AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: CRESTOR™
ACTIVE INGREDIENT: Rosuvastatin

Study No: D4411M00010
Exploratory study of new imaging biomarkers for measurement of carotid plaque inflammation

Developmental phase: Exploratory study

Study Completion Date: Last Subject's last visit 11 June 2009

Date of the Study Report: 29 April 2010

OBJECTIVES

Primary:

- Comparison between the active and the placebo group regarding changes in MRI contrast enhancement in terms of the transfer constant (K^{trans}) for the carotid region

Secondary:

- Comparison between the active and the placebo group regarding changes in MRI contrast enhancement measured as fractional plasma volume (V_p) and changes in ^{18}FDG uptake in terms of standardised uptake value (SUV)*, respectively
- Change in carotid MRI contrast enhancement in terms of K^{trans} and V_p after 3 months within group compared to baseline
- Change in ^{18}FDG uptake in terms of SUV* within group after 3 months compared to baseline in the carotid and aorta regions, respectively

* SUV, as defined in the study protocol, was replaced by maximum Tissue-to-Background Ratio (TBR) in the analyses, prior to unblinding of the data. TBR is the SUV value normalized to the activity of blood in each patient

TREATMENTS

The study medication used in this study consisted of 40 mg rosuvastatin tablets and the matching placebo tablets. Rosuvastatin/placebo was administrated orally once daily in the morning for 3 months.

Table 1 Identities of the Investigational Products

Investigational Product	Dosage form and strength	Manufacturer	Formulation number	Batch number	Expiry date (Use before end of)
Rosuvastatin	Tablet 40 mg	AstraZeneca, Canovanas, Puerto Rico	H 1935-01-02	H 1935-01-02-01	2010-01-01
Placebo to 40 mg	Tablet	AstraZeneca, Canovanas, Puerto Rico	H 1942-01-01	H 1942-01-01-01	2010-01-01

METHODS

Study design:

This was a single centre, double-blind, placebo-controlled, randomised, parallel-group 3-month study evaluating different imaging techniques for measurement of atherosclerosis and inflammatory activity in carotid arteries after statin treatment.

The baseline MRI measurement was performed at a separate visit during the enrolment period and the baseline PET/CT scan was performed at the randomisation visit. Three (3) months after randomisation the procedures were repeated.

Imaging methods:

1. MRI K^{trans} and V_p plaque
   MRI scanning for plaque composition was performed in the left and the right carotid region, centred at the bifurcation and extending approximately 20 mm in both cranial and caudal directions. The scan was centred on the index side. Vessel permeability and blood volume were assessed using dynamic contrast-enhanced MRI with kinetic modelling, calculating fractional plasma volume (V_p) and a transfer constant (K^{trans}).

2. PET/CT - max TBR
   Subjects were imaged, after a fast of at least 4 hours. Subjects were injected intravenously in an antecubital fossa vein with 2.7 MBq/kg ^{18}FDG after which they rested. The PET/CT acquisition was performed 90 minutes after the injection of ^{18}FDG. PET images were acquired from the carotid and aortic regions in two separate stations. Arterial FDG uptake was quantified by drawing a region of interest (ROI) around the artery on every slice. Maximum TBR was calculated by dividing the max SUV in the plaque by the SUV measured in a large vein.

Statistical methods:

Primary and secondary objectives were primarily analyzed using an ANCOVA model with change from baseline to 3 months as response variable, the baseline value as covariate and the treatment group as factor. If model assumptions for ANCOVA analysis were not fulfilled, a pre-specified alternative analysis approach, Mann-Whitney's U-test, was used for comparison of treatment effect.

RESULTS

Subject population

The study population consisted of non-diabetic subjects with asymptomatic carotid atherosclerosis, with no severe hypercholesterolemia and without history of cardiovascular disease. A total of 138 subjects were enrolled and 73 subjects were randomised. No subjects discontinued the study after randomisation.

Table 2 Baseline characteristics

	Active (n=36)	Placebo (n=37)
Age (years)[a]	65.3 (65-67)	65.3 (65-67)
Sex (male)[b]	36	37
BMI (kg/m^2)	25.6 (2.76)	26.1 (3.76)
SBP (mmHg)	143.0 (16.25)	143.7 (18.21)
DBP (mmHg)	81.8 (8.19)	80.7 (8.24)
C-reactive protein (mg/L)[c]	1.5 (0.2-12.0)	1.8 (0.2-11.0)
LDL cholesterol (mmol/L)	3.6 (0.63)	3.6 (0.79)

Mean (SD) except for: [a] mean (range), [b] number, and [c] median (range)

Summary of efficacy results

At the 3-month assessment, all 73 randomised subjects were evaluated for the MRI variables and 58 subjects for the PET/CT max TBR. According to the study protocol subjects with a negative PET/CT scan at baseline were excluded from the follow-up PET/CT scan in order to avoid unnecessary exposure to radiation.

Primary objective:

- No change in MRI contrast enhancement, K^{trans} plaque, could be seen for rosuvastatin group compared to placebo group after 3 months of treatment, -0.0013 (95% CI: -0.0114 to 0.0089).

Secondary objectives:

- No change in MRI V_p plaque could be seen for rosuvastatin compared to placebo after 3 months of treatment, -0.0027 (95% CI: -0.0235 to 0.0182).
  No change in max TBR could be seen for rosuvastatin compared to placebo after 3 months of treatment in the baseline adjusted ANCOVA analysis. However the model assumptions for the ANCOVA analysis of max TBR were not fully fulfilled and the pre-specified alternative analysis, a Mann-Whitney's U-test, indicated a significant decrease in max TBR at 3 months for rosuvastatin compared to placebo ($p = 0.024$).
- There were no significant changes in K^{trans} plaque at 3 months within any of the treatment groups; 0.0047 (95% CI: -0.0025 to 0.0119) for the rosuvastatin group and 0.0060 (95% CI: -0.0011 to 0.0131) for the placebo group.
  There were no significant changes in V_p plaque at 3 months within any of the treatment groups; 0.0003 (95% CI: -0.0145 to 0.0151) for the rosuvastatin group and -0.0030 (95% CI: -0.0116 to 0.0175) for the placebo group

- A median change in max TBR of -0.200 (range: -1.060 to 0.880) was observed in the rosuvastatin group compared to 0.115 (range: -1.280 to 1.470) in the placebo group.

Safety results
No serious AEs (SAEs) were reported in this study and no randomised subjects were discontinued due to AEs. Rosuvastatin was well tolerated and the reported AEs do not change the known safety profile of this drug.

List of abbreviations:

AE = adverse event

ANCOVA = analysis of covariance

BMI = body mass index

CI = confidence interval

CT = computerized tomography

DBP = diastolic blood pressure

FGD = fluorodeoxyglucose

K^{trans} = transfer constant

LDL = low density lipoprotein

MRI = magnetic resonance imaging

PET = positron emission tomography

SAE = serious adverse event

SBP = systolic blood pressure

SUV = standardised uptake value

TBR = tissue-to-background ratio

V_p = fractional plasma volume