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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Lipitor®/Atorvastatin

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

NATIONAL CLINICAL TRIAL NO.: NCT00728988

PROTOCOL NO.: A2581161

PROTOCOL TITLE: A Prospective Randomized, Open-Label, Parallel-Group Comparative Study: Atorvastatin Pre-Treatment Versus Usual Care in Asian Patients with Acute Coronary Syndromes Undergoing Early Percutaneous Coronary Intervention

Study Centers: A total of 27 study centers took part in the study, including 15 in the Republic of Korea and 12 in China.

Study Initiation Date and Primary Completion or Completion Dates:
13 November 2008 to 26 April 2010

Phase of Development: Phase 4

Study Objectives:

Primary Objective: the primary objective of the study was to evaluate the efficacy of atorvastatin in reducing cardiovascular outcomes in Asian subjects with non-ST-segment elevation (NSTE)-acute coronary syndrome (ACS) following hospital admission for early percutaneous coronary intervention (PCI).

Secondary Objectives: the secondary objectives of the study were:

- To evaluate the effects of atorvastatin on biomarker levels (troponin I, creatine kinase [CK]-MB, myoglobin, and C-reactive protein [CRP]) in this subject population;
- To evaluate the safety and tolerability profile of atorvastatin in the presence of underlying usual care in this subject population.

METHODS

Study Design: The study was a 30 day prospective, multi-country, multi-center, randomized, open-label study with 2 equally sized parallel treatment groups: atorvastatin versus usual care. The study population consisted of Asian subjects with NSTE-ACS

following hospital admission for early percutaneous coronary intervention (PCI). Screening (Visit 0) was to take place no more than 72 hours before PCI. Eligible subjects were randomized after Screening (Visit 0) to either the atorvastatin treatment group (subjects received atorvastatin plus usual care) or the usual care treatment group (subjects received usual care only). Subjects were assessed 12 hours pre-PCI (Visit 1), 2 hours pre-PCI (Visit 2), 8 hours post-PCI (Visit 3), 24 hours post-PCI (Visit 4), and 30 days post-PCI/End of Treatment (Visit 5).

Assessments included vital signs, physical examination, electrocardiogram (ECG), and clinical laboratory tests (including hematology, lipids, biochemistry, CRP, urinalysis, and cardiac biomarkers). All subjects received usual care treatment, including aspirin and clopidogrel pre-PCI and continued through to study completion (Day 30). Subjects also received enoxaparin or dalteparin via subcutaneous injection before PCI. Enoxaparin and dalteparin could have been administered post-PCI at the discretion of the investigator, if required. All subjects received atorvastatin (40 mg) post-PCI, starting 24 hours post-PCI and continued through to study completion. The atorvastatin treatment group received all of the usual care treatments and an additional 2 doses of atorvastatin pre-PCI (80 mg 12 hours pre-PCI, and 40 mg 2 hours pre-PCI).

Number of Subjects (Planned and Analyzed): It was planned that a total of 251 subjects would be enrolled into each treatment group in the study to allow for approximately 158 evaluable subjects per treatment group. Of the 505 subjects who were screened, 499 met the criteria for inclusion into the study and were assigned to study treatment (247 subjects were randomized to the atorvastatin treatment group and 252 subjects were randomized to the usual care treatment group).

Diagnosis and Main Criteria for Inclusion: Subjects were Asian, aged ≥18 years. Subjects had to have NSTE-ACS with either: unstable angina (with the subject undergoing coronary angiography within 72 hours of the onset of symptoms of instability), or NSTE acute myocardial infarction ([MI] with the subject undergoing coronary angiography within 72 hours of the onset of symptoms). Subjects also had to have low density lipoprotein-cholesterol (LDL-C) ≥80 mg/dL at Screening (Visit 0).

Study Treatment: The usual care treatment group received: aspirin (200 to 300 mg loading dose for aspirin naïve subjects according to local practice) pre-PCI and 100 to 200 mg daily thereafter according to local practice. Subjects already on aspirin treatment at Screening (Visit 0) continued according to their usual pre-study regimen; clopidogrel 300 mg loading dose was administered at least 3 hours pre-PCI and 75 mg daily thereafter; subcutaneous heparin administered as either enoxaparin (1mg/kg weight-adjusted, every 12 hours pre-PCI [dose was to be modified to 1 mg/kg every 24 h if the estimated creatinine clearance was less than 30 mL/min]) or dalteparin (120 IU/kg weight-adjusted, every 12 hours pre-PCI [maximum dose 10000 IU, per 12 hours]); and oral atorvastatin 40 mg daily post-PCI for 30 days. If required, enoxaparin or dalteparin could have been administered post-PCI at the discretion of the investigator.

The atorvastatin treatment group received: usual care treatment outlined above, plus atorvastatin 80 mg (4 tablets of 20 mg) 12 hours pre-PCI and 40 mg (2 tablets of 20 mg) 2 hours pre-PCI.

Usual care treatments were supplied to subjects in accordance with the American College of Cardiology /American Heart Association 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction. Commercial supplies of atorvastatin (20 mg) were provided by the sponsor in China and Korea.

Efficacy Evaluations: The primary efficacy assessment was the combined incidence of major adverse cardiac events (MACE) (death, MI, and target vessel revascularization) within 30 days post-PCI. Secondary efficacy assessments included the incidence of MACE within 8 hours and 24 hours post-PCI; the proportion of subjects with any elevated biomarkers of myocardial injury (troponin I, CK-MB, and myoglobin) above the upper limit of normal (ULN) at 8 hours, 24 hours, and 30 days post-PCI when compared with Baseline (Visit 1); and the change from Visit 1 in CRP at 8 hours, 24 hours, and 30 days post-PCI. Efficacy assessments were performed at Visit 1, 8 hours post-PCI (Visit 3), 24 hours post-PCI (Visit 4), and 30 days post-PCI (Visit 5 or End of Treatment Visit).

Safety Evaluations: Adverse events (AEs) were recorded and evaluated throughout the study and up Visit 5. Clinical laboratory tests, vital signs (pulse rate, body temperature, respiratory rate, and supine systolic and diastolic blood pressures [BP]), and 12 lead ECG were performed at Screening and Visits 1, 2 (vital signs only), 3, 4, and 5. A physical examination was performed at Screening and at Visit 5. A 2-dimensional Doppler examination and left ventricular ejection fraction (LVEF) measurement (echocardiogram) was performed at Screening.

Statistical Methods:

Efficacy Analyses: The efficacy analysis was performed on the full analysis set (FAS) and per protocol (PP) analysis set, with the FAS as the primary analysis set. The FAS included all subjects who received at least 1 dose of study treatment and who received PCI. The FAS was used for both primary and secondary efficacy analyses. The PP analysis set included all subjects who: received at least 1 dose of study treatment; were treated for at least 14 days or discontinued before this time due to treatment failure; were >80% and <120% compliant with the randomized treatment; underwent PCI within a maximum of 72 hours of the onset of symptoms and a maximum of 24 hours after the first dose of atorvastatin; did not violate any inclusion or exclusion criteria that could affect the efficacy results. The PP analysis set was used for the primary efficacy analysis only.

The incidence of MACE within 30 days post-PCI in each treatment group was summarized and the number and percentage of subjects with MACE were presented. The difference in incidence rates and the p-value for testing this difference between the treatment groups against 0 and the 95% confidence intervals (CIs) for the true difference were presented. Because MACE was composed of 3 events (death, MI, and target vessel revascularization), additional analyses were conducted on these events separately, if applicable. A sensitivity analysis was also performed on these data.

The odds ratio of MACE within 30 days post-PCI and the 95% CIs were calculated using a logistic regression analysis, with the usual care treatment group as the reference group.

An unadjusted odds ratio and 95% CIs were calculated by including treatment group as the only covariate in the logistic regression model. An adjusted odds ratio and 95% CIs were calculated by including treatment group and the following potential confounding covariates in the logistic regression model: age, gender, country, NSTEMI, LVEF ≤40%, use of beta-blockers, use of angiotensin-converting enzyme-inhibitors, use of angiotensin receptor blockers, use of calcium channel antagonists, and use of diuretics. These logistic regression analyses were also applied to the 3 events (death, MI, and target vessel revascularization) separately, if applicable. Parameter estimates for the intercept and covariates of interest were presented in addition to the associated standard error (SE) and p-values. Odds ratios and 95% CIs of the covariates were also presented.

MACE event free comparison up to 30 days post-PCI between treatment groups was analyzed using the Kaplan-Meier method with a log-rank test. The Kaplan-Meier analysis with a log-rank test was also applied to MI events up to 30 days post-PCI. A Kaplan-Meier plot and the p-values of the log-rank test were presented.

All secondary efficacy analyses were performed on the FAS. Summaries of the overall incidence rate or MACE within 8 and 24 hours post-PCI were produced by treatment group and visit. The p-values for testing the difference in the incidence rate between the treatment groups against 0 and the 95% CIs for the true differences were presented. A line plot of the incidence rate of MACE by visit was presented, with separate lines representing the different treatment groups. Summaries of the proportions of subjects with any elevated biomarkers of myocardial injury above the ULN range (CK-MB, troponin I, and myoglobin) from baseline at 8 hours, 24 hours, and 30 days post-PCI were produced by treatment group and visit and the difference in the proportions was analyzed for each visit. The p-values for testing the difference in the proportions between the treatment groups against 0 and the 95% CIs for the true differences were presented. A line plot of the proportion of subjects with elevated biomarkers by visit was presented, with separate lines representing the different treatment groups.

On 09 September 2009, Siemens Healthcare Diagnostics issued an Urgent Field Safety Notice (3001-0902) stating that certain identified lots of high sensitivity (hs)-CRP reagents were found to demonstrate instability, leading to an overall 20% average positive bias. In order to evaluate the impact of the affected samples, a sensitivity analysis was performed to compare the results of the following 3 groups: all samples including the affected samples with appropriate data correction; unaffected samples; and affected samples with data correction. Percent change in CRP from baseline at 8 hours, 24 hours, and 30 days post-PCI was analyzed in each sample group and summaries of the change from baseline in CRP level were produced by treatment group for each visit. The analysis of variance model was used to test the difference between treatment groups. Least squares (LS) mean percent change from baseline along with the 95% CIs for each comparison (using the usual care treatment group as reference), and LS mean with SE for each treatment group was presented. A line plot of the mean change from baseline in CRP by visit was presented, with separate lines

representing each treatment group, and box plots of the change from baseline in CRP by visit were presented for each treatment group.

Safety Analyses: The safety analysis set included all subjects who received at least 1 dose of study treatment. Safety results were listed and summarized in accordance with the sponsor's reporting standards.

RESULTS

Subject Disposition and Demography: Of the 505 subjects who were screened, a total of 499 subjects at 27 centers were randomized to either the atorvastatin treatment group (247 subjects) or the usual care treatment group (252 subjects). In the atorvastatin treatment group, 90 (36.4%) subjects were included in the PP analysis set and 163 (66.0%) subjects were included in the FAS. In the usual care treatment group, 114 (45.2%) subjects were included in the PP analysis set and 172 (68.3%) subjects were included in the FAS. The number of subjects treated, completed, and discontinued from the study are summarized for each treatment group in Table 1.

Table 1. Subject Disposition

	Atorvastatin n (%)	Usual Care n (%)
Assigned to study treatment	247	252
Treated	245	250
Completed[a]	154 (62.3)	164 (65.1)
Discontinued[a]	91 (36.8)	86 (34.1)
Subject died[b,c]	1 (0.4)	1 (0.4)
Not related to study treatment[b]	90 (36.7)	85 (34.0)
AE[b]	3 (1.2)	2 (0.8)
Other[b]	85 (34.7)	77 (30.8)
Subject no longer willing to participate in the study[b]	2 (0.8)	6 (2.4)
Analyzed for efficacy		
PP analysis set[a]	90 (36.4)	114 (45.2)
FAS[a]	163 (66.0)	172 (68.3)
Analyzed for safety		
AEs[a]	245 (99.2)	250 (99.2)
Laboratory data[a]	238 (96.4)	245 (97.2)

AE = adverse event; FAS = full analysis set; n = number of subjects with an observation; PP = per protocol.
[a]Percentage of subjects was calculated based on the number of subjects assigned to treatment.
[b]Percentage of subjects was calculated based on the number of subjects treated.
[c]One additional death (in the usual care treatment group) was recorded in the safety database that was not captured in the CRF or clinical database because it occurred after the subject's last visit.

The pre- and post-PCI reasons for discontinuation from the study for both treatment groups are summarized in Table 2.

Table 2. Discontinuations from Study

	Atorvastatin n (%)	Usual Care n (%)
Number of subjects discontinued after screening but pre-PCI	82	78
Insufficient clinical response	0	0
AE	1 (1.2)	1 (1.3)
Subject died	0	0
Protocol violation	0	1 (1.3)
Lost to follow up	0	0
Did not meet entrance criteria	1 (1.2)	1 (1.3)
Subject no longer willing to participate	1 (1.2)	3 (3.8)
Other[b]	79 (96.3)	72 (92.3)
Number of subjects discontinued post-PCI	9	8
Insufficient clinical response	0	0
AE	2 (22.2)	1 (12.5)
Subject died[a]	1 (11.1)	1 (12.5)
Protocol violation	0	0
Lost to follow up	0	0
Did not meet entrance criteria	3 (33.3)	1 (12.5)
Subject no longer willing to participate	1 (11.1)	3 (37.5)
Other	2 (22.2)	2 (25.0)

AE = adverse event; CRF = case report form; n = number of subjects with an observation; PCI = percutaneous coronary intervention.
[a]One additional death (in the usual care treatment group) was recorded in the safety database that was not captured in the CRF or clinical database because it occurred after the subject's last visit.
[b]This number included the subjects who were considered not to require PCI.

In the FAS, the majority of subjects assigned to study treatment were males (116 males versus 47 females and 126 males versus 46 females in the atorvastatin and usual care treatment groups, respectively); all subjects were Asian; and subjects ranged in age from 35 to 85 years, with a body mass index (BMI) between 14.9 and 37.0 kg/m^2. For all randomized subjects, the majority of subjects assigned to study treatment were males (166 males versus 81 females and 175 males versus 77 females in the atorvastatin and usual care treatment groups, respectively); all subjects were Asian; and subjects ranged in age from 35 to 85 years, with a BMI between 14.0 and 37.0 kg/m^2.

Efficacy Results: In the FAS, the incidence of MACE within 30 days post-PCI, was similar in the atorvastatin and usual care treatment groups and the 2-sided 95% CIs included 0, suggesting no statistically significant difference between the atorvastatin and usual care treatment groups. The odds ratio of MACE within 30 days post-PCI, calculated using a logistic regression analysis, showed no statistically significant difference between the atorvastatin and usual care treatment groups. There was no statistically significant difference between the atorvastatin and usual care treatment groups in MACE event-free curves (investigated using survival analysis and log-rank test). The sensitivity analysis showed no statistically significant difference between the atorvastatin and usual care treatment groups in the incidence of MACE within 30 days post-PCI, which was calculated using the Kaplan-Meier method. The results were similar for the PP analysis set.

The incidence of MACE was similar in the atorvastatin and usual care treatment groups at 8 hours and 24 hours post-PCI and the 2-sided 95% CIs included 0, suggesting no statistically significant difference between the atorvastatin and usual care treatment groups.

The proportion of subjects with elevated biomarkers of myocardial injury CK-MB, troponin-I, and myoglobin) was similar in the atorvastatin and usual care treatment groups at all time points during the study and the 95% CIs included 0, suggesting no statistically significant difference between the atorvastatin and usual care treatment groups.

In all samples (refers to all CRP samples tested, including samples that were affected by the defective high sensitivity [hs]-CRP reagents with appropriate data correction), unaffected samples (refers to the CRP samples tested that were not affected by the defective hs-CRP reagents), and affected samples (refers to the CRP samples tested that were affected by the defective hs-CRP reagents with appropriate data correction), the 95% CIs of the LS mean change from Baseline included 0 at all time points, suggesting no statistically significant difference between the atorvastatin and usual care treatment groups.

Safety Results: The proportion of subjects reporting treatment-emergent AEs (TEAEs) (all causality) was similar in the atorvastatin and usual care treatment group (116 [47.3%] subjects and 119 [47.6%] subjects, respectively). The proportion of subjects reporting treatment-related TEAEs was slightly higher in the atorvastatin treatment group (40 [16.3%] subjects) compared with the usual care treatment group (31 [12.4%] subjects). The proportion of subjects reporting treatment-emergent severe TEAEs (all causality) was similar in the atorvastatin and usual care treatment groups (8 [3.3%] subjects and 9 [3.6%] subjects, respectively).

In both treatment groups, the most commonly reported TEAEs were in the General disorders and administration site conditions system organ class (SOC) (36 [14.7%] subjects and 36 [14.4%] subjects in the atorvastatin and usual care treatment groups, respectively). The most commonly reported preferred term (PT) TEAE in both treatment groups was headache (29 [11.8%] subjects and 18 [7.2 %] subjects in the atorvastatin and usual care treatment groups, respectively). In the atorvastatin treatment group, the most commonly reported treatment-related TEAEs were in the Cardiac disorders SOC (12 [4.9%] subjects) and in the usual care treatment group, the most commonly reported treatment-related TEAEs were in the Gastrointestinal disorders SOC (9 [3.6%] subjects). The most commonly reported PT treatment-related TEAE in the atorvastatin treatment group was myocardial infarction (10 [4.1%] subjects versus 6 [2.4%] subjects in the usual care treatment group) and the most commonly reported PT treatment-related TEAE in the usual care treatment group was alanine aminotransferase (ALT) increased (7 [2.8%] subjects versus 4 [1.6%] subjects in the atorvastatin treatment group).

TEAEs (all causality) summarized by SOC and reported for ≥5% of subjects in either treatment group are summarized in Table 3.

Table 3. Treatment-Emergent Adverse Events (All Causality) Reported for ≥5% of Subjects in Either Treatment Group

System Organ Class[a]	Atorvastatin (N = 245) n (%)	Usual Care (N = 250) n (%)
Cardiac disorders	31 (12.7)	28 (11.2)
Gastrointestinal disorders	26 (10.6)	25 (10.0)
General disorders and administration site conditions	36 (14.7)	36 (14.4)
Investigations	10 (4.1)	21 (8.4)
Musculoskeletal and connective tissue disorders	18 (7.3)	16 (6.4)
Nervous system disorders	35 (14.3)	27 (10.8)
Vascular disorders	7 (2.9)	14 (5.6)

Subjects were only counted once per treatment for each row.
All data collected since the first dose of study treatment is included.
N = number of subjects in the evaluable population.
[a] AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v13.0).

Three (1.2%) subjects in the atorvastatin treatment group and 2 (0.8%) subjects in the usual care treatment group discontinued from the study due to AEs (all causality). Subjects who withdrew permanently from the study due to AEs are summarized in Table 4.

Table 4. Permanent Discontinuations due to Adverse Events.

MedDRA Preferred Term	Study Start[a]/Stop Day[a]	Severity	Outcome	Causality	SAE
Atorvastatin treatment group					
Chest pain	7/10	Moderate	Resolved	Disease under study	No
Gastrointestinal haemorrhage	1/5	Mild	Resolved	Background study drug-antiplatelet therapy	No
Haematoma	2/2	Mild	Resolved	Background study drug-aspirin, clopidogrel, heparin	No
Usual Care treatment group					
Cerebrovascular accident	2/>30	Severe	Still present	Concomitant treatment-coronary angiography	Yes
ALT increased	3/>12	Mild	Still present	Other illness-a cold	No

ALT = alanine aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities (v13.0); SAE = serious adverse event.
[a] Day relative to the start of study treatment. First day of treatment = Day 1.

No subject was recorded as having a dose reduction or temporary discontinuation due to TEAEs.

Differences exist between the safety database listings of SAEs and deaths and the clinical study database. The reason for the differences is that SAEs are reported separately in the case report form (CRF) and in the AE monitoring system. Instances of SAEs occurring after the subject's last visit cannot be captured in the CRF and are therefore not included in the clinical database. However, these AEs are included in the safety database.

Two deaths were recorded in the clinical database (death and angina unstable). One additional subject was recorded as having died in the safety database but was not recorded as

having died in the clinical database. The subject died from acute myocardial infarction, ischaemia, renal failure acute and rhabdomyolysis. The 3 deaths recorded in the safety database are presented in Table 5.

Table 5. Deaths

Events with Fatal Outcome MedDRA Preferred Term	Study Treatment[a]	Therapy Stop Date	Date of Death[b]
Death	Atorvastatin calcium	05 Oct 2009	06 Oct 2009
Angina unstable	Atorvastatin calcium	NA	08 Mar 2009
Acute myocardial infarction Ischaemia Renal failure acute Rhabdomyolysis	No subject drug	NA	26 Jun 2009

MedDRA = Medical Dictionary for Regulatory Activities (v13.0); NA = not available; OC = Oracle Clinical; PIMS = Phase I Management System; SDW = safety data warehouse.
[a] The source of the actual treatment group or sequence is the OC or PIMS and the source of the suspect drug is from SDW.
[b] Death period is calculated as SDW death date minus OC first active therapy date + 1.

The proportion of subjects reporting serious adverse events (SAEs) (all causality) was similar in the atorvastatin and usual care treatment groups (16 subjects each, 6.5% and 6.4%, respectively, according to the clinical database). One additional subject in each treatment group was recorded as having an SAE in the safety database (35 SAEs [18 and 17 SAEs in the atorvastatin and usual care treatment groups, respectively]) that was not captured in the clinical database. One subject (atorvastatin treatment group) reported SAEs of chest pain and dyspnoea on Day 6 of the study and one subject (usual care treatment group) reported SAEs of acute myocardial infarction, ischaemia, renal failure acute, and rhabdomyolysis on Day 9 of the study. Only 1 subject in the usual care treatment group reported an SAE (ALT increased on Day 7) that was considered by the investigator to be related to the study treatment. The most frequently reported PT SAEs were posted post procedural myocardial infarction.

SAEs including fatal SAEs are presented in Table 6.

Table 6. Serious Adverse Events

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Study Drug(s)[a] and Unit Dose[b]	Therapy Stop Day[c]	Event Onset Day[d]	MedDRA Preferred Term	Causality	Clinical Outcome	Seriousness
Atorvastatin treatment group						
40 mg Atorvastatin	32	2	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
40 mg Atorvaststin	29	2	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 60 mg Enoxaparine/ 75 mg Clopidogrel	2	6	Chest pain Dyspnoea	Unrelated	Recovered/resolved	Hospitalization
200 mg Aspirin/ 75 mg Clopidogrel	34	1	Pleural effusion	Unrelated	Recovered/resolved	Hospitalization
40 mg Atorvastatin	33	3	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
200 mg Aspirin/ 75 mg Clopidogrel	1	19	Atrial fibrillation	Unrelated	Recovered/resolved	Hospitalization
200 mg Aspirin/ 75 mg Clopidogrel	25	26	Death	Unrelated	Fatal	Fatal
100 mg Aspirin/ 75 mg Clopidogrel	8	9	Acute myocardial infarction	Unrelated	Recovered/resolved	Hospitalization
40 mg Atorvastatin	34	2	Myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 75 mg Clopidogrel	36	3	Myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 75 mg Clopidogrel	29	3	Myocardial infarction	Unrelated	Recovered/resolved	Important medical event

ID = identification; MedDRA = Medical Dictionary for Regulatory Activities (v13.0); NA = not available; OC = Oracle Clinical; PIMS = Phase I Management System; SDW = safety data warehouse.

[a] The source of the actual treatment group or sequence is the OC or PIMS and the source of the suspect drug is from SDW.

[b] Dose of treatment at the earliest onset date.

[c] Therapy stop day = SDW therapy stop date minus OC first active therapy date + 1.

[d] Onset study day = SDW onset date – (OC first active therapy date + 1).

Table 6. Serious Adverse Events (continued)

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Study Drug(s)[a] and Unit Dose[b]	Therapy Stop Day[c]	Event Onset Day[d]	MedDRA Preferred Term	Causality	Clinical Outcome	Seriousness
200 mg Aspirin	1	17	Cerebral infarction	Unrelated	Recovered/resolved	Hospitalization
200 mg Aspirin/ 75 mg Clopidogrel	1	10	Palpitations	Unrelated	Recovered/resolved	Hospitalization
200 mg Aspirin/ 75 mg Clopidogrel	1	9	Visual impairment	Unrelated	Recovered/resolved	Hospitalization
40 mg Atorvastatin	32	26	Gastritis	Unrelated	Not recovered/ not resolved	Hospitalization
	32	26	Gastritis erosive	Unrelated	Not recovered/ not resolved	Hospitalization
	1	1	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
200 mg Aspirin/ 75 mg Clopidogrel	28	6	Hepatitis acute	Unrelated	Recovered/resolved	Hospitalization
40 mg Atorvastatin/ 100 mg Aspirin/ 75 mg Clopidogrel	1	7	Chest pain	Unrelated	Recovered/resolved	Hospitalization
Usual Care treatment group						
73 mg Enoxaparine	32	2	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
40 mg Atorvastatin	NA	3	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
40 mg Atorvastatin/ 200 mg Aspirin/ 75 mg Clopidogrel	32	9	Chest pain	Unrelated	Recovered/resolved	Hospitalization

ID = identification; MedDRA = Medical Dictionary for Regulatory Activities (v13.0); NA = not available; OC = Oracle Clinical; PIMS = Phase I Management System; SDW = safety data warehouse.

[a] The source of the actual treatment group or sequence is the OC or PIMS and the source of the suspect drug is from SDW.

[b] Dose of treatment at the earliest onset date.

[c] Therapy stop day = SDW therapy stop date minus OC first active therapy date + 1.

[d] Onset study day = SDW onset date – (OC first active therapy date + 1).

Table 6. Serious Adverse Events (continued)

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Study Drug(s)[a] and Unit Dose[b]	Therapy Stop Day[c]	Event Onset Day[d]	MedDRA Preferred Term	Causality	Clinical Outcome	Seriousness
75 mg Clopidogrel	32	3	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin	29	3	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 75 mg Clopidogrel	NA	2	Cerebrovascular accident	Unrelated	Recovering/resolving	Important medical event
100 mg Aspirin/ 20000 IU Dalteparin sodium	NA	4	Myocardial infarction	Unrelated	Recovered/resolved with sequelae	Hospitalization
75 mg Clopidogrel	8	7	Alanine aminotransferase increased	Related	Recovered/resolved	Hospitalization
200 mg Aspirin/ 150 mg Clopidogrel	NA	2	Angina unstable	Unrelated	Fatal	Fatal
200 mg Aspirin/ 75 mg Clopidogrel	31	3	Myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 75 mg Clopidogrel	35	3	Myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 75 mg Clopidogrel	NA	2	Myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 75 mg Clopidogrel	NA	9	Ischaemia	Unrelated	Fatal	Fatal
	NA	9	Rhabdomyolysis	Unrelated	Fatal	Fatal
	NA	9	Renal failure acute	Unrelated	Fatal	Fatal
	NA	9	Acute myocardial infarction	Unrelated	Fatal	Fatal
60 mg Enoxaparine	NA	3	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event

ID = identification; MedDRA = Medical Dictionary for Regulatory Activities (v13.0); NA = not available; OC = Oracle Clinical; PIMS = Phase I Management System; SDW = safety data warehouse.

[a] The source of the actual treatment group or sequence is the OC or PIMS and the source of the suspect drug is from SDW.

[b] Dose of treatment at the earliest onset date.

[c] Therapy stop day = SDW therapy stop date minus OC first active therapy date + 1.

[d] Onset study day = SDW onset date – (OC first active therapy date + 1).

Table 6. Serious Adverse Events (continued)

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Study Drug(s)[a] and Unit Dose[b]	Therapy Stop Day[c]	Event Onset Day[d]	MedDRA Preferred Term	Causality	Clinical Outcome	Seriousness
120 mg Enoxaparine	NA	3	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
120 mg Enoxaparine	NA	2	Post procedural myocardial infarction	Unrelated	Recovered/resolved	Important medical event
100 mg Aspirin/ 75 mg Clopidogrel	NA	9	Chest discomfort	Unrelated	Recovered/resolved	Hospitalization

ID = identification; MedDRA = Medical Dictionary for Regulatory Activities (v13.0); NA = not available; OC = Oracle Clinical; PIMS = Phase I Management System; SDW = safety data warehouse.

[a] The source of the actual treatment group or sequence is the OC or PIMS and the source of the suspect drug is from SDW.

[b] Dose of treatment at the earliest onset date.

[c] Therapy stop day = SDW therapy stop date minus OC first active therapy date + 1.

[d] Onset study day = SDW onset date – (OC first active therapy date + 1).

The most frequently reported laboratory abnormality (with normal baseline) in both treatment groups was glucose >1.5 x ULN (30/108 [28%] subjects and 34/115 [30%] subjects in the atorvastatin and usual care treatment groups, respectively), and the number of subjects with laboratory abnormalities was comparable between the atorvastatin and usual care treatment groups.

The most frequently reported urinalysis (dipstick) abnormalities (with normal baseline) were urine blood (37/219 [17%] and 42/221 [19%] subjects in the atorvastatin and usual care treatment groups, respectively) and urine glucose (35/220 [16%] and 37/226 [16%] subjects in the atorvastatin and usual care treatment groups, respectively). The most frequently reported urinalysis (microscopy) abnormality (with normal baseline) was urine red blood cells in the atorvastatin treatment group (16/105 [15%] subjects versus 17/118 [14%] subjects in the usual care treatment group) and urine white blood cells in the usual care treatment group (30/120 [25%] subjects versus 15/104 [14%] subjects in the atorvastatin treatment group). Overall, single elevations in liver function tests (>3.0x ULN) were reported in <5% of subjects in this study.

With the exception of LDL-C, which decreased from baseline by 58 mg/dL and 48 mg/dL in the atorvastatin and usual care treatment groups, respectively, and creatine kinase, which decreased from baseline by 12 U/L and 18 U/L in the atorvastatin and usual care treatment groups, respectively, there were no notable median changes from baseline to last observation in any laboratory parameter in either treatment group. The most commonly reported laboratory test TEAE (all causality and treatment related) in both treatment groups was ALT increased (4 [1.6%] subjects and 9 [3.6%] subjects in the atorvastatin and usual care treatment groups, respectively [all causality], and 4 [1.6%] subjects and 7 [2.8%] subjects in the atorvastatin and usual care treatment groups, respectively [treatment related]).

Vital signs absolute values were comparable between the atorvastatin and usual care treatment groups for all parameters analyzed (pulse rate, body temperature, respiratory rate, and systolic and diastolic BP) with no or small mean changes from baseline observed during the study for each vital signs parameter.

For the brief physical examination findings, 1 (0.4%) subject and 2 (0.8%) subjects in the atorvastatin and usual care treatment groups, respectively, had significant changes from baseline at the final visit.

The proportion of subjects with normal or abnormal (not clinically significant) ECG results was comparable between the atorvastatin and usual care treatment groups at all time points during the study. The proportion of subjects with abnormal (clinically significant) ECG results was lower in the atorvastatin treatment group compared to the usual care treatment group at all time points during the study.

CONCLUSIONS:

- While other studies evaluating the use of statins before an invasive cardiovascular procedure have suggested a clinical benefit, there was no significant difference in the incidence of MACE within 30 days post-PCI between the atorvastatin and usual care

treatment groups, when atorvastatin was administered pre-procedurally in subjects with NSTE-ACS.

- There were no significant differences in the proportions of subjects who had elevated levels of troponin-I, CK-MB, and myoglobin post-PCI between the atorvastatin and usual care treatment groups.

- There were no significant differences in the mean percentage change from baseline in CRP between the atorvastatin and usual care treatment groups.

- The summaries of safety data suggest that atorvastatin, in conjunction with usual care, is safe and well tolerated. The overall incidence of laboratory test (all causality and treatment-related) AEs was low, and the incidence of increased liver enzymes and increased blood creatinine AEs was similar between the atorvastatin and usual care treatment groups, suggesting that atorvastatin was well tolerated in the group of Asian subjects treated in this study, in accordance with the product labeling.