AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Rosuvastatin
Study Code	D356FC00003
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A 12-week Open-label, Randomised, Parallel-group, Multicentre, Phase IIIb Study to Compare the Efficacy and Safety of Rosuvastatin (CRESTOR™) 10 mg and 20 mg in Combination with Ezetimibe 10 mg and Simvastatin 40 mg and 80 mg in Combination with Ezetimibe 10 mg (fixed dose combination) in Patients with Hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent, Atherosclerosis or a 10-year CHD Risk of >20%

GRAVITY – Gauging the lipid effects of **R**osuv**A**statin plus ezetimibe **V**ersus s**I**mvastatin plus ezetimibe **T**herap**Y**

Study dates:	First patient enrolled: 29 August 2007 Last patient completed: 03 September 2008
Phase of development:	Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

There were 111 study centres: 56 in the USA, 13 in Peru, 12 in the Netherlands, 8 in Colombia, 8 in Argentina, 6 in Brazil, 4 in Chile and 4 in Lithuania.

The first patient was enrolled on 29 August 2007.

Last patient completed the study on 03 September 2008.

Publications

None at the time of writing this report.

Objectives

Primary objectives

The primary objective of this study was to evaluate the LDL-C lowering efficacy of rosuvastatin (CRESTOR™) 10 mg and 20 mg in combination with ezetimibe relative to that of simvastatin in a fixed dose combination with ezetimibe. This objective had 3 specific components:

1. Percentage change from baseline in LDL-C for rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

2. Percentage change from baseline in LDL-C for rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

3. Percentage change from baseline in LDL-C for rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

Secondary objectives

If statistical significance was reached for any of the components of the primary objective, the following secondary objectives (1 to 6) were formally tested (secondary objectives 7 and 8 and the exploratory objective were tested even if statistical significance was not reached):

1. To assess and compare the effects of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on percentage LDL-C reduction after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

2. To assess and compare the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg and 80 mg in combination with ezetimibe 10 mg on percentage change in HDL-C, total cholesterol (TC), TG, non-HDL-C, apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I); TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I and high sensitivity C-reactive protein (hs-CRP) from baseline after 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

3. To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

4. To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

5. To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

6. To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

7. To assess the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs the same dose of rosuvastatin 10 mg and 20 mg alone on percentage change in LDL-C, HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I; TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I and hs-CRP from baseline and on current American and European guideline lipid goal achievement after 6 weeks monotherapy and 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy was used)

8. To assess the safety and tolerability of rosuvastatin in combination with ezetimibe vs simvastatin in combination with ezetimibe by observing adverse events, changes in laboratory safety variables and discontinuations over 6 weeks of combination therapy

Exploratory objective

The exploratory objective of this study was as follows:

- To assess and compare the effects of rosuvastatin or simvastatin alone or in combination with ezetimibe, an additional sample was also drawn for possible analysis following review of the principal findings of the study. **Biomarker results were reported separately from the clinical study report (CSR).**

Study design

This was a 12-week open-label, randomised, parallel-group, multicentre, phase IIIb study to compare the efficacy and safety of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg and simvastatin 40 mg and 80 mg in fixed dose combination with ezetimibe 10 mg in patients with hypercholesterolaemia and CHD or a CHD risk equivalent, atherosclerosis or a 10-year CHD risk of >20%. Patients underwent 6 weeks of monotherapy followed by 6 weeks of combination therapy.

Target healthy volunteer population and sample size

Subjects 18 years of age and older, with a history of CHD or a CHD risk equivalent and patients with a reasonable likelihood of attaining LDL-C values of ≥ 130 mg/dL to <220 mg/dL at Visit 2, in the opinion of the Investigator.

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

AstraZeneca provided open-labelled clinical study material, including rosuvastatin 10 mg, rosuvastatin 20 mg, simvastatin 40 mg, simvastatin 80 mg, ezetimibe 10 mg, the combination product of ezetimibe 10 mg/simvastatin 40 mg and the combination product of ezetimibe 10 mg/simvastatin 80 mg. Materials were labelled with a two-panel open tear-off label.

The details of the investigational products and any study treatment are given in Table 1.

Table 1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule and route of administration	Manufacturer	Manufacturer lot number
Rosuvastatin	10 mg tablet od orally	AstraZeneca Pharmaceuticals	107008
	20 mg tablet od orally		107194
Simvastatin	40 mg tablet od orally	Merck	U6369
	80 mg tablet od orally		X3612
Ezetimibe	10 mg tablet od orally	Schering	7EZP615A1
Ezetimibe/ Simvastatin	10/40 mg tablet od orally	Merck/ Schering	X3074
	10/80 mg tablet od orally		X3392

All investigational products were to be kept in a secure place under appropriate storage conditions.

Duration of treatment

This was a 12-week, parallel group study. Potentially eligible patients underwent screening procedures (Week –6; Visit 1), and entered a 6-week dietary lead-in period. Those who fulfilled all eligibility criteria (Week -6; Visit 1) and had qualifying lipid values at Visit 2 were randomly allocated (1:1:1:1) to 1 of 4 treatments for a period of 12 weeks.

Criteria for evaluation - efficacy and safety (main variables)

Table 2 Efficacy variables

Objective	Variable(s)
Primary	The percentage change in LDL-C from baseline to 6 weeks (mean value of 4 and 6 weeks of combination therapy was used). The primary variable was assessed after 6 weeks of combination therapy.
Secondary	LDL-C, HDL-C, TC, TG, non HDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I, hs-CRP; and the corresponding measures of effects are the respective changes from baseline.
	Therapeutic lipid goals of LDL-C, as described in American and European guidelines, with the corresponding measures of effect being the proportions of patients at the goal.
Exploratory	Change in biomarkers (sitosterol, lanosterol, plasma C4, LpPLA2 and biomarkers related to atherosclerosis and lipid fractions). Biomarker results are presented separately from the CSR.

Table 3 Safety variables

Objective	Variable(s)
AEs	AEs, SAEs, other significant adverse events
Vital signs	Blood pressure, pulse rate
Physical examination	Normal/abnormal physical examination findings
Laboratory measurements	Haematology, clinical chemistry, abbreviated clinical chemistry, urinalysis

Statistical methods

All efficacy measurements were summarised by randomised treatment group. Safety data were summarized by the actual treatment received. In this study, all baseline and on-treatment effects were assessed as the mean of two consecutive measurements made 2 weeks apart. For reporting purposes, the average of weeks 4 and 6 was termed the effect after 6 weeks of treatment.

Analysis of covariance (ANCOVA) was used as the primary analysis. The response variable was the logarithm of the ratio of the treatment value divided by the corresponding baseline value in LDL-C levels with a main effect for treatment, centre and baseline level of LDL-C as a covariates. To address the apparent multiple comparisons of rosuvastatin/ezetimibe combinations there was a 'family of tests' approach using the Hochberg procedure to control for multiple comparisons.

Data from all patients who entered the dietary lead-in period was included in the evaluation of safety. Those patients who withdrew during the dietary lead-in period and those who withdrew after randomisation were summarised separately.

All AEs were categorized by MedDRA system organ class (SOC) and preferred term and listed for each patient. In the randomised safety population, treatment-emergent events were reported as frequencies in each treatment group. Tests of statistical significance were not performed.

Haematology and clinical chemistry data were listed for each patient and summarized for each treatment group at each visit. Values outside laboratory reference ranges were highlighted.

Patient population

Patients who fulfilled all eligibility criteria and had qualifying lipid values at Visit 2 (LDL-C $\geq$ 130 to <220 mg/dL; triglyceride < 400 mg/dL) were randomised to the 12-week treatment phase.

A total of 1743 patients entered the study, of which 51 withdrew from the screening phase and 859 withdrew from the dietary lead-in phase. A total of 833 patients were randomised to the treatment phase.

Summary of efficacy results

Table 4 Efficacy objectives, variables and conclusions

Objective	Outcome Variable	Conclusion
Percentage change from baseline in LDL-C for rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).	Percentage change in LDL-C lowering.	A greater percentage change reduction in LDL-C from baseline to combination therapy was observed in the R20+E10 treatment group (-63.48%) than in the S40+E10 treatment group (-55.22%) and this difference was statistically significant ($p<0.001$).
Percentage change from baseline in LDL-C for rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).	Percentage change in LDL-C lowering.	A greater percentage change reduction in LDL-C from baseline to combination therapy was observed in the R10+E10 treatment group (-59.72%) than in the S40+E10 treatment group (-55.22%) and this difference was statistically significant ($p=0.002$).
Percentage change from baseline in LDL-C for rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).	Percentage change in LDL-C lowering.	A greater percentage change reduction in LDL-C from baseline to combination therapy was observed in the R20+E10 treatment group (-63.48%) than in the S80+E10 treatment group (-57.42%) and this difference was statistically significant ($p<0.001$).

Table 4 Efficacy objectives, variables and conclusions

Objective	Outcome Variable	Conclusion
To assess and compare the effects of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on percentage LDL-C reduction after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).	Percentage change in LDL-C lowering.	A greater percentage change reduction in LDL-C after combination therapy was observed in the R10+E10 treatment group (-59.72%) than in the S80+E10 treatment group (-57.42%) but this difference was not statistically significant (p=0.497).
To assess and compare the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg and 80 mg in combination with ezetimibe 10 mg on percentage change in HDL-C, total cholesterol, TG, nonHDL-C, apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I); TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, TG/HDL-C, ApoB/ApoA-I and hs-CRP from baseline after 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy was used).	HDL-C, Total Cholesterol, TG, Non-HDL-C, ApoB, ApoA-I, Total Cholesterol/HDL-C, LDL-C/HDL-C, Non-HDL-C/HDL-C, ApoB/ApoA-I, hs-CRP, TG/HDL-C.	Statistically greater decreases in percentage change for Total Cholesterol, TG, Non-HDL-C, ApoB, Total Cholesterol/HDL-C, LDL-C/HDL-C, Non-HDL-C/HDL-C, ApoB/ApoA-I and TG/HDL-C were seen in the R10+E10 treatment group than in the S40+E10 treatment group. Statistically greater increases in percentage change for HDL-C and decreases in percentage change for Total Cholesterol, TG, Non-HDL-C, ApoB, Total Cholesterol/HDL-C, LDL-C/HDL-C, Non-HDL-C/HDL-C, ApoB/ApoA-I and TG/HDL-C were seen in the R20+E10 treatment group than in the S40+E10 and S80+E10 treatment groups.
To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).	LDL-C goals (American and European guidelines).	Statistically greater frequencies of patients achieved all lipid goals under both American and European guidelines in the R20+E10 treatment group than in the S40+E10 treatment group.

Table 4 Efficacy objectives, variables and conclusions

Objective	Outcome Variable	Conclusion
To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).		Statistically greater frequencies of patients achieved the LDL-C <100 mg/dL (p=0.030) lipid goal under American and European guidelines and the LDL-C <80 mg/dL (p=0.004) lipid goal under European guidelines in the R10+E10 treatment group than in the S40+E10 treatment group.
To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).		Statistically greater frequencies of patients achieved all lipid goals in the R20+E10 treatment group than in the S80+E10 treatment group except for the LDL-C <130 mg/dL lipid goal (p=0.078) under American guidelines.
To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy was used).		Greater frequencies of patients achieved each of the lipid goals under American and European guidelines in the R10+E10 treatment group than in the S80+E10 treatment group (with the exception of a marginally lower percentage in the R10+E10 treatment group for the LDL-C <70 mg/dL lipid goal under American guidelines) but none of the differences were found to be statistically significant.

Table 4 Efficacy objectives, variables and conclusions

Objective	Outcome Variable	Conclusion
To assess the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs the same dose of rosuvastatin 10 mg and 20 mg alone on percentage change in LDL-C, HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I; TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, TG/HDL-C, ApoB/ApoA-I and hs-CRP from baseline and on current American and European guideline lipid goal achievement after 6 weeks monotherapy and 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy was used).	HDL-C, Total Cholesterol, TG, Non-HDL-C, ApoB, ApoA-I, Total Cholesterol/HDL-C, LDL-C/HDL-C, Non-HDL-C/HDL-C, ApoB/ApoA-I, hs-CRP, TG/HDL-C.	Statistically greater decreases in percentage change for Total Cholesterol, TG, Non-HDL-C, ApoB, Total Cholesterol/HDL-C, LDL-C/HDL-C, Non-HDL-C/HDL-C, ApoB/ApoA-I, and TG/HDL-C were observed in the R10+E10 and R20+E10 treatment groups than during monotherapy.
To assess the efficacy of rosuvastatin 10 mg and 20 mg vs simvastatin 40 mg and 80 mg on the proportion of patients achieving lipid goals (American and European guideline) after monotherapy.	LDL-C goals (American and European guidelines).	Statistically greater frequencies of patients achieved all lipid goals at completion of monotherapy in the R20 treatment group than in the S40 and S80 treatment groups. Statistically greater frequencies of patients in the R10 treatment group achieved the LDL-C <100 mg/dL lipid goal under American and European guidelines, the LDL-C <70 mg/dL lipid goal under American guidelines and the LDL-C <80 mg/dL lipid goal under European guidelines, than in the S40 treatment group.

Table 4 Efficacy objectives, variables and conclusions

Objective	Outcome Variable	Conclusion
To assess the efficacy of rosuvastatin 10 mg and 20 mg vs simvastatin 40 mg and 80 mg on the proportion of patients with LDL-C ≥ 160 mg/dL at baseline achieving lipid goals (American and European guideline) after monotherapy.	LDL-C goals (American and European guidelines).	Statistically greater frequencies of patients with LDL-C ≥ 160 mg/dL achieved the majority of lipid goals in the R20 treatment group than in the S40 and S80 treatment groups, except compared to the S80 treatment group for the LDL-C <130 mg/dL lipid goal (p=0.233) under American guidelines and the LDL-C <115 mg/dL lipid goal (p=0.081) under European guidelines. Statistically greater frequencies of patients in the R10 treatment group achieved the LDL-C <100 mg/dL lipid goal (p=0.004) under American and European guidelines and the LDL-C <80 mg/dL lipid goal (p=0.034) under European guidelines, than in the S40 treatment group.

Summary of pharmacokinetic results

Not applicable.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

Table 5 Safety objectives, variables and conclusions

Objective	Variable	Conclusion
To assess the safety and tolerability of rosuvastatin in combination with ezetimibe vs simvastatin in combination with ezetimibe by observing adverse events, changes in laboratory safety variables and discontinuations over 6 weeks of combination therapy.	Incidence and severity of AEs, SAEs and abnormal laboratory values.	Treatment-emergent AEs were reported by 243 patients (31.4%) during the combination therapy phase. Similar frequencies of patients experienced treatment-emergent AEs across treatment groups during combination therapy. By preferred term, the most frequently experienced treatment-emergent AE was myalgia. The highest frequency of patients experiencing treatment-emergent drug-related AEs was seen in the S80+E10 treatment group. During combination therapy a total of 16 patients (2.1%) experienced a treatment-emergent SAE. By preferred term, the most frequently experienced treatment-emergent SAE was unstable angina. During combination therapy, a total of 12 patients (1.5%) experienced a treatment-emergent laboratory abnormality leading to withdrawal. Shifts in haematology, clinical chemistry and urinalysis parameters outside of the reference were observed in all treatment groups. Treatment-emergent laboratory abnormalities related to haematology, clinical chemistry and urinalysis parameters were infrequent, with no such abnormalities occurring in greater than 1% of patients and with no notable differences between treatment groups. No patients died during the study.