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**PROPRIETARY DRUG NAME<sup>®</sup> / GENERIC DRUG NAME:** Lipitor<sup>®</sup> / Atorvastatin calcium

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI

**NCT #:** 00163163

**PROTOCOL NO.:** A2581051

**PROTOCOL TITLE:** Carotid Atorvastatin Study in Hyperlipidemic Post-MENopausal Women: a Randomised Evaluation of Atorvastatin Versus Placebo (CASHMERE)

**Study Centres:** A total of 12 centres in Belgium, 54 centres in France and 3 centres in The Netherlands enrolled subjects into the study.

**Study Initiation and Completion Dates:** 17 January 2003 – 14 July 2006

**Phase of Development:** Phase 3

**Study Objectives:** To evaluate the effect of atorvastatin 80 mg versus placebo, given for 12 months, on carotid intima-media thickness (IMT) in post-menopausal women with moderate hypercholesterolaemia.

To compare the change of the following parameters in each group (and in a subgroup analysis according to HRT status; results to be presented in a separate report):

- Echographic parameters measured at the site of the carotid artery: internal diameter (DI), wall cross-sectional area (WCSA), arterial mass (AM), pulse pressure (PP), cross-sectional distensibility (DC) and cross-sectional compliance (CC) and pulse wave velocity (PWV).
- Lipids: Total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and triglycerides (TG).
- C-reactive protein.

## METHODS

**Study Design:** The study was originally designed to compare atorvastatin, HRT and the combination of atorvastatin and HRT versus placebo in a 2 x 2 factorial design, however,

following Protocol Amendment No. 5, the 2 treatment groups including HRT were withdrawn from the study modifying the design to a 12-month multicentre, prospective, randomised, double-blind study to compare atorvastatin versus placebo in post-menopausal women with moderate hypercholesterolaemia. After Protocol Amendment No. 5, a total of 400 subjects were planned to be enrolled, 200 per treatment group. However, with Amendment No. 10, the number of subjects to be screened was raised to 665, in order to recruit 430 subjects.

For each subject, the study consisted of 7 visits: screening (Week 1 to -6), randomisation (Week 0), dose titration (Week 4), then 1 visit every 3 months (Months 4, 7 and 10) until the end of the study (Month 12). Visits were to occur within  $\pm 7$  days of the planned visit.

At Week 0, subjects were randomised to receive either atorvastatin 40 mg or placebo for 28 days. At Week 4, all subjects were switched to either atorvastatin 2 x 40 mg, or placebo and were to remain on this treatment until the end of the study. Subjects were instructed to follow dietary recommendations throughout the study.

**Number of Subjects (Planned and Analysed):** The study was designed to include approximately 400 subjects. A total of 665 subjects were screened and of these, 399 were assigned to treatment (192 to atorvastatin and 206 subjects to placebo). One subject in the placebo treatment group did not have a validated IMT value and subsequently did not receive any treatment and was excluded from the ITT analysis.

On 12 December 2005, active treatment and placebo were received at the study centres. On 14 December 2005, the Contract Research Organisation discovered that the treatment (active or placebo) was mentioned on the acknowledgement of receipt for the courier. This involved 32 centres and 152 subjects. The Scientific Committee was informed and acknowledged being aware of this situation. The Scientific Committee concluded that there was no significant impact on the study results.

As a result of the potential unblinding, separate analyses excluding the affected subjects were performed. This sub-population (ITT sensitivity [ie, blinded] population) consisted of 124 atorvastatin subjects and 122 placebo subjects.

**Diagnosis and Main Criteria for Inclusion:** The study enrolled post-menopausal women aged  $\leq 70$  years with fasting LDL-C  $\geq 130$  mg/dL (3.37 mmol/L) and  $\leq 190$  mg/dL (4.92 mmol/L), and TG  $\leq 4$  g/L (4.52 mmol/L), after 6 weeks following the recommended diet. Subjects were excluded if they had been treated with any hydroxymethylglutaryl-CoA reductase inhibitor for more than 3 months in the year prior to randomisation or any lipid lowering drugs within 6 weeks prior to randomisation.

**Study Treatment:** At Week 0 (Visit 2), subjects were randomised to receive either 1 x 40 mg atorvastatin tablet or a matching placebo tablet for 28 days. The tablets were to be swallowed with a glass of water at bedtime.

At Week 4 (Visit 3), for subjects not experiencing any treatment related AEs, the atorvastatin dose was increased to 80 mg. Subjects received either 2 x 40 mg atorvastatin tablets or 2 matching placebo tablets for a further 11 months.

If a subject experienced an intolerable side-effect believed to be related to study drug while receiving atorvastatin 80 mg, the investigator could instruct the subject to return to atorvastatin 40 mg and the change in dose would be documented.

**Efficacy Evaluations: Primary:** Mean change in carotid IMT from baseline to Month 12.

**Secondary:** Mean change from baseline to Month 12 of DI, WCSA, AM, PP, DC, CC, PWV, lipid profile (TC, LDL-C, HDL-C and TG) and C-reactive protein.

**Safety Evaluations:** At each visit the following were evaluated: reported AEs, physical examinations, vital signs and biological laboratory test results.

**Statistical Methods:** The main analyses used the ITT population (any subject who received at least 1 dose of investigational product) and each cohort was analysed separately. The primary efficacy parameter (mean change in carotid IMT from baseline to Month 12) was compared for atorvastatin and placebo by analysis of covariance. The covariable was the baseline value. Factors were yes/no for atorvastatin treatment. A factor centre was included in the model.

For continuous variables, the change from baseline and percent change from baseline to Month 12 was analysed by analysis of covariance as described for IMT.

Given that the treatment unblinding potentially affected 152 subjects, sensitivity analyses were also performed on the blinded population. The sensitivity analyses were the same as the main analyses but excluded all subjects who were potentially unblinded to treatment. The sensitivity analyses were for the primary endpoint, and the key secondary endpoints DI, WCSA, DC and PWV.

Safety data were summarised using Worldwide Safety Standards.

## RESULTS

**Subject Disposition and Demography:** Subject disposition is summarised by treatment in Table S1 for the planned analyses and in Table S2 for the sensitivity analyses. All subjects in this study were post-menopausal women. Demographic characteristics were similar for each treatment group, summarised in Table S3 for the planned analyses. Subjects' medical history was similar between the atorvastatin and placebo treatment groups, and was consistent with expectations for the study population; the most frequently experienced conditions, in both treatment groups, were hypertension, osteoarthritis, venous insufficiency and depression.

Mean duration of study treatment for the atorvastatin and placebo treatment groups was 341 days and 343.5 days, respectively.

There were more discontinuations in the atorvastatin group than the placebo group (63/192 [32.8%] versus 46/206 [22.3%], respectively, for the planned analyses). The reasons for discontinuation are shown in Table S1 and Table S2.

In general, concomitant medication taken during the study was similar between the atorvastatin and placebo treatment groups; the most frequently taken concomitant medications were female sex hormones and antagonists, analgesics for mild to moderate pain, beta blocking drugs – single agents (taken by less subjects in the atorvastatin group than in the placebo group), anxiolytics, and ulcer healing drugs (see Table S4).

**Table S1. Subject Disposition**

Number (%) of Subjects	Atorvastatin	Placebo
Screened		665
Randomised		399
Treated	192	206
Completed study	129 (67.2)	160 (77.7)
Discontinued treatment	63 (32.8)	46 (22.3)
Adverse event	24 (12.5)	20 (9.7)
Laboratory abnormality	18 (9.4)	2 (1.0)
Subject defaulted	11 (5.7)	15 (7.3)
Other	10 (5.2)	9 (4.4)
Evaluated for Efficacy		
ITT	192 (100)	206 (100)
Per Protocol	109 (56.8)	131 (63.6)
Evaluated for Safety		
Adverse Events	192 (100)	206 (100)
Laboratory Tests	191 (99.5)	203 (98.5)

ITT = intention-to-treat

PPROT = per protocol

**Table S2. Subject Disposition for Sensitivity Analyses (Blinded Population)**

Number (%) of Subjects	Atorvastatin	Placebo
Screened		513
Randomised		247
Treated	124	122
Completed study	73 (58.9)	85 (69.7)
Discontinued treatment	51 (41.1)	37 (30.3)
Adverse event	18 (14.5)	16 (13.1)
Laboratory abnormality	14 (11.3)	1 (0.8)
Subject defaulted	10 (8.1)	12 (9.8)
Other	9 (7.3)	8 (6.6)
Evaluated for Efficacy		
ITT sensitivity population	124 (100)	122 (100)
Evaluated for Safety	124 (100)	122 (100)

ITT = intention-to-treat

**Table S3. Demographic and Baseline Characteristics**

	Atorvastatin	Placebo
Number of subjects	192	206
Mean age (range), years	57.7 (42-70)	57.1 (44-69)
Mean weight (range, kg)	65.4 (45.0-92.0)	65.2 (44.2-88.0)
Mean height (range), cm	161.5 (144.0-176.0)	161.1 (139.5-176.0)
Race, n		
Not specified	192	206
Carotid internal diameter, $\mu\text{m}$	5501.7	5552.5
Carotid wall cross-sectional area, $\mu\text{m}^2$	13626401	13386852
Carotid arterial mass, $\mu\text{kg}$	14443985	14190063
Carotid pulse pressure, mmHg	48.1	46.7
Carotid cross-sectional distensibility, L/kPa	0.0027590	0.0026304
Carotid cross-sectional compliance, $\text{m}^2/\text{kPa}$	99673	97912
Carotid pulse wave velocity, m/s	9.52	9.55
TC, mmol/L	6.465	6.496
HDL-C, mmol/L	1.738	1.716
LDL-C, mmol/L	4.108	4.148
TG, mmol/L	1.351	1.356
C-reactive protein, nmol/L	21.708	19.306

TC = total cholesterol; HDL-C = high density lipid cholesterol; LDL-C = low density lipid cholesterol;  
 TG = triglycerides

**Table S4. Most Common Concomitant Drug Treatments for at least 10% of Subjects Reporting in Each Group, n (%)**

Drug Treatment	Atorvastatin N=192	Placebo N=206
Analgesics used for mild to moderate pain	44 (22.9)	58 (28.2)
Selective serotonin reuptake inhibitors and related antidepressants	26 (13.5)	29 (14.1)
Beta-blocking drugs – single agents	22 (11.5)	42 (20.4)
Corticosteroids	15 (7.8)	23 (11.2)
Antihistamines used in allergic disorders	14 (7.3)	23 (11.2)
Anti-inflammatory analgesics	59 (30.7)	72 (35)
Anxiolytics	33 (17.2)	35 (17)
Hypnotics and sedatives	20 (10.4)	20 (9.7)
Female sex hormones and antagonists	58 (30.2)	75 (36.4)
Thyroid hormones	20 (10.4)	20 (9.7)
Ulcer-healing drugs, gastrointestinal	29 (15.1)	34 (16.5)

**Efficacy Results: Primary endpoint:** There was no statistically significant treatment difference in the mean change in carotid IMT from baseline to Month 12 (Table S5). The mean (95% CI) difference between atorvastatin and placebo in mean change from baseline to Month 12 was not statistically significant ( $p=0.2875$ ).

With regards to the sensitivity analyses which included only the blinded population, results for the primary endpoint were similar to those for the ITT population: The mean, adjusted

for baseline and centre, (95% CI) difference between atorvastatin and placebo in mean change from baseline to Month 12 in carotid IMT was not statistically significant at  $-0.8 \mu\text{m}$  ( $-27.7, 26.1$ ) (Table S6).

**Table S5. Mean Change in Carotid IMT from Baseline to Month 12 – ITT population**

	Atorvastatin	Placebo
Baseline		
Number of subjects	192	205
Carotid IMT in $\mu\text{m}$ , mean (SD)	698.6 (118.23)	682.5 (104.00)
Month 12		
Number of subjects	182	187
Carotid IMT in $\mu\text{m}$ , mean (SD)	710.2 (116.79)	696.0 (117.74)
Difference <sup>a</sup> , Month 12-baseline	13.5 (90.89)	11.4 (103.63)
Percentage change from baseline to Month 12	2.9 (13.06)	2.5 (14.84)
Treatment difference in IMT (atorvastatin-placebo)		
n		369
Least squares mean <sup>b</sup>		10.7
95% CI		(-9.0, 30.4)
p-value		0.2875

<sup>a</sup> unadjusted mean

<sup>b</sup> mean change adjusted for baseline and centre

IMT = intima media thickness

CI = confidence interval

**Table S6. Mean Change in Carotid IMT from Baseline to Month 12 – ITT population (Sensitivity Analyses of the Blinded Population)**

	Atorvastatin	Placebo
Baseline		
Number of subjects	124	121
Carotid IMT in $\mu\text{m}$ , mean (SD)	702.9 (122.62)	676.8 (101.50)
Month 12		
Number of subjects	116	107
Carotid IMT in $\mu\text{m}$ , mean (SD)	705.7 (120.47)	696.4 (122.87)
Difference <sup>a</sup> , Month 12-baseline	4.2 (90.57)	15.3 (108.31)
Percentage change from baseline to Month 12	1.6 (12.81)	3.0 (15.63)
Treatment difference in IMT (atorvastatin-placebo)		
n		223
Least squares mean <sup>b</sup>		-0.8
95% CI		(-27.7, 26.1)
p-value		0.9537

<sup>a</sup> unadjusted mean

<sup>b</sup> mean change adjusted for baseline and centre

IMT = intima media thickness

CI = confidence interval

**Secondary Endpoints:** The mean (95% CI) differences between atorvastatin and placebo in mean change from baseline to Month 12 for LDL-C, TG and TC were statistically significant

(p-values <0.0001) at -1.656 mmol/L (-1.848, 1.464), -0.316 mmol/L (-0.410, -0.222) and -1.809 mmol/L (-2.017, -1.601), respectively (see Table S7). The mean change from baseline to Month 12 for the remaining secondary endpoints was similar for atorvastatin and placebo; there were no statistically significant differences.

Sensitivity analyses results (on the blinded population) for the key secondary endpoints DI, WCSA, DC and PWV, were similar to those for the ITT population: The differences between atorvastatin and placebo in mean changes from baseline to Month 12 for blinded subjects were not statistically significant.

**Table S7. Summary of Difference in Mean Change from Baseline to Month 12 between Atorvastatin and Placebo in Secondary Endpoints**

Secondary Endpoint, unit	Atorvastatin N=192		Placebo N=205		n	Treatment Difference		
	Baseline (mean)	Month 12 (mean)	Baseline (mean)	Month 12 (mean)		Adjusted Mean Difference	95% CI	p-value
Carotid internal diameter, µm	5501.7	5519.0	5552.5	5573.9	369	-41.0	(-148.8, 66.8)	0.4551
Carotid wall cross-sectional area, µm <sup>2</sup>	13626401	13962813	13386852	13722445	369	223718	(-286240, 733676)	0.3886
Carotid arterial mass, µkg	14443985	14800582	14190063	14545792	369	237141	(-303414, 777697)	0.3886
Carotid pulse pressure, mmHg	48.1	45.6	46.7	46.0	367	-1.9	(-4.5, 0.8)	0.1756
Carotid cross-sectional distensibility, L/kPa	0.0027590	0.0028168	0.0026304	0.0026298	365	0.0001503	(-0.0000902, 0.00039080)	0.2196
Carotid cross-sectional compliance, m <sup>2</sup> /kPa	99673	104944	97912	99205	365	4659	(-3642, 12960)	0.2702
Carotid pulse wave velocity, m/s	9.52	9.45	9.55	9.61	362	-0.21	(-0.53, 0.11)	0.1976
TC, mmol/L	6.465	4.629 <sup>a</sup>	6.496	6.373 <sup>a</sup>	385	-1.809	(-2.017, -1.601)	<0.0001
HDL-C, mmol/L	1.738	1.773 <sup>a</sup>	1.716	1.754 <sup>a</sup>	385	-0.027	(-0.077, 0.022)	0.2768
LDL-C, mmol/L	4.108	2.363 <sup>a</sup>	4.148	3.978 <sup>a</sup>	384	-1.656	(-1.848, 1.464)	<0.0001
TG, mmol/L	1.351	1.084 <sup>a</sup>	1.356	1.406 <sup>a</sup>	385	-0.316	(-0.410, -0.222)	<0.0001
C-reactive protein, nmol/L	21.708	24.617	19.306	22.752	237	1.765	(-7.267, 10.796)	0.7002

<sup>a</sup> LOFC

TC = total cholesterol; HDL-C = high density lipid cholesterol; LDL-C = low density lipid cholesterol; TG = triglycerides

**Safety Results:** There were no deaths during the study.

A total of 18 subjects (10 atorvastatin subjects and 8 placebo subjects) reported 21 SAEs during the treatment phase of the study (see Table S8). One SAE was considered treatment-related by the investigator: a subject receiving atorvastatin 40 mg experienced severe myalgia on Day 155; for which she was permanently discontinued from the study on Day 169. The event subsequently resolved.

In total, 3 subjects (2 subjects in the atorvastatin treatment group and 1 subject in the placebo group) were permanently discontinued from the study as a result of SAEs.

**Table S8. Serious Adverse Events**

Event <sup>a</sup>	Severity	Outcome
<b>Atorvastatin 40 mg</b>		
Myalgia <sup>c</sup>	Severe	Resolved
Epistaxis	Severe	Resolved
<b>Atorvastatin 80 mg</b>		
Pyelonephritis	Severe	Resolved
Malaise	Mild	Resolved
Cholelithiasis	Moderate	Resolved
Epilepsy	Severe	Resolved
Appendicitis	Severe	Resolved
Rectosigmoid cancer <sup>c</sup>	Severe	Resolved
Hysterectomy <sup>c</sup>	Severe	Still present
Viral infection	Severe	Resolved
Osteoarthritis	Severe	Recovering
<b>Placebo</b>		
Pneumonia	Moderate	Still present
Myocardial infarction <sup>c</sup>	Severe	Resolved
Arthralgia	Mild	Resolved
Abdominal pain	Severe	Still present
Psychosomatic disease	Severe	Still present
Psychosomatic disease	Severe	Still present
Bronchopneumonia	Moderate	Resolved
Atrial fibrillation	Severe	Resolved
Knee operation	Mild	Resolved
Viral infection	Moderate	Resolved

<sup>a</sup> MedDRA (v10.0) coding dictionary applied.

<sup>b</sup> Day relative to start of study treatment. First day of study treatment = Day 1

<sup>c</sup> SAEs leading to permanent discontinuation

During the study, 41/192 subjects (21.4%) in the atorvastatin treatment group permanently discontinued due to treatment emergent AEs compared to 22/206 subjects (10.7%) in the placebo group. For 35 subjects (18.2%) in the atorvastatin group the AEs were considered related to treatment compared to 16 subjects (7.8%) in the placebo group. The most common treatment related AE leading to treatment discontinuation for 9 subjects (4.7%) in the atorvastatin group and 1 subject (0.5%) in the placebo group was LDL-C decreased (<0.5 g/L, as defined in the protocol). Table S9 lists treatment related AEs which led to discontinuation for AEs reported by  $\geq 2$  subjects, regardless of treatment.

**Table S9. Discontinuations Due to Treatment Related Adverse Events**

Adverse Event <sup>a</sup>	Atorvastatin				Placebo			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
LDL-C decreased	8	1		9	1			1
Myalgia	2		2	4	1		1	2
Alanine aminotransferase increased		3		3				
Transaminases increased	1	1	1	3				
Nausea	1	1	1	3			1	1
Fatigue		1	2	3				
Pruritus		2		2				
Muscle spasms			2	2		2		2
Diarrhoea	1	1		2				
Hepatic cytolysis	1	1		2				
Liver function test abnormal	1		1	2				
Insomnia			1	1	1			1
Creatine phosphokinase increased	1			1	1		1	2
Vomiting						1	1	2
Vertigo					1		1	2
Headache						1	1	2

Those AEs which led to discontinuation for more than 1 subject per treatment group are included

Subjects may have discontinued because of more than 1 AE

<sup>a</sup> MedDRA (v10.0) coding dictionary applied.

A similar number of subjects in the atorvastatin and placebo treatment groups experienced treatment emergent AEs during the study, 154/192 subjects (80.2%) and 159/206 subjects (77.2%), respectively. Adverse events were considered treatment related for 64/192 subjects (33.3%) in the atorvastatin treatment group compared to 42/206 subjects (20.4%) in the placebo group. The most frequently reported AE in the atorvastatin group was LDL-C decreased (<0.5 g/L, as defined in the protocol) which was reported by 14 subjects (7.3%) compared to 1 subject (0.5%) in the placebo group; all events were considered treatment related. All other AEs which were considered treatment related were reported by similar numbers of subjects in the atorvastatin and placebo groups.

A summary of treatment emergent AEs occurring in at least 4% of subjects in any treatment group in the first phase is shown in Table S10.

**Table S10. Number of Subjects (%) with Treatment Emergent Adverse Events Reported by ≥4% of Subjects in Any Treatment Group**

Adverse Events <sup>a</sup>	Atorvastatin N=192		Placebo N=206	
	All causality	Treatment related	All causality	Treatment related
Number of AEs	410	99	438	65
Subjects with AEs	154 (80.2)	64 (33.3)	159 (77.2)	42 (20.4)
Subjects with SAEs	10 (5.2)	1 (0.5)	8 (3.9)	0
Subjects with severe AEs	25 (13.0)	15 (7.8)	27 (13.1)	9 (4.4)
Subjects discontinued due to AEs	41 (21.4)	35 (18.2)	22 (10.7)	16 (7.8)
Subjects with reduced/temporarily discontinued dose due to AEs	19 (9.9)	8 (4.2)	14 (6.8)	6 (2.0)
LDL-C decreased	14 (7.3)	14 (7.3)	1 (0.5)	1 (0.5)
Bronchitis	13 (6.8)	0	14 (6.8)	0
Nasopharyngitis	11 (5.7)	0	16 (7.8)	0
Back pain	10 (5.2)	0	15 (7.3)	0
Headache	9 (4.7)	1 (0.5)	11 (5.3)	3 (1.5)
Muscle spasms	9 (4.7)	0	11 (5.3)	0
Cystitis	8 (4.2)	0	4 (1.9)	0
Gastroenteritis	8 (4.2)	0	3 (1.5)	0
Myalgia	8 (4.2)	6 (3.1)	11 (5.3)	5 (2.4)
Rhinitis	7 (3.6)	0	11 (5.3)	0
Abdominal pain upper	6 (3.1)	3 (1.6)	10 (4.9)	3 (1.5)
Vertigo	5 (2.6)	1 (0.5)	10 (4.9)	3 (1.5)
Insomnia	5 (2.6)	2 (1.0)	10 (4.9)	2 (1.0)
Arthralgia	3 (1.6)	0	11 (5.3)	0
Hot flush	2 (1.0)	0	9 (4.4)	1 (0.5)

<sup>a</sup> MedDRA (v10.0) coding dictionary applied.

The incidence of laboratory abnormalities was similar between the atorvastatin and placebo treatment groups overall considering the underlying disease. The most commonly reported laboratory abnormality, from normal baseline, in the atorvastatin treatment group was ALT increased experienced by 9/175 subjects (5%) compared to 1/178 subjects (1%) in the placebo group. During the study, 16/192 subjects (8.3%) in the atorvastatin treatment group permanently discontinued due to treatment related laboratory abnormalities compared to 2/206 subjects (1%) in the placebo group.

There were no clinically significant changes from baseline for heart rate or blood pressure in either treatment group.

### CONCLUSIONS:

During this study, there was no observable difference between atorvastatin and placebo in mean change from baseline to Month 12 in carotid IMT in post-menopausal women with moderate hypercholesterolaemia. The mean change in carotid IMT from baseline to Month 12 was similar for atorvastatin (13.5 µm; from 698.6 to 710.2 µm) and placebo (11.4 µm; from 682.5 to 696.0 µm) and the mean difference was not statistically significant at 10.7 µm (95% CI: -9.0, 30.4). The sensitivity analyses performed showed that the conclusion for the primary analysis was robust to the removal of those subjects who were potentially unblinded.

Significant differences between atorvastatin and placebo in the change from baseline to Month 12 for the secondary endpoints LDL-C, TG and TC were observed (all p-values were <0.001). The mean change from baseline to Month 12 for the remaining secondary endpoints was similar for atorvastatin and placebo; there were no statistically significant differences. The sensitivity analyses performed showed that the conclusions for the key secondary endpoints DI, WCSA, DC and PWV were robust to the removal of those subjects who were potentially unblinded.

There were no deaths during the study. A total of 18 subjects (10 atorvastatin subjects and 8 placebo subjects) reported 21 SAEs during the treatment phase of the study. One SAE was considered treatment-related by the investigator: a subject receiving atorvastatin 40 mg experienced severe myalgia on Day 155; for which she was permanently discontinued from the study on Day 169. The event subsequently resolved. Three subjects were permanently discontinued from the study as a result of SAEs.

The most common treatment related AE leading to treatment discontinuation for 9 subjects in the atorvastatin group and 1 subject in the placebo group was LDL-C decreased (<0.5 g/L, as defined in the protocol). A decrease in LDL-C reflects the expected pharmacological activity of atorvastatin. Accordingly, the most frequently reported AE in the atorvastatin group was LDL-C decreased (<0.5 g/L, as defined in the protocol) which was considered related to study treatment and was reported by a further 5 subjects - a total of 14 subjects (7.3%) compared to 1 subject in the placebo group. All other AEs which were considered treatment related were reported by similar numbers of subjects in the atorvastatin and placebo groups.

For cholesterol, LDL-C, and TG, large median decreases from baseline were observed in the atorvastatin group compared to placebo. The observed decrease from baseline in LDL-C was an expected pharmacological effect of atorvastatin.