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Report with Randomized Treatment and Extension Phase Data

A 12-Week, Randomized, Open-label, 3-Arm Parallel-group, Multicenter, Phase IIIb Study Comparing the Efficacy and Safety of Rosuvastatin with Atorvastatin and Simvastatin Achieving NCEP ATP III LDL-C Goals in High-risk Subjects with Hypercholesterolemia in the Managed Care Setting (SOLAR Study)

Coordinating investigator

None

Study centers

The randomized period of this study was conducted at 145 centers in the United States of America (USA); patients from 140 of these centers entered the open-label extension (OLE) period.

Publications

None at issue

Study dates		**Phase of development**
First patient enrolled	05 June 2002	Therapeutic confirmatory (IIIb)
Last patient completed randomized treatment phase	12 July 2004	
Last patient completed extension phase	06 October 2004	

Objectives

The primary objective of the study was to compare the efficacy of rosuvastatin 10 mg with atorvastatin 10 mg and simvastatin 20 mg prescribed in the managed care setting in high-risk patients (as defined by National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III]) by measuring the percentage of patients who achieved NCEP ATP III low-density lipoprotein cholesterol (LDL-C) goal (<100 mg/dL) after 6 weeks of treatment.

Secondary objectives of the randomized treatment phase of the study were to evaluate the efficacy and safety of treatment with rosuvastatin 10 mg compared with atorvastatin 10 mg and simvastatin 20 mg in high-risk patients who were given a fixed starting dose for 6 weeks. If goal was attained at 6 weeks, patients were to maintain their original dose through Week 12. If goal was not achieved by Week 6, patients were to receive 1 dose titration (ie, dose-doubling) at Week 6. Efficacy and safety were assessed by evaluating:

- Percentage change from baseline in LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), nonHDL-C, and nonHDL-C/HDL-C after 6 and 12 weeks of treatment
- Percentage of patients who achieve NCEP ATP III LDL-C goal (<100 mg/dL) after 12 weeks of treatment
- Percentage of patients with TG >200 mg/dL at baseline who achieve both NCEP ATP III LDL-C (<100 mg/dL) and nonHDL-C goals (<130 mg/dL) after 6 and 12 weeks of treatment
- The incidence and severity of adverse events (AEs), physical examination, and abnormal laboratory values through 12 weeks of treatment

The secondary safety objective of the OLE phase of the study was to assess safety by evaluating the incidence and severity of AEs, physical examination, and abnormal laboratory values from Week 12 through the duration of the OLE phase.

Efficacy data continued to be collected during the OLE phase, but there were no efficacy objectives.

Study design

This was a 12 week, randomized, open-label, 3-arm parallel-group, multicenter, Phase IIIb study comparing the efficacy and safety of rosuvastatin to atorvastatin and simvastatin prescribed in the managed care setting in achieving NCEP ATP III target LDL-C goal in high-risk patients with hypercholesterolemia. Patients who completed the randomized treatment phase of the study could then elect to participate in the rosuvastatin OLE phase.

Target patient population and sample size

This study recruited men and non-pregnant women (ages ≥18 years) with primary hypercholesterolemia who were at high risk for coronary heart disease (CHD) events (CHD or

CHD risk equivalent) according to NCEP ATP III guidelines, who had fasting LDL-C ≥130 mg/dL and <250 mg/dL. All patients had fasting TG concentrations <400 mg/dL.

The size of the study population was calculated to detect a difference of 10% in the proportion of patients reaching NCEP ATP III LDL-C goal at Week 6 (as when one treatment brings 45% of patients to goal, and the other brings 55% to goal) with a power of 80%. Based on these assumptions, 494 evaluable patients were required in each treatment group. To allow for a dropout rate of approximately 10% during treatment (withdrawal rate was to be approximately 63% during the dietary lead-in period), it was planned to randomize 548 patients to each treatment group. Therefore, a total of 1644 patients were to be randomized into the study.

Investigational product and comparators: dosage, mode of administration and batch numbers

For the randomized phase: rosuvastatin calcium 10 mg, atorvastatin 10 mg, and simvastatin 20 mg as start dose titrated at Week 6, as needed, to rosuvastatin 20 mg, atorvastatin 20 mg, and simvastatin 40 mg, respectively. For the OLE phase: rosuvastatin 10 mg, 20 mg, and 40 mg. Doses of all study drugs were to be taken orally, once daily, as a single tablet. (Atorvastatin and simvastatin were supplied as commercially available tablets through the local retail pharmacy). Batch numbers for rosuvastatin 10 mg (formulation 12672) were 2000027483, 2000029413, 2000047329, 2000053019, for rosuvastatin 20 mg (formulation 12673) were 2000027496, 2000031849, 2000047327, and for rosuvastatin 40 mg (formulation 12821) were 2000027508, 2000033813, 2000034639, 2000036167.

Duration of treatment

After a 6-week dietary lead-in period, eligible patients were randomized to 12 weeks of treatment with an option of entering an OLE phase to receive rosuvastatin for at least 12 weeks.

Criteria for evaluation (main variables)

Efficacy

The primary study variable was the percentage of high-risk patients who achieve NCEP ATP III LDL-C goal (<100 mg/dL) at Week 6 with rosuvastatin 10 mg compared with atorvastatin 10 mg and simvastatin 20 mg

Secondary study variables in the randomized phase were:

- Percent change from baseline in LDL-C, TC, HDL-C, TG, nonHDL-C, and nonHDL-C/HDL-C levels in high-risk patients with hypercholesterolemia after 6 and 12 weeks of treatment
- Percentage of patients who achieve NCEP ATP III target LDL-C levels after 12 weeks of treatment

- Percentage of patients with TG levels above 200 mg/dL at baseline who achieve both NCEP ATP III target LDL-C (<100 mg/dL) and nonHDL-C levels (<130 mg/dL) after 6 and 12 weeks of treatment

Secondary study variables in the OLE phase were:

- Percentage of patients that achieve their established NCEP ATP III LDL-C goal (<100 mg/dL) at each visit
- Percentage change from baseline in LDL-C, TC, TG, HDL-C, nonHDL-C, and nonHDL-C/HDL-C at each visit
- Percentage of patients with TG levels above 200 mg/dL at baseline who achieve both NCEP ATP III target LDL-C (<100 mg/dL) and nonHDL-C levels (<130 mg/dL) at each visit

Safety

Secondary variables in the randomized phase were safety and tolerability evaluations, as determined by adverse events, physical examination findings, and laboratory data. Secondary study variables in the OLE phase were safety and tolerability evaluations, as determined by adverse events, physical examination findings, and laboratory data from Week 12 through the duration of the OLE phase (physical examinations were performed at the final visit only).

Statistical methods

(a) Analysis of efficacy

The comparison of the proportion of patients in the randomized phase who met and who did not meet NCEP ATP III LCL-C target goal was between the rosuvastatin group and each of the atorvastatin and simvastatin groups at Weeks 6 and 12 as analyzed by logistic regression. Values of secondary lipid variables in the randomized phase were analyzed using an analysis of covariance (ANCOVA) models with factors fitted for treatment (ie, rosuvastatin, atorvastatin, and simvastatin), center, and the baseline lipid parameter value as a covariate. Values of secondary lipid variables in the OLE phase were analyzed descriptively.

(b) Analysis of safety

All AEs, AEs leading to death, serious adverse events (SAEs), treatment-related AEs, and AEs leading to discontinuation (DAEs) were summarized by treatment received according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. Summaries of all adverse events, adverse events leading to death, serious adverse events, drug related adverse events, and adverse events leading to withdrawal were presented for all patients on rosuvastatin during the randomized and OLE phases.

Hematology and clinical chemistry values were summarized descriptively using means, medians, standard deviations (SDs), minima, maxima, and number of patients at each visit.

Hepatic biochemistry and creatine kinase (CK) values, as well as their changes from baseline, were summarized by descriptive statistics at each visit. Elevations of ALT (>3 times upper limit of normal [ULN]), CK (>5 x ULN, >10 x ULN) and percentage increases in serum creatinine above 30% for rosuvastatin patients at any time point were highlighted and summarized by current dose. Elevations of ALT values above 3 x ULN on 2 consecutive visits, CK values above 10 x ULN, and increases from baseline serum creatinine values exceeding 100% were considered clinically important and were to be summarized by treatment group.

Urinalysis results for continuous variables were summarized by means, SDs, minima, maxima, and numbers of patients at each visit. Qualitative urinalysis results were summarized in shift tables. Additional categorical urinalysis results in patients with an increase in urine protein to ++ or greater, including quantitative urine protein and quantitative urine protein/creatinine ratio were to be summarized for current-dose group. Vital signs and weight were summarized with descriptive statistics. Abnormal physical examination findings at baseline and new or aggravated abnormalities at Week 12 and the final visit were listed.

Patient population

The first patient was enrolled in the study on 05 March 2002 and the last patient completed the study on 06 October 2004. In total, 4161 patients entered the dietary lead-in period, 1632 patients were randomized to study treatment, and 1364 patients entered the OLE phase. Patients had generally comparable demographic and baseline characteristics among treatment groups and the patient population enrolled in this study was representative of the target population (ie, high-risk patients with hypercholesterolemia in the managed care setting). The mean and median age were approximately 62 years in each treatment group in the randomized phase, ranging from 22 to 91 years; approximately 42% of patients in each treatment group were at least 65 years. The majority of patients in the randomized phase were Caucasian (approximately 82% in each treatment group) and there were more men than women enrolled in each treatment group, approximately 58% men and 42% women. Approximately 47% of patients were obese (BMI >30), from 41.9% to 51.1% in each treatment group. Most (53.6%) patients in the randomized phase had documented CHD, 1482 (90.8%) patients had either CHD or at least 1 CHD risk equivalent. The most common CHD risk equivalent was diabetes mellitus (41.3%). Baseline CHD/CHD risk equivalents were comparable among treatment groups. Sixty-six (4.0%) randomized patients were assessed not to be at high risk by the NCEP ATP III criteria: 18 (3.3%) patients randomized to rosuvastatin, 23 (4.2%) randomized to atorvastatin, and 25 (4.6%) randomized to simvastatin; these patients were excluded from the per-protocol population.

The mean age of patients in the cumulative safety population at Week 0 was 62.6, ranging from 22 to 91 years (median age 62.5 years). The majority of patients (approximately 57%) were between 18 and 64 years of age. There were more men than women in the cumulative safety population, approximately 58% men versus approximately 42% women. The majority of patients were Caucasian (approximately 83%). The demographics of patients in the cumulative safety population, CHD and CHD risk equivalents, major CHD risk factors, and

Framingham 10-year risk percentages were generally similar to those patients in the randomized phase.

Efficacy results

A greater proportion of patients with hypercholesterolemia at high risk for CHD events in the managed care setting achieved NCEP ATP III LDL-C goal (<100 mg/dL) after 6 weeks of treatment with the recommended starting dose of rosuvastatin 10 mg than with recommended starting doses of atorvastatin 10 mg or simvastatin 20 mg: 65.2% of patients in the rosuvastatin treatment group versus 41.3% and 39.0% of patients in the atorvastatin and simvastatin treatment groups, respectively, achieved goal ($p<0.0001$). Within the same period, significantly greater reductions in LDL-C, TC, nonHDL-C, and nonHDL-C/HDL-C were achieved in patients randomized to rosuvastatin relative to the comparator statins ($p\leq0.0001$); reductions in TG were achieved in patients randomized to rosuvastatin relative to simvastatin ($p<0.0001$).

Patients who took rosuvastatin in the randomized phase experienced reductions from baseline in LDL-C, TC, TG, nonHDL-C, and nonHDL-C/HDL-C at the Week 6 visit of –45.4%, –32.4%, –20.3%, –41.2%, and –44.3%, respectively, and increases from baseline in HDL-C of 6.7%. Patients who took rosuvastatin in the randomized phase experienced reductions from baseline in LDL-C, TC, TG, nonHDL-C, and nonHDL-C/HDL-C at the Week 12 visit of –48.1%, –33.9%, –21.9%, –43.8%, and –48.2%, respectively, and increases from baseline in HDL-C of 9.4%. Patients who took rosuvastatin in the OLE phase experienced reductions from baseline in LDL-C, TC, TG, nonHDL-C, and nonHDL-C/HDL-C at the final visit of –48.4%, –33.9%, –18.7%, –43.4%, and –47.2%, respectively, and increases from baseline in HDL-C of 8.8%. Changes of this magnitude are consistent with lipid levels generally thought to be of significant clinical applicability.

A greater proportion of patients with hypercholesterolemia at high risk for CHD events in the managed care setting achieved NCEP ATP III LDL-C goal (<100 mg/dL) after 12 weeks of treatment with rosuvastatin than with atorvastatin or simvastatin: 75.6% of patients in the rosuvastatin treatment group versus 58.1% and 52.9% of patients in the atorvastatin and simvastatin treatment groups, respectively, achieved goal ($p<0.0001$). The percentage of ITT patients taking rosuvastatin in the OLE who met the NCEP ATP III LCL-C goal increased from 61.7% at the last visit of the randomized phase to 79.6% at the final visit. A greater proportion of high-risk patients with hypercholesterolemia in the managed care setting, who also had TG levels exceeding 200 mg/dL at the baseline visit, achieved NCEP ATP III goals for both LDL-C and nonHDL-C after 6 weeks of treatment with rosuvastatin than with simvastatin: 43.9% of patients in the rosuvastatin treatment group versus 19.4% of patients in the simvastatin treatment group achieved goal ($p<0.0001$). Patients who had TG levels exceeding 200 mg/dL at the baseline visit achieving NCEP ATP III goals for both LDL-C and nonHDL-C after 6 weeks of treatment were numerically higher in the rosuvastatin treatment group than in the atorvastatin treatment group, 43.9% versus 22.4%, respectively, but this difference was not statistically significant. A greater proportion of high-risk patients with hypercholesterolemia in the managed care setting, who also had TG levels exceeding 200 mg/dL at the baseline visit, achieved NCEP ATP III goals for both LDL-C and

nonHDL-C after 12 weeks of treatment with rosuvastatin than with simvastatin: 56.5% of patients in the rosuvastatin treatment group versus 30.9% of patients in the simvastatin treatment group achieved goal (p=0.0002). Patients who had TG levels exceeding 200 mg/dL at the baseline visit achieving NCEP ATP III goals for both LDL-C and nonHDL-C after 12 weeks of treatment were numerically higher in the rosuvastatin treatment group than in the atorvastatin treatment group, 56.5% versus 35.9%, respectively, but this difference was not statistically significant. Overall, 65.8% of patients with TG levels exceeding 200 mg/dL at baseline who took rosuvastatin in the OLE phase achieved both NCEP ATP III LDL-C and nonHDL-C goals at the final visit.

Safety results

The median duration of exposure to study drug was 84 days (12 weeks) for patients in the randomized phase, and 170 days (24 weeks) for patients taking rosuvastatin in the randomized or OLE phases. The frequency of treatment-emergent AEs associated with each treatment group in the randomized phase was approximately 53%, ranging from 51.9% to 55.1%. Three deaths occurred in the randomized phase (all on atorvastatin); none were attributed to study drug by the investigator. The frequency of treatment-emergent SAEs and treatment-emergent DAEs in the randomized phase was approximately 3% each and similar among treatment groups. The frequency of treatment-related treatment-emergent AEs in the randomized phase was approximately 8% and similar among treatment groups, 10.1% in the cumulative safety population; the frequency of AEs was similar among treatment groups and rosuvastatin doses. Of the 1444 patients in the cumulative safety population, 3 died during the OLE phase (all on rosuvastatin 10 mg). No patient who administered rosuvastatin in this study experienced a treatment-related SAE. The frequency of treatment-emergent DAEs among patients who took rosuvastatin in the randomized or OLE phases was 5.4%; the frequency of treatment-related DAEs was 3.5%.

The majority of patients with treatment-emergent AEs experienced AEs that were mild or moderate in severity, and most patients with treatment-emergent AEs experienced AEs that were considered by the investigator to be unrelated to study treatment. None of the AEs that occurred in either the randomized or OLE treatment phase was unexpected given the underlying medical conditions of the patient population. The overall AE profile associated with each treatment group and across the rosuvastatin dose groups was similar. The most common categories of treatment-emergent AEs reported in at least 15% of patients during the randomized treatment phase were infections and infestations (15.2%) and musculoskeletal and connective tissue disorders (15.0%). The most common treatment-emergent AEs experienced by at least 2% of patients during the randomized treatment phase were upper respiratory tract infections (4.4%), myalgia (3.9%), arthralgia (3.5%), urinary tract infections (2.1%), and back pain, CK elevation, and headache (2.0% each). The most common categories of treatment-emergent AEs reported in more than 20% of patients who received rosuvastatin during the randomized or OLE treatment phases were infections and infestations (28.6%) and musculoskeletal and connective tissue disorders (22.9%). The most common treatment-emergent AEs experienced by at least 5% of patients who received rosuvastatin were upper respiratory tract infections (7.4%), arthralgia (5.5%), and myalgia (5.1%). For any

individual dose group, the maximum frequency of occurrence for any of these AEs was 6.4% (patients in the 40 mg rosuvastatin group experienced upper respiratory tract infections).

Changes in hematology, clinical laboratory, and urine test results were generally small and comparable among treatment groups and rosuvastatin doses. Three patients experienced clinically important elevations in ALT (>3 x ULN on 2 consecutive visits), 1 receiving atorvastatin and 2 receiving rosuvastatin. In the randomized phase, 1 patient experienced an AE of acute renal failure (simvastatin 20 mg) and 2 patients experienced AEs of renal insufficiency (atorvastatin 10 mg and simvastatin 20 mg). One patient experienced hepatitis C while taking rosuvastatin 10 mg during the OLE phase. In the OLE phase, 2 patients experienced renal insufficiency while taking rosuvastatin 10 mg; the investigator did not attribute either event to study drug. One patient who received study drug during the randomized treatment phase (rosuvastatin) and 1 patient who received rosuvastatin during the OLE phase of the study experienced elevations in CK exceeding 10 x ULN; neither of these reported AEs relating to skeletal muscle. No patient who received study drug in the randomized phase and 1 patient who received rosuvastatin in the OLE phase experienced an elevation from baseline serum creatinine exceeding 100%; no AEs related to the renal system were experienced by this patient. Changes in urinalysis findings were infrequent and similar among treatment groups and rosuvastatin doses. At Week 6, 4 patients each taking rosuvastatin and simvastatin, and 5 patients taking atorvastatin experienced shifts in urine blood from none or trace at baseline to ++ or greater; 2 patients taking rosuvastatin experienced comparable shifts in urine protein. At Week 12, 4 patients taking rosuvastatin, 7 patients taking atorvastatin, and 8 patients taking simvastatin experienced shifts in urine blood from none or trace at baseline to ++ or greater; 1 patient taking rosuvastatin experienced a comparable shift in urine protein. During the randomized or OLE phase, 26 patients taking rosuvastatin 10 mg, 6 patients taking rosuvastatin 20 mg, and none taking rosuvastatin 40 mg experienced shifts in urine blood from none or trace at baseline to ++ or greater; 7 patients taking rosuvastatin 10 mg, 5 patients taking rosuvastatin 20 mg, and 1 taking rosuvastatin 40 mg experienced comparable shifts in urine protein. There was no clinically relevant difference among treatment groups or rosuvastatin doses in the proportions of patients with abnormal vital signs measurements or adverse changes from baseline physical examination findings.

Date of the report

21 July 2005