AstraZeneca

Drug product:	CRESTOR™	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium		
Document No.:			
Edition No.:			
Study code:	D3560C00034/4522IL0034		
Date:	06 December 2005		

An Open-label, Multinational, Multicenter Extension Trial to Assess the Long-term Safety and Efficacy of ZD4522 in Subjects in the ZD4522 Clinical Trial Program

International coordinating investigator

Study center(s)

This global study was conducted at 311 centers in the United States of America (USA) and Australia, Canada, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Poland, Scotland, South Africa, Spain, Sweden, and the United Kingdom.

Publications

Ose L, Tonstad S, Harris S, Marotti M. Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: Effects on lipid measures and C-reactive protein. Atheroscler Suppl 2005; 6(1):117 (Abstract W16-P-064).

Stein EA, Harris S, Schleman M, Sager PT. Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: Effects on low-density lipoprotein cholesterol and C-reactive protein. J Am Coll Cardiol 2005;45(Suppl 1):392A (Abstract 1070-129).

Study dates		**Phase of development**
First patient enrolled	25 August 1999	Therapeutic confirmatory (III)
Last patient completed	10 January 2005	

Objectives

The primary objective of this trial was to assess the long-term safety of ZD4522 (rosuvastatin).

The secondary objective of this trial was to assess the long-term efficacy of ZD4522 (rosuvastatin) through the evaluation of patients achieving National Cholesterol Education

Program (NCEP) Adult Treatment Panel III (ATP III) and triglyceride (TG) goals and by measuring the percentage change from baseline in lipid and lipoprotein fractions.

Study design

This was an open-label, multinational, multicenter safety and efficacy extension clinical study.

Target patient population and sample size

Patients who successfully completed a study of origin (Phase II or III study in the rosuvastatin clinical study program used for baseline data in this extension study) were eligible to participate. Entry criteria were dependent upon which study the patient had completed. In addition, Safety Study Eligible (SSE) patients, those in the dietary lead-in phase of any of these studies when randomization to the study closed, were eligible if they met the criteria and completed all assessments at the randomization visit of the study of origin.

Patients were divided into 3 groups depending upon which study they originated from: Group 1 consisted of patients with Fredrickson Type IIa/IIb (isolated hypercholesterolemia/ mixed dyslipidemia) from Studies 23 to 28 and 30 to 33; Group 2 consisted of patients with Fredrickson Type IV (isolated hypertriglyceridemia) from Studies 29, 35, and 36; and, Group 3 had patients with homozygous familial hypercholesterolemia from Study 54. (Although patients from Study 44 were eligible to enter this study, no patients from Study 44 enrolled in Study 34, and thus were not included in any Group 1 analysis).

No sample size estimation was carried out since the primary objective of the study was non-comparative and sample size was limited to the available patients from Phase II and III studies. A minimum of 3500 patients had the potential to enter into this extension study.

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

The investigational product was rosuvastatin calcium (CRESTOR™) 5, 10, 20, 40, and 80 mg. Rosuvastatin was supplied by AstraZeneca; doses were to be taken orally, once daily, as a single tablet. The following rosuvastatin batches were used: 5 mg: 2000000727, 2000001876, 2000001877, 2000008672, 2000013718, 2000030291, 2000061389, 993033A, 993034A, 993085A, 993095A; 10 mg: 2000002090, 2000002702, 2000008252, 2000008293, 2000009588, 2000013183, 2000013779, 2000013793, 2000015589, 2000016325, 2000019795, 2000021506, 2000023980, 2000030317, 2000032458, 2000033995, 2000034438, 2000053807, 993046A, 993047A, 993088A, 993096A, 993104A, 993145B; 20 mg: 2000002948, 2000007481, 2000013832, 2000027365, 2000028497, 2000030816, 2000033038, 2000036071, 993086A, 993108A, 993146B; 40 mg: 2000001059, 2000003533, 2000006825, 2000009534, 2000014308, 2000018684, 2000030899, 2000033203, 2000033991, 2000034122, 2000034548, 2000034555, 993087A, 993109A, 993110A; and 80 mg: 2000000805, 2000003241, 2000006125, 2000007097, 2000008001, 2000010220, 2000011035, 2000011995, 2000014428, 2000017415, 2000018194, 2000018615, 2000020806, 993151B. For patients in Group 2, combination therapy may also have been supplied by AstraZeneca. For some of these patients, Fenofibrate 67 mg (batch number 016),

Niaspan (batch number 100002A), or Questran light (batch number GO9975A) may have been administered concomitantly with rosuvastatin treatment.

Duration of treatment

Visit 1 of this study normally corresponded to the last visit of the study of origin (feeder trial). In the event study entry was delayed, or for SSE patients having >2 weeks between the last visit of the study of origin and Day 1 of this study, specific assessments from the last visit of the study of origin were repeated within 2 weeks prior to their scheduled Study 34 Visit 1. The next scheduled visit was planned at 2 weeks for measuring liver function tests (LFTs) and low-density lipoprotein cholesterol (LDL-C) levels. All patients returned after a further 4 weeks (Visit 2.1). Patients who had not yet achieved NCEP ATP III guidelines had their doses titrated up at 6-week intervals until these goals were achieved (Group 2: TG was <200 mg/dL [<2.26 mmol/L]) or titration reached maximum dose. Thereafter, patients returned at 12-week intervals. If patients' LDL-C levels decreased to <50 mg/dL (1.29 mmol/L), they may have been down-titrated.

Criteria for evaluation (main variables)

The primary variable of the study was safety, as determined by adverse events (AEs), laboratory data, physical examination (vital signs and weight), and electrocardiogram (ECG).

The secondary variables of the study were:

- Percent change from baseline in LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TG, non-high-density lipoprotein cholesterol (non-HDL-C), LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C at 12 months and at each scheduled timepoint (Groups 1, 2, and 3)

- Success or failure in achieving NCEP ATP III LDL-C goal at 12 months and at each scheduled timepoint (Groups 1 and 3)

- Success or failure in achieving NCEP ATP III LDL-C/TG combined goal at 12 months and at each scheduled timepoint (Group 2)

Patients from Studies 24 and 27, and from Studies 26 and 28, were combined, and the number and percentage of patients reaching NCEP ATP III LDL-C targets were presented for each visit by treatment and dose received in the study of origin.

Statistical methods

The Eating Pattern Assessment Tool (EPAT) Section 1 scores were summarized using descriptive statistics. All dietary data were reviewed and analyzed by Radiant Research and the results were reported separately.

All efficacy measures were summarized using descriptive statistics or frequency distributions for the raw data; no formal statistical analyses were conducted. The Friedewald value was the

primary efficacy measure for LDL-C, except at those visits where TG was ≥400 mg/dL (4.52 mmol/L), when the β-quantification measurement was used.

The baseline values for LDL-C, TC, HDL-C, TG, non-HDL-C, and all related ratios were those determined from the study of origin carried over to this extension study. These values were calculated by averaging the available readings obtained at the last 3 consecutive visits during the dietary lead-in phase of the study of origin. In the event that lipid measurements were repeated at an extension study visit, the scheduled value (ie, first value) was used in the analysis of observed data. Descriptive statistics on the percentage change from baseline in lipid variables were performed at all scheduled timepoints in the Intent-to-Treat (ITT) population for Groups 1, 2, and 3.

Descriptive statistics on the percentage of patients reaching target NCEP ATP III goals were presented, overall and by risk category, for the percent of patients reaching target NCEP ATP III LDL-C goals (Group 1 and 3) and the percent of patients reaching combined target NCEP ATP III LDL-C/TG goals (Group 2). Patients from Studies 24 and 27, and from Studies 26 and 28, were also combined, and the number and percentage of patients reaching NCEP ATP III LDL-C targets were presented for each visit by treatment and dose received in the study of origin.

Data from all patients in the database who received study drug were included in the evaluation of safety. Adverse events were classified as treatment-emergent and observed. The incidence of treatment-emergent AEs was tabulated according to the Medical Dictionary for Regulatory Activities, System Organ Class and preferred term, with summaries for all AEs, deaths, serious AEs (SAEs), treatment-related AEs, and AEs leading to study discontinuation (DAEs).

Hematology, hepatic biochemistry, creatine kinase (CK), and serum creatinine values, as well as their changes from both baseline and Week 0 of the titration phase were summarized using descriptive statistics at each visit. Laboratory values outside the reference ranges were highlighted and clinically significant elevations in alanine aminotransferase (ALT), CK, and serum creatinine were summarized. Urinalysis results were summarized using descriptive statistics; qualitative urinalysis results summarized the shift from qualitative category at baseline to qualitative category at a particular visit.

Vital signs and weight were summarized with descriptive statistics. ECG data were summarized according to the number of patients with or without clinically significant changes from screening in the study of origin to Week 0 of the titration phase (Visit 1) and to the final study visit.

Patient population

The first patient was enrolled in the study on 25 August 1999 and the last patient completed the study on 10 January 2005. In total, 3015 patients entered this study; 956 patients (31.7%) discontinued the study, which appears in line with the extended study duration. The most common reasons for study discontinuation were informed consent withdrawn (10.3%) and adverse events (10.1%).

The overall age range of patients in the study was 9 to 86 years; the overall median age was 57 years. The age range of patients in Group 3 was 9 to 64 years; the median age was 30 years and 5 patients were less than 18 years of age. The majority of patients were Caucasian (93.3%); 52.8% of the study population was male and 47.2% was female overall. Group 1 had a nearly equal proportion of males and females; in Groups 2 and 3, the majority of the study population was male. The patient population enrolled in this study was representative of the target population for rosuvastatin (ie, had baseline lipid and lipoprotein levels consistent with hypercholesterolemia). Coronary heart disease (CHD) risk factors, high CHD risk factors, and major CHD risk factors were also representative of the target population for their respective study groups. Dietary data, as evaluated by mean EPAT scores, were similar across the dose groups from Week 0 to the final dose of the final study visit.

Of the 3015 patients entering this extension study, 2990 patients were included in the ITT population and 3009 patients were included in the safety population. Patients received an average of 1306.7 treatment days on rosuvastatin. The majority of patients had durations of rosuvastatin exposure between 216 and 251 weeks.

Efficacy and pharmacokinetic results

The efficacy results of this extension study are based on the laboratory values of 2990 patients treated with rosuvastatin 5 to 80 mg (40 mg maximum post Amendment 11) who were in the ITT population. Patients were divided into 3 groups depending upon which study they originated from: Group 1 (Studies 23 to 28 and 30 to 33); Group 2 (Studies 29, 35, and 36); and, Group 3 (Study 54). Patients from Studies 24 and 27, and from Studies 26 and 28, were also combined for additional NCEP ATP III analyses.

Results for Group 1 (n=2506)

Rosuvastatin treatment resulted in mean reductions from baseline to the final study visit in LDL-C (45.83%), TC (33.60%), TG (15.70%), non-HDL-C (42.00%), LDL-C/HDL-C (48.51%), TC/HDL-C (37.26%), and non-HDL-C/HDL-C (44.75%). HDL-C increased by 8.49%. Overall, on the basis of descriptive statistics, the majority of patients (72.1%) numerically reached their target NCEP ATP III LDL-C goals at the final visit. For all doses, 82.3% of low risk, 74.9% of medium risk, and 60.3% of high-risk patients numerically met goal. Overall, 81.7% in the 5 mg group, 84.5% in the 10 mg group, 78.7% in the 20 mg group, 59.1% in the 40 mg group, and 37.7% in the 80 mg group of rosuvastatin numerically reached their target NCEP ATP III LDL-C goals overall at the final visit.

Results for Group 2 (n=454)

Rosuvastatin treatment resulted in mean reductions from baseline to the final study visit in LDL-C (38.86%), TC (31.47%), TG (31.66%), non-HDL-C (39.35%), LDL-C/HDL-C (44.86%), TC/HDL-C (37.96%), and non-HDL-C/HDL-C (44.49%). HDL-C increased by 14.52%. Overall, on the basis of descriptive statistics, 39.4% of patients numerically reached their combined target NCEP ATP III LDL-C and TG goals at the final visit and 47.3% numerically reached their NCEP ATP III LDL-C goal. For all doses, 32.5% of low risk, 35.4% of medium risk, and 42.3% of high-risk patients numerically met their combined target NCEP ATP III LDL-C and TG goals overall at the final visit and 65.0% of low risk, 54.6% of

medium risk, and 41.2% of high-risk patients numerically met their NCEP ATP III LDL-C goal.

Results for Group 3 (n=30)
Rosuvastatin treatment resulted in mean reductions from baseline to the final study visit in LDL-C (22.09%), TC (19.45%), TG (9.27%), non-HDL-C (20.74%), LDL-C/HDL-C (18.10%), TC/HDL-C (15.74%), and non-HDL-C/HDL-C (16.64%). HDL-C increased by 3.89%. No patients (0/30) in Group 3 numerically reached their target NCEP ATP III LDL-C goal, overall or by risk category, at the final visit.

Results for Studies 24 and 27
The majority of patients, on the basis of descriptive statistics, numerically reached their target NCEP ATP III LDL-C goals overall, by start dose in the study of origin and final dose in this study, from start doses of rosuvastatin 5 mg and 10 mg in this study, when comparing results from the first visit of the titration phase to the first visit of the fixed dose period. As many of the sample numbers were low, results should be interpreted with caution.

Results for Studies 26 and 28
The majority of patients, on the basis of descriptive statistics, numerically reached their target NCEP ATP III LDL-C goals overall, by final dose in the study of origin and final dose in this study, from start doses of rosuvastatin 10 mg and 80 mg in this study, when comparing results from the first visit of the titration phase to the first visit of the fixed dose period. As many of the sample numbers were low, results should be interpreted with caution.

Safety results

Patients received an average of 1306.7 treatment days on rosuvastatin. The majority of patients had durations of rosuvastatin exposure between 216 and 251 weeks.

The frequency of AEs associated with each rosuvastatin dose group was similar. The 5 most commonly occurring AEs were: arthralgia (19.8%), nasopharyngitis (17.0%), upper respiratory tract infection (15.8%), back pain (13.6%), pain in extremity (12.0%), and urinary tract infection (12.0%). The frequency of deaths (1.2%), nonfatal SAEs (23.8%), DAEs (9.5%) and treatment-related AEs (25.2%) did not appear unusual in an open-label study of this extended duration. The majority of AEs were mild to moderate in severity; there was no evidence of dose-related concerns in the marketed 5 to 40 mg rosuvastatin dose groups. None of the AEs that occurred in this study was unexpected for this study population.

Of hepatic events examined, 1 patient (<0.05%) had an AE of hepatic failure and a concomitant event of renal failure; both events were considered not treatment-related by the investigator. Three patients (0.1%) had AEs of hepatitis, 2 patients (0.1%) had AEs of Hepatitis A, and 1 patient (<0.05%) had an AE of Hepatitis B. Of these 6 hepatitis patients, 5 experienced these hepatic events while on the unmarketed 80 mg rosuvastatin dose. The remaining hepatitis patient receiving 20 mg rosuvastatin plus gemfibrozil had a reported drug-induced hepatitis during a simultaneous event of rhabdomyolysis. Regarding other hepatic events, 2 patients (0.1%) had AEs of jaundice: 1 of these was receiving rosuvastatin 80 mg.

The other patient, receiving rosuvastatin 20 mg, had a concomitant AE of acute cholecystitis. Both jaundice events were considered not treatment-related by the investigator.

Regarding skeletal muscle events, 6 patients (0.2%) had AEs of rhabdomyolysis. Five of these events occurred on the unmarketed rosuvastatin 80 mg dose. The remaining rhabdomyolysis event occurred on 20 mg and was considered a drug interaction with gemfibrozil by the investigator. (This patient also had hepatitis reported during this event, and was discussed above in the paragraph on hepatic events). One patient (<0.05%) had an AE of myopathy, but there was no concomitant CK value >10 x ULN, thus this case did not meet AstraZeneca's internal criteria for myopathy (CK value >10 x ULN plus muscle symptoms). Four patients (0.1%) had AEs of myositis: 3 of these patients had events that were neither considered serious nor treatment-related by the investigator and, in fact, these patients recovered while continuing in the study. The fourth patient was receiving the 80 mg dose. The frequency of reported events of myalgia (a recognized statin class effect) ranged from 3.1% (rosuvastatin 20 mg) to 8.0% (rosuvastatin 80 mg), with the unmarketed 80 mg dose group having the highest frequency.

Of renal events examined, 7 patients (0.2%) had AEs of acute renal failure: 3 of these patients experienced these events in conjunction with AEs of rhabdomyolysis at the unmarketed rosuvastatin 80 mg dose (discussed above under skeletal muscle events). The events of the remaining 4 patients were not considered treatment-related by the investigator: 3 of these patients were concomitantly hospitalized with other serious AEs (ie, congestive heart failure and ischemic cardiomyopathy, pyelonephritis, nephrolithiasis and hypovolemia); and, 1 patient's event of acute renal failure was not considered serious and resolved while the patient continued in the study. Nine patients (0.3%) had AEs of non-specific renal failure: 1 of these had a concomitant event of hepatic failure (mentioned above); the 8 remaining patients' events were not considered treatment-related by the investigator. Of these 8 patients' events: 2 occurred at the 80 mg rosuvastatin dose; 1 was not considered serious and serum creatinine levels remained within normal limits; 1 was a decompensation of renal insufficiency in a diabetic patient; 1 patient experienced nausea, vomiting, and a urinary tract infection immediately preceding the event; 1 patient had concomitant events of congestive heart failure, hypoxia, pancreatitis and cholecystitis; 1 patient died of a co-occurring myocardial infarction; and, 1 patient died shortly afterward from metastatic hepatic cancer. One patient (<0.05%) had an AE of acute prerenal failure (prerenal azotemia) and 1 patient (<0.05%) had an AE of chronic renal failure, actually a transient exacerbation of chronic renal insufficiency in a diabetic; both events were not considered treatment-related by the investigator. Three patients (0.1%) had AEs of renal impairment: these events for 2 patients were neither considered serious nor treatment-related by the investigator. A third patient had an AE of renal impairment, which was actually a component of a co-occurring AE of rhabdomyolysis. This patient was receiving the unmarketed 80 mg dose. One patient (<0.05) had an AE of interstitial nephritis and 1 patient (<0.05) had an AE of glomerulonephritis; both of these events occurred on the rosuvastatin 80 mg dose. The overall frequency of investigator-reported events of proteinuria (in contrast to actual proteinuria detected by urinalysis) was 2.4%; the rosuvastatin 80 mg dose group had the highest frequency (2.6%).

The overall frequency of reported events of hematuria was low (3.1%) and generally similar across the dose groups.

Changes in clinical laboratory results were generally small and showed no dose-related effects in the marketed 5 to 40 mg rosuvastatin dose range. Thirty patients (1.0%) had ALT values >3 x ULN on 2 consecutive visits (the internal AstraZeneca definition of clinically important); the majority of these patients (66.7%) had the elevations occur while receiving the unmarketed rosuvastatin 80 mg dose. Overall, 48 patients (1.6%) had a CK elevation that met the internal AstraZeneca definition of clinically important (>10 x ULN). The majority of patients (51.0%) maintained or had a decrease in serum creatinine; however, 18 patients (0.6%) experienced an increase in serum creatinine >100% from baseline (the internal AstraZeneca definition of clinically important). Of these 18 patients, only 3 had increases in dipstick urine protein from none or trace at baseline to ++ or greater at the final visit, and only 1 patient had an increase in dipstick urine blood from none or trace at baseline to ++ or greater at the final visit. While 231 patients (8.8%) experienced an increase in dipstick urine protein from none or trace at baseline to ++ or greater at any visit, only 26 patients (1.0%) had such an increase remaining at the final visit. Similarly, of 317 patients (11.9%) with an increase in urine blood from none or trace at baseline to ++ or greater at any visit, only 45 patients (1.7%) had such an increase remaining at the final visit. Overall, the number of clinically notable elevations was low, especially given the extended duration of this study.

There were no treatment-associated changes in vital signs, ECG, and weight during the study.

Date of the report

06 December 2005