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For publications based on this study, see associated bibliography.

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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NATIONAL CLINICAL TRIAL NO.: NCT00174304

PROTOCOL NO.: A3841029 (interim)

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

Study Centers: The study was carried out in 110 centers distributed in 11 countries: Austria – 4 centers; Belgium – 10 centers; Finland – 9 centers; Greece – 9 centers; Hungary – 9 centers; Ireland – 3 centers; Italy – 35 centers; Portugal – 13 centers; Slovenia – 5 centers; Spain – 6 centers; and Switzerland – 7 centers.

Study Initiation and Completion Dates: 12 October 2004 – 31 August 2005

This PhRMA Web Synopsis summarizes the interim results of the core study and includes data relating to visits/events on or before Visit 7. The last subject visit for the core study occurred on 31 August 2005. The results for subjects who entered the extension phase will be reported separately.

Phase of Development: Phase 3

Study Objectives:

Primary: To evaluate the effectiveness of amlodipine/atorvastatin therapy by assessing the percentage of subjects who reached goal for blood pressure and low-density lipoprotein cholesterol (LDL-C) targets as defined by their governing (European) guidelines

Secondary:

- To assess changes from baseline to end of treatment for the following efficacy parameters: LDL-C, total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), HDL-C/LDL-C ratio, TC/HDL-C ratio, systolic blood pressure (SBP) and diastolic blood pressure (DBP)

- To evaluate the safety of amlodipine/atorvastatin with titration of amlodipine and atorvastatin doses sufficient to reach blood pressure and LDL-C therapeutic targets

- To validate a newly developed questionnaire, Expectations and Satisfaction with Treatment Questionnaire (ESTQ-SF).

Tertiary:

To assess the following efficacy endpoints by country: the percentage of subjects who reached target blood pressure and LDL-C targets according to the governing guidelines; and the changes from baseline to end of treatment for LDL-C, TC, triglycerides, HDL-C, HDL-C/LDL-C ratio, TC/HDL-C ratio, SBP and DBP

METHODS

Study Design: The JEWEL II study was a 16-week, international, multicenter, open-label study to assess the effectiveness of the amlodipine/atorvastatin single pill in achieving blood pressure and LDL-C targets, in line with European guidelines [European Journal of Cardiovascular Prevention and Rehabilitation 2003, 10 (Suppl 1): 1-78; available at www.escardio.org], in subjects with hypertension and dyslipidemia. In addition to appropriate life-style modifications, drug treatment consisted of the amlodipine/atorvastatin single pill in 8 different dosage strengths: 5/10 mg, 10/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg, 5/80 mg and 10/80 mg. The study consisted of a screening visit, a baseline enrollment visit and 5 follow-up assessment visits at Weeks 4, 6, 10, 12, and 16. The screening visit was performed to determine subject suitability. Subjects underwent a second blood pressure evaluation for eligibility during the enrollment phase. Each subject had to have 2 qualifying blood pressure measurements to be eligible for enrollment. The blood pressure level used for eligibility assessment was the average of the levels obtained at the screening (or interim) and enrollment visits. The LDL-C level used for eligibility assessment was a single fasting value obtained from the serum sample collected at screening. Assessment of blood pressure was performed at Weeks 4, 6, 10, 12, and 16 and assessment of LDL-C was performed at Weeks 4, 10, and 16. In addition, optional assessments of LDL-C could be conducted at Weeks 6 and 12 based on investigator discretion and clinical need. Up titration of the subject's medication occurred at Weeks 6, 10 and 12 if the subject had not reached targets as defined by the guidelines. Downward titration of either component was acceptable if clinically indicated and appropriately documented. Efficacy, outcomes and safety evaluations were conducted.

Number of Subjects (Planned and Analyzed): The study was designed to include approximately 1220 subjects. A total of 1466 subjects were screened and of these, 1120 were assigned to treatment. A total of 1107 took at least one dose of treatment.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were men and women aged $\geq$ 18 and $\leq$ 80 years old who had provided written informed consent and had a diagnosis of concurrent hypertension and dyslipidemia that qualified for drug treatment according to the guidelines in Europe. This was defined as those with a blood pressure level not at the target with or without medication, and LDL-C levels at target on medication or not at target with or

without medication. For subjects taking dyslipidemia and/or antihypertensive therapy at screening, the doses of medication had to be stable for at least 6 weeks prior to baseline assessments.

Study Treatment: The amlodipine/atorvastatin single pill was available in 8 dosage strengths: 5/10 mg, 10/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg, 5/80 mg and 10/80 mg. During the 16-week treatment phase of the study, each subject was instructed to take the study medication once daily at the same time each day. Doses were titrated over the 16 weeks in an effort to achieve both blood pressure and lipid targets as defined by European guidelines (see table below).

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.
BP = blood pressure

A subject's initial dose of amlodipine/atorvastatin was based on the level of both blood pressure and LDL-C control and the use of blood pressure and/or lipid lowering medications at screening and enrollment. The amlodipine component of the single pill was initial or substitution therapy for Istin®/Norvasc®, switch therapy for other calcium channel blockers (CCBs) or add-on therapy to other antihypertensive agents. The atorvastatin component of the therapy was initial or substitution therapy for Lipitor® or switch therapy for other lipid lowering agents; it could not have been add-on therapy or used with other lipid lowering agents during this 16-week study.

Efficacy Evaluations:

Blood Pressure Measurements: At each visit, following a 5-minute seated rest period, 3 seated blood pressure readings were obtained at 2-minute intervals.

Twelve-hour Fasting Serum Lipid Profile: The complete serum profile (serum total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C, the HDL/LDL-C ratio, the TC/HDL-C ratio and apolipoprotein B) was determined from blood samples taken at screening, enrollment and at Weeks 4, 10 and 16.

Outcomes Research:

Expectations and Satisfaction with Treatment Questionnaire (ESTQ): The results of the questionnaire will be reported separately.

Safety Evaluations: Clinical and adverse event (AE) monitoring was performed at all visits. Physical examinations were performed at screening and final assessment. Laboratory tests were performed at screening, enrollment and final assessment. Additionally, clinical chemistry tests were performed at Weeks 6 and 12, and optionally at Week 10. Pregnancy testing was carried out on females of child bearing potential at screening (additional pregnancy testing was required in Austria).

Statistical Methods: For continuous data, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) were presented. For categorical data, the number and percentage of subjects were summarized. In addition, for the efficacy endpoints, 95% confidence intervals (CIs) were computed for the mean changes from baseline to end of treatment, and for the percentage of responders who reached blood pressure and LDL-C targets; CIs were based on the Normal distribution. For the mean changes from baseline to end of treatment, CIs that included zero were interpreted as not showing a statistically significant change from baseline.

Efficacy analyses were done for both the full analysis set (FAS) and per protocol population (PP). The FAS was the Intent-to-Treat (ITT) population, which consisted of all enrolled subjects who received at least one dose of study medication and had post-enrolment efficacy data. The FAS/ITT population was the primary population for the assessment of efficacy. The PP population comprised those subjects in the ITT population who had taken at least 80% of the intended medication and had completed 16 weeks of treatment (i.e., had not discontinued treatment). Safety analyses were performed using the safety population, which consisted of all subjects who were known to have received at least one dose of study medication.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized by treatment in the table below.

Table S2. Subject Disposition and Subjects Analysed

Numbers 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*	502	363	192	76
Completed	446 (88.8)	334 (92.0)	178 (92.7)	71 (93.4)
Discontinued	56 (11.2)	29 (8.0)	14 (7.3)	5 (6.6)
Analysed for efficacy:				
FAS/ITT	491 (97.8)	359 (98.9)	189 (98.4)	75 (98.7)
PP	422 (84.1)	314 (86.5)	164 (85.4)	66 (86.8)
Analysed for safety:				
Adverse events	502 (100)	363 (100)	192 (100)	76 (100)
Laboratory data	484 (96.4)	351 (96.7)	187 (97.4)	74 (97.4)
	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*	204	154	88	37
Completed	187 (91.7)	147 (95.5)	84 (95.5)	34 (91.9)
Discontinued	17 (8.3)	7 (4.5)	4 (4.5)	3 (8.1)
Analysed for efficacy:				
FAS/ITT	202 (99.0)	153 (99.4)	87 (98.9)	37 (100)
PP	183 (89.7)	137 (89.0)	78 (88.6)	32 (86.5)
Analysed for safety:				
Adverse events	204 (100)	154 (100)	88 (100)	37 (100)
Laboratory data	201 (98.5)	151 (98.1)	87 (98.9)	36 (97.3)

*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. Consequently, the calculation of percent discontinuations contains a variable unavoidable degree of underestimation.

Within the FAS/ITT population, the majority of all subjects were white (99.3%); 55.7% of subjects were male (mean age: 59 years, range 33–85) and 44.3% female (mean age: 62 years, range 31–85). All subjects had been diagnosed with concurrent hypertension and dyslipidemia with mean durations since first diagnosis of 8.1 and 4.7 years, respectively.

A total of 135 subjects (12.2%) withdrew from the study during the active treatment. Reasons for withdrawal are presented by treatment below. Of the subjects who withdrew due to AEs, the largest proportion was in the 5 mg/10 mg group.

Table S3. Reasons for Withdrawal from Study

Numbers 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
Total withdrawn	56 (11.2)	29 (8.0)	14 (7.3)	5 (6.6)
Adverse event	18 (3.6)	17 (4.7)	4 (2.1)	3 (3.9)
Laboratory abnormality	5 (1.0)	1 (0.3)	0	0
Other*	3 (0.6)	1 (0.3)	2 (1.0)	1 (1.3)
Subject defaulted**	30 (6.0)	10 (2.8)	8 (4.2)	1 (1.3)
	Amlodipine 10 mg / Atorvastatin 10 mg	**Amlodipine 10 mg / Atorvastatin 20 mg**	**Amlodipine 10 mg / Atorvastatin 40 mg**	**Amlodipine 10 mg / Atorvastatin 80 mg**
Total withdrawn	17 (8.3)	7 (4.5)	4 (4.5)	3 (8.1)
Subject death	1 (0.5)	0	0	0
Adverse Event	8 (3.9)	2 (1.3)	1 (1.1)	0
Laboratory abnormality	2 (1.0)	0	0	1 (2.7)
Other*	1 (0.5)	0	2 (2.3)	0
Subject defaulted**	5 (2.5)	5 (3.2)	1 (1.1)	2 (5.4)

*Other includes changing concomitant medication during hospitalization, protocol violators, lack of effect, low/on compliance and a subject who moved.
**Defaulted includes subjects who withdrew consent and subjects lost to follow up.

Efficacy Results:

Primary Endpoint: For the FAS, 51% of subjects on any treatment and 52% of subjects on amlodipine 5 or 10 mg/atorvastatin 10 mg achieved both blood pressure and lipid targets. The percentages were slightly higher for the PP analysis set.

Table S4. The Percentage of Subjects Achieving Both Blood Pressure and Lipid Treatment Targets

	Amlodipine / Atorvastatin All Treatments	Amlodipine (5 mg or 10 mg) / Atorvastatin 10 mg
FAS, N	1084	478
Number of subjects achieving both BP and LDL-C targets [95% CI]	548 (50.6%) [47.5%, 53.6%]	248 (51.9%) [47.3%, 56.4%]
PP, N	936	408
Number of subjects achieving both BP and LDL-C targets [95% CI]	503 (53.7%) [50.5%, 57.0%]	228 (55.9%) [50.9%, 60.8%]

The primary endpoint was also summarized by subgroups of interest. The results from these subgroup analyses showed that, for all treatments (FAS/ITT), both blood pressure and lipid targets were also achieved for:

- 53%, 50% and 50% of subjects who had previously used amlodipine, other CCB treatment, or other non-CCB treatment, respectively, versus 52% of subjects who were naïve to prior antihypertensive use
- 40%, 54% and 27% of subjects who had previously used atorvastatin, other statin treatment, or other non-statin treatment, respectively, versus 52% of subjects who were naïve to prior lipid lowering use

- 51% and 49% of subjects with a primary and secondary prevention of CVD classification, respectively
- 29% of subjects with diabetes versus 59% of subjects without diabetes
- 48% of subjects with metabolic syndrome versus 58% without metabolic syndrome, as defined by the new International Diabetes Federation criteria
- 46% of subjects with metabolic syndrome versus 55% without metabolic syndrome, as defined by the National Cholesterol Education Program (NCEP) adult treatment panel (ATP) III criteria
- 57% of subjects at LDL-C goal at baseline and 49% of subjects not at LDL-C goal at baseline
- 51% of White subjects (N = 1076), 50% of Black subjects (N = 6), and 50% of subjects of other ethnicity (N = 2)
- 40% of subjects with total cholesterol below 6.5 mmol/L with at least 3 additional defined risk factors and 54% without total cholesterol below 6.5 mmol/L and at least 3 additional defined risk factors
- 59% of subjects aged 18–44 years, 53% of subjects aged 45–64 years and 45% aged at least 65 years
- 50% of males and 51% of females

The results were similar for the PP analyses.

Secondary Endpoints: For all treatments (FAS/ITT), the mean change from baseline to end of treatment for: LDL-C was a decrease of 1.09 mmol/L; for TC was a decrease of 1.26 mmol/L; for triglycerides was a decrease of 0.32 mmol/L; for HDL-C was a marginal decrease of 0.03 mmol/L; for the HDL-C/LDL-C ratio was an increase of 0.18; for the TC/HDL-C ratio was a decrease of 0.83; for SBP was a decrease of 21.8 mmHg; and for DBP was a decrease of 12.6 mmHg. In total, 89% of subjects achieved either blood pressure or lipid targets on any treatment. The results were similar for the PP analyses.

Tertiary Endpoints: In all countries, apart from Finland, Ireland, Italy and Switzerland, at least 50% of subjects on all treatments achieved country specific blood pressure and lipid targets. For Finland, Ireland, Italy and Switzerland, 37 – 47% of subjects on all treatments achieved country specific blood pressure and lipid targets.

Safety Results: Two subjects died: 1 subject during active treatment with amlodipine 10 mg/atorvastatin 10 mg (acute myocardial infarction) and 1 subject 24 days after discontinuing treatment with amlodipine 5 mg/atorvastatin 10 mg (metastatic cancer of the omentum, left lung, and neck and small bowel obstruction that lead to sudden death post-therapy). None of the deaths was attributed to study drug by the investigator.

A total of 24 subjects experienced at least 1 serious adverse event (SAE) during the study. The SAEs are listed below. None of the SAEs were considered to be treatment-related by the investigator.

Table S5 Summary of SAEs

SAE	Outcome
Amlodipine 5 mg/Atorvastatin 10 mg	
Trauma*	Recovered
Accidental fall*	Recovered
Chest pain*	Recovered
Myocardial infarction†	Recovered
Collapse	Recovered
Gastric polyps	Not recovered
Ulnar neuritis	Recovered
Atrial fibrillation*	Recovered with sequelae
Suspicion of pneumonia	Recovered
Clinical diagnosis of tuberculosis	Not recovered
Pain in the right shoulder	Recovered
Lesion in the rotary artery	Unknown
Syncope	Recovered
Recurring episode of bradycardia	Recovered
Bilateral renal stagnation	Not recovered
Small bowel obstruction*	Not recovered
Metastatic carcinoma, omentum*	Not recovered
Metastatic carcinoma, lymph node neck*	Not recovered
Metastatic carcinoma, left lung*	Not recovered
Sudden death†	Death
Worsening of neurosis	Not recovered
Panic attack	Recovered
Depression	Not recovered
Worsening of hypertension	Recovered
Phlegmon	Recovered with sequelae
Amlodipine 5 mg/Atorvastatin 20 mg	
Adenocarcinoma of colon*	Recovered with sequelae
Myocardial infarction*	Recovered
Syncope*	Recovered
Ventricular tachycardia*	Recovered
Coronary artery stenosis†	Recovered
Amlodipine 5 mg/Atorvastatin 40 mg	
Atrial fibrillation*	Recovered
Congestive heart failure*	Recovered
Hemorrhagic uterine fibroma*	Recovered
Acute cholecystitis	Recovered
Deep venous thrombosis	Recovering
Suspected pulmonary embolism	Recovering
Amlodipine 5 mg/Atorvastatin 80 mg	
Esophagitis	Recovered
Gastric ulcer	Recovered
Gastrointestinal bleeding	Recovered
Amlodipine 10 mg/Atorvastatin 10 mg	
Critical stenosis of right coronary vessel	Recovered
Cystis synovialis	Recovered
Acute myocardial infarction	Death
Amlodipine 10 mg/Atorvastatin 40 mg	
Derangement of lateral right meniscus, surgical removal	Recovered
Angina*	Recovered with sequelae
Angina unstable*	Recovered
Amlodipine 10 mg/Atorvastatin 80 mg	

Carotid sinus syndrome	Recovered
Hyperreflexia	
Syncope	Recovered
Carotid sinus hyperreflexia	Unknown
*SAEs leading to permanent discontinuations	
Amlodipine 5 mg / Atorvastatin 10 mg and Amlodipine 10 mg / Atorvastatin 10 mg	
Phlegmon	Recovered with sequelae
Accidental fall	Recovered
Critical stenosis of the right coronary vessel	Recovered
*SAEs leading to permanent discontinuations	
†Post-therapy	

A total of 69 subjects (6.2%) permanently discontinued the study as a result of treatment-emergent AEs during the study; the AEs for 51 subjects (4.6%) were considered to be related to treatment by the investigator. Treatment-related AEs leading to discontinuation are summarized below. The most common treatment-related AE from any treatment group was peripheral edema.

Table S6 Discontinuation Due to Treatment-related Adverse Events by Treatment [Number of Subjects]

Event	Mild	Moderate	Severe	Total
Amlodipine 5 mg/Atorvastatin 10 mg				
Peripheral Edema	7	3	1	11
Increased CK	3		1	4
Myalgia			1	1
Pruritus		1		1
Amlodipine 5 mg/Atorvastatin 20 mg				
Peripheral Edema	2	4	1	7
Myalgia	1			1
Pruritus		1		1
Headache		1		1
Vertigo	1			1
Amlodipine 5 mg/Atorvastatin 40 mg				
Peripheral Edema	1			1
Edema	1			1
Amlodipine 5 mg/Atorvastatin 80 mg				
Peripheral Edema		1		1
Pruritus		1		1
Headache		1		1
Vertigo		1		1
Amlodipine 10 mg/Atorvastatin 10 mg				
Peripheral Edema	1	4	2	7
Increased CK	1			1
Myalgia			1	1
Edema		1		1
Amlodipine 10 mg/Atorvastatin 20 mg				
Peripheral Edema		1		1
Amlodipine 10 mg/Atorvastatin 40 mg				
Peripheral Edema			1	1

Subjects may have discontinued because of more than 1 event

A total of 362 subjects (32.7%) had at least 1 treatment-emergent AE. The incidence of AEs for all treatments is listed below. The majority of AEs were mild to moderate in severity. The

most common AE was peripheral edema, which was also the most common treatment-related AE. Treatment-related AEs were reported by 224 subjects (20.2%).

Table S7 Summary of Treatment-emergent Adverse Events for All Treatments (All Causality)*

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 = 502	N = 363	N = 192	N = 76
Peripheral edema	35 (7.0)	26 (7.2)	8 (4.2)	5 (6.6)
Influenza	9 (1.8)	5 (1.4)	4 (2.1)	1 (1.3)
Dizziness	3 (0.6)	5 (1.4)	3 (1.6)	0
Increased GGT	2 (0.4)	1 (0.3)	0	0
Treatment-related				
Peripheral Edema	35 (7.0)	26 (7.2)	8 (4.2)	5 (6.6)
All Causality	**Amlodipine 10 mg/ Atorvastatin 10 mg**	**Amlodipine 10 mg/ Atorvastatin 20 mg**	**Amlodipine 10 mg/ Atorvastatin 40 mg**	**Amlodipine 10 mg/ Atorvastatin 80 mg**
	N = 204	N = 154	N = 88	N = 37
Peripheral Edema	43 (21.1)	19 (12.3)	12 (13.6)	4 (10.8)
Influenza	3 (1.5)	1 (0.6)	1 (1.1)	2 (5.4)
Dizziness	1 (0.5)	1 (0.6)	4 (4.5)	0
Increased GGT	1 (0.5)	0	0	2 (5.4)
Treatment-related				
Peripheral edema	42 (20.6)	18 (11.7)	12 (13.6)	4 (10.8)

*Reported in at least 3% of subjects for any of the treatments. Events are sorted by decreasing frequency in the amlodipine 5 mg /atorvastatin 10 mg group.
If the same subject in a given treatment had more than 1 occurrence of the same AE, only the most severe occurrence was counted
GGT = gamma-glutamyl transferase

The most commonly reported laboratory abnormalities were increased triglycerides, increased potassium and increased blood urea nitrogen. Six subjects also discontinued with treatment-related laboratory abnormalities; 5 of which referred to raised liver enzymes.

CONCLUSIONS:

Single-pill (amlodipine/atorvastatin) therapy was an effective and well-tolerated treatment, which treated subjects so that they achieved both blood pressure and LDL-C targets recommended by European guidelines to improve management of total CV risk in subjects requiring blood pressure- and lipid-lowering therapy. It was also effective and safe for reducing blood pressure and LDL-C to target levels in subjects with diabetes and/or metabolic syndrome.