AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Crestor
ACTIVE INGREDIENT: Rosuvastatin

Study No: NL401017
Crestor in patients with diabetes mellitus type 2: lowering of LDL-C levels to European guidelines (DIALOOG)

Developmental phase: IV
Study Completion Date: 01-27-2006
Date of Report: 06-26-2007

OBJECTIVES:

In an observational multi-centre study (DIALOOG), the effects of treatment with 10, 20 and 40 mg rosuvastatin were assessed on low-density lipoprotein cholesterol (LDL-C) goal achievement in patients with diabetes mellitus type II (DM II) who had not been treated with cholesterol reducing drugs during at least the past three months. Proportional changes in LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG) and the ratio TC/HDL-C were also studied, as well as investigator satisfaction with patient cholesterol levels.

METHODS:

Study design & patients

The DIALOOG study is an observational study conducted in different centres in the Netherlands, representing daily practice implying that no rules of conduct are imposed upon the physician and patient, and that no actions are demanded from the patient beyond standard practice. All patients consented to placing anonymous results at the disposal of AstraZeneca. The centres consisted of general practitioner, cardiologist or internist practices. In total 2,410 patients were included in the study.
Patients eligible for the study were DM II patients with an LDL-C $\geq$ 2.5 mmol/l, who were treated with anti-diabetic medication or diet for at least three months previously. Patients had to be statin naïve and not treated with a statin for the last three months preceding inclusion. The general practitioner or specialist made the decision to start treatment with rosuvastatin 10 mg irrespective of study participation. Exclusion criteria included patients with symptoms of myalgia, myopathy or liver function insufficiency (including raised serum transaminases) which bear a causal relation to the treatment with statins, patients with familiar dyslipideamia and/or patients with contra-indications for treatment with rosuvastatin. Patients with pre-disposed factors for myopathy were not eligible. Patients were their own historical control and were treated in accordance with the physician's standards.

At baseline, date of the visit, patient characteristics, year of diagnose of DM II, anti-diabetic medication, HbA_{1C} level, medical history, smoking behaviour and the lipid profile were obtained. Rosuvastatin treatment with 10 mg was started.
The second visit took place when a reliable value of LDL-C was obtained during treatment with 10 mg. If determined, other lipid values were documented. The maximum effect of treatment with rosuvastatin is expected to be obtained after four weeks. Such as in the case of daily practice, the time between the two visits was variable, but was minimised to four weeks. When the general practitioner or specialist decided to continue rosuvastatin 10 mg treatment, the second visit was the final visit. This was also the case when the patient switched to alternative cholesterol lowering therapy, or started treatment with additional cholesterol lowering drugs. The efficacy of rosuvastatin 10 mg was determined and documented. In the case of the rosuvastatin treatment being increased to 20 mg, visit 3 was planned according to daily practice, but minimally 4 weeks following the second visit taking place when a reliable value of LDL-C was obtained during treatment with 20 mg. If determined, other lipid values were documented. When the general practitioner or specialist decided to continue rosuvastatin 20 mg treatment or when the patient switched to another cholesterol lowering therapy, or started treatment with additional cholesterol lowering drugs, the third visit was the final visit. The efficacy of rosuvastatin 20 mg was determined and documented. If a raise of the dosage to 40 mg was considered by the general practitioner the patient was referred to a specialist, the third visit being the final one. In the case of the specialist deciding to adapt the rosuvastatin treatment to 40 mg, visit 4 was planned according to daily practice. The fourth visit took place when a reliable value of LDL-C was obtained during treatment with 40 mg. If determined, other lipid values were documented. The efficacy of rosuvastatin 40 mg was documented and evaluation was terminated following the fourth visit.

Efficacy
The efficacy analysis was performed on intention-to-treat basis (ITT). Patients satisfying the inclusion criteria were included. Primary efficacy measure was the proportion of patients reaching the target of LDL-C < 2.5 mmol/l at visit 2 (treatment with rosuvastatin 10 mg) and visit 3 (treatment with rosuvastatin 20 mg). The goal of LDL-C < 2.5 mmol/l has been recently formulated for high-risk patients by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. In case LDL-C was unknown, patients were evaluated as not reaching LDL-C target.
Secondary efficacy measures included the proportion of patients reaching the target of LDL-C < 2.5 mmol/l at visit 4 (treatment with rosuvastatin 40 mg). The proportion of patients reaching this target was also determined at visit 2, 3 and 4 in patients with $HbA_{1c} \leq 8\%$ and in patients with $HbA_{1c} > 8\%$ at visit 1. Furthermore, secondary efficacy measures included the proportional change from baseline of LDL-C, HDL-C, TC, TG and TC/HDL-C at visits 2, 3 and 4 and finally the proportion of general practitioners or specialists that was satisfied with the patients levels of LDL-C, HDL-C, TC and TG at visit 2, 3 and 4.

Safety
Standard safety assessments included the registration of all SAEs which were to be documented and reported within one day to AstraZeneca, and adverse events resulting in discontinuation (DAE) of rosuvastatin. A SAE was defined as an AE leading to death, life-threatening situation, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, a congenital abnormality/birth defect, or an important medical event. All patients were evaluated for safety (irrespective of the inclusion criteria).

Sample size
The primary end point for the evaluation of the efficacy was based on the proportion of patients reaching LDL-C < 2.5 mmol/l at visit 2 (rosuvastatin 10 mg) or visit 3 (rosuvastatin 20 mg). It was assumed that 17% of all patients would eventually be treated with rosuvastatin 20 mg and the proportion of these patients with LDL-C < 2.5 mmol/l was expected to be 50% at visit 3. These assumptions were based on both marketing and clinical research with rosuvastatin.
The sample size was based on obtaining a two-sided confidence interval of 95% ($\alpha = 0.05$) for a single proportion using the large sample normal approximation. The confidence interval would extend to 0.05 of the observed proportion, for an expected proportion of 0.50. Therefore the total sample size had to be 385 / 17 x 100 = 2,265 evaluable patients. Corrected for an expected dropout of 10%, it was planned to include 2,500 patients.

Statistical analysis
All data were analysed according to the Intention To Treat (ITT) principle. The ITT analysis set was defined as all DM II patients having LDL-C $\geq$ 2.5 mmol/l, measured at a time point that the patient was not treated with cholesterol reducing medication. Last Observation Carried Forward (LOCF) was not used to replace missing values, as between each visit the patients used differing doses of rosuvastatin. If LDL-C was unknown at a certain visit, the patient was regarded as having a LDL-C above the target at that particular visit. If it was not known whether the physician was satisfied or not with the level of LDL-C, HDL-C, TG or TC at a certain visit, this was regarded as being not satisfied with the level at this visit.
The analyses of the primary end point consisted of calculating a 95% confidence interval using the large sample normal approximation for the proportion of patients having a LDL-C < 2.5 mmol/l after treatment at visit 2 (rosuvastatin 10 mg) or visit 3 (rosuvastatin 20 mg). The same was done for the secondary variables: (1) the proportion of patients with LDL-C < 2.5 mmol/l at visit 4 (rosuvastatin 40 mg), and (2) the proportion of general practitioners or specialists that was satisfied with the patient levels of LDL-C, HDL-C, TC and TG at visit 2, 3 and 4. The proportional change from baseline of LDL-C, HDL-C, TC, TG and TC/HDL-C at visits 2, 3 and 4 was analysed by calculating 95% confidence intervals for the mean change. The proportions of patients with LDL-C < 2.5 mmol/l at visits 2, 3 and 4 in patients with HbA_{1c} $\leq$ 8% at visit 1 were compared to patients with HbA_{1c} > 8% at visit 1. This analyses was performed by χ^2 (Chi squared) test. For the proportion within each subgroup and for the difference between the subgroups, 95% confidence intervals were calculated.

RESULTS:

Characteristics
General practitioners, cardiologists and internists from 275 different centres enrolled a total number of 2,410 diabetic type II patients in the study. Diabetic patients had to be treated with medication or diet for at least the previous three months. Furthermore, they had to be statin naïve or not treated with a statin for the three months preceding inclusion. The physician made the decision irrespective of study participation to start treatment with rosuvastatin 10 mg. In order to imitate the practical situation as closely as possible, no demands were made on the physician with regard to target cholesterol value.
A total of 87 of 2,410 patients (3.6%) did not meet the inclusion criterion of LDL-C $\geq$ 2.5 mmol/l (in 67 patients LDL-C was unknown and in 20 patients LDL-C < 2.5 mmol/l).
From the remaining 2,323 patients, 17 (0.7% of all included patients) were not treated with diabetic medication or diet. These patients were not excluded from the ITT population, so 2,323 patients remained in the ITT population.

The baseline characteristics are depicted in Table 1 and are mainly based on these 2,323 patients. However, sex and smoking habits were unknown in 2 and 10 patients respectively and lipid levels were incomplete for HDL-C, TC, TG and the ratio TC/HDL-C. As a result, the number of patients may slightly vary between the different parameters.

Table 1. Baseline characteristics

Characteristics	Numbers (%)
Number of patients (ITT)	2,323
Male	1,223 (52.6)
Female	1,098 (47.3)
Unknown*	2 (0.1)
Age (years ± sd)	60.9 (10.3)
Male (years ± sd)	59.8 (10.1)
Female (years ± sd)	62.1 (10.4)
Diabetes Mellitus II	
Diagnosed (years ± sd)	4.6 (5.5)
Latest HbA_{1c}	7.3 (2.1)
Current antidiabetic treatment	
Only diet	313 (13.5)
Insulin	399 (17.2)
Metformin	1,382 (59.5)
Sulfonylurea derivate	824 (35.5)
Acarbose	23 (1.0)
Thiazolidinedione	253 (10.9)
Other	111 (4.8)
No medical treatment or diet	17 (0.7)
Medical History	
Myocardial infarction	136 (5.9)
PTCA and/or CABG	74 (3.2)
Angina pectoris	141 (6.1)
CVA	64 (2.8)
TIA	88 (3.8)
PVD	210 (9.0)
Hypertension	1,225 (52.7)
Nephropathy	119 (5.1)
Neuropathy	100 (4.3)
Retinopathy	105 (4.5)
None of the above	751 (32.3)
Smoking behaviour	
Yes	518 (22.3)
No	1,795 (77.3)
Unknown*	10 (0.4)

Characteristics	Numbers (%)
Lipid levels (mmol/l ± sd)	
LDL-C (N = 2,323)	4.03 (0.85)
HDL-C (N = 2,289)	1.27 (0.51)
TC (N = 2,313)	6.25 (1.58)
TG (N= 2,280)	2.32 (2.30)
TC / HDL-C (ratio) (N = 2,285)	5.34 (2.26)

** These data are not available.*

CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Cholesterol goal achievement

The mean time between the first and second visit was 91 days with a standard deviation (sd) of ± 72.7. The second visit was the final visit, when the general practitioner or specialist decided to continue rosuvastatin 10 mg treatment, the patient switched to another cholesterol reducing therapy, or started treatment with additional cholesterol reducing drugs. The majority of patients did not receive higher doses of rosuvastatin: only 241 patients received 20 mg rosuvastatin (10.4%). The mean time between the second and third visit was 80 days (± 56.1). The third visit was the final visit when the patient continued rosuvastatin 20 mg treatment. Only 8 patients (0.3%) received the highest dose of 40 mg, prescribed by a specialist, after the third visit. The mean time between the first and last visit, for all ITT patients, was 96 days (± 76.9).

In Table 2 the proportion of patients reaching LDL-C goal < 2.5 mmol/l are depicted.

Table 2. Proportion of patients with LDL-C < 2.5 mmol/l

Dose	*HbA_{1c}*	*Total*	*Success*	*Unknown*	*LDL-C < 2.5 mmol/l*
Mg		*N*	*N*	*N (%)*	*proportion (95% CI)*
10	*Total*	*2,323*	*1,488*	*110 (4.7)*	*64.1 (62.1 – 66.0)*
	≤ 8 %	*1,848*	*1,172*	*83 (4.5)*	*63.4 (61.2 – 65.6)*
	> 8 %	*418*	*278*	*21 (5.0)*	*66.5 (62.0 – 71.0)*
	Difference[1]				*-3.1 (-8.1 – 1.9) [ns]*
20	*Total*	*241*	*112*	*21 (8.7)*	*46.5 (40.2 – 52.8)*
	≤ 8 %	*192*	*87*	*12 (6.3)*	*45.3 (38.3 – 52.4)*
	> 8 %	*47*	*23*	*9 (19.1)*	*48.9 (34.6 – 63.2)*
	Difference[1]				*-3.6 (-19.6 – 12.3) [ns]*
10/20	*Total*	*2,323*	*1,576 [2]*	*125 (5.4)*	*67.8 (65.9 – 69.7)*
	≤ 8 %	*1,848*	*1,241*	*92 (5.0)*	*67.2 (65.0 – 69.3)*
	> 8 %	*418*	*295*	*27 (6.5)*	*70.6 (66.2 – 74.9)*
	Difference[1]				*-3.4 (-8.3 – 1.4) [ns]*

[1] The difference between HbA_{1c} ≤ 8 % and HbA_{1c} > 8 % was tested with a Chi-square test

2 Number of successes of 10 mg and 20 mg do not add up to number of successes in 10/20 mg as 24 patients started using rosuvastatin 20 mg although they had already reached the target after treatment with rosuvastatin 10 mg
[ns] Not significant

In the case of LDL-C being unknown, patients were evaluated as not reaching LDL-C targets. In the 10 mg rosuvastatin group LDL-C goal was reached in 64.1% (95% CI: 62.1-66.0). In the group where the dosage was raised to 20 mg rosuvastatin at the second visit, LDL-C goal < 2.5 mmol/l was reached in 46.5% (95% CI: 40.2-52.8). In the group of patients treated with 10 mg rosuvastatin and if necessary with 20 mg, this goal was reached in 67.8% (95% CI: 65.9-69.7). HbA_{1c} subgroup analyses showed no significant differences in the well regulated ($HbA_{1c} \leq 8\%$) compared to the less well regulated diabetic group ($HbA_{1c} > 8\%$ group), both for the 10 mg, 20 mg and the combination (10/20 mg) group (Table 2). The target of LDL-C < 2.5 mmol/l was respectively reached by 63.4% (10 mg), 45.3% (20 mg) and 67.2% (10/20 mg) for the $HbA_{1c} \leq 8\%$ group, and by 66.5% (10 mg), 48.9% (20 mg) and 70.6% (10/20 mg) for the $HbA_{1c} > 8\%$ group. The 40 mg rosuvastatin group was too small (N=8) to give reliable results. In 6 of these 8 patients, no information of LDL-C was gathered following treatment with rosuvastatin 40 mg.

Table 3. Proportional lipid changes (95% CI) from baseline for different rosuvastatin dosages.

	N_{V2}	Visit 2 (10 mg)	N_{V3}	Visit 3 (20 mg)	$N_{V2,3}$	Visit 2 & 3 (10/20 mg)[3]
LDL-C [1]	2,211	-43.7% (-44.6 – -42.8)	221	-39.8% (-42.2 – -37.3)	2,214	-45.5% (-46.3 – -44.7)
HDL-C [1]	2,159	9.4% (3.9 – 14.9)	210	15.2% (11.2 – 19.2)	2,167	10.1% (4.6 – 15.6)
TC [1]	2,199	-30.6% (-31.6 – -29.6)	219	-27.3% (-29.9 – -24.7)	2,200	-31.8% (-32.8 – -30.8)
TG [1]	2,134	-17.6% (-19.6 – -15.6)	201	-16.7% (-22.2 – -11.3)	2,140	-18.7% (-20.7 – -16.7)
TC/HDL-C [2]	2,152	-28.5% (-33.5 – -23.6)	210	-33.6% (-36.9 – -30.2)	2,160	-29.9% (-34.8 – -25.0)

[1] LDL-C, HDL-C, TC and TG are depicted in mmol/l .
[2] TC/HDL-C is a ratio.
[3] Change from visit 1 to last available measurement of Visit 2 and Visit 3.
*[ns] Not significant, * p < 0.0001.*

Lipid changes

At visit 2, rosuvastatin 10 mg reduced LDL-C by 43.7% (95% CI: 42.8-44.6), TC by 30.6% (95% CI: 29.6-31.6), TG by 17.6% (95% CI: 15.6-19.6) and the ratio TC/HDL-C by 28.5% (95% CI: 23.6-33.5). HDL-C increased by 9.4% (95% CI: 3.9-14.9). The 95% confidence intervals did not include zero and were therefore statistically significant. These results, as well as those for the 20 mg treatment group and the combination (10/20 mg) group are given in Table 3. The results for the combination group are quite similar to the 10 mg rosuvastatin group. The decline in LDL-C was 45.5% (95% CI: 44.7-46.3), in TC 31.8% (95% CI: 30.8-32.8), in TG 18.7% (95% CI: 16.7-20.7) and in the ratio TC/HDL-C 29.9% (95% CI: 25.0-34.8). HDL-C increased 10.1% (95% CI: 4.6-15.6). The results for the 20 mg rosuvastatin group show the same trend as for the 10 mg group. The decline in LDL-C was 39.8% (95% CI: 37.3-42.2), in TC 27.3% (95% CI: 24.7-29.9), in TG 16.7% (95% CI: 11.3-22.2) and in the ratio TC/HDL-C 33.6% (95% CI: 30.2-36.9). HDL-C increased by 15.2% (95% CI: 11.2-19.2). The results of the 40 mg rosuvastatin group are not demonstrated, due to the fact that only in case of 2 patients lipid levels were known.

Absolute reductions in LDL-C from baseline for the 10 mg (visit 2) and 20 mg (visit 3) rosuvastatin groups were respectively 1.79 mmol/l (95% CI: 1.75-1.84) and 1.76 (95% CI: 1.63-1.89).

The proportions of general practitioners or specialists that were satisfied with the patient levels of LDL-C, HDL-C, TC and TG at visit 2 (10 mg), 3 (20 mg) and 4 (40 mg) are demonstrated in Table 4.

Table 4. Proportion of patients investigator is satisfied with their lipid levels for different rosuvastatin dosages.

Dose *mg*	***Lipid***	***Total*** *N*	***Success*** *N*	***Unknown*** *N (%)*	***Satisfaction investigator*** *proportion (95% CI)*
10	*LDL-C*	*2,323*	*1,883*	*114 (4.9)*	*81.1 (79.5 – 82.7)*
	HDL-C	*2,323*	*1,889*	*195 (8.4)*	*81.3 (79.7 – 82.9)*
	TC	*2,323*	*1,881*	*178 (7.7)*	*81.0 (79.4 – 82.6)*
	TG	*2,323*	*1,771*	*241 (10.4)*	*76.2 (74.5 – 78.0)*
20	*LDL-C*	*241*	*187*	*23 (9.5)*	*77.6 (72.3 – 82.9)*
	HDL-C	*241*	*188*	*35 (14.5)*	*78.0 (72.8 – 83.2)*
	TC	*241*	*179*	*28 (11.6)*	*74.3 (68.8 – 79.8)*
	TG	*241*	*157*	*44 (18.3)*	*65.1 (59.1 – 71.2)*

In the case of lipid level satisfaction being unknown, evaluations were reported as not satisfied. Approximately 81% of the investigators were satisfied with the LDL-C, HDL-C and TG values for the 10 mg dose of rosuvastatin, whereas 76% were satisfied regarding the value of TG. For the 20 mg rosuvastatin dose, 78% were satisfied regarding the LDL-C and HDL-C values, 74% regarding the TC value and 65% regarding the TG value. It must be noted that a considerable number of unknown values were seen in all groups, but most pronounced in the TG group. The number of patients in the 40 mg rosuvastatin dose were again too small to give reliable results.

Safety
All patients (N=2,410) were included for safety assessment. SAE's were reported in 9 patients (0.4%). One patient died, due to sudden cardiac death. The other reported SAE's were cerebrovascular accident (N=2), myocardial infarction, bronchial carcinoma, carcinoid tumour of the pancreas, abdominal upper pain, diplopia and pneumonia.
In 2.4% of the patients (N=58), rosuvastatin treatment was stopped during the study due to an AE. In this group 85 DAE's were reported. The most frequently reported DAE's are shown in Table 5.

Table 5. Most frequent reported adverse events leading to discontinuation of medication.

Adverse event (DAE)	***Frequency***
Myalgia	*17 (0.7%)*
Headache	*6 (0.2%)*
Nausea	*6 (0.2%)*
Musculoskeletal discomfort	*4 (0.2%)*
Stomach discomfort	*4 (0.2%)*
Dizziness	*3 (0.1%)*
Fatigue	*3 (0.1%)*
Malaise	*3 (0.1%)*