AstraZeneca

Clinical Study Report

Drug substance:	Rosuvastatin
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Study code:	D3560L00011
Date:	*30 June 2006*

An open-label, randomised, multi-centre, phase IIIb/IV, parallel group study to compare the efficacy and safety of rosuvastatin and atorvastatin in patients with type IIa and IIb hypercholesterolaemia

Study dates: First subject enrolled: *26 June 2003*
Last subject enrolled: *07 July 2004*

Phase of development: IIIb/IV

Co-ordinating investigators:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice.

Drug product:	<<>>	**SYNOPSIS**	
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An open-label, randomised, multi-centre, phase IIIb/IV, parallel group study to compare the efficacy and safety of rosuvastatin and atorvastatin in patients with type IIa and IIb hypercholesterolaemia

International co-ordinating investigators

Study centre(s)

The study was conducted in 99 centres in Belgium and Luxembourg.

Publications

Abstract accepted for Poster publication. Belgian Society of Cardiology. Brussels. February 2006.

Study dates

First subject enrolled *26 June 2003*

Last subject completed *21 December 2004*

Phase of development

Therapeutic confirmatory (III)
Therapeutic use (IV)

Objectives

Primary objective

The primary objective of the study is to compare the efficacy of rosuvastatin 10 mg with atorvastatin 10 mg by assessment of the percentage of patients who reach the EUROPEAN LDL-C target goal after 12 weeks of therapy.

Secondary objectives

1. To compare the efficacy of rosuvastatin 10 mg with atorvastatin 10 mg by assessment of the percentage of patients who reach the EUROPEAN TC treatment goal after 12 weeks of therapy.
2. To compare the percentage change from baseline (week -2) in LDL-C, TC, HDL-C and TG at 12 weeks. This will be performed separately for the switched and the naïve patients.
3. To compare the efficacy of rosuvastatin 10 mg with atorvastatin 10 mg in modifying lipids and lipid ratios (Non-HDL-C, TC/HDL-C, LDL-C/ HDL-C, non-HDL-C/HDL-C) at week 12. This will be performed separately for the switched and the naïve patients.
4. To compare rosuvastatin 10 mg with atorvastatin 10 mg after 12 weeks of treatment with respect to the incidence and severity of adverse events and abnormal laboratory values.
5. To assess the incidence and severity of adverse events and abnormal laboratory values of rosuvastatin 10 mg and 20 mg after 24 weeks of treatment.
6. To evaluate the percentage of patients who reach the EUROPEAN LDL-C treatment goal at week 24 after initially treated with atorvastatin 10 mg, but not reaching the EUROPEAN LDL-C treatment goal and therefore switched to rosuvastatin 10 mg.

Study design

This is a randomised, multi-centre, open-label, 2-arm parallel group study in patients with type IIa and IIb hypercholesterolaemia performed in Belgium and Luxembourg.

One thousand seventy eight patients with hypercholesterolaemia were to be enrolled. Lipid-lowering therapy naïve patients or patients on a "usual Belux starting dose" for minimum 4 weeks of any lipid-lowering therapy which is ineffective (have not reached the target LDL-C goal) could be entered. The newly treated patients should have received at least 4 weeks dietary advice before entering the study

Patients meeting the entry criteria were randomised to receive 12 weeks of open-label treatment with either rosuvastatin 10 mg od or atorvastatin 10 mg od.

At the end of the 12 weeks it was decided whether or not the subject could enter the follow-up period depending on the LDL-C value.

In the follow-up period, if patients achieved EUROPEAN LDL-C goals on rosuvastatin 10 mg od they were to continue this therapy. If patients did not achieve their EUROPEAN LDL-C goals on rosuvastatin 10 mg they were to be treated with rosuvastatin 20 mg od. Patients on atorvastatin 10 mg could continue on rosuvastatin 10 mg od if EUROPEAN LDL-C goals were not achieved.

Fasting lipids and laboratory safety parameters were measured throughout the study.

Target subject population and sample size

Patients to be enrolled in the study were male or female, 18 years or older, with primary hypercholesterolaemia and with the following characteristics:

- Patients switched from start doses of any lipid lowering therapy with an LDL-C level > 120 mg/dL (3.1 mmol/L)
- Lipid-lowering therapy naïve patients with an LDL-C level > 130 mg/dL (3.5 mmol/L) and a Total-Cholesterol > 190 mg/dL (5.0 mmol/L)
- 10 year CV risk > 20 % or >20% if projected to age 60 (as defined in The Joint European Guidelines) and/or type 2 diabetes and/or a history of CHD or other established atherosclerotic disease.

Key exclusion criteria were: History of SAE with another HMG-CoA reductase inhibitor; active liver disease; unstable cardiovascular disease; severe renal or hepatic impairment; treatment with cyclosporin or any disallowed drug.

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

Rosuvastatin 10 mg once daily in oral tablet form.

Batch Number ZD4522 10MG : EO1811-04L01, E01811-06L01.

Rosuvastatin 20 mg once daily in oral tablet form in the follow-up period:

Batch Number ZD4522 20MG : EO1811-04L04, E01811-05L04, EO1811-035L03.

Atorvastatin 10 mg once daily in oral tablet form.

Lipitor 10 mg 0243122, 02I12A, 02I25A, 01H09, 01J08, 0487092, 0567073B.

Duration of treatment

Patients were to be treated for 12 weeks with rosuvastatin 10 mg or atorvastatin 10 mg therapy once daily.

After the 12 first weeks of treatment, patients could continue on rosuvastatin treatment in a follow-up period for another 12 weeks.

- Patients who achieved EUROPEAN LDL-C target goal of < 115 mg/dL (3.0 mmol/L) on rosuvastatin 10 mg od were to continue on this dose of rosuvastatin.
- Patients who did not achieve the EUROPEAN LDL-C target goal of < 115 mg/dL (3.0 mmol/L) on rosuvastatin 10 mg od were to be treated with rosuvastatin 20 mg od.
- Patients who did not achieve the EUROPEAN LDL-C target goal of < 115 mg/dL (3.0 mmol/L) on atorvastatin 10 mg od were to be treated with rosuvastatin 10 mg od.
- Patients who achieved the EUROPEAN LDL-C target goal on atorvastatin 10 mg od were to end the study and return to normal clinical practice.

Criteria for evaluation (main variables)

Efficacy

- Primary variable:

  Reaching the EUROPEAN LDL-C target at week 12.

- Secondary variables:

1. Reaching the EUROPEAN TC target at week 12.
2. Percentage change from baseline in LDL-C, TC, HDL-C and TG (week –2) at 12 weeks, assessed separately for switched and naïve patients.
3. Percentage change from baseline (week –2) in lipid ratios (Non-HDL-C, TC/HDL-C, LDL-C/ HDL-C, non-HDL-C/HDL-C) at 12 weeks, assessed separately for switched and naïve patients.
4. Percentage of patients reaching EUROPEAN LDL-C treatment goal at week 24 after initially treated with atorvastatin 10 mg, but not reaching the EUROPEAN LDL-C treatment goal and therefore switched to rosuvastatin 10 mg.

Safety

1. Incidence and severity of adverse events and abnormal laboratory values of rosuvastatin 10 mg and atorvastatin 10 mg after 12 weeks.
2. Incidence and severity of adverse events and abnormal laboratory values of rosuvastatin 10 mg and 20 mg after 24 weeks.

Statistical methods

Efficay is evaluated on an intention to treat (ITT) basis by randomised treatment. The ITT population consists of patients who have a baseline reading of any lipid variable, one post-baseline reading of any lipid variable and have received at least one dose of trial medication.If a subject is withdrawn prior to week 12, the last post baseline assessment was carried forward as the week 12 value. Since this is an open study, additional analyses were also performed excluding those patients who were misrandomised.

The evaluation of safety during the first 12-week period is based upon the safety population. This population consists of patients who took at least one dose of trial medication in the period from week 0 (Visit 2) to week 12 (Visit 3). Only data concerning this period are considered in the analysis. In the safety population treatment arms are defined based on the treatment actually received by the subject.

The evaluation of safety during the follow-up period is based upon the follow-up safety population. This population consists of patients who have taken at least one dose of trial medication in the period from week 12 (Visit 3) to week 24 (Visit 4). Only data concerning this period are considered in the follow-up safety analysis.

The analysis is both descriptive and inferential. Statistical tests were performed two-sided at the 5% level of significance. Statistical testing includes logistic regression analysis for modeling the binary variables and ANCOVA for the evaluation of continuous variables.

The primary efficacy variable was analysed using a logistic regression model with factors fitted for treatment, subject type (naïve or switched), centre, treatment-by-subject type interaction, treatment-by-centre interaction and the pre-dose LDL-C value (week -2) fitted as a covariate. Small centers in which not both treatment arms are represented, were regrouped as one center. If an interaction term was found to be significant ($p \leq 0.05$), the nature of the interaction was investigated, otherwise the term was dropped from the final model. The results are presented as odds ratios, with associated 95% confidence interval and p-value. The same approach was also used for secondary binary efficacy variables concerning reaching targets based on LDL-C.

The analyses of percentage change in lipids and modifying lipid parameters from pre-dose (week –2) to week 12 was performed separately for the switched patients and the naïve patients. The analysis was carried out using an ANCOVA model, with factors fitted for treatment and centre. Small centres in which not both treatment arms were represented, were regrouped as one centre. The results are presented in terms of LSmeans and the difference between the treatment LSmeans, with p-values and associated 95% confidence intervals. In case of non-normality of the residuals of the model, the two treatment arms were compared using a Cochran-Mantel-Haenszel test, controlled for center.

The evaluation of safety is only performed in a descriptive way. Adverse events were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). The incidence of adverse events by MedDRA preferred term is summarised by treatment and treatment dose. The number of patients who withdraw or die due to adverse events is described. For laboratory safety data, the change from baseline and percentages of values out-of-range are described. For vital signs, the change from baseline is described.

Subject population

Of the 1201 patients screened for the study, 938 were randomised (78.1%).

All randomised patients were administered study medication, but one of the patients who was randomised to receive atorvastatin was administered rosuvastatin. Therefore, the safety population consists of 938 patients, 479 patients of whom received rosuvastatin and 459 of whom received atorvastatin to start the treatment with.

Post-baseline laboratory assessments were available for 877 of the 938 randomised patients (93.5%): 458 (52.2%) to receive rosuvastatin and 419 (47.8%) to receive atorvastatin. These patients constitute the Intention to Treat Population.

Five hundred and seventy (570) patients were entered in the follow-up phase of the study and were administered study medication. Five hundred and eight (508) patients were assigned to receive rosuvastatin 10 mg and 62 to receive rosuvastatin 20 mg. However, 506 received rosuvastatin 10 mg and 64 received rosuvastatin 20 mg. The safety follow-up population thus consists of 570 patients: 506 in the rosuvastatin 10 mg and 64 in the rosuvastatin 20 mg group.

The demographic and key baseline characteristics are comparable in the two treatment groups, except for TC and LDL-C in the switched patients for which the baseline value is on average about 10 mg/dL higher in the rosuvastatin group than in the atorvastatin group.

Efficacy results

The results of the primary efficacy variable are summarised in Table S1.

Table S1 Reaching EUROPEAN LDL-C target (<115mg/dL) at week 12 (Intention to Treat Population)

Subject Type	Visit	Treatment (Randomised to)			
		Rosuvastatin 10 mg (N = 458)		Atorvastatin 10 mg (N = 419)	
		N	%	N	%
All patients	Week 12	384	84.6	277	67.4
Naïve Patients	Week 12	318	88.8	237	69.7
Switched Patients	Week 12	66	68.8	40	56.3

Data derived from Table, Section 11.2.1.1A, 11.2.1.1B

In the rosuvastatin group, 84.6% of all patients reached the EUROPEAN LDL-C goal at week 12, while in the atorvastatin group, only 67.4% of all patients reached the target. These percentages were higher for naïve patients than for switched patients: respectively 88.8% versus 68.8% for the rosuvastatin group and 69.7% versus 56.3% for the atorvastatin group.

Rosuvastatin enabled a greater proportion of patients to achieve EUROPEAN LDL-C goals compared with atorvastatin (OR = 3.32, 95%CI = [2.31; 4.84] and $p < 0.001$). Rosuvastatin reduced LDL-C significantly more than atorvastatin and thereby may reduce the need for dose titration in clinical practice. The subject type was also significant (OR switched versus naïve = 0.24, 95%CI = [0.16; 0.36] and $p < 0.001$): naïve patients reached significantly more frequently the EUROPEAN LDL-C target than switched patients. A higher baseline EUROPEAN LDL-C level lowered significantly the probability of reaching the EUROPEAN LDL-C target ($p<0.001$).

For LDL-C and TC, the results of the comparison of the two treatments are markedly different in naïve and in switched patients. For naïve patients, the percentages of decrease in LDL-C and TC are significantly more important with rosuvastatin than with atorvastatin ($p < 0.001$), as for switched patients, the difference between the two treatment groups is not statistically significant ($p = 0.082$ for LDL-C and $p = 0.091$ for TC). For HDL-C and TG, the results of the comparison of the two treatments are comparable in naïve and in switched patients. For HDL-C, the slight increase was similar in the two treatment groups (p-values for naïve and switched patients respectively 0.895 and 0.565). The percentage of decrease of TG was also comparable in both treatment groups (p-values for naïve and switched patients respectively 0.641 and 0.848).

The frequency of patients that reached the goals at the end of the follow-period is given in Table S2, broken down by the reaching of the EUROPEAN LDL-C goal at week 12.

Further up-titration of uncontrolled patients from rosuvastatin 10 mg towards 20 mg lead to an additional 57% of patients achieving LDL goals.

Switch of uncontrolled patients from atorvastatin 10 mg towards rosuvastatin 10 mg lead to an additional 65% of patients achieving LDL goals.

Of the controlled patients who continued on rosuvastatin 10 mg, 91% remained controlled at the end of the follow-up.

Table S2 Reaching EUROPEAN LDL-C target at week 24 (Intention to Treat population)

	Treatment assigned to at week 12			
Treatment assigned to before week 12	**Rosuvastatin 10 mg (N = 478)**		**Rosuvastatin 20 mg (N = 60)**	
	N	**%**	**N**	**%**
LDL-C goal not reached at week 12				
Rosuvastatin 10 mg	3	75.0	31	57.4
Atorvastatin 10 mg	71	64.6	2	66.7
LDL-C goal reached at week 12				
Rosuvastatin 10 mg	318	90.9	2	100.0
Atorvastatin 10 mg	13	92.9	0	0.0

Data derived from Table, Section 11.2.1.2J

Safety results

Adverse events were reported by 17.1% of the patients on rosuvastatin and by 16.1% of the patients on atorvastatin.

During the follow-up period, the frequency of patients reporting adverse events was 13.4% for the patients who continued on rosuvastatin 10 mg, 23.7% for the patients who increased the dose from 10 mg to 20 mg rosuvastatin, and 9.1% for the patients who switched from atorvastatin 10 mg to rosuvastatin 10 mg. The tolerability profile of rosuvastatin at week 24 was comparable with the results seen in the overall clinical trial program of rosuvastatin and atorvastatin

The most frequent types of adverse eventswere myalgia, diarrhoea, fatigue, nausea, and muscle cramp. The incidence of these events is comparable in the two treatment groups. It thus appears that rosuvastatin 10 mg was well tolerated with an adverse event profile comparable with atorvastatin 10 mg.

Abnormal ALT/AST values (> 3 ULN) newly occurring during the study were observed for 4 patients, for 3 patients after 24 weeks of treatment with rosuvastatin 10 mg, and for one patient after 12 weeks of treatment with atorvastatin 10 mg.

Abnormal creatinine values (> 100% increase from baseline) occurring during the study, were observed for 3 patients after treatment with rosuvastatin 10 mg, and for none of the patients after treatment with atorvastatin 10 mg.

Abnormal CK values (> 10 ULN) newly occurring during the study were observed for 1 patient at the end of 24 weeks of treatment with rosuvastatin 10 mg.

Date of the report

30 June 2006