Clinical Study Report ROMEO	
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A 6-week, randomised, open-label, parallel group, multi-centre study to compare the efficacy of rosuvastatin 10mg with atorvastatin 10mg in the treatment of metabolic syndrome subjects with raised LDL-C;

ROsuvastatin in MEtabolic syndrOm (ROMEO)

Study dates:	First patient enrolled: 18 September 2006 Last patient completed: 13 June 2008
Phase of development:	IV
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

SYNOPSIS

A 6-week, randomised, open-label, parallel group, multi-centre study to compare the efficacy of rosuvastatin 10mg with atorvastatin 10mg in the treatment of metabolic syndrome subjects with raised LDL-C (ROMEO)

Coordinating Investigator

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Study Centres

Subjects were recruited from a total of 13 centres in Korea. A total of 613 subjects were enrolled, of whom 258 were randomised.

Publications

None at the time of writing this report

Study dates

First patient enrolled	18 September 2006
Last patient completed	13 June 2008

Phase of development

IV

Objectives

Primary:

The primary objective of this study was to compare the effect of rosuvastatin 10mg with atorvastatin 10mg after 6 weeks of treatment in the ratio of ApoB/ApoA1 in subjects with metabolic syndrome.

Secondary:

The secondary objectives of this study were to compare the effects of rosuvastatin 10mg with atorvastatin 10mg, after 6 weeks of, on:

1. Bringing subjects to their NCEP ATP III LDL-C target goal
2. Bringing subjects to their NCEP ATP III LDL-C and nonHDL-C target goal
3. Glucose and Insulin resistance
4. Percentage reduction of LDL-C
5. Modifying other lipids and lipoproteins
6. Modifying inflammatory markers
7. Safety

Study design

This was a randomised, multi-centre, open-label, parallel-group study to compare the efficacy and safety of rosuvastatin compared with atorvastatin in the treatment of metabolic syndrome subjects with raised LDL-C. The study comprised the following 2 periods:

- 6 weeks dietary run-in period (week -6 to 0)
- 6 weeks randomised treatment period (week 0 to 6)

Target subject population and sample size

Male or female subjects, 18 years or older, with metabolic syndrome (as defined by the NCEP-ATP III guidelines) and a raised LDL-C [≥130mg/dL (3.36 mmol/L) < 220mg/dL (5.69 mmol/L)].

The size of the study population was calculated to detect a clinically meaningful difference in efficacy between rosuvastatin and atorvastatin, and was based on the primary endpoint, the percentage change from baseline in ApoB/ApoA1 ratio. It was estimated that 232 evaluable subjects would be required to achieve 90% power for a two-sided significance level of 5%. To allow for a dropout rate of 10% during the study, it was planned to randomise 258 subjects into the study, and allowing also for a withdrawal rate of 60% between visit 1 and subsequent radomisation at visit 2, to enroll approximately 645 subjects into the study.

Investigational product and comparator: dosage and mode of administration

Rosuvastatin 10mg once daily in oral tablet form

Atorvastatin 10mg once daily in oral tablet form

Duration of treatment

Subjects were randomised to be treated for 6 weeks with rosuvastatin 10mg or atorvastatin 10mg therapy once daily

Endpoints

Primary endpoint:

Percentage change from baseline in ratio of AopB/ApoA1 at week 6

Secondary endpoints

1. Percentage of subjects reaching their NCEP ATP III LDL-C target goal after 6 weeks of treatment
2. Percentage of subjects reaching their NCEP ATP III LDL-C and nonHDL-C target goal after 6 weeks of treatment [subjects with baseline TGs≥200mg/dL (2.26 mmol/L) only]
3. Percentage change from baseline in glucose and insulin resistance at week 6.
4. Percentage change from baseline in LDL-C at week 6
5. Percentage change from baseline(week 0) in TC, HDL-C, TG and lipoproteins at week 6
6. Percentage change from baseline in hs-CRP(C-reactive protein) at week 6
7. Safety evaluation as determined by the incidence and severity of adverse events and abnormal laboratory data

Statistical methods

The primary analysis population was intention to treat (ITT) population. This included all subjects with a baseline and at least one post-baseline lipid measurement. For the primary objective of comparing rosuvastatin 10mg with atorvastatin 10mg effects on percentage change in ApoB/ApoA1 ratio, an analysis of variance model with terms for centre and treatment were used. The result was presented as an estimate of the treatment effect (adjusted difference between the treatment groups) together with its 95% confidence intervals. A similar analysis of variance was also used to analyse the percentage change from baseline in other lipids and lipoproteins.

For secondary endpoints 1 and 2, logistic regression models with effects for baseline LDL-C, NCEP ATP III target, centre and treatment were used and the results were presented in terms of odds ratios, associated 95% confidence intervals, and p-values.

Numbers and percentages of subjects experiencing adverse events were summarised for subjects in the dietary lead-in safety population, and also in the randomised safety population. Laboratory safety data were tabulated. No statistical testing was performed on the safety endpoints.

The non-parametric Wilcoxon rank sum test was used to test for differences between treatments in their effect on inflammatory marker (hs-CRP). Data summaries including medians and interquartile ranges were also provided by treatment group.

All glucose and insulin assessments were done using laboratory data. The percentage change from baseline for glucose was calculated and insulin resistance was calculated using HOMA-R, QUICKI index. Glucose and insulin resistance summaries including medians and interquartile ranges were also provided by treatment.

Study population

The subject population and disposition were presented in Table S1. A total of 613 subjects were enrolled in the study at 13 centres, of whom 258 were randomised in approximately 1:1 ratio to treatment with rosuvastatin (n=132) or atorvastatin (n=126). Among 355 subjects not randomised, the most common reason not proceeding was a failure to meet the eligibility criteria.

Overall, the two treatment groups were not balanced in terms of several demographic characteristics (gender, age, weight and height).

Table S1 Subject population and disposition (randomised set)

		Rosuvastatin	Atorvastatin	Total
Randomised		132	126	258
Gender	Male	58(43.9%)	38(30.2%)	96(37.2%)
(n and % of subjects)	Femle	74(56.1%)	88(69.8%)	162(62.8%)
Age(years)	Mean (SD)	57.5(10.4)	60.4(9.8)	58.9(10.2)
	Range	29 to 79	33 to 84	29 to 84
Origin	Korean	132(100.0%)	126(100.0%)	258(100.0%)
(n and % of subjects)	Other	0	0	0
Weight(kg)	Mean (SD)	70.8(11.8)	67.8(10.0)	69.3(11.0)
	Range	44 to 108	45 to 97	44 to 108
Height(cm)	Mean (SD)	160.9(8.2)	158.8(8.1)	159.7(8.3)
	Range	140 to 178	142 to 178	140 to 178
Waist(cm)	Mean (SD)	93.3(7.0)	92.5(7.3)	92.9(7.2)
	Range	78 to 110	77 to 125	77 to 125
BMI(kg/m^2)	Mean (SD)	27.2(3.2)	27.0(3.2)	27.1(3.2)
	Range	21.1 to 38.1	20.3 to 38.1	20.3 to 38.1

Efficacy results

Rosuvastatin was significantly more effective than atorvastatin in reducing ratio of ApoB/ApoA1 from baseline (-45.9% vs -38.1%, $p<0.0001$). Similarly, rosuvastatin was significantly more effective than atorvastatin in reducing LDL-C and TC levels (-46.5% vs -39.0 for LDL-C, $p<0.0001$; -34.6% vs -29.4% for TC, $p=0.0003$).

A significantly greater proportion of subjects receiving rosuvastatin reached their LDL-C goal at week 6 than did so receiving atorvastatin (88.2% vs 75.4%, $p=0.0067$).

Table S2 Summary of major efficacy results (ITT analysis set)

		Rosuvastatin N=127	Atorvastatin N=122
Ratio of ApoB/ApoA1	LS mean % change	-45.9	-38.1
		rosuvastatin vs atorvastatin p<0.0001	
Percentage of subjects reaching their LDL-C target goal	n(%)	112(88.2)	92(75.4)
		rosuvastatin vs atorvastatin p=0.0067	
Percentage of subjects reaching their LDL-C and non-HDL goal	n/N(%)	41/52(78.8)	32/48(66.7)
		rosuvastatin vs atorvastatin p=0.1458	
LDL-C	LS mean % change	-46.5	-39.0
		rosuvastatin vs atorvastatin p<0.0001	
TC	LS mean % change	-34.6	-29.4
		rosuvastatin vs atorvastatin p=0.0003	

Safety results

Both study treatments were generally well tolerated, and the incidence of adverse events (AEs), and possibly related AEs, serious AEs, and AEs that led to their permanently discontinuing study treatment were low (Table S3). Only 4 subjects (3.2%) in the atorvastatin treatment group reported a non-fatal treatment-emergent SAE during the course of the study. These SAEs were assessed by investigator as having been unrelated to study medication.

Table S3 Number (%) of subjects who had at least one treatment-emergent adverse event in any category, and total number of adverse events (safety analysis set)

	Rosuvastatin n=129	Atorvastatin n=124
Number of subjets		
Any adverse event	18(14.0%)	18(14.5%)
Possibly related adverse event	8(6.2%)	4(3.2%)
Serious adverse event	0	4(3.2%)
Discontinuation of study treatment due to AEs	4(3.1)	2(1.6%)
Number of adverse events		

Any adverse event	21	23
Possibly related adverse event	9	5
Serious adverse event	0	5
Discontinuation of study treatment due to AEs	6	2