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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Lipitor[™]/atorvastatin calcium

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00540293

PROTOCOL NO.: A2581157

PROTOCOL TITLE: A Multicenter, Eight-Week Treatment, Single-Step Titration, Open-Label Study Assessing the Percentage of Korean Dyslipidemic Patients Achieving LDL Cholesterol Target with Atorvastatin Starting Doses of 10 mg, 20 mg and 40 mg

Study Centers: 20 centers in Korea

Study Initiation and Completion Dates: 10 October 2007 to 16 May 2008

Phase of Development: Phase 4

Study Objectives:

• **Primary Objective:**

To evaluate the percentage of Korean dyslipidemic subjects in the total group and each cardiovascular risk group achieving low density lipoprotein-cholesterol (LDL-C) target as defined by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria at starting doses of 10 mg, 20 mg and 40 mg of atorvastatin at Week 8.

• **Secondary Objectives:**

1. To evaluate the percentage of Korean dyslipidemic subjects in the total group and each cardiovascular risk group achieving LDL-C target as defined by NCEP ATP III criteria at starting doses of 10 mg, 20 mg and 40 mg of atorvastatin at Week 4.
2. To evaluate the changes and percent changes in lipid parameters in Korean dyslipidemic subjects in the total group and each cardiovascular risk group treated with atorvastatin at starting doses of 10 mg, 20 mg and 40 mg at Weeks 4 and 8.

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3. To evaluate the proportion of subjects who achieved the LDL-C target with no titration and the proportion of subjects who achieved the LDL-C target with 1 step titration of atorvastatin at starting doses of 10 mg, 20 mg and 40 mg at Week 8.
4. To evaluate the changes and percent changes in high sensitive circulating C-reactive protein (hs-CRP) at Weeks 4 and 8 and other selected inflammatory markers at Week 8 in Korean dyslipidemic subjects treated with atorvastatin at starting doses of 10 mg, 20 mg and 40 mg.
5. To evaluate the safety and tolerability of atorvastatin in Korean dyslipidemic subjects at starting doses of 10 mg, 20 mg and 40 mg.

METHODS

Study Design: This was a prospective, multicenter, single-step titration, open-label study assessing the percentage of Korean dyslipidemic subjects achieving LDL-C target with atorvastatin starting doses of 10 mg, 20 mg, and 40 mg. The starting dose depended on a subject's cardiovascular risk assessment and LDL-C measurement at baseline. After enrollment, the subjects were treated with atorvastatin for 8 weeks.

The subjects eligible at screening were separated into 2 groups:

1. Those who were on antilipidemic medications at the time of screening and therefore required a 6-week washout period. There were a total of 4 visits at Weeks -6, 0, 4 and 8.
2. Those who were not on antilipidemic medications at the time of screening and therefore did not require washout. There was a maximum of 4 visits at Weeks -1, 0, 4 and 8.

During the initial 4-week open-label treatment period, subjects were assigned to receive 10 mg, 20 mg, or 40 mg atorvastatin once daily. For the next 4 weeks of open-label treatment, subjects who achieved their LDL-C target at Week 4 continued with their starting dose for the final 4 weeks, and subjects who did not meet their LDL-C target received atorvastatin at the next higher dose (e.g., 80 mg [2 x 40 mg tablets] for those started with 40 mg).

Number of Subjects (Planned and Analyzed):

Approximately 416 subjects were planned to be enrolled.

At the end of the study, 425 subjects were enrolled and included into the safety and Full Analysis Set (FAS) analysis populations, and 358 subjects into the efficacy evaluation (EVAL) analysis population.

Diagnosis and Main Criteria for Inclusion: Korean outpatients, aged ≥ 18 and ≤ 80 years, with a diagnosis of dyslipidemia at baseline (LDL-C ≤ 220 mg/dL and triglyceride [TG] level ≤ 600 mg/dL), who were eligible for LDL-lowering drug therapy defined by NCEP ATP III were included in this study. Subjects were required to follow the Therapeutic Lifestyle Changes (TLC) diet throughout the study. Female subjects of child bearing potential were

required to use reliable methods of birth control. No antilipidemic medications were allowed for the 6-week washout period.

Study Treatment: Commercial atorvastatin (Lipitor™) oral white, oval and film-coated tablets (10 mg, 20 mg and 40 mg) were used as study treatment. Study treatment was provided in the blister card for 30-day supply and was administered once daily for a maximum of 8 weeks.

Efficacy Evaluations:

- **Primary Efficacy Variable**

The primary efficacy variable was the percentage of subjects achieving their LDL-C target at Week 8. It was assessed for subjects in the total group and repeated for subjects in each cardiovascular risk group.

- **Secondary Efficacy Variables**

1. Percentage of subjects in the total group and each cardiovascular risk group achieving their LDL-C target at Week 4.
2. Change and percent change from baseline to Weeks 4 and 8 for LDL-C, high density lipoprotein-cholesterol (HDL-C), non-HDL-C, LDL-C/HDL-C ratio, total cholesterol (TC), and TG for subjects in the total group and each cardiovascular risk group.
3. Percentage of subjects who achieved LDL-C target with no titration and after 1 step titration of atorvastatin.
4. Change and percent change from baseline to Weeks 4 and 8 for hs-CRP.
5. Change and percent change from baseline to Week 8 for monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) (these inflammation markers were not measured at Week 4).

Safety Evaluations: Safety evaluations included adverse events (AEs), discontinuations, clinical laboratory test results, physical examinations, vital signs and body weight.

Statistical Methods:

- **Sample Size:** A sample size of approximately 416 subjects was considered for enrollment to provide a precise estimate of the overall treatment response rate (the percentage of subjects achieving their LDL-C target at Week 8). Precision was measured by the width of the 95% confidence interval (CI) for the response rate. The proposed sample size gave a 95% CI of less than 7.5% in width based on the Clopper-Pearson method, assuming a 10% dropout and an observed overall response rate of 85%.
- **Analysis Populations:** This study included 1 safety population and 2 efficacy analysis populations: FAS population and EVAL population. All efficacy variables were

analyzed for FAS population and any analysis results using the EVAL population were intended to give further support to conclusions based on the FAS. Safety data were analyzed using the safety population.

- **Subgroup Analyses:** Subjects were classified into 3 risk groups (low risk, medium risk and high risk), and for each efficacy parameter, subgroup analyses were performed on each of the risk groups. The 3 risk groups were defined according to cardiovascular risk category.
- **Efficacy Analysis:** For binary endpoints, the proportion of interest was estimated and a 95% CI for the proportion was calculated using the exact (Clopper-Pearson) method. For endpoints based on continuous data, descriptive statistics on the data were given including mean, standard deviation (SD), median, 25th and 75th percentiles, minimum and maximum. Additionally, to gauge the precision of the appropriate location parameter estimates (mean or median), 95% CIs were provided. Missing values were imputed by last observation carried forward (LOCF) unless otherwise specified.
- **Safety Analysis:** Safety was analyzed for the following parameters: baseline and demographic characteristics, subject disposition, reasons for discontinuations, medical history, previous and concomitant drug treatment, treatment duration, AEs, laboratory parameters, vital signs, physical examinations.

RESULTS

Subject Disposition and Demography: Among a total population of 425 subjects who enrolled, 29, 45 and 351 were classified into low risk, medium risk and high risk group, respectively, based on their cardiovascular risk category and starting LDL-C. In the same study population, 253 (59.5%), 63 (14.8%) and 109 (25.6%) subjects were assigned at baseline to 10 mg, 20 mg and 40 mg atorvastatin, respectively. A higher proportion of subjects (31.1%) in the high risk group were assigned to 40 mg at baseline compared with the low and medium risk groups which had no subject assigned to this dose. Among a total of 395 subjects who were assigned to titration dose at Week 4, 56 (14.2%) were titrated 1 step up. The number of subjects assigned to 10 mg, 20 mg, 40 mg and 80 mg atorvastatin at Week 4 was 215 (54.4%), 77 (19.5%), 77 (19.5%) and 26 (6.6%), respectively. No subject in the low or medium risk groups was titrated to 80 mg at Week 4; however, 26 in the high risk group were. All subjects were analyzed for safety and were included in the FAS analysis population, whereas 358 subjects were included in the EVAL analysis population.

Subject disposition is summarized in the table below:

Table S1. Subject Disposition

Number (%) of Subjects	Atorvastatin
Screened:	574
Treated	425
Completed	390 (91.8)
Discontinued	35 (8.2)
Analyzed for safety	
Adverse events	425 (100)
Laboratory data	415 (97.6)

A total of 35 (8.2%) subjects prematurely discontinued from the study. The majority of discontinuations (n=25) were not related to study drug, whereas 10 discontinuations were related to study drug. There were 17 (4.0 %) subjects who discontinued from the study due to AEs, of which 10 were related and 7 were unrelated to study drug. The proportion of subjects who discontinued was similar across risk groups.

All subjects in the study were Asian. The mean age for the total study population was 61 years and 54% of subjects were male.

Efficacy Results:

- **Percentage of LDL-C Responders at Weeks 4 and 8:** The percentage of LDL-C responders at Weeks 4 and 8 (primary objective) is summarized by risk group in FAS population in the following table.

Table S2. LDL-C Responders* by Visit and by Risk Group - FAS

	Total % (N=425) (95% CI)	Low Risk % (N=29) (95% CI)	Medium Risk % (N=45) (95% CI)	High Risk % (N=351) (95% CI)
n	415	28	44	343
Responders*				
- Week 4	81.9 (77.9, 85.5)	85.7 (67.3, 96.0)	95.5 (84.5, 99.4)	79.9 (75.2, 84.0)
- Week 8**	86.0 (82.3, 89.2)	92.9 (76.5, 99.1)	95.5 (84.5, 99.4)	84.3 (80.0, 87.9)

*Responders= % subjects who achieved LDL-C target; **Week 8= primary objective for this study; LDL-C= low density lipoprotein-cholesterol; CI= confidence interval; FAS= Full Analysis Set; N= number of subjects in the FAS population; n= number of subjects with on-treatment lipid measures (missing values imputed by last observation carried forward).

In the total FAS population, 81.9% (95% CI: 77.9, 85.5) of subjects achieved their LDL-C target at Week 4, which was sustained through to Week 8 (86.0%, 95% CI: 82.3, 89.2).

- **Change and Percent Change from Baseline to Weeks 4 and 8 in Lipid Parameters (LDL-C, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC and TG):** The main results are summarized in the following table.

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Table S3. Mean Baseline, Change and Percent Change from Baseline in Lipid Parameters by Risk Group-FAS

	Total (N=425) Mean (95% CI)	Low Risk (N=29) Mean (95% CI)	Medium Risk (N=45) Mean (95% CI)	High Risk (N=351) Mean (95% CI)
n	415	28	44	343
LDL-C (mg/dL)				
Baseline	151.7 (149.1,154.4)	187.0 (179.8, 194.1)	160.6 (154.3, 167.0)	147.7 (144.9, 150.5)
Week 4	-63.5 (-66.2, -60.8)	-73.8 (-82.7, -64.8)	-65.1 (-73.5, -56.7)	-62.4 (-65.4, -59.4)
Week 8	-65.3 (-68.0, -62.5)	-77.6 (-88.3, -66.9)	-64.2 (-72.4, -56.0)	-64.4 (-67.4, -61.4)
% Change from baseline				
Week 4	-40.9 (-42.3, -39.5)	-39.5 (-44.1, -35.0)	-39.6 (-43.8, -35.5)	-41.2 (-42.8, -39.6)
Week 8	-42.0 (-43.4, -40.7)	-41.2 (-46.6, -35.8)	-39.3 (-43.5, -35.1)	-42.5 (-44.0, -41.0)
HDL-C (mg/dL)				
Baseline	48.3 (47.3, 49.3)	50.5 (47.4, 53.7)	48.0 (45.5, 50.5)	48.2 (47.0, 49.3)
Week 4	0.1 (-0.7, 0.9)	-0.8 (-3.6, 2.0)	3.3 (0.9, 5.7)	-0.2 (-1.1, 0.7)
Week 8	0.5 (-0.4, 1.3)	2.1 (-1.6, 5.9)	3.0 (0.9, 5.1)	0.0 (-1.0, 1.0)
% Change from baseline				
Week 4	1.7 (0.0, 3.4)	-0.2 (-6.0, 5.6)	7.7 (2.3, 13.1)	1.1 (-0.8, 2.9)
Week 8	2.6 (0.8, 4.4)	5.6 (-2.1, 13.2)	6.7 (2.3, 11.1)	1.8 (-0.2, 3.9)
Non-HDL-C (mg/dL)				
Baseline	175.5 (172.5, 178.5)	209.9 (201.0, 218.8)	187.1 (179.9, 194.4)	171.1 (167.9, 174.4)
Week 4	-69.4 (-72.3, -66.5)	-75.4 (-87.8, -63.1)	-71.3 (-80.2, -62.5)	-68.6 (-71.8, -65.4)
Week 8	-70.7 (-73.7, -67.7)	-80.9 (-93.9, -67.8)	-72.1 (-80.3, -64.0)	-69.7 (-73.0, -66.4)
% Change from baseline				
Week 4	-38.7 (-40.1, -37.4)	-35.5 (-40.9, -30.1)	-37.7 (-41.5, -33.8)	-39.1 (-40.6, -37.7)
Week 8	-39.4 (-40.7, -38.1)	-38.2 (-44.1, -32.2)	-38.3 (-42.1, -34.5)	-39.7 (-41.1, -38.2)
LDL-C/HDL-C Ratio (Scalar)				
Baseline	3.2 (3.1, 3.3)	3.7 (3.4, 4.0)	3.4 (3.2, 3.6)	3.2 (3.1, 3.3)
Week 4	-1.4 (-1.4, -1.3)	-1.4 (-1.7, -1.1)	-1.5 (-1.7, -1.3)	-1.3 (-1.4, -1.3)
Week 8	-1.4 (-1.5, -1.3)	-1.6 (-1.9, -1.2)	-1.5 (-1.7, -1.3)	-1.4 (-1.5, -1.3)
% Change from baseline				
Week 4	-41.3 (-43.0, -39.7)	-36.7 (-44.3, -29.0)	-44.1 (-48.9, -39.3)	-41.4 (-43.2, -39.6)
Week 8	-42.6 (-44.3, -40.9)	-41.6 (-49.5, -33.7)	-42.9 (-48.0, -37.7)	-42.6 (-44.5, -40.8)
TC (mg/dL)				
Baseline	223.9 (220.8, 227.0)	262.3 (253.9, 270.8)	235.1 (228.0, 242.3)	219.3 (216.0, 222.6)
Week 4	-69.4 (-72.4, -66.4)	-78.2 (-89.3, -67.1)	-68.0 (-77.2, -58.8)	-68.8 (-72.2, -65.5)
Week 8	-70.4 (-73.4, -67.3)	-80.7 (-94.2, -67.3)	-69.1 (-77.2, -61.1)	-69.7 (-73.1, -66.2)
% Change from baseline				
Week 4	-30.3 (-31.4, -29.2)	-29.7 (-33.6, -25.7)	-28.5 (-31.9, -25.2)	-30.6 (-31.9, -29.3)
Week 8	-30.7 (-31.9, -29.6)	-30.4 (-35.2, -25.5)	-29.2 (-32.3, -26.2)	-31.0 (-32.2, -29.7)
TG (mg/dL)				
Baseline	154.1 (146.2, 162.1)	150.7 (128.6, 172.8)	152.3 (130.3, 174.2)	154.7 (145.6, 163.7)
Week 4	-29.1 (-35.5, -22.7)	-11.5 (-43.0, 20.0)	-16.6 (-31.4, -1.8)	-32.1 (-39.2, -25.1)
Week 8	-29.3 (-37.9, -20.7)	-20.9 (-51.3, 9.5)	-18.5 (-36.3, -0.7)	-31.4 (-41.3, -21.5)
% Change from baseline				
Week 4	-8.2 (-12.9, -3.6)	4.4 (-18.5, 27.3)	-8.3 (-17.7, 1.2)	-9.3 (-14.4, -4.1)
Week 8	-9.8 (-14.9, -4.8)	-6.3 (-27.0, 14.5)	-7.0 (-20.4, 6.4)	-10.5 (-16.2, -4.8)

FAS= Full Analysis Set; CI= confidence interval; LDL-C= low density lipoprotein-cholesterol; HDL-C= high density lipoprotein-cholesterol; TC= total cholesterol; TG= triglyceride; N= number of subjects in the FAS population; n= number of subjects with on-treatment lipid measures so that post baseline changes could be determined (missing values imputed by last observation carried forward).

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In the total study population, over 30% reduction was observed in LDL-C, non-HDL-C, LDL-C/HDL-C ratio and TC over time during the study with the greatest decrease in the first 4 weeks of treatment; similar changes were also seen across risk groups. TG was also reduced by approximately 10% by Week 8; this varied somewhat across risk groups with the main decrease seen in high risk group (10.5% at Week 8). HDL-C was only slightly increased over 8 weeks (2.6% at Week 8); this result varied across risk groups, with the main increase observed in the medium risk group (6.7% at Week 8).

- **Percentage of LDL-C Responders at Week 8 with No Titration and with 1 Step Titration:** In the total FAS population, 89.1% (95% CI: 85.3, 92.2) of subjects who were not titrated achieved their LDL-C target at Week 8 and 82.1% (95% CI: 69.6, 91.1) of subjects who were titrated 1 step up achieved their LDL-C target at Week 8.
- **Change and Percent Change in hs-CRP at Weeks 4 and 8 and in Other Inflammatory Markers (MCP-1, IL-6 and TNF- α) at Week 8:** Median (not mean) changes are reported here as data in these parameters contained extreme values. There was some degree of decrease in hs-CRP (12.3% at Week 4 and 18.6% at Week 8) and some degree of increase in MCP-1 (14.0% at Week 8); however, the results varied across risk groups. No change was observed in IL-6 and TNF- α during the study.

Safety Results: Overall, a total of 69 (16.2%) subjects experienced 86 AEs, among which 32 were considered treatment related. The majority of AEs were in the high risk group as expected, since over 80% of the subjects belonged to this group. Only 3 severe AEs were reported and not related to study treatment. The most common treatment related AEs were nausea (4 events), headache (4 events) and nasopharyngitis (2 events), none of which were severe or serious. Three serious AEs (1 wrist fracture and 2 cerebral infarctions) were reported, which were not related to study treatment and 1 of them resulted in death. A total of 35 (8.2%) subjects discontinued early from this study. Seventeen (4.0%) subjects discontinued due to AEs, of which 10 were related to treatment; and 2 subjects temporarily discontinued due to AEs, of which 1 was related to treatment. Overall, the incidence of AEs was generally low during this study.

Two incidences of premature discontinuations in the study were due to abnormal laboratory test results, 1 of which was related to study treatment. No cases of rhabdomyolysis or myopathy were reported. Four subjects presented abnormal creatine phosphokinase (CPK), yet none of them were CPK > 5 x upper limit of normal (ULN). For the most part, abnormal laboratory test results were unremarkable. Findings for vital signs and weight were unremarkable. Eight subjects experienced significant changes during physical examinations, and 6 incidences were related to study treatment.

CONCLUSIONS: In summary, atorvastatin at the appropriate starting dose (10-40 mg/day) and the titration dose (up to 80 mg/day) was found to be an effective, safe and well tolerated statin treatment for dyslipidemia in this Korean population. The majority of subjects achieved LDL-target as defined by NCEP ATP III criteria as early as Week 4 during this 8-week study, regardless of risk categorization. LDL-C was effectively reduced over time and changes for other lipid parameters (HDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC and TG)

were within expected ranges as observed in other studies carried out in Asian populations. Change in selected inflammatory markers (hs-CRP, MCP-1, IL-6 and TNF- α) in this population was not clinically significant. All findings from this study provide additional data on the efficacy and safety of atorvastatin in Korean subjects, as well as providing a recommended starting dose of atorvastatin to attain LDL-C target according to NCEP ATP III criteria.