AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: CRESTOR™
ACTIVE INGREDIENT: Rosuvastatin

Study No: D1840M00006
A randomised, double-blind, placebo-controlled study to evaluate the transthoracic Doppler echocardiography method as a non-invasive method for coronary function measurements; ability to detect short-term statin effects in patients with increased cardiovascular risk

Developmental phase: Exploratory study
Study Completion Date: Last Subject's last visit 7 May 2009
Date of the Study Report: 17 March 2010

OBJECTIVES

Primary:

- Change in coronary flow reserve (CFR) peak velocity within rosuvastatin group after 1 month of treatment compared to baseline
- Comparison of treatment effects on CFR peak velocities between groups after 1 month of treatment

Secondary:

- Changes in CFR peak velocity within the rosuvastatin group after 3 months compared to baseline and to 1 month
- Changes in other CFR parameters after one month rosuvastatin or placebo treatment; comparisons within groups and between groups
- Changes in plasma lipids, lipoproteins and other cardiovascular biomarkers after 1 month of treatment with rosuvastatin or placebo; comparisons within groups and between groups

TREATMENTS

Rosuvastatin and matching placebo tablets were used as tool compounds for evaluation of the echocardiography method of interest in this study. Dosing: 1 tablet of rosuvastatin or placebo once daily for 1 month (double blind) + 1 tablet rosuvastatin once daily for additional 2 months (open label). Total treatment period with rosuvastatin was 3 months and with placebo 1 month.

Table 1 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number	Expiry date (Use before end of)
Rosuvastatin	film-coated tablets 40 mg (as rosuvastatin calcium 41.6 mg)	IPR Pharmaceuticals Inc. Puerto Rico	H 1935-01-03	H 1935-01-03-01	May 2009
Rosuvastatin PLACEBO	film-coated tablets 40 mg (as rosuvastatin calcium 41.6 mg) PLACEBO	IPR Pharmaceuticals Puerto Rico	H 1942-01-02	H 1942-01-02-01	May 2009

METHODS

Study design:
This was a double-blind, randomised, placebo-controlled 1-month study with parallel groups and with a 2-month open-label extension of the active arm.

Imaging methods – Echocardiography and CFR:
A duplex ultrasound system (Acuson Sequoia 512, Mountainview, CA) equipped with a 4V1C transducer allowing Doppler frequencies of up to 3.5 MHz and pulsed-wave spectral Doppler frequency of 1.75 MHz was used. A modified parasternal long-axis projection was used for Doppler recording of the blood flow velocity in the mid or distal part of the left anterior descending coronary artery (LAD). After blood flow in the anterograde direction was interrogated, baseline LAD flow velocities were recorded with an angle between the LAD course and the Doppler beam typically below 45°. Thereafter, 140 µg/kg/min adenosine (ITEM Development, Stocksund, Sweden) was administered intravenously to cause coronary hyperaemia, and the peak hyperaemic flow velocity was recorded in the same vascular segment during unforced post-exhalation apnoea (or shallow respirations if no variation in peak flow velocity was observed) after 1 minute and between 2-3 minutes of adenosine. Five sonographers were involved in the study.

Efficacy biomarkers:
Plasma lipids, lipoproteins and other cardiovascular biomarkers.

Statistical methods:
Changes in CFR parameters were analysed using a linear model (ANCOVA) with within subject change as the response, and baseline value and treatment as explanatory variables, with the results presented using confidence intervals (CI) and p-values.
Changes in plasma lipids, lipoproteins and other cardiovascular biomarkers from baseline to 1 month were analysed on a relative scale using geometric mean ratios based on a linear (ANCOVA) model with log-transformed values as the response variable, and baseline value, treatment, and visit as explanatory variables.
The results concerning the secondary objectives are presented in terms of point estimates, standard deviations and 95% CI, and no adjustments for multiplicity were done.

RESULTS

Subject population:
Study population consisted of subjects with carotid and/or femoral atherosclerotic plaques and dyslipidaemia. One-hundred and forty three (143) subjects were enrolled and

73 were randomised (37 to rosuvastatin and 36 to placebo) out of the planned total of 80 subjects. During the 1 month double-blind period, 3 subjects were prematurely discontinued, 1 on active treatment and 2 on placebo.

Table 2 Baseline characteristics

	Unit	Rosuvastatin n=37	Placebo n=36
Age	Years	70 (0.8)	70 (1.7)
Sex	M / F	16 / 21	24 / 12
Body weight	kg	79.8 (16.3)	78.8 (16.7)
Waist/hip ratio	ratio	1 (0.1)	0.9 (0.1)
LDL-C	mmol/L	3.7 (0.6)	3.6 (0.8)
Triglycerides	mmol/L	1.4 (0.7)	1.2 (0.5)
ApoB/ApoA1	ratio	0.8 (0.2)	0.8 (0.2)
hsCRP	mg/L	4.5 (10.9)	2.7 (3.6)
FPG (fasting plasma glucose)	mmol/L	5.2 (0.8)	5.4 (1)
CFR peak velocity	ratio	3.1 (0.9)	3.1 (0.9)

Frequencies and mean (SD) values are presented in the table

Summary of efficacy results:

Primary objectives:

- The mean change in CFR peak velocity within rosuvastatin group after 1 month was 0.23 (95% CI: -0.03 to 0.48; p value=0.079). The mean difference in change in CFR peak velocity after 1 month of rosuvastatin treatment compared to placebo was 0.07 (95% Confidence Interval (CI)): -0.30 to 0.44; p value=0.700).

Secondary objectives:

- In the rosuvastatin group, the CFR peak velocity was increased at 3 months compared to baseline, but no significant difference was seen between 3 months and 1 month.
- No significant changes were seen either within or between groups in other CFR parameters (maximum CFR velocity (V_{max}) or Velocity Time Interval (VTI)) at the 1 month assessment versus baseline.
- Changes in the cardiovascular plasma biomarkers within and between treatment groups after 1 month of treatment:
  - Total cholesterol, LDL-C, ApoB, hsCRP and triglycerides decreased after rosuvastatin compared to placebo. HDL-C and ApoA1 increased in both groups.
  - There were no significant effects on other inflammatory markers

Summary of safety results:

There were no serious adverse events (SAEs) after randomisation. Rosuvastatin was well tolerated and the reported AEs do not change the known safety profile of this drug.