AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Rosuvastatin
Study Code	DM-CRESTOR-0003
Edition Number	1
Date	2-Dec-2011

Effectiveness of rosuvastatin versus the fixed dose combination of ezetimibe/simvastatin to reduce cholesterol levels in outpatients in a naturalistic environment: A retrospective study

Study dates:	First subject enrolled: 3-april-2009 Last subject last visit: 27-december-2010
Phase of development:	Therapeutic use (IV)
International Co-ordinating Investigator:	Not applicable

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 and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the effectiveness of rosuvastatin (RSV) versus ezetimibe/simvastatin (E/S) to bring outpatients to their ATP III cholesterol goals (2001) in a naturalistic environment.	Percentage of patients who achieved NCEP ATP III goal (2001)	
Secondary	**Secondary**	
1. To compare the effectiveness of RSV versus E/S to:		
(a) Achieve ATP III cholesterol goals with the more strict criteria from 2004 in a naturalistic setting Grundy SM et al 2004.	Percentage of patients who achieved NCEP ATP III goal (2004)	
(b) Changes in the atherogenic lipids profile (Total Cholesterol(TC); Low Density Lipoprotein Cholesterol(LDL-C); High Density Lipoprotein Cholesterol(HDL-C); Triglycerides(TGs); percentage of reduction or increase.	Percent and mean change of TC, LDL-C, HDL-C and TGs.	
(c) Changes in the clinical chemistry laboratory parameters such as Glucose, HbA1c, Creatinine, Urea, TGO, TGP, GGT, TSH, CK, Cholesterol No- HDL.	Mean change of the clinical chemistry laboratory parameters: Glucose, HbA1c, Creatinine, Urea, TGO, TGP, GGT, TSH, CK, Cholesterol No- HDL.	
2. To demonstrate that RSV is a more cost-effective therapy than E/S in patients with dislipidemias in a naturalistic environment in Mexico.	Average treatment cost, Cost per 1% LDL-C decrease , cost per patient to achieve NCEP ATP III goal 2001 , cost per patient to achieve NCEP ATP III goal 2004 , Incremental Cost-Effectiveness Ratio(ICER) for NCEP ATP III goal 2001, ICER for NCEP ATP III goal 2004, and the cost-effectiveness acceptability curve (CEAC)	

Study design

This was a clinical, retrospective file review, parallel groups, comparative, national, multicentre, phase IV study and transversal analysis to evaluate the effectiveness of RSV versus E/S in outpatients with dislipidemia in a naturalistic environment.

Target subject population and sample size

From January 2004 to December 2010, outpatient medical records in 15 Hospitals and clinics in Mexico were reviewed to identify patients according to the following criteria: patients who had an established dyslipidemia diagnosis with no dyslipidemic treatment in the previous three months; serum lipid measurements (TC,LDL-C,HDL-C and TG) before receiving drug therapy with either oral RSV once daily, or oral E/S once daily; no other concomitant lipid-lowering treatment such as: fibrates, nicotinic acid, etc. had been administered; and lipid levels for at least 8 weeks (± 7 days) of treatment had been recorded.

The study sample included 402 clinical files, to achieve an 80% power and an alpha of 0.05%; assuming a 10% of non evaluable clinical files, we planned to ended up with 362 evaluable clinical files. A total of 15 sites from all over Mexico participated in the study, each of them participated with about 30 clinical files.

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

The details of the investigational products are given in Table S2.

Because of the retrospective nature of the study design, then formulation number and batch number of the investigational products are unknown.

Table S2 Details of investigational product and any other study treatments

Investigational product	Route of administration	Dosage form	Dosing schedule	Manufacturer
RSV	Oral	Tablet	One tablet per day	AstraZeneca
E/S	Oral	Tablet	One tablet per day	Unknown

The doses of the study treatments are as follows. In all cases the dosing schedule was one tablet per day. Doses for RSV: 5 mg, 10 mg, and 20 mg. Doses for E/S: 5/5 mg, 10/10 mg, 10/20 mg, and 20/40 mg

Duration of treatment

The study treatments were administered for at least 8 weeks (± 7 days).

Statistical methods

The primary efficacy end point (percentage of patients who achieved NCEP ATP III LDL-C cholesterol goals (2001) at follow up) was assessed using a univariate multiple logistic regression model of that endpoint, with the treatment group as a fixed effect and baseline LDL-C level, age, gender and CHD risk level as covariates. The main secondary efficacy end

point (percentage of patients who achieved NCEP ATP III LDL-C cholesterol goals (2004) at follow up) was assessed using the same statistical analysis used for the Primary Efficacy End Point. All other secondary efficacy end points (Percentage and mean change of lipid parameters (LDL-C, HDL-C,TC and TG) from baseline to week 8 of treatment; and mean change in other laboratory parameters) were assessed using an analysis of covariance (ANCOVA) model of that endpoint, with the treatment group as a fixed effect and baseline LDL-C level, age, gender and CHD risk level as covariates. Within the framework of the ANCOVA model, point estimates for the mean change and Least square mean within each treatment group were calculated. The analyses of safety and tolerability endpoints were summarized by descriptive statistics or frequency tables. There were no hypotheses proposed a priori for these safety endpoints.

The cost and cost-effectiveness analysis was conducted from an institutional perspective using drug costs only, and using the exchange rate from August 2011 of 12.2424 Mexican pesos/US dollar (www.bangico.org.mx).

Subject population

Only those patients that satisfied all inclusion/exclusion criteria were considered valid to be included in the study population. Thus, there is only one data set of 268 valid patients in the study population. This data set was regarded as the primary analysis set and was used for all safety and efficacy analyses. However, all outputs for the cost-effectiveness analysis were generated on the basis of the 11-week analysis set. The 11-week analysis set was defined as those patients for which the treatment duration was less than or equal than 105 days. The rational for the definition of the 11-week analysis set was to include as many patients as possible from the primary analysis set, in such a way that the average treatment duration within groups were very similar for the two treatment groups, and also that the average treatment duration within groups were similar to the recommended treatment duration (8-12 weeks) to obtain significant reductions in the lipid profile. The total number of patients in the 11-week analysis set was 87 and the average treatment duration for RSV and E/S were 75.6 days and 76.3 days, respectively. That is, the average treatment duration are very similar for both treatment groups and approximately equal to 11 weeks.

Out of the 268 valid patients, 150 patients (56%) received Rosuvastatin (RSV) and 118 patients (44%) received a combination of ezetimibe and simvastatin (E/S). Patients from both treatment groups (RSV and E/S) had similar baseline characteristics. The majority of the patients were Hispanics, mean age of 59 years, about 60% were female. Physically, on average they were a little over 160 cm high, weighted about 75 kg and have about 96 cm waist. Their mean vital signs were about 130 mmHg SBP and 80 mmHg DBP, with a mean pulse of 73 bpm. The most frequent baseline diagnoses were check-up (a little over 20%), followed by arterial hypertension and diabetes mellitus (a little over 10%), isquemic cardiopathy and dyslipidemia. About 90% of the patients had a significant medical history at baseline. Close to 50% had arterial hypertension and close to 30% had diabetes mellitus. The only statistically significant different baseline characteristic between treatment groups was the percentage of patients who had isquemic cardiopathy history, being this percentage greater among the RSV group (17%) compared to the E/S group (7%) p-value = 0.0100.

Summary of efficacy results

Patients from both treatment groups benefit from their treatment. Regarding treatment efficacy, about 80% of the patients from each treatment group achieved NCEP ATP III LDL-C cholesterol goal (2001) and about 60% achieved a stricter NCEP ATP III LDL-C cholesterol goal (2004). Patients experienced a mean decrease after 8-weeks of treatment compared to their baseline values for all the evaluated lipids parameters (except for HDL cholesterol). In particular, LDL cholesterol important decrease (about 60 mg/dL) and HDL-C increase (although only slightly, about 2.5 mg/dL) are positive treatment effects. No statistically significant differences between treatment groups were identified regarding clinical efficacy variables, however, the average treatment cost per an 11-week supply was statistically significant higher for E/S patients (239.49 USD) compared to 192.74 USD for RSV patients (p-value=0.0033). Also, costs per patient to achieve NCEP ATP III goal (2001 and 2004), and cost per 1% LDL-C decrease, were also higher among E/S patients as compared to RSV patients, which means that RSV was more cost-effective than E/S.

Summary of safety results

Extent of exposure at the most frequent treatment dose was longer for RSV patients (26 weeks median exposure time) compared to E/S patients (18 weeks median exposure time).

Incidence of adverse events was slightly higher among E/S patients (19.5% vs. 15.3% for RSV patients). For both treatment groups, adverse events were predominantly mild (about 10% of the patients). The most frequently reported adverse events by the RSV patients were respiratory, thoracic and mediastinal disorders (4.0%) and metabolism and nutrition disorders (2.7%; by E/S patients were psychiatric disorders (5.1%), Musculoskeletal, connective tissue and bone disorders and nervous system disorders (4.2% each). None of the reported adverse events were judged to be related to study treatment. There were two serious adverse event reported, one per treatment group. One was a female patient in the RSV treatment group who underwent a left hemithyroidectomy . The other was a female patient in the E/S group who had moderate uncontrolled hypertension that required treatment . No deaths were reported.

Regarding the laboratory parameters evaluated, other than those evaluated for treatment efficacy, their mean increase/decrease either was too small (without clinical significance) or estimation was based on information for very few patients. For both treatment groups there was a slight decrease in vital signs mean values between baseline and follow-up. This decrease in mean value was not considered to have clinical relevance. Overall it can be concluded that RSV patients had a slightly better safety profile than E/S patients.