AstraZeneca

Drug product	CRESTOR•	**SYNOPSIS**	
Drug substance	Rosuvastatin (ZD4522)		
Document No.	4522IL/0050		
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Study code	4522IL/0050		
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Principal Investigator

Study center

This study was a single-center study conducted at the Stanford University School of Medicine, Stanford, California.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	22 May 2000	Therapeutic confirmatory (III)
Last patient completed	18 May 2002	

Objectives

The primary objective of the trial was to compare the effect of rosuvastatin (ZD4522) and gemfibrozil on the fasting and postprandial triglyceride (TG) profile following 12 weeks of treatment. The secondary objectives of this trial were to compare the effects of rosuvastatin and gemfibrozil on other lipid and lipoprotein fractions; plasma glucose and insulin concentration, insulin resistance/sensitivity, and free fatty acids (FFA); the concentration of soluble adhesion molecules; and safety and tolerability.

Study design

This was an 18-week, randomized, open-label, parallel-group, single-center trial designed to compare the effects of rosuvastatin (40 mg once daily [qd] and gemfibrozil (600 mg twice daily [bid]) on fasting and postprandial TG profiles in the treatment of patients with combined hyperlipidemia for 12 weeks after a 6-week dietary lead-in period.

Target patient population and sample size

Nondiabetic male and female patients at least 18 years of age with combined hyperlipidemia (fasting total cholesterol [TC] of >200 mg/dL and TG concentrations >200 mg/dL and <600 mg/dL); a body mass index (BMI) <33 kg/m^2; and not taking any medication likely to affect glucose or lipid metabolism were recruited for this study.

Approximately 90 patients were to be entered into the dietary lead-in period. It was calculated that, with a 60% drop-out rate during the screening process, approximately 36 patients would be randomized. A projected on-treatment drop-out rate of 15% yields 15 evaluable patients per treatment group for the 12-week treatment period, which was required to have at least 80% power to detect a difference of 1.5 mmol.h/L between the 2 treatment arms in the area under the concentration (AUC) change from baseline.

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

Rosuvastatin, 40 mg orally with water qd before bedtime (3 hours after the evening meal), or gemfibrozil, 600 mg orally with water bid (30 minutes before the morning and evening meals). Formulation and batch numbers were: rosuvastatin (given as one 40 mg encapsulated tablet) F12566, 2000000666; gemfibrozil (given as one 600 mg tablet) supplied locally.

Duration of treatment

The duration of treatment was 12 weeks, following a 6-week dietary lead-in period to wash out any other lipid-lowering therapy and to stabilize the patient's diet. The dietary lead-in period could be 4 weeks if the patient was not on statin/lipid lowering drugs.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: Percentage change from baseline to Week 12 in the AUC of the postprandial TG levels across the rosuvastatin and gemfibrozil treatment groups.

Secondary variables are as follows:

- Percent change from baseline to Week 12 in AUC for glucose, insulin, FFA, apolipoprotein-B100 (ApoB100), apolipoprotein E (ApoE), apolipoprotein CIII (ApoCIII), remnant lipoproteins, factor XII, and the lipid nuclear magnetic resonance (NMR) profile at Week 12

- Percent change from baseline to Week 12 in AUC for TC, low-density lipoprotein cholesterol (LDL-C), low-density lipoprotein triglyceride (LDL-TG), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, high-density lipoprotein triglyceride (HDL-TG), very-low density lipoprotein cholesterol (VLDL-C), VLDL-TG, apolipoprotein A-I (ApoA-I), and lipoprotein a [Lp(a)]

- Percent change from baseline to Week 12 in LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and ApoB100/ApoA-I

- Percent change from baseline in insulin sensitivity, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, C-reactive protein (CRP), and interleukin-6 (IL-6) at Week 12

- Percentage of patients brought within National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines at Week 12.

In addition, the following variables were added as part of the Statistical Analysis Plan (SAP):

- Absolute change from baseline to Week 12 in AUC of TG, TC, HDL-C, and LDL-C in the intention-to-treat (ITT) and per-protocol (PP) populations.

- Absolute change from baseline to Weeks 2, 6, 10, and 12 in the fasting levels of TG, TC, HDL-C, and LDL-C in the ITT and PP populations.

- Percent change from baseline to Weeks 2, 6, 10, and 12 in the fasting levels of TG, TC, HDL-C, and LDL-C in the ITT and PP populations.

- Percentage of patients brought within European Atherosclerosis Society (EAS) target LDL-C levels at Week 12 in the ITT population.

Safety

Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, creatine kinase [CK], renal biochemistry, hematology, urinalysis), vital signs, electrocardiograms (ECGs), physical examination, and chest x-ray.

Statistical methods

The efficacy data were analyzed based on ITT and PP populations. The ITT population consisted of all randomized patients who received study therapy and had a baseline reading and at least one post baseline reading for one or more lipid variables. The PP population included patients who were not major protocol violators or deviators.

The assumptions of normality and homogeneity of variance were explored using probability and residual plots. If any of the assumptions were found to be violated, an appropriate transformation of the data or nonparametric test was to be performed. The Kruskal-Wallis nonparametric test was used for the primary endpoint variable.

For nonpostprandial evaluations, the Friedewald Equation provided the measure of LDL-C concentration, except when TG exceeded 400 mg/dL the •-quantification method was used. For postprandial evaluations, the •-quantification method was used for all lipid and lipoprotein measurements. Analysis of the primary endpoint was performed using analysis of variance (ANOVA) with treatment as the factor. P-values and associated 95% confidence intervals of the difference of treatment least square means (LS means) were reported.

All secondary endpoints and additional variables involving percent or absolute change from baseline in the AUC at Week 12 used the same analysis approach used for the primary endpoint. However, main-effect covariates determined to be significant in the exploratory analysis of the primary endpoint were included here as covariates along with the treatment factor in the analysis of covariance (ANCOVA) or ANOVA (if no covariates were significant) model. For the ANCOVA model, main-effect covariates along with their interaction terms were not found to be significant (Table T10.1.2), and were dropped from the analyses performed on the secondary variables. Because the covariate terms were not significant, the originally planned ANCOVA analyses are thus referred to as ANOVA analyses. For all secondary endpoints and additional variables added to the SAP involving percent and absolute change from baseline at Weeks 2, 6, 10, and 12, main effect covariates were handled as previously described. Results were presented as F-test statistics and least square means. P-values and associated 95% confidence intervals (CIs) of the difference of treatment least square means were reported at Week 12 only.

In the ITT population, descriptive statistics were used to summarize the percentage of patients reaching NCEP ATP III target LDL-C levels at Weeks 2, 6, and 12 by treatment and for the overall percentage of patients within each NCEP ATP III risk category reaching NCEP targets.

Data from all patients who received at least 1 dose of randomized trial therapy were included in the evaluation of safety. All adverse events (AEs), adverse events resulting in death, serious adverse events (SAEs), drug-related adverse events, and adverse events leading to withdrawal were summarized. Hematology, clinical chemistry, urine pH, and specific gravity were summarized using descriptive statistics. The remaining urinalysis assessments (glucose, blood, ketones, protein, and bilirubin) were summarized according to the numbers of patients with results of none, trace, +, ++, +++, or ++++. Vital signs, weight, and ECG data were also summarized. Descriptive statistics were used to summarize the Eating Pattern Assessment Tool (EPAT) score for each treatment.

Patient population

All 40 patients screened at 1 study center were eligible for randomization following the dietary lead-in period. Half (20) of the patients were given rosuvastatin 40 mg qd and 20 were given gemfibrozil 600 mg bid. During randomized treatment, 1 patient in the rosuvastatin treatment group was lost to follow-up and 1 patient in the gemfibrozil group was discontinued because of adverse events. There were 40 patients in the safety population and 39 in the ITT and PP population for the primary endpoint.

Demographic characteristics were generally balanced between the treatment groups. The majority of the patients were Caucasians between 18 and 64 years of age, with a mean BMI of 28.67 kg/m². The treatment groups were comparable with respect to coronary heart disease risk factors, history of atherosclerosis, and total triglyceride and cholesterol concentrations.

Efficacy and pharmacokinetic results

Pharmacokinetic parameters of rosuvastatin and gemfibrozil were not assessed during this study. Rosuvastatin was not significantly more effective than gemfibrozil in reducing the AUC of postprandial TG levels (the primary variable of the study) over 12 weeks of treatment in patients with combined hyperlipidemia. Results of the primary endpoint are presented in the following table.

Table S1 Triglyceride profile: Analysis of percentage change from baseline AUC at Week 12 in postprandial TG levels

Statistic	Rosuvastatin 40 mg (N=20)	Gemfibrozil 1200 mg (N=19)
Postprandial TG levels		
n	20	19
Baseline (mean [mg/dL.H], SD)	3246.7 (931.0)	2941.1 (742.9)
Baseline median (mg/dL.H)	3442.0	2788.5
n	19	19
Final (mean [mg/dL.H], SD)	2167.7 (655.3)	1757.1 (656.1)
Final median (mg/dL.H)	2163.0	1615.0
Analysis:		
n	19	19
lsmean of % change (SE)	-28.92 (5.57)	-38.20 (5.57)
LCL, UCL	-40.21, -17.63	-49.49, -26.92
p-value of difference	NA	0.246[a], 0.274[b]

Data derived from Table T10.1.1.
[a] Main ANOVA of observed data from the ITT population.
[b] Kruskal-Wallis test of observed data from the ITT population.
UCL Upper 95% confidence interval limit; LCL Lower 95% confidence interval limit; lsmean Least squares mean; SD Standard deviation; SE Standard error; NA Not Applicable.

Results of the secondary endpoints are summarized as follows:

Treatment with rosuvastatin produced improvements in the atherogenic profile for several lipid and lipoprotein fractions that were significantly better than those produced by treatment with gemfibrozil.

Both rosuvastatin and gemfibrozil increased the AUC values for HDL-C, ApoA-I, and Lp(a) after 12 weeks, and these increases were not significantly different between the treatments. Both rosuvastatin and gemfibrozil lowered the AUC values for LDL-TG, TC, ApoB100, ApoE, non-HDL-C, and RLP-C after 12 weeks, but significantly greater decreases ($p<0.05$) were produced by rosuvastatin. Rosuvastatin lowered the AUC for LDL-C, whereas gemfibrozil increased it; these changes were significantly different ($p<0.001$).

Both rosuvastatin and gemfibrozil also lowered the AUC values for HDL-TG, VLDL-TG, VLDL-C, ApoCIII, ApoCIII:B, and ApoCIII:non-B after 12 weeks, but these decreases were not significantly different between the treatments. Rosuvastatin produced a significantly greater reduction ($p<0.05$) in AUC values for L2 and LDL particle concentration, and significantly greater increases ($p<0.05$) in AUC values for H4 and HDL size than gemfibrozil.

Gemfibrozil produced a significantly greater increase ($p<0.05$) in AUC values for LDL size than observed for rosuvastatin, although both treatments increased the AUC value for LDL size over the 12 weeks of treatment. Significant differences in AUC values ($p<0.05$) were observed for V2, L3, and H1 by using the Kruskal-Wallis test, but not for the ANOVA analyses, indicating that these data were highly skewed.

Both rosuvastatin and gemfibrozil had similar effects on AUC values for postprandial glucose, insulin, free fatty acids, and activated factor XII from baseline to Week 12. Both rosuvastatin and gemfibrozil slightly increased the mean values for steady-state plasma glucose concentration (SSPG) and steady-state plasma insulin concentration (SSPI) from baseline to Week 12; these changes were not significantly different between treatments.

Rosuvastatin and gemfibrozil had only minor effects on the mean concentrations of the soluble adhesion molecules (ICAM-1, VCAM-1, E-selectin, CRP, and IL-6); the changes produced were not significantly different between the treatments. Rosuvastatin had a significantly greater effect on lowering the AUC for both TC and LDL-C (both $p<0.001$) than gemfibrozil. Both treatments also reduced the AUC for TG and increased the AUC values for HDL-C, but these changes were not significantly different from one another.

Treatment with rosuvastatin resulted in greater percent reductions in the LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C ratios at Weeks 2, 6, and 10, in addition to Week 12, which was significantly greater ($p<0.001$), indicating an improvement in the atherogenic profile was observed at all timepoints for rosuvastatin. Treatment with rosuvastatin also had a significantly greater clinical effect at Week 12 ($p<0.001$) on the ApoB100/ApoA-I ratio.

Both treatments reduced absolute TG and TC levels during the study. Although the reductions in TG were not significantly different at Week 12, rosuvastatin had a significantly ($p<0.001$) greater effect in reducing TC levels at Week 12. Both treatments increased HDL-C levels during the study, and these increases were not significantly different from one another at

Week 12. Rosuvastatin produced decreases in LDL-C levels during the study, whereas treatment with gemfibrozil produced increases in LDL-C; these changes were significantly different ($p<0.001$) at Week 12. Overall results for the percent change from baseline to Weeks 2, 6, 10, and 12 in the fasting levels of TG, TC, HDL-C, and LDL-C were the same observed for the absolute changes from baseline.

A higher percentage of patients achieved NCEP ATP III guideline targets for LDL-C levels with rosuvastatin (100%, all risk levels) than with gemfibrozil (78.9%) at Week 12, which was also evident at Weeks 2 and 6. Also, a higher percentage of patients reached the LDL-C and non-HDL-C target levels with rosuvastatin than with gemfibrozil regardless of week or NCEP ATP III risk category. Overall, based on last observation carried forward (LOCF) data for all risk categories at Week 12, a higher percentage of patients in the rosuvastatin group (94.4%) than in the gemfibrozil group (70.6%) reached the NCEP ATP III targets for LDL-C and non-HDL-C levels.

A higher proportion of patients achieved EAS treatment guideline targets for LDL-C with rosuvastatin than with gemfibrozil, regardless of risk category. Overall, based on LOCF data for both risk categories at Week 12, a higher percentage of patients in the rosuvastatin group (100%) than in the gemfibrozil group (31.6%) reached the EAS target for LDL-C levels.

Safety results

Overall, rosuvastatin was well tolerated. There were no unexpected findings when reviewing the overall adverse events for the 2 treatment groups. The type, incidence, and non-serious nature of the events were similar. Adverse events were reported by similar proportions of patients who took rosuvastatin (80%) or gemfibrozil (85%). The most common AEs (reported by 4 or more patients in either group) were known effects of this class of compounds and included headache, diarrhea, pharyngitis, nausea, and myalgia. There were no deaths, no SAEs, and no other significant adverse events. Only 1 patient, in the gemfibrozil group, discontinued study treatment due to adverse events (abdominal bloating and stomach cramping), which were reported by the investigator as treatment-related.

There were also no unexpected findings resulting from analyses of hematology, hepatic biochemistry, or clinical biochemistry, with laboratory results that supported a safety profile for rosuvastatin comparable to that of gemfibrozil. The safety profile observed during this study is as expected for statins, with little cause for concern when considering hepatic toxicity (ie, increases in alanine aminotransferase [ALT] levels were not clinically meaningful).

Date of the report

10 April 2003