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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00530946

PROTOCOL NO.: A3841058

PROTOCOL TITLE: A Multi-Center, Randomized Study to Evaluate Efficacy and Safety of a Fixed Combination Therapy of Amlodipine and Atorvastatin in the Treatment of Concurrent Hypertension and Hyper-LDL-Cholesterolemia

Study Center(s): Twenty (20) centers in Japan

Study Initiation and Completion Dates: 21 September 2007 to 02 April, 2008

Phase of Development: Phase 3

Study Objective(s):

Primary Objective: To evaluate the change in the trough systolic blood pressure (SBP) and the percent change in low density lipoprotein-cholesterol (LDL-C) from baseline (the average value of Week -1 and Week 0) to Week 8 in 4 doses of CI-1038 (amlodipine/atorvastatin: 2.5 mg/5 mg, 2.5 mg/10 mg, 5 mg/5 mg and 5 mg/10 mg).

Secondary Objectives:
1. To evaluate the changes from baseline in SBP (except Week 8 of treatment), diastolic blood pressure (DBP), LDL-C /HDL-C (high density lipoprotein-cholesterol) ratio, TC (total cholesterol) /HDL-C ratio and apolipoprotein B to each assessment time point, as well as the percent changes from baseline in LDL-C (except to Week 8 of treatment), TC, HDL-C and TG (triglycerides).

2. To evaluate the safety of 4 doses of CI-1038 during the 8-week treatment period.

METHODS

Study Design: This study was conducted as a multi-center, randomized, open, parallel-group comparative study in patients with concurrent hypertension and hyper-LDL-cholesterolemia. Investigators were instructed not to disclose the treatment allocation of each subject until the

database was locked to keep the data blind as much as possible. The study period consisted of a 6-week diet observation period and an 8-week treatment period. Subjects were expected to make 5 visits (Weeks -6, -4, -2, -1 and 0) during the diet observation period, and those who met the criteria for entering the treatment period at the end of the diet observation period (Week 0) were randomized into 1 of 4 CI-1038 dose groups (2.5 mg/5 mg, 2.5 mg/10 mg, 5 mg/5 mg and 5 mg/10 mg). Subjects were expected to make 3 visits (Weeks 2, 4 and 8) during the treatment period, during which efficacy and the safety were evaluated.

Number of Subjects (Planned and Analyzed):
Planned: A total of 160 patients (40 patients in each treatment group)
Analyzed: A total of 165 patients (43 patients in the 2.5 mg/5 mg, 41 patients in the 2.5 mg/10 mg, 41 patients in the 5 mg/5 mg and 40 patients in the 5 mg/10 mg treatment groups)

Diagnosis and Main Criteria for Inclusion:
Diet observation period: Male or female outpatients aged 20 to < 80 years with concurrent hypertension and hyper-LDL-cholesterolemia at Visit 1 (Week -6), and with following condition: (1) patients untreated with antihypertensive medication should have an SBP of 140 to <180 mmHg at Visit 1 (Week -6), (2) patients untreated with lipid lowering medication should have an LDL-C of 140 to <250 mg/dL and a TG of <400 mg/dL at Visit 1 (Week -6), (3) patients on antihypertensive medication or lipid lowering medication, no criteria for SBP and LDL-C were set, and it was required to discontinue the antihypertensive medication prior to Visit 2 (Week -4) and the lipid lowering medication prior to Visit 1 (Week -6), respectively.

Treatment period: The SBP at both Visits 4 (Week -1) and 5 (Week 0) was in the range from 140 to <180 mmHg, with the difference in SBP between Visits 4 (Week -1) and 5 (Week 0) within ± 10 mmHg; the LDL-C at Visits 3 (Week -2) and 4 (Week -1) was in the range from 140 to <250 mg/dL, with the change in LDL-C between Visit 3 (Week -2) and Visit 4 (Week -1) within ± 15%; and the TG was <400 mg/dL.

Study Treatment: One CI-1038 tablet (2.5 mg/5 mg tablet, 2.5 mg/10 mg tablet, 5 mg/5 mg tablet or 5 mg/10 mg tablet) was taken orally once daily, after breakfast for 8 weeks.

Efficacy Evaluations:

Primary endpoint: The change in SBP and the percent change in LDL-C from baseline to Week 8 of treatment.

Secondary endpoints: The changes from baseline in SBP (except Week 8 of treatment), DBP, LDL-C/HDL-C ratio, TC/HDL-C ratio and apolipoprotein B, as well as the percent changes from baseline in LDL-C (except Week 8 of treatment), TC, HDL-C and TG to each assessment time point.

Safety Evaluations: Adverse events (AEs), laboratory test values, pulse rate and 12-lead electrocardiogram (ECG)

Statistical Methods:
Efficacy: The efficacy analysis set (full analysis set: FAS) consisted of all randomized subjects who took at least one dose of the study drug and had both SBP and LDL-C observations at both baseline (the mean of the values obtained at Week -1 and Week 0) and post baseline.

As the primary analysis of the primary endpoint, the change in SBP and the percent change in LDL-C from baseline to Week 8 were analyzed using an analysis of covariance (ANCOVA) with baseline measurement as a covariate, and amlodipine dose, atorvastatin dose, and their interaction as factors. In the analysis, least square means and their two-sided 95% confidence intervals (CIs) in each treatment group were calculated. In addition, differences between the groups in the least square mean and their two-sided 95% CIs were calculated: (1) to compare the SBP change across the amlodipine dose groups and to assess the effect of the atorvastatin dose on the SBP, (2) to compare the LDL-C percent change across the atorvastatin dose groups, and to assess the effect of the amlodipine dose on the LDL-C.

As secondary analyses, the analyses using the ANCOVA model were performed by age category (<65 years, ≥65 years), by the presence or absence of previous treatment for hypertension or hyperlipidemia, and by the presence or absence of a history of cerebrovascular and cardiovascular diseases.

For the secondary endpoints (DBP, TC, HDL-C, TG, LDL-C/HDL-C ratio, TC/HDL-C ratio and apolipoprotein B), the data obtained at Week 8 were analyzed using the same model employed in the primary analysis of the primary endpoint. Also, for the changes or percent changes from baseline to each assessment time point in SBP, LDL-C and the secondary endpoints, summary statistics and two-sided 95% CIs of the means were calculated for each treatment group.

Safety: The safety analysis set consisted of all randomized subjects who took at least one dose of the study drug. AEs, laboratory test values, pulse rate and 12-lead ECG were analyzed by means of descriptive statistics. Summary tables were prepared by treatment group. AEs were classified and tabulated based on MedDRA (Version 11.0).

RESULTS

Subject Disposition and Demography: Of 301 subjects who entered the diet observation period, 165 subjects who met all the inclusion criteria for the treatment period and had no conflict to exclusion criteria were randomized to 4 CI-1038 groups. All subjects were treated with the study drug, and were analyzed for efficacy and safety. The disposition of subjects was similar across the treatment groups (Table S1).

Table S1. Subject Disposition and Subjects Analyzed

	CI-1038 treatment groups (amlodipine/ atorvastatin)			
	2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
Subjects who entered the diet observation period (N=301)				
Subjects randomized for the treatment period (N=165)	43	41	41	40
Subjects treated	43 (100)	41 (100)	41 (100)	40 (100)
Completed subjects	41 (95.3)	39 (95.1)	40 (97.6)	38 (95.0)
Discontinued subjects	2 (4.7)	2 (4.9)	1 (2.4)	2 (5.0)
Reason for discontinuation				
Adverse events	1	2	1	1
Not treatment-related	0	0	0	0
Treatment-related	1	2	1	1
Noncompliance	1	0	0	0
Protocol deviations	0	0	0	1
Analyzed for efficacy				
Full analyses set	43 (100)	41 (100)	41 (100)	40 (100)
Analyzed for safety				
Adverse events	43 (100)	41 (100)	41 (100)	40 (100)
Laboratory data	43 (100)	41 (100)	41 (100)	40 (100)

Subjects (%)

Males accounted for 40.6% of all subjects. The mean age was 59.4 years, and subjects aged ≥65 years accounted for 35.2%. The mean body weight in all the subjects was 64.8 kg, with the mean body mass index (BMI) of 25.4 kg/m^2. The analysis by treatment group showed no major imbalance in demographic characteristics among the treatment groups.

Efficacy Results:
Primary endpoints**:** The least square means of the change in the trough SBP from baseline to Week 8 were decreases of 16.6, 15.9, 21.8 and 18.9 mmHg in the CI-1038 2.5 mg/5 mg, 2.5 mg/10 mg, 5 mg/5 mg and 5 mg/10 mg groups, respectively (Table S2).

In the secondary analyses by age category (<65 years, ≥65 years) and by the presence or absence of previous treatment for hypertension, the decrease in SBP in all subgroups was greater in the higher amlodipine dose (5 mg) groups than in the lower amlodipine dose (2.5 mg) groups. In the analysis by the presence or absence of a history of cerebrovascular and cardiovascular diseases, no assessment was possible because of a limited number of subjects with a history of these diseases.

Table S2. Change in SBP From Baseline to Week 8 (FAS-Last Observation Carried Forward)

	CI-1038 treatment groups (amlodipine/ atorvastatin)			
	2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	151.7 (9.57)	151.7 (8.34)	151.5 (8.86)	152.0 (9.78)
Week 8	N=43	N=41	N=41	N=40
Mean (SD)	135.1 (13.78)	135.8 (12.22)	129.8 (11.63)	133.0 (11.18)
Change from baseline to Week 8	N=43	N=41	N=41	N=40
Mean (SD)	-16.5 (11.74)	-15.9 (11.77)	-21.7 (10.32)	-19.0 (11.27)
Least square mean of the change (SE)	-16.6 (1.65)	-15.9 (1.69)	-21.8 (1.69)	-18.9 (1.71)
95% CI	(-19.8, -13.3)	(-19.3, -12.6)	(-25.1, -18.4)	(-22.3, -15.5)

FAS = Full analysis set, Baseline = The average value of Week -1 and Week 0, N = Number of subjects assessed, SD = Standard deviation, SE = Standard error, Unit of blood pressure = mmHg
Least square means and their two-sided 95% CIs were calculated using an ANCOVA model with baseline measurement as a covariate and amlodipine dose, atorvastatin dose, and their interaction as factors.

The least square means of the percent change in LDL-C from baseline to Week 8 were decreases of 37.2%, 42.5%, 34.3% and 40.6% in the CI-1038 2.5 mg/5 mg, 2.5 mg/10 mg, 5 mg/5 mg and 5 mg/10 mg groups, respectively (Table S3).

In the secondary analyses by age category (<65 years, ≥65 years) and by the presence or absence of previous treatment for hypertension, the decrease in LDL-C in all subgroups was greater in the higher atorvastatin dose (10 mg) groups than in the lower amlodipine dose (5 mg) groups. In the analysis by the presence or absence of a history of cerebrovascular and cardiovascular diseases, no assessment was possible because of a limited number of subjects with a history of these diseases.

Table S3. Percent Change in LDL-C From Baseline to Week 8 (FAS-Last Observation Carried Forward)

	CI-1038 treatment groups (amlodipine/ atorvastatin)			
	2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	173.9 (21.60)	170.1 (22.28)	173.0 (23.36)	173.1 (20.19)
Week 8	N=43	N=41	N=41	N=40
Mean (SD)	109.0 (18.84)	97.8 (21.17)	113.2 (20.21)	102.9 (23.38)
Percent change from baseline to Week 8	N=43	N=41	N=41	N=40
Mean (SD)	-37.3 (8.27)	-42.4 (10.22)	-34.4 (9.19)	-40.6 (11.08)
Least square mean of the percent change (SE)	-37.2 (1.49)	-42.5 (1.52)	-34.3 (1.52)	-40.6 (1.54)
95% CI	(-40.2, -34.3)	(-45.5, -39.5)	(-37.3, -31.3)	(-43.6, -37.6)

FAS = Full analysis set, Baseline = The average value of Week -1 and Week 0, N= Number of subjects assessed, SD= Standard deviation, SE= Standard error, Unit of LDL-C = mg/dL
Least square means and their two-sided 95% CIs were calculated using an ANCOVA model with baseline measurement as a covariate and amlodipine dose, atorvastatin dose, and their interaction as factors.

Secondary endpoints: Results are summarized in Table S4.

Table S4. Secondary Endpoints: Change or Percent Change From Baseline to Each Observation Point (FAS[a])

	CI-1038 treatment groups (amlodipine/ atorvastatin)			
	2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
SBP (mmHg)				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	151.7 (9.57)	151.7 (8.34)	151.5 (8.86)	152.0 (9.78)
Change from baseline				
Week 2	N=42	N=41	N=40	N=40
Mean (SD)	-12.8 (9.63)	-13.5 (10.18)	-19.2 (10.53)	-16.0 (9.01)
95% CI	(-15.8, -9.8)	(-16.7, -10.3)	(-22.6, -15.9)	(-18.9, -13.1)
Week 4	N=42	N=41	N=41	N=38
Mean (SD)	-14.2 (10.26)	-14.6 (12.33)	-20.2 (11.08)	-19.6 (11.03)
95% CI	(-17.4, -11.0)	(-18.5, -10.7)	(-23.7, -16.7)	(-23.2, -16.0)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-16.8 (11.40)	-15.3 (11.59)	-21.3 (10.07)	-18.7 (11.24)
95% CI	(-20.4, -13.2)	(-19.0, -11.5)	(-24.5, -18.1)	(-22.4, -15.0)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-16.5 (11.74)	-15.9 (11.77)	-21.7 (10.32)	-19.0 (11.27)
95% CI	(-20.1, -12.9)	(-19.6, -12.2)	(-25.0, -18.5)	(-22.6, -15.4)
DBP (mmHg)				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	89.9 (7.73)	88.8 (8.31)	88.6 (7.82)	91.0 (8.34)
Change from baseline				
Week 2	N=42	N=41	N=40	N=40
Mean (SD)	-4.9 (6.23)	-6.0 (6.05)	-8.1 (6.24)	-8.2 (6.38)
95% CI	(-6.9, -3.0)	(-7.9, -4.1)	(-10.0, -6.1)	(-10.2, -6.2)
Week 4	N=42	N=41	N=41	N=38
Mean (SD)	-5.3 (4.96)	-8.2 (7.13)	-9.4 (6.19)	-9.2 (6.62)
95% CI	(-6.9, -3.8)	(-10.5, -6.0)	(-11.3, -7.4)	(-11.3, -7.0)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-7.7 (6.34)	-8.7 (8.06)	-12.0 (6.31)	-9.9 (6.57)
95% CI	(-9.7, -5.7)	(-11.3, -6.1)	(-14.0, -10.0)	(-12.1, -7.8)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-7.6 (6.53)	-8.7 (7.87)	-12.0 (6.24)	-9.8 (6.68)
95% CI	(-9.6, -5.6)	(-11.2, -6.2)	(-13.9, -10.0)	(-11.9, -7.7)
LDL-C（mg/dL）				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	173.9 (21.60)	170.1 (22.28)	173.0 (23.36)	173.1 (20.19)
Percent change from baseline				
Week 2	N=43	N=41	N=41	N=40
Mean (SD)	-34.8 (9.11)	-42.5 (11.00)	-32.8 (9.15)	-40.2 (13.52)
95% CI	(-37.6, -32.0)	(-45.9, -39.0)	(-35.6, -29.9)	(-44.5, -35.9)
Week 4	N=42	N=41	N=41	N=39
Mean (SD)	-37.4 (7.67)	-43.8 (9.30)	-35.0 (9.19)	-41.8 (9.53)
95% CI	(-39.7, -35.0)	(-46.8, -40.9)	(-37.9, -32.1)	(-44.9, -38.7)

FAS = Full analysis set, N = Number of subjects assessed, SD = Standard deviation, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, Baseline = The average value of Week -1 and Week 0.

Least square means and their two-sided 95% CIs were calculated using an ANCOVA model with baseline measurement as a covariate and amlodipine dose, atorvastatin dose, and their interaction as factors.

[a] Results of observed cases are shown otherwise specified.

Table S4 (cont). Secondary Endpoints: Change or Percent Change From Baseline to Each Observation Point (FAS[a])

	CI-1038 treatment groups (amlodipine/ atorvastatin)			
	2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
LDL-C（mg/dL）(cont)				
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-37.6 (7.80)	-42.9 (10.28)	-34.2 (9.22)	-40.8 (11.28)
95% CI	(-40.1, -35.2)	(-46.2, -39.6)	(-37.1, -31.2)	(-44.5, -37.1)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-37.3 (8.27)	-42.4 (10.22)	-34.4 (9.19)	-40.6 (11.08)
95% CI	(-39.8, -34.7)	(-45.7, -39.2)	(-37.3, -31.5)	(-44.2, -37.1)
TC（mg/dL）				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	251.3 (26.37)	251.0 (26.10)	251.9 (24.78)	254.9 (23.72)
Percent change from baseline				
Week 2	N=43	N=41	N=41	N=40
Mean (SD)	-24.2 (6.86)	-30.5 (8.44)	-23.0 (7.22)	-28.3 (10.04)
95% CI	(-26.3, -22.1)	(-33.1, -27.8)	(-25.3, -20.8)	(-31.5, -25.1)
Week 4	N=42	N=41	N=41	N=39
Mean (SD)	-26.6 (6.36)	-31.5 (7.08)	-24.7 (7.64)	-28.6 (7.44)
95% CI	(-28.6, -24.6)	(-33.7, -29.3)	(-27.1, -22.3)	(-31.0, -26.2)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-26.1 (6.01)	-30.0 (8.43)	-23.4 (7.78)	-28.2 (8.73)
95% CI	(-28.0, -24.2)	(-32.7, -27.2)	(-25.8, -20.9)	(-31.1, -25.4)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-25.7 (6.98)	-29.6 (8.36)	-23.5 (7.71)	28.1 (8.56)
95% CI	(-27.8, -23.5)	(-32.3, -27.0)	(-25.9, -21.0)	(-30.8, -25.4)
HDL-C（mg/dL）				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	59.6 (14.28)	61.5 (17.68)	60.7 (16.84)	60.7 (13.42)
Percent change from baseline				
Week 2	N=43	N=41	N=41	N=40
Mean (SD)	7.7 (12.11)	8.3 (10.70)	6.6 (9.12)	9.9 (10.32)
95% CI	(3.9, 11.4)	(4.9, 11.6)	(3.7, 9.5)	(6.6, 13.2)
Week 4	N=42	N=41	N=41	N=39
Mean (SD)	7.2 (8.16)	7.9 (13.03)	9.3 (13.24)	11.9 (13.28)
95% CI	(4.7, 9.7)	(3.7, 12.0)	(5.2, 13.5)	(7.6, 16.2)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	7.2 (10.86)	7.5 (13.27)	9.7 (10.59)	10.8 (9.66)
95% CI	(3.8, 10.7)	(3.2, 11.8)	(6.3, 13.1)	(7.6, 13.9)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	7.6 (11.10)	7.3 (12.97)	9.8 (10.47)	10.9 (9.42)
95% CI	(4.2, 11.1)	(3.2, 11.4)	(6.5, 13.1)	(7.9, 13.9)

FAS = Full analysis set, N = Number of subjects assessed, SD = Standard deviation, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, Baseline = The average value of Week -1 and Week 0.

Least square means and their two-sided 95% CIs were calculated using an ANCOVA model with baseline measurement as a covariate and amlodipine dose, atorvastatin dose, and their interaction as factors.

[a] Results of observed cases are shown otherwise specified.

Table S4 (cont). Secondary Endpoints: Change or Percent Change From Baseline to Each Observation Point (FAS[a])

	CI-1038 treatment groups (amlodipine/ atorvastatin)			
	2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
TG（mg/dL）				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	140.6 (50.01)	146.9 (71.26)	143.7 (66.30)	165.9 (61.89)
Percent change from baseline				
Week 2	N=43	N=41	N=41	N=40
Mean (SD)	-15.1 (33.82)	-27.4 (22.48)	-16.2 (20.00)	-23.9 (24.51)
95% CI	(-25.5, -4.7)	(-34.5, -20.3)	(-22.5, -9.9)	(-31.8, -16.1)
Week 4	N=42	N=41	N=41	N=39
Mean (SD)	-14.2 (25.31)	-25.7 (18.15)	-15.1 (22.42)	-23.2 (28.55)
95% CI	(-22.1, -6.3)	(-31.4, -19.9)	(-22.2, -8.0)	(-32.4, -13.9)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-14.1 (19.72)	-21.1 (21.68)	-10.8 (31.42)	-24.0 (25.15)
95% CI	(-20.3, -7.9)	(-28.1, -14.1)	(-20.9, -0.8)	(-32.3, -15.7)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-14.4 (19.29)	-20.3 (21.62)	-10.8 (31.02)	-23.8 (24.88)
95% CI	(-20.3, -8.5)	(-27.1, -13.5)	(-20.6, -1.0)	(-31.8, -15.9)
LDL-C/HDL-C ratio				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	3.1 (0.79)	3.0 (0.80)	3.1 (0.93)	3.0 (0.77)
Change from baseline				
Week 2	N=43	N=41	N=41	N=40
Mean (SD)	-1.2 (0.58)	-1.4 (0.42)	-1.1 (0.49)	-1.3 (0.53)
95% CI	(-1.4, -1.0)	(-1.5, -1.2)	(-1.3, -1.0)	(-1.5, -1.2)
Week 4	N=42	N=41	N=41	N=39
Mean (SD)	-1.3 (0.41)	-1.4 (0.42)	-1.2 (0.56)	-1.4 (0.49)
95% CI	(-1.4, -1.1)	(-1.5, -1.2)	(-1.4, -1.1)	(-1.6, -1.3)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-1.2 (0.37)	-1.4 (0.44)	-1.2 (0.52)	-1.4 (0.52)
95% CI	(-1.4, -1.1)	(-1.5, -1.2)	(-1.4, -1.1)	(-1.5, -1.2)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-1.2 (0.38)	-1.4 (0.44)	-1.2 (0.52)	-1.4 (0.50)
95% CI	(-1.4, -1.1)	(-1.5, -1.2)	(-1.4, -1.1)	(-1.5, -1.2)
TC/HDL-C ratio				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	4.4 (0.97)	4.3 (1.01)	4.4 (1.15)	4.4 (0.98)
Change from baseline				
Week 2	N=43	N=41	N=41	N=40
Mean (SD)	-1.3 (0.71)	-1.6 (0.49)	-1.2 (0.61)	-1.5 (0.64)
95% CI	(-1.5, -1.0)	(-1.7, -1.4)	(-1.4, -1.1)	(-1.7, -1.3)

FAS = Full analysis set, N = Number of subjects assessed, SD = Standard deviation, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, Baseline = The average value of Week -1 and Week 0.

Least square means and their two-sided 95% CIs were calculated using an ANCOVA model with baseline measurement as a covariate and amlodipine dose, atorvastatin dose, and their interaction as factors.

[a] Results of observed cases are shown otherwise specified.

Table S4 (cont). Secondary Endpoints: Change or Percent Change From Baseline to Each Observation Point (FAS[a])

	CI-1038 treatment groups (amlodipine/ atorvastatin)			
	2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
TC/HDL-C ratio (cont)				
Week 4	N=42	N=41	N=41	N=39
Mean (SD)	-1.4 (0.48)	-1.6 (0.49)	-1.4 (0.69)	-1.6 (0.59)
95% CI	(-1.5, -1.2)	(-1.7, -1.4)	(-1.6, -1.2)	(-1.8, -1.4)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-1.3 (0.43)	-1.5 (0.51)	-1.4 (0.65)	-1.5 (0.62)
95% CI	(-1.5, -1.2)	(-1.7, -1.3)	(-1.6, -1.1)	(-1.7, -1.3)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-1.3 (0.43)	-1.5 (0.51)	-1.4 (0.64)	-1.5 (0.60)
95% CI	(-1.5, -1.2)	(-1.6, -1.3)	(-1.6, -1.2)	(-1.7, -1.3)
Apolipoprotein B（mg/dL）				
Baseline	N=43	N=41	N=41	N=40
Mean (SD)	126.5 (14.05)	125.6 (14.75)	125.9 (15.04)	128.9 (14.02)
Change from baseline				
Week 2	N=43	N=41	N=41	N=40
Mean (SD)	-36.6 (12.55)	-45.8 (12.11)	-33.5 (9.86)	-44.4 (15.46)
95% CI	(-40.5, -32.7)	(-49.7, -42.0)	(-36.7, -30.4)	(-49.3, -39.4)
Week 4	N=42	N=41	N=41	N=39
Mean (SD)	-40.1 (10.94)	-47.2 (10.20)	-36.6 (11.36)	-45.8 (13.79)
95% CI	(-43.5, -36.7)	(-50.4, -43.9)	(-40.2, -33.0)	(-50.2, -41.3)
Week 8	N=41	N=39	N=40	N=38
Mean (SD)	-40.2 (9.65)	-46.4 (10.87)	-36.6 (12.27)	-45.1 (14.39)
95% CI	(-43.3, -37.2)	(-49.9, -42.9)	(-40.5, -32.7)	(-49.9, -40.4)
Week 8-LOCF	N=43	N=41	N=41	N=40
Mean (SD)	-39.9 (9.77)	-45.9 (10.83)	-36.7 (12.16)	-44.7 (14.15)
95% CI	(-42.9, -36.9)	(-49.3, -42.5)	(-40.6, -32.9)	(-49.3, -40.2)

FAS = Full analysis set, N = Number of subjects assessed, SD = Standard deviation, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, Baseline = The average value of Week -1 and Week 0.
Least square means and their two-sided 95% CIs were calculated using an ANCOVA model with baseline measurement as a covariate and amlodipine dose, atorvastatin dose, and their interaction as factors.
[a] Results of observed cases are shown otherwise specified.

Safety Results: No deaths occurred in this study. Other serious AEs were observed in 2 subjects, both events occurred before the start of study treatment, and these subjects were not randomized to the study treatment. Study treatment was discontinued due to AEs in 5 subjects (3.0%) (1 to 2 subjects in each treatment group). For all AEs that led to the discontinuation of study treatment (abdominal distention/ nausea, blood pressure increased, and headache/ migraine/ dizziness/ insomnia), the causal relationship to the study drug could not be ruled out. All these AEs were resolved after the discontinuation of study drug.

A summary of AEs is shown in Table S5. The incidence of AEs was similar across the treatment groups.

Table S5. Summary of Adverse Events

	All subjects	CI-1038 treatment groups (amlodipine/ atorvastatin)			
		2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
	N=165	N=43	N=41	N=41	N=40
No. of adverse events					
All-causality	99	26	30	24	19
Treatment-related	30	8	10	6	6
No. of subjects with an adverse event					
All-causality	67 (40.6)	18 (41.9)	16 (39.0)	17 (41.5)	16 (40.0)
Treatment-related	22 (13.3)	6 (14.0)	6 (14.6)	5 (12.2)	5 (12.5)
No. of subjects with a severe adverse event					
All-causality	1 (0.6)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Treatment-related	1 (0.6)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
No. of subjects who discontinued study treatment due to adverse events					
All-causality	5 (3.0)	1 (2.3)	2 (4.9)	1 (2.4)	1 (2.5)
Treatment-related	5 (3.0)	1 (2.3)	2 (4.9)	1 (2.4)	1 (2.5)

N = Number of subjects assessed Subjects (%)

AEs occurred in 3% or more in any treatment group are shown in Table S6. The most frequently observed all-causality AE was nasopharyngitis. There was no great difference in the type or frequency of AEs between the doses of amlodipine or atorvastatin.

Table S6. Adverse Events Occurred in 3% or More in Any Treatment Group

Adverse events (MedDRA 11.0)	All subjects	CI-1038 treatment groups (amlodipine/ atorvastatin)			
System organ class		2.5 mg/5 mg	2.5 mg/10 mg	5 mg/5 mg	5 mg/10 mg
Preferred term	N=165	N=43	N=41	N=41	N=40
Gastrointestinal disorders					
Nausea	2 (1.2)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)
Immune system disorders					
Seasonal allergy	2 (1.2)	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)
Infections and infestations					
Nasopharyngitis	21 (12.7)	6 (14.0)	3 (7.3)	5 (12.2)	7 (17.5)
Musculoskeletal and connective tissue disorders					
Pain in extremity	3 (1.8)	0 (0.0)	2 (4.9)	1 (2.4)	0 (0.0)
Nervous system disorders					
Headache	3 (1.8)	0 (0.0)	2 (4.9)	0 (0.0)	1 (2.5)

N = Number of subjects assessed Subjects (%)

Except for lipid parameters (TC, HDL-C, LDL-C, and TG), median changes in laboratory test values from baseline to the final test were small in all treatment groups, showing no clinically significant changes, and there was no great difference between the treatment groups. Laboratory abnormalities reported as AEs were ALT increased (1 event), ALP increased (1 event), eosinophil count increased (1 event), HDL decreased (1 event), and liver function test abnormal (2 events) in all subjects.

In the median pulse rate change from baseline after the start of treatment, an increase of 2.0 bpm in all subjects, and an increase of 1.5 to 2.5 bpm in each treatment group were observed at Week 2 of treatment. The median change from baseline to the final assessment time point was 0 bpm in all subjects, and -1.0 to 1.0 bpm in each treatment group, showing no distinctive differences between the treatment groups.

Twelve-lead ECG findings were assessed by investigators as normal, or abnormal but clinically insignificant in all except 2 subjects. Clinically significant abnormalities were reported in 1 subject in the CI-1038 2.5 mg/5 mg group as a transient atrial fibrillation before the start of study treatment, and the subject had a normal finding at Week 8, and another subject in the CI-1038 5 mg/5 mg group showed an ST-segment elevation at Week 8.

CONCLUSION(S): The efficacy and the safety of 4 doses of CI-1038 (amlodipine/atorvastatin: 2.5 mg/5 mg, 2.5 mg/10 mg, 5 mg/5 mg and 5 mg/10 mg) were evaluated in 165 patients with concurrent hypertension and hyper-LDL-cholesterolemia. The results obtained in this study are as follows:

- Independent of the atorvastatin doses, the decrease in SBP was greater in subjects receiving amlodipine 5 mg than in subjects receiving amlodipine 2.5 mg.

- Independent of the amlodipine doses, the decrease in LDL-C was greater in subjects receiving atorvastatin 10 mg than in subjects receiving atorvastatin 5 mg.

- The majority of AEs were mild to moderate in severity. There was no great difference in the type or frequency of AEs between the doses of amlodipine or atorvastatin.

- In this study, there were no deaths, and no serious AEs occurred after the start of study treatment. Study treatment was discontinued in 5 subjects (in no more than 2 subjects in each treatment group). All the AEs that led to the discontinuation of study treatment resolved after the discontinuation of the study drug.

In summary, CI-1038, an amlodipine/atorvastatin combination drug, showed antihypertensive and lipid-lowering effects as the main actions of the respective drugs in a dose-dependent manner. The dose of atorvastatin had no evident effect on the change in SBP, and the dose of amlodipine had no evident effect on the percent change in LDL-C. There were no concerns regarding the safety of CI-1038 in all treatment groups.