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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Caduet®/Amlodipine Besylate and Atorvastatin Calcium

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert

NATIONAL CLINICAL TRIAL NO.: NCT00407537

PROTOCOL NO.: A3841047

PROTOCOL TITLE: A Cluster Randomized Trial on Cardiovascular Risk Factor Management: Caduet® Versus Usual Care in Subjects with Hypertension and Additional Cardiovascular Risk Factors in Clinical Practice

Study Centers: A total of 140 investigators (referred to as sites hereafter) were randomized and 136 of these treated subjects: 6 sites in Costa Rica, 18 sites in Croatia, 11 sites in the Czech Republic, 3 sites in the Dominican Republic, 8 sites in Indonesia, 4 sites in Jordan, 18 sites in the Republic of Korea, 2 sites in Kuwait, 4 sites in Lebanon, 6 sites in Malaysia, 9 sites in Mexico, 2 sites in Panama, 6 sites in the Philippines, 14 sites in the Russian Federation, 8 sites in Taiwan, 3 sites in Thailand, 6 sites in Turkey, 4 sites in the United Arab Emirates, and 4 sites in Venezuela.

Study Initiation Date and Primary Completion or Completion Dates: 01 March 2007 to 06 October 2009

Phase of Development: Phase 4

Study Objectives: To investigate whether a Caduet®-based multi-factorial risk factor management strategy resulted in greater reduction in total cardiovascular (CV) risk as compared with a usual care strategy after 1 year of treatment in subjects with hypertension and ≥3 additional risk factors, but no coronary heart disease (CHD) and baseline cholesterol ≤6.5 mmol/L (250 mg/dL), a population similar to that recruited into the Anglo-Scandinavian Cardiac Outcomes Trial, which demonstrated the CV outcomes benefit of aggressive multi-factorial risk factor treatment with amlodipine and atorvastatin.

METHODS

Study Design: This was a prospective, cluster randomized, open-label study with 2 equally-sized parallel groups, comparing a Caduet-based multi-factorial risk factor management strategy with usual care in clinical practice in hypertensive subjects with 3 or more additional CV risk factors but no known CHD. The investigators in this study were to

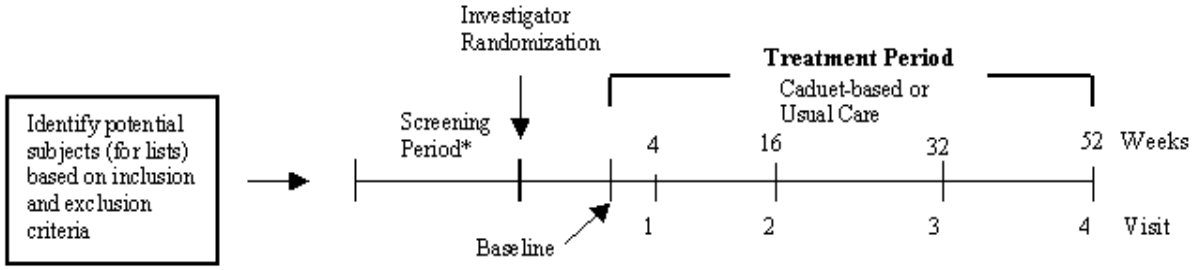
be general practitioners or outpatient primary care physicians. Subjects were treated for 12 months according to the randomization group of the site. The site was to be assigned a randomization group after all 12 subjects in the site cluster were screened and deemed eligible. The 2 planned parallel groups were:

- Group I (Caduet): 82 sites, representing 984 subjects, were to be randomized to use Caduet.
- Group II (usual care): 82 sites, representing 984 subjects, were to be randomized to usual care.

The study design consisted of 6 visits: screening, Week 0 (baseline), Week 4 ±7 days (Visit 1), Week 16 ±14 days (Visit 2), Week 32 ±14 days (Visit 3), and Week 52 ±14 days (final visit; Visit 4). All efforts were to be made by each site to complete screening of the subjects in the site cluster within 3 months. Eligible subjects were dispensed study treatment (for subjects in the Caduet group) or prescribed usual care (for subjects in the usual care group) at baseline, Week 4, Week 16, and Week 32. In addition, optional visits could be performed at any point during the treatment period.

The study design is presented in Figure S1.

Figure S1. Study Design



*12 subjects per site were to be screened and deemed eligible before the site was randomly assigned to a group.

Number of Subjects (Planned and Analyzed): It was planned that 1968 subjects would be recruited by 164 sites. At total of 136 sites treated subject (72 sites in the Caduet group and 64 sites in the usual care group), 1531 subjects were assigned to treatment, and 1461 subjects were treated: 783 of the treated subjects were assigned to Caduet and 678 of the treated subjects were assigned to usual care. Of these, 779 subjects were treated with Caduet and 682 subjects were treated with usual care. Four subjects who were assigned to Caduet were treated with usual care.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, aged 35 to 79 years at baseline, with hypertension (untreated systolic blood pressure [SBP] ≥160 mm Hg and/or diastolic blood pressure [DBP] ≥100 mm Hg or treated SBP ≥140 mm Hg and/or DBP ≥90 mm Hg [or SBP >130 mm Hg and/or DBP >80 mm Hg in the presence of diabetes]) and total cholesterol (TC) ≤6.5 mmol/L (250 mg/dL) were enrolled. The subjects were to have no history of CHD and had 3 or more additional CV risk factors.

Study Treatment: Four doses of Caduet were provided to the Caduet treatment group for use in this study: amlodipine/atorvastatin 5/10 mg, 5/20 mg, 10/10 mg, and 10/20 mg. All Caduet tablets containing 5 mg amlodipine (regardless of atorvastatin content) were white, non-debossed, and oval-shaped. All Caduet tablets containing 10 mg amlodipine (regardless of atorvastatin content) were blue, non-debossed, and oval-shaped.

Each subject assigned to the Caduet group was instructed to take Caduet once daily at the same time each day during the 52-week treatment phase of the study. At Week 0 (baseline) and Week 4 (Visit 1), Caduet 5/10 mg or 10/10 mg was administered as directed by the blood pressure (BP) target. Caduet could be given as initial or additional treatment with other anti-hypertensive drugs to control BP, or, if the subject was already receiving a calcium channel blocker, Caduet could substitute for this while other anti-hypertensive drugs were added on as required to control BP.

At Week 16 (Visit 2) through Week 52 (Visit 4), if cholesterol was controlled, Caduet containing 10 mg atorvastatin (either 5/10 mg or 10/10 mg Caduet) was continued in all countries. If cholesterol was not controlled, Caduet was increased to doses of 5/20 mg or 10/20 mg in countries where Caduet containing 20 mg atorvastatin was approved. In countries where only Caduet containing 10 mg atorvastatin was approved (Caduet 5/10 mg and 10/10 mg), Caduet discontinuation was to be considered. If Caduet was discontinued, any anti-hypertensive and lipid lowering drugs (eg, amlodipine and atorvastatin) were to be administered, as required to control BP and cholesterol.

In the usual care group, from Week 0 (baseline) through Week 52 (Visit 4), investigators prescribed usual care from a full choice of any locally approved (and not contraindicated) anti-hypertensive and/or lipid lowering drugs, including, but not limited to, amlodipine and atorvastatin, according to local clinical practice. No study drug was provided to subjects in the usual care group.

Efficacy Evaluations: The investigator collected the necessary information to assess the CV risk factors (age, sex, current smoking behavior, diabetes, BP, and lipid parameters [TC, triglycerides, high density lipoprotein [HDL] cholesterol, and low density lipoprotein [LDL] cholesterol {calculated}]).

Safety Evaluations: Safety was evaluated by monitoring of adverse events (AEs), clinical laboratory tests (serum chemistry), BP, and heart rate.

Statistical Methods: Two analysis sets were identified: the full analysis set (FAS; all subjects who had BP and lipid parameter data from at least 1 post baseline visit) and the safety analysis set (all subjects in the Caduet group who received at least 1 dose of Caduet and all subjects in the usual care group). All efficacy analyses were based on the FAS and safety analyses were based on the safety analysis set.

The primary and continuous secondary endpoints were analyzed using a mixed-effects linear model which included baseline value, country, treatment, and site as covariates. A compound-symmetry variance-covariance matrix was used for subjects from the same site, and subjects' site was treated as a random effect in the mixed-effects model. Statistical

testing was 2-sided and was evaluated at the 5% significance level. Where appropriate, a 95% confidence interval (CI) was provided along with point estimates. Discrete secondary endpoints variables were analyzed using a generalized linear mixed model with generalized estimating equations method that included compound-symmetry covariance matrix for subjects from the same site. Each analysis included country, site, and group. The estimated odds ratio, its 95% CI, and the corresponding p-value were reported.

Safety data were summarized and presented by group according to the sponsor's data standards.

RESULTS

Subject Disposition and Demography: Subject disposition and randomized groups are summarized in Table S1.

Table S1. Subject Disposition and Evaluation Groups

	Caduet n (%)	Usual Care n (%)
Site Distribution (assigned)	72	64
Screened 2514		
Assigned to treatment[a] 1531		
Treated (assigned)[b]	783	678
Treated (actual)[b]	779	682
Completed	686 (88.1)	638 (93.5)
Discontinued	93 (11.9)	44 (6.5)
Subject died	5 (0.6)	2 (0.3)
Related to study treatment	27 (3.5)	0
AE	27 (3.5)	0
Not related to study treatment	61 (7.8)	42 (6.2)
AE[d]	9 (1.2)	0
Lost to follow-up	12 (1.5)	19 (2.8)
Other	6 (0.8)	7 (1.0)
Subject no longer willing to participate	34 (4.4)	16 (2.3)

AE = adverse event; n = number of subjects/sites.

[a] All eligible subjects within a randomized cluster who attended the baseline visit. Some subjects who attended a baseline visit were not treated. One subject, who withdrew participation after screening/randomization but before receiving treatment, is not included in assigned to treatment.

[b] Four subjects were randomized to receive Caduet; however, they received usual care during the study. These subjects were analyzed in the usual care group for safety and in the Caduet group for efficacy. All other subjects treated at the same site received Caduet as randomized; therefore, one site was included in both the Caduet and usual care group for safety analyses.

All subjects were included in the safety analysis set and were analyzed for AEs. A similar percentage of subjects in each group were included in the FAS (760 [97.6%] subjects in the Caduet group and 657 [96.3%] subjects in the usual care group). However, there were missing data at some visits (the visit was missed or assessments were not performed) for some subjects, which affected the number of observation available for analysis.

Both groups had similar mean (standard deviation [SD]) age (60.0 [10.0] years in the Caduet group and 60.3 [10.2] years in the usual care group), weight (77.9 [16.1] kg in the Caduet group and 78.0 [16.1] kg in the usual care group), height (164.5 [10.1] cm in the Caduet group and 164.2 [10.1] cm in the usual care group), and race distribution. As defined in the protocol, approximately 50% of the enrolled subjects were female. A similar mean duration since first diagnosis of hypertension was observed for each group (8.8 years in the Caduet group and 8.6 years in the usual care group).

Baseline values for Framingham 10-year risk of total CHD, European SCORE and Framingham 10-year risk of CV disease, Framingham 10-year risk of stroke, systolic and diastolic BP, and lipid parameters are summarized in Table S2.

Table S2. Mean Baseline Values for Framingham 10-Year Risk of Total Coronary Heart Disease, European Systematic Coronary Risk Evaluation and Framingham 10-Year Risk of Cardiovascular Disease, Framingham 10-Year Risk Of Stroke, Systolic and Diastolic Blood Pressure, and Lipid Parameters

		Caduet (N = 760)	Usual Care (N = 657)
Framingham 10-year risk of total CHD	Mean (SD)	20.0 (11.17)	18.1 (11.13)
European SCORE 10-year risk of CV disease	Mean (SD)	5.0 (5.03)	4.6 (4.50)
Framingham 10-year risk of CV disease	Mean (SD)	31.1 (17.37)	29.7 (17.64)
Framingham 10-year risk of stroke	Mean (SD)	5.8 (2.95)	5.6 (2.93)
Systolic BP (mm Hg)	Mean (SD)	150.4 (14.84)	144.3 (14.46)
Diastolic BP (mm Hg)	Mean (SD)	89.7 (9.22)	86.5 (9.13)
TC (mg/dL)	Mean (SD)	199.4 (29.97)	197.3 (29.93)
LDL cholesterol (mg/dL)	Mean (SD)	119.4 (27.08)	118.0 (27.75)
HDL cholesterol (mg/dL)	Mean (SD)	47.6 (13.58)	47.8 (13.70)
Triglycerides (mg/dL)	Mean (SD)	167.0 (85.73)	161.2 (80.1)

BP = blood pressure; CHD = coronary heart disease; CV = cardiovascular; HDL = high density lipoprotein; LDL = low density lipoprotein; N = number of subjects in the full analysis set; SCORE = Systematic Coronary Risk Evaluation; SD = standard deviation; TC = total cholesterol.

Subjects enrolled in the Caduet group compared with the usual care group had higher mean BP (systolic and diastolic), triglycerides, Framingham 10-year risk of total CHD, and European SCORE and Framingham 10-year risk of CV disease at baseline. Mean Framingham 10-year risk of stroke, TC, LDL cholesterol, and HDL cholesterol were comparable between groups at baseline.

The distribution of study defined CV risk factors at baseline is summarized in Table S3.

Table S3. Distribution of Cardiovascular Risk factors at Baseline: All Treated Subjects (Actual Treatment)

	Caduet (N = 779) n (%)	Usual Care (N = 682) n (%)
Family history of premature CHD in a first degree relative (<55 years old)	455 (58.41)	364 (53.37)
Age male and female (males >55 years; females >65 years)	411 (52.76)	383 (56.16)
Left-ventricular hypertrophy	369 (47.37)	337 (49.41)
Type 2 diabetes	336 (43.13)	286 (41.94)
Smoking	317 (40.69)	246 (36.07)
Other specified abnormalities on ECG	211 (27.09)	259 (37.98)
Plasma TC/HDL ratio ≥6 or HDL <40 mg/dL	203 (26.06)	157 (23.02)
Peripheral vascular disease	201 (25.8)	130 (19.06)
Previous stroke or transient ischemic attack	108 (13.86)	98 (14.37)

CHD = coronary heart disease; ECG = electrocardiogram; HDL = high density lipoprotein; N = number of subjects in each group as assigned to treatment; n = number of subjects with an observation; TC = total cholesterol.

The 3 most frequently observed risk factors for CV disease in both groups were family history of premature CHD in a first degree relative, age, and left-ventricular hypertrophy. At baseline, the groups were comparable for the incidence of left-ventricular hypertrophy, type 2 diabetes, and previous stroke or transient ischaemic attack; however, a higher percentage of subjects in the Caduet group compared with the usual care group had a family history of premature CHD in a first degree relative, were smokers, had plasma TC/HDL ratio ≥6 or HDL <40 mg/dL, or had peripheral vascular disease. A higher percentage of subjects in the usual care group compared with the Caduet group were males >55 years or females >65 years, or had other specified abnormalities on ECG.

A similar median (range) duration of treatment was observed in the Caduet (352.0 [1 to 410] days) and usual care groups (365.0 [2 to 507] days).

Efficacy Results: *Primary Efficacy Results:* Change from baseline in Framingham 10-year risk of total CHD at Week 52 is summarized in Table S4.

Table S4. Framingham 10-Year Risk of Total Coronary Heart Disease at Baseline and Week 52, and Change from Baseline to Week 52

Framingham 10-Year Risk of total CHD		Caduet (N = 760)	Usual Care (N = 657)
Baseline	Mean (SD)	20.0 (11.17)	18.1 (11.13)
Week 52	Mean (SD)	12.5 (8.26)	16.3 (10.51)
Change from baseline to Week 52	LSM (95% CI)	-7.24 (-7.87, -6.61)	-2.52 (-3.19, -1.84)
Caduet vs usual care*	LSM (95% CI)	-4.72 (-5.55, -3.89)	
	p-value	<0.001	

* The difference in LSM, its 95% CI, and the corresponding p-value were calculated based on a mixed-effects linear model.

CHD = coronary heart disease; CI = confidence interval; LSM = least-square mean; N = number of subjects in the full analysis set; SD = standard deviation; vs = versus.

A mean decrease from baseline to Week 52 in Framingham 10-year risk of total CHD was observed in both groups. In the Caduet group, the percentage change in Framingham 10-year risk of total CHD from baseline to Week 52 was -33.0% compared with -4.0% in the usual care group. The adjusted difference between groups for absolute change and the percentage change from baseline to Week 52 was -4.72 (95% CI: -5.55, -3.89 [p<0.001]; Table S4) and -27.09% (95% CI: -31.71, -22.48 [p<0.001]), respectively.

Secondary Efficacy Results: A decrease from baseline to Week 16 in mean Framingham 10-year risk of total CHD was observed in both groups. In the Caduet group the percentage change from baseline to Week 16 was -33.4% compared with -5.1% in the usual care group. The adjusted difference between groups for absolute change from baseline to Week 16 was -4.76 (95% CI: -5.58, -3.93 [p<0.001])

A decrease from baseline to Week 16 and Week 52 in mean European SCORE 10-year risk of CV disease was observed in both groups. In the Caduet group the percentage change from baseline to Week 16 and Week 52 was -34.8% and -36.4%, respectively, compared with -12.9% and -12.5%, respectively, in the usual care group. The adjusted difference between groups for absolute change from baseline to Week 16 and Week 52 was -0.88 (95% CI: -1.16, -0.59 [p<0.001]) and -0.97 (95% CI: -1.23, -0.72 [p<0.001]), respectively.

A decrease from baseline to Week 16 and Week 52 in mean Framingham 10-year risk of CV disease was observed in both groups. In the Caduet group the percentage change from baseline to Week 16 and Week 52 was -35.9% and -35.4%, respectively, compared with -9.6% and -9.0%, respectively, in the usual care group. The adjusted difference between groups for absolute change from baseline to Week 16 and Week 52 was -7.16 (95% CI: -8.29, -6.03 [p<0.001]) and -7.13 (95% CI: -8.21, -6.05 [p<0.001]), respectively.

A decrease from baseline to Week 16 and Week 52 in mean Framingham 10-year risk of stroke was observed in both groups. In the Caduet group the percentage change from baseline to Week 16 and Week 52 was -35.9% and -35.4%, respectively, compared with -9.6% and -9.0%, respectively, in the usual care group. The adjusted difference between groups for absolute change from baseline to Week 16 and Week 52 was -1.35 (95% CI: -1.57, -1.14) and -1.35 (95% CI: -1.56, -1.15), respectively. Since the Framingham 10-year risk of stroke was calculated from the CV disease risk function using the gender specific 'calibration factor', no formal statistical testing was performed.

Decreases in mean SBP and DBP were observed in both groups at Week 16. Mean SBP decreased from 150.4 mm Hg to 133.5 mm Hg in the Caduet group (LSM [95% CI] change from baseline: -15.31 [-17.02, -13.60]) and from 144.3 mm Hg to 134.5 mm Hg in the usual care group (LSM [95% CI] change from baseline: -12.16 [-14.00, -10.32]). The mean change from baseline to Week 16 comparison between groups was statistically significant (p=0.007). Mean DBP decreased from 89.7 mm Hg to 80.7 mm Hg in the Caduet group (LSM [95% CI] change from baseline: -8.30 [-9.24, -7.36]) and from 86.5 mm Hg to 81.1 mm Hg in the usual care group (LSM [95% CI] change from baseline: -6.69 [-7.70, -5.68]). The mean change from baseline to Week 16 comparison between groups was statistically significant (p=0.011).

Subjects in the Caduet group but not the usual care group experienced additional decreases in both SBP and DBP from Week 16 to Week 52. At Week 52, mean SBP decreased to 130.6 mm Hg in the Caduet group and to 134.3 mm Hg in the usual care group. Mean DBP decreased to 79.2 mm Hg in the Caduet group and to 81.1 mm Hg in the usual care group. The LSM (95% CI) difference between groups for the change from baseline was -5.75 (-8.00, -3.50) for SBP and -3.17 (-4.42, -1.92) for DBP, both of which were statistically significant ($p<0.001$).

Similar percentages of subjects in the Caduet and usual care groups were at BP goals at Week 16 whether a standard definition (<140/90 mm Hg) (65.2% and 62.6%, respectively) or more strict guidelines for diabetics (<140/90 mm Hg or <130/80 mm Hg for diabetics) (48.6% and 46.0%, respectively) were used. At Week 52, higher percentages of subjects in the Caduet group compared with usual care were at BP goals (76.1% and 60.6%, respectively for standard goals; 58.2% and 47.5% for the more strict goals for diabetics) and the differences between groups were statistically significant ($p\leq0.005$).

Both groups had similar mean values for all lipid parameters at baseline. Clinically and statistically significant decreases in mean TC, LDL cholesterol, and triglycerides were observed in the Caduet group, whereas these parameters showed modest change in the usual care group. At Week 16, mean TC in the Caduet group was 156.0 mg/dL compared with 195.2 mg/dL in the usual care group (Caduet vs usual care for mean change from baseline: $p<0.001$). At Week 52, the difference between groups was maintained (163.3 mg/dL in the Caduet group compared with 196.6 mg/dL in the usual care group; Caduet vs usual care for mean change from baseline: LSM [95% CI] of -33.07 [-37.57, -28.56]; $p<0.001$). A difference between groups was also observed for LDL cholesterol at Week 16 and Week 52. At Week 16, mean LDL cholesterol in the Caduet group was 80.9 mg/dL compared with 116.4 mg/dL in the usual care group (Caduet vs usual care for mean change from baseline: $p<0.001$). At Week 52 the difference between groups was maintained (87.1 mg/dL in the Caduet group compared with 117.3 mg/dL in the usual care group; Caduet vs usual care for mean change from baseline: LSM [95% CI] of -29.83 [-33.70, -25.95]; $p<0.001$). The same trend was observed for triglycerides. At Week 16, mean triglycerides in the Caduet group was 143.5 mg/dL compared with 164.8 mg/dL in the usual care group (Caduet vs usual care for mean change from baseline: $p<0.001$). At Week 52, there was also a statistically significant difference between groups (151.5 mg/dL in the Caduet group compared with 166.4 mg/dL in the usual care group; Caduet vs usual care for mean change from baseline: LSM [95% CI] of -18.27 [-28.72, -7.81]; $p<0.001$).

A higher percentage of subjects in the Caduet group compared with the usual care group were at LDL cholesterol goals as defined for subjects at high risk of CV disease according to United States National Cholesterol Education Program Adult Treatment Panel III criteria (<100 mg/dL) (77.3% and 28.2%, respectively, at Week 16; 71.9% and 28.8%, respectively, at Week 52) and the European Society of Cardiology guidelines (<80 mg/dL) (52.4% and 13.3%, respectively, at Week 16; 46.7% and 11.5%, respectively, at Week 52) at Week 16 and Week 52, and the differences between groups were statistically significant ($p<0.001$).

Subjects in both the Caduet and usual care groups took anti-hypertensive and lipid lowering drug treatments (excluding study provided Caduet) during the study: ~86% subjects and

~97% subjects, respectively, at both Week 16 and Week 52 received anti-hypertensive treatments only; ~6% subjects and ~31% subjects, respectively, at both Week 16 and Week 52 received lipid lowering treatments only; and ~6% subjects and ~30% subjects, respectively, at both Week 16 and Week 52 received both anti-hypertensive and lipid lowering treatments. The most frequently reported classes of anti-hypertensive or lipid lowering treatment (excluding study provided Caduet) at Week 16 and Week 52 were agents acting on the renin-angiotensin system (~62%) and beta blocking agents (~33%) in the Caduet group, and agents acting on the renin-angiotensin system (~76%) and CCBs (~52%) in the usual care group.

A low percentage of subjects in the Caduet (~0.5%) and usual care groups (~7%) had their dose of anti-hypertensive or lipid lowering drug treatments (excluding study provided Caduet) increased between baseline and Week 16.

Safety Results: Safety was monitored in the study by investigator reported treatment-emergent adverse events (referred to as AEs hereafter) and protocol specified safety assessments. Only subjects in the Caduet group received study treatment. Therefore, in the usual care group, AEs were not related to a protocol specified treatment, but were reported based on continuance of previous therapy. The majority of investigators in the usual care group reported little change in anti-hypertensive and lipid lowering treatments and several drugs were used with no study defined guidance or standardization for dose adjustments. For these reasons, comparisons of AEs between the Caduet and usual care groups cannot be made in the same manner as in a study with 2 or more study defined treatments, particularly for treatment-related AEs. The open-label nature of this study has introduced additional bias to the AE reporting pattern.

AEs were reported for 680 subjects from 122 sites. Fifteen sites (3 sites in the Caduet group and 12 sites in the usual care group) did not report any AEs for all enrolled subjects. The percentage of subjects who had all causality AEs was 48.8% in the Caduet group and 44.0% in the usual care group. The percentage of subjects who had investigator reported treatment-related AEs was 15.9% in the Caduet group and 4.3% in the usual care group. A low percentage of subjects in each group had all causality and treatment-related severe AEs (5.5% and 1.3%, respectively, in the Caduet group, and 2.3% and 0%, respectively, in the usual care group).

The incidence of AEs reported for ≥1% of subjects in either group is summarized in Table S5.

Table S5. Incidence of Adverse Events Reported for ≥1% Subject in Either Group

MedDRA System Organ Class Preferred Term	Caduet (N = 779) n (%)	Usual Care (N = 682) n (%)
Cardiac disorders		
Palpitations	9 (1.2)	5 (0.7)
Gastrointestinal disorders		
Abdominal pain upper	7 (0.9)	7 (1.0)
Constipation	9 (1.2)	4 (0.6)
Dyspepsia	5 (0.6)	10 (1.5)
General disorders and administration site conditions		
Chest pain	18 (2.3)	10 (1.5)
Oedema	12 (1.5)	1 (0.1)
Oedema peripheral	53 (6.8)	11 (1.6)
Infections and infestations		
Bronchitis	12 (1.5)	15 (2.2)
Nasopharyngitis	22 (2.8)	10 (1.5)
Pharyngitis	6 (0.8)	13 (1.9)
Respiratory tract infection viral	1 (0.1)	7 (1.0)
Upper respiratory tract infection	16 (2.1)	14 (2.1)
Investigations		
Blood creatine phosphokinase increased	15 (1.9)	5 (0.7)
Blood glucose increased	8 (1.0)	3 (0.4)
Blood triglycerides increased	11 (1.4)	14 (2.1)
Metabolism and nutrition disorders		
Dyslipidaemia	0	11 (1.6)
Hypercholesterolaemia	1 (0.1)	12 (1.8)
Hyperglycaemia	7 (0.9)	8 (1.2)
Hyperlipidaemia	0	10 (1.5)
Hypertriglyceridaemia	2 (0.3)	7 (1.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	10 (1.3)	8 (1.2)
Back pain	12 (1.5)	6 (0.9)
Osteoarthritis	10 (1.3)	8 (1.2)
Nervous system disorders		
Dizziness	17 (2.2)	9 (1.3)
Headache	23 (3.0)	15 (2.2)
Hypoaesthesia	8 (1.0)	0
Psychiatric disorders		
Insomnia	8 (1.0)	11 (1.6)
Respiratory, thoracic and mediastinal disorders		
Cough	9 (1.2)	8 (1.2)
Vascular disorders		
Hypertension	6 (0.8)	12 (1.8)
Hypotension	9 (1.2)	4 (0.6)

Note: Subjects were counted only once per treatment in each row.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the safety analysis set; n = number of subjects with an event.

The AE profile observed in this study was consistent with the previous safety experience for the drug and the labeling.

The percentage of subjects in the Caduet group and the usual care group who were permanently discontinued because of all causality AEs was 6.7% and 0.6%, respectively. The percentage of subjects in the Caduet group and the usual care group who were permanently discontinued because of treatment-related AEs was 4.7% and 0.1%, respectively., The percentage of subjects in the Caduet group who had their dose reduced or were temporarily discontinued because of all causality and treatment-related AEs was 3.5% and 1.5%, respectively) and the percentage of subjects in the usual care group who were temporarily discontinued because of all causality and treatment-related AEs was 0.9% and 0.4%, respectively). Permanent discontinuations due to AEs are presented in Table S6.

Table S6. Permanent Discontinuations due to Adverse Events

Page 1 of 2					
MedDRA Preferred term	**Start Day/ Stop Day[a]**	**Severity**	**Outcome**	**Causality**	**SAE?**
Caduet					
Oedema	100/[>229]	Moderate	Still present	Study drug	No
Oedema peripheral	161/191	Moderate	Resolved	Study drug	No
Oedema	72/79	Severe	Resolved	Study drug	Yes
Oedema	36/113	Severe	Resolved	Study drug	No
Cardiac arrest	51/101	Severe	Resolved	Disease under study	Yes
Blood creatinine increased	29/[>77]	Moderate	Still present	Disease under study	No
Myocardial infarction	69/91	Severe	Resolved	Other illness	Yes
Oedema peripheral	242/242	Mild	Resolved	Study drug	No
Oedema peripheral	81/93	Moderate	Resolved	Study drug	Yes
Oedema peripheral	310/330	Moderate	Resolved	Study drug	No
Oedema peripheral	256/256	Mild	Resolved	Study drug	No
Erythema	317/353	Severe	Resolved	Study drug	No
Oedema peripheral	26/[>71]	Mild	Still present	Other illness	No
Balance disorder	133/[>221]	Mild	Still present	Other	No
Constipation	21/23	Mild	Resolved	Study drug	No
Myalgia	21/23	Mild	Resolved	Study drug	No
Rash	169/183	Moderate	Resolved	Study drug	No
Oedema peripheral	70/80	Mild	Resolved	Study drug	No
Oedema peripheral	133/158	Mild	Resolved	Study drug	No
Dizziness	2/24	Severe	Resolved	Other	No
Oedema peripheral	54/112	Mild	Resolved	Study drug	No
Hyperglycaemia	366/378	Severe	Resolved	Study drug	Yes
Arthralgia	8/24	Severe	Resolved	Study drug	No
Myalgia	8/24	Severe	Resolved	Study drug	No
Hypertension	8/24	Moderate	Resolved	Study drug	No
Bradycardia	109/128	Severe	Resolved	Other illness	Yes
Renal failure	111/123	Moderate	Resolved	Other illness	Yes
Oedema peripheral	42/63	Moderate	Resolved	Study drug	No
Generalised oedema	7/13	Moderate	Resolved	Study drug	No
Blood CPK increased	117/124	Moderate	Resolved	Study drug	No
Oedema peripheral	161/211	Moderate	Resolved	Study drug	No
Headache	197/199	Severe	Resolved	Study drug	No
Oedema peripheral	219/323	Moderate	Resolved	Study drug	No
Oedema peripheral	63/[>63]	Severe	Still present	Study drug	No
Oedema peripheral	67/76	Severe	Resolved	Study drug	No
Hypersensitivity	2/11	Moderate	Resolved	Study drug	No
Non-Hodgkin's lymphoma	284/298	Severe	Resolved	Other illness	Yes
Blood glucose increased	106/[>394]	Moderate	Unknown	Other illness	No
Hepatic function abnormal	47/119	Severe	Resolved	Other illness	Yes
Blood triglyceride increased	363/363	Mild	Resolved	Study drug	No
Nausea	5/11	Moderate	Resolved	Study drug	No
Palpitations	8/10	Mild	Resolved	Study drug	No

Note: Values in brackets were imputed from incomplete dates.
ALT = alanine aminotransferase; CPK = creatine phosphokinase; MedDRA = Medical Dictionary for Regulatory Activites; SAE = serious adverse event.
[a] Day relative to the start of study treatment.

Table S6. Permanent Discontinuations due to Adverse Events (continued)

Page 2 of 2					
MedDRA Preferred term	**Start Day/ Stop Day[a]**	**Severity**	**Outcome**	**Causality**	**SAE?**
Caduet (continued)					
Headache	55/57	Mild	Resolved	Study drug	No
Erectile dysfunction	121/130	Moderate	Resolved	Study drug	No
Myalgia	12/29	Moderate	Resolved	Study drug	No
Dizziness	12/29	Severe	Resolved	Study drug	No
Headache	12/29	Severe	Resolved	Study drug	No
Flushing	12/29	Moderate	Resolved	Study drug	No
Oedema peripheral	9/19	Moderate	Resolved	Study drug	No
Acute myocardial infarction	24/25	Severe	Resolved	Other illness	Yes
ALT increased	237/[>363]	Moderate	Still present	Study drug	No
Blood creatinine increased	237/[>363]	Moderate	Still present	Study drug	No
Acute myocardial infarction	130/136	Moderate	Resolved	Other illness	Yes
Ischaemic stroke	40/54	Moderate	Resolved	Other illness	Yes
Oedema peripheral	299/307	Moderate	Resolved	Study drug	No
Myocardial infarction	89/112	Severe	Resolved	Other illness	Yes
Oedema mouth	6/6	Mild	Resolved	Study drug	No
Vertigo	17/17	Mild	Resolved	Study drug	No
Oedema peripheral	6/[>29]	Moderate	Still present	Study drug	No
Tachycardia	83/85	Mild	Resolved	Study drug	No
Usual Care					
Hypertension	1/113	Mild	Resolved	Disease under study	No
Oedema peripheral	124/140	Moderate	Resolved	Study drug	No
Acute myocardial infarction	270/373	Severe	Resolved	Disease under study	Yes
Acute myocardial infarction	237/281	Severe	Resolved	Disease under study	Yes

Note: Values in brackets were imputed from incomplete dates.
ALT = alanine aminotransferase; CPK = creatine phosphokinase; MedDRA = Medical Dictionary for Regulatory Activites; SAE = serious adverse event.
[a] Day relative to the start of study treatment.

Four subjects in the Caduet group and 2 subjects in the usual care group died during the study or within 30 days of permanent discontinuation from the study. In the Caduet group, 1 subject died from sudden cardiac death, 1 subject died from non-Hodgkin's lymphoma, 1 subject died from pancreatic carcinoma and sepsis, and 1 subject died from acute myocardial infarction. In the usual care group, 1 subject died from metastases to liver and metastases to peritoneum and 1 subject died from rectal cancer. None of the events leading to death were considered to be related to study treatment. Further details of each death are presented in Table S7 (see fatal events).

Seventy five SAEs were reported for 55 subjects in the Caduet group and 30 SAEs were reported for 22 subjects in the usual care group. Post randomization SAEs are presented in Table S7.

Table S7. Serious Adverse Events

Page 1 of 4					
MedDRA Preferred term	**Start Day[a]**	**Causality**	**Clinical Outcome**	**Seriousness**	**Action Taken (Drug Level)**
Caduet					
Appendicitis	47	Unrelated	Recovered/resolved with sequel	Hospitalization, life-threatening, important medical event	Dose not changed
Renal cyst	113	Unrelated	Recovered/resolved with sequel	Hospitalization, life-threatening	Dose not changed
Oedema	72	Related	Recovered/resolved	Hospitalization	Permanently withdrawn
Uterine neoplasm	34	Unrelated	Recovered/resolved	Hospitalization, important medical event	Permanently withdrawn
Cerebellar infarction	211	Unrelated	Recovered/resolved with sequel	Hospitalization, life-threatening, important medical event	Dose increased
Acute coronary syndrome	214	Unrelated	Recovered/resolved with sequel	Hospitalization, disability, life-threatening, important medical event	Dose increased
Adrenal adenoma	59	Unrelated	Recovered/resolved with sequel	Hospitalization, important medical event	Dose not changed
Benign prostatic hyperplasia	224	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Prostatitis	244	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Angina unstable	4	Unrelated	Recovered/resolved	Hospitalization	Temporarily withdrawn
Renal mass	335	Unrelated	Not recovered/not resolved	Hospitalization	Dose not changed
Hydronephrosis	335	Unrelated	Not recovered/not resolved	Hospitalization	Dose not changed
Hyperglycaemia	224	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Hernia	NA	Unrelated	Recovered/resolved	Hospitalization	Temporarily withdrawn
Cerebrovascular accident	181	Unrelated	Recovered/resolved with sequel	Hospitalization	Dose not changed
Acute pulmonary oedema	203	Unrelated	Recovering/resolving	Hospitalization	Dose not changed
Lipoma	87	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Macular hole	192	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Pancreatic carcinoma	NA	Unrelated	Not recovered/not resolved	Hospitalization	Dose not changed
Dysphagia	NA	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Angina pectoris	117	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Reflux oesophagitis	NA	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Vitreous haemorrhage	168	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Normal tension glaucoma	168	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Cardiac arrest	51	Unrelated	Recovered/resolved with sequel	Hospitalization, life-threatening	Permanently withdrawn
Cardiac failure	14	Unrelated	Recovered/resolved	Hospitalization	Temporarily withdrawn
Acute myocardial infarction	69	Unrelated	Recovered/resolved	Hospitalization, life-threatening	Permanently withdrawn

MedDRA = Medical Dictionary for Regulatory Activites; NA = not available or not applicable.
[a] Day relative to the start of study treatment.

Table S7. Serious Adverse Events (continued)

Page 2 of 4					
MedDRA Preferred term	**Start Day[a]**	**Causality**	**Clinical Outcome**	**Seriousness**	**Action Taken (Drug Level)**
Caduet (continued)					
Oedema peripheral	81	Related	Recovered/resolved	Important medical event	Permanently withdrawn
Fall	41	Unrelated	Recovered/resolved	Important medical event	Dose not changed
Hand fracture	41	Unrelated	Recovered/resolved	Important medical event	Dose not changed
Chest discomfort	344	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Urinary tract infection	286	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Urinary tract infection	266	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Sudden cardiac death	137	Unrelated	Fatal	Fatal	Dose not changed
Chest pain	26	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Ischaemic stroke	100	Unrelated	Recovered/resolved	Hospitalization, important medical event	Temporarily withdrawn
Chest pain	169	Unrelated	Recovered/resolved	Hospitalization, important medical event	Temporarily withdrawn
Cerebrovascular accident	40	Unrelated	Recovered/resolved	Hospitalization	Temporarily withdrawn
Central nervous system lesion	40	Unrelated	Recovered/resolved	Hospitalization	Temporarily withdrawn
Hemiparesis	40	Unrelated	Recovered/resolved	Hospitalization	Temporarily withdrawn
Biliary colic	13	Unrelated	Recovered/resolved	Disability	Dose not changed
Liver disorder	56	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Hyperglycaemia	366	Unrelated	Recovered/resolved	Hospitalization, important medical event	Permanently withdrawn
Bradycardia	109	Unrelated	Recovered/resolved	Hospitalization, important medical event	Permanently withdrawn
Renal failure	111	Unrelated	Recovered/resolved	Important medical event	Permanently withdrawn
Non-Hodgkin's lymphoma	284	Unrelated	Fatal	Fatal	Dose not changed
Appendicitis	96	Unrelated	Recovered/resolved	Hospitalization, life-threatening	Dose not changed
Jaundice	47	Unrelated	Not recovered/not resolved	Hospitalization, important medical event	Permanently withdrawn
Choluria	47	Unrelated	Not recovered/not resolved	Hospitalization, important medical event	Permanently withdrawn
Pancreatic carcinoma	91	Unrelated	Fatal	Fatal	Permanently withdrawn
Sepsis	91	Unrelated	Fatal	Fatal	Permanently withdrawn
Lower respiratory tract infection	NA	Unrelated	Not recovered/not resolved	Hospitalization	Permanently withdrawn
Renal failure acute	NA	Unrelated	Not recovered/not resolved	Hospitalization	Permanently withdrawn
Hepatic function abnormal	47	Unrelated	Recovered/ resolved	Important medical event	Permanently withdrawn
Thrombophlebitis	84	Unrelated	Recovered/resolved	Hospitalization	Dose not changed

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[a] Day relative to the start of study treatment.

Table S7. Serious Adverse Events (continued)

Page 3 of 4					
MedDRA Preferred term	**Start Day[a]**	**Causality**	**Clinical Outcome**	**Seriousness**	**Action Taken (Drug Level)**
Caduet (continued)					
Hypertensive crisis	88	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Lower respiratory tract infection	88	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Depression	88	Unrelated	Unknown	Important medical event	Dose not changed
Rotator cuff syndrome	217	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Urinary tract infection	191	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Acute myocardial infarction	24	Unrelated	Fatal	Hospitalization, disability, life-threatening, important medical event	Dose not changed
Pneumonia	36	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Myocardial infarction	130	Unrelated	Recovered/resolved	Hospitalization	Permanently withdrawn
Ischaemic stroke	40	Unrelated	Recovered/resolved	Hospitalization, important medical event	Permanently withdrawn
Pneumonia	125	Unrelated	Recovered/resolved	Hospitalization, important medical event	Dose not changed
Atrial fibrillation	223	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Coronary heart disease	98	Unrelated	Recovered/resolved	Hospitalization, disability, important medical event	Dose not changed
Myocardial infarction	89	Unrelated	Recovered/resolved	Hospitalization, disability, important medical event	Permanently withdrawn
Sinusitis	131	Unrelated	Recovered/resolved	Important medical event	Dose not changed
Hypertriglyceridaemia	362	Unrelated	Recovered/resolved	Important medical event	Post therapy
Arthritis infective	101	Unrelated	Recovering/resolving	Hospitalization, important medical event	Dose not changed
Bursitis	128	Unrelated	Recovered/resolved	Important medical event	Dose not changed
Vertigo	132	Unrelated	Recovered/resolved	Important medical event	Dose not changed
Usual Care					
Myocardial ischaemia	41	Unrelated	Recovered/resolved	Important medical event	Temporarily withdrawn
Arteriosclerosis coronary artery	54	Unrelated	Recovered/resolved	Hospitalization, important medical event	Temporarily withdrawn
Lung neoplasm malignant	190	Unrelated	Not recovered/not resolved	Hospitalization	Dose not changed
Fracture coccyx	371	Unrelated	Recovering/resolving	Hospitalization	Dose not changed
Cataract	NA	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Cardiac failure congestive	56	Unrelated	Not recovered/not resolved	Hospitalization	Dose not changed
Renal disorder	231	Unrelated	Not recovered/not resolved	Hospitalization	Dose not changed
Anaemia	231	Unrelated	Recovering/resolving	Hospitalization	Dose not changed
Head injury	230	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Humerus fracture	45	Unrelated	Recovered/resolved	Hospitalization	Dose not changed

MedDRA = Medical Dictionary for Regulatory Activites; NA = not available or not applicable.
[a] Day relative to the start of study treatment.

Table S7. Serious Adverse Events (continued)

Page 4 of 4					
MedDRA Preferred term	**Start Day[a]**	**Causality**	**Clinical Outcome**	**Seriousness**	**Action Taken (Drug Level)**
Usual Care (continued)					
Transient ischaemic attack	252	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Angina unstable	NA	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Facial palsy	282	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Ovarian cyst	209	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Chronic obstructive pulmonary disease	145	Unrelated	Recovered/resolved	Hospitalization	Dose not changed
Upper limb fracture	75	Unrelated	Recovered/resolved with sequel	Hospitalization	Dose not changed
Panic attack	56	Unrelated	Not recovered/not resolved	Important medical event	Dose not changed
Hip fracture	340	Unrelated	Recovered/resolved with sequel	Hospitalization	Dose not changed
Metastases to peritoneum	392	Unrelated	Fatal	Hospitalization, important medical event	Dose not changed
Metastases to liver	392	Unrelated	Fatal	Hospitalization, important medical event	Dose not changed
Infection	NA	Unrelated	Recovered/resolved	Important medical event	Dose not changed
ECG T wave inversion	NA	Unrelated	Not recovered/not resolved	Hospitalization	Dose not changed
Rectal cancer	NA	Unrelated	Fatal	Fatal	Dose not changed
Atrial fibrillation	38	Unrelated	Recovered/resolved	Important medical event	Dose not changed
Acute myocardial infarction	270	Unrelated	Recovered/resolved	Hospitalization, life-threatening, important medical event	Permanently withdrawn
Acute myocardial infarction	237	Unrelated	Recovered/resolved with sequel	Hospitalization, life-threatening, important medical event	Permanently withdrawn
Myocardial iscaemia	176	Unrelated	Recovered/resolved	Hospitalization, important medical event	Dose not changed
Cerebrovascular disorder	18	Unrelated	Recovered/resolved	Hospitalization	Dose not changed

MedDRA = Medical Dictionary for Regulatory Activites; NA = not available or not applicable.
[a] Day relative to the start of study treatment.

The most frequently reported laboratory test abnormality was triglycerides >1.3 x the upper limit of normal (27% subjects in the Caduet group and 39% subjects in the usual care group). The most frequently reported laboratory test-related AEs in both groups were blood CPK increased (1.9% in the Caduet group and 0.7% in the usual care group) and blood triglycerides increased (1.4% in the Caduet group and 2.1% in the usual care group). No other laboratory test-related AE was reported for >1% of subjects in either group.

Similar and small median changes from baseline at Week 4, Week 16, and Week 52 were observed in heart rate in both groups.

CONCLUSIONS:

- The primary objective of this study was met. The study demonstrated that a Caduet-based clinical management approach was more effective in reducing the total CV risk compared with usual care after 1 year of treatment in subjects with hypertension and ≥3 additional risk factors, but no known CHD and baseline cholesterol ≤6.5 mmol/L (250 mg/dL).

- In subjects with hypertension and ≥3 additional risk factors, but no known CHD and baseline cholesterol ≤6.5 mmol/L (250 mg/dL), a Caduet-based clinical management approach was more effective than usual care as early as Week 16 and was maintained up to Week 52, in decreasing:

    - Framingham 10-year risk of total CHD at Week 16.
    - European SCORE 10-year risk of fatal CV disease.
    - Framingham 10-year risk of fatal CV disease.
    - Framingham 10-year risk of stroke.
    - Systolic and diastolic BP.
    - TC, LDL cholesterol, and triglycerides.

- The percentage of subjects reaching goal was significantly higher in the Caduet group compared with the usual care group for the following endpoints:

    - BP goal at Week 52.
    - LDL cholesterol goal at Week 16 and Week 52.

- Subjects in both the Caduet and usual care groups took anti-hypertensive and lipid lowering drug treatments (excluding study provided Caduet) during the study and a low percentage of subjects in the Caduet and usual care groups had their dose of anti-hypertensive or lipid lowering drug treatments (excluding study provided Caduet) increased between baseline and Week 16.

- Caduet was well tolerated and no new safety signals emerged during the conduct of the study.