Drug Substance	Rosuvastatin	**SYNOPSIS**	
Study Code	4522SP/0001		
Date	18 January 2007		

"A multicenter, randomized, double-blind, parallel-group, dose titration (10 mg and 20 mg) study to compare the efficacy and safety of Rosuvastatin versus Atorvastatin in patients with primary hypercholesterolemia"

Investigator

A total of 41 investigators participated in the study.

Study centre(s)

Forty-one Spanish centers participated in this multicenter study.

Study dates

First subject enrolled 9 May 2003

Last subject completed 2 September 2004

Objectives

Primary objective

To compare the efficacy of Rosuvastatina 10 mg versus Atorvastatin 10 mg by assessing:

- The proportion of patients achieving the NCEP ATP III LDL-C goal after 12 weeks of treatment.
- The percent decrease in individual LDL-C levels after 12 weeks of treatment.

Secondary objectives

- To evaluate and compare the efficacy of Rosuvastatin 10 mg versus Atorvastatin 10 mg
- The comparative safety of Rosuvastatin versus Atorvastatin by recording adverse events occurring with each drug.

Study design

A phase IIIb multicenter, randomized, double-blind, parallel-group, dose titration (10 mg and 20 mg) study to compare the efficacy and safety of Rosuvastatin versus Atorvastatin in patients with primary hypercholesterolemia after 12 and 24 weeks of treatment.

-{}-The study consisted of a 4-week run-in or pre-randomization period and a 24-week active treatment period. Written informed consent was obtained from each patient before participation in the study. During the run-in period, patients followed the prescribed diet as indicated by the DCC-E and did not take any lipid lowering treatment.

After the run-in period, patients meeting the screening criteria were randomized to Rosuvastatin 10 mg or Atorvastatin 10 mg for 12 weeks. In patients who did not achieve the NCEP ATP III LDL-C goal after 12 weeks of treatment, the dose of Rosuvastatin or Atorvastatin was increased to 20 mg and this dose was maintained for the last 12 weeks of treatment. Patients who reached such goal continued on the same dose of the study drug (10 mg) until week 24.

Medication was administered by the oral route as a once daily capsule, approximately 3 hours after the evening meal.

A total of 7 visits were scheduled to occur during the clinical trial: two visits in the run-in period (Visits 0 and 1) and five visits in the active treatment period (Visits 2 to 6). Drug treatment randomization occurred at Visit 2.

Target subject population and sample size

The protocol estimated that 225 patients would have to be randomized to each of the groups. A total of 722 patients signed the informed consent, but only 631 of these met all run-in criteria and formed the safety population.

Investigational product and comparator(s). Duration of treatment

The study medication consisted of oral Rosuvastatin 10 mg once daily for 24 weeks. Patients who did not achieve the NCEP ATP III LDL-C goal after 12 weeks of treatment were titrated to 20 mg daily for the last 12 weeks of treatment. Patients who achieved the LDL-C goal continued on 10 mg. Rosuvastatin treatment was administered as capsules 3 hours after the evening meal.

Rosuvastatin is a member of the class of HMG CoA reductase inhibitors (therapeutic class C10AA).

The control drug was oral Atorvastatin 10 mg once daily for 24 weeks. Patients who did not achieve the NCEP ATP III LDL-C goal after 12 weeks of treatment were titrated to 20 mg daily for the last 12 weeks of treatment. Patients who achieved the LDL-C goal continued on 10 mg. Atorvastatin treatment was administered as capsules with an identical appearance to Rosuvastatin capsules 3 hours after the evening meal.

Atorvastatin is a member of the class of HMG CoA reductase inhibitors (therapeutic class C10AA).

Variables

Primary assessment variable:

- Proportion of patients achieving the NCEP ATP III LDL-C goal after 12 weeks of treatment.
- Percent decrease in individual LDL-C levels after 12 weeks of treatment.

Secondary efficacy variables:

- Proportion of patients achieving the DCC-E LDL-C goal after 12 weeks of treatment.
- Proportion of patients achieving the JTFE-2 LDL-C goal after 12 weeks of treatment.
- Percent change in total cholesterol, HDL-C, triglycerides, Apo B, and Apo-AI levels after 12 weeks of treatment.
- Proportion of patients achieving the NCEP ATP III LDL-C goal after 12 additional weeks of treatment with Rosuvastatin 20 mg or Atorvastatin 20 mg.
- Percent change in total cholesterol, HDL-C, triglycerides, Apo B, and Apo-AI levels after 12 additional weeks of treatment with Rosuvastatin 20 mg or Atorvastatin 20 mg.
- Percent change in LDL-C, total cholesterol, HDL-C, triglycerides, Apo B, and Apo-AI levels at week 24.
- Proportion of patients achieving the NCEP ATP III LDL-C goal at week 24.
- Change in levels of vascular inflammation biomarkers (CRP, ICAM-1, IL-6) and coagulation factors (Fi, PAI-1, thrombin) with Rosuvastatin or Atorvastatin treatment.

Safety variables

All adverse events occurring in both the pre-randomization and randomization phases were recorded.

Statistical methods:

Efficacy analysis

For statistical analysis, the baseline LDL-C value was the one obtained in the test performed for Visit 2.

The ITT population-LOCF and the Cochran-Mantel-Haenszel general association statistic, after adjustment for treatment and centre, were used to compare the proportions of patients achieving the NCEP ATP II therapeutic objectives with both treatments. For subgroup comparisons, a logistic regression model containing the effects of centre and treatment group was used, and a Fisher's exact test (two-tailed) or the standard logaritmic transformation was used as appropriate.

For analysis of the percent change in LDL-C, an analysis of variance (ANOVA) on the LOCF data of the ITT population was used, including in the model the treatment, the centre, and the centre-treatment interaction term. In the event that the interaction term had substantially contributed to the model ($p<0.05$), the nature of the interaction had to be investigated and an evaluation had to be made as to whether the inferences made about the main effects of treatment were appropriate. If the interaction term was not significant, it was withdrawn from the model. The tests were performed with a one-sided α level = 0.025 and are presented at a two-sided α level = 0.05. Results of each model are presented in terms of F tests, means adjusted by least squares, and the corresponding 95% confidence interval and significance level.

The analysis by observed cases is secondary and is supplemental to the LOCF analysis. Descriptive statistics and graphic representations of all relevant data are also given.

Safety analysis

Data from all patients entering the run-in period with diet were evaluated in the safety analysis. Patients withdrawn during the run-in period with diet and those withdrawn after randomization should be separately analyzed.

Adverse events reported during the study were coded using the WHOART dictionary. The incidence of adverse events for each treatment group was displayed in tabular form by organs and systems using the preferred term. All adverse events reported during the run-in period with diet were listed by organs and systems and preferred term.

A listing per patient of hematology, chemistry, vascular inflammation markers, and coagulation data was provided. These data were also summarized for all patients using the mean, minimum, maximum, and number of patients. Hematology and chemistry values outside the normal range of the central laboratory were highlighted. Changes in liver function and CPK levels and their changes from baseline were summarized using descriptive statistics at each visit

Efficacy results:

Thirty-four percent (210/631) of patients enrolled in the study showed a positive response to the diet followed and required no drug treatment. Thus, these patients were not randomized to any drug treatment.

Demographic and baseline characteristics were similar for both therapeutic groups. Most patients randomized belonged to the category with a lower cardiovascular risk or C (51.71% in the Atorvastatin group and 56.94% in the Rosuvastatin group). The proportions of patients in category B were 27.8% in the Atorvastatin group and 25.36% in the Rosuvastatin group, while the proportions of patients in category A, those with a higher cardiovascular risk, were 20.49% in the Atorvastatin group and 17.7% in the Rosuvastatin group.

After 12 weeks of treatment, the percent change in LDL-C levels from Visit 2 was statistically higher for the Rosuvastatin group (IT LOCF: -42.18 versus -34.86 for the Atorvastatin group, $p<0.0001$; PP: -42.01 versus -35.38 for Atorvastatin). Similarly, the proportion of patients achieving the NCEP ATP III LDL-C goal after 12 weeks of treatment was statistically higher in the Rosuvastatin group both for the ITT population (ITT LOCF: 55.5% in the Rosuvastatin group versus 39.5% in the Atorvastatin group; ITT with actual values: 55.5% Rosuvastatin versus 41.1% Atorvastatin; ITT with values for all visits: 56.2% Rosuvastatin versus 40.6% Atorvastatin) and the PP population (PP with actual values: 56.9% Rosuvastatin versus 40.3% Atorvastatin; PP with values for all visits: 57.9% versus 40.2% Atorvastatin). Statistically significant differences favoring Rosuvastatin were also seen for the proportions of patients who achieved the JTFE-3 LDL-C goal after 12 weeks of treatment (ITT LOCF: 56.5% in the Rosuvastatin group versus 42.0% in the Atorvastatin group; ITT with actual values: 54.5% Rosuvastatin versus 37.4% Atorvastatin; ITT with values for all visits: 55.7% Rosuvastatin versus 36.9% Atorvastatin). By contrast, the proportions of patients achieving the DDC-E LDL-C goal after 12 weeks of treatment (ITT LOCF: 92.3% in the Rosuvastatin group versus 86.8% in the Atorvastatin group; ITT with actual values: 92.0% Rosuvastatin versus 87.9% Atorvastatin; ITT with values for all visits: 92.8% Rosuvastatin versus 88.2% Atorvastatin) or the NCEP ATP III LDL-C goal after 24 weeks of treatment (ITT LOCF: 55.2% in the Rosuvastatin group versus 47.6% in the Atorvastatin group) were similar for both groups.

After 12 weeks of treatment, percent changes in levels of total cholesterol (ITT LOCF: -30.87 for Rosuvastatin versus -25.69 for Atorvastatin), Apo AI (ITT LOCF: 7.66 for Rosuvastatin versus 5.14 for Atorvastatin), and Apo B (ITT LOCF: -32.45 for Rosuvastatin versus -26.83 for Atorvastatin) were significantly higher for the Rosuvastatin group. By contrast, percent changes in levels of triglycerides (ITT LOCF: -16.50 for Rosuvastatin versus -13.01 for Atorvastatin) and HDL-C (ITT LOCF: 4.20 for Rosuvastatin versus 3.52 for Atorvastatin) were similar for both groups.

After 24 weeks of treatment, percent changes in LDL-C, total cholesterol, and Apo B levels remained higher ($p<0.0001$) for Rosuvastatin, but this did not occur for levels of triglycerides ($p=0.977$), HDL-C ($p=0.831$), or Apo AI ($p=0.124$).

No significant changes were seen in levels of inflammation markers (ICAM-1, IL-6, and CRP) or coagulation factors (fibrinogen, PAI-1, and thrombin) during the study in any of the therapeutic groups.

Safety results:

One or more adverse events occurred during the study in 150 patients. Of the 256 adverse events recorded (9 in the non-randomized group, 122 in the Rosuvastatin group, and 125 in the Atorvastatin group), 29 (11.33%) were related to Rosuvastatin (13) or Atorvastatin (16). Adverse events related to treatment administered included: myalgia (1.4% of patients in the Rosuvastatin group and 1.4% in the Atorvastatin group), headache (0.95% in the Rosuvastatin group and 0.48% in the Atorvastatin group), malaise (0.95% in the Atorvastatin group), and paresthesia (0.48% in the Rosuvastatin group and 0.48% in the Atorvastatin group).

There were 10 serious adverse events, 2 in the non-randomized group and 3 and 5 in the Rosuvastatin and Atorvastatin groups respectively. Only two serious adverse events were related to the treatment given: increased SGPT levels related to Rosuvastatin, and increased GPT levels related to Atorvastatin.

Eighteen patients were withdrawn from the study for adverse events. Of these, 8 patients had been randomized to Rosuvastatin, and 8 to Atorvastatin. The remaining 2 patients were withdrawn during the period between Visit 1 and Visit 2, before randomization to a drug treatment. Four of the adverse events causing patient withdrawal were related to Rosuvastatin, and 4 to Atorvastatin.

No significant changes were seen in mean lipid or hematological values or in chemistry values during the study. However, a patient from each therapeutic group showed creatinine levels exceeding by more than 30% the values found at Visit 2. These levels were from 50% to 100% higher than those seen at Visit 2 for both patients. The patient from the Atorvastatin group showed these levels at visit 3, and the patient from the Atorvastatin group at Visit 6.

Moreover, in the Rosuvastatin group, a patient showed ALAT values 3 times the ULN at Visit 4, and another patient at Visit 6. In the Atorvastatin group, one of the patients also had ALAT values 3 times the ULN. While no patient in the Rosuvastatin group had CPK levels 10 times the ULN during the study, such levels were found in 5 patients from the Atorvastatin group (3 patients at Visit 5, and 2 at Visit 6).

Both drugs were generally well tolerated, with a similar safety and tolerability profile.