 g/ L -

An autopsy revealed evidence of repeated ischemic brain infarction (a cyst in the left frontal lobe and encephalomalacia on the right cerebral hemisphere), hypertensive disease (eccentric myocardial hypertrophy), arteriolonephrosclerosis, atherosclerosis (arteries of the skull base), internal carotid arteries (50% stenosis), aorta and coronary arteries (50% stenosis), pancreatic cancer (with metastases in the liver, lymph nodes and stomach lumen), microfocal pneumonia of the right side, acute erosions and ulcers of the stomach with bleeding, pulmonary edema, brain edema, postinfarction cardiosclerosis, parietal thrombosis of the aortic valve flaps and numerous kidney infarcts.

In the investigator's opinion, death was due to the serious adverse events of ischemic stroke, cardiac failure, and pancreatic cancer. The ischemic stroke most likely represented a progression of the underlying disease of hypertension, the cardiac failure a complication of the underlying cardiovascular disease, and the pancreatic and liver cancers most likely represented intercurrent illness. All of the serious adverse events were considered to be unrelated to the study medication.

The subject had completed the course of study medication at the time of onset of the serious adverse events.

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Medical problems present at study entry included coronary artery disease (stable grade II angina pectoris), chronic cholecystitis, arterial hypertension, hyperlipidemia, adenoma of the prostate, and headaches.

Concomitant medications included acetylsalicylic acid, and nitroglycerin.

Subject ID: 1326- 0934 AER Case No.: 2003014578

This 61- year- old white male with a history of sleep apnea (surgery in 1989, 1993, and 2002) received double- blind, double- dummy atorvastatin 40 mg once daily from 03 Feb 2003 to 20 Mar 2003 (46 days).

Early in the morning on [redacted] the subject experienced chest pain (musculoskeletal, non-cardiac), for which he was hospitalized later that day; the chest pain was reported gone at the time of hospitalization. Blood pressure was 194/ 107, and 3 electrocardiograms (dates and times unspecified) were negative for both ischemia and infarction (normal sinus rhythm); blood samples

(unspecified) were normal. On [redacted], the subject was considered recovered and was discharged from the hospital.

Study medication was permanently discontinued on 20 Mar 2003 due to this adverse event.

According to the investigator the serious adverse event, chest pain musculoskeletal non- cardiac, was caused by an intercurrent illness and was not related to the study medication.

Medical problems present at study entry included heartburn.

Concomitant medications included esomeprazole and orlistat.

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PLACEBO TREATMENT GROUP

Subject ID: 1005- 2939 AER Case No.: 2002072387

This 75- year- old white male with a history of stroke, MI, benign prostatic hypertrophy, inguinal hernia, cataract, and glaucoma received double- blind, double- dummy placebo from 21 Nov 2002 to 16 Dec 2002 (26 days).

On 11 Dec 2002 (Day 21 of treatment), after standing for 1 hour, the subject experienced left knee pain. The subject and was unable to stand or walk, and was assisted in an emergency room (date unspecified) but not hospitalized. On 17 Dec 2002, during his study visit, the subject presented with blood pressure >160/ 100 mm Hg and with pain in his left knee; there was no inflammation or sign of fever. The non- serious event of high blood pressure was considered resolved the same day and no further instances of high blood pressure were observed (no dates or results of further blood pressure readings were reported). On 02 Jan 2003 the subject saw a rheumatologist, who indicated that the pain presented as osteoarthirits that had become acute and was therefore arthralgia; the arthralgia was treated with unspecified anti- inflammatory medications and physical therapy and was considered resolved on 16 Jan 2003.

Study medication was permanently discontinued on 16 Dec 2002 in order to begin treatment with a steroidal anti- inflammatory medication not allowed per protocol.

According to the investigator the serious adverse event, arthralgia, most likely represented an intercurrent illness and was not related to study medication.

Medical problems present at study entry included osteoarthritis (knees), systemic arterial hypertension, hyperlipidemia, sporadic constipation, and coronary artery disease.

Concomitant medications included acetylsalicylic acid.

Subject ID: 0011- 1990 AER Case No.: 2002063854

This 65- year- old white female with a history of vertigo received double- blind, double-dummy placebo from 1 Jul 2002 to 25 Aug 2002 (56 days).

The subject developed vertigo on 19 Aug 2003, and was hospitalized on [redacted] for further diagnosis of vertigo. She was discharged from the hospital on [redacted] and the vertigo was considered resolved on that date.

The subject had completed the course of study medication at the time of onset of the serious adverse event of progression of vertigo.

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In the investigator's opinion, the serious adverse event of progression of vertigo most likely represented the intercurrent illness of hidden depression with somatization and was not related to the study medication. Medical problems present at study entry included vertigo, vegetative dystonia, cholecystitis, type 2 diabetes mellitus, autoimmune thyroiditis, and varicosis. Concomitant medications included sulpiride (Day 50 through Day 61), vertigoheel, cralonin (Day 54 to Day 57), jodthyrox, and dimetindene maleate.

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1 This table includes narratives of subjects who discontinued due to adverse events during the double- blind phase of the RESPOND Study. Adverse events include adverse events as well as laboratory, ECG, or vital sign abnormalities, or any other abnormal objective test findings, regardless of relationship to treatment or onset relative to the initiation of study drug treatment. Event terms in these narratives are those used by the investigator (with the COSTART preferred term given in parentheses when different from the investigator term). Source: Subjects' case report forms, which are provided in Section 12 of this study report, and the following data listings, which are provided in Section 13 of this study report: Listings 3, 6, 8, 11, 12, 13, 14. 1, 15, 16, and 17.

TABLE 6.7 OTHER ADVERSE EVENT NARRATIVES 1

Placebo Treatment Group

Subject randomization number: 0491

This 55- year- old White female with comorbid hypertension and hyperlipidemia took double- blind, double- dummy placebo once daily beginning on 05 Nov 2002 (Day 1) for a total of 42 days. On Day 26, the subject began to experience headache of moderate severity. The event resolved on Day 31, but recurred and was severe in intensity on Day 40. Because of the headache, study medication was discontinued and the subject was withdrawn from the study. In the opinion of the investigator, neither occurrence of headache was due to the study medication; the first was related to stress, and the second, to the underlying disease.

Medical problems present at study entry included anxiety, asthma, ankle edema, familial tremor, fatigue, osteoarthritis, right hip and knee pain, insomnia, and recurrent urinary tract infection. Past medical history included headache, upper respiratory tract infection (2000), recurrent bronchitis (1999), gallstones (1976), constipation (1956), neck pain with early degenerative disc changes (2000), eye floater (2002), vaginal dysplasia (1999), heartburn (1981), cerumen impaction (2000), uterine fibroids (1999), angina (2002), sinus bradycardia (2002), thyroid disease (1950s), appendectomy (1976), cholecystectomy (1976), right foot fracture with surgery (1986), tubal ligation (1976), and tonsillectomy (1956). Physical examination at screening was remarkable for mild to moderate familial tremor and osteoarthritis of the hands.

Concomitant medications included aspirin, ibuprofen, and senna.

The only other on- treatment adverse event reported for this subject was constipation.

Subject randomization number: 1591

This 60- year- old White male with comorbid hypertension and hyperlipidemia took double- blind, double- dummy placebo once daily beginning on 10 Jan 2003 (Day 1) for a total of 3 days. On Day 1, the subject developed flush (preferred term, vasodilatation) of moderate severity. Because of this event, study medication was discontinued and the subject was withdrawn from the study.

The event resolved without treatment 1 day after the last dose of study medication (Day 4). In the opinion of the investigator, the event was most likely due to the study medication.

No past medical history was reported, and no medical problems were reported at study entry. Physical examination at screening revealed no abnormalities.

Appendix 3: Protocol Synopsis of ongoing GEMINI Study

Title: Clinical Utility Of Amlodipine/ Atorvastatin To Improve Concomitant Cardiovascular Risk Factors Of Hypertension And Dyslipidemia (Gemini)

Protocol Identifier: A3 841012

Rationale: Within the United States approximately twenty seven million people have concomitant hypertension and dyslipidemia. Both NorvascB, a calcium channel blocker, and Lipitor", an hydroxymethylglutary1 CoA- reductase inhibitor, have generated extensive safety and efficacy data, as well as worldwide clinical experience, for the treatment of hypertension and dyslipidemia respectively. The purpose of this study is to gain clinical experience in dosing a single pill partnering the two complementary drugs to treat the cardiovascular risk factors of hypertension and dyslipidemia in a naturalistic clinical setting.

Rationale for Amendment # 1 (November 22, 2002):

The GEMINI protocol is being amended in order to offer subjects the option of participating in an open- label extension phase of study for a duration of36 weeks (approximately 9 months).

This amendment further incorporates administrative changes .

Objectives: Primary: To evaluate the efficacy of amlodipine/ atorvastatin therapy by assessing the percentage of intent- to- treat subjects achieving both blood pressure and lipid treatment goals as defined by Joint National Committee (JNC) Guidelines and National Cholesterol Education Program (NCEP) Guidelines.

Secondary: To assess the percentage of subjects achieving treatment goals as defined by the JNC Guidelines stratified by baseline levels of systolic blood pressure (SBP) and diastolic blood pressure @BP). To assess the percentage of subjects achieving treatment goals as defined by the NCEP Guidelines stratified by baseline level of low- density lipoprotein cholesterol (LDL- C). To assess changes from baseline in LDL- C, total cholesterol, triglycerides, high- density lipoprotein cholesterol (HDL- C), HDL- C/ LDL- C ratio, SEP, DBP, pulse pressure, and global risk factor scores after 14 weeks of open- label treatment. To evaluate the safety of dual therapy with titration of amlodipine and atorvastatin doses to reach blood pressure (BP) and LDL- C therapeutic targets. The assessments above may also be reassessed using other regional guidelines as necessary.

In addition, physician and subject compliance rates will be evaluated

Please see Appendix I for Extension Phase Objectives. From the statistical and reporting prospective, extension phase of the GEMINI study will be considered as a separate study.

Subjects and Centers: Approximately 1000 subjects at approximately 250 US sites will be enrolled. Subjects will include those with concomitant hypertension and dyslipidemia that require treatment with drug therapy.

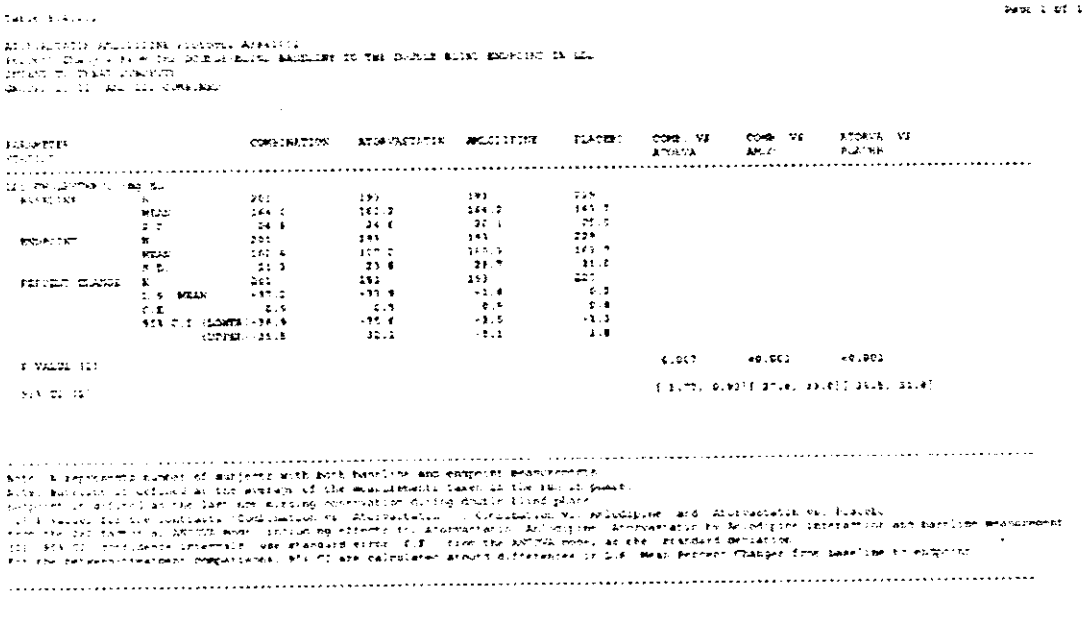
Inclusion/ Exclusion Key Inclusion Criteria: Subjects must have a diagnosis of concurrent Criteria: hypertension and dyslipidemia that qualifies for drug therapy. Blood pressure must be not at goal

as defined by JNC Guidelines with or without medication; LDL- C may be at goal as defined by NCEP Guidelines on medication or not at goal with or without medication. Any pre- enrollment therapies for hypertension and/ or dyslipidemia must be stable for at least 6 weeks before baseline assessments.

Inclusion/ Exclusion Key Exclusion Criteria: Subjects whose BP is adequately maintained at Criteria: (cont'd) goal with or without medication; subjects who are currently treated with both amlodipine and atorvastatin; subjects who are being treated with maximum dose calcium channel blockade therapy, or have a serum LDL- C concentration 2 100mg/ dL while being treated with atorvastatin 80mg.

Other Therapy: Prior statin therapy is allowed but will be discontinued and replaced with the atorvastatin component of the single pill, following enrollment. Prior therapy with non- calcium channel blocker antihypertensive therapy should continue as concomitant therapy to maintain baseline level of BP control and the amlodipine component of the single pill will be added on following enrollment to improve BP control; prior calcium channel blocker therapy will be replaced with the amlodipine component of the single pill following enrollment. No washout period will be required for prior BP or lipid lowering therapies.
Study Design: This is a 14- week, open- label trial to gain clinical experience with a single pill combining amlodipine and atorvastatin for the treatment of concomitant hypertension and dyslipidemia in a naturalistic clinical setting.
Efficacy Measures: Efficacy measures include blood pressure and lipid levels.
Safety: Routine clinical and laboratory safety will be monitored.
Decision Statistical methods are described in the protocol. No sample size Points/ Statistical calculations are provided for this non- comparative, open- label study. No methods/ Interim interim analysis is planned for termination of this study. analysis :
Study Medication Eight dosage strengths of the amlodipine/ atorvastatin single pill will be Regimens: available for use in this open- label study. Subjects will be dispensed study medication at an appropriate dose for their current blood pressure level, lipid levels and concomitant therapies; doses will be titrated over the 14 weeks to improve both blood pressure and lipid control as necessary.
Dates: The study will start during third quarter of 2002. Recruitment will continue for approximately three months. The last visit by the last subject in the core study is estimated to occur during first quarter of 2003. The last patient visit for the extension study will occur in the fourth quarter of 2003.
Special No special equipment/ measures will be required for this study. Equipment/ Measures:

Appendix 4 Changes from baseline to double blind endpoint in LDL - RESPOND



Appendix 5:Serious Adverse events in > 2 cases RESPOND

Table 4. Serious Adverse Events by MedDRA System Organ Class, With Preferred Event Terms for Serious Adverse Events Reported in ≥2 Cases

(Page 4 of 4)

System Organ Class MedDRA Preferred Event Term	AVALON DB Placebo N = 239[a]	AVALON DB Amlo N = 201[b]	AVALON DB Ator N = 200[c]	AVALON DB + AVALON SB + GEMINI[d] Amlo + Ator N = 2010[e]	RESPOND + MARGAUX + DEAAL Blinded N = 1931[f]
Respiratory, Thoracic, and Mediastinal Disorders	1	0	0	3	4
Pulmonary Embolism	1	0	0	0	2
Skin and Subcutaneous Tissue Disorders	0	0	0	0	1
Vascular Disorders	0	0	0	1	3
TOTAL CASES	6	2	2	70	30
TOTAL EVENTS REPORTED	8	2	2	101	51

DB = Double-blind period; SB = Single-blind period; Amlo = Amlodipine (any dose); Ator = Atorvastatin (any dose); NOS = Not otherwise specified

[a] Includes serious adverse events for 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006)

[b] N = Number of patients who took at least 1 dose of the indicated study medication during the AVALON double-blind treatment period (Study A3841001)

[c] N = Number of patients who took at least 1 dose of either concurrent amlodipine + atorvastatin or Caduet (amlodipine/atorvastatin combination tablet) during the single-blind treatment period of AVALON (Study A3841001) or the open-label dose-titration period of GEMINI (Study A3841012), plus 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

[d] N = Number of patients randomized to blinded study medication (placebo, amlodipine, atorvastatin, or amlodipine + atorvastatin) in RESPOND (Study A3841003), MARGAUX (Study A0531006), and DEAAL (Study A0531031), less 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and less 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006)

Appendix 6 :Summary of drug exposure- AVALON

Of the 847 patients who took at least 1 dose of study medication during the double-blind treatment period of AVALON (Study A3841001), 207 patients took concurrent amlodipine 5 mg QD + atorvastatin 10 mg QD; the median exposure to double-blind treatment was 56 days (Table 6).

Table 6. Summary of Exposure to Study Medication by Treatment Group: AVALON (Study A3841001) Double-Blind Treatment Period

[Number of Patients]

	Placebo N = 239	Amlo N = 201	Ator N = 200	Amlo + Ator N = 207
Total Exposure Time				
≤1 Days	0	3	0	2
2 to 7 Days	0	0	0	1
2 to 7 Days	3	2	3	0
15 to 28 Days	7	3	6	8
29 to 60 Days	214	179	176	188
61 to 90 Days	15	14	15	8
≥90 Days	0	0	0	0
Median Duration (Days)	56.0	56.0	56.0	56.0
Range (Days)	12-70	1-64	9-84	1-74

Amlo = Amlodipine 5 mg QD; Ator = Atorvastatin 10 mg QD.

3.2. Demographics and Baseline Characteristics of the Study Population

Patients who took at least 1 dose of study medication during the double-blind treatment period of AVALON (Study A3841001) were predominantly white and predominantly male, with a mean age of approximately 55 years (Table 7). At baseline, patients who took concurrent amlodipine 5 mg QD + atorvastatin 10 mg QD had a mean LDL-C of 163.9 mg/dL, a mean systolic blood pressure of 146.6 mm Hg, and a mean diastolic blood pressure of 92.1 mm Hg.

Appendix 7: Patient enrollment for Amlodipine /Atorvastatin Clinical Studies ongoing as of April 4 2003

Table 2. Patient Enrollment for Amlodipine/Atorvastatin Clinical Studies Ongoing as of 04 April 2003

Study ID / Treatment Period	N Randomized: 15 Jul 2002	N Randomized: 04 Apr 2003[a]	N Completed: 04 Apr 2003[a]	First Patient Enrolled[a]	Enrollment Complete[a]	Last Patient Visit
Ongoing Efficacy and Safety Studies: Caduet™ Clinical Development Program						
AVALON (A3841001)						
Double-Blind	562	848	779	01 Feb 2001	01 Oct 2002	29 Nov 2002
Single-Blind Open-Label Dose-Titration	N A	783	Ongoing	15 May 2001	26 Nov 2002	N A
Open-Label Extension	N A	292	Ongoing	25 Sep 2002	N A	N A
RESPOND (A3841003)						
Double-Blind	75	1640	1466[b]	25 Mar 2002	3 Jan 2003	28 Mar 2003
Open-Label Extension	N A	213	Ongoing	31 Jan 2003	28 Mar 2003	N A
GEMINI (A3841012)						
Open-Label Dose-Titration	N A	1221	1096	05 Aug 2002	27 Nov 2002	19 Mar 2003
Open-Label Extension	N A	975	Ongoing	03 Dec 2002	19 Mar 2003	N A
Ongoing Efficacy and Safety Studies: Amlodipine Clinical Development Program						
MARGAUX (A0531006)	127	144	Ongoing[b]	25 Oct 2000	N A	N A
DE AAL (A0531031)	74	123	Ongoing[b]	11 Jul 2001	N A	N A
TOTAL Unique Patients	836	3976				

N = Number of patients; N A = Not applicable

[a] Dates are approximate; actual dates of enrollment figures and milestones may vary slightly.

[b] At the time of the 04 April 2003 cutoff, the sponsor remained blinded to randomized treatment assignments; treatments assigned in these studies included placebo, amlodipine monotherapy, atorvastatin monotherapy, and concurrent amlodipine + atorvastatin. Five patients in RESPOND (Study A3841003) and 1 patient in MARGAUX (Study A0531006) who had serious adverse events are known to have taken amlodipine + atorvastatin.

Appendix 8: Serious adverse events in the CADUET program

Table 4. Serious Adverse Events by MedDRA System Organ Class, With Preferred Event Terms for Serious Adverse Events Reported in ≥2 Cases

(Page 2 of 4)

System Organ Class / MedDRA Preferred Event Term	AVALON DB: Placebo N = 239[a]	AVALON DB: Amlo N = 201[b]	AVALON DB: Ator N = 200[b]	AVALON DB + AVALON SB + GEMINI: Amlo + Ator N = 2610[c]	RESPOND + MARGAUX + DE AAL: Blinded[d] N = 1903[e]
General Disorders and Administration Site Conditions	1	0	0	5	4
Chest Pain	0	0	0	2	3
Fall	1	0	0	2	0
Hepatobiliary Disorders	0	0	0	2	0
Infections and Infestations	0	0	1	5	3
Cellulitis	0	0	0	1	1
Pneumonia NOS	0	0	0	2	1
Urosepsis	0	0	0	1	1
Injury, Poisoning, and Procedural Complications	0	0	0	2	1
Rib Fracture	0	0	0	1	1
Investigations	0	0	0	1	1
Metabolism and Nutrition Disorders	0	0	0	3	0

DB = Double-blind period; SB = Single-blind period; Amlo = Amlodipine tany dose); Ator = Atorvastatin (any dose); NOS = Not otherwise specified

[a] Includes serious adverse events for 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

[b] N = Number of patients who took at least 1 dose of the indicated study medication during the AVALON double-blind treatment period (Study A3841001).

[c] N = Number of patients who took at least 1 dose of either concurrent amlodipine + atorvastatin or Caduet (amlodipine atorvastatin combination tablet) during the single-blind treatment period of AVALON (Study A3841001) or the open-label dose-titration period of GEMINI (Study A3841012), plus 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

[d] N = Number of patients randomized to blinded study medication (placebo, amlodipine, atorvastatin, or amlodipine + atorvastatin) in RESPOND (Study A3841003), MARGAUX (Study A0531006), and DE AAL (Study A0531031), less 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and less 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

Appendix 9: Serious Adverse events in the CADUET program

Table 4. Serious Adverse Events by MedDRA System Organ Class, With Preferred Event Terms for Serious Adverse Events Reported in ≥2 Cases

(Page 3 of 4)

System Organ Class MedDRA Preferred Event Term	AVALON DB Placebo N = 239[a]	AVALON DB Amlo N = 201[b]	AVALON DB Ator N = 200[c]	AVALON DB + AVALON SB + GEMINI Amlo + Ator N = 2010	RESPOND + MARGAUX + DUAAL Blinded N = 1901[d]
Musculoskeletal and Connective Tissue Disorders	1	0	0	6	2
Joint Disorder NOS	0	0	0	2	0
Myalgia	0	0	0	2	0
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	0	0	0	8	2
Lung Cancer Stage I unspecified (Excl Metastatic Tumors to Lung)	0	0	0	2	0
Nervous System Disorders	0	1	0	8	3
Syncope	0	0	0	3	1
Renal and Urinary Disorders	0	0	0	2	1
Reproductive System and Breast Disorders	0	0	0	1	1

DB = Double-blind period, SB = Single-blind period, Amlo = Amlodipine (any dose), Ator = Atorvastatin (any dose), NOS = Not otherwise specified

[a] Includes serious adverse events for 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006)

[b] N = Number of patients who took at least 1 dose of the indicated study medication during the AVALON double-blind treatment period (Study A3841011)

[c] N = Number of patients who took at least 1 dose of either concurrent amlodipine + atorvastatin or Caduet (amlodipine atorvastatin combination tablet) during the single-blind treatment period of AVALON (Study A3841011) or the open-label dose-titration period of GEMINI (Study A3841012), plus 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

[d] N = Number of patients randomized to blinded study medication (placebo, amlodipine, atorvastatin, or amlodipine + atorvastatin) in RESPOND (Study A3841003), MARGAUX (Study A0531006), and DUAAL (Study A0531031), less 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and less 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006)

Appendix 10: Serious adverse events in CADUET program

Table 4. Serious Adverse Events by MedDRA System Organ Class, With Preferred Event Terms for Serious Adverse Events Reported in ≥2 Cases

(Page 1 of 4)

System Organ Class MedDRA Preferred Event Term	AVALON DB Placebo N = 239[a]	AVALON DB Amlo N = 201[b]	AVALON DB Ator N = 200[c]	AVALON DB + AVALON SB + GEMINI Amlo + Ator N = 2010[d]	RESPOND + MARGAUX + DUAAL Blinded N = 1901[d]
Cardiac Disorders	4	0	0	24	12
Acute Myocardial Infarction	0	0	0	5	2
Angina Pectoris	0	0	0	2	3
Angina Unstable	1	0	0	0	2
Atrial Fibrillation	1	0	0	7	1
Congestive Cardiac Failure Aggravated	0	0	0	3	0
Coronary Artery Disease NOS	0	0	0	2	0
Myocardial Infarction	1	0	0	5	3
Pulmonary Edema NOS	0	0	0	2	1
Sick Sinus Syndrome	0	0	0	2	0
Ventricular Tachycardia	0	0	0	2	0
Ear and Labyrinth Disorders	0	0	1	0	1
Endocrine Disorders	0	0	0	0	1
Gastrointestinal Disorders	0	1	0	14	2

DB = Double-blind period, SB = Single-blind period, Amlo = Amlodipine (any dose), Ator = Atorvastatin (any dose), NOS = Not otherwise specified

[a] Includes serious adverse events for 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006)

[b] N = Number of patients who took at least 1 dose of the indicated study medication during the AVALON double-blind treatment period (Study A3841011)

[c] N = Number of patients who took at least 1 dose of either concurrent amlodipine + atorvastatin or Caduet (amlodipine atorvastatin combination tablet) during the single-blind treatment period of AVALON (Study A3841011) or the open-label dose-titration period of GEMINI (Study A3841012), plus 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006).

[d] N = Number of patients randomized to blinded study medication (placebo, amlodipine, atorvastatin, or amlodipine + atorvastatin) in RESPOND (Study A3841003), MARGAUX (Study A0531006), and DUAAL (Study A0531031), less 5 patients known to have taken amlodipine + atorvastatin during RESPOND (Study A3841003) and less 1 patient known to have taken amlodipine + atorvastatin during MARGAUX (Study A0531006)

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