AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Rosuvastatin calcium
Study Code	D3560L00060
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A phase IV, 6-week, randomised, double-blind, multicentre, parallel group, comparative study to evaluate the efficacy of rosuvastatin 5 mg and atorvastatin 10 mg in UK Asian subjects with primary hypercholesterolaemia

SHUKRA - Study of Asian patients with Hypercholesterolaemia in the UK-Rosuvastatin 5 mg versus Atorvastatin 10 mg

Study dates: First patient enrolled: 20 December 2006
Last patient completed: 19 February 2008

Phase of development: Therapeutic use (IV)

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

Publications

None at the time of writing this report.

Objectives

Primary Objective

The primary objective of this UK study was to compare the efficacy of rosuvastatin 5 mg with atorvastatin 10 mg in reducing low-density lipoprotein cholesterol (LDL-C) in Asian subjects with primary hypercholesterolaemia after 6 weeks of treatment.

Secondary Objectives

The secondary objectives of the study were to compare the efficacy of rosuvastatin 5 mg with atorvastatin 10 mg in Asian subjects with primary hypercholesterolaemia by assessing:

1. The percentage of subjects reaching the General Medical Services (GMS) contract target of total cholesterol (TC) <5 mmol/L, after 6 weeks of treatment.

2. The percentage of subjects reaching the Joint British Societies' Guideline (JBS 2) targets of TC <4 mmol/L and LDL-C <2 mmol/L, after 6 weeks of treatment.

3. The percentage of subjects reaching the European (European Atherosclerosis Society, EAS) targets of LDL-C<2.5 or 3.00 mmol/L, depending on risk category, and the combined LDL-C and TC target of LDL-C<2.5 or 3.0 mmol/L and TC<4.5 or 5.0 mmol/L, both depending on risk category.

4. The percentage change from baseline in TC, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-C, apolipoprotein-B (ApoB), apolipoprotein-A1 (ApoA1), LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio and ApoB/ApoA1 ratio after 6 weeks of treatment.

5. The safety and tolerability of treatment with rosuvastatin and atorvastatin during the 6-week treatment period with respect to the incidence and severity of adverse events and abnormal laboratory values.

Study design

This was a randomised, double-blind, comparative, multicentre, parallel group study designed to evaluate the efficacy of rosuvastatin 5 mg and atorvastatin 10 mg in Asian patients.

Patients entered a 6-week dietary run-in period, after which eligible patients (fasting LDL-C level of 3.5-5.7 mmol/L and a TG level of <4.52 mmol/L determined from blood samples taken 10-14 days prior to the 6-week visit) were randomised to receive treatment with either rosuvastatin 5 mg (plus atorvastatin placebo) or atorvastatin 10 mg (plus rosuvastatin placebo) for 6 weeks.

Target patient population and sample size

The target patient population was self described Asian (i.e., first or second generation including origin of India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan, Japan, China, Philippines, Vietnam, Korea, Indonesia and Malaysia), male and female patients, aged 18 years or older with primary hypercholesterolaemia. To enter the dietary run-in period, patients were required to have a fasting LDL-C of 3.5–5.7 mmol/L (statin naïve patients) or 2.6-4.2 mmol/L (in patients who had taken a statin within 4 weeks of Visit 1) and TG <4.52 mmol/L (all patients) determined from blood samples collected at screening (Day 0, Visit 1).

The sample size was determined based on the primary efficacy variable, the percentage change in LDL-C from baseline (week 6, Visit 2) to week 12 (Visit 3). A treatment difference between the 2 medications of 3% was deemed to be clinically significant. Assuming a standard deviation of 14%, to detect a difference of 3% with 80% power, for a 2-sided significance level of 5% (alpha=0.05) requires 343 randomised patients per group. To allow for a withdrawal rate of 10%, it was planned to recruit a total of 762 patients.

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

All study drugs were administered orally, once daily.

Rosuvastatin (as calcium salt, ZD4522) film coated 5 mg tablets, formulation number F12671, batch number TT005X manufactured by iPR Pharmaceuticals Ltd, Puerto Rico.

Atorvastatin (as calcium trihydrate) 10 mg encapsulated tablets, formulation number F12513, PL number 16051/0001, Pfizer Ltd. Tablets were encapsulated by AstraZeneca to ensure blinding.

Placebo to match rosuvastatin film coated tablet, formulation number F12830

Placebo to match atorvastatin encapsulated tablet, formulation number F12545

Duration of treatment

6 weeks

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

- Primary outcome variable: Percentage reduction in LDL-C from baseline (week 6) to week 12

- Secondary outcome variables:

  - The percentage of patients reaching the current GMS target of TC <5 mmol/L, after 6 weeks of treatment

  - The percentage of patients reaching the JBS 2 targets of TC <4 mmol/L and LDL-C <2 mmol/L, after 6 weeks of treatment

  - The percentage of patients reaching the EAS targets of LDL-C <2.5 or 3.0 mmol/L, depending on risk category, and the combined LDL-C and TC target of LDL-C <2.5 or 3.0 mmol/L and TC <4.5 or 5.0 mmol/L, both depending on risk category, after 6 weeks of treatment

  - The percentage change from baseline in TC, HDL-C, TG, non-HDL-C, ApoB, ApoA1, LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio and ApoB/ApoA1 ratio after 6 weeks of treatment.

Criteria for evaluation - safety (main variables)

- Secondary outcome variables:

  - Adverse events (AEs) including overall incidence, serious AEs, discontinuations due to AEs, other significant AEs and causally related AEs

  - Clinical chemistry and haematology laboratory values including number (%) of patients with clinically important laboratory values. These were defined as those values fulfilling any of the following criteria: alanine aminotransferase (ALT) >3 x upper limit of normal (ULN), aspartate aminotransferase (AST) >3 x ULN, bilirubin >3 x ULN, creatine kinase (CK) >5 x ULN or creatinine >177 μmol/L

– Physical examination and vital signs.

Statistical methods

Efficacy

As only 55 of the planned target of 686 patients were randomised, the study did not have the pre-planned power of 80% to meet its primary objective. Hence, no statistical testing was performed on the efficacy data.

The primary and secondary efficacy variables were summarised by standard descriptive statistics using the intention-to-treat (ITT) analysis set, which included all randomised patients.

The percentage changes from baseline to end of treatment for lipids and lipid ratios, derived from the Analysis of Covariance (ANCOVA) model of the percentage change from baseline to end of treatment, with the baseline value included as a covariate and treatment group included as a factor were also summarised descriptively (the least squares mean [LSMEAN] and standard error [SE] of the percentage change in each treatment group, the estimated treatment difference and the associated 95% confidence interval [CI]).

The odds ratio (OR) and 95% confidence interval for the OR, derived from the logistic regression model of the percentage of patients to target, with the baseline lipid (LDL-C and/or TC as appropriate) and treatment group fitted as factors were also summarised. For the analysis of the percentage of patients achieving EAS targets, the LDL-C and/or TC target, as derived according to the patient's risk category, was also included as a factor in the model. The risk category was derived from the patient's baseline LDL-C and TC measurements, cardiovascular disease history, diabetic status, smoking status, baseline blood pressure and demographic information.

Safety

The safety variables were summarised descriptively using the safety analysis set, which included all randomised patients who took at least one dose of study medication.

Patient population

The patient population and disposition are shown in Table S1. One hundred and seventy-five (175) patients were enrolled into the study and 55 patients were randomised to rosuvastatin (30 patients) or atorvastatin (25 patients). The first patient received study drug on 1 February 2007 and the last patient completed the study on 19 February 2008. Forty-nine (89.1%) patients completed the study.

A total of 120 patients were not randomised to treatment, mainly due to incorrect enrolment (104 patients) with patients not meeting the inclusion criterion of fasting LDL-C of 3.5-5.7 mmol/L and TG of <4.52 mmol/L determined from blood samples at the end of the dietary run-in.

As the study was closed early due to inadequate recruitment, it failed to achieve its target sample size with only 23% and 8% of the planned numbers of enrolled and randomised patients respectively.

Table S1 Patient population and disposition

	Number (%) of patients		
	Rosuvastatin 5 mg	**Atorvastatin 10 mg**	**Total**
Patients planned enrolled			762
Patients planned randomised	343	343	686
Disposition			
Patients enrolled [a] (% of planned)			175 (23.0)
Patients randomised	30 (100)	25 (100)	55 (100)
Patients who were not randomised			120
Incorrect enrolment			104
Adverse event			1
Voluntary discontinuation by subject			6
Subject lost to follow up			4
Severe non-compliance			1
Other			4
Patients received treatment	29 (96.7)	25 (100)	54 (98.2)
Patients who completed treatment/study	28 (93.3)	21 (84.0)	49 (89.1)
Patients who discontinued treatment/study	2 (6.7)	4 (16.0)	6 (10.9)
Adverse event	2 (6.7)	0	2 (3.6)
Voluntary discontinuation	0	3 (12.0)	3 (5.5)
Other	0	1 (4.0)	1 (1.8)
Analysis sets			
Patients included in safety analysis set	29 (96.7)	25 (100)	54 (98.2)
Patients included in ITT analysis set	30 (100.0)	25 (100)	55 (100.0)

[a] Informed consent received
[b] Percentages calculated are based on the number of patients randomised
ITT Intention to treat

The patient demographics and baseline characteristics are shown in Table S2. All patients were of South Asian origin, except for 2 patients who were of Asian (Chinese origin). The majority of South Asian patients were of Indian or Pakistani sub group (see Table 2, Section

11). The demographic and baseline characteristics were generally comparable for the 2 treatment groups. However, a higher proportion of patients were randomised to rosuvastatin with a history of cardiovascular disease than to atorvastatin.

Table S2 Demographic and baseline characteristics, ITT analysis set

	Rosuvastatin 5 mg (N=30)	**Atorvastatin 10 mg (N=25)**
Demographic characteristics		
Sex: n (%)		
Male	17 (56.7%)	14 (56.0%)
Female	13 (43.3%)	11 (44.0%)
Age (years)		
N	30	25
Mean (SD)	50.3 (11.3)	53.3 (11.1)
Median	49.0	53.0
Range	26-74	35-74
Origin: n (%)		
Asian	2 (6.7%)	0
South Asian	28 (93.3%)	25 (100.0%)
Baseline patient characteristics: n (%)		
Current smoker	5 (16.7%)	2 (8.0%)
Statin naïve [a]	23 (76.7%)	20 (80.0%)
History of cardiovascular disease	8 (26.7%)	3 (12.0%)
Diabetic (type I or II)	3 (10.0%)	4 (16.0%)
Baseline lipid characteristics: Mean (SD)		
LDL-Cholesterol (mmol/L)	4.29 (0.48)	4.43 (0.56)
Total Cholesterol (mmol/L)	6.49 (0.66)	6.45 (0.61)
HDL-Cholesterol (mmol/L)	1.34 (0.32)	1.27 (0.26)
Triglycerides (mmol/L)	1.89 (0.78)	1.63 (0.64)
EAS LDL-Cholesterol (LDL-C)target: n (%)		
<3.0 mmol/L [b]	19 (63.3%)	18 (72.0%)
<2.5 mmol/L [c]	11 (36.7%)	7 (28.0%)
EAS Total Cholesterol (TC) target: n (%)		
<5.0 mmol/L [b]	19 (63.3%)	18 (72.0%)

	Rosuvastatin 5 mg (N=30)	Atorvastatin 10 mg (N=25)
<4.5 mmol/L [c]	11 (36.7%)	7 (28.0%)

[a] Statin naïve was defined for this study as any patient who had not taken a statin within 4 weeks of enrolment.

[b] For Risk categories:
- Asymptomatic, total risk <5%
- Asymptomatic, total risk ≥5%, baseline LDL-C ≥3 mmol/L or baseline TC ≥5 mmol/L

[c] For Risk categories:
- Symptomatic (Patients were defined as symptomatic if they met at least 1 of the following criteria: history of cardiovascular disease, type II diabetes or diabetes of unknown type, baseline total cholesterol ≥8 mmol/L, baseline LDL-C ≥6 mmol/L, baseline systolic BP ≥180 mmHg, baseline diastolic BP ≥110 mmHg).
- Asymptomatic, total risk ≥5%, baseline LDL-C <3 mmol/L and baseline TC <5 mmol/L

The methods used to calculate the total risk are given in the statistical analysis plan (Appendix 12.1.9)
EAS European Atherosclerosis Society

Summary of efficacy results

Primary variable

The primary variable, the percentage change in LDL-C from baseline to end of treatment (6 weeks) showed a numerically greater reduction in the atorvastatin treatment group (LS mean -36.92) than in the rosuvastatin treatment group (LS mean –33.28; Table S4).

Secondary variables

The percentage of patients reaching the GMS contract target of TC <5 mmol/L, the JBS 2 target of TC<4 mmol/L, the JBS 2 target of LDL-C<2 mmol/L and achieving the EAS LDL-C and TC targets are shown in Table S3.

The proportions of patients achieving their LDL-C targets in the 2 treatment groups were similar, although a numerically higher proportion of patients achieved their TC targets in the atorvastatin treatment group compared with the rosuvastatin treatment group.

Table S3 Number (%) of patients reaching lipid target goals after 6 weeks of treatment, ITT analysis set

Lipid target	Number(%) of patients [a]		Treatment difference	
	Rosuvastatin 5 mg (N=30)	Atorvastatin 10 mg (N=25)	Odds ratio	95% CI
TC <5 mmol/L (GMS contract target)	15 (50.0%)	16 (64.0%)	0.43	[0.12, 1.50]
TC <4 mmol/L (JBS 2 target)	5 (16.7%)	7 (28.0%)	0.44	[0.11, 1.78]
LDL-C <2 mmol/L (JBS 2 target)	4 (13.3%)	3 (12.0%)	0.90	[0.17, 4.83]
EAS LDL-C target met [b]	17 (56.7%)	14 (56.0%)	0.88	[0.18, 4.33]
EAS LDL-C and TC targets met [b, c]	13 (43.3%)	12 (48.0%)	0.73	[0.18, 2.92]

[a] The percentages are based on the total number of patients in the treatment groups for the ITT analysis set and include 3 patients in both treatment groups with missing end of treatment data.
[b] The EAS target for LDL-C is <2.5 or <3.0 mmol/L, dependant on risk category.
[c] The EAS target for TC is <4.5 or <5.0 mmol/L, dependant on risk category.

The percentage changes in lipids and lipid sub-fractions from baseline after 6 weeks of treatment are shown in Table S4.

Table S4 Percentage changes in lipids and lipid sub-fractions from baseline after 6 weeks of treatment, ITT analysis set

Percentage change in lipids	Rosuvastatin 5 mg (N=30)		Atorvastatin 10 mg (N=25)		Treatment difference [a]	
	N	LSMean (SE)[a]	N	LSMean (SE)[a]	LS Mean (SE)	95%CI
LDL-C	27	-33.28 (3.67)	22	-36.92 (4.07)	3.64 (5.52)	[-7.46, 14.74]
TC	27	-23.03 (2.71)	22	-26.88 (3.01)	3.85 (4.05)	[-4.31, 12.00]
HDL-C	27	4.46 (2.40)	22	3.15 (2.66)	1.31 (3.58)	[-5.89, 8.52]
Triglycerides	27	-3.67 (4.66)	22	-14.35 (5.17)	10.67 (7.01)	[-3.44, 24.79]
Non-HDL-C	27	-29.72 (3.42)	22	-34.09 (3.78)	4.37 (5.10)	[-5.90, 14.64]
LDL-C/HDL-C	27	-34.75 (3.92)	22	-38.45 (4.35)	3.70 (5.90)	[-8.17, 15.57]
TC/HDL-C	27	-24.99 (3.04)	22	-28.42 (3.37)	3.43 (4.55)	[-5.73, 12.59]
Non-HDL-C/HDL-C	27	-31.05 (3.85)	22	-35.48 (4.26)	4.44 (5.76)	[-7.15, 16.02]
ApoB	27	-25.96 (3.01)	22	-28.67 (3.34)	2.71 (4.50)	[-6.35, 11.76]
ApoA-1	27	-0.55 (1.83)	22	1.89 (2.04)	-2.44 (2.80)	[-8.07, 3.20]
ApoB/ApoA-1	27	-22.89 (4.01)	22	-28.75 (4.46)	5.86 (6.10)	[-6.42, 18.14]

[a] Least squares mean (LSMean), standard errors (SE), treatment difference and 95% CI obtained from ANCOVA model with treatment as a factor and baseline lipid as a covariate

Summary of safety results

The median overall exposure to rosuvastatin and atorvastatin was 42 days. A summary of AEs in each category is given in Table S5.

The overall incidence of AEs in the 2 treatment groups was similar and none of the AEs reported was unexpected for the study population. One patient, a 66-year-old male treated with rosuvastatin had a non-fatal SAE of cerebrovascular accident, which the investigator considered to be unrelated to the study therapy. Two (6.9%) patients discontinued study treatment with rosuvastatin due to AEs (1 due to the SAE of cerebrovascular accident; 1 due to dizziness). One patient treated with rosuvastatin experienced 2 AEs (fatigue and dizziness) and 2 patients with atorvastatin experienced 4 AEs (tension and libido decreased; thirst and pollakiuria) considered to be related to study therapy.

One patient also discontinued the study due to an AE (hypothyroidism) prior to randomisation.

Table S5 Number (%) of patients who had a treatment emergent adverse event in any category, safety analysis set

	Number (%) of patients [a]	
Category of adverse event	**Rosuvastatin 5 mg (N=29)**	**Atorvastatin 10 mg (N=25)**
Any Adverse Event	11 (37.9%)	10 (40.0%)
Serious adverse events:		
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	1 (3.4%)	0
Discontinuation due to adverse events	2 (6.9%)	0
Causally related AEs	1 (3.4%)	2 (8.0%)

[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 these categories

Dizziness (rosuvastatin 3 patients, 10.3%; atorvastatin 1 patient, 4.0%) and headache (rosuvastatin 1 patient, 3.4%; atorvastatin 2 patients, 8.0%) were the most commonly reported AEs.

Changes in clinical laboratory results were generally small and showed no treatment related trends. One patient in the rosuvastatin treatment group had a clinically important abnormality of raised AST (125 IU/L) during the dietary run-in phase.