CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-540

STATISTICAL REVIEW(S)

NDA 21-540
CADUET (amlodipine besylate and atorvastatin calcium)
Pfizer Inc.

Four-month Safety Update

See page 61 of Dr. William's review dated December 5, 2003.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-540

Drug Name: Caduet (amlodipine bysylate / atorvastatin calcium)

Indication(s): [redacted]

Applicant: Pfizer Inc.

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Review Priority: Standard

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Keywords: combination therapy

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Combination therapy of amlodipine and atorvastatin had a significantly higher percentage of patients who achieved JNC goals compared to atorvastatin alone treatment, and a significantly higher percentage of patients who achieved NCEP LDL-C goals compared to amlodipine alone treatment. It was also shown that the combination treatment had a significantly greater effect on reducing systolic blood pressure compared to atorvastatin alone treatment, and on reducing LDL-C level compared to amlodipine alone treatment. The secondary analyses showed that amlodipine did not modify the effect of atorvastatin on LDL-C and atorvastatin did not modify the effect of amlodipine on systolic blood pressure when the two treatments were co-administered. In conclusion, it was shown that combination treatment had a significantly better antihypertensive effect than atorvastatin and a significantly better anti-hyperlipidemic effect than amlodipine. And, there was no evidence that coadministration with atorvastatin modified the blood pressure-lowering effect of amlodipine and that coadministration with amlodipine modified the lipid-lowering effect of atorvastatin.

1.2 Brief Overview of Clinical Studies

This NDA contained 3 Phase III studies for evaluation of the efficacy and safety of the dual therapy of atorvastatin and amlodipine in the simultaneous treatment of coexisting hyperlipidemia and hypertension. AVALON (Study A3841001) was a Phase 3, double-blind, placebo-controlled and open-label phases, randomized, North-America, multi-center study with efficacy to be evaluated primarily in terms of percentages of patients who achieve JNC (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) blood pressure and NCEP (National Cholesterol Education Program) low-density lipoprotein cholesterol (LDL-C) goals. This study had placebo, amlodipine 5mg, atorvastatin 10mg, and amlodipine 5mg+atorvastatin 10mg treatment arms. ACCESS (Study 981-176) was a 54-week, randomized, open-label study that evaluated the lipid-lowering efficacy of atorvastatin vs. other statins in dyslipidemic patients. Among the patients in ACCESS, there were 232 hypertension angina patients who took prescription amlodipine concurrently. This study was used to support the results of other phase 3 studies. RESPOND (Study A3841003) was a Phase 3, double-blind, placebo-controlled and open-label phases, randomized, multi-national study with efficacy to be evaluated primarily in terms of changes in systolic blood pressure (SBP) and LDL-C level. This study had all 15 possible combination treatment arms of amlodipine dosages (0mg, 5mg, 10mg) and atorvastatin (0mg, 10mg, 20mg, 40mg, 80mg) dosages. This reviewer evaluated the AVALON and the RESPOND studies for statistical review.

1.3 Statistical Issues and Findings

The primary analyses of the AVALON study showed a significantly greater percentage of amlodipine + atorvastatin patients achieving JNC blood pressure goals versus atorvastatin-only patients (51.0% vs. 32.3%, $p<0.0001$), and a significantly greater percentage of amlodipine +

atorvastatin patients achieving NCEP LDL-C goals versus amlodipine-only patients (82.1% vs. 12.4%, p<0.0001). The following table summarizes the results of the primary analyses.

Table 1: Patient Achieving JNC and NCEP goals – The AVALON Study
(Source: Sponsor's analysis confirmed by reviewer's analysis)

					AML+ATO	
	Placebo	AML	ATO	AML+ATO	vs. AML	vs. ATO
Patients Achieving JNC Goals						
N	236	198	198	204		
n (%)	70 (29.7)	107 (54.0)	64 (32.3)	104 (51.0)		
p-value					0.52	0.0002
Patients Achieving NCEP Goals						
N	229	193	193	201		
n (%)	15 (6.6)	24 (12.4)	151 (78.2)	165 (82.1)		
p-value					<0.0001	0.23

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

The secondary analyses of this study confirmed the results of the primary analyses results. In addition, the secondary analyses showed that atorvastatin 10mg did not modify the systolic blood pressure lowering efficacy of amlodipine 5mg, and amlodipine 5mg did not modify the LDL-C lowering efficacy of atorvastatin 10mg when the two treatments were co-administered.

For the primary analyses of the RESPOND study on LDL-C showed that (1) atorvastatin overall (p<0.0001), as well as (2) each active atorvastatin dosage combined across amlodipine doses (80mg, p<0.0001; 40mg, p<0.0001; 20mg, p<0.0001; 10mg, p<0.0001), had a statistically significant treatment effect on LDL-C. Results for (3) the third set of eight comparisons showed that the least square mean percent changes from baseline in LDL-C in each of the eight combination treatment groups was significantly greater (p<0.0001 for all comparisons) than that in the corresponding amlodipine-alone treatment group. The analysis results on systolic blood pressure showed that (1) amlodipine overall (p<0.0001), as well as (2) each active amlodipine dosage combined across atorvastatin doses (10mg, p<0.0001; 5mg, p<0.0001), had a statistically significant treatment effect on systolic blood pressure. Results for (3) the third set of eight comparisons showed that the least square mean changes from baseline in systolic blood pressure in each of the eight combination treatment groups was significantly greater (p<0.0001 for all comparisons) than that in the corresponding atorvastatin-alone treatment group. The results of the final set of eight comparisons for LDL-C and SBP are shown below.

Table 2: Efficacy of Combined Treatment in Reducing LDL-C and Systolic Blood Pressure – The RESPOND Study *(Source: Sponsor's analysis confirmed by reviewer's analysis)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
Least Square Mean Percent Changes of LDL-C						
AML 0mg	Change	-1.2	-33.5	-39.5	-43.1	-47.0
AML 5mg	Change	-0.1	-39.0	-42.2	-44.9	-48.2
	Difference		-38.9	-42.2	-44.8	-48.2
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
AML 10mg	Change	-2.6	-36.6	-38.6	-43.2	-49.2
	Difference		-34.0	-36.0	-40.6	-46.6
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
Least Square Mean Changes of Systolic Blood Pressure						
AML 0mg	Change	-2.9	-4.3	-6.1	-6.2	-6.6
AML 5mg	Change	-12.6	-13.6	-15.3	-12.8	-12.6
	Difference		-9.3	-9.2	-6.6	-6.0
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
AML 10mg	Change	-16.5	-15.9	-16.0	-16.5	-17.5
	Difference		-11.6	-9.9	-10.3	-11.0
	p-value		<0.0001	<0.0001	<0.0001	<0.0001

AML=amlodipine, ATO=atorvastatin

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2. INTRODUCTION

2.1 Overview

Hypertension and hyperlipidemia are two of the most common and major independent risk factors for developing cardiovascular disease (CVD). They frequently co-exist and together contribute at least additive but possibly synergistic risk. However, there are currently no single-drug products indicated for concurrent treatment of multiple coronary vascular disease risk factors.

Atorvastatin has proven to be safe and effective therapy for hyperlipidemia. At the recommended starting dose of 10mg once daily, low-density lipoprotein cholesterol (LDL-C) and total cholesterol are each reduced by 39% and 29% respectively. The higher doses of 20mg, 40mg, and 80mg are still more effective. Similarly, amlodipine has proven to be an effective antihypertensive agent by systolic and diastolic blood pressure reductions of around 13mmHg and 7mmHg respectively. Since there are no contraindications to the concomitant use of these agents it is considered the simultaneous use in the challenging clinical setting of coexisting hyperlipidemia and hypertension.

Caduet is a combination product containing both amlodipine and atorvastatin in the following 8 respective oral dose combinations: 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, and 10/80 mg. This new drug application (NDA) is for an approval to market caduet for the indication of

This NDA contained 3 Phase III studies for evaluation of the efficacy and safety of the combined treatment of atorvastatin and amlodipine in the simultaneous treatment of coexisting hyperlipidemia and hypertension. AVALON (Study A3841001) was a Phase 3, double-blind, placebo-controlled and open-label phases, randomized, North-America, multi-center study. RESPOND (Study A3841003) was a Phase 3, double-blind, placebo-controlled and open-label phases, randomized, multi-national study. ACCESS (Study 981-176) was a 54-week, randomized, open-label study that evaluated the lipid-lowering efficacy of atorvastatin vs. other statins in dyslipidemic patients. Among the patients in ACCESS, there were 232 hypertension/angina patients who took prescription amlodipine concurrently. This study was used to support the results of other phase 3 studies. This reviewer evaluated the AVALON and the RESPOND studies for statistical review.

The AVALON study was undertaken to evaluate the safety and efficacy of combined treatment with atorvastatin 10mg and amlodipine 5mg once daily. The atorvastatin 10mg and amlodipine 5mg dosages were chosen because they were the approved starting doses at the time the protocol was designed and because they together comprise the lowest dose in the amlodipine/atorvastatin single-tablet drug product. This reviewer evaluated the double-blind, placebo-controlled phase which was 8-week, North America, multi-center, randomize study. A total of 848 patients were randomized in 1:1:1:1 ratio to treatment with placebo, atorvastatin 10mg, amlodipine 5mg, and atorvastatin 10mg+amlodipine 5mg.

The RESPOND study was undertaken to evaluate the safety and efficacy of combined treatment with all 15 combinations of the dosages of amlodipine (0mg, 5mg, 10mg) and atorvastatin (0mg, 10mg, 20mg, 40mg, 80mg). The evaluated phase of this study was a multi-national, eight-week, randomized, double-blind, multi-center, placebo-controlled study. A total of 1660 patients were randomized to one of the 15 possible combinations of amlodipine and atorvastatin.

2.2 Data Sources

Data used for review were from the electronic submission received on 6/30/03 for the AVALON study and on 10/20/03 for the RESPOND study. The network path was

[redacted] The following volumes were reviewed: 1 and 2.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The overall results of the efficacy for the AVALON and the RESPOND studies are discussed in this section. The reviews of the two individual studies are included in appendix.

3.1.1 AVALON

3.1.1.1 Objective of the Study

The primary objective of this study was to determine whether co-administration of atorvastatin 10mg and amlodipine 5mg was superior to amlodipine 5mg in the treatment of hyperlipidemia and superior to atorvastatin 10mg in the treatment of hypertension. The most important secondary objective was to provide statistical assessment of the possible synergistic effect of the dual therapy in reducing systolic blood pressure.

3.1.1.2 Endpoints

The primary endpoints were the percentage of patients reaching JNC (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) goal and the percentage of patients reaching NCEP (National Cholesterol Education Program) goal.

3.1.1.3 Primary and Secondary Efficacy Results

The demographic and other baseline characteristics between the treatment groups were balanced. Patients in each group were predominantly male, white, and in Group II risk factor category, which include patients with hypertension and hyperlipidemia plus one additional CV risk factor excluding known coronary heart disease (CHD) and diabetes mellitus (DM). Also, the baseline LDL-C level and systolic blood pressure were similar across the treatment groups. The table (i.e. Table 2) showing the demographic and baseline characteristics of patients in each treatment group can be found in appendix 1.

The primary efficacy variable was analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test for general association with groups stratified by baseline global risk factor scores as strata. The primary efficacy results showed that the percentage of combination-treated patients who reached their NCEP LDL-C goals was significantly greater than that of amlodipine-only treated patients ($p<0.0001$). Also, the percentage of combination-treated patients who reached the JNC blood pressure goals was significantly greater than that of patients treated with atorvastatin alone ($p=0.0002$). These results showed that the combination therapy was significantly more effective in lowering LDL-C levels than amlodipine alone, and significantly more effective on lowering blood pressure levels than atorvastatin alone. The following table shows the results of the primary efficacy analyses.

Table 3: Patients Reaching JND and NCEP Goals – The AVALON Study

(Source: Sponsor's analysis confirmed by reviewer's analysis)

	Placebo	AML	ATO	AML+ATO	AML+ATO	
					vs. AML	vs. ATO
Patients Achieving JNC Blood Pressure Goal						
N	236	198	198	204	-	-
n(%)	70 (29.7)	107 (54.0)	64 (32.3)	104 (51.0)	-	-
p-value	-	-	-	-	-	0.0002
Patients Achieving NCEP LDL-C Goal						
N	229	193	193	201	-	-
n(%)	15 (6.6)	24 (12.4)	151 (78.2)	165 (82.1)	-	-
p-value	-	-	-	-	<0.0001	-

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

As the secondary analysis, the comparisons of the percentage of patients reaching JNC goals and the changes in blood pressure parameters (systolic blood pressure, diastolic blood pressure, and pulse pressure) in the combination and amlodipine only treatments were performed to confirm additional beneficial effect of atorvastatin when added to amlodipine. The results of the analysis showed that the percentage of patients achieving JNC goals and the least square mean changes in the blood pressure parameters between the combination treatment and the amlodipine only treatment were similar. The results suggested that atorvastatin 10mg did not modify the blood pressure lowering efficacy of amlodipine 5mg when the two treatments were combined. The following table summarizes the results.

Table 4: Efficacy of Combined Treatment vs. Amlodipine on Blood Pressure – The AVALON Study *(Source: Sponsor's analysis confirmed by reviewer's analysis)*

	AML	AML+ATO	AML+ATO vs. AML
N	198	204	-
Patients achieving JND goal			
n (%)	107 (54.0)	104 (51.0)	
p-value			0.52
Systolic Blood Pressure			
LS mean change	-14.3	-12.7	-
p-value	-	-	0.12
Diastolic Blood Pressure			
LS mean change	-8.9	-8.2	-
p-value	-	-	0.27
Pulse Pressure			
LS mean change	-5.4	-4.5	-
p-value	-	-	0.28

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

The comparisons of the percentages of patients reaching NCEP goals and the least square mean percent changes of LDL-C in the combination and atorvastatin only treatments were performed for an assessment of the possible synergistic effect of the combined treatment in LDL-C. The least squares mean percent changes in LDL-C between the two treatment groups were significantly different (p=0.0067) where the greater reduction of LDL-C observed in the combination treatment group. The sponsor stated in the report that the difference was not considered clinically meaningful because the observed percent changes of the combination therapy group was similar to those seen in other 4 Pfizer-sponsored studies of atorvastatin. The percentages of patients reaching NCEP goals between the two treatment groups were not significantly different (p=0.23). The following table shows the analysis results.

Table 5: Efficacy of Combined Treatment vs. Atorvastatin on LDL-C – The AVALON Study *(Source: Sponsor's analysis confirmed by reviewer's analysis)*

	ATO	AML+ATO	AML+ATO vs. ATO
N	193	201	-
Patients Reaching NCEP Goals			
n (%)	151 (78.2)	165 (82.1)	-
p-value	-	-	0.23
LDL-C			
LS mean % change	-33.9	-37.2	-
p-value	-	-	0.0067

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

Other lipid parameters (total cholesterol, triglycerides, apolipoprotein B, and HDL-C) were analyzed to confirm the findings of above secondary analyses. The least squares mean percent

changes of total cholesterol and apolipoprotein B were statistically significantly greater in the combination treatment group compared to the atorvastatin only treatment group (total cholesterol, p=0.0004; triglycerides, p=0.075; apolipoprotein B, p=0.013; HDL-C, p=0.54). The sponsor also stated that the LS mean % changes of total cholesterol and apolipoprotein B were in the range of those found in the 4 Pfizer-sponsored studies on atorvastatin. The table showing results of these analyses can be found in Table 8 of appendix 1.

As secondary analyses, comparisons between combination treatment and amlodipine-alone treatment on lipid parameters, comparisons between combination treatment and atorvastatin-alone treatment on blood pressure parameters were performed. These analyses confirmed the results of the primary analyses. The efficacy of combined treatment on reaching both NCEP and JNC goals as well as reducing global risk factor scores were also analyzed by comparing with both the amlodipine-alone treatment group and the atorvastatin-alone treatment group. These analyses showed that the percentage of patients reaching both NCEP and JNC goals were significantly greater in the combination treatment group compared to either atorvastatin-alone treatment group or amlodipine-alone treatment group ($p<0.0001$). The least square mean changes in global risk scores were also significantly greater in the combination treatment group compared to either atorvastatin-alone treatment group or amlodipine-alone treatment group ($p\leq0.0046$). The discussion in detail and the tables can be found in section Secondary Efficacy Results in appendix 1.

3.1.2 RESPOND

3.1.2.1 Objective of the Study

The primary objective of this study was to demonstrate superiority of the combination therapy over amlodipine only therapy in reducing LDL-C, and to demonstrate superiority of combination therapy over atorvastatin only therapy in reducing 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.

3.1.2.2 Endpoints

The primary endpoints were LS mean percent changes of LDL-C at week 8 and LS mean changes of systolic blood pressure at week 8.

3.1.2.3 Primary and Secondary Efficacy Results

There was no significantly different distribution of age, gender, race, risk group, LDL-C baseline, and systolic blood pressure baseline between the treatment groups. The majority of patients in each treatment group were white, and about 48% of patients were in Group II (including patients with hypertension and hyperlipidemia plus one additional cardiovascular risk factor excluding known CHD and DM), and about 49% of patients were in Group III (including

patients with hypertension and hyperlipidemia and CHD, DM or other atherosclerotic disease). The table (i.e. Table 4) summarizing the demographic and baseline characteristics can be found in appendix 2.

The primary endpoints were evaluated by using a step-down approach utilizing closed testing procedures as shown in the table below.

Table 6: Primary Efficacy Analyses Methods – The RESPOND Study

Efficacy of combined treatment in reducing LDL-C	Efficacy of combined treatment in reducing SBP
1. Null hypothesis of "no overall atorvastatin effect on LDL-C" was test. If rejected. then: ↓	1. Null hypothesis of "no overall amlodipine effect on SBP" was tested. If rejected, then: ↓
2. Hypothesis of "no individual atorvastatin dose effect on LDL-C" was tested (ie, each active atorvastatin dose, combined across placebo and amlodipine doses, was compared with atorvastatin placebo combined across all amlodipine doses). If rejected for all 4 active atorvastatin doses, from high to low, then: ↓	2. Hypothesis of "no individual amlodipine dose effect on SBP" was tested (ie, each active amlodipine dose, combined across placebo and active atorvastatin doses, was compared with amlodipine placebo combined across all atorvastatin doses). If rejected for both active amlodipine doses, form high to low, then: ↓
3. Hypothesis of "no individual combination treatment effect on LDL-C" was tested (ie, each of the 8 combination treatments was compared with the corresponding amlodipine treatment).	3. Hypothesis of "no individual combination treatment effect on SBP" was tested (ie, each of the 8 combination treatments was compared with the corresponding atorvastatin treatment).

The first analysis of testing overall atorvastatin effect on LDL-C showed a statistically significant effect of combination treatment ($p<0.0001$) as well as the second analysis for each active atorvastatin dosage combined across amlodipine doses (80mg, $p<0.0001$; 40mg, $p<0.0001$; 20mg, $p<0.0001$; 10mg, $p<0.0001$). The third analyses of comparisons between each of the 8 combination treatment groups with the corresponding amlodipine-alone treatment also showed the significantly greater effect on LDL-C of the combination treatment ($p<0.0001$ for all comparisons). The table below shows the second and the third analyses results.

Table 7: Primary Efficacy Analysis of Combined Treatments in Reducing LDL-C- The RESPOND Study *(Source: Sponsor's analysis confirmed by reviewer's analysis)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean % change	-1.2	-33.5	-39.5	-43.1	-47.0
AML 5mg	LS mean % change	-0.1	-39.0	-42.2	-44.9	-48.3
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
AML 10mg	LS mean % change	-2.6	-36.6	-38.6	-43.2	-49.2
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
Total	LS mean % change	-1.3	-36.4	-40.1	-43.7	-48.2
	p-value		<0.0001	<0.0001	<0.0001	<0.0001

AML=amlodipine, ATO=atorvastatin

The first analysis of overall amlodipine effect on systolic blood pressure showed a statistically significant greater effect of combination treatment on reducing systolic blood pressure ($p<0.0001$) as well as the second analysis for each active amlodipine dosage combined across atorvastatin doses (10mg, $p<0.0001$; 5mg, $p<0.0001$). The final analysis on each of 8 combination treatment groups vs. the corresponding atorvastatin-alone treatment groups also showed the significantly greater effects of combination treatment on reducing systolic blood pressure ($p<0.0001$ for all comparisons). The results of the second and the third analyses are summarized in the table below.

Table 8: Primary Efficacy Analysis of Combined Treatments in Reducing Systolic Blood Pressure - The RESPOND Study

(Source: Sponsor's analysis confirmed by reviewer's analysis)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg	Total
AML 0mg	LS mean change	-2.9	-4.3	-6.1	-6.2	-6.6	-5.2
AML 5mg	LS mean change	-12.6	-13.6	-15.3	-12.8	-12.6	-16.5
	p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
AML 10mg	LS mean change	-16.5	-15.9	-16.0	-16.5	-17.5	-13.4
	p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

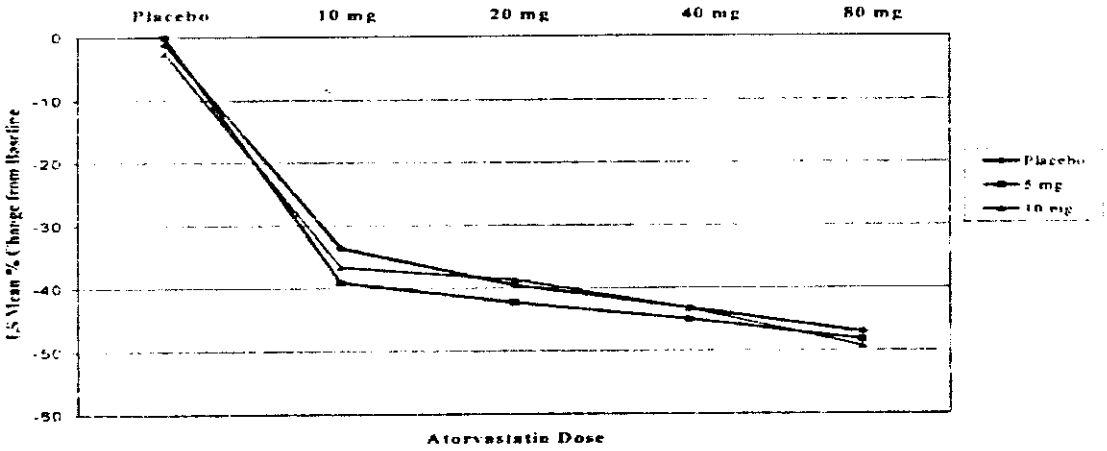
AML=amlodipine, ATO=atorvastatin

The primary analyses showed that all combination treatments were significantly more effective on the hypertension compared to atorvastatin-alone treatment and on the hyperlipidemia compared to amlodipine-alone treatment.

The secondary analyses on evaluating whether amlodipine modified the effect of atorvastatin on LDL-C and whether atorvastatin modified the effect of amlodipine on systolic blood pressure were done using graphs and linear regression analysis as well as the comparisons of mean changes.

For the analysis on the effect of the amlodipine on the LDL-C lowering efficacy of atorvastatin, separate lines for the LS mean % changes of LDL-C levels for amlodipine 0mg, amlodipine 5mg and amlodipine 10mg across the atorvastatin dosages were drawn as shown in the following figure.

Figure 1: Effect of Amlodipine on the Atorvastatin Dose Response- LDL-C - The RESPOND Study *(Source: Sponsor's analysis confirmed by reviewer's analysis)*



A linear regression analysis of the lines in the above figure showed that there was no significant difference between the lines (p=0.51). This analysis showed that the percent change of LDL-C of any four atorvastatin doses were similar across the amlodipine dosages.

In addition, an analysis was done by combining atorvastatin four doses for amlodipine 5mg and 10mg, and comparing those groups with atorvastatin only treated groups. This analysis showed that the effect on LDL-C of amlodipine 10mg combined across active atorvastatin dosages was not significantly different from that of the atorvastatin treatment alone (-40.8 vs. –41.9;p=0.24). However, when amlodipine 5mg was combined across active atorvastatin dosages, this combined group showed statistically greater effect on reduction of LDL-C level compared to the atorvastatin-alone treated group (-40.8 vs. –43.6; p=0.0078). The discussions in detail about this secondary analysis and the table showing the results can be found in the section 11.2 Secondary Efficacy Results and Table 7 in appendix 2.

For the analysis on the effect of the atorvastatin on the systolic blood pressure lowering efficacy of amlodipine, the LS mean changes from baseline of each of the 15 treatment groups were illustrated as shown in Figure 2.

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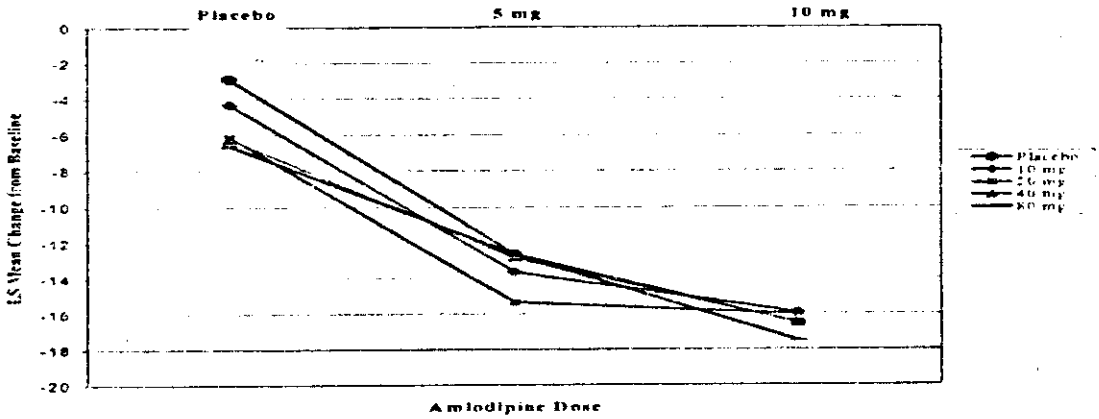
Figure 2: Effect of Atorvastatin on the Amlodipine Dose Response –Systolic BP – The RESPOND Study *(Source: Sponsor's analysis confirmed by reviewer's analysis)*



As the above figure shows, the reductions in systolic blood pressure of any atorvastatin doses combined across amlodipine doses were similar. The linear regression analysis of these lines showed that there was no difference among the five lines (p=0.48).

It was further analyzed by comparing the LS mean changes in systolic blood pressure for the "high" atorvastatin doses (40mg and 80mg) and "low" atorvastatin doses (10mg and 20mg) with amlodipine treatment alone. The analysis showed that the effect on systolic blood pressure of "high" doses of atorvastatin and "low" doses of atorvastatin were not significantly different from that of the amlodipine treatment alone ("high": -14.4 vs. –14.8; p=0.75, "low": -14.4 vs. –15.2; p=0.49). These comparisons also showed that atorvastatin did not modify the systolic blood pressure lowering effect of amlodipine. The discussions in detail and table summarizing the results of this secondary analysis can be found in the section 11.2 Secondary Efficacy Results and in Table 8 in appendix 2.

As secondary analyses, efficacy of the combined treatment on other blood pressure parameters (diastolic blood pressure, and pulse pressure) and other lipid parameters (HDL-C, total cholesterol, and triglycerides) were analyzed as well as on global risk factor scores. These analyses confirmed the conclusions of the primary and the secondary analyses discussed above. The discussion of those secondary analyses can be found in the section 11.2 Secondary Efficacy Results in appendix 2.

3.2 Evaluation of Safety

Please refer to the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor did not perform the subgroup analysis. This reviewer performed the subgroup analysis to explore the consistency of efficacy of the combined treatment vs. amlodipine alone treatment on hypertension and vs. atorvastatin alone treatment on hyperlipidemia.

4.1 Gender, Race and Age

Subgroup analyses on gender, race, and age are discussed in this section.

4.1.1 AVALON

There was no difference between the gender and the race on reaching JNC and NCEP goals. However, there were differences seen in age groups. The patients in ≥ 65 years old group showed much less efficacy of the amlodipine + atorvastatin treatment on hypertension and on hyperlipidemia compared to the patients in the amlodipine-alone and atorvastatin-alone treatment groups, respectively. Only 40.9% of the patients in the combined treatment group reached JNC goal when 56.1% of the patients in the amlodipine group reached JNC goal. Also, 76.7% of the patients in the combined treatment group reached NCEP goals when 88.9% of the patients in the atorvastatin group reached the goal. This is somewhat different findings compared to other age groups where the combination therapy showed similar or slightly greater efficacy on hypertension and hyperlipidemia. The effect of atorvastatin on hypertension also showed differences among the age groups. The percentage of patients reaching JNC goal in the atorvastatin group reduced as the patients got older (<45; 39.1%, 45 to 59; 36.5%, 60 to 64; 26.7%, and ≥65; 10.7%). However, the sample size was too small to draw any conclusion. The following table presents the primary endpoint (reaching JNC blood pressure goal and NCEP LDL-C goal at Week 8) by their subgroup categories.

Table 9: Subgroup Analysis on Gender, Race, and Age – The AVALON Study

(Source: reviewer's analysis only)

	Placebo		AML		ATO		AML + ATO	
	n/N	%	n/N	%	n/N	%	n/N	%
Gender								
Male								
JNC	42/149	28.2	57/117	48.7	30/110	27.8	68/132	51.5
NCEP	10/143	7.0	15/114	13.2	84/107	78.5	110/129	85.3
Female								
JNC	28/87	32.2	50/81	81.3	34/88	38.6	36/72	50.0
NCEP	5/86	5.8	9/79	11.4	67/86	77.9	55/72	76.4
Race								
White								
JNC	59/191	30.9	88/166	53.0	55/165	33.3	88/172	51.2
NCEP	13/184	7.1	22/161	13.7	129/161	80.1	140/169	82.8
Black								
JNC	5/27	18.5	13/18	72.2	7/22	31.8	11/23	47.8
NCEP	2/27	7.4	2/18	11.1	15/21	71.4	17/23	73.9
Asian								
JNC	0/3	0	3/4	75	1/2	50	2/6	33.3
NCEP	0/3	0	0/4	0	1/2	50	5/6	83.3
Other								
JNC	6/15	40	3/10	30	1/9	11.1	3/3	100
NCEP	0/15	0	0/10	0	6/9	66.7	3/3	100
Age								
<45								
JNC	6/26	23.1	13/27	48.2	9/23	39.1	13/24	54.2
NCEP	3/27	11.1	3/24	12.5	17/23	73.9	20/24	83.3
45 to 59								
JNC	35/122	28.7	48/89	53.9	38/104	36.5	52/99	52.5
NCEP	9/118	7.6	14/87	16.1	82/102	80.4	79/96	82.3
60 to 64								
JNC	8/33	24.2	15/28	53.6	8/30	26.7	12/22	54.6
NCEP	3/32	9.4	2/29	6.9	17/28	60.7	20/23	87.0
≥65								
JNC	10/40	25	23/41	56.1	3/28	10.7	18/44	40.9
NCEP	0/37	0	4/40	10	24/27	88.9	33/43	76.7

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

4.1.2 RESPOND

The subgroup analysis on age, gender, and race showed that there was no statistically significant difference between the subgroups on reducing LDL-C level and systolic blood pressure. The following tables show the results of the subgroup analyses.

Table 10: Subgroup Analysis on Age – The RESPOND Study
(Source: reviewer's analysis only)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	<45					
	N	6	10	7	6	11
	LDL-C	3.7	-20.7	-40.0	-41.3	-52.1
	SBP	-11.2	-2.9	-8.6	-9.6	-2.3
	45 – 59					
	N	44	47	48	51	52
	LDL-C	-2.9	-35.4	-36.7	-44.7	-44.7
	SBP	-2.1	-6.2	-4.7	-6.7	-7.6
	60-64					
	N	28	23	26	23	20
	LDL-C	-0.1	-32.5	-38.8	-36.5	-51.9
	SBP	-3.3	-1.7	-7.2	-2.2	-6.7
	≥ 65					
	N	33	10	30	31	27
	LDL-C	-0.8	-35.0	-44.3	-45.4	-45.9
	SBP	-2.4	-3.6	-7.1	-7.4	-6.0
AML 5mg	<45					
	N	10	6	9	5	13
	LDL-C	5.9	-31.6	-48.7	-46.9	-51.3
	SBP	-15.4	-11.7	-13.7	-13.9	-14.1
	45 – 59					
	N	41	48	49	57	49
	LDL-C	-2.6	-39.1	-40.2	-44.2	-45.7
	SBP	-12.1	-13.6	-15.0	-12.9	-10.5
	60-64					
	N	26	19	24	19	23
	LDL-C	2.1	-39.2	-41.4	-43.4	-50.0
	SBP	-14.0	-11.7	-12.8	-9.3	-16.0
	≥ 65					
	N	33	38	29	29	26
	LDL-C	-0.4	-39.9	-44.5	-46.9	-49.9
	SBP	-11.4	-15.1	-18.4	-14.6	-12.3
AML 10mg	<45					
	N	11	2	5	8	8
	LDL-C	2.6	-35.0	-25.0	-45.3	-49.5
	SBP	-9.6	-22.6	-14.6	-14.0	-9.6
	45 – 59					
	N	46	55	57	54	52
	LDL-C	-3.3	-38.2	-38.3	-44.6	-50.2
	SBP	-16.4	-17.2	-13.2	-17.6	-20.1

	60-64					
	N	22	26	16	19	20
	LDL-C	-5.0	-38.4	-39.8	-39.5	-54.9
	SBP	-20.5	-13.2	-19.6	-17.6	-15.3
	≥ 65					
	N	32	27	32	30	31
	LDL-C	-1.9	-31.7	-40.9	-42.4	-49.7
	SBP	-16.3	-15.3	-19.2	-14.2	-16.8

Table 11: Subgroup Analysis on Gender – The RESPOND Study

(Source: reviewer's analysis only)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	Male					
	N	52	66	56	51	46
	LDL-C	-0.7	-30.2	-40.0	-43.3	-50.3
	SBP	-3.1	-5.1	-4.5	-5.6	-5.4
	Female					
	N	59	45	55	60	64
	LDL-C	-1.6	-38.4	-39.0	-42.9	-44.7
	SBP	-2.7	-3.0	-7.9	-6.8	-7.6
AML 5mg	Male					
	N	62	60	54	58	68
	LDL-C	0.2	-36.7	-41.2	-45.1	-48.4
	SBP	-11.8	-12.5	-13.3	-13.4	-11.3
	Female					
	N	48	51	57	52	43
	LDL-C	-0.5	-41.5	-43.2	-44.6	-48.0
	SBP	-13.8	-14.9	-17.3	-12.2	-14.3
AML 10mg	Male					
	N	60	61	62	71	57
	LDL-C	-2.9	-35.4	-39.9	-46.2	-47.7
	SBP	-14.6	-12.5	-16.6	-16.5	-16.9
	Female					
	N	51	49	48	40	54
	LDL-C	-2.3	-38.2	-36.8	-37.9	-50.9
	SBP	-18.7	-20.0	-15.3	-16.3	-18.3

Table 12: Subgroup Analysis on Race – The RESPOND Study

(Source: reviewer's analysis only)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	White					
	N	104	101	102	104	99
	LDL-C	-1.0	-34.0	-39.8	-43.9	-46.8
	SBP	-2.7	-4.5	-5.6	-6.3	-6.5
	Black					
	N	3	3	4	2	5
	LDL-C	4.7	-23.4	-43.2	-25.2	-44.7
	SBP	0.3	3.5	-10.6	5.5	-2.9
	Asian					
	N	1	1	4	1	3
	LDL-C	-9.6	-37.5	-41.9	-42.2	-55.7
	SBP	-14.2	13.6	-16.4	-4.3	-6.8
	Other					
	N	3	6	1	4	3
	LDL-C	-10.9	-27.3	16.3	-30.3	-51.9
	SBP	-7.7	-8.1	-6.4	-10.9	-12.5
AML 5mg	White					
	N	107	102	103	101	105
	LDL-C	-0.4	-39.0	-42.0	-45.9	-48.2
	SBP	-12.9	-13.4	-14.8	-12.8	-12.5
	Black					
	N	2	4	2	3	2
	LDL-C	27.1	-32.2	-31.6	-34.8	-50.5
	SBP	-7.8	-14.8	-13.9	-17.2	-15.3
	Asian					
	N	1	4	3	3	2
	LDL-C	-19.8	-41.2	-54.2	-42.1	-56.9
	SBP	2.3	-16.2	-22.8	-14.2	-9.8
	Other					
	N	0	1	3	3	2
	LDL-C	-	-57.3	-49.5	-24.3	-36.2
	SBP	-	-10.3	-25.6	-9.8	-19.1
AML 10mg	White					
	N	102	100	98	100	104
	LDL-C	-2.4	-36.3	-39.1	-42.8	-48.9
	SBP	-16.3	-15.3	-15.8	-16.0	-17.3
	Black					
	N	5	3	5	5	0
	LDL-C	-9.1	-39.8	-27.2	-43.3	-
	SBP	-25.1	-23.1	-13.2	-18.6	-
	Asian					
	N	1	2	2	3	4
	LDL-C	-1.8	-41.9	-23.8	-54.4	-55.8
	SBP	-14.0	-17.3	-14.0	-28.1	-21.4
	Other					
	N	3	5	5	3	3
	LDL-C	-2.9	-38.6	-46.0	-41.2	-54.2

	SBP	-7.9	-22.0	-23.5	-18.0	-19.8

4.2 Other Special/Subgroup Populations

Subgroup analyses on region are discussed in this section.

4.2.1 AVALON

The AVALON study was conducted in Canada and U.S. Overall, greater percentages of patients in Canada reached the JNC and NCEP goals compared to those of patients in U.S. across all groups except the patients in the combination group on reaching NCEP goals. However, no conclusion was drawn from this finding due to small sample sizes of patients in Canada. The result of this subgroup analysis is shown in the table below.

Table 13: Subgroup Analysis on Country – The AVALON Study
(Source: reviewer's analysis only)

	Placebo		AML		ATO		AML + ATO	
	n/N	%	n/N	%	n/N	%	n/N	%
Canada								
JNC	19/49	38.8	29/39	74.4	9/33	27.3	26/43	60.5
NCEP	5/48	10.4	8/38	21.1	26/32	81.3	32/42	76.2
U.S.A.								
JNC	51/187	27.3	78/159	49.1	55/165	33.3	78/161	48.5
NCEP	10/187	5.5	16/155	10.3	125/161	77.6	133/159	83.7

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

4.2.2 RESPOND

The countries in the RESPOND study were grouped as Europe, North America, Russia, South Africa, and South America in this reviewer's subgroup analysis. There was no trend or difference seen between the subgroups on the LS mean change of systolic blood pressure and LS mean % change of LDL-C. The results are shown in the table below.

Table 14: Subgroup Analysis on Region – The RESPOND Study

(Source: reviewer's analysis only)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	Europe					
	N	46	37	43	41	42
	LDL-C	-2.0	-35.1	-40.9	-46.4	-47.2
	SBP	-2.0	-3.5	-2.0	-6.6	-5.8
	N. America					
	N	20	24	21	22	19
	LDL-C	0.7	-31.1	-34.3	-41.0	-47.3
	SBP	4.1	-4.4	-6.5	-2.4	-9.2
	Russia					
	N	34	36	35	34	36
	LDL-C	-0.1	-32.7	-40.0	-42.3	-43.3
	SBP	-7.0	-6.1	-7.2	-6.3	-4.4
	S. Africa					
	N	6	9	8	6	8
	LDL-C	-4.2	-35.0	-46.0	-36.1	-56.6
	SBP	-6.6	-0.48	-16.6	-9.8	-1.7
	S. America					
	N	5	5	4	8	5
	LDL-C	-5.1	-35.2	-31.9	-40.6	-48.9
	SBP	-3.4	-1.6	-18.5	-11.2	-12.7
AML 5mg	Europe					
	N	43	46	43	39	43
	LDL-C	-2.7	-39.0	-45.1	-49.2	-50.9
	SBP	-14.0	-13.8	-15.4	-12.6	-11.2
	N. America					
	N	19	20	20	22	19
	LDL-C	5.0	-35.7	-38.2	-37.9	-44.8
	SBP	-9.9	-7.7	-12.9	-12.1	-14.7
	Russia					
	N	35	34	35	34	36
	LDL-C	-0.6	-41.5	-41.0	-49.1	-46.1
	SBP	-11.1	-16.0	-15.4	-14.3	-12.5
	S. Africa					
	N	8	9	9	11	8
	LDL-C	1.1	-41.5	-43.0	-38.2	-49.1
	SBP	-12.2	-17.0	-19.2	-13.0	-11.8
	S. America					
	N	5	2	4	4	5
	LDL-C	4.9	-19.3	-45.4	-21.3	-53.0
	SBP	-21.2	-9.1	-18.8	-6.2	-17.1
AML 10mg	Europe					
	N	45	40	47	46	45
	LDL-C	-2.4	-34.0	-38.1	-44.6	-47.1
	SBP	-16.7	-13.7	-15.4	-15.4	-17.5
	N. America					
	N	16	23	17	17	18
	LDL-C	-0.5	-37.3	-37.4	-43.0	-48.6

	SBP	-15.6	-15.5	-16.9	-13.3	-14.9
	Russia					
	N	36	35	34	36	35
	LDL-C	-3.5	-39.3	-39.9	-40.3	-49.5
	SBP	-15.3	-16.2	-15.7	-17.6	-17.6
	S. Africa					
	N	6	7	6	9	9
	LDL-C	-3.7	-40.5	-37.2	-45.9	-55.5
	SBP	-18.0	-23.8	-11.8	-23.6	-19.4
	S. America					
	N	8	5	6	3	4
	LDL-C	-6.2	-33.2	-41.1	-48.6	-55.9
	SBP	-21.7	-23.4	-23.1	-21.1	-22.1

AML=amlodipine. ATO=atorvastatin

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary analysis of the AVALON study showed that a significantly greater percentage of patients in the combined treatment group achieved JNC blood pressure goals vs. patients in the atorvastatin alone treatment group (51.0% vs. 32.3%, p<0.0001). The primary analysis also showed that a significantly greater percentage of patients in the combined treatment group achieved NCEP LDL-C goals vs. patients in the amlodipine alone treatment group (82.1% vs. 12.4%, p<0.0001). The following table summarizes the results of the primary analyses.

Table 15: Patient Achieving JNC and NCEP goals – The AVALON Study
(Source: sponsor's analysis confirmed by reviewer's analysis)

					AML+ATO	
	Placebo	AML	ATO	AML+ATO	vs. AML	vs. ATO
Patients Achieving JNC Goals						
N	236	198	198	204		
n (%)	70 (29.7)	107 (54.0)	64 (32.3)	104 (51.0)		
p-value					0.520	<0.001
Patients Achieving NCEP Goals						
N	229	193	193	201		
n (%)	15 (6.6)	24 (12.4)	151 (78.2)	165 (82.1)		
p-value					<0.001	0.225

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

The secondary analyses of this study confirmed the results of the primary analyses. In addition, the secondary analyses showed that atorvastatin 10mg did not modify the systolic blood pressure lowering efficacy of amlodipine 5mg, and amlodipine 5mg did not modify the LDL-C lowering efficacy of atorvastatin 10mg when the two treatments were combined. One of the secondary analyses showed that the combination treatment had the significantly greater effect on reducing

LDL-C, total cholesterol, and apolipoprotein B compared to atorvastatin alone treatment (LDL-C: p=0.0067, total cholesterol; p=0.0004, apolipoprotein B; p=0.013). However, the sponsor stated that LS mean % changes of those lipid parameters of the combined treatment in the AVALON Study were similar to those seen in other 4 Pfizer-sponsored studies of atorvastatin.

In the RESPOND study, the primary analysis results on LDL-C showed that (1) atorvastatin overall ($p<0.0001$), as well as (2) each active atorvastatin dosage combined across amlodipine doses (80mg, $p<0.0001$; 40mg, $p<0.0001$; 20mg, $p<0.0001$; 10mg, $p<0.0001$), had a statistically significant treatment effect on LDL-C. Results for (3) the third set of eight comparisons showed that the least square mean percent changes from baseline in LDL-C in each of the eight combination treatment groups was significantly greater ($p<0.0001$ for all comparisons) than that in the corresponding amlodipine-alone treatment group. The analysis results on systolic blood pressure showed that (1) amlodipine overall ($p<0.0001$), as well as (2) each active amlodipine dosage combined across atorvastatin doses (10mg, $p<0.0001$; 5mg, $p<0.0001$), had a statistically significant treatment effect on systolic blood pressure. Results for (3) the third set of eight comparisons showed that the least square mean changes from baseline in systolic blood pressure in each of the eight combination treatment groups was significantly greater ($p<0.0001$ for all comparisons) than that in the corresponding atorvastatin-alone treatment group. The results of the final set of eight comparisons are shown below.

Table 16: Efficacy of Combined Treatment in Reducing LDL-C and Systolic Blood Pressure – The RESPOND Study
(Source: sponsor's analysis confirmed by reviewer's analysis)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
Least Square Mean Percent Changes of LDL-C						
AML 0mg	Change	-1.2	-33.5	-39.5	-43.1	-47.0
AML 5mg	Change	-0.1	-39.0	-42.2	-44.9	-48.2
	Difference		-38.9	-42.2	-44.8	-48.2
	p-value		<0.001	<0.001	<0.001	<0.001
AML 10mg	Change	-2.6	-36.6	-38.6	-43.2	-49.2
	Difference		-34.0	-36.0	-40.6	-46.6
	p-value		<0.001	<0.001	<0.001	<0.001
Least Square Mean Changes of Systolic Blood Pressure						
AML 0mg	Change	-2.9	-4.3	-6.1	-6.2	-6.6
AML 5mg	Change	-12.6	-13.6	-15.3	-12.8	-12.6
	Difference		-9.3	-9.2	-6.6	-6.0
	p-value		<0.001	<0.001	<0.001	<0.001
AML 10mg	Change	-16.5	-15.9	-16.0	-16.5	-17.5
	Difference		-11.6	-9.9	-10.3	-11.0
	p-value		<0.001	<0.001	<0.001	<0.001

AML=amlodipine, ATO=atorvastatin

5.2 Conclusions and Recommendations

The primary analysis of the AVALON study showed that combination therapy of amlodipine 5mg and atorvastatin 10mg had a significantly higher percentage of patients who achieved JNC goals compared to atorvastatin 10mg treatment, and achieved NCEP LDL-C goals compared to amlodipine 5mg treatment. The primary analysis of the RESPOND study showed that the combined treatment with each of the eight active amlodipine and atorvastatin dosage combination had a significantly greater effect on reducing systolic blood pressure compared to atorvastatin alone treatment, and on reducing LDL-C level compared to amlodipine alone treatment. The secondary analyses of two studies showed that amlodipine did not modify the effect of atorvastatin on LDL-C and atorvastatin did not modify the effect of amlodipine on systolic blood pressure when the two treatments were co-administered. Thus, it can be concluded that the AVALON and the RESPOND studies showed that combination treatment had the significantly better effect than atorvastatin on hypertension and the significantly better effect than amlodipine on hyperlipidemia, and neither amlodipine nor atorvastatin modifies the treatment effect of the other when both are administered in combination.

Appendix 1. AVALON Study

1. Study Design

The AVALON Study is a Phase III trial that consists of four phases and one sub-study. This study is the 8-week, North America, multi-center, randomized, double-blind, double-dummy, placebo-controlled phase. The patients were randomized 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. There were three different subject populations as characterized at the time of screening. GROUP I include subjects with hypertension and hyperlipidemia only. GROUP II include subjects with hypertension and hyperlipidemia plus one additional cardiovascular risk factor excluding known coronary heart disease (CHD) and diabetes mellitus (DM). GROUP III includes subjects with hypertension and hyperlipidemia and CHD, DM or other atherosclerotic disease. There were four on-treatment visits that occurred at two-week intervals during which efficacy and safety assessments were performed.

2. Objective of the Study

Primary Objective

- To determine whether co-administration of atorvastatin 10 mg and amlodipine 5 mg QD was superior to amlodipine 5 mg QD in the treatment of hyperlipidemia and superior to atorvastatin 10 mg QD in the treatment of hypertension.

Secondary Objective

1. To provide statistical assessment of the possible synergistic effect of the dual therapy in reducing systolic blood pressure. To demonstrate additional beneficial effects of atorvastatin when added to amlodipine, by comparing changes in systolic blood pressure after 8 weeks of double-blind treatment between the dual therapy and amlodipine 5 mg treatment groups.

2. To provide comparative evaluation of the 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.

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

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

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

This objective was not specified in the protocol, but requested by the FDA to evaluate whether there were pharmacodynamic interactions between atorvastatin 10 mg and amlodipine 5 mg when administered in combination that would reduce the effect size of either.

3. Sample Size

A sample size of 1000 subjects (250 subjects per treatment group) was originally planned. Based on information from publications, 84% of subjects with mild-to-moderate diastolic hypertension who were treated with amlodipine 5mg reached JNC diastolic therapeutic goals. For subjects taking atorvastatin 10mg, 71% reached NCEP therapeutic goals after 12 weeks. A sample size of 1000 subjects (250 subjects per treatment group) was estimated to have approximately 90% power to detect around 15% difference between atorvastatin 10mg + amlodipine 5mg (combination therapy) and amlodipine 5mg treatment groups for reaching NCEP therapeutic goals, and to detect around 13% difference between atorvastatin 10mg + amlodipine 5mg (combination therapy) and atorvastatin 10mg treatment groups for reaching JNC therapeutic goals. This power calculation was based on the chi-square test (two-sided, with significance level α =0.05) and assumed that 10% of randomized subjects would not be included in the intent-to-treat evaluation of efficacy.

For the evaluation of the additional effect of the combination therapy in reducing systolic blood pressure, expected difference in the mean change in the systolic blood pressure from baseline to the double-blind endpoint between atorvastatin 10 mg + amlodipine 5 mg (combination therapy) and amlodipine 5 mg treatment groups is 3.5 mmHg. The estimated standard deviation for the change in systolic blood pressure is 10.9 mmHg. It was assumed that 10% of randomized subjects would not be included in the intent-to-treat evaluation of efficacy. With the above assumptions, it was estimated that a sample size of 250 randomized subjects per treatment group would provide 92% power (two-sided test, significance level α =0.05) to detect statistically significant treatment difference in systolic blood pressure.

Although the planned sample size in the final protocol was 1000, the sample size was reduced to approximately 800 subjects (200 subjects per treatment group) for administrative reasons such as slow enrollment. Any decision to reduce sample size was not to be based on any interim data analysis (no interim data analysis was planned for this study). With 200 randomized subjects per treatment group, there would be approximately 90% power to detect around 17% difference between atorvastatin 10 mg + amlodipine 5 mg (combination therapy) and amlodipine 5 mg treatment groups for reaching NCEP therapeutic goals, and to detect around 15% difference between atorvastatin 10 mg + amlodipine 5mg (combination therapy) and atorvastatin 10 mg treatment groups for reaching JNC therapeutic goals. This power calculation also assumed that 10% of randomized subjects would not be included in the intent-to-treat evaluation of efficacy. For the statistical evaluation of additional effect of combination therapy in reducing systolic blood pressure, with 200 randomized subjects per treatment group and the same assumptions as in the original power calculations, the power to detect treatment difference of 3.5 mmHg was estimated to be approximately 85%.

4. Primary Efficacy Parameters

- Percentage of patients reaching JNC goals
- Percentage of patients reaching NCEP LDL-C goals

5. Primary Efficacy Analysis

- Comparison of percentage of subjects reaching NCEP therapeutic targets in the atorvastatin 10 mg + amlodipine 5mg treatment group vs. amlodipine 5mg treatment group

- Comparison of percentage of subjects reaching JNC therapeutic targets in the atorvastatin 10mg + amlodipine 5mg group vs. atorvastatin 10mg treatment group

Results of both comparisons had to be statistically significant for the combination therapy to be considered efficacious. This approach is recommended for the statistical assessment of efficacy of a combination therapy when each component makes a contribution to a different outcome.

6. Secondary Efficacy Analyses

- Comparison of the changes from baseline to endpoint in blood pressure parameters (systolic blood pressure, diastolic blood pressure, and pulse pressure) in the combination and amlodipine treatment groups.
- Comparison of the changes from baseline to endpoint in lipid parameters (LDL-C, Total Cholesterol, Triglycerides, HDL-C, and Apolipoprotein B) in the combination and amlodipine treatment groups.
- Comparison of changes from baseline to endpoint in blood pressure parameters in the combination and atorvastatin treatment groups.
- Comparisons of the percentages of subjects reaching both NCEP and JNC therapeutic goals at endpoint in (1) the combination and atorvastatin treatment groups, and (2) the combination and amlodipine treatment groups.
- Comparison of least square mean changes from baseline to endpoint in the global risk factor scores in (1) the combination and atorvastatin treatment groups, and (2) the combination and amlodipine treatment groups.
- Association between subjects' ability to reach NCEP and JNC therapeutic goals at endpoint (assessed for the combination treatment group only).

7. Statistical Methods

The primary efficacy analysis was done on intent-to-treat (ITT) population including 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, subjects in Group I, II, and III were combined.

If a patient discontinued the study before completion of 8 weeks of double-blind therapy, the last non-missing, post-baseline observation was carried forward (LOCF)

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 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 α=0.05 and no adjustments were made for multiple comparisons. 95% confidence intervals around between-treatment differences in least square mean percent changes and least square mean changes from baseline to endpoint were also used. For correlation analyses, Pearson correlation coefficients were reported and simple linear regression models were fitted for the change in blood pressure as the response variable and the percent change in LDL-C as the predictor variable. The association between subjects' ability to reach NCEP and JNC therapeutic goals at endpoint was assessed for the combination treatment group using continuity-adjusted chi-square test.

8. Differences between the Protocol and Statistical Analysis Plan

Secondary evaluations for Groups I, II, and III were not performed for the individual groups. This was a deviation from the statistical methods section of the protocol. The reason for the deviation was that during the double-blind review of the data before database release, it was learned that a majority of subjects were from Group II (approximately 80% of all subjects). Therefore, selected primary and secondary efficacy evaluations were performed for groups of subjects stratified by baseline global risk factor scores. The following cohorts were evaluated: (1) subjects from Groups I and II with baseline global risk factor scores of =7; (2) subjects from Groups I and II with baseline global risk factor scores from 7 to 9 (inclusive); (3) subjects from groups I and II with baseline global risk factor scores =10; (4) subjects from Group III with a baseline global risk score of any value. No statistical comparisons were made in this evaluation.

9. Patient Disposition

A total of 848 patients were randomized to treatment. Of these, 847 patients (combination, N=207; atorvastatin, N=200; amlodipine, N=201; placebo, N=239) took at least one dose of the double-blind study medication. 841 patients (combination, N=205; atorvastatin, N=199; amlodipine, N=199; placebo, N=238) were included in the efficacy analyses. Similar proportions of patients discontinued from the study prematurely among the treated groups, and so were the proportions of the patients who completed the study. This is shown in Table below.

Table 1: Patient Disposition (Source: sponsor's analysis only)

	Combination (N=207)		Atorvastatin (N=200)		Amlodipine (N=201)		Placebo (N=239)	
	n	(%)	n	(%)	n	(%)	n	(%)
Discontinued	16	(7.7)	15	(7.5)	14	(7.0)	23	(9.6)
Completed	191	(92.3)	185	(92.5)	187	(93.0)	216	(90.4)
ITT efficacy population	205	(99.0)	199	(99.5)	199	(99.0)	238	(99.6)
Safety population	207	(100.0)	200	(100.0)	201	(100.0)	239	(100.0)

10. Demography and Baseline Characteristics

Patients who entered the study were predominantly male, white, with a mean age of approximately 55 years, and met criteria for inclusion in the Group II risk factor category. Baseline global risk scores in the four treatment groups ranged from 7.2 to 7.6 for males and from 10.4 to 11.1 for females, which according to the Framingham CHD score sheet indicate that on average, male and female subjects had an estimated 10-year CHD risk of between 14-18% and 11-13%, respectively. Statistical comparison of group risk categories across treatment groups did not reveal any statistically significant differences. There were also no statistically significant between-group differences in LDL-C levels, blood pressure, or global risk scores. Demographic and key baseline characteristics are summarized in Table below.

Table 2: Baseline Characteristics by Treatment Group
(Source: sponsor's analysis confirmed by reviewer's analysis)

Parameter	Combination (N=207)	Atorvastatin (N=200)	Amlodipine (N=201)	Placebo (N=239)
Gender				
Male (n [%])	135 (65.2)	111 (55.5)	117 (58.2)	151 (63.2)
Female (n [%])	72 (34.8)	89 (44.5)	84 (41.8)	88 (36.8)
Age (years)				
Mean (SD)	55.6 (9.9)	55.1 (9.3)	56.2 (10.3)	55.3 (9.2)
Race				
White (n [%])	173 (83.6)	167 (83.5)	169 (84.1)	193 (80.8)
Black (n [%])	24 (11.6)	22 (11.0)	18 (9.0)	27 (11.3)
Asian (n [%])	6 (2.9)	2 (1.0)	4 (2.0)	3 (1.3)
Other (n [%])	4 (1.9)	9 (4.5)	10 (5.0)	16 (6.7)
Weight (kg)				
Mean (SD), for males	95.0 (17.2)	96.1 (18.1)	93.3 (18.5)	94.0 (16.7)
Mean (SD), for females	81.4 (17.2)	83.4 (17.4)	81.2 (17.8)	82.2 (17.2)
Height (cm)				
Mean (SD), for males	177.3 (5.9)	177.0 (7.1)	175.8 (7.7)	176.8 (7.2)
Mean (SD), for females	161.4 (6.2)	163.5 (6.6)	162.1 (7.0)	162.4 (6.7)
Duration of primary diagnoses (years)				
Mean (range), for hypertension	5.9 (0.0-41.1)	5.6 (0.0-49.2)	5.9 (0.0-37.7)	7.6 (0.0-51.5)
Mean (range), for hyperlipidemia	4.5 (0.0-30.7)	4.2 (0.0-25.5)	4.2 (0.0-31.9)	4.6 (0.0-25.7)
Risk factor group assignment				
Group I (n [%])[1]	14 (6.8)	11 (5.5)	18 (9.0)	9 (3.8)
Group II (n [%])[1]	155 (74.9)	160 (80.0)	143 (71.1)	189 (79.1)
Group III (n [%])[1]	38 (18.4)	29 (14.5)	40 (19.9)	41 (17.2)
Efficacy parameters				
Mean (SD) LDL-C (mg/dL)[1]	163.9 (25.0)	161.7 (24.6)	164.3 (26.0)	163.3 (24.8)
Mean (SD) systolic BP (mmHg)[1]	146.6 (12.3)	147.1 (10.9)	147.6 (10.0)	146.7 (10.8)
Mean (SD) diastolic BP (mmHg)[1]	92.1 (7.2)	91.4 (7.7)	92.6 (6.9)	92.4 (6.2)
Mean (SD) GRF score – males[1]	7.4 (2.2)	7.2 (2.0)	7.5 (2.2)	7.6 (2.0)
Mean (SD) GRF score – females[1]	11.1 (3.6)	10.6 (2.9)	10.5 (3.6)	10.4 (3.6)

LDL-C indicates low-density lipoprotein cholesterol; BP, blood pressure; GRF, global risk factor.
[1] There were no statistically significant differences among treatment groups for these parameters.

11. Efficacy Results

11.1 Primary Efficacy Results

The primary efficacy results show 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%). Also, 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%). These results indicate that combined 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. Table summarizes the results of the primary efficacy analyses.

Table 3: Patients Achieving JNC and NCEP Goals
(Source: sponsor's analysis confirmed by reviewer's analysis)

	Placebo	AML	ATO	AML+ATO	AML + ATO	
					vs. AML	vs. ATO
Patients Achieving JNC Blood Pressure Goal						
N	236	198	198	204	-	-
n (%)	70 (29.7)	107 (54.0)	64 (32.3)	104 (51.0)	-	-
95% C.I.	-	-	-	-	-	9.2, 28.1
p-value	-	-	-	-	-	0.0002
Patients Achieving NCEP LDL-C Goal						
N	229	193	193	201	-	-
n (%)	15 (6.6)	24 (12.4)	151 (78.2)	165 (82.1)	-	-
95% C.I.	-	-	-	-	62.6, 76.7	-
p-value	-	-	-	-	<0.0001	-

AML=amlodipine only treatment, ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

11.2 Secondary Efficacy Results

Efficacy of combined treatment vs. amlodipine on blood pressure parameters

The most important secondary evaluation of efficacy was the assessment of the possible synergistic effect of the combined treatment in reducing systolic blood pressure. To confirm additional beneficial effect of atorvastatin, when added to amlodipine, changes from baseline to endpoint in systolic blood pressure, diastolic blood pressure, pulse pressure, and percentage of patients reaching JNC goal were compared between the combined treatment group and amlodipine treatment group. The following table summarizes the analysis results.

Table 4: Efficacy of Combined Treatment vs. Amlodipine on Blood Pressure
(Source: sponsor's analysis confirmed by reviewer's analysis)

	Placebo	AML	AML+ATO	AML + ATO vs. AML
N	236	198	204	-
Patients achieving JNC goal				
n (%)	70 (29.7)	107 (54.0)	104 (51.0)	-
95% C.I.		-	-	-12.8, 6.7
p-value		-	-	0.52
Systolic blood pressure				
LS Mean changes	-5.4	-14.3	-12.7	-
95% C.I.	-6.8, -4.0	-15.9, -12.9	-14.2, -11.2	-0.4, 3.8
p-value				0.12
Diastolic blood pressure				
LS Mean changes	-3.3	-8.9	-8.2	-
95% C.I.	-4.2, -2.5	-9.9, -8.0	-9.1, -7.3	-0.6, 2.1
p-value				0.27
Pulse pressure				
LS Mean changes	-2.2	-5.4	-4.5	-
95% C.I.				-0.8, 2.7
p-value				0.28

AML=amlodipine only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

As shown in the table, the least square mean changes in systolic blood pressure of the combined treatment group and the amlodipine treated group were –12.7 and –14.3 mmHg, respectively, and, in diastolic blood pressure, -8.2 and –8.9 mmHg, respectively (systolic, p=0.12; diastolic, p=0.27). The blood pressure reductions between the two groups were not statistically significant. There was also no statistically significant difference between the two treatment groups in the least square mean changes from baseline in pulse pressure (p=0.28) or in the percentages of patients who reached their JNC blood pressure goals (p=0.52). The results provide no statistical evidence that atorvastatin 10mg enhanced or otherwise modified the blood pressure lowering efficacy of amlodipine 5mg when the two treatments were combined.

Efficacy of combined treatment vs. amlodipine on lipid parameters

Changes of the lipid parameters (LDL-C, Total Cholesterol, Triglycerides, HDL-C, and Apolipoprotein B) were compared between the atorvastatin + amlodipine treatment group and the amlodipine treatment group. The results of the analysis are shown in below.

Table 5: Efficacy of Combined Treatment vs. Amlodipine on Lipid Parameters
(Source: sponsor's analysis confirmed by reviewer's analysis)

	Placebo	AML	AML+ATO	AML + ATO vs. AML
N	229	193	201	-
LDL-C (mg/dL)				
LS Mean % change	0.2	-1.8	-37.2	-
95% C. I.	-	-	-	-37.8, -33.0
p-value	-	-	-	<0.0001
Total Cholesterol (mg/dL)				
LS mean % change	-0.9	-2.1	-27.7	-
95% C.I.	-	-	-	-27.4, -23.8
p-value	-	-	-	<0.0001
Triglycerides (mg/dL)				
LS mean % change	-0.1	-2.3	-23.0	-
95% C.I.	-	-	-	-27.0, -14.4
P-value	-	-	-	<0.0001
Apolipoprotein B (mg/dL)				
LS mean % change	-1.0	-1.7	-30.7	-
95% C.I.	-	-	-	-31.2, -26.8
P-value	-	-	-	<0.0001
HDL- Cholesterol (mg/dL)				
LS mean % change	0.2	0.0	5.0	-
95% C.I.	-	-	-	2.1, 7.8
P-value	-	-	-	0.0006

AML=amlodipine only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

As can be seen in the table above, combination-treated subjects experienced highly statistically significantly greater least square mean percent changes from baseline compared with amlodipine-treated subjects in LDL-C (combination, -37.2%; amlodipine, -1.8%; p<0.0001). There were also statistically significantly (p<0.0001) greater least square mean percent changes in the combination treatment group compared with the amlodipine treatment group in all other lipid parameters analyzed in this study, e.g., total cholesterol, triglycerides, apolipoprotein B, and HDL-C. These results indicate that the combined treatment was statistically significantly more effective than amlodipine in lowering lipid levels in these patients with hyperlipidemia and hypertension.

Efficacy of combined treatment vs. atorvastatin on blood pressure parameters

Changes of the blood pressure parameters (systolic blood pressure, diastolic blood pressure, and pulse pressure) were compared between the atorvastatin + amlodipine treatment group and the atorvastatin treatment group. The results of the analysis are shown in below.

Table 6: Efficacy of Combined Treatment vs. Atorvastatin on Blood Pressure
(Source: sponsor's analysis confirmed by reviewer's analysis)

	Placebo	ATO	AML+ATO	AML + ATO vs. ATO
N	236	198	204	-
Systolic blood pressure				
LS Mean changes	-5.4	-5.9	-12.7	-
95% C.I.				-8.9, -4.6
p-value				<0.0001
Diastolic blood pressure				
LS Mean changes	-3.3	-4.2	-8.2	-
95% C.I.				-5.4, 2.7
p-value				<0.0001
Pulse pressure				
LS Mean changes	-2.2	-1.7	-4.5	-
95% C.I.				-4.5, -1.0
p-value				0.0012

ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

As shown in Table 6, patients in the combination-treated groups showed significantly greater least square mean reductions in systolic blood pressure (combination, -12.7 mmHg; atorvastatin, -5.9 mmHg: $p<0.0001$), diastolic blood pressure (combination, -8.2 mmHg; atorvastatin, -4.2 mmHg: $p<0.0001$), and pulse pressure (combination, -4.5 mmHg; atorvastatin, -1.7 mmHg; $p=0.0012$) compared to the patients in the atorvastatin group. These results indicate that the combination therapy was statistically significantly more effective than atorvastatin in the treatment of hypertension in the patients with hypertension and hyperlipidemia.

Efficacy of combined treatment vs. atorvastatin on LDL-C

This reviewer performed the comparisons between the combined treatment and atorvastatin-only treatment on the least squares mean percent changes in LDL-C and percentages of patients reaching NCEP goals for an assessment of the possible synergistic effect of the combined treatment in LDL-C. The table below summarizes the results of the analysis.

Table 7: Efficacy of Combined Treatment vs. Atorvastatin on LDL-C
(Source: sponsor's analysis confirmed by reviewer's analysis)

	Placebo	ATO	AML+ATO	AML + ATO vs. ATO
N	229	193	201	-
Patients achieving NCEP LDL-C goal				
n (%)	15 (6.6)	151 (78.2)	165 (82.1)	-
95% C.I.	-	-	-	-4.0, 11.7
p-value	-	-	-	0.23
LDL-C, mg/dL				
LS mean % change	0.2	-33.9	-37.2	-
95% C.I.	-1.3, 1.8	-35.6, -32.1	-38.9, -35.5	-5.8, -0.9
P-value	-	-	-	0.0067

The least squares mean percent changes in LDL-C were –37.2% and –33.9%, for amlodipine + atorvastatin patients and atorvastatin-only patients, respectively. And, the difference seen between the two treatment groups were statistically significant (p=0.0067). The sponsor stated in the report that these results were consistent with those of 4 Pfizer-sponsored studies of atorvastatin where the reduced LDL-C levels were 35-39%, therefore, the difference seen in AVALON study was not considered clinically meaningful. There was no statistically significant difference in percentages of patients reaching NCEP LDL-C goals when amlodipine + atorvastatin patients were compared with atorvastatin-only patients (p=0.23).

The efficacy of amlodipine + atorvastatin treatment and the atorvastatin-only treatment on hyperlipidemia was further analyzed by comparing percent changes from baseline to endpoint in lipid parameters such as Total Cholesterol (TC), Triglycerides (TG), Apolipoprotein B (apo B), and HDL-C. The following table shows the results of the analysis.

Table 8: Changes in Lipid Parameters from Baseline to Endpoint
(Source: sponsor's analysis confirmed by reviewer's analysis)

	Placebo	ATO	AML+ATO	AML + ATO Vs. ATO
N	229	193	201	-
Total Cholesterol (mg/dL)				
LS mean % change	-0.9	-24.4	-27.7	-
95% C.I.	-	-	-	-5.0, -1.5
p-value	-	-	-	0.0004
Triglycerides (mg/dL)				
LS mean % change	-0.1	-17.2	-23.0	-
95% C.I.	-	-	-	-12.0, 0.6
P-value	-	-	-	0.075
Apolipoprotein B (mg/dL)				
LS mean % change	-1.0	-27.9	-30.7	-
95% C.I.	-	-	-	-5.0, -0.6
P-value	-	-	-	0.013
HDL- Cholesterol (mg/dL)				
LS mean % change	0.2	4.1	5.0	-
95% C.I.	-	-	-	-1.9, 3.7
P-value	-	-	-	0.54

ATO=atorvastatin only treatment, AML+ATO=combined treatment of amlodipine and atorvastatin

The differences in least squares mean percent changes for other lipid parameters had a pattern similar to that observed in the analyses for LDL-C. There were statistically significant differences in least squares mean percent changes from baseline in the combined treatment group compared to the atorvastatin treatment group for TC (-27.7% vs. –24.4%; p= 0.0004) and apo B (-30.7% vs. –27.9%; p=0.013). And, there was a trend toward greater changes in the combined treatment group compared to the atorvastatin treatment group for TG (-23.0% vs. –17.2%; p=0.075). There was no statistically significant difference between the two groups for mean percent change in HDL-C (5.0% vs. 4.1%; p=0.54). As was the case for LDL-C, the sponsor stated that these results were consistent with those of 4 Pfizer-sponsored studies of atorvastatin 10 mg in patients with hyperlipidemia that are reported in the current Lipitor package insert. In these 4 studies. atorvastatin 10 mg reduced TC by 25% to 29%, apo B by 27% to 34%, and TG by 17% to 23%, and increased HDL-C by 6-7%. Therefore, the amlodipine 5 mg had no clinically meaningful impact on the lipid-lowering efficacy of atorvastatin 10 mg when the two treatments were administered together.

Since there were statistically significant differences between the combined treatment group and the atorvastatin-only group on lipid parameters, this reviewer analyzed the efficacy of atorvastatin-only treatment on hyperlipidemia by comparing the placebo group and the atorvastatin-only group. The analyses showed that atorvastatin group had statistically significant changes on all lipid parameters compared to the placebo group. The results of the analyses are summarized in the table below.

Table 9: Efficacy of Atorvastatin Group on Changes in Lipid Parameters
(Source: sponsor's analysis confirmed by reviewer's analysis)

	Placebo	ATO	ATO vs. Placebo
N	229	193	-
LDL-C (mg/dL)			
LS mean % change	0.2	-33.9	-
95% C.I.	-	-	-36.5, -31.8
p-value	-	-	<0.0001
Total Cholesterol (mg/dL)			
LS mean % change	-0.9	-24.4	-
95% C.I.	-	-	-25.3, -21.8
p-value	-	-	<0.0001
Triglycerides (mg/dL)			
LS mean % change	-0.1	-17.2	-
95% C.I.	-	-	-23.3, -11.1
P-value	-	-	<0.0001
Apolipoprotein B (mg/dL)			
LS mean % change	-1.0	-27.9	-
95% C.I.	-	-	-29.0, -24.7
P-value	-	-	<0.0001
HDL-C (mg/dL)			
LS mean % change	0.2	4.1	-
95% C.I.	-	-	1.2, 6.7
P-value	-	-	0.0049

ATO=atorvastatin only treatment

Efficacy of combined treatment on reaching both NCEP and JNC goals

In a secondary efficacy analysis of the percent-to-goals parameters, the percentage of combination-treated subjects who reached both NCEP *and* JNC therapeutic goals (45.5%) was highly statistically significantly greater ($p<0.0001$) than the percentages of either atorvastatin-treated subjects (28.6%) or amlodipine-treated subjects (8.3%) who reached both NCEP and JNC goals.

13. Conclusion

The results of the primary and the secondary analyses showed that combined treatment with atorvastatin 10mg and amlodipine 5mg was an effective treatment in patients with comorbid hypertension and hyperlipidemia. Further, administration of the two treatments together showed no evidence modifying either the blood pressure-lowering efficacy of amlodipine 5mg or the lipid-lowering efficacy of atorvastatin 10mg.

Appendix 2. RESPOND Study

1. Study Design

The RESPOND Study is a multi-national, randomized, double-blind, multi-center, double-dummy, placebo-controlled study. This study has an eight-week, double-blind treatment phase and an ongoing 60-week, open-label extension phase. At the screening visit, eligible subjects were preliminarily assigned to one of three groups (Group I, II, and III) on the basis of their risk for developing coronary heart disease (CHD). Subjects who met cardiovascular (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 (0mg, 5mg, 10mg) and atorvastatin (0mg, 10,mg, 20mg, 40mg, 80mg), where 0mg denotes placebo. The 15 treatment groups are summarized in the table below.

Table 1: Treatment Groups in RESPOND Study

	ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	0+0 mg	0+10 mg	0+20 mg	0+40 mg	0+80 mg
AML 5mg	5+0 mg	5+10 mg	5+20 mg	5+40 mg	5+80 mg
AML 10mg	10+0 mg	10+10 mg	10+20 mg	10+40 mg	10+80 mg

AML=amlodipine; ATO=atorvastatin

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.

2. Objective of the Study

Primary Objective

The primary objective of the RESPOND study was to evaluate efficacy of different dose combinations of atorvastatin and amlodipine. To demonstrate superiority of amlodipine atorvastatin combination therapy over amlodipine only treatment in reducing low-density lipoprotein cholesterol (LDL-C) by comparing:

- the dual therapies of atorvastatin 10mg, 20mg, 40mg, and 80mg each with amlodipine 5mg, to amlodipine 5mg only; and
- the dual therapies of atorvastatin 10mg, 20mg, 40mg, and 80mg each with amlodipine 10mg to amlodipine 10mg only.

To demonstrate superiority of amlodipine/atorvastatin combination therapy over atorvastatin only treatment in reducing systolic blood pressure (SBP) by comparing:

- the dual therapies of amlodipine 5mg and 10mg each with atorvastatin 10mg to atorvastatin 10mg only; and

- the dual therapies of amlodipine 5mg and 10mg each with atorvastatin 20mg to atorvastatin 20mg only; and
- the dual therapies of amlodipine 5mg and 10mg each with atorvastatin 40mg and to atorvastatin 40mg only; and
- the dual therapies of amlodipine 5mg and 10mg each with atorvastatin 80mg to atorvastatin 80mg only.

Secondary Objective

- 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.

- To provide comparative evaluation of efficacy of different dose combinations of atorvastatin and amlodipine by assessing percentages of subjects reaching NCEP, JNC, EAS and WHO-ISH therapeutic targets, changes in lipid parameters, systolic and diastolic blood pressure, pulse pressure and global risk factor scores.

- To investigate atorvastatin and amlodipine dose-response curves. To determine whether atorvastatin has impact on the blood pressure parameters and if there is any synergistic effect. To provide similar evaluation of the impact of amlodipine on the lipid parameters.

- To assess effect of atorvastatin on the blood pressure parameters by comparing changes from baseline between atorvastatin only treatment groups and double-placebo (atorvastatin 0mg and amlodipine 0mg) treatment group.

- To provide comparative evaluation of the safety profile of different dose combinations of atorvastatin and amlodipine versus atorvastatin only treatment and amlodipine only treatment.

- To provide comparative evaluation of the safety profile of the different doses of atorvastatin only treatment and amlodipine only treatment.

3. Sample Size

Power calculations for the changes in LDL-C and systolic blood pressure were performed for the primary comparisons involving low doses of atorvastatin (10mg) and amlodipine (5mg). Because greater treatment differences were expected for the higher doses of amlodipine and atorvastatin, the power to detect statistically significant results should be higher than for the low dose comparisons. A sample size of 1500 subjects (100 subjects per treatment arm) was originally planned.

The expected mean percent change from baseline to endpoint in LDL-C in subjects treated with atorvastatin 10mg and amlodipine 5mg was 36.9%, with a standard deviation of 11.8%. The

mean percent change from baseline to endpoint in LDL-C in subjects treated with amlodipine 5mg alone was expected to be zero. The expected mean change from baseline to endpoint in systolic blood pressure in subjects treated with atorvastatin 10mg and amlodipine 5mg was 16.0mmHg, and in subjects treated with atorvastatin 10mg alone, 6.2mmHg. The estimated standard deviation for the change in systolic blood pressure was 10.9 mmHg.

It was also assumed that 10% of randomized subjects would not meet criteria for inclusion in the intent-to-treat evaluation of efficacy. With these assumptions, a sample size of 100 randomized subjects per treatment group would provide 99% power (2-sided t-test, significance level=0.05) to detect statistically significant treatment differences in LDL-C and systolic blood pressure.

4. Primary Efficacy Parameters

- Percent change from baseline to 8-week in LDL-C
- Change from baseline to 8-week in systolic blood pressure

5. Secondary Efficacy Parameters

- Absolute change from baseline to 8-week in LDL-C, as well as the percent and absolute change from baseline to 8-week in other lipid parameters (HDL-C, total cholesterol, HDL-C/LDL-C ratio, VLDL-C, triglycerides, and apolipoprotein B).
- Changes from baseline to 8-week in diastolic blood pressure and pulse pressure.
- Changes from baseline to 8-week in global risk factor score.

6. Primary Efficacy Analyses

The primary analyses evaluated the efficacy of the combination treatments in reducing LDL-C and systolic blood pressure. A step-down approach utilizing closed testing procedures was followed as shown in below Table.

Table 2: Primary Efficacy Analyses

Efficacy of combined treatment in reducing LDL-C	Efficacy of combined treatment in reducing SBP
1. Null hypothesis of "no overall atorvastatin effect on LDL-C" was test. If rejected, then: ↓	1. Null hypothesis of "no overall amlodipine effect on SBP" was tested. If rejected, then: ↓
2. Hypothesis of "no individual atorvastatin dose effect on LDL-C" was tested (i.e., each active atorvastatin dose, combined across placebo and amlodipine doses, was compared with atorvastatin placebo combined across all amlodipine doses). If rejected for all 4 active atorvastatin doses, from high to low, then: ↓	2. Hypothesis of "no individual amlodipine dose effect on SBP" was tested (i.e., each active amlodipine dose, combined across placebo and active atorvastatin doses, was compared with amlodipine placebo combined across all atorvastatin doses). If rejected for both active amlodipine doses, form high to low, then: ↓
3. Hypothesis of "no individual combination treatment effect on LDL-C" was tested (i.e., each of the 8 combination treatments was compared with the corresponding amlodipine treatment).	3. Hypothesis of "no individual combination treatment effect on SBP" was tested (i.e., each of the 8 combination treatments was compared with the corresponding atorvastatin treatment).

7. Secondary Efficacy Analyses

- The main secondary analyses evaluated whether amlodipine modified the effect of atorvastatin on LDL-C and whether atorvastatin modified the effect of amlodipine on systolic blood pressure.

- Comparison of the absolute change from baseline to endpoint in LDL-C as well as the percent and absolute changes from baseline to endpoint in other lipid parameters in each of the eight combination treatment groups and the respective amlodipine treatment group.

- Comparison of the change from baseline to endpoint in diastolic blood pressure and pulse pressure in each of the eight combination treatment groups and the respective atorvastatin treatment group.

- Comparison of the changes from baseline to endpoint in global risk factor scores in each of the eight combination treatment groups and the respective amlodipine treatment group and in each of the eight combination treatment groups and the respective atorvastatin treatment group. Only Group I and II subjects were included in these analyses.

8. Statistical Methods

The primary efficacy analysis was done on intent-to-treat (ITT) population that included all randomized subjects who took at least one dose of assigned treatment during the double-blind phase of the study and had at least one post-randomization efficacy assessment during this phase. For the missing values, last observation carried forward (LOCF) method was used.

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 3x5 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. Unless otherwise noted, subjects from Groups I, II, and III combined were included.

9. Patient Disposition

A total of 1660 subjects were randomized to treatment. Of these, 1594 subjects were included in the ITT (efficacy) population. All treated subjects were included in the safety population. There was no notable rate of discontinuation in any of the treatment group. The table below shows the disposition of the patients across the treatment groups.

Table 3: Patient Disposition *(Source: sponsor's analysis only)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	Randomized (N)	111	111	111	111	111
	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(n,%)	111 (100)	111 (100)	111 (100)	111 (100)	111 (100)
	Safety (n,%)	111 (100)	111 (100)	111 (100)	111 (100)	111 (100)
AML 5mg	Randomized (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(n,%)	110 (100)	110 (99.1)	111 (100)	109 (99.1)	111 (100)
	Safety(n,%)	110 (100)	111 (100)	111 (100)	110 (100)	111 (100)
AML 10mg	Randomized (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(n,%)	109 (98.2)	108 (98.2)	110 (100)	111 (100)	111 (100)
	Safety(n,%)	111 (100)	110 (100)	110 (100)	111 (100)	111 (100)

AML=amlodipine; ATO=atorvastatin

10. Demography and Baseline Characteristics

There was no significantly different distribution of age, gender, race, risk group, LDL-C, and systolic blood pressure between the groups. The majority of subjects were white (92.3%) across the treatment groups, and approximately 48% of subjects were in Group II, and approximately 49% of all subjects were in Group III. Demographic and key baseline characteristics are summarized in Table 4 below.

Table 4: Demographic and Baseline Characteristics

(Source: sponsor's analysis confirmed by reviewer's analysis)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	**Age**					
	Mean (SD)	59.55 (9.2)	58.58 (9.2)	58.71 (8.9)	59.92 (9.3)	58.75 (8.5)
	Gender n(%)					
	Male	52 (46.9)	66 (59.5)	56 (50.5)	51 (46.0)	46 (41.8)
	Female	59 (53.2)	45 (40.5)	55 (49.4)	60 (54.1)	64 (58.2)
	Race n(%)					
	White	104 (93.7)	101 (91.0)	102 (91.9)	104 (93.7)	99 (90.0)
	Black	3 (2.7)	3 (2.7)	4 (3.6)	2 (1.8)	5 (4.6)
	Asian	1 (0.9)	1 (0.9)	4 (3.6)	1 (0.9)	3 (2.7)
	Other	3 (2.7)	6 (5.4)	1 (0.9)	4 (3.6)	3 (2.7)
	Group					
	Group I	3 (2.7)	5 (4.5)	6 (5.4)	3 (2.7)	3 (2.7)
	Group II	49 (44.1)	52 (46.9)	57 (51.4)	55 (49.6)	56 (50.9)
	Group III	59 (53.2)	54 (48.7)	48 (43.3)	53 (47.8)	51 (46.4)
	LDL-C					
	Mean (SD)	180.5 (27.7)	180.5 (23.7)	182.5 (22.4)	181.8 (27.4)	185.6 (26.2)
	SBP					
	Mean (SD)	149.0 (8.8)	149.3 (10.1)	148.6 (8.8)	148.5 (9.8)	147.8 (9.0)
AML 5mg	**Age**					
	Mean (SD)	59.3 (9.7)	60.2 (8.7)	58.1 (10.2)	58.0 (8.5)	57.2 (9.7)
	Gender n(%)					
	Male	62 (56.4)	60 (54.1)	54 (48.7)	58 (52.7)	68 (61.3)
	Female	48 (43.6)	51 (46.0)	57 (51.4)	52 (47.3)	43 (38.7)
	Race n(%)					
	White	107 (97.3)	102 (91.9)	103 (92.8)	101 (91.8)	105 (94.6)
	Black	2 (1.8)	4 (3.6)	2 (1.8)	3 (2.7)	2 (1.8)
	Asian	1 (0.9)	4 (3.6)	3 (2.7)	3 (2.7)	2 (1.8)
	Other	0 (0)	1 (0.9)	3 (2.7)	3 (2.7)	2 (1.8)
	Group					
	Group I	5 (4.6)	2 (1.8)	4 (3.6)	3 (2.7)	4 (3.6)
	Group II	53 (48.2)	46 (41.4)	53 (47.8)	58 (52.7)	46 (41.4)
	Group III	52 (47.3)	63 (56.8)	54 (48.7)	49 (44.6)	61 (55.0)
	LDL-C					
	Mean (SD)	182.83 (26.2)	178.11 (27.8)	183.45 (27.3)	181.85 (25.6)	185.54 (26.8)
	SBP					
	Mean (SD)	149.29 (9.9)	148.93 (8.7)	148.36 (8.6)	147.89 (10.9)	146.90 (8.8)
AML 10mg	**Age**					
	Mean (SD)	58.21 (9.7)	59.76 (7.7)	58.87 (9.2)	58.31 (9.4)	59.26 (8.7)
	Gender n(%)					
	Male	60 (45.1)	61 (55.5)	62 (56.4)	71 (64.0)	57 (51.4)
	Female	51 (46.0)	49 (44.6)	48 (43.6)	40 (36.0)	54 (48.7)
	Race n(%)					

	White	102 (91.9)	100 (90.9)	98 (89.1)	100 (90.1)	104 (93.7)
	Black	5 (4.5)	3 (2.7)	5 (4.6)	5 (4.5)	0 (0)
	Asian	1 (0.9)	2 (1.8)	2 (1.8)	3 (2.7)	4 (3.6)
	Other	3 (2.7)	5 (4.6)	5 (4.6)	3 (2.7)	3 (2.7)
	Group					
	Group I	3 (2.7)	3 (2.7)	2 (1.8)	3 (2.7)	3 (2.7)
	Group II	55 (49.6)	58 (52.7)	56 (50.9)	58 (52.3)	57 (51.4)
	Group III	53 (47.8)	49 (44.6)	52 (47.3)	50 (45.1)	51 (46.0)
	LDL-C					
	Mean (SD)	179.59 (24.0)	180.88 (26.5)	182.32 (23.9)	181.42 (23.3)	179.74 (25.5)
	SBP					
	Mean (SD)	147.24 (8.5)	148.62 (9.6)	148.81 (10.6)	147.81 (10.5)	148.75 (10.3)

AML=amlodipine; ATO=atorvastatin

11. Efficacy Results

11.1 Primary Efficacy Results

Efficacy of the combined treatments in reducing LDL-C

The first analysis of overall atorvastatin effect on LDL-C showed a statistically significant effect of combination therapy ($p<0.0001$) as well as the second analysis for each active atorvastatin dosage combined across amlodipine doses (80mg, $p<0.0001$; 40mg, $p<0.0001$; 20mg, $p<0.0001$; 10mg. $p<0.0001$). The final set of comparisons that the least square mean percent changes from baseline in LDL-C in each of the eight combination treatment groups was significantly greater ($p<0.0001$ for all comparisons) than that in the corresponding amlodipine-alone treatment group. These results indicated that all eight combination groups were superior to amlodipine alone in reducing LDL-C. The results of the second and the third analyses are presented in table below.

Table 5: Primary Efficacy Analysis of Combined Treatments in Reducing LDL-C
(Source: sponsor's analysis confirmed by reviewer's analysis)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean % change	-1.2	-33.5	-39.5	-43.1	-47.0
AML 5mg	LS mean % change	-0.1	-39.0	-42.2	-44.9	-48.3
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
AML 10mg	LS mean % change	-2.6	-36.6	-38.6	-43.2	-49.2
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
Total	LS mean % change	-1.3	-36.4	-40.1	-43.7	-48.2
	p-value		<0.0001	<0.0001	<0.0001	<0.0001

AML=amlodipine; ATO=atorvastatin

Efficacy of the combined treatments in reducing systolic blood pressure

The first analysis of overall amlodipine effect on systolic blood pressure showed a statistically significant effect of combination ($p<0.0001$) as well as the second analysis for each active amlodipine dosage combined across atorvastatin doses (10mg, $p<0.0001$; 5mg, $p<0.0001$). The final set of comparisons that the least square mean changes from baseline in systolic blood pressure in each of the eight combination treatment groups was significantly greater ($p<0.0001$ for all comparisons) compared with the corresponding atorvastatin-alone treatment group. This showed that all eight combination groups were superior to atorvastatin alone in lowering systolic blood pressure. The results of the second and the third analyses are shown in Table 6.

Table 6: Primary Efficacy Analysis of Combined Treatments in Reducing Systolic Blood Pressure *(Source: sponsor's analysis confirmed by reviewer's analysis)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg	Total
AML 0mg	LS mean change	-2.9	-4.3	-6.1	-6.2	-6.6	-5.2
AML 5mg	LS mean change	-12.6	-13.6	-15.3	-12.8	-12.6	-16.5
	p-value		<0.0001	<0.0001	<0.0001	0.0001	<0.0001
AML 10mg	LS mean change	-16.5	-15.9	-16.0	-16.5	-17.5	-13.4
	p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

AML=amlodipine; ATO=atorvastatin

The primary analyses of the percent change in LDL-C and changes in systolic blood pressure showed that all combination treatments were significantly effective in the hypertension compared to atorvastatin-only treatment and in the hyperlipidemia compared to amlodipine-only treatment.

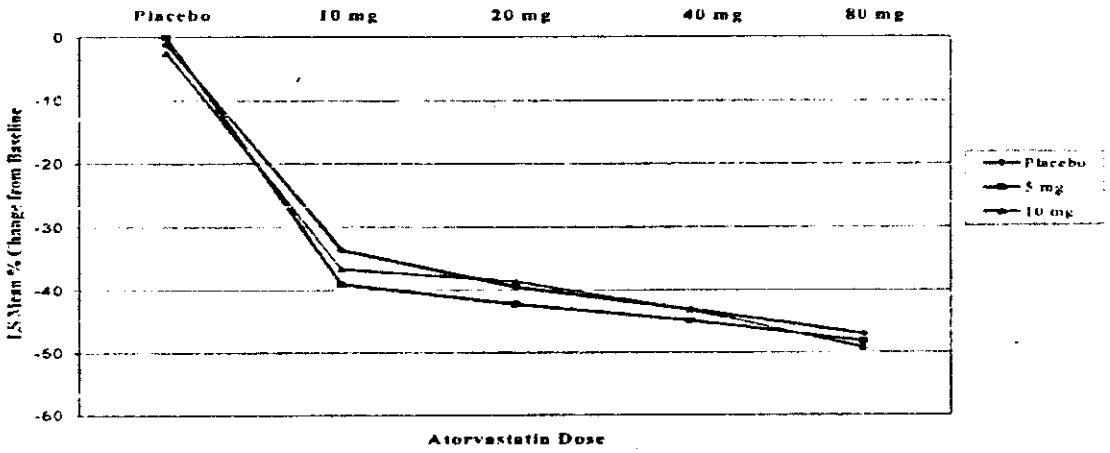
11.2 Secondary Efficacy Results

The main secondary analyses evaluated whether amlodipine modified the effect of atorvastatin on LDL-C and whether atorvastatin modified the effect of amlodipine on systolic blood pressure.

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

To analyze the effect of amlodipine on the LDL-C lowering efficacy of atorvastatin, the following graph was drawn and regression analysis was performed.

Figure 1: Effect of Amlodipine on the Atorvastatin Dose Response Curve- LDL-C
(Source: sponsor's analysis confirmed by reviewer's analysis)



The graphs in Figure 1 showed that the percent change of LDL-C of any four atorvastatin doses with amlodipine 5mg or amlodipine 10mg was similar to the percent change of LDL-C when any of the four atorvastatin dosages were treated alone. A linear regression analysis of these lines showed that there was no difference (p=0.51) among the three regression lines with respect to percent changes in LDL-C.

The effect of amlodipine on the LDL-C lowering effect of atorvastatin was further analyzed by combining atorvastatin four doses for amlodipine 10mg and amlodipine 5 mg and comparing those groups with atorvastatin only treated groups.

The analysis showed that the effect on LDL-C of amlodipine 10mg combined across active atorvastatin dosages was not significantly different from that of the atorvastatin treatment alone (P=0.24). However, there was a significant difference (p=0.0078) in the reductions in LDL-C between amlodipine 5mg combined across all atorvastatin dosages and the atorvastatin doses alone. Further analysis on comparisons between each of eight combination groups vs. corresponding atorvastatin alone treatment groups showed that the least square mean percent change from baseline in LDL-C observed when amlodipine 5mg was added to atorvastatin 10mg (-39.0%) was significantly greater (p=0.0072) than that seen when atorvastatin 10mg was administered alone (-33.5%). The results of these analyses are presented in the table below.

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Table 7: Effect of Amlodipine on LDL-C Lowering Efficacy of Atorvastatin
(Source: sponsor's analysis confirmed by reviewer's analysis)

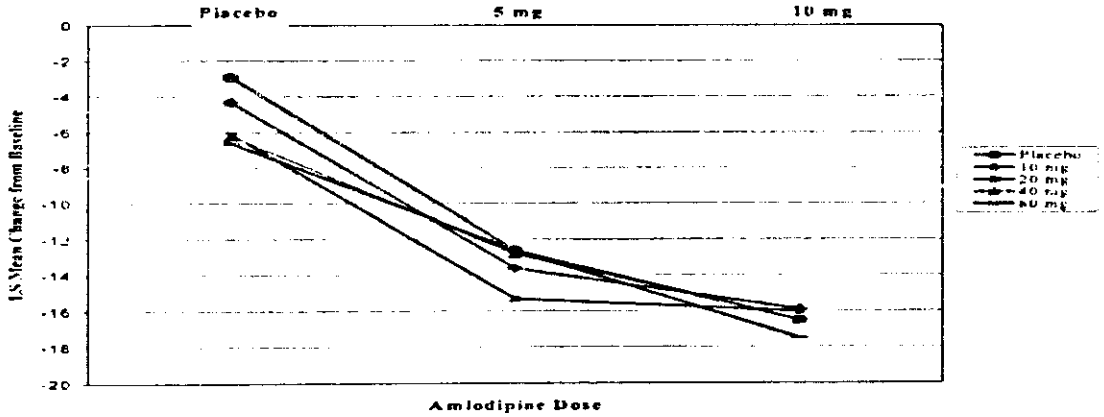
		ATO 10mg, 20mg, 40mg, and 80mg			
AML 0mg	LS mean % change	-40.8			
AML 5mg	LS mean % change p-value	-43.6 0.0078			
AML 10mg	LS mean % change p-value	-42.0 0.24			
		ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean % change	-33.5	-39.5	-43.1	-47.0
AML 5mg	LS mean % change	-39.0 0.0072	-42.2 0.17	-44.9 0.37	-48.2 0.55
AML 10mg	LS mean % change	-36.6 0.13	-38.6 0.67	-43.2 0.97	-49.2 0.28

AML=amlodipine; ATO=atorvastatin

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

As done for the analysis of effect of amlodipine on LDL-C lowering efficacy of atorvastatin, the least square mean changes from baseline in systolic blood pressure in each of the 15 treatment groups were illustrated in the following Figure.

Figure 2: Effect of Atorvastatin on the Amlodipine Dose Response Curve-Systolic Blood Pressure *(Source: sponsor's analysis confirmed by reviewer's analysis)*



The figure above showed that the reductions in systolic blood pressure when amlodipine 5mg or 10mg was administered with any of the atorvastatin doses were similar to the reductions seen when amlodipine 5mg or 10mg was administered alone. A linear regression analysis of these data showed that there was no difference (p=0.48) among the five regression lines with respect to change in systolic blood pressure.

The effect of atorvastatin on the systolic blood pressure lowering effect of amlodipine was further analyzed by conducting two comparisons. The least square mean changes in systolic blood pressure for the "high" atorvastatin doses (40mg and 80mg) were combined over both amlodipine doses and the "low" atorvastatin doses (10gm and 20mg) were combined over both amlodipine doses. These groups were compared to those in the groups treated with amlodipine alone. These comparisons showed no difference between the compared groups.

The least square mean of the systolic blood pressure changes of eight combination groups were also compared with those of the corresponding amlodipine dosage alone groups. The comparisons also showed that the effect on systolic blood pressure observed when any of the atorvastatin dosages was co-administered with amlodipine 5mg or 10mg was no different from that observed when the corresponding amlodipine dosage was administered alone. The following table shows the results of the analysis.

Table 8: Effects of Atorvastatin on Systolic Blood Pressure Lowering Efficacy of Amlodipine *(Source: sponsor's analysis confirmed by reviewer's analysis)*

		ATO 0mg	ATO 10mg+20mg		ATO 40mg+80mg	
AML 5mg+10mg	LS mean change p-value	-14.4	-15.2 0.49		-14.8 0.75	
		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 5mg	LS mean change p-value	-12.6	-13.6 0.52	-15.3 0.081	-12.8 0.89	-12.6 0.97
AML 10mg	LS mean change p-value	-16.5	-15.9 0.703	-16.0 0.76	-16.5 0.99	-17.5 0.49

AML=amlodipine; ATO=atorvastatin

Efficacy of the combined treatments in reducing other lipid parameters

Percent changes of other lipid parameters such as HDL-C, total cholesterol, and triglycerides were analyzed using the same analytical methods for the primary analyses, which was done by step-down approach utilizing closed testing procedures. The following table summarizes the third analysis results.

Table 9: Efficacy of Combined Treatment in Reducing Lipid Parameters
(Source: sponsor's analysis confirmed by reviewer's analysis)

HDL-C						
		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean % change	1.3	5.4	5.0	3.4	2.7
AML 5mg	LS mean % change	3.3	5.7	5.9	3.5	6.6
	p-value		0.26	0.23	0.91	0.13
AML 10mg	LS mean % change	4.1	6.0	6.7	4.5	5.3
	p-value		0.39	0.25	0.85	0.59
Total Cholesterol						
		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean % change	-0.1	-24.0	-29.4	-32.6	-35.6
AML 5mg	LS mean % change	0.7	-28.2	-31.0	-33.6	-36.2
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
AML 10mg	LS mean % change	-2.4	-27.1	-28.5	-32.5	-37.3
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
Triglycerides						
		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean % change	8.5	-10.7	-21.4	-24.7	-27.4
AML 5mg	LS mean % change	4.4	-19.8	-22.7	-24.5	-26.3
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
AML 10mg	LS mean % change	-4.4	-18.6	-22.2	-21.3	-33.4
	p-value		0.0005	<0.0001	<0.0001	<0.0001

AML=amlodipine; ATO=atorvastatin

Secondary analyses of percent changes in other lipid parameters yielded results similar to the primary efficacy results on LDL-C. As seen in the above table, all eight combination treatments were shown to be significantly more effective than amlodipine alone in reducing total cholesterol, and triglycerides. The least square mean percent increases in HDL-C were higher in each of the combination treatment group than in the corresponding amlodipine-alone treatment group, but the differences did not reach statistical significance.

Efficacy of the combined treatments in reducing other blood pressure parameters

The least squares mean changes of diastolic blood pressure and pulse pressure were analyzed as done for the primary analyses and other lipid parameters. The results of the third analysis are summarized in the table below.

Table 10: Efficacy of Combined Treatment in Reducing Blood Pressure Parameters
(Source: sponsor's analysis confirmed by reviewer's analysis)

Diastolic Blood Pressure						
		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean change	-3.3	-3.9	-3.8	-5.1	-4.1
AML 5mg	LS mean change	-7.6	-8.2	-9.4	-7.7	-8.5
	p-value		<0.0001	<0.0001	0.0050	<0.0001
AML 10mg	LS mean change	-10.4	-8.9	-10.5	-9.8	-11.0
	p-value		<0.0001	<0.0001	<0.0001	<0.0001
Pulse Pressure						
		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean change	0.5	-0.3	-2.3	-1.1	-2.5
AML 5mg	LS mean change	-4.9	-5.4	-5.9	-5.2	-4.1
	p-value		<0.0001	0.0034	0.0013	0.19
AML 10mg	LS mean change	-6.1	-6.9	-5.4	-6.7	-6.6
	p-value		<0.0001	0.012	<0.001	0.0009

AML=amlodipine; ATO=atorvastatin

Secondary analyses of changes in diastolic blood pressure and pulse pressure showed the results similar to the primary efficacy results on systolic blood pressure. As seen in above table, all eight combination treatments were shown to be superior to atorvastatin alone in reducing diastolic blood pressure. All combination treatments except amlodipine 5mg+atorvastatin 80mg group also showed the similar results in reducing pulse pressure.

Efficacy of Combination Treatment in Reducing Global Risk Factor Scores

As a secondary analysis, the efficacy of the combination treatments in reducing patients' Framingham CHD global risk factor scores were analyzed. The risk scores were based on patients' gender, age, LDL-C, HDL-C, systolic and diastolic blood pressure, smoking status, and the presence of diabetes, and they were used to provide an estimate of a patient's risk for developing CHD. Since patients in Group III had either CHD or a CHD risk equivalent at study entry, patients in Group III were not included in this analysis. The changes of global risk factor scores were analyzed by the same statistical method as done for the primary analyses. The following table shows the least square mean changes of global risk factor scores for each treatment group and the analysis results.

Table 11: Efficacy of Combined Treatment in Reducing Global Risk Factor Score
(Source: sponsor's analysis confirmed by reviewer's analysis)

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	LS mean change	-0.5	-2.7	-2.9	-3.5	-3.6
AML 5mg	LS mean change	-1.4	-3.8	-4.2	-4.4	-5.2
	p-value(vs. aml only)		<0.0001	<0.0001	<0.0001	<0.0001
	p-value(vs. ato only)		0.0102	0.0004	0.019	<0.0001
AML 10mg	LS mean change	-1.9	-3.4	-4.2	-4.4	-5.0
	p-value(vs. aml only)		0.0002	<0.0001	<0.0001	<0.0001
	p-value(vs. ato only)		0.108	0.0004	0.022	0.0001

AML=amlodipine; ATO=atorvastatin

The results showed that atorvastatin overall ($p<0.0001$), as well as each active atorvastatin dosage combined across amlodipine doses (80mg, $p<0.0001$; 40mg, $p<0.0001$; 20mg, $p<0.0001$; 10mg, $p<0.0001$), had a statistically significant treatment effect on the global risk factor scores. Also, the changes in all of eight combination treatment groups were statistically significantly greater ($p\leq0.0002$ for all comparisons) than that in the corresponding amlodipine-alone treatment group. The analysis with the atorvastatin-alone treatment showed the similar results. Amlodipine overall ($p<0.0001$), as well as each active amlodipine dosage combined across atorvastatin doses (10mg, $p<0.0001$; 5mg, $p<0.0001$), had a significant treatment effect on the scores. In addition, the least square mean changes in the scores in all of the combination treatment group except the amlodipine 10mg+atorvastatin 10mg group ($p=0.108$) were significantly greater than that in the corresponding atorvastatin-alone treatment group. This secondary analysis indicated that combination treatments were significantly more effective in reducing the global risk factor scores than either amlodipine alone or atorvastatin alone.

12. SUBGROUP ANALYSIS

12.1 Age, Gender, and Race

Subgroups of gender, race, and age were analyzed to explore the consistency of efficacy of the combined treatment vs. amlodipine-alone treatment on hypertension, and vs. atorvastatin-alone treatment on hyperlipidemia. There were no statistically significant differences between the gender, race, and age groups on reducing LDL-C level and systolic blood pressure. The following tables show the results of the subgroup analyses.

Table 12: Subgroup Analysis on Age *(Source: reviewer's analysis only)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	<45					
	N	6	10	7	6	11
	LDL-C	3.7	-20.7	-40.0	-41.3	-52.1
	SBP	-11.2	-2.9	-8.6	-9.6	-2.3
	45 – 59					
	N	44	47	48	51	52
	LDL-C	-2.9	-35.4	-36.7	-44.7	-44.7
	SBP	-2.1	-6.2	-4.7	-6.7	-7.6
	60-64					
	N	28	23	26	23	20
	LDL-C	-0.1	-32.5	-38.8	-36.5	-51.9
	SBP	-3.3	-1.7	-7.2	-2.2	-6.7
	≥ 65					
	N	33	10	30	31	27
	LDL-C	-0.8	-35.0	-44.3	-45.4	-45.9
	SBP	-2.4	-3.6	-7.1	-7.4	-6.0
AML 5mg	<45					
	N	10	6	9	5	13
	LDL-C	5.9	-31.6	-48.7	-46.9	-51.3
	SBP	-15.4	-11.7	-13.7	-13.9	-14.1
	45 – 59					
	N	41	48	49	57	49
	LDL-C	-2.6	-39.1	-40.2	-44.2	-45.7
	SBP	-12.1	-13.6	-15.0	-12.9	-10.5
	60-64					
	N	26	19	24	19	23
	LDL-C	2.1	-39.2	-41.4	-43.4	-50.0
	SBP	-14.0	-11.7	-12.8	-9.3	-16.0
	≥ 65					
	N	33	38	29	29	26
	LDL-C	-0.4	-39.9	-44.5	-46.9	-49.9
	SBP	-11.4	-15.1	-18.4	-14.6	-12.3
AML 10mg	<45					
	N	11	2	5	8	8
	LDL-C	2.6	-35.0	-25.0	-45.3	-49.5
	SBP	-9.6	-22.6	-14.6	-14.0	-9.6
	45 – 59					
	N	46	55	57	54	52
	LDL-C	-3.3	-38.2	-38.3	-44.6	-50.2
	SBP	-16.4	-17.2	-13.2	-17.6	-20.1
	60-64					
	N	22	26	16	19	20
	LDL-C	-5.0	-38.4	-39.8	-39.5	-54.9
	SBP	-20.5	-13.2	-19.6	-17.6	-15.3
	≥ 65					
	N	32	27	32	30	31
	LDL-C	-1.9	-31.7	-40.9	-42.4	-49.7
	SBP	-16.3	-15.3	-19.2	-14.2	-16.8

Table 13: Subgroup Analysis on Gender *(Source: reviewer's analysis only)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	Male					
	N	52	66	56	51	46
	LDL-C	-0.7	-30.2	-40.0	-43.3	-50.3
	SBP	-3.1	-5.1	-4.5	-5.6	-5.4
	Female					
	N	59	45	55	60	64
	LDL-C	-1.6	-38.4	-39.0	-42.9	-44.7
	SBP	-2.7	-3.0	-7.9	-6.8	-7.6
AML 5mg	Male					
	N	62	60	54	58	68
	LDL-C	0.2	-36.7	-41.2	-45.1	-48.4
	SBP	-11.8	-12.5	-13.3	-13.4	-11.3
	Female					
	N	48	51	57	52	43
	LDL-C	-0.5	-41.5	-43.2	-44.6	-48.0
	SBP	-13.8	-14.9	-17.3	-12.2	-14.3
AML 10mg	Male					
	N	60	61	62	71	57
	LDL-C	-2.9	-35.4	-39.9	-46.2	-47.7
	SBP	-14.6	-12.5	-16.6	-16.5	-16.9
	Female					
	N	51	49	48	40	54
	LDL-C	-2.3	-38.2	-36.8	-37.9	-50.9
	SBP	-18.7	-20.0	-15.3	-16.3	-18.3

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Table 14: Subgroup Analysis on Race *(Source: reviewer's analysis only)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	White					
	N	104	101	102	104	99
	LDL-C	-1.0	-34.0	-39.8	-43.9	-46.8
	SBP	-2.7	-4.5	-5.6	-6.3	-6.5
	Black					
	N	3	3	4	2	5
	LDL-C	4.7	-23.4	-43.2	-25.2	-44.7
	SBP	0.3	3.5	-10.6	5.5	-2.9
	Asian					
	N	1	1	4	1	3
	LDL-C	-9.6	-37.5	-41.9	-42.2	-55.7
	SBP	-14.2	13.6	-16.4	-4.3	-6.8
	Other					
	N	3	6	1	4	3
	LDL-C	-10.9	-27.3	16.3	-30.3	-51.9
	SBP	-7.7	-8.1	-6.4	-10.9	-12.5
AML 5mg	White					
	N	107	102	103	101	105
	LDL-C	-0.4	-39.0	-42.0	-45.9	-48.2
	SBP	-12.9	-13.4	-14.8	-12.8	-12.5
	Black					
	N	2	4	2	3	2
	LDL-C	27.1	-32.2	-31.6	-34.8	-50.5
	SBP	-7.8	-14.8	-13.9	-17.2	-15.3
	Asian					
	N	1	4	3	3	2
	LDL-C	-19.8	-41.2	-54.2	-42.1	-56.9
	SBP	2.3	-16.2	-22.8	-14.2	-9.8
	Other					
	N	0	1	3	3	2
	LDL-C	-	-57.3	-49.5	-24.3	-36.2
	SBP	-	-10.3	-25.6	-9.8	-19.1
AML 10mg	White					
	N	102	100	98	100	104
	LDL-C	-2.4	-36.3	-39.1	-42.8	-48.9
	SBP	-16.3	-15.3	-15.8	-16.0	-17.3
	Black					
	N	5	3	5	5	0
	LDL-C	-9.1	-39.8	-27.2	-43.3	-
	SBP	-25.1	-23.1	-13.2	-18.6	-
	Asian					
	N	1	2	2	3	4
	LDL-C	-1.8	-41.9	-23.8	-54.4	-55.8
	SBP	-14.0	-17.3	-14.0	-28.1	-21.4
	Other					
	N	3	5	5	3	3
	LDL-C	-2.9	-38.6	-46.0	-41.2	-54.2
	SBP	-7.9	-22.0	-23.5	-18.0	-19.8

12.2 Region

The countries in the RESPOND study were grouped as Europe, North America, Russia, South Africa, and South America. There was no trend or difference seen between the regions on the LS mean change of systolic blood pressure and LS mean % change of LDL-C. The results are shown in the table below.

Table 15: Subgroup Analysis on Region *(Source: reviewer's analysis only)*

		ATO 0mg	ATO 10mg	ATO 20mg	ATO 40mg	ATO 80mg
AML 0mg	Europe					
	N	46	37	43	41	42
	LDL-C	-2.0	-35.1	-40.9	-46.4	-47.2
	SBP	-2.0	-3.5	-2.0	-6.6	-5.8
	N. America					
	N	20	24	21	22	19
	LDL-C	0.7	-31.1	-34.3	-41.0	-47.3
	SBP	4.1	-4.4	-6.5	-2.4	-9.2
	Russia					
	N	34	36	35	34	36
	LDL-C	-0.1	-32.7	-40.0	-42.3	-43.3
	SBP	-7.0	-6.1	-7.2	-6.3	-4.4
	S. Africa					
	N	6	9	8	6	8
	LDL-C	-4.2	-35.0	-46.0	-36.1	-56.6
	SBP	-6.6	-0.48	-16.6	-9.8	-1.7
	S. America					
	N	5	5	4	8	5
	LDL-C	-5.1	-35.2	-31.9	-40.6	-48.9
	SBP	-3.4	-1.6	-18.5	-11.2	-12.7
AML 5mg	Europe					
	N	43	46	43	39	43
	LDL-C	-2.7	-39.0	-45.1	-49.2	-50.9
	SBP	-14.0	-13.8	-15.4	-12.6	-11.2
	N. America					
	N	19	20	20	22	19
	LDL-C	5.0	-35.7	-38.2	-37.9	-44.8
	SBP	-9.9	-7.7	-12.9	-12.1	-14.7
	Russia					
	N	35	34	35	34	36
	LDL-C	-0.6	-41.5	-41.0	-49.1	-46.1
	SBP	-11.1	-16.0	-15.4	-14.3	-12.5
	S. Africa					
	N	8	9	9	11	8
	LDL-C	1.1	-41.5	-43.0	-38.2	-49.1
	SBP	-12.2	-17.0	-19.2	-13.0	-11.8
	S. America					
	N	5	2	4	4	5
	LDL-C	4.9	-19.3	-45.4	-21.3	-53.0
	SBP	-21.2	-9.1	-18.8	-6.2	-17.1

AML 10mg	Europe					
	N	45	40	47	46	45
	LDL-C	-2.4	-34.0	-38.1	-44.6	-47.1
	SBP	-16.7	-13.7	-15.4	-15.4	-17.5
	N. America					
	N	16	23	17	17	18
	LDL-C	-0.5	-37.3	-37.4	-43.0	-48.6
	SBP	-15.6	-15.5	-16.9	-13.3	-14.9
	Russia					
	N	36	35	34	36	35
	LDL-C	-3.5	-39.3	-39.9	-40.3	-49.5
	SBP	-15.3	-16.2	-15.7	-17.6	-17.6
	S. Africa					
	N	6	7	6	9	9
	LDL-C	-3.7	-40.5	-37.2	-45.9	-55.5
	SBP	-18.0	-23.8	-11.8	-23.6	-19.4
	S. America					
	N	8	5	6	3	4
	LDL-C	-6.2	-33.2	-41.1	-48.6	-55.9
	SBP	-21.7	-23.4	-23.1	-21.1	-22.1

AML=amlodipine, ATO=atorvastatin

13. Conclusion

The results of the primary analysis indicated 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 subject's LDL-C levels, and significantly more effective than atorvastatin alone in lowering patients' SBP. The secondary analysis showed that amlodipine did not modify the LDL-C lowering efficacy of atorvastatin, and atorvastatin did not modify the SBP lowering efficacy of amlodipine when the two treatments were co-administered. Additional secondary analyses confirmed the results from the primary analysis. In conclusion, the RESPOND study showed that treatment with each of the eight dose combination of amlodipine and atorvastatin was effective in the concurrent treatment of hyperlipidemia and hypertension, and that neither amlodipine nor atorvastatin modifies the treatment effect of the other when both are administered in combination.

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