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PROPRIETARY DRUG NAME/INN: Caduet[®]/Amlodipine-atorvastatin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT #: NCT00174330

PROTOCOL NO.: A3841026

PROTOCOL TITLE: A Multi-Center, Randomized, Open-label Study to Evaluate the Efficacy and Safety of Dual Therapy With Atorvastatin Plus Amlodipine When Compared to Amlodipine Therapy Alone in the Treatment of Subjects With Concurrent Hyperlipidemia and Hypertension

Study Center(s): Fifteen (15) study centers in China

Study Initiation and Completion Dates: 27 May 2005 to 28 February 2006

Phase of Development: Phase 4

Study Objective(s):

Primary: To evaluate efficacy of the dual therapy of atorvastatin 10 mg or 20 mg + amlodipine 5 mg or 10 mg versus amlodipine 5 mg or 10 mg alone (the evaluation of efficacy was based on the comparisons of mean change from baseline to Week 8 in blood pressure [{BP} systolic and diastolic]) and to investigate whether atorvastatin when co-administered with amlodipine modified the BP-lowering efficacy of amlodipine

Secondary:

- (1) To provide comparative evaluation of the safety profile of 8 weeks of the dual therapy with atorvastatin + amlodipine versus amlodipine alone
- (2) To provide comparative evaluation of efficacy by assessing percentages of subjects reaching systolic BP goal and diastolic BP goal, separately, after 8 weeks treatment of the dual therapy with atorvastatin + amlodipine versus amlodipine alone
- (3) To provide comparative evaluation of the percent change from baseline to week 8 in low density lipoprotein cholesterol (LDL-C) after 8 weeks of the dual therapy with atorvastatin + amlodipine versus amlodipine alone

METHODS

Study Design:

This was a randomized, open-label and active-controlled evaluation of the efficacy and safety of dual therapy with atorvastatin and amlodipine compared with amlodipine therapy alone in the treatment of subjects with comorbid hyperlipidemia and hypertension.

Subjects were required to visit the center on 5 occasions: screening, washout, baseline (Week 0), Week 4, and Week 8/early termination. Study duration was 8 weeks.

Number of Patients (planned and analyzed):

Planned: A sample size of 300 subjects was planned for this study.

Analyzed: A total of 377 patients were randomized. A total of 375 patients consisting of 254 patients in the amlodipine-atorvastatin group and 121 patients in the amlodipine group were treated.

Diagnosis and Main Criteria for Inclusion:

Chinese subjects, aged 18 to 75 years of age, who were diagnosed with concurrent hypertension and hyperlipidemia and who completed the relevant washout period for lipid-lowering and antihypertensive therapy taken at screening were eligible for entry into this study.

Study Treatment:

Subjects received atorvastatin 10 mg plus amlodipine 5 mg or amlodipine 5 mg alone once daily at baseline (Week 0) for a period of 4 weeks. At Week 4, subjects were assessed for possible titration of the amlodipine and/or atorvastatin dose. Doses were titrated up if a subject had not reached their BP and lipid goals: BP goal, systolic BP <140 mmHg and diastolic BP <90 mmHg; LDL-C goal, ≤ 120 mg/dL (3.1 mmol/L). All subjects who reached the lipid and BP goals maintained their dose. For the remaining 4 weeks, subjects received atorvastatin 10 or 20 mg plus amlodipine 5 or 10 mg or amlodipine 5 or 10 mg alone.

Efficacy Evaluations:

Primary: The primary efficacy endpoints were mean changes in systolic and diastolic BPs from baseline to Week 8. The average of 2 recorded values was used for statistical analyses, assessment of inclusion criteria and assessment of BP goals.

Secondary: The secondary endpoints were percent of subjects reaching systolic and/or diastolic BP goals (<140 / <90 mmHg) and the percent change from baseline to Week 8 in LDL-C.

Safety Evaluations: Safety was assessed by adverse events (AEs), physical examination, laboratory parameters, electrocardiograms and heart rate measurement.

Statistical Methods:

Analysis Populations: This study included the safety, per protocol (PP) and modified intent-to-treat (MITT) population. The safety population included all subjects who took at least 1 dose of study medication. The MITT population consisted of all randomized subjects in the safety population who had at least 1 dose of assigned treatment and had at least 1 post-randomization measurement of lipid and/or BP parameters. The PP population included all randomized and correctly-included subjects who received at least 1 dose of assigned treatment and reasonably adhered to the protocol. The primary analysis of the primary endpoints was performed in the PP population and was repeated in the MITT population. Other efficacy endpoints were analyzed using the MITT population.

Efficacy Analysis: For the primary endpoint, the treatment difference, corresponding 95% confidence interval (CI) and p-value for the primary efficacy endpoints were calculated (amlodipine/atorvastatin minus amlodipine alone) based on the analysis of covariance (ANCOVA) model with treatment and center as factors, and the baseline value as a covariate. The secondary efficacy endpoints were summarized for each treatment group and were compared using a chi-square test or Fisher's Exact test (for cases when the expected frequency per cell was less than 5). The estimated difference between groups in percent change from baseline to Week 8 in LDL-C with 2-sided 95% CI and p-value were calculated based on an ANCOVA model similar to the one for the primary endpoint, which included the baseline measure as a covariate and treatment and center as factors.

Safety Analysis: Safety evaluations included the number and percentage of AEs by relationship to study medication (all causality and treatment-emergent) and AEs by severity and by whether or not they led to discontinuation. Mean changes in heart rate and physical examination findings were summarized. In addition, the incidence of laboratory parameters was presented.

RESULTS

Subject Disposition and Demography:

Subject disposition is shown below in Table S1.

Table S1 Subject Disposition

	Amlodipine/Atorvastatin n (%)	Amlodipine n (%)
Treated	254	121
Completed Study	241 (94.9%)	113 (93.4)
Discontinued	13 (5.1)	8 (6.6)
Evaluated for Efficacy:		
PP Population	217 (86.8)	107 (90.7)
MITT Population	250 (98.8%)	118 (96.7)
Assessed for Safety:		
Adverse Events	254 (100%)	121 (100.0)
Laboratory Tests	248 (97.6%)	117 (96.7)

PP= per protocol, MITT= modified intent-to-treat.

All subjects were Asian and, in total, more male (55%) subjects entered the study than female (45%). Subject demographic results are summarized in Table S2.

Table S2 Subject Demographic Characteristics

	Amlodipine/Atorvastatin			Amlodipine		
	Male N=143 n (SD)	Female N=111 n (SD)	Total N=254 n (SD)	Male N=63 n (SD)	Female N=58 n (SD)	Total N=121 n (SD)
Age, years mean	53.6 (10.6)	57.0 (8.6)	55.1 (9.9)	54.0 (11.4)	55.6 (7.7)	54.7 (9.8)
Weight, kg	74.7 (9.9)	63.8 (8.6)	69.9 (10.8)	75.8 (8.0)	61.3 (8.8)	68.8 (11.1)
Height, cm	171.2 (5.9)	158.8 (5.0)	165.8 (8.3)	172.8 (5.7)	159.0 (5.1)	166.2 (8.8)

SD= standard deviation.

At screening, subjects had their BP and LDL-C levels recorded; treatment groups were comparable. No notable differences between treatment groups in any demographic measures were observed.

Efficacy Results:

A significant reduction in systolic and diastolic BP from baseline to Week 8 was observed for subjects in both treatment groups and the magnitude of this reduction was comparable across treatment groups. The difference in LS mean BP changes between the groups was small and was not statistically significant. Furthermore, the confidence intervals (CIs) associated with these estimates were narrow and excluded clinically meaningful values. These results indicated that atorvastatin did not modify the BP-lowering effect of amlodipine. Table S3 summarizes the changes from baseline in BP.

**Table S3 Mean Change from Baseline to Week 8 in Blood Pressure Parameters
 – PP Population**

	Absolute Value		Change from Baseline	
	Amlodipine/ Atorvastatin n=217	Amlodipine n=107	Amlodipine/ Atorvastatin n=217	Amlodipine n=107
Systolic BP (mmHg)				
Baseline (Week 0)				
Mean (SD)	149.4 (11.04)	150.7 (10.92)	—	—
Week 4,* mean (SD)	134.1 (12.17)	135.7 (13.37)	-15.2 (11.84)	-14.9 (12.31)
Week 8, mean (SD)	129.8 (9.26)	130.8 (11.46)	-19.6 (12.28)	-19.9 (13.24)
Adjusted Week 8:				
LS Mean (SE)			-19.9 (0.65)	-19.5 (0.93)
p-value			<0.001	<0.001
Change from baseline (amlodipine/atorvastatin)	Difference in LS Means -0.4	SE 1.11	95% CIs -2.6 to 1.8	p-value 0.700
Diastolic BP (mmHg)				
Baseline (Week 0)				
Mean (SD)	93.5 (6.85)	93.0 (6.66)	—	—
Week 4,* mean (SD)	85.0 (7.99)	85.7 (8.00)	-8.6 (7.33)	-7.3 (7.36)
Week 8, mean (SD)	82.1 (5.56)	82.3 (7.73)	-11.4 (7.38)	-10.8 (6.73)
Adjusted Week 8:				
LS Mean (SE)			-11.4 (0.43)	-10.9 (0.62)
p-value			<0.001	<0.001
Change from baseline (amlodipine/atorvastatin)	Difference in LS Means -0.4	SE 0.74	95% CIs -1.9 to 1.0	p-value 0.568

*At Week 4, n=210 and 104 for the amlodipine/atorvastatin and amlodipine groups, respectively.
 BP= blood pressure, PP= per protocol, SD= standard deviation, SE= standard error, LS= least squares,
 CIs= confidence intervals.

Secondary Efficacy:

Blood Pressure Goals: At Week 4, similar proportions of subjects between treatment groups reached BP goals. The proportion increased at Week 8: 78% and 71% of subjects who received combination treatment and amlodipine treatment reached both BP goals, respectively. No statistically significant difference was observed at Week 8/LOCF. The results are summarized in Table S4.

**Table S4 Percentage of Subjects Who Reached Blood Pressure Goals–
 MITT Population**

	Amlodipine/Atorvastatin n (%)	Amlodipine n (%)	p-value
Baseline, n	250	118	
Reached systolic BP goal	34 (13.6)	16 (13.6)	
Reached diastolic BP goal	42 (16.8)	25 (21.2)	
Reached both BP goals	0	0	
Week 4, n	242	116	
Reached systolic BP goal	162 (66.9)	71 (61.2)	
Reached diastolic BP goal	168 (69.4)	72 (62.1)	
Reached both BP goals	135 (55.8)	62 (53.4)	
Week 8 (LOCF), n	249	118	
Reached systolic BP goal	210 (84.3)	91 (77.1)	0.093
Reached diastolic BP goal	219 (88.0)	95 (80.5)	0.058
Reached both BP goals	193 (77.5)	83 (70.3)	0.137

Systolic and diastolic blood pressure goals were <140 / <90 mmHg.

MITT= modified intent-to-treat, BP= blood pressure, LOCF= last observation carried forward.

Percent Change in LDL-C: Significant reductions in LDL-C over the 8-week treatment period were observed for both treatment groups. However, subjects who received amlodipine/atorvastatin experienced a significantly greater reduction in LDL-C compared with the amlodipine group; the difference in percent reduction to Week 8/LOCF was -28.9 (95% CI -32.9 – -24.8, p <0.001). Results are shown in Table S5.

**Table S5 Mean Percent Change from Baseline to Week 8 in LDL-C
 – MITT Population**

	Absolute Value		Change from Baseline	
	Amlodipine/Atorvastatin	Amlodipine	Amlodipine/Atorvastatin	Amlodipine
LDL-C (mg/dL)				
Baseline (Week 0), n	250	118	—	—
Mean (SD)	129.8 (5.88)	129.6 (5.57)	—	—
Week 4, n	236	110	236	110
Mean (SD)	88.8 (27.02)	127.0 (23.89)	-31.5 (21.12)	-2.0 (18.42)
Week 8, n	238	114	238	114
Mean (SD)	85.1 (22.86)	122.5 (25.16)	-34.3 (17.87)	-5.3 (19.68)
Week 8/LOCF, n	247	117	247	117
Mean (SD)	85.6 (22.90)	123.0 (25.19)	-33.9 (17.94)	-4.8 (19.86)
Adjusted Week 8/LOCF: LS Mean (SE)			-33.7 (1.19)	-4.8 (1.73)
p-value			<0.001	0.006
Change from baseline/LOCF (amlodipine/atorvastatin)	Difference in LS Means -28.9	SE 2.06	95% CIs -32.9 to -24.8	p-value <0.001

LDL-C= low density lipoprotein-cholesterol, MITT= modified intent-to-treat, SD= standard deviation, LS= least squares, SE= standard error, LOCF= last observation carried forward, CI= confidence interval.

As expected, a greater proportion of subjects in the combination treatment group achieved the LDL-C goal compared with those in the amlodipine group (Table S6). This data supports

the significant difference observed in LS mean LDL-C reduction at Week 8 between the 2 treatment groups.

Table S6 Percent of Subjects Who Reached Lipid Goal – MITT Population

	Amlodipine/Atorvastatin n (%)	Amlodipine n (%)
Baseline, n	250	118
At LDL-C goal	0	0
Week 4, n	241	115
Reached LDL-C goal	215 (89.2)	38 (33.0)
Atorvastatin upward titrated	1	
Atorvastatin dose maintained	214	
Did not reach LDL-C goal	26 (10.8)	77 (67.0)
Atorvastatin upward titrated	21	
Atorvastatin dose maintained	4	
Atorvastatin titrated downwards	1	
Week 8, n	246	116
Reached LDL-C goal	230 (93.5)	50 (43.1)
Week 8/LOCF, n	247	117
Reached LDL-C goal	229 (92.7)	50 (42.7)

LDL-C goal was ≤ 120 mg/dL (3.1 mmol/L).

MITT= modified intent-to-treat, LDL-C= low density lipoprotein-cholesterol, LOCF= last observation carried forward.

Safety Results:

The proportion of subjects who experienced a treatment-related AE was slightly higher in the combination group than the amlodipine group: 13.4% (n=34) and 9.1% (n=11), respectively. The most frequent AEs, regardless of system organ class, are presented in Table S7. The incidence of all causality treatment-related AEs was similar between treatment groups.

Table S7 Treatment-Related Adverse Events (> 1% in Any Treatment Group) – Safety Population

	Amlodipine/Atorvastatin N=254 n (%)	Amlodipine N=121 n (%)
Subjects with adverse events	34 (13.4)	11 (9.1)
Peripheral edema	5 (2.0)	2 (1.7)
Abnormal ALT	4 (1.6)	0 (0.0)
ALT increased	5 (2.0)	1 (0.8)
Dizziness	4 (1.6)	1 (0.8)
Headache	3 (1.2)	2 (1.7)

ALT= alanine aminotransferase.

Nine subjects permanently discontinued due to an AE: 7 (3%) from the combination group and 2 (2%) from amlodipine group. Seven subjects discontinued due to a treatment-related AE: 6 (2%) from the combination group and 1 (1%) from the amlodipine group. All discontinuations due to AEs are summarized in Table S8.

**Table S8 Permanent Discontinuations Due to Adverse Events
 – Safety Population**

Treatment	Adverse Event	Severity	Outcome
Amlodipine	Chest pain	Moderate	Resolved
Amlodipine	Dizziness*	Mild	Resolved
Aml/atorvastatin	Pyrexia*	Mild	Resolved
Aml/atorvastatin	Myalgia*	Moderate	Resolved
Aml/atorvastatin	Hypertension	Moderate	Still present
Aml/atorvastatin	Upper abdominal pain*	Moderate	Resolved
Aml/atorvastatin	Cough*	Severe	Resolved
Aml/atorvastatin	Pruritus*	Moderate	Resolved
Aml/atorvastatin	Dizziness*	Moderate	Still present
Aml/atorvastatin	Dysuria*	Moderate	Resolved

*Treatment-related adverse events. Aml= amlodipine.

There were no deaths or serious adverse events in this study.

Comparable proportions of subjects had a laboratory abnormality (without regard for baseline): amlodipine/atorvastatin 59% (n=147) and amlodipine 62% (n=73). No laboratory abnormality was considered clinically significant; however, one patient had elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels.

One subject in each treatment group had a significant change from baseline in physical examination findings; one subject had swelling of the right eyelid while receiving amlodipine/atorvastatin and another subject had a cardiac arrhythmia while receiving treatment with amlodipine.

CONCLUSION(S):

Atorvastatin combined with amlodipine as a dual therapy did not modify the BP-lowering efficacy of amlodipine in this sample population with comorbid hypertension and hyperlipidemia. Amlodipine/atorvastatin dual therapy and amlodipine single therapy significantly reduced BP at Week 8. In support of the primary finding, no significant treatment difference was observed. There were no unexpected safety events and all but 2 AEs were mild to moderate in severity. This study provides important information on the use of dual amlodipine/atorvastatin therapy to treat comorbid hypertension and hyperlipidemia.