AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Crestor
ACTIVE INGREDIENT: Rosuvastatin

Study No: D3560L00079
Open-labelled, single arm, Phase IV clinical study to evaluate the impact of rosuvastatin on lipid levels in patients with metabolic syndrome

Developmental Phase: Therapeutic confirmatory (IV)
Study Completion Date: 25 March 2010
Date of Report: 07 March 2011

OBJECTIVES:

Primary objectives:

To evaluate the efficacy of rosuvastatin therapy on plasma lipid profile (LDL, HDL and total cholesterol, triglyceride) in patients with metabolic syndrome.

Secondary objectives:

- To evaluate the efficacy of rosuvastatin therapy on the following parameters:
    - Small dense LDL and subfractions of HDL
    - Inflammation markers (IL 1, 6, 8 , 10, TNF, hsCRP)
    - Percentage of patients reaching treatment goals at the end of treatment
- To assess safety profile of rosuvastatin therapy in the study population.

Compliance to dietary limitations and life style modifications were also questioned.

METHODS:

Study design

This study was designed as a prospective, single-arm, open-labelled clinical study to investigate the impact of rosuvastatin on lipid profile in patients with metabolic syndrome.

The study duration was planned to be 11 months (8 months for patient enrolment and 3 months for drug therapy). However, patient recruitment was prolonged for 3 months in order to reach the targeted patient number.

A total of 5 visits were performed: Screening visit (visit 1, -2. week) and initial visit (visit 2, 0. week) before and at 6. (visit 3), 9. (visit 4) and 12. (visit 5) weeks after the initiation

of rosuvastatin treatment. All patients fulfilling the selection criteria were started rosuvastatin treatment at a dose of 10 mg at visit 2, and the dose was doubled at 6 weeks (visit 3) to 20 mg.

Target subject population and sample size

Patients with metabolic syndrome who met the following inclusion and exclusion criteria were enrolled in the study:

Inclusion criteria:

Patients who meet all the following criteria will be included in the study:

- Aged 18 – 69 years,
- Both males and females,
- With a diagnosis of "Metabolic Syndrome" according to NCEP ATP III criteria,
- LDL-Cholesterol >130 mg/dl,
- HDL-Cholesterol<40 mg/dl in males and <50 mg/dl in females,
- Triglycerides <400 mg/dl,
- Agreed to give Written Informed Consent

Exclusion criteria:

Patients who meet any of the following exclusion criteria will be excluded from the study:

- Concomitant coronary artery disease (Coronary artery disease is defined as having unstable angina, angina pectoris with an evidence of MI, hospitalization due to coronary revascularization or >50% stenosis in one or more than one of the major epicardial coronary arteries or history of MI.)
- Currently under statin therapy or previously treated with statins within the last 6 months
- Uncontrolled hypertension
- Homozygous familial hypercholesterolemia
- Uncontrolled hypothyroidism (TSH≥ 1.5xULN)
- History of renal failure or serum creatinine >176μmol/L (2.0mg/dL)
- History of myocardial infarction
- Abnormal liver function tests
- History of severe arrhythmia
- Heart failure
- History of syncope
- History of malignancy (unless a documented disease free period exceeding 5-years is present) with the exception of basal cell or squamous cell carcinoma of the skin. Women with a history of cervical dysplasia would be permitted to enter the study provided they had 3 consecutive clear Papanicolaou (Pap) smears.

- History of statin induced myopathy or serious hypersensitivity reaction to other HMG CoA reductase inhibitors (statins) including rosuvastatin
- Current active liver disease (ALT/SGPT >2xULN or severe hepatic impairment *(to protect patient safety as directed on the labels of currently approved statins)*
- Unexplained creatine kinase (CK≥ 3xULN) *(To protect patient safety)*
- Use of lipid lowering drugs other than statins in the previous 3 months
- History of alcohol or drug abuse within the last 5 years *(this may affect compliance)*
- Pregnant women, women who are breast feeding, and women of childbearing potential who are not using chemical or mechanical contraception or have a positive serum pregnancy test (a serumβ-human chorionic gonadotrophin [β-HCG] analysis)
- Concomitant medications with warfarin, cyclosporin, gemfibrozil, antacids.
- Participation in another investigational drug study less than 4 weeks before enrolment in the study, or according to subjects local ethics committee requirements where a larger period is stipulated *(to avoid potential misinterpretation of overlapping adverse events)*

A sample size of 100 were estimated to achieve 80% power to detect a difference of 10% between baseline and after treatment lipid/marker levels with the assumption that standard deviation is 33% of mean and with a significance level (type 1 error) of 0.05 and %20 drop out rate, using a two-sided hypothesis

Investigational product and comparator(s)

The study drug was rosuvastatin. The initial dose of rosuvastatin (Crestor 10 mg tablet) was 10 mg/day. After the first 6 weeks on 10 mg/day, rosuvastatin dose was doubled to 20 mg. There was no comparator drug in this study

Duration of treatment

The treatment period lasted for 12 weeks (3 months).

Variables

Efficacy

- Change of LDL-cholesterol levels from baseline after 3 months of rosuvastatin treatment
- Change of HDL-cholesterol levels from baseline after 3 months of rosuvastatin treatment
- Change of IL 1, 6, 8, 10, TNF, and hs-CRP levels from baseline after 3 months of rosuvastatin treatment
- Change of sdLDL and HDL subfraction levels from baseline after 3 months of rosuvastatin treatment
- Percentage of patients reaching treatment goals at the end of 6 weeks and 12 weeks of treatment

Safety

- Abnormal physical examination findings

- Adverse events
- Abnormal laboratory findings (clinical chemistry, hematology)
- Abnormal vital signs

Statistical Methods

Patient characteristics were summarized using descriptive statistics and expressed as mean, standard deviation, median, minimum and maximum values for continuous variables; and as numbers and percentages for categorical variables. Subsequent measurements of continuous primary variables that show normal distribution patterns were compared by paired t-test, while variables with non-normal distribution were analyzed by Wilcoxon test. ANOVA for repeated measures were used to analyze the change in various dependent variables in time. Subgroup analysis were performed using parametric or non-parametric tests depending on the variable. Analysis of efficacy outcome variables were also performed using 'last observational carried forward' technique and compared with results of intent-to-treat population.

In addition to standard efficacy analysis; percentage of patients at whom treatment goal achieved were also calculated regarding time. Target levels were set as follows:

- LDL-cholesterol <100
- HDL-colesterol: kadında >50; erkekte >40
- Non-HDL-cholesterol (total cholesterol – HDL-cholesterol): <130

The analysis of secondary objectives regarding measurement times (changing in small dense LDL and subfractions of HDL and inflammation markers) were evaluated either by ANOVA for repeated measures or Friedman variance analysis according to the distribution pattern (normal or non-normal) of the variables. Safety analysis included summaries of the adverse event rates and listings and frequency tables of adverse events.

RESULTS:

Subject population

Patient flow, demographic characteristics and analysis sets are shown in Table S1.

Table S1. Patient flow

	n	**Percentage**
Screened (Visit 1)	161	100.0
Enrolled	97	60.3
- Visit 2	97	100.0
- Visit 3	85	87.6
- Visit 4	76	78.4
- Visit 5	81	83.5
Completed	74	46.0
Discontinued	23	14.3
- Adverse event	9	

	n	Percentage
- ICF withdrawal*	9	
- Lost-to-follow-up	4	
- Protocol violation**	1	

*Two patients who withdrew their consent because of AEs are included in this group.
**Not fulfilling patient selection criteria.

Demographic features and clinical background

Table S2 Demographic and baseline characteristics of the full data set

	Mean (SD)	Median (Min-max)
Age (year)	50.9 (9.5)	52 (19-69)
Gender	**Sayı**	**%**
Female	57	58.8
Male	40	41.2
Concomitant disease other than hyperlipidemia and metabolic syndrome	**n**	**Percentage**
No	40	41.2
Yes	57[a]	58.8
Vital ve antropometric findings	**Mean (SD)**	**Median (min-max)**
Pulse (beat/min)	77.6 (9.6)	77 (52-110)
Systolic blood pressure (mmHg)	141.9 (16.5)	140 (102-195)
Diastolic blood pressure (mmHg)	90.4 (10.1)	90 (60-110)
Body weight (kg)	89.5 (15.4)	86 (60-152)
Waist circumference (cm)	106.4 (11.7)	104 (85-151)

[a]A total of 84 concomitant diseases in 57 patients.

Summary of efficacy results

Primary efficacy variables

Lipid levels measured at all study visits are given at Table S3. When compared to the basal values, rosuvastatin treatment resulted in significant increase in HDL-cholesterol, and decrease in LDL-cholesterol, total cholesterol, non-HDL-cholesterol ve trigliceride levels ($p<0.001$).

Table S3. Effect of rosuvastatin on lipid profile[a]

	Basal[b]	Visit 3 (6. week)	Visit 4 (9. week)	Visit 5 (12. week)	LOCF	Basal-Visit 5 (percent change)	Basal-LOCF percent change)
	Mean (standard deviation)						
LDL-cholesterol (mg/dL)	165.5 (32.0)	91.8 (38.5)*	89.5 (40.4)*	89.0 (40.5)*	98.3 (44.8)*	- 46.5 (25.2)	- 40.2 (26.4)
HDL-cholesterol (mg/dL)	39.5 (6.5)	44.2 (10.2)*	43.5 (9.7)*	44.0 (10.8)*	43.4 (9.8)*	+ 10.3 (16.4)	+ (9.3) 15.2
Total cholesterol (mg/dL)	236.5 (38.2)	159.8 (44.4)*	154.8 (42.6)*	157.1 (44.5)*	166.2 (47.7)*	- 34.1 (17.7)	- 29.4 (19.2)
Non-HDL-cholesterol (mg/dL)	197.0 (38.0)	116 (46.0)*	111.0 (43.0)*	113.0 (45.0)*	123.0 (48.0)*	- 43.0 (21.0)	- 37.0 (23.0)
Triglyceride (mg/dL)	195.1 (65.3)	153.1 (76.8)*	143.0 (67.3)*	150.2 (63.5)*	154.7 (69.3)*	- 21.0 (30.5)	- 18.3 (30.1)

[a]Number of patients attended to the follow-up visits was varying. The minimum and maximum numbers of patients included in the analysis for each lipid parameter were as follows: LDL-cholesterol: 65-97, HDL-cholesterol, total cholesterol , trygliseride and non-HDL-cholesterol: 66-97.
[b]Mean of screening visit (visit 1) and initial visit (visit 2) measurements
*$p<0.001$ vs basal values; Friedman and Wilcoxon tests
LOCF: last observation carried forward.

Secondary efficacy variables

sdLDL subtypes and HDL fractions (Table S4)

When compated to the initial values, rosuvastatin resulted in significant decrease in LDL-3 and LDL-4 subtypes at 6. (visit 3) and 12. (visit 5) weeks of treatment and for LOCF values ($p<0.001$; for each). Decrease in LDL-5 levels compared to initial visit was significant at the 6. Week pf the treatment ($p<0.01$) and for LOCF values ($p<0.05$) but could not reach the level of significance at visit 5. No significant change in LDL-7 levels under rosuvastatin treatment was observed.

Regarding HDL fractions, there was a significant increase in only large-HDL at the 12. week (visit 5 $p<0.01$) and for LOCF values ($p<0.01$).

Table S4. Effect of rosuvastatin on LDL subtypes and HDL fractions[a]

	Visit 2 (initial)	Visit 3 (6. week)	Visit 5 (12. week)	LOCF	Basal-Visit 5 (percent change)	Basal-LOCF (percent change)
	Mean (standard deviation)				Median (min; max)	
LDL subtype						
LDL 3 (mg/dL)	15.5 (9.5)	8.2 (6.5)*	8.2 (7.5)*	8.8 (7.9)*	-51 (-100;2200)	-50 (-100;2200)
LDL 4 (mg/dL)	7.9 (9.6)	3.0 (4.7)*	3.3 (4.6)*	3.5 (4.8)*	-46 (-100;1400)	-44 (-100;1400)

	Visit 2 (initial)	Visit 3 (6. week)	Visit 5 (12. week)	LOCF	Basal-Visit 5 (percent change)	Basal-LOCF (percent change)
LDL 5 (mg/dL)	2.7 (7.1)	0.8 (2.1)$^{+}$	1.5 (3.8)	1.3 (3.5)^{q}	0 (-100;2000)	0 (-100;2000)
LDL 6 (mg/dL)	0.5 (2.6)	0.0 (0.1)	0.4 (1.7)	0.3 (1.5)	0 (-100;100)	0 (-100;100)
LDL 7 (mg/dL)	0.5 (3.0)	0.0 (0.0)	0.7 (5.0)	0.8 (5.3)	0 (-100;200)	0 (-100;100)
HDL fraction						
Large (mg/dL)	15.0 (6.4)	15.4 (8.9)	16.3 (7.2)^{q}	17.6 (7.6)$^{+}$	12 (-95;300)	8 (-59;300)
Intermediate (mg/dL)	18.9 (5.7)	20.5 (6.7)	20.4 (5.8)	19.9 (6.1)	6 (-67;1100)	5 (-67;1100)
Small (mg/dL)	6.2 (4.2)	7.3 (4.9)	7.0 (4.4)	6.6 (4.6)	-9 (-100;800)	0 (-100;800)

[a]Number of patients attended to the follow-up visits was varying. The minimum and maximum numbers of patients included in the analysis for each lipid parameter were as follows: LDL subtypes: 72-90; HDL fractions: 58-83.
^{q}p<0.05; $^{+}$p<0.01ve *p<0.001; vs initial visit measurement. Friedman and Wilcoxon tests.
LOCF: last observation carried forward.

IL-1, IL-6, IL-8, IL-10, TNF, and hsCRP (Table S5)

There was no significant change in IL-1, IL-6 ve IL-8 levels with rosuvastatin treatment. IL-10 level was higher compared to the initial measurement at 12. Week, but p value could only reach 0.059. TNF was significantly higher for LOCF calculation compared to the initial measurement (p=0.004); and LOCF value of hs-CRP was significantly lower than the initial (p=0.002).

Table S5. Effect of rosuvastatin on inflammation markers

	Visit 2 (initial; N=97)	Visit 3 (6. week; N=85)	Visit 5 (12. week; N=81)	LOCF (N=97)	Basal-Visit 5 (percent change)	Basal-LOCF (percent change)
	Mean (standard deviation)				Median (min; max)	
IL-1 (pg/mL)	4.1 (2.3)	4.1 (2.2)	4.0 (2.4)	4.1 (2.2)	0 (-100;20)	0 (-100;500)
IL-6 (pg/mL)	2.6 (2.1)	2.5 (1.9)	2.6 (2.3)	2.8 (2.4)	0 (-100;230)	0 (-100;475)
IL-8 (pg/mL)	10.7 (5.1)	14.5 (5.4)	12.9 (14.4)	12.7 (13.3)	2 (-100;939)	0 (-100;939)
IL-10 (pg/mL)	4.2 (2.1)	4.1 (2.0)	4.8 (4.2)^{q}	4.8 (3.9) ^{q}	0 (-100;600)	0 (-100;600)
TNF (pg/mL)	10.8 (5.3)	11.9 (7.3)	14.1 (10.1)	12.9 (9.2)$^{+}$	8 (-70;746)	4 (-70;746)
hs-CRP[b] (mg/dL)	8.3 (7.2)	6.8 (4.7)*	--	6.7 (5.6)$^{+}$	--	--

[a]Number of patients attended to the follow-up visits was varying. The minimum and maximum numbers of patients included in the analysis for each lipid parameter were as follows: IL-1: 61-79; IL-6: 62-79; IL-8: 34-78; IL-10: 64-79; TNF: 45-60; hsCRP: 43-79.
[b]Number of patient whose hs-CRP levels could have been measured at visit 5 was only 4; therefore these measurments were not included in the analysis.
^{q}p=0.059; *p=0.002; $^{+}$p=0.004, vs initial measurements. Friedman and Wilcoxon tests.
LOCF: last observation carried forward.

Achivement to target levels

The rate of patients who reached the target levels for LDL-cholesterol and non-HDL cholesterol after 12 weeks of rosuvastation treatment was 73.8 ve 77.3%, respectively, and for HDL-cholesterol 59.1% (Table S6).

Table S6. Number of patients who reached the target levels with rosuvastatin treatment

	Patients who reached the target levels at Visit 5 (week 12) (n (percent))*
LDL-cholesterol	48/65 (73.8)
HDL-cholesterol	39/66 (59.1)
Non-HDL-cholesterol	51/66 (77.3)

***Target level: LDL-cholesterol: <100 mg/dL; HDL-cholesterol: males >40 mg/dL, females >50 mg/dL; non-HDL-cholesterol: <130 mg/dL.

Summary of safety results

Advers events (AEs) are summarized at Table S7. A total of 29 AEs were observed in 24 patients. No serious AE (SAE) was reported. Nine patients discontinued before completion due to AEs (DAEs).

Table S7 Number (%) of patients who had a serious adverse event or event leading to study discontinuation (safety analysis set)

	Number of patients in each category of AE[a]	
AE category	**n**	**percent**
Any AE	24	24.7
SAE	0	0
DAE	9	9.3
Other important AE	0	0
	Total number of AEs	
AE	29	
SAE	0	
DAE	9	

[a] Subjects with events in more than 1 category are counted once in each of those categories.