AstraZeneca

Clinical Study Report

Drug substance:	Rosuvastatin
Document No.:	D3560L00038
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Study code:	D3560L00038
Date:	29 November 2005

Evaluation of the hs-CRP reducing Effect of Rosuvastatin – a placebo controlled randomized multicentre phase IIIb study in hypertensive patients with an increased global risk of developing fatal cardiovascular disease - the ELECTRA study

Study dates: First patient enrolled: 10 May 2004
Last patient enrolled: 11 Nov 2004

Phase of development: IIIb

Co-ordinating Investigator:

Sponsor's Responsible Medical Officer: Dr Björn E Eriksson MD, PhD

This study was performed in compliance with Good Clinical Practice.

Drug product:	Crestor	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin		
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Evaluation of the hs-CRP reducing Effect of Rosuvastatin – a placebo controlled randomized multicentre phase IIIb study in hypertensive patients with an increased global risk of developing fatal cardiovascular disease - the ELECTRA study

Co-ordinating investigator

Study centre(s)

36 in Sweden

Publications

None at the time of writing of this report.

Study dates		**Phase of development**
First patient enrolled	10 May 2004	IIIb
Last patient completed	7 April 2005	

The decision to terminate the study prematurely was taken 28 October 2004 due to problems in finding enough patients eligible for randomisation.

Objectives

The primary objective was to compare the efficacy of rosuvastatin vs. placebo in reducing hs-CRP in hypertensive patients with an increased global risk of developing atherosclerotic cardiovascular disease during 18 weeks of treatment.

Secondary objectives of the study were (during 18 weeks of treatment)

- To compare the efficacy of the treatment regimes and between treatments regimes on the reduction
    - of the global risk of developing atherosclerotic cardiovascular disease
    - in the number of features of the metabolic syndrome
- To compare the efficacy between treatments regimes on the reduction
    - in the global risk of developing atherosclerotic cardiovascular disease to a level below 5 %
- To investigate any relationship between the
    - changes in global risk, and the reduction in hs-CRP value and between randomized treatments
    - changes in the numbers of features of the metabolic syndrome and the reduction in hs-CRP and between randomized treatments
    - hs-CRP levels and levels of LDL-C, HDL-C, TG, TC, TC/HDL-C, non-HDL, LDL/HDL, non-HDL/HDL, Apo B, Apo A1 and ApoB/ApoA1, and combined
    - change of hs-CRP levels and changes of LDL-C, HDL-C, TG, TC, TC/HDL-C, non-HDL, LDL/HDL, non-HDL/HDL, Apo B, Apo A1 and ApoB/ApoA1
- To compare the efficacy of life style advice vs life style advice in combination with once daily treatment with rosuvastatin 10 mg
    - in reducing LDL-C below 3.0 mmol/L
    - on LDL-C, HDL-C, TG, TC, TC/HDL-C, non-HDL, LDL/HDL, non-HDL/HDL, Apo B, Apo A1 and ApoB/ApoA1
- To investigate number of patients reaching target blood pressure below 130/85 mmHg at the end of the study

- To investigate the titration schedule for the antihypertensive treatment

- To determine the safety of rosuvastatin, candesartan and felodipine by evaluating the incidence and severity of adverse events, and abnormal laboratory values

Many of the combined planned objectives above have been omitted due to the low number of evaluable patients included in the study.

Study design

This was a 18 week, randomized, double-blind, placebo controlled, multicentre, phase IIIb study comparing the CRP lowering potential of once daily treatment with rosuvastatin 10 mg vs. placebo in hypertensive patients with an increased global risk of developing atherosclerotic cardiovascular disease (CVD).

Target patient population and sample size

Men and women aged 18 years and older with treated or untreated primary hypertension, and absolute risk of fatal CVD of $\underline{\geq}$ 5% over 10 years or will exceed 5% if projected to age 60 years according to SCORE (Systematic Coronary Risk Evaluation) as presented in the ESC Guidelines 2003 (De Backer et al., 2003) and with a hs-CRP value between 3.0 –10.0 mg/L were eligible for the study.

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

Double-blind randomized treatment: Rosuvastatin 10 mg oral tablet o.d. or placebo (batch number E02790-001L01)

Open-label treatment: Candesartan 16 mg oral tablet o.d. (batch number E02790-001L02, commercial packs)

Felodipine 2.5 or 5 mg oral tablet o.d. (batch number E02790-002L01 and E02790-002L02, commercial packs) was to be added if mean sitting blood pressure was ≥ 130/85 mm Hg at visits 4-6

Duration of treatment

18 weeks

Criteria for evaluation (main variables)

Efficacy

Primary variable:

- Change in hs-CRP

Secondary variables:

- Change in global risk of developing atherosclerotic cardiovascular disease
- Change in number of features of the metabolic syndrome *
- Change in the number of patients with a global risk of developing atherosclerotic cardiovascular disease to a level below 5 %
- Number of patients reaching target blood pressure below 130/85 mmHg
- The titration schedule for the antihypertensive treatment

* Waist circumference > 102 cm in males > 88 cm in females, serum triglycerides (TG) $\geq$ 1.7 mmol/L, High Density Lipoprotein cholesterol (HDL-C) < 1 mmol/L in males and <1.3 mmol/L in females, blood pressure $\geq$ 130/85 mmHg and a plasma glucose $\geq$ 6.1 mmol/L (National Institutes of Health, 2002)

Safety

Standard safety assessments included adverse event reports, clinical laboratory data (haematology and clinical chemistry) and vital signs.

Statistical methods

The study was terminated prematurely because of problems in finding enough patients eligible for randomization in time; hence the number of evaluable patients became so low that no formal statistical analyses were meaningful. All results are therefore only presented descriptively according to the intention to treat approach and no statistical inference has been performed.

Patient population

The study was originally planned for a recruitment of 501 randomized patients. However, due to problems in finding enough patients eligible for randomization, the study was prematurely terminated.

In total, 377 patients were enrolled but only 87 were randomized. The main reason for discontinuation before randomization was hs-CRP level not between 3-10 mg/L. Out of the 87 randomized patients, 42 were randomized to rosuvastatin and 45 to placebo. However, one patient in the rosuvastatin arm took study treatment but had no efficacy data and is therefore not included in the efficacy population and analysis. For this reason the patient is included in the safety results but not in e.g. table S1.

The number of discontinuations was somewhat higher in the placebo group compared to the rosuvastatin group (12 vs. 8). Except for “Treated for hypertension”, the treatment groups were comparable regarding demographic and baseline characteristics.

The randomized patients were representative of a hypertensive population with increased cardiovascular risk. Fifty-seven percent were males and the average age was 62 years.

Table S1 Patient population and disposition

		Rosuvastatin 10 mg		Placebo		Total	
Population							
N randomized (N planned)		41	(251)	45	(250)	86	(501)
Demographic characteristics							
Sex (n and % of patients)	Male	24	(59%)	25	(56%)	49	(57%)
	Female	17	(41%)	20	(44%)	37	(43%)
Age (years)	Mean (SD)	62.4	(8.71)	62.6	(8.51)	62.5	(8.55)
	Range	47 to 80.5		39.3 to 76.8		39.3 to 80.5	
Race (n and % of patients)	Caucasian	41	(100%)	45	(100%)	86	(100%)
Baseline characteristics							
Mean (SD) CRP (g/L)		4.80	(1.79)	5.23	(1.84)	5.02	(1.82)
Smoking:							
Yes		15	(17.4%)	15	(17.4%)	30	(34.9%)
No		26	(30.2%)	30	(34.9%)	56	(65.1%)
Treated for hypertension							
Untreated		31	(36.0%)	6	(7.00%)	16	(18.6%)
Treated		10	(11.6%)	39	(45.4%)	70	(81.4%)
SCORE absolute (mean/SD)		7.90	(4.55)	8.62	(6.29)	8.28	(5.51)
SCORE predicted (mean/SD) N = 9		6.78	(2.73)	6.89	(2.26)	6.83	(2.43)

		Rosuvastatin 10 mg		Placebo		Total	
Blood pressure diastolic sitting mean visit 3 (mean/SD)		88.2	(11.0)	89.5	(8.83)	88.9	(9.87)
Blood pressure systolic sitting mean visit 3 (mean/SD)		153.9	(13.2)	154.8	(16.0)	154.4	(14.7)
Heart rate sitting visit 3		75.7	11.5	72.9	11.2	74.2	11.4
Disposition							
N (%) of patients who	Completed	34	(39.5%)	33	(38.3%)	67	(78 %)
	Discontinued	7	(8.1 %)	12	(14.0%)	20	(22 %)
N analysed for safety[a]		42		45		87	
N analysed for efficacy (ITT)		41		45		86	

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number

Baseline data derived from **Error! Reference source not found.**11.1, Section **Error! Reference source not found.**

Efficacy results

Table S2 Descriptive statistics with absolute change and pct change for hs-CRP (mg/L). ITT population.

	Rosuvastatin		Placebo	
hs-CRP (mg/L)	Abs change	Pct change	Abs change	Pct change
n	39	39	42	42
Missing	2	2	3	3
Mean	-0.6	1.845	0.245	2.828
SD	7.594	212.3	3.675	59.74
Median	-1.8	-41	-0.5	-10.2
Min	-6.7	-84.7	-6.1	-76.3
Max	42.7	1256	12.9	195.5
P10	-5.1	-81.3	-3.3	-53.1
P25	-2.9	-60	-1.5	-41.5
P75	-0.6	-12.8	1.3	24.56
P90	3.8	82.43	4.3	81.82

Safety results

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]					
	Rosuvastatin 10 mg (N=42)		Placebo (N=45)		Total (N=87)	
Any adverse events	24	(57.1%)	26	(57.8%)	50	(57.5%)
Serious adverse events	0	(0%)	0	(0%)	0	(0%)
Discontinuations of study treatment due to adverse events	2	(4.8%)	2	(4.4%)	4	(4.6%)
Other significant adverse events	0	(0%)	0	(0%)	0	(0%)
	Total number of adverse events					
Adverse events	44		42		86	

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Table S4 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)						
	Rosuvastatin 10 mg (n=42)		Placebo (n=45)		Total (n=87)	
Nasopharyngitis	6	(14.3%)	7	(15.6%)	13	(14.9%)
Dizziness	3	(7.1%)	1	(2.2%)	4	(4.6%)
Headache	2	(4.8%)	2	(4.4%)	4	(4.6%)
Vertigo	1	(2.4%)	3	(6.7%)	4	(4.6%)

[a] Events with a total frequency of ≥4% across all treatment groups are included in this table.

Overall, rosuvastatin was well tolerated. A similar proportion of patients reported adverse events on rosuvastatin and placebo (approximately 58%). There were no serious adverse events. Discontinuations of study treatment due to adverse events were 4 patients in all (4.6%): 2 in the rosuvastatin arm and 2 in the placebo arm.

Date of the report

29 November 2005