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**PROPRIETARY DRUG NAME:** Caduet/Amlodipine/Atorvastatin

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI

**PROTOCOL NO.** A3841003

**PROTOCOL TITLE:** A multi-national, prospective, randomized, double-blind, multi-center, placebo-controlled study to evaluate the efficacy and safety of a fixed combination therapy of amlodipine and atorvastatin in the treatment of concurrent hypertension and hyperlipidemia. *The Respond Trial.*

**Study Center(s):** Two hundred and nineteen (219) study centers internationally

**Study Initiation and Completion Dates:** 25 March 2002 to 28 March 2003

**Phase of Development:** Phase 3

**STUDY OBJECTIVE(S):**

*Primary objectives:*

1. To evaluate efficacy of different dose combinations of atorvastatin and amlodipine. To demonstrate superiority of amlodipine and atorvastatin combination therapy over amlodipine only treatment in reducing baseline LDL-cholesterol 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.
2. To demonstrate superiority of amlodipine and atorvastatin combination therapy over atorvastatin only treatment in reducing baseline systolic blood pressure 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 to atorvastatin 40mg only; and
  - the dual therapies of amlodipine 5mg and 10mg each with atorvastatin 80mg to atorvastatin 80mg only.

*Secondary Objectives:*

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1. 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.

Other secondary objectives were:

2. 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.
3. To assess association between subjects' ability to reach NCEP and JNC targets within each dose combination of atorvastatin and amlodipine and for all dose combinations combined. The same assessment will be performed for EAS and WHO-ISH therapeutic targets.
4. 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.
5. 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.
6. To provide comparative evaluation of the safety profile of different dose combinations of atorvastatin and amlodipine versus atorvastatin only treatment and amlodipine only treatment.
7. To provide comparative evaluation of the safety profile of the different doses of atorvastatin only treatment and amlodipine only treatment.

## METHODS

### Study Design:

The Respond Trial is a multi-national, prospective, randomized, double-blind, placebo-controlled study consisting of a screening visit, a taper/washout, a run-in/qualification period, an eight-week double-blind treatment phase, and a 60-week, open-label extension, which is ongoing. (1) At the screening visit, eligible subjects were preliminarily assigned to one of three groups (Groups I, II, III) on the basis of their risk for developing coronary heart disease (CHD). (2) Subjects then underwent a taper/washout (if required) of antihypertensive and lipid-lowering medications lasting at least three weeks and six weeks, respectively. (3) During the two-to-three visit run-in/qualification period, additional baseline efficacy assessments were performed. Subjects at this point could be reassigned to another cardiovascular (CV) risk group depending on their baseline HDL-C levels. (4) Subjects who met CV group-specific blood pressure and LDL-C criteria based on the run-in measurements, as well as all other study entry criteria, were randomized to treatment with one of the 15 possible combinations of amlodipine (0 mg, 5 mg, 10 mg) and atorvastatin (0 mg, 10 mg, 20 mg, 40 mg, 80 mg), where 0 mg denotes placebo. The 15 treatment groups are summarized in the panel below.

**Panel 1. Double-Blind Treatments**

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

0 mg denotes placebo; AML, amlodipine; ATO, atorvastatin  
Shaded area indicates eight combination study treatments.

The investigational products utilized in the double-blind phase were:

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- amlodipine besylate 5 mg capsules
- amlodipine besylate 10 mg capsules
- atorvastatin 10 mg tablets \*
- atorvastatin 40 mg tablets \*
- placebo matching atorvastatin 10 mg and 40 mg tablets
- placebo matching amlodipine 5 mg and 10 mg capsules

\* = tablets of different size

Study drug was administered in double-blind, double-dummy fashion. Patients were instructed to take:

- One amlodipine active or matching placebo capsule plus four atorvastatin active and/or matching placebo tablets once daily, at the same time every day, throughout the eight-week double-blind study period.
- The total duration of treatment was 8 weeks.

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. (5) 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.

**Diagnoses and Criteria for Inclusion of Subjects:** Subjects were men and women from 18 to 75 years of age with both hyperlipidemia and hypertension. At screening, subjects were preliminarily assigned to one of three groups based on their risk for developing CHD, as defined in the panel below.

**Panel 2. CV Risk Factors Required for Inclusion in CV Risk Groups I, II, and III**

Group I	Group II	Group III
Hypertension and hyperlipidemia only	Hypertension, hyperlipidemia, and $\geq 1$ of the following: <ul style="list-style-type: none"> <li>• <math>\geq 45</math> yrs if male</li> <li>• <math>\geq 55</math> yrs if female</li> <li>• family history of premature CHD</li> <li>• current smoker</li> <li>• HDL-C <math>&lt; 40</math> mg/dL<sup>1</sup></li> </ul>	Hypertension, hyperlipidemia and CHD, diabetes mellitus, or other atherosclerotic disease

CV indicates cardiovascular; HDL-C, high-density lipoprotein-cholesterol; CHD, coronary heart disease.

<sup>1</sup> An HDL-C of  $\geq 60$  mg/dL (1.6 mmol/L) was considered a negative risk factor. In this situation, the subject was required to have two of the above risk factors to be included in Group II.

In order to be eligible for randomization, subjects were further required to meet group-specific LDL-C and blood pressure criteria, based on measurements collected during the run-in/qualification period. These criteria are presented in the panel below.

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**Panel 3. CV Risk Group–Specific LDL-C and Blood Pressure Criteria**

	Group I	Group II	Group III
Fasting LDL-C <sup>1</sup>	190-250 mg/dL (4.9–6.5 mmol/L)	160-250 mg/dL (4.1–6.5 mmol/L)	130-250 mg/dL (3.4–6.5 mmol/L)
Blood Pressure <sup>1</sup>	Systolic, 140-179 mmHg <i>and/or</i> Diastolic, 90-109 mmHg	Systolic, 140-179 mmHg <i>and/or</i> Diastolic, 90-109 mmHg	Systolic, 130-159 mmHg <i>and/or</i> Diastolic, 85-99 mmHg

<sup>1</sup> Average of measurements collected at two (or three) pre-randomization visits occurring seven  $\pm$ 2 days apart. LDL-C indicates low-density lipoprotein-cholesterol. CV indicates cardiovascular.

CV risk group criteria were based on the NCEP ATP III guidelines for the treatment of high blood cholesterol <sup>1</sup> and the JNC VI guidelines for the treatment and prevention of high blood pressure <sup>2</sup>.

Subjects were excluded from the study if they had a history of myocardial or cerebral infarction within six and three months, respectively, of screening and a history of other serious cardiovascular disease.

**Efficacy Evaluations:** Efficacy was assessed through the collection of serum lipid levels (fasting) and blood pressure measurements obtained at 9 AM  $\pm$  3 hours at each of the run-in qualification (baseline) visits and at the end of eight weeks of double-blind treatment and, for blood pressure only, at the end of one week of double-blind treatment.

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

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

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

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

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

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

### **RESULTS**

**Subject Disposition and Demography:** Subject disposition is summarized by treatment group in the panel below.

**Panel 4. Subject Disposition**

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

One subject was randomized to combined treatment with amlodipine 10 mg and atorvastatin 80 mg but received treatment with amlodipine 5 mg and atorvastatin 0 mg. In all analyses, the subject's data were included in the treatment group to which the subject was randomized.

Within the population of all treated subjects, there were slightly more males than females, and over 90% of subjects were White. The mean age was 58 years, and the average subject was overweight based on his or her BMI. All subjects had comorbid hypertension and hyperlipidemia. Approximately 49% of all subjects had one or more additional CV risk factors (i.e., they were Group II subjects), and approximately 48% of all subjects had CHD or a CHD risk equivalent (i.e., they were Group III subjects).

**Efficacy Results: Primary efficacy results.** In analyses evaluating the efficacy of the combination treatments in reducing LDL-C, the appropriate comparisons from a 3x5 factorial ANCOVA model were specified, and were made utilizing a step-down approach with closed testing procedures. The results show that (1) atorvastatin overall ( $p < 0.001$ ), as well as (2) each active atorvastatin dosage combined across amlodipine doses (80 mg,  $p < 0.001$ ; 40 mg,  $p < 0.001$ , 20 mg,  $p < 0.001$ , 10 mg,  $p < 0.001$ ), had a statistically significant treatment effect on LDL-C. Results for (3) the third set of eight comparisons show that the least square mean percent changes from baseline in LDL-C in each of the eight combination treatment groups was significantly greater ( $p < 0.001$  for all comparisons) than that in the corresponding amlodipine-alone treatment group. Results of this last set of comparisons are shown below.

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**Panel 5. Primary Efficacy Analysis: Efficacy of the Combined Treatments in Reducing LDL-C (Percent Change from Baseline)**

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

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

As in the analyses described above, analyses evaluating the efficacy of the combination treatments in reducing systolic blood pressure utilized the appropriate comparisons from a 3x5 factorial ANCOVA model and a step-down approach with closed testing procedures. The results show that (1) amlodipine overall ( $p < 0.001$ ), as well as (2) each active amlodipine dosage combined across all atorvastatin doses (10 mg,  $p < 0.001$ ; 5 mg,  $p < 0.001$ ), had a statistically significant treatment effect on systolic blood pressure. Results of (3) the third set of eight comparisons show that there were significantly greater least square mean changes from baseline in systolic blood pressure in each of the eight combination treatment groups ( $p < 0.001$  for all comparisons) compared with the corresponding atorvastatin-alone treatment group. Results of this final set of eight comparisons are shown below.

**Panel 6. Primary Efficacy Analysis: Efficacy of the Combined Treatments in Reducing Systolic Blood Pressure (mmHg)**

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

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

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

Secondary efficacy results. In analyses evaluating whether amlodipine modifies the LDL-C-lowering efficacy of atorvastatin, the appropriate, specified comparisons from a 3x5 factorial ANCOVA model were made. For two of the comparisons, the least square mean percent changes from baseline in LDL-C for (1) amlodipine 10 mg combined over all atorvastatin doses and (2) amlodipine 5 mg combined over all atorvastatin doses were compared to those in the groups of subjects treated with active atorvastatin alone. In the remaining comparisons, (3) each of the eight amlodipine and atorvastatin dose combination groups was compared with the group receiving the corresponding amlodipine dose alone. Results are shown below.

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**Panel 7. Effect of Amlodipine on the LDL-C–Lowering Efficacy of Atorvastatin (Percent Change from Baseline)**

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

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

Results of the comparison described in (1) above and presented in the panel show that the effect on LDL-C of amlodipine 10 mg combined across active atorvastatin dosages was not significantly different from that of the active atorvastatin dosages alone ( $p=0.250$ ). This indicates that amlodipine 10 mg when administered in combination with the active atorvastatin dosages did not alter the LDL-C–lowering efficacy of atorvastatin. The comparison described in (2) above reveals that there was a significant difference ( $p=0.006$ ) in the reductions in LDL-C between amlodipine 5 mg combined across all active atorvastatin dosages and the active atorvastatin doses alone. In addition, the least square mean percent change from baseline in LDL-C observed when amlodipine 5 mg was added to atorvastatin 10 mg (-39.0%) was significantly greater ( $p=0.007$ ) than that seen when atorvastatin 10 mg was administered alone (-33.5%). None of the other comparisons described in (3) above reveals a significant treatment effect for either amlodipine 5 mg or amlodipine 10 mg. The data demonstrate that there was no overall modification of atorvastatin’s effect on LDL-C when the drug was taken in combination with amlodipine.

Analyses evaluating the effect of atorvastatin on the systolic blood pressure–lowering efficacy of amlodipine consisted of the appropriate comparisons from a 3x5 factorial ANCOVA model. For two of the comparisons, the least square mean changes in systolic blood pressure for (1) the “high” atorvastatin doses (ie, 80 mg or 40 mg) combined over both amlodipine doses and (2) the “low” atorvastatin doses (ie, 20 mg or 10 mg) combined over both amlodipine doses were compared to those in the groups treated with amlodipine alone. In the remaining eight comparisons, (3) each of the eight amlodipine and atorvastatin dose combination groups was compared with the group receiving the corresponding atorvastatin dose alone. Results are shown in the panel below.

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**Panel 8. Effect of Atorvastatin on the Systolic Blood Pressure–Lowering Efficacy of Amlodipine (mmHg)**

Parameter / Analysis		ATO 0 mg	ATO 10 mg and 20 mg combined		ATO 40 mg and 80 mg combined	
AML 5 mg and 10 mg	LS mean change /	-14.4	-15.2		-14.8	
	P-value		0.490		0.746	
	LS mean difference		-0.7		-0.3	
	95% CI		-2.5, 1.2		-2.2, 1.5	
Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 5 mg	LS mean change /	-12.6	-13.6	-15.3	-12.8	-12.6
	P-value		0.522	0.081	0.892	0.972
	LS mean difference		-1.0	-2.7	-0.2	0.1
	95% CI		-4.0, 2.0	-5.7, 0.3	-3.2, 2.8	-3.0, 3.1
AML 10 mg	LS mean change /	-16.5	-15.9	-16.0	-16.5	-17.5
	P-value		0.703	0.761	0.995	0.485
	LS mean difference		0.6	0.5	0.0	-1.1
	95% CI		-2.5, 3.6	-2.6, 3.5	-3.0, 3.0	-4.1, 1.9

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

Results of the comparisons described in (1) and (2) above and presented in the panel show that there was no significant difference between the groups in the least square mean changes from baseline in systolic blood pressure ( $p=0.746$  and  $p=0.490$ , respectively). This indicates that when co-administered with amlodipine, neither the “high” atorvastatin dosages nor the “low” atorvastatin dosages altered the systolic blood pressure–lowering efficacy of amlodipine. Results of the remaining eight comparisons described in (3) above show that the effect on systolic blood pressure observed when any of the active atorvastatin dosages was co-administered with amlodipine 5 mg or 10 mg was no different from that observed when the corresponding amlodipine dosage was administered alone. The data thus provide no evidence that atorvastatin modified amlodipine’s effect on systolic blood pressure when the two drugs were taken in combination.

Secondary analyses of changes in other lipid and blood pressure parameters yielded results similar to the primary efficacy results described above. All eight combination treatments were shown to be significantly more effective than amlodipine alone in reducing total cholesterol, VLDL-C, triglycerides, and apolipoprotein B as well as in raising the HDL-C/LDL-C ratio (but not HDL-C), and significantly more effective than atorvastatin in reducing diastolic blood pressure. Additional analyses evaluating the efficacy of the combination treatments in reducing subjects’ Framingham CHD global risk factor scores showed that the combination treatments were significantly more effective than amlodipine alone and atorvastatin alone in reducing subjects’ risk scores. The risk scores are based on subjects’ gender, age, LDL-C, HDL-C, blood pressure, smoking status, and the presence of diabetes, and they are used to provide an estimate of a subject’s risk for developing CHD. In addition, significantly higher percentages of subjects treated with amlodipine and atorvastatin reached their therapeutic NCEP goals for LDL-C, their therapeutic JNC goals for blood pressure, as well as both their LDL-C and blood pressure goals than subjects treated with either amlodipine alone or atorvastatin alone.

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

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

Three deaths were reported in the double-blind portion of the study, including one each of: cancer, sudden cardiac death and myocardial infarction. All three deaths were subjects treated with atorvastatin alone. None of these deaths was due to events considered to be causally-related to the study treatment.

The majority of the 25 SAEs reported in this study were hospitalizations due to events that in the investigator's opinion were related to intercurrent illnesses, and unrelated to the study treatment. Only one SAE was considered related to treatment: postural hypotension, in a 53-year-old male subject randomized to amlodipine 5 mg and atorvastatin 20 mg, was considered to be related to treatment with amlodipine. Thus, none of the SAEs reported in this study was considered to be related to concurrent treatment with the combination of amlodipine and atorvastatin.

**Panel 9. Incidences of Liver Enzyme Abnormalities without Regard to Baseline that Occurred in  $\geq 2\%$  of Subjects in a Combination Treatment Group**

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

As can be seen in the panel above, the incidences of on-treatment GGT abnormalities were slightly higher in subjects treated concurrently with amlodipine and atorvastatin 80 mg than in subjects treated with amlodipine alone or atorvastatin 80 mg alone. The incidences of SGOT and SGPT abnormalities in combination-treated subjects were not very different from those in subjects treated with atorvastatin alone. Review of subjects' laboratory data revealed that the magnitude of the elevations in GGT, SGPT, and SGOT values were generally similar, regardless of the subject's study treatment.

**Panel 10. Incidences of Creatine Kinase Abnormalities without Regard to Baseline that Occurred in  $\geq 2\%$  of Subjects in a Combination Treatment Group**

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

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

## CLINICAL STUDY SYNOPSIS

**Panel 11. Incidences of Renal Function Test Abnormalities without Regard to Baseline that Occurred in  $\geq 2\%$  of Subjects in a Combination Treatment Group**

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

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

**Panel 12. Incidences of Other Clinical Chemistry Abnormalities without Regard to Baseline that Occurred in  $\geq 2\%$  of Subjects in a Combination Treatment Group**

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

The incidences of potassium and glucose (fasting) abnormalities do not reveal any apparent drug- or dose-related patterns.

**Panel 13. Incidences of Urinalysis Laboratory Abnormalities without Regard to Baseline that Occurred in  $\geq 2\%$  of Subjects in a Combination Treatment Group**

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

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

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

**Based on a report completed on:** 3 October 2003.