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STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Crestor
ACTIVE INGREDIENT: Rosuvastatin

Study No: NL401142
REALISTIC: Protocol for an observational study in high risk patients switched from higher doses of other statins to Crestor on the percentage of patients reaching the new EAS LDL-C target goal

Developmental phase: IV
Study Completion Date: 07-24-2006
Date of Report: 07-31-2008

OBJECTIVES:

The REALISTIC study was an observational study performed by specialists only (internal specialists and cardiologists). The main objective of the REALISTIC study was to investigate the percentage of patients reaching LDL-C < 2.5 mmol/L in subjects at high risk of a cardiovascular event who were switched from higher doses of other statins to rosuvastatin 10 mg or after increase of dose to 20 mg. The effects of the 40 mg dose were also investigated.

METHODS:

Study design and patients

This study was an observational, non-interactive study in the daily practice of cardiologists and internal specialists. They were asked to record patient data on at least two Visits. These Visits took place according to normal routine clinical practice and the treating physician decided when these Visits took place.

Visit 1 took place when the physician had decided to start treatment with rosuvastatin 10 mg. The values of LDL-C, and if available, the value of other lipids (TC, HDL-C, Tg) were recorded in the CRF. Thereafter rosuvastatin treatment was started according to the SmPC.

Visit 2 took place when the value of LDL-C on treatment with rosuvastatin 10 mg was available. If available, also the value of other lipids (TC, HDL-C, Tg) on treatment with rosuvastatin 10 mg was recorded. The efficacy of rosuvastatin 10 mg was evaluated, and it was decided whether treatment with rosuvastatin 20 mg would be started or whether rosuvastatin 10 mg should be continued after Visit 2.

Visit 3 took place when the value of LDL-C on treatment with rosuvastatin 20 mg was available. If available, also the value of other lipids (TC, HDL-C, Tg) on treatment with rosuvastatin 20 mg was recorded. The efficacy of rosuvastatin 20 mg was evaluated, and it was decided whether treatment with rosuvastatin 40 mg would be started or whether rosuvastatin 20 mg should be continued after Visit 3.

Visit 4 took place when the value of LDL-C on treatment with rosuvastatin 40 mg was available. If available, also the value of other lipids (TC, HDL-C, Tg) on treatment with rosuvastatin 40 was recorded. The efficacy of rosuvastatin 40 mg was evaluated.

In this study, patients in Dutch daily practice of cardiologists and internal specialists who were switched from higher doses of other statins to rosuvastatin 10 mg were included. An LDL-C value at start of the study had to be available before inclusion in the study.

Inclusion criteria

1. Patient had documented coronary heart disease, peripheral artery disease, cerebrovascular disease, diabetes mellitus type 2 or diabetes mellitus type 1 with microalbuminuria.
2. Patient was being treated with either atorvastatin 20, 40 or 80 mg, pravastatin 40 mg, or simvastatin 20, 40 or 80 mg.
3. An LDL-C value was present for the dose of the statin used at Visit 1.
4. Decision had already been taken to start rosuvastatin treatment.
5. Patient was willing to give permission that recorded data would become available to AstraZeneca.

Exclusion criteria

1. Patient was known to have complaints of muscle pain, myopathy or liver function disorders (including elevation of serum transaminases) causally related to statin use.
2. Contra-indications for rosuvastatin 10 mg treatment (see SmPC).
3. Patient had a familial dyslipidemia like FH or FCH
4. Presence of pre-disposing factors for myopathy (creatinin clearance <60 ml/min, hypothyroidia, genetic muscle disease in medical history, muscular toxicity with other HMG-coA reductase inhibitors or fibrates, alcohol abuse, situations in which an increased plasma level may occur, Japanese or Chinese subjects, concomitant use of fibrates, age > 70 years).

Treatment

Rosuvastatin is a potent inhibitor of HMG-CoA reductase. Dosages of 10 mg (Visit 1), 20 mg (Visit 2) and 40 mg (Visit 3) were administered to the patients in this study.

Dosage regimen and dosing conditions

Patients switching from another statin to rosuvastatin started with a dose of 10 mg. If the LDL-C value at Visit 2 was not below 2.5 mmol/L, the physician could decide to increase the dose to 20 mg. If the LDL-C value at Visit 3 was not below 2.5 mmol/L, the physician could decide to increase the dose to 40 mg.

Prior and concomitant therapy

Except for the previous used statin, other prior or concomitant medication was not recorded in this study.

Treatment compliance

Treatment compliance was assessed by the physician. In case of non-compliance the physician noted this in most cases.

Study variables

Study assessments by visit

	Visit 1	Visit 2	Visit 3	Visit 4
General patient information	X			
Medical history	X			
Previous treatment	X			
Lipid profile	X	X	X	X
Medication	X	X	X	X
Serious adverse events	◄	———	———	——►
Adverse events (leading to discontinuation)		◄	———	——►

Primary Efficacy Variable (s)

The primary efficacy variable was the LDL-C value assessed at Visit 2, 3 and 4.

Secundary Efficacy Variable (s)

The efficacy variables HDL-C, TC and Tg were recorded as well at Visit 2, 3 and 4. The HDL-C/TC value was calculated from these data. The change from baseline was assessed as the level at visit 2, 3 or 4 minus the level at visit 1 divided by the level at visit 1.

Study subjects

Disposition of subjects

The disposition of subjects is presented in Table 1.

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Table 1: Disposition safety set

		Previous Treatment							
	All Subjects	Atorvastatin 20 mg	Atorvastatin 40 mg	Simvastatin 20 mg	Simvastatin 40 mg	Pravastatin 40 mg	Atorvastatin 80 mg	Simvastatin 80 mg	NK
Visit	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1	1602	192 (12.0)	150 (9.4)	350 (21.8)	291 (18.2)	573 (35.8)	25 (1.6)	13 (0.8)	8 (0.5)
2	1602	192 (12.0)	150 (9.4)	350 (21.8)	291 (18.2)	573 (35.8)	25 (1.6)	13 (0.8)	8 (0.5)
3	342	44 (12.9)	62 (18.1)	49 (14.3)	78 (22.8)	86 (25.1)	13 (3.8)	7 (2.0)	3 (0.9)
4	98	12 (12.2)	12 (12.2)	16 (16.3)	23 (23.5)	25 (25.5)	4 (4.1)	4 (4.1)	2 (2.0)

N = Total number of subjects, n = number of subjects in specified group,
Calculations based on N (n/N), NK = Not known

The corresponding demographic characteristics are presented in Table 2.

Table 2: Demographics safety set

Parameter			All subjects (N=1602)
Age (years)			
		n	1601
		mean	62.0
		SD	10.1
		minimum	17
		median	63.0
		maximum	86
		NK	1
Sex			
	Male	n (%)	1039 (64.9)
	Female	n (%)	560 (35.0)
	NK	n (%)	3 (0.2)
Smoking			
	Yes	n (%)	322 (20.1)
	No	n (%)	1176 (73.4)
	NK	n (%)	104 (6.5)

SD = standard deviation, N = total number of subjects, n = number of subjects; NK = Not Known
Calculation of percentages based on N (for age with non-missing values)
Age was calculated as: the date of visit 1 - the year of birth

A summary of the medical history data is presented in Table 3, a summary of the main reason for starting rosuvastatin is presented in Table 4.

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Table 3: Medical History safety set

		Previous Treatment							
Result	All Subjects n (%)	Atorvastatin 20 mg n (%)	Atorvastatin 40 mg n (%)	Simvastatin 20 mg n (%)	Simvastatin 40 mg n (%)	Pravastatin 40 mg n (%)	Atorvastatin 80 mg n (%)	Simvastatin 80 mg n (%)	Not defined n (%)
Myocardial infarction	547 (34.1)	64 (33.3)	49 (32.7)	89 (25.4)	102 (35.1)	225 (39.3)	11 (44.0)	6 (46.2)	1(12.5)
PTCA and/or CABG	593 (37.0)	63 (32.8)	66 (44.0)	94 (26.9)	127 (43.6)	224 (39.1)	10 (40.0)	6 (46.2)	3(37.5)
Angina pectoris	388 (24.2)	62 (32.3)	26 (17.3)	81 (23.1)	81 (27.8)	126 (22.0)	8 (32.0)	3 (23.1)	1(12.5)
CVA	72 (4.5)	5 (2.6)	4 (2.7)	17 (4.9)	12 (4.1)	32 (5.6)	1 (4.0)	1 (7.7)	0(0.0)
TIA	75 (4.7)	4 (2.1)	7 (4.7)	23 (6.6)	17 (5.8)	22 (3.8)	1 (4.0)	1 (7.7)	0(0.0)
Peripheral Vascular Disease	198 (12.4)	32 (16.7)	24 (16.0)	46 (13.1)	25 (8.6)	61 (10.6)	5 (20.0)	4 (30.8)	1(12.5)
Hypertension	590 (36.8)	82 (42.7)	54 (36.0)	142 (40.6)	109 (37.5)	184 (32.1)	11 (44.0)	4 (30.8)	4(50.0)
Diabetes mellitus type 2	385 (24.0)	56 (29.2)	29 (19.3)	97 (27.7)	71 (24.4)	122 (21.3)	7 (28.0)	2 (15.4)	1(12.5)
Diabetes mellitus type 1 with microalbuminuria	14 (0.9)	1 (0.5)	3 (2.0)	3 (0.9)	5 (1.7)	2 (0.3)	0 (0.0)	0 (0.0)	0(0.0)

n = number of subjects in specified group
Calculation of percentages based on disposition at visit 1 (safety set

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Table 4: Reason to start with rosuvastatin safety set

		Previous Treatment							
Result	All Subjects n (%)	Atorvastatin 20 mg n (%)	Atorvastatin 40 mg n (%)	Simvastatin 20 mg n (%)	Simvastatin 40 mg n (%)	Pravastatin 40 mg n (%)	Atorvastatin 80 mg n (%)	Simvastatin 80 mg n (%)	NK n(%)
Doctor not satisfied with lipid values obtained with current statin	1359 (84.8)	141 (73.4)	113 (75.3)	308 (88.0)	236 (81.1)	529 (92.3)	19 (76.0)	8 (61.5)	5 (62.5)
Side effects with current statin	161 (10.0)	42 (21.9)	27 (18.0)	19 (5.4)	37 (12.7)	30 (5.2)	3 (12.0)	2 (15.4)	1 (12.5)
At request by patient	31 (1.9)	5 (2.6)	2 (1.3)	10 (2.9)	7 (2.4)	7 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Interaction with other medication	14 (0.9)	3 (1.6)	2 (1.3)	2 (0.6)	4 (1.4)	1 (0.2)	2 (8.0)	0 (0.0)	0 (0.0)
Other	36 (2.2)	1 (0.5)	6 (4.0)	11 (3.1)	7 (2.4)	6 (1.0)	1 (4.0)	3 (23.1)	1 (12.5)
NK	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)

n = number of subjects in specified group, NK = Not Known

Calculation of percentages based on disposition at visit 1 (safety set)

All subjects included in the study are included in the safety set. Subjects for whom an LDL-C value was recorded at Visit 1 are included in the ITT set.

Safety set
The total number of subjects in the safety set was 1602. The mean age of this set was 62.0 years (17 - 86 years). Of these subjects 65% were male, and 35% female. Of this set, just over 20% (20.1%) were smokers, and 73.5% non-smokers (for 6.5% it was not known whether they smoke or not). The largest part of these subjects (35.8%) previously received 40 mg pravastatin. Simvastatin 20 mg (21.8%) and simvastatin 40 mg (18.2%) were also regularly reported as previous treatment. Atorvastatin 20 mg (12.0%) and 40 mg (9.4%) were less often given previous treatments. The smallest part of the subjects previously received 80 mg atorvastatin (1.6%) or 80 mg simvastatin (0.8%).

Myocardial infarction (34.1%), PTCA and/or CBAG (37.0%) and hypertension (36.8%) were all reported by more than one third of the subjects. Angina pectoris (24.2%) and diabetes mellitus type 2 (24.0%) were reported by almost a quarter of the subjects. CVAs (4.5%), TIAs (4.7%) and Diabetes Mellitus type 1 with microalbuminuria (0.9%) were only reported in a small proportion of the study population. Hypertension and Diabetes mellitus type 2 were more often reported by subjects who previously received 20 mg doses of atorvastatin and simvastatin but also by patients who received 80 mg atorvastatin. Subjects with a previous treatment of 80 mg simvastatin or atorvastatin more often reported myocardial infarction and Peripheral Vascular Disease.

The main reason to start with rosuvastatin was that the physician was not satisfied with lipid values obtained with the current statin (85% of the subjects). For another 10% of the subjects the main reason was the side effects that occurred with the current statin. Other reasons to start with rosuvastatin were only reported for small percentages of subjects (0.9 to 2.2%).

At Visits 1 and 2 there were 1602 subjects included in the safety set. At Visit 3 this number decreased to 342, and at Visit 4 it decreased again to 98 subjects.

ITT set
For 17 subjects no LDL-C value was reported at baseline. Therefore, they were not included in the ITT set. The remaining number of subjects that were included in the ITT set was 1585.
The mean age of these subjects was 62.1 years (17 - 86 years). Of these subjects, 65% were male and 35% female. Just under 20% (19.9%) were smokers and 73.6% non-smokers (it was not known if the remaining 6.4% were smokers or not). Data regarding previous treatment, reported medical history and reason to start with rosuvastatin were similar to those of the safety set.
At Visits 1 and 2 there were 1585 subjects included in the ITT set. 302 of these subjects for whom the dosage was increased continued with the study and returned on visit 3. Thereafter, 42 subjects for whom the dosage was increased to 40 mg continued with the study and returned at visit 4.

RESULTS:

Mean lipid values at Visit 1 are presented in Table 5. Mean lipid values at baseline were within the same range for all previous treatment groups. However, the subjects receiving 80 mg atorvastatin or 80 mg simvastatin showed a trend to higher LDL-C, Tg and TC

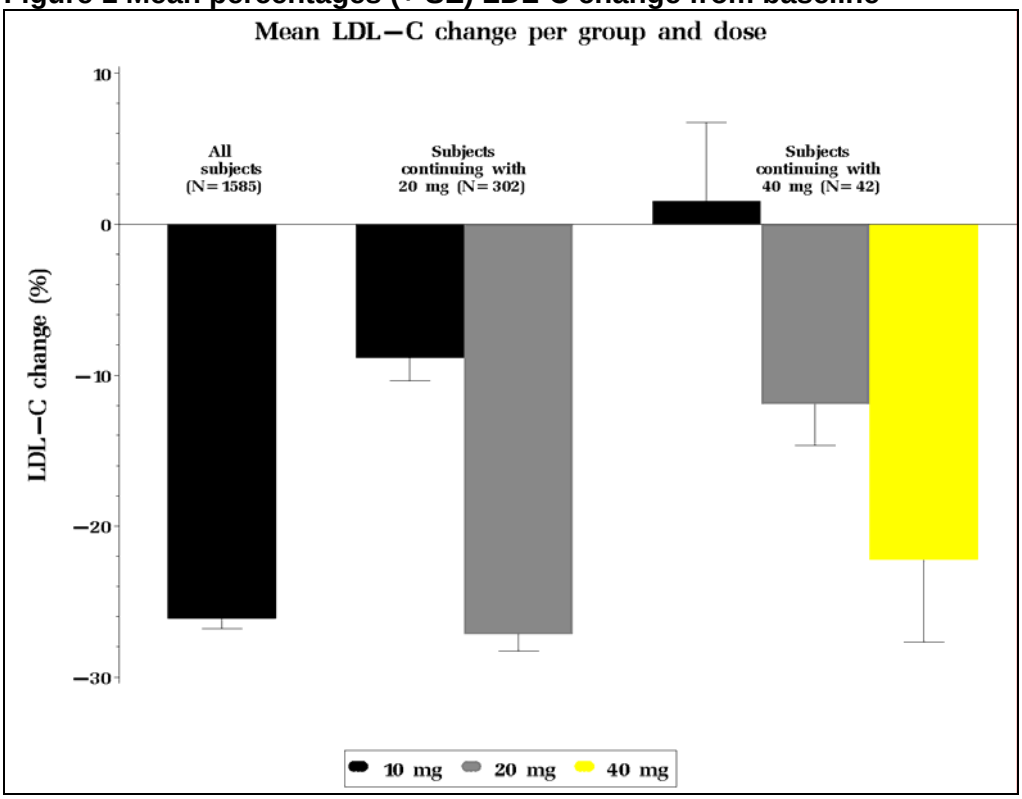
values and lower HDL-C values at baseline than the subjects in the other groups. The mean ratio HDL-C/TC at baseline was also higher for these subjects.

Table 5 Mean (SD) lipid values at Visit 1

Parameter / Previous treatment	LDL-C (mmol/L)	HDL-C (mmol/L)	TC/HDL-C ratio	TC (mmol/L)	Tg (mmol/L)
Atorvastatin 20 mg	3.39 (0.98)	1.28 (0.69)	4.60 (1.45)	5.41 (1.15)	1.98 (1.19)
Atorvastatin 40 mg	3.31 (0.96)	1.26 (0.35)	4.49 (1.38)	5.34 (1.15)	1.94 (1.17)
Simvastatin 20 mg	3.49 (0.82)	1.33 (0.41)	4.52 (1.71)	5.56 (0.94)	1.90 (1.20)
Simvastatin 40 mg	3.35 (0.85)	1.31 (0.37)	4.53 (2.03)	5.45 (0.99)	2.05 (2.21)
Pravastatin 40 mg	3.44 (0.71)	1.32 (0.35)	4.46 (1.29)	5.57 (0.95)	1.95 (1.22)
Atorvastatin 80 mg	3.68 (1.72)	1.15 (0.46)	5.49 (2.18)	5.70 (1.65)	2.08 (1.27)
Simvastatin 80 mg	3.67 (1.18)	1.23 (0.32)	5.04 (2.25)	5.66 (0.88)	1.91 (0.93)
All	3.42 (0.85)	1.31 (0.42)	4.52 (1.60)	5.51 (1.02)	1.96 (1.44)

The mean percentage LDL-C change from baseline values are presented in Figure 1.

Figure 1 Mean percentages (+ SE) LDL-C change from baseline



<u>10 mg rosuvastatin treatment</u>

All subjects started with 10 mg rosuvastatin at Visit 1. After receiving this treatment, the LDL-C values decreased on average with 26% (SD 25%). In total 53% of the subjects in the ITT set reported LDL-C values below 2.5 mmol/L at this visit.

An overview of percentages of subjects with LDL-C values below 2.5 mmol/L at visit 2 is shown in Table 6. Significantly more than half of the subjects who previously received 40 mg pravastatin (58 %) or 20 mg simvastatin (59%) showed a LDL-C value below 2.5 mmol/L. Of the other previous treatment groups atorvastatin 20 mg (49%) and simvastatin 40 mg (47%) showed slightly lower results which were still significantly higher than 40%. In addition, 37% of the subjects who previously received 40 mg atorvastatin also showed LDL-C levels below 2.5 mmol/L. The results in the 80 mg

atorvastatin and 80 mg simvastatin groups were lower. However, only few subjects were included in those groups.

Table 6 Percentage (95% CI) of patients with LDL-C below 2.5 mmol/L at Visit 2

Previous treatment	n visit 2	LDL-C < 2.5 mmol/L % (95% CI)	number of subjects uptitrated to 20 mg n (%)	Subjects without dosage increase and LDL-C >= 2.5 mmol/L (n, %)
Atorvastatin 20 mg	187	49 (42-56)	38 (20%)	51 (27%)
Atorvastatin 40 mg	148	37 (30-45)	59 (40%)	30 (20%)
Simvastatin 20 mg	347	58 (53-63)	43 (12%)	100 (29%)
Simvastatin 40 mg	289	47 (41-53)	72 (25%)	79 (27%)
Pravastatin 40 mg	571	59 (55-63)	71 (12%)	142 (25%)
Atorvastatin 80 mg	25	24 (11-44)	13 (52%)	5 (20%)
Simvastatin 80 mg	12	33 (13-62)	5 (42%)	2 (17%)
All subjects	1585	53 (50-55)	302 (19%)	410 (26%)

For in total 302 subjects (19%), the dosage was increased to 20 mg rosuvastatin. However, 26% of the patients showed LDL-C values equal to or above 2.5 mmol/L but did not receive a higher rosuvastatin dose. For most of these subjects (284) LDL-C levels between 2.5 and 3.0 mmol/L were reported. Most of the subjects for whom the dosage was not increased continued with rosuvastatin. A few subjects stopped because the physician was not satisfied with the effect (2 with levels above 3.5 mmol/L), because of an AE or SAE, or because of lost to follow up or lack of compliance.

<u>20 mg rosuvastatin treatment</u>

For 302 subjects the dosage rosuvastatin was increased to 20 mg. As can be seen from Figure 5.1, these subjects showed a mean decrease of 9% in LDL-C values after the 10 mg treatment. After the increase in dosage to 20 mg rosuvastatin, the LDL-C values dropped further to -27%. In total 41% of these subjects reported LDL-C values below 2.5 mmol/L after receiving 20 mg rosuvastatin.

An overview of percentages of subjects with LDL-C values below 2.5 mmol/L at visit 3 is shown in Table 7. Although less subjects were included, the results were similar to the results of the 10 mg treatment at visit 2. The subjects previously receiving 20 mg simvastatin showed the best results with 56% of the subjects below 2.5 mmol/L. The other previous treatment groups also showed good results with the percentage subjects below 2.5 mmol/L varying between 36% (40 mg simvastatin group) and 48% (20 mg atorvastatin group). The results in the 80 mg Atorvastatin and 80 mg Simvastatin groups were again lower. However, only few subjects were included in those groups.

Table 7 Percentage (95% CI) of patients with LDL-C below 2.5 mmol/L at Visit 3

Previous treatment	n visit 3	LDL-C < 2.5 mmol/L % (95% CI)	number of subjects uptitrated to 40 mg n (%)	Subjects without dosage increase and LDL-C >= 2.5 mmol/L (n, %)
Atorvastatin 20 mg	38	48 (30-61)	3 (8%)	16 (42%)
Atorvastatin 40 mg	59	37 (26-50)	8 (14%)	26 (44%)
Simvastatin 20 mg	43	56 (41-70)	7 (16%)	9 (21%)
Simvastatin 40 mg	72	36 (26-48)	11 (15%)	28 (39%)
Pravastatin 40 mg	71	45 (34-57)	5 (7%)	26 (37%)
Atorvastatin 80 mg	13	23 (7-52)	4 (31%)	6 (46%)
Simvastatin 80 mg	5	20 (3-69)	4 (80%)	0 (0%)
All subjects	302	41 (36-47)	42 (14%)	112 (37%)

For in total 42 subjects (14%), the dosage was increased to 40 mg rosuvastatin. However, 37% of the patients showed LDL-C values equal to or above 2.5 mmol/L but

did not receive a higher rosuvastatin dose. For about half of these subjects LDL-C levels between 2.5 and 3 mmol/L were reported at visit 3.

40 mg rosuvastatin treatment

For 42 subjects the dosage rosuvastatin was increased to 40 mg. These subjects did not show a significant increase or decrease after the 10 mg treatment. After the increase in dosage to 20 mg rosuvastatin, the LDL-C values decreased with 12% compared to the baseline values at visit 1. After a further dosage increase to 40 mg rosuvastatin the LDL-C values dropped to -22% of the baseline value at visit 1. In total 29% (12 out of 42) of these subjects reported LDL-C values below 2.5 mmol/L at visit 4. These were subjects previously receiving 40 mg atorvastatin (2 of 12), 20 mg simvastatin (4 of 16), 40 mg simvastatin (3 of 23), 80 mg atorvastatin (1 of 4) and 80 mg simvastatin (2 of 4).

TC values also decreased during the study and showed similar patterns as the LDL-C values. The mean TC decrease at Visit 2 (10 mg rosuvastatin) and Visit 3 (20 mg rosuvastatin) was 17% (SD 29%). For the subjects receiving 40 mg rosuvastatin, the decrease was 20% at visit 4. On average, HDL-C values were slightly increased at Visit 2 (3%) and a little more for the remaining subjects at Visit 3 and 4 (7% for both Visits). The ratio TC/HDL-C decreased by 16% (SD 41%) at Visit 1 and 20% for the remaining subjects at Visit 3 and 4.
A clear effect on Tg values could not be observed in this study.

Safety

In total 44 adverse events were reported by 38 subjects that lead to discontinuation of the study drug. Most reported adverse events were musculoskeletal connective tissue disorders (14) including myalgia (13) and pain in extremity (1), gastrointestinal disorders (10), headache (6, one including dizziness) and skin and subcutaneous tissue complaints (6, 3 pruritis, 2 rash, 1 face swelling). Another three subjects reported malaise. Other events were only reported once.
Eight (8) serious adverse events were reported that were not related to study medication. Four of these events resulted in dead, another event resulted in persistent disability.
In general, no serious adverse event was observed which was regarded causally related to study medication. The frequently reported adverse events that lead to study discontinuation are all known side effects of statin treatments.