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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Caduet® / Amlodipine besylate & atorvastatin calcium

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: N/A

PROTOCOL NO.: A3841029 Extension

PROTOCOL TITLE: An international, multicentre, open label study to assess the effectiveness of amlodipine/atorvastatin combination in subjects with hypertension and dyslipidaemia. (The JEWEL II Study – extension phase)

Study Centers: Greece – 9 centers; Italy – 4 centers; and Switzerland – 7 centers

Study Initiation and Completion Dates: 17 March 2005 – 19 September 2006

(The study terminated early in Greece because Greece did not approve a marketing authorisation for Caduet® and hence the sponsor withdrew the application; the last patient visit in Greece was 04 January 2006.)

Phase of Development: Phase 3

Study Objective: The 54 week (approximately 12 months) open-label extension study was designed to evaluate the long-term safety and effectiveness of amlodipine/atorvastatin therapy in the treatment of simultaneous dyslipidemia and hypertension.

METHODS

Study Design: This was an open-label, multicenter extension phase study continuing from the initial 16 week-treatment period in the core phase. The extension phase consisted of up to 54 additional weeks of therapy, with study visits every 18 weeks and the final visit 70 weeks from the start of treatment in the preceding protocol. If required to attain blood pressure targets, additional blood pressure lowering medications could be administered as adjunctive therapy during the extension phase of the study (following Visit 7 of the core phase)**.** The first visit of the extension phase of the study was scheduled to coincide with the final visit (Visit 7) of the core phase.

Following blood pressure and lipid assessments, study medication was dispensed at Visits 7, 8 and 9 for approximately 18 weeks of single tablet dual therapy with amlodipine and

atorvastatin in accordance with dosing requirements to reach therapeutic targets. Subjects retained their targets, as defined by the governing European guidelines (see Table S1), determined at the enrollment visit for the core phase. Efficacy and safety assessments were planned.

Table S1. European Blood Pressure and Lipid Level Targets*

BP	**Non Diabetic** **Diabetic**	SBP < 140mmHg, DBP < 90mmHg SBP < 130mmHg, DBP < 80 mmHg
Lipid	**Group** General Asymptomatic subjects with total risk remaining ≥5%** over 10 years despite continuous lifestyle advice and after annual follow-up Subjects with established CVD or diabetes	**Target LDL-C** <115 mg/dL (<3 mmol/L) <100 mg/dL (<2.5 mmol/L) <100 mg/dL (<2.5 mmol/L)

*See European Journal of Cardiovascular Prevention and Rehabilitation 2003, 10 (Suppl 1): 1-78.
**High fatal CVD risk ≥5% over 10 years corresponded to the formerly used 20% absolute risk of a composite of coronary heart disease events

Number of Subjects (Planned and Analyzed): There was no planned number of subjects since this was an extension of a core phase. A total of 157 subjects from the core phase of the study continued in this extension phase. Of the 157 subjects who received study medication, 111 (70.7%) withdrew during the study and 46 subjects (29.3%) completed the study.

Diagnosis and Main Criteria for Inclusion: Only subjects who were enrolled in the core phase and had completed the 16-week open label treatment period at participating centers were eligible to enter the extension phase. Subjects could only enter the extension phase at the same time as they had completed the core study. Subjects were not allowed to enter the extension phase after the final study visit for the core study had passed. The inclusion criteria for entry into the core phase were:

- Subjects were men and women aged ≥18 and ≤ 80 years old.
- Women who were of childbearing potential had a negative serum pregnancy test and were using adequate measures of contraception (as determined by the investigator) to avoid pregnancy and must have been highly unlikely to conceive during the study period.
- Written informed consent was obtained for all subjects.
- Treated or untreated subjects were diagnosed with concurrent hypertension and dyslipidemia, qualifying for drug treatment according to the governing guidelines.
    - The blood pressure level used for eligibility assessment was the average of the levels obtained at the qualifying visits. Blood pressure was not at the target defined by governing guidelines.
    - The LDL-C level used for eligibility assessment was a single value obtained at screening. LDL-C could have been at target on medication or not at target with or without medication as defined by governing guidelines.
- For subjects on treatment for dyslipidemia and/or antihypertensive therapy at screening, the doses of medication were to have been stable for at least 6 weeks prior to baseline assessments.

Study Treatment: As for the core study, 8 dosage strengths of amlodipine/atorvastatin (single tablet) were used: 5 mg/10 mg, 10 mg/10 mg, 5 mg/20 mg, 10 mg/20 mg, 5 mg/40 mg, 10 mg/40 mg, 5 mg/80 mg and 10 mg/80 mg. During this extension phase, each subject was instructed to take the study medication once daily at the same time each day. Subjects were initially dispensed study medication at the start of the core phase at an appropriate dose based upon baseline blood pressure level, lipid levels and concomitant therapies. Assessment for dose titration was performed at Weeks 16, 34 and 52 (counting from the start of the core phase) in an effort to achieve both blood pressure and lipid targets as defined by European guidelines.

Efficacy Evaluations: Efficacy data were not reported because no meaningful analysis was possible given the small number of subjects who participated.

Safety Evaluations: Safety evaluations including clinical and adverse event (AE) monitoring, physical examinations and laboratory testing were done at all visits. Pregnancy testing was carried out on females of child bearing potential at all visits.

Statistical Methods: Efficacy data were not reported as no meaningful analysis could be made given the small number of subjects in the extension phase. Adverse events, laboratory and other safety data were clinically reviewed, listed and summarized.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized by treatment in Table S2, below.

Table S2. Subject Disposition and Subjects Analyzed

Number of Subjects (%)	Amlodipine 5 mg/ Atorvastatin 10 mg	Amlodipine 5 mg/ Atorvastatin 20 mg	Amlodipine 5 mg/ Atorvastatin 40 mg	Amlodipine 5 mg/ Atorvastatin 80 mg
Treated*	58	66	32	11
Completed	30 (51.7)	35 (53.0)	20 (62.5)	5 (45.5)
Discontinued	28 (48.3)	31 (47.0)	12 (37.5)	6 (54.5)
Analysed for safety:				
Adverse events	58 (100)	66 (100)	32 (100)	11 (100)
Laboratory data	58 (100)	66 (100)	32 (100)	11 (100)
	Amlodipine 10 mg/ Atorvastatin 10 mg	**Amlodipine 10 mg/ Atorvastatin 20 mg**	**Amlodipine 10 mg/ Atorvastatin 40 mg**	**Amlodipine 10 mg/ Atorvastatin 80 mg**
Treated*	24	30	14	7
Completed	8 (33.3)	18 (60.0)	12 (85.7)	3 (42.9)
Discontinued	16 (66.7)	12 (40.0)	2 (14.3)	4 (57.1)
Analysed for safety:				
Adverse events	24 (100)	30 (100)	14 (100)	7 (100)
Laboratory data	24 (100)	30 (100)	14 (100)	7 (100)

*A subject contributed to a treatment group if they have spent any time on that therapy during the study. Therefore, a subject who was titrated contributed to more than 1 treatment group

Of the 985 subjects who completed the core study, 157 (16%) continued in this extension phase study. Of the 157 subjects, 111 (70.7%) withdrew from the study. Seven subjects (4.5%) withdrew due to an AE, 71 subjects (45.2%) were withdrawn when the sponsor terminated the study at all the centers in Greece, 32 subjects (20.4%) defaulted and 1 subject

(0.6%) was lost to follow-up. In total, 46 subjects (29.3%) completed the study. Reasons for withdrawal are presented by treatment in Table S3.

Table S3. Reasons for Withdrawal from Study

No. of Subjects (%)	Amlodipine 5 mg/ Atorvastatin 10 mg	Amlodipine 5 mg/ Atorvastatin 20 mg	Amlodipine 5 mg/ Atorvastatin 40 mg	Amlodipine 5 mg/ Atorvastatin 80 mg
Related to Drug	16 (27.6)	20 (30.3)	8 (25.0)	4 (36.4)
Adverse events	0	0	2 (6.3)	1 (9.1)
Other	16 (27.6)	20 (30.3)	6 (18.8)	3 (27.3)
Not Related to Drug	12 (20.7)	11 (16.7)	4 (12.5)	2 (18.2)
Adverse events	0	0	0	0
Other	0	1 (1.5)	0	0
Subject defaulted	12 (20.7)	10 (15.2)	4 (12.5)	2 (18.2)
Total	**28 (48.3)**	**31 (47.0)**	**12 (37.5)**	**6 (54.5)**
No. of Subjects (%)	**Amlodipine 10 mg/ Atorvastatin 10 mg**	**Amlodipine 10 mg/ Atorvastatin 20 mg**	**Amlodipine 10 mg/ Atorvastatin 40 mg**	**Amlodipine 10 mg/ Atorvastatin 80 mg**
Related to Drug	12 (50.0)	11 (36.7)	2 (14.3)	2 (28.6)
Adverse events	0	0	1 (7.1)	0
Other	12 (50.0)	11 (36.7)	1 (7.1)	2 (28.6)
Not Related to Drug	4 (16.7)	1 (3.3)	0	2 (28.6)
Adverse events	3 (12.5)	0	0	0
Other	0	0	0	0
Subject defaulted	1 (4.2)	1 (3.3)	0	2 (28.6)
Total	**16 (66.7)**	**12 (40.0)**	**2 (14.3)**	**4 (57.1)**

Efficacy Results: There were not enough subjects to perform a meaningful efficacy analysis.

Safety Results: There were no deaths. A total of 11 subjects experienced at least 1 serious adverse event (SAE) during the study. The SAEs are listed in Table S4 below.

Table S4. Serious Adverse Events

Event	Event onset*	Outcome
Amlodipine 5 mg/Atorvastatin 10 mg		
Breast cancer**	Day 18	Recovered with sequalae
Spinal osteoarthritis	Day 436	Not recovered
Gastric polyps	Day 43	Not recovered
Peripheral neuropathy	Day 90	Recovered
Pneumonia	Day 233	Not recovered
Tuberculosis	Day 251	Not recovered
Amlodipine 5 mg/Atorvastatin 20 mg		
Coronary artery bypass	Day 330	Recovered
Amlodipine 5 mg/Atorvastatin 80 mg		
Gastrointestinal hemorrhage	Day 31	Recovered
Esophagitis	Day 28	Recovered
Gastric ulcer	Day 31	Recovered
Amlodipine 10 mg/Atorvastatin 10 mg		
Musculoskeletal pain	Day 199	Recovered
Rotator cuff syndrome	Day 199	Recovered
Syncope	Day 97	Recovered
Bradycardia	Day 100	Recovered
Coronary artery stenosis**	Day 251	Recovered
Amlodipine 10 mg/Atorvastatin 40 mg		
Stent placement	Day 373	Recovered
Syncope	Day 120	Recovered
Carotid sinus syndrome	Day 114	Recovered

*Relative to the start of the core phase (Day 1)
**Subject discontinued

None of the SAEs were considered to be treatment-related by the investigator.

There were 7 subjects (4.5%) who permanently discontinued due to treatment-emergent AEs during the study (Table S5). The AEs leading to discontinuation were considered to be related to treatment by the investigator in 4 subjects (2.5%). No subjects discontinued because of laboratory abnormalities.

Table S5. Discontinuation Due to Adverse Events for All Treatments

Event	Severity	Causality	SAE
Amlodipine 5 mg/Atorvastatin 40 mg			
Increased ALT and AST	Mild	Study drug	No
Myalgia	Mild	Study drug	No
Breast mass	Severe	Illness-cancer	Yes
Peripheral edema	Moderate	Study drug	No
Amlodipine 5 mg/Atorvastatin 80 mg			
Muscle spasms	Mild	Study drug	No
Amlodipine 10 mg/Atorvastatin 10 mg			
Coronary artery stenosis	Moderate	Illness-CV disease	Yes
Back pain	Moderate	Other event	No
Amlodipine 10 mg/Atorvastatin 40 mg			
Edema	Mild	Study drug	No

ALT = alanine aminotransferase, AST = aspartamine aminotransferase

A summary of treatment-emergent AEs occurring in more than 1 subject in any treatment group is shown in Table S6. Peripheral edema, the only AE occurring in at least 4% of all subjects, was reported overall by 19 subjects (12.1%) regardless of treatment. The incidence of peripheral edema was considered to be related to treatment for 18 of these subjects (11.5%).

Table S6. Summary of Treatment-emergent Adverse Events*: [Number (%) of Subjects]

All Causality	**Amlodipine 5 mg/ Atorvastatin 10 mg**	**Amlodipine 5 mg/ Atorvastatin 20 mg**	**Amlodipine 5 mg/ Atorvastatin 40 mg**	**Amlodipine 5 mg/ Atorvastatin 80 mg**
	N = 58	**N = 66**	**N = 32**	**N = 11**
Peripheral edema	4 (6.9)	4 (6.1)	2 (6.3)	0
Back pain	1 (1.7)	0	2 (6.3)	0
Headache	0	2 (3.0)	1 (3.1)	0
Upper RTI	0	2 (3.0)	0	0
RTI	0	1 (1.5)	1 (3.1)	0
Dizziness	0	1 (1.5)	0	0
Hypertension	0	1 (1.5)	0	0
Treatment-related				
Peripheral edema	4 (6.9)	4 (6.1)	2 (6.3)	0
All Causality	**Amlodipine 10mg/ Atorvastatin 10 mg**	**Amlodipine 10mg/ Atorvastatin 20 mg**	**Amlodipine 10mg/ Atorvastatin 40 mg**	**Amlodipine 10 mg/ Atorvastatin 80 mg**
	N = 24	**N = 30**	**N = 14**	**N = 7**
Peripheral edema	7 (29.2)	5 (16.7)	1 (7.1)	2 (28.6)
Back pain	2 (8.3)	0	0	0
Headache	0	0	0	0
Upper RTI	0	0	0	0
RTI	2 (8.3)	0	0	0
Dizziness	0	0	2 (14.3)	0
Hypertension	0	2 (6.7)	0	0
Treatment-related				
Peripheral edema	6 (25.0)	5 (16.7)	1 (7.1)	2 (28.6)

*Reported in at least 2 subjects for any of the treatments. If the same subject in a given treatment had more than one occurrence of the same AE, only the most severe occurrence was counted.
RTI = respiratory tract infection

There were no clinically significant laboratory abnormalities.

CONCLUSIONS:

Single pill (amlodipine/atorvastatin) therapy was safely administered at doses between 5 mg/10 mg and 10 mg/80 mg in subjects with simultaneous dyslipidemia and hypertension and was generally well-tolerated.