The study listed may include approved and nonapproved uses, formulations, or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this registry, healthcare professionals should consult prescribing information for the product approved in their country.

Title of Study: An Open-Label, Randomized, Parallel-Group, Multicenter Study to Compare the Efficacy and Safety of "Switching" to Rosuvastatin 10 Mg Daily Versus Atorvastatin 10 Mg Daily With Ezetimibe 10 Mg Daily Versus Doubling the Dose of Atorvastatin to 20 Mg Daily in Subjects With Hypercholesterolemia and Atherosclerotic or Coronary Vascular Disease or Diabetes Mellitus Who Have Not Achieved Study Target LDL-C Goal While Dosing With Atorvastatin 10 Mg Daily (Protocol No. P03708)

Studied Period: 10/7/04-8/8/05 | **Clinical Phase:** IV

Objective(s):

Primary. To compare the LDL-C lowering efficacy of ezetimibe 10 mg daily plus atorvastatin 10 mg daily versus rosuvastatin 10 mg daily from baseline at the end of treatment (means of Week 5 and Week 6 values).

Secondary. 1) To compare the LDL-C lowering efficacy of ezetimibe 10 mg daily plus atorvastatin 10 mg daily versus atorvastatin 20 mg daily at the end of treatment from baseline; 2) To compare between treatments the percent changes from baseline at the end of treatment in the concentrations of total cholesterol (TC), non-HDL-C, apolipoprotein B (apo B), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C ratio, and TC/HDL-C ratio; 3) To evaluate the safety and tolerability of each treatment.

Methodology: Randomized, multicenter, open-label, parallel-group study in conformance with Good Clinical Practices.

Number of Subjects: anticipated 553 randomized; 525 evaluable; however, due to the early termination of the study, 87 subjects were randomized and analyzed as the ITT and Safety population.

Diagnosis and Criteria for Inclusion:
Subjects were eligible to participate in the study providing that they met the following criteria:

- 18 years to 75 years of age;
- Stabilized on atorvastatin 10 mg daily and by subject reported history has taken at least 80% of daily doses at least for the 4 weeks preceding Visit 1;
- LDL-C concentration greater than or equal to 2.5 mmol/L to less than or equal to 160 mg/dL (less than or equal to 4.1 mmol/L) based on blood specimens taken at Visit 1, using the Friedewald calculation as described in the Protocol, Section 8.8. The lipid profiles at Visit 3 (baseline) and all subsequent visits were kept "blinded" until data analysis;
- Triglyceride concentration of less than 350 mg/dL (less than 3.99 mmol/L) based on blood specimens taken at Visit 1;
- Documented atherosclerotic disease, CHD, or diabetes mellitus;
- Liver transaminases (ALT, AST) less than 50% above the upper limit of normal, with no active liver disease, and CPK less than 50% above the upper limit of normal as tested in blood specimens taken at Visit 1;
- Clinical laboratory tests (CBC, blood chemistries, urinalysis) taken at Visit 1 must have been within normal limits or clinically acceptable to the Investigator;
- Had previously been prescribed a cholesterol lowering diet and exercise program at least 4 weeks prior to Visit 1 and had been advised to continue the same diet and exercise program during the study;
- Reported a stable weight history for at least 4 weeks prior to randomization at Visit 3 (baseline visit);
- Women receiving hormonal therapy, including hormone replacement, any estrogen antagonist/agonist, or oral contraceptives, must have been maintained on a stable dose and regimen for at least 8 weeks and willing to continue the same regimen for the duration of the study;
- Women of childbearing potential (includes women who were less than 1 year postmenopausal and women who became sexually active) must have been using an acceptable method of birth control (for example, hormonal contraceptive, medically prescribed IUD, condom in combination with spermicide) or been surgically sterilized (for example, hysterectomy or tubal ligation).
- Free of any clinically significant diseases other than hyperlipidemia, CHD, or diabetes mellitus that would interfere with study evaluations;
- Understood and able to adhere to the dosing and visit schedules, and demonstrated their willingness to participate in the study and comply with its procedures by signing a written informed consent.

Duration of Treatment: 6 weeks

Test Product, Dose, Mode of Administration: Ezetimibe 10 mg daily

Reference Therapy, Dose, Mode of Administration, Batch No(s): Rosuvastatin 10 mg daily; atorvastatin 10 mg daily; atorvastatin 20 mg daily

Criteria for Evaluation:

Efficacy: The lipid profile data, including LDL-C (using Friedewald calculation), HDL-C, triglycerides, total cholesterol, and Apo B, were measured at Visit 1, 3, 4, and 5. All the lipid data were included for the efficacy analysis.

Safety: The test results of complete blood count (differential, white blood count, platelet count, hemoglobin, hematocrit), chemistry (fasting glucose, HbA 1c (for subjects with diabetes mellitus), blood urea nitrogen (BUN), uric acid, total bilirubin, alkaline phosphate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), serum creatinine, thyroid stimulating hormone (TSH) [Visit 1 only], creatine phosphokinase (CPK), and urinalysis (gross, included specific gravity, blood, ketones, protein, glucose; micro included white blood cells, red blood cells) were performed at Visits 1 and 5. Safety assessment also consisted of monitoring all adverse events and serious adverse events (SAEs).

Statistical Methods:

Efficacy: The analysis of percent change of LDL-C from baseline was based on an ANCOVA model containing two fixed effects of treatment and center, and baseline as covariate. Since the data may be unbalanced among centers, and the interest is to test the un-weighted hypothesis of the treatment effect, the interaction term was not applied in the model. The LS Mean and the 95% confidence interval were calculated.
The efficacy variables involving the other lipids (total cholesterol, HDL-cholesterol, non-HDL-cholesterol, Apo B, and triglycerides) were analyzed similar to that of the primary endpoint.

Safety: Shift tables of laboratory values which were within normal range at baseline but move outside the normal limits at post-treatment were presented. In particular, the number (proportion) of subjects with proteinuria, AST and/or ALT of greater than or equal to 3 times the upper limit of normal (ULN) on two consecutive occasions, and with CPK greater than or equal to 10 times ULN was tabulated.

SUMMARY – CONCLUSIONS:

RESULTS:

Efficacy:

This study randomized 87 subjects distributed among ezetimibe 10 mg plus atorvastatin 10 mg treatment (N=38), rosuvastatin 10 mg treatment (N=35), and atorvastatin 20 mg treatment (N=14). All randomized subjects received at least one dose of study medication, had post-baseline assessment and belonged to the safety/ITT population.

The ezetimibe 10 mg plus atorvastatin 10 mg group showed a statistically significantly greater mean percent decrease from baseline in LDL-C than either the rosuvastatin 10 mg ($p=0.022$) or the atorvastatin 20 mg group ($p<0.001$), which indicated that ezetimibe 10 mg plus atorvastatin 10 mg was superior to treatment with either rosuvastatin 10 mg or atorvastatin 20 mg daily for lowering LDL-C level in this study.

The LDL-C achieved at endpoint was assessed within the treatment groups with patients either reaching the target level of <100 mg/dL or remaining >=100 mg/dL. There were 8/14 (57.14%) of subjects in the atorvastatin 20 mg treatment group with LDL-C <100 mg/dL, and 27/35 (77.14%) of subjects in the rosuvastatin 10 mg group with LDL-C <100 mg/dL compared with 35/38 (92.11%) of subjects in the ezetimibe 10 mg plus atorvastatin 10 mg treatment.
The difference for target-goal acheivement between the ezetimibe 10 mg plus atorvastatin 10 mg and rosuvastatin 10 mg groups, 92 % vs. 77%, did not reach statistical significance ($p=0.104$); while a significant difference was shown between ezetimibe 10 mg plus atorvastatin 10 mg and atorvastatin 20 mg ($p=0.008$).

The ezetimibe 10 mg plus atorvastatin 10 mg group also showed a statistically significantly greater mean percent decreases from baseline in total cholesterol, non-HDL-C, LDL-C/HDL-C ratio, and TC/HDL-C ratio than either the rosuvastatin 10 mg or atorvastatin 20 mg treatment groups.

The ezetimibe 10 mg plus atorvastatin 10 mg group presented a statistically significantly greater mean percent decrease from baseline in Apo B compared with the atorvastatin 20 mg treatment group.

There were no significant differences for the LS mean percent changes in HDL-C and triglycerides between ezetimibe 10 mg plus atorvastatin 10 mg treatment versus either rosuvastatin 10 mg treatment or atorvastatin 20 mg treatment.

Safety:

There was one severe AE (cataract operation) in the ezetimibe 10 mg plus atorvastatin 10 mg group. All treatment-associated AEs were mild or moderate, and similar among the three treatment groups. One subject discontinued from the study because of AE: fatigue, which was possibly related to treatment in the ezetimibe 10 mg plus atorvastatin 10 mg treatment group. One serious AE (viral infection) occurred in the rosuvastatin 10 mg group, which was determined by the Investigator as unlikely related to treatment. One death occurred more than 30 days after the subject failed to meet protocol eligibility. There were no subjects in any of the treatment groups with elevations of ALT≥3XULN, AST≥3XULN, or CPK≥10XULN at the end of treatment. Among the subjects with proteinuria test at both Visit 1 and Visit 5, the normal result at Visit 1 was changed to abnormal at Visit 5 for 13.3% of the ezetimibe 10 mg plus atorvastatin 10 mg subjects, 16.6% of the rosuvastatin 10 mg subjects, and 16.7% of the atorvastatin 20 mg subjects.

CONCLUSIONS:

The primary efficacy analysis demonstrated that ezetimibe 10 mg plus atorvastatin 10 mg treatment was superior to both rosuvastatin 10 mg and atorvastatin 20 mg treatment for lowering LDL-C. In addition, the rate of LDL-C target-goal (<100 mg/dL) acheivement was better for the ezetimibe 10 mg plus atorvastatin 10 mg compared with the rosuvastatin 10 mg group, 92 % vs. 77%, but the difference did not reach statistical significance (p=0.104). However, a significant difference was shown between the ezetimibe 10 mg plus atorvastatin 10 mg and atorvastatin 20 mg treatment groups (p=0.008).

The secondary efficacy analyses showed that: 1) the ezetimibe 10 mg plus atorvastatin 10 mg treatment significantly lowered total cholesterol, non-HDL-C, LDL-C/HDL-C ratio, and TC/HDL-C ratio compared with either rosuvastatin 10 mg or atorvastatin 20 mg treatment, as determined by LS mean percent changes from baseline at the end of treatment; 2) the ezetimibe 10 mg plus atorvastatin 10 mg treatment resulted in a significantly greater mean percent decrease from baseline in Apo B compared with the atorvastatin 20 mg group. Due to the small number of subjects (n=14) in the atorvastatin 20 mg treatment group and the apparent lack of effect of doubling the dose of atorvastatin from 10 mg to 20 mg in this study, the results of the comparisons between the ezetimibe 10 mg plus atorvastatin 10 mg and the atorvastatin 20 mg group should be interpreted with caution.

All three treatments were safe and well-tolerated in this study.

Date of the Report: 3/29/06