Clinical Study Report Synopsis

Drug Substance	Rosuvastatin
Study Code	D356FC00007
Edition Number	1.0
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A randomised, double-blind trial to compare the efficacy of rosuvastatin 5 and 10 mg to atorvastatin 10 mg in the treatment of high risk patients with hypercholesterolemia followed by an open label treatment period with rosuvastatin up-titrated to the maximum dose of 20 mg for those patients who do not achieve goal

Study dates: First subject enrolled: 27 May 2008
Last subject last visit: 16 Jul 2009

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted at 13 investigational sites in China. The first patient was enrolled on 27 May 2008, the last patient was completed on 16 Jul 2009.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives of this study are summarized in the Table S1 below.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
• To compare the efficacy of rosuvastatin 5mg and 10mg with atorvastatin 10mg by assessing the percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) concentration in patients with hypercholesterolemia and either a history of coronary heart disease (CHD) or a CHD risk equivalent, or clinical evidence of atherosclerosis or a 10 year CHD risk of ≥10%, following 6-week treatment.	- Percentage change from baseline in LDL-C concentration after 6 weeks of treatment, comparing rousuvastatin 5mg with atorvastatin 10mg - Percentage change from baseline in LDL-C concentration after 6 weeks of treatment, comparing rousuvastatin 10mg with atorvastatin 10mg	Efficacy
Secondary	**Secondary**	

Objectives	Outcome variables	Type
• To compare the efficacy of rosuvastatin 5mg and 10 mg with atorvastatin 10mg in modifying high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), nonHDL-C, Apolipoprotein B (ApoB), Apolipoprotein A-I (ApoA-I), TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I following 6-week treatment. • To compare the efficacy of rosuvastatin 5mg and 10mg with atorvastatin 10mg in achieving LDL-C and nonHDL-C goals according to National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) guidelines (2001) following 6-week treatment • For those patients not achieving goal in the double blind phase: - To describe the percentage of patients achieving LDL-C goal after titration from rosuvastatin 5 mg to 10mg - To describe the percentage of patients achieving LDL-C goal after titration from rosuvastatin 10 mg to 20mg	- Percentage change from baseline in HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I at 6 weeks. - Percentage of patients achieving NCEP ATP III guideline (2001) LDL-C goal and nonHDL-C goal at 6 weeks: Moderately high risk: 2+ risk factors (10-year risk 10%-20%): LDL-C goal < 3.36mmol/L (130mg/dL); non-HDL-C goal < 4.14mmol/L (160mg/dL) High risk: CHD or CHD risk equivalents (10-year risk >20%): LDL-C goal < 2.60mmol/L (100mg/dL); non-HDL-C goal < 3.36mmol/L (130mg/dL) - For those patients not achieving goal in the double blind phase: Percentage of patients achieving NCEP ATP III LDL-C goal after titration from rosuvastatin 5 mg to 10mg Percentage of patients achieving NCEP ATP III LDL-C goal after titration from rosuvastatin 10 mg to 20mg	Efficacy
• To assess the safety and tolerability of rosuvastatin versus atorvastatin by observing adverse events, changes in laboratory safety variables and discontinuations.	- Adverse events (AEs) - Laboratory variables: Haematology and urinalysis Clinical Chemistry: creatine kinase(CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (BIL), creatinine(Cr), fasting plasma glucose (FPG) - Discontinuations - Other safety measurements: Physical examination ECG (electrocardiogram)	Safety

Study design

This was a multi-centre, randomised, double-blind, 3-arm, parallel-group, comparator trial for the 6-week period, investigating the efficacy and safety of rosuvastatin 5mg and 10mg vs. atorvastatin 10mg once daily in moderately high risk and high risk patients with hypercholesterolemia as described below. Patients entered a 4-week dietary lead-in period (dietary counselling and other non-drug treatment, discontinue all cholesterol lowering drugs), after which eligible patients received their randomly assigned treatment. Patients in the rosuvastatin 5mg and 10mg group who did not achieve ATP III LDL-C goal at week 6

continued to an open-label, non-comparator extension treatment, which was either titration to rosuvastatin 10mg (rosuvastatin 5mg group) or to rosuvastatin 20mg (rosuvastatin 10mg group) once daily for another 6 weeks. Patients in the atorvastatin group did not continue to the extension treatment period irrespective if they achieved goal. Their treatment regimens were decided by the investigators after 6 weeks of study treatment.

Target subject population and sample size

Male and female patients (aged 18 years old or above) with hypercholesterolemia (excluding homozygous familial hypercholesterolemia) LDL-C concentration ≥ 3.36mmol/L (130mg/dL) and < 6.50 mmol/L (250 mg/dl), fasting TG concentrations of < 4.52 mmol/L (400 mg/dl) and either a history of CHD or a CHD risk equivalent, or clinical evidence of atherosclerosis or a 10 year CHD risk of ≥10% as described in NCEP ATP III guideline.

To demonstrate non-inferiority of rosuvastatin 5 mg versus atorvastatin 10 mg, a sample size of 121 patients per treatment group was required to have 80% power to reject inferiority for a two-sided t test at significance level of 2.5%, assuming the real difference in percent changes from baseline in LDL-C between rosuvastatin 5mg and atorvastatin 10mg is 0, the non-inferiority margin was -6%, and the standard deviation was 15 % (based upon ZD4522 Phase I data on file and Nawrocki et al 1995), with the treatment allocation ratio of 1:1.

To demonstrate superiority of rosuvastatin 10 mg over atorvastatin 10 mg, the same sample size as for non-inferiority test, i.e. 121 patients per treatment group, was needed to have 80% power to detect a difference of 6% in percent changes from baseline in LDL-C between rosuvastatin 10 mg and atorvastatin 10 mg at two-sided significance level of 2.5%, assuming a real difference between these two treatments was at least 6% and the standard deviation was 15 %, with the treatment allocation ratio of 1:1.

To take a dropout rate of 10% into consideration, about 135 patients were expected to be randomized to each treatment group so as to have 121 evaluable patients per group. Therefore, in total 405 patients were required to enter the randomised treatment period.

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

Randomised treatment period (from week 1 to week 6)

Rosuvastatin 5mg and 10mg were supplied as encapsulated tablets, taken orally one tablet once daily.

Extension treatment period (from week 7 to week 12)

Rosuvastatin 10mg and 20mg were taken orally one tablet once daily. Both were supplied as tablets without encapsulation.

Atorvastatin 10mg was supplied as encapsulated tablets, with the same appearance as rosuvastatin 5mg and 10mg and they were undifferentiated from each other.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Rosuvastatin	Capsule/5mg/ randomised treatment period: one capsule once daily/ oral	Astrazeneca	ST76064-001-FA05 ST76064-001-FA08 TX27037	1419 1634
Rosuvastatin	Capsule/10mg/ randomised treatment period: one capsule once daily; open label extension treatment period: one tablet once daily/oral	Astrazeneca	ST75033-001-FA11 ST75033-001-FA13 51865I07	1419 1420 1634 1616
Rosuvastatin	Capsule/20mg/ randomised treatment period: one capsule once daily; open label extension treatment period: one tablet once daily/oral	Astrazeneca	60035F08	1421 1617
Atorvastatin	Capsule/10mg/ randomised treatment period: one capsule once daily/oral	Pfizer	ST73060-001-FB15 ST73060-001-FB16	1419 1634

Duration of treatment

Any previous lipid-lowering therapies were stopped at visit 1. Patients initially underwent a 4-week dietary lead-in period where they were asked to follow the therapeutic lifestyle change (TLC) diet.

At the end of the 4-week dietary lead-in period, eligible patients were randomised in 1:1:1 ratio to rosuvastatin 5 mg or rosuvastatin 10mg or atorvastatin 10 mg group. The duration of treatment was 6 weeks. Patients in the rosuvastatin 5mg and 10mg group who did not achieve the ATP III guideline (2001) LDL-C goal by week 6, continued to the extension treatment period, and were treated with rosuvastatin 10mg and 20mg respectively for 6 weeks. Safety variables were observed in the extension period.

Patients in atorvastatin 10mg group finished the study by week 6.

Patients in rosuvastatin 5mg or 10mg group who reached ATP III guideline (2001) LDL-C goal by week 6, and those who finished the 6 weeks extension treatment period either with rosuvastatin 10mg or 20mg would finish the study

For all patients finishing the study, their further treatment regimens were decided by investigators.

Statistical methods

The primary analyses of efficacy data were restricted to the intention-to-treat (ITT) population. The patients in ITT were analysed by randomised treatment group. In addition, secondary analyses were carried out using the per-protocol (PP) population to assess whether the conclusions from the primary analysis were robust. The ITT population consistes of all randomised patients who had received at least one dose of any study treatment, who had measurements at baseline for one or more lipid variables and at least one post baseline measurement for the same one or more lipid variables in the randomised treatment period. PP population was defined as all ITT patients with no major protocol deviations. The analysis of safety data were performed in the safety population which consisted of all patients that had received at least one dose of the study medication. The patients in the safety population endpoints were evaluated according to the treatment they actually received.

The analyses to determine the effect of treatment on percentage change from baseline in lipid concentration at 6 weeks used the analysis of covariance (ANCOVA) model with factors fitted for treatment, centre, risk factor, lipid concentration at baseline, treatment by centre and treatment by risk factor. If the interaction terms were found to contribute substantially to the model ($p<0.05$), the nature of the interactions would be investigated and the appropriateness of inferences made regarding treatment main effects would be evaluated; otherwise these terms were dropped from the model. The results were presented in terms of lsmeans and the difference between the lsmeans, with associated nominal 95% confidence intervals. The contrasts of interest were the treatment differences between each dose of rosuvastatin (5 mg and 10 mg) and atorvastatin 10mg, which were calculated from the same ANCOVA model. The Bonferroni method was used for adjustment for multiplicity when performing the primary analyses, i.e the significance level alpha was adjusted to 0.025 for each comparison.

In this study, the non-inferiority margin for percentage change from baseline in LDL-C between rosuvastatin 5 mg and atorvastatin 10 mg was set to -6% . To facilitate the result explanation of non-inferiority, additional 97.5% confidence intervals for the lsmeans of treatment difference was also presented. If the lower limit of 97.5% confidence intervals for the difference between rosuvastatin 5 mg and atorvastatin 10 mg was greater than -6%, clinical non-inferiority would be claimed.

For superiority test between rosuvastatin 10 mg and atorvastatin 10 mg in percentage change from baseline in LDL-C, if there was a statistically significant difference at 2-sided significance level of 0.025 between rosuvastatin 10mg and atorvastatin 10 mg, i.e. $P<0.025$, superiority would be claimed.

No confirmatory claim was made for the secondary variables and therefore no adjustments for multiplicity were made for these secondary analyses. However, the interpretation of the data had taken the risk of multiplicity errors into consideration.

The number and percentage of patients reaching LDL-C goal (as described in NCEP ATP III) were summarised for ITT population and PP population for rosuvastatin and atorvastatin at week 6 for overall patients. Treatment comparisons were performed using a logistic regression model with factors fitted for treatment, centre, risk factor and baseline LDL-C. The incidence and severity of adverse events were summarized by body system and preferred term for each of the 3 randomised treatment group. All other safety data including physical examination, vital signs and laboratory data were summarized using descriptive statistics statistics and frequency distribution (whichever appropriate). Categorical variables were summarized by frequency and percent of population.

Laboratory values outside the normal reference ranges were highlighted. No formal treatment comparisons were performed.

The demographic and baseline measurements were summarized in the ITT population using descriptive statistics and frequency distribution (whichever appropriate).

One blood sample was drawn at visit 2. This sample was divided into two tubes for measurements. One sample measured the levels of TC, TG, LDL-C and HDL-C. Another one measured the level of LDL-C only. The mean LDL-C value of the two measurements was used for eligibility evaluation and baseline.

Subject population

In the present study, in total 934 patients were enrolled to the study, and of them 436 patients from 14 study sites were randomized.

The patient population and disposition is presented in Table S2. The treatment groups were well balanced with respect to demographic and baseline characteristics.

There were no clinically important differences in the composition of the populations among the treatment groups. The study population met the specifications as defined in the protocol and is therefore appropriate for the evaluation of the efficacy of Rosuvastatin in management of lipids level in patients with hypercholesterolemia and either a history of CHD or a CHD risk equivalent, or clinical evidence of atherosclerosis or a 10 year CHD risk of ≥10%, following 6-week treatment.

Table S2 Patient population and disposition

	Rosuvastatin 5mg	Rosuvastatin 10mg	Atorvastatin 10mg	Total
Disposition	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Number of patients enrolled				934

	Rosuvastatin 5mg	Rosuvastatin 10mg	Atorvastatin 10mg	Total
Disposition	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Number of patients not randomized				498
Number of patients randomized	145	145	146	436
Number of patients received treatment	145(100.0%)	145(100.0%)	146(100.0%)	436(100.0%)
Number of patients completed study[1]	139(95.9%)	143(98.6%)	140(95.9%)	422(96.8%)
Number of patients discontinued study[2]	6 (4.1%)	2 (1.4%)	6 (4.1%)	14 (3.2%)
Number of patients entered into the extension treatment period	36	23		59
Number of patients completed the extension treatment period	33	23		56
Analysis population				
Patient included in safety population	145(100.0%)	145(100.0%)	146(100.0%)	436(100.0%)
Patient included in ITT population	136(93.8%)	139(95.9%)	139(95.2%)	414(95.0%)
Patient included in PP population	128(88.3%)	133(91.7%)	129(88.4%)	390(89.4%)
Baseline characteristics (ITT set)				
Age (years)				
Mean(SD)	60.4(8.51)	59.7(10.57)	58.4(9.29)	59.5(9.51)
Min-Max	36-80	29-87	34-77	29-87
Sex (n (%))				
Male	52 (38.2%)	54 (38.8%)	62 (44.6%)	168(40.6%)
Female	84 (61.8%)	85 (61.2%)	77 (55.4%)	246(59.4%)
Race (n (%))				
Oriental	136(100.0%)	139(100.0%)	139(100.0%)	414(100.0%)
Baseline LDL-C level (mmol/L)				
N	136	139	139	
Mean (SD)	4.242 (0.6769)	4.131 (0.6818)	4.213 (0.6617)	
Range[3]	2.95-6.73	2.66-6.80	2.28-5.95	
Baseline TG level (mmol/L)				

	Rosuvastatin 5mg	Rosuvastatin 10mg	Atorvastatin 10mg	Total
Disposition	**N (%)**	**N (%)**	**N (%)**	**N (%)**
N[4]	135	139	139	
Mean (SD)	1.921 (0.7825)	2.042 (0.9164)	2.061 (0.8971)	
Range[3]	0.64-4.27	0.63-5.97	0.42-5.48	

1. Number of patients completed study: it refers to the number of patients who completed the randomized treatment period of the study.
2. Number of patients discontinued study: it refers to the number of patients who discontinued the study before completion of the randomized treatment period.
3. Based on the old versions of protocol (prior to version 4.0) there were two visits in dietary run-in phase data and visit 3 data were used as baseline, while in the updated protocol there were only one visit in dietary run-in phase data and visit 2 data were used as baseline. Among patients used the old version of CRF, there were some cases that LDL-C or TG levels were out of the range defined in the inclusion criteria at visit 3 (the baseline) but were normal at visit 2, and these patients were eligible according to the protocol and randomized in the study.
4. The patient E0012005 had LDL-C evaluation data at visit2 but missed lipids results in Visit 3, therefore the number of patients in Rosuvastatin 5mg group at baseline TG was 135.
Data derived from the Appendix 12.2.1.1 - 12.2.1.2, the Appendix 12.2.3.1-12.2.3.5, and the Appendix 12.2.4.1, 12.2.9, and 12.2.8.3.

Summary of efficacy results

The first primary efficacy variable for the study was the percentage change from baseline in LDL-C concentration after 6 weeks of treatment, comparing rousuvastatin 5mg with atorvastatin 10mg (from week 0 to week 6). The percentage changes from baseline in LDL-C concentration (LSmeans (SE)) after 6 weeks of treatment were -41.70% (2.62) and -38.67% (2.64) in the rosuvastatin 5mg and atorvastatin 10mg groups respectively, the LSmeans of treatment difference was 3.03 % (97.5% CI -1.49%, 7.54%) between rosuvastatin 5mg and atorvastatin 10mg groups. There was no significant difference in percentage change from baseline in LDL-C concentration between rosuvastatin 5mg and atorvastatin 10mg groups after 6 weeks of treatment in ITT population (See Table S3).

Table S3 Analysis of percentage change from baseline in LDL-C concentration at Week 6 comparing rosuvastatin 5mg with atorvastatin 10mg (ITT Population)

LDL-C (mmol/L)	Rosuvastatin 5mg (N=136)	Atorvastatin 10mg (N=139)
Baseline		

LDL-C (mmol/L)	**Rosuvastatin 5mg (N=136)**	**Atorvastatin 10mg (N=139)**
n	136	139
mean	4.242	4.213
SD	0.6769	0.6617
median	4.14	4.07
range	2.95-6.73	2.28-5.95
Week 6		
n	136	139
mean	2.534	2.660
SD	0.7174	0.7997
median	2.45	2.47
range	1.17-5.11	1.49-6.02
Percentage change from baseline (%)		
n	136	139
mean	-39.715	-36.486
SD	16.5545	17.4926
median	-42.50	-40.80
range	-76.00-24.00	-62.60-44.60
LSmeans(SE)	-41.70(2.62)	-38.67(2.64)
LSmeans of treatment difference (97.5% CI Contrast to Atorvastatin 10mg)	3.03(-1.49,7.54)	
P value(Contrast to Atorvastatin 10mg)	0.1323	

The analyses method was analysis of covariance (ANCOVA) model with factors fitted for treatment, centre, risk factor, LDL-C concentration at baseline, treatment by centre and treatment by risk factor.
If the interaction terms are found no significance ($p \geq 0.05$), these terms will be dropped from the model.
Treatment difference is calculated as Atorvastatin10mg minus Rosuvastatin 5mg
Data derived from the Appendix 12.2.8.3

The second primary efficacy variable for the study was the percentage change from baseline in LDL-C concentration after 6 weeks of treatment, comparing rousuvastatin 10mg with atorvastatin 10mg (from week 0 to week 6). The percentage changes from baseline in LDL-C concentration (LSmeans (SE)) after 6 weeks of treatment were -46.28% (2.62) and -38.67% (2.64) in the rosuvastatin 10mg and atorvastatin 10mg groups respectively, the LSmeans of treatment difference was 7.61% (97.5% CI 3.11%, 12.11%) (P=0.0002) between rosuvastatin 10mg and atorvastatin 10mg groups. The difference in percentage change from baseline in LDL-C concentration was significantly larger in the rosuvastatin 10mg group compared with the atorvastatin 10mg group after 6 weeks of treatment in ITT population (See Table S4).

Table S4 Analysis of percentage change from baseline in LDL-C concentration at Week 6 comparing rosuvastatin 10mg with atorvastatin 10mg (ITT Population)

LDL-C (mmol/L)	**Rosuvastatin 10mg (N=139)**	**Atorvastatin 10mg (N=139)**
Baseline		
n	139	139
mean	4.131	4.213
SD	0.6818	0.6617
median	3.96	4.07
range	2.66-6.80	2.28-5.95
Week 6		
n	139	139
mean	2.296	2.660
SD	0.6963	0.7997
median	2.12	2.47
range	1.37-4.91	1.49-6.02

LDL-C (mmol/L)	**Rosuvastatin 10mg (N=139)**	**Atorvastatin 10mg (N=139)**
Percentage change from baseline (%)		
n	139	139
mean	-43.944	-36.486
SD	17.3252	17.4926
median	-47.40	-40.80
range	-63.60-44.00	-62.60-44.60
LSmeans(SE)	-46.28(2.62)	-38.67(2.64)
Lsmeans of treatment difference (97.5%CI Contrast to Atorvastatin 10mg)	7.61(3.11,12.11)	
P value(Contrast to Atorvastatin 10mg)	0.0002	

The analyses method was analysis of covariance (ANCOVA) model with factors fitted for treatment, centre, risk factor, LDL-C concentration at baseline, treatment by centre and treatment by risk factor.
If the interaction terms are found no significance ($p \geq 0.05$), these terms will be dropped from the model.
Treatment difference is calculated as Atorvastatin10mg minus Rosuvastatin 10mg
Data derived from the Appendix 12.2.8.3

There were no significant differences (LSmeans of treatment difference) between rosuvastatin 5mg and atorvastatin 10mg in percentage change from baseline in HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I at week 6, while the percentage changes from baseline in TC, nonHDL-C, ApoB, TC/HDL-C, LDL-C/HDL-C, and ApoB/ApoA-I at week 6 were significantly larger in rosuvastatin 10mg group than in the atorvastatin 10mg group ($P<0.025$). The percentage changes from baseline in HDL-C, TG, ApoA-I, and nonHDL-C/HDL-C at week 6 were similar in the rosuvastain10mg and atorvastatin 10mg groups.

The LDL-C and nonHDL-C goal attainment according to ATP III guideline (2001) at week 6 were numerically greater in rosuvastatin 5mg group compared with atorvastatin 10mg group, while significantly greater in rosuvastatin 10mg group than atorvastatin 10mg group.

Among those patients who did not achieve goal in the double blind phase, there were 41.2% (14 patients) achieved LDL-C goal after dose titration from rosuvastatin 5mg to 10mg, and

47.6% (10 patients) achieved LDL-C goal after dose titration from rosuvastatin 10mg to 20mg.

Summary of safety results

Table S5 and S6 summarized AEs occurring during the randomized treatment period and extension treatment period respectively.

During the randomized treatment period, percentages of patients with adverse events (AEs) were slightly higher in the rosuvastatin 5mg (12.4%) and 10mg (11.7%) treatment groups than the atorvastatin 10mg group (8.9%). Study drug related AEs were also slightly higher in the rosuvastatin 5mg (4.8%) and 10mg (3.4%) treatment groups than the atorvastatin 10mg group (1.4%). There was no death in the study, the percentage of patients with serious AE (SAE) were 0.7%, 0, 0.7% in the rosuvastatin 5mg, rosuvastatin 10mg and atorvastatin 10mg groups respectively. Percentages of patients discontinue from the investigational products due to an AE (DAE) were similar in the rosuvastatin 5mg (1.4%) and atorvastatin 10mg (1.4%) groups which were higher than that of rosuvastatin 10mg group (0%). Percentages of patients with other significant AE (OAE) were 3.4%, 2.1%, and 0.0% in the rosuvastatin 5mg, rosuvastatin 10mg and atorvastatin 10mg groups respectively.

Overall, treatment with rosuvastatin 5mg-20mg were well tolerated over the 6-week randomized treatment period and 6-week extension treatment period in patients with hypercholesterolaemia. The tolerability of rosuvastatin 5mg and 10mg was comparable to atorvastatin 10mg during the randomized treatment period, with low incidence of DAEs.

In the study, there were no serious liver, renal and skeletal muscle injury occurred over the whole study period.

Table S5 Overview of Adverse Events during randomized treatment period (Safety population)

Category of adverse event	Rosuvastatin 5mg (N=145) N (%)	Rosuvastatin 10mg (N=145) N (%)	Atorvastatin 10mg (N=146) N (%)	Total (N=436) N (%)
Number of reported adverse events (AE)	31	22	17	70
Number of patients with at least one AE	18 (12.4%)	17 (11.7%)	13 (8.9%)	48 (11.0%)
Number patients with at least one severe adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number Patients with at least one study drug related AE	7 (4.8%)	5 (3.4%)	2 (1.4%)	14 (3.2%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Category of adverse event	Rosuvastatin 5mg (N=145) N (%)	Rosuvastatin 10mg (N=145) N (%)	Atorvastatin 10mg (N=146) N (%)	Total (N=436) N (%)
Number of patients with at least one serious adverse event (SAE) other than death	1 (0.7%)	0 (0.0%)	1 (0.7%)	2 (0.5%)
Number of patients with at least one adverse event leading to discontinuation of investigational drug (DAE)	2 (1.4%)	0 (0.0%)	2 (1.4%)	4 (0.9%)
Number of patients with at least one other significant adverse event (OAE)	5 (3.4%)	3 (2.1%)	0 (0.0%)	8 (1.8%)

Definition of other significant adverse event: 1.AEs leading to discontinuation of the subject from study treatment, other than SAE 2.AEs leading to dosing adjustment, other than SAE.
Data derived from the Appendix 12.2.7.1

Table S6 Overview of Adverse Events during extension treatment period (Safety population)

	Rosuvastatin titrated from 5mg to 10mg (N=36)	Rosuvastatin titrated from 10mg to 20mg (N=23)	Total (N=59)
Number of reported adverse events (AE)	4	1	5
Number of patients with at least one AE	2 (5.6%)	1 (4.3%)	3 (5.1%)
Number patients with at least one severe adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number Patients with at least one study drug related AE	1 (2.8%)	1 (4.3%)	2 (3.4%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of patients with at least one serious adverse event (SAE) other than death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of patients with at least one adverse event leading to discontinuation of investigational drug (DAE)	1 (2.8%)	0 (0.0%)	1 (1.7%)
Number of patients with at least one other significant adverse event (OAE)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Definition of other significant adverse event: 1.AEs leading to discontinuation of the subject from study treatment, other than SAE 2.AEs leading to dosing adjustment, other than SAE.

Data derived from the Appendix 12.2.7.1