AstraZeneca

CLINICAL STUDY REPORT

DRUG SUBSTANCE	Rosuvastatin Calcium
STUDY CODE	NIS-CGR-CRE-2007/1
VERSION NUMBER	3.0
DATE	14 October 2009

Study Title: A multi-centre, open label, non-randomized, non interventional, 24-week study for the assessment of efficacy, safety and tolerability of rosuvastatin (Crestor®) following its administration in hypercholesterolaemic patients, in real life clinical practice in Greece

STUDY DATES	Date of 1st Patient enrolled: *01 December 2007* Date of Last Patient Completed: *21 December 2008*
PHASE OF DEVELOPMENT:	Observational, Non Interventional, Phase IV Study

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and specific terms are used in the present clinical study report

Abbreviation	Explanation
AE	Adverse Event
CK	Creatinine Kinase
CRF	Case Report Form
EAS	European Atherosclerosis Association
EOF	National Organization for Medicines (in Greece)
GCP	Good Clinical Practice
HDL	High Density Lipoprotein
HDL-C	HDL-Cholesterol
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board (Hospital Scientific Committee/Administrative Council)
ITT	Intention To Treat
LDL-C	Low Density Lipoprotein - Cholesterol
OR	Odds Ratio
SAE	Serious Adverse Event
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPC	Summary of Product Characteristics
TC	Total Cholesterol
TG	Triglycerides
TJETF	Third Joint European Task Force
WHO	World Health Organization

1 ETHICS

1.1 Review and approval by the competent authorities

The final study protocol, including the final version of the Patient's Informed Consent Form, have been approved by the competent IRB (Scientific Committee/Administrative Council) of the participating coordinating Hospital Sites and the National Organization for Medicines (EOF), before the enrolment of any patient into the study and the performance of any study related procedure. All study amendments and/or administrative changes pertaining to the approved protocol have been also submitted to EOF for approval.

1.2 Ethical conduct of the study

The study has been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (ICH-GCP guidelines), all applicable national and E.U. laws and regulations, and AstraZeneca policy on Bioethics.

1.3 Subject information and consent

Prior to the conduct of any study-related procedure, investigators ensured that each potential participating patient had been provided with accurate and adequate oral and written information about the nature, purpose, possible risks and benefits of the present study. Additionally, patients were informed regarding their right to discontinue their participation in the study at any time and for any reason. They have been given the opportunity to ask questions on the nature and purpose of the study and all study-related procedures, as well as adequate time for consideration whether or not they wish to participate in the study. The patient's signed informed consent form (ICF) was obtained in duplicate before enrolling the patient into the study. The original signed ICF was archived by the investigator while a copy of the signed ICF was given to the patient.

2 INTRODUCTION

Several clinical studies have demonstrated the efficacy of statins in reducing low-density lipoprotein cholesterol (LDL-C) and risk of cardiovascular disease. However, in routine clinical practice many patients receiving statin therapy fail to achieve their LDL-C goals, set by European guidelines, probably due to suboptimal titration schedules. A number of factors may limit dose titration in clinical practice, while the choice of statin appears to play the most important role in the outcome of statin therapy. In the primary care setting, the availability of

hypolipidemic agents, such as rosuvastatin, which due to its pharmacological profile, allow patients to achieve their LDL-C goals with decreased need for dose titration, is particularly important for the optimization of treatment outcomes and the maximization of clinical benefit for this subject population. This study aimed at demonstrating the efficacy profile of rosuvastatin (Crestor®) in Greek subjects with hypercholesterolemia, in real life clinical practice.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study primary objective and primary endpoints

The primary objective of the study was the assessment of rosuvastatin efficacy, measured by the change in LDL-cholesterol (LDL-C) levels, from baseline (before the commencement of rosuvastatin administration) to Week 12 of the study.

The primary endpoints were the following:

- The percentage change in LDL-C levels from baseline to Week 12
- The percentage of patients reaching the LDL-C target levels (according to EAS guidelines) at Week 12.

3.2 Study secondary objectives and secondary endpoints

Secondary objectives were the assessment of the efficacy of treatment with rosuvastatin in modifying other lipids and lipoprotein fractions, as well as the evaluation of safety and tolerability profile of rosuvastin when administered in hypercholesterolaemic subjects in real life clinical setting.

Secondary endpoints were the following:

- The percentage change in HDL-C, total cholesterol (TC) and fasting triglycerides (TG) levels from the period prior to rosuvastatin therapy initiation (baseline values - historical data) to Week 12 of the study
- The percentage change in LDL-C levels from Week 12 to Week 24 of the study and from the period prior to rosuvastatin therapy initiation (baseline values - historical data) to Week 24 of the study
- The percentage change in HDL-C, total cholesterol (TC) and fasting triglycerides (TG) levels from Week 12 to Week 24 of the study and from the period prior to rosuvastatin therapy initiation (baseline values - historical data) to Week 24 of the study

- The dose titration schedule followed until the achievement of LDL-C target levels, in real life clinical practice
- The percentage of patients reaching the LDL-C goal (as defined by the EAS guidelines) at Week 24
- Identification of risk factors associated with potential failure to attain LDL-C goals in routine clinical practice
- Assessment of rosuvastatin safety profile, by evaluating the incidence and severity of adverse events throughout the study
- Evaluation of rosuvastain tolerability profile by assessing the treatment compliance rate among the study population, throughout the study.

4 INVESTIGATIONAL PLAN AND PROCEDURES

4.1 Overall study design and flow chart

This is an open label, non-interventional, non randomized, observational study for the evaluation of efficacy and safety profile of rosuvastatin (Crestor®), administered once daily, in Greek hypercholesterolemic subjects who were already treated with rosuvastatin therapy prior to their enrollment in the study.

The study was initially planned to be conducted with the participation of 130 private office-based physicians (comprising of private practice general practitioners, specialists in internal medicine and cardiologists), under the coordination of 9 hospital centers. Additionally, the recruitment of up to 910 patients was anticipated.

Overall, 116 physicians finally participated in the study (coordinated by 9 hospital sites) and 810 patients were enrolled.

Following study initiation (Day 0 - Visit 1), follow-up visits were performed on Weeks 12 and 24 (visit 2 and 3 respectively). Investigators also retrospectively collected relevant data of the lipidaemic profile of patients during the period prior to rosuvastatin therapy initiation (if available).

Adverse Events (AEs) and Serious Adverse Events (SAEs) were collected and reported by the investigators over the whole study duration.

The study flowchart is summarized in Table 1.

Table 1 Study Flowchart

	Initial Visit	Follow-up Visit	Final Visit
Procedures	**Visit 1** Week 0	**Visit 2** Week 12 +/- 3 days	**Visit 3** Week 24 +/- 3 days
Subject's Informed Consent	X		
Inclusion/Exclusion criteria	X		
Demographic data (date of birth, gender, ethnicity, height)	X		
Demographic data (Weight)	X	X	X
History of smoking/alcohol consumption and dietary habits	X		
Vital Signs[1]	X	X	X
Concomitant diseases/Concomitant medications	X	X	X
Medical history of hypercholesterolemia	X		
Current concomitant hypolipidemic medication	X	X	X
Date of Crestor® therapy initiation and prescribed dosage	X		
Subject's lipidemic profile[2] prior to Crestor® therapy commencement	X		
Subject's lipidemic profile[2], within 4 weeks prior to Visit		X	X
Biochemistry[3] (if available)	X	X	X
Study drug	X	X	X
Assessment of patient's compliance with therapy	X	X	X
Record of adverse drug reactions (related to the study drug)		<----------X---------->	
Record of all adverse events		<----------X---------->	

[1] Vital signs include the measurement and record of arterial pressure (SAP and DAP) and heart rate
[2] Lipidemic profile includes the record of LDL-C, HDL-C, total cholesterol and triglycerides levels
[3] Biochemistry: Transaminases (SGOT, SGPT) and CK (if available)

4.2 Discussion of study design and non-interventional type of the study

This is a non-interventional study evaluating the efficacy and safety of Crestor® when administered in patients with hypercholesterolemia, who were already being treated with rosuvastatin prior to their enrolment into the study.

The observance of the following rules has ensured the non-interventional character of this project:

- Rosuvastatin (Crestor®) was already administered to the participating patients prior to their enrollment into study and according to the currently approved labeling (SPC). Upon their enrollement, dose titration (if required) was performed depending on patients' clinical response and tolerability, as well as physicians' clinical judgment.
- The participating patients did not undergo diagnostic or follow-up procedures other than those usually implemented by their treating physician.
- Statistical analysis of collected data was performed with the use of appropriate descriptive statistical methods.

The study has been designed to follow up patients for 24 weeks (6 months). This time period is considered adequate to allow the manifestation and the documentation of the efficacy and safety profile of study medication.

4.3 Selection of study population

4.3.1 Inclusion criteria

- Any subject with hypercholesterolemia who was already in treatment with rosuvastatin, according to the product's SPC, within the last month prior to study entry, and for whom data regarding his/her lipidemic profile before rosuvastatin therapy commencement were available.
- Adult outpatients of both genders, aged between 18 - 80 years.
- Patients who were able to read and understand the *Patient Information Sheet*.
- Patients who had signed the *Informed Consent Form*.
- Patients who were willing to comply will all study requirements.

4.3.2 Exclusion criteria

- Subjects who were unlikely to comply with protocol requirements (e.g., non-cooperative behavior, inability to attend the required by the protocol visits).
- Subjects who were currently participating or had participated in other interventional study the last 3 months prior to their enrolment.
- Women who were pregnant, breast feeding or had the intention of becoming pregnant during their participation in the study.
- Women of childbearing potential who were not using effective and medically acceptable methods of contraception
- Subjects who were meeting any of the contraindications of the study medication according to the approved SPC.

4.3.3 Subjects' withdrawal of treatment or assessment

Subjects were free to discontinue their participation in the study at any time, and without prejudice to their future treatment. Subjects who discontinued the study were asked about the reason(s) for their discontinuation and about the presence of any adverse events and, if possible, were seen and assessed by the investigator. Adverse Events were followed up until resolution or stabilization.

4.4 Treatment regimen

4.4.1 Identity of study medication

Name:	Crestor®, film-coated tablets for oral use
Stength:	According to the approved Summary of Product Characteristics
Manufacturer/MAH:	AstraZeneca

4.4.2 Dosage of the study prescribed medication

For details regarding the administered dosage of study medication please refer to section 8 of Clinical Study Protocol.

4.4.3 Pre-study, concomitant and post-study treatment(s)

All concomitant medications received by the patient were recorded in the Case Report Form (CRF) throughout the study.

4.4.4 Treatment compliance

Patients were asked at each study visit if they had taken their medication as prescribed by the investigator, and their compliance was recorded in the CRF.

5 STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE DETERMINATION

As this is a non-interventional study, statistical analysis of collected data, including baseline demographic and somatometric data, reports of AEs/SAEs, as well as study endpoints and outcome variables, was performed using appropriate descriptive statistical methods.

5.1 Determination of sample size

It was anticipated that the enrolment of 820 subjects would provide a probability of > 95% to detect a 40% difference in the primary endpoint, which was the change in LDL-C levels from baseline (prior to Crestor® therapy commencement) to Week 12 of the study. Taking into consideration a drop out rate of 10%, the final sample size was estimated to be 910 subjects in order to secure the afore-mentioned sample size for the final statistical analysis. Based on these estimations, the final sample size of 810 evaluable patients is considered sufficient to meet the primary objective of this protocol with a high statistical power.

5.2 Statistical and analytical methods

Summary statistics were used to present the data of this study. Specifically, the mean value, the standard deviation, the median value and the range (minimum - maximum values) were used for the analysis and the presentation of continuous variables. Categorical variables were summarized as frequency distribution tables and relevant percentages.

In order to assess the mean change in the continuous variables between the study visits, the paired t-test was used. The difference in the distribution of the categorical variables between the study groups was analyzed using the chi-square test.

All tests were two-tailed and statistical significance level was set at a=0.05.

Data processing and analysis were performed using the statistical package SPSS v. 17.0.

5.3 Description of analysis sets

Statistical Analysis was performed for the total of 810 subjects who participated in the study, as anticipated by the clinical study protocol.

A post hoc secondary analysis of the primary variables was performed in the population with no violation/deviation from the protocol-defined eligibility criteria.

5.4 Statistical and analytical considerations

For the analysis of safety data and efficacy measures the 'Intention to Treat Population, ITT' was used, which is defined as the patients who took at least one dose of the study medication and had at least one post-baseline efficacy assessment. Missing data were not imputed.

6 STUDY SUBJECTS

6.1 Subjects who participated and completed the study

Overall 810 subjects participated in the present study, and were enrolled by 116 investigational sites. All subjects met the eligibility criteria for study entry. Overall 787 (97.2%) subjects completed the study.

6.2 Protocol deviations

Overall 185 patients* violated/deviated from the study protocol regarding eligibility. More specifically:

- 108 patients had baseline LDL-C value which was after rosuvastatin treatment commencement.
- 15 patients performed visit 1 (initial visit) before rosuvastatin treatment commencement.
- 74 subjects started rosuvastatin more than 1 month before visit 1.

**More than one of the aforementioned violations/deviations were observed in some patients.*

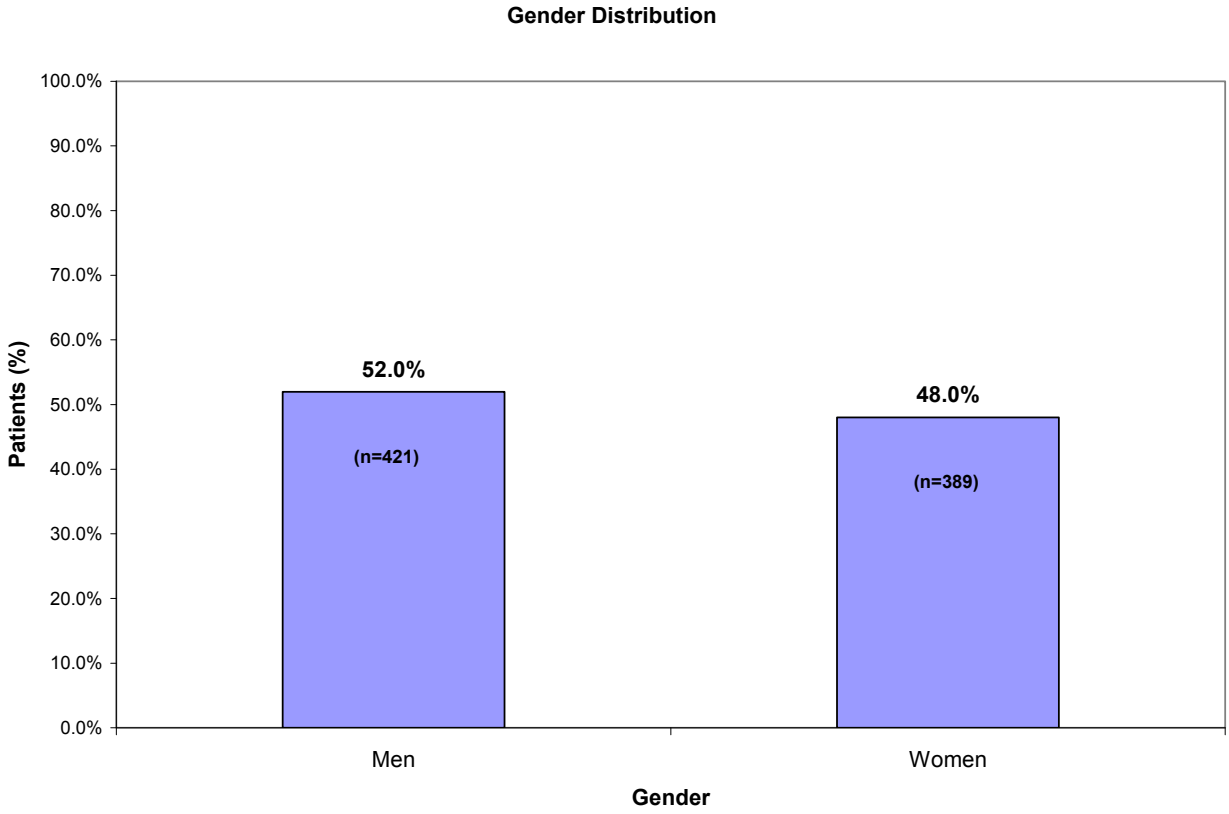
6.3 Subjects analyzed

Overall 810 subjects were analyzed.

6.4 Subjects demographic and baseline characteristics

A slight preponderance of men over women 52.0%/48.0% was observed among the study population [Figure 1].

Figure 1 Frequency distribution of subjects' gender



Almost all the patients participating in the study were Caucasians (96.4%) [Table 2].

Table 2 Frequency distribution of subjects' race

Race	n	%
Caucasian	781	96.4%
Black	2	0.2%
Asian	2	0.2%
Other	0	0.0%
Missing Data	25	3.1%

Table 3 presents the summary statistics of subjects' demographic and baseline data. Subjects that participated in the study had a mean age of 59.1±10.9 years [Table 3]. Except of a subject with body weight of 129 kilograms, for the rest of the study participants no extreme values regarding their height and weigh were reported. The mean BMI indicates that study population was mainly

overweight [Table 3]. Mean systolic and diastolic blood pressures were 132.7mmHg and 81.1mmHg, respectively [Table 3].

Table 3 Summary statistics of subjects' demographic and baseline data

Variable	Mean	Std Dev	Median	Minimum	Maximum	N
Age (years)	59.1	10.9	59.0	25.0	83.0	810
Weight (kg)	79.7	12.9	79.0	40.0	129.0	810
Height (cm)	168.8	8.6	168.0	140.0	194.0	809
BMI (kg/m^2)	27.9	3.8	27.0	18.0	50.0	809
Heart rate (beats/min)	75.3	8.8	75.0	50.0	172.0	806
Systolic BP (mmHg)	132.7	13.5	130.0	95.0	195.0	810
Diastolic BP (mmHg)	81.1	8.3	80.0	60.0	115.0	810

6.5 Dietary habits and history of smoking/alcohol consumption

More than half of subjects participated in the study (65.1%) reported moderate consumption of foods high in saturated fatty acids, while 62.6% of them were following a balanced diet according to their treating physician's recommendation [Table 4].

Table 4 Dietary habits

Dietary Habits	n	%
Consumption of foods high in saturated fatty acids		
High	158	19.5%
Moderate	527	65.1%
None	95	11.7%
Missing	30	3.7%
Balanced diet after medical advice		
Yes	507	62.6%
No	272	33.6%
Missing	31	3.8%

31.0% of the patients were current smokers [Table 5], while almost 1/5 of them were consuming alcohol [Table 6]. The daily average alcohol intake was 2.1 glasses/day.

Table 5 Smoking habits

Smoking Habits	n	%
Current Smoker	251	31.0%
Non smoker	559	69.0%
Past-smoker	120	14.8%

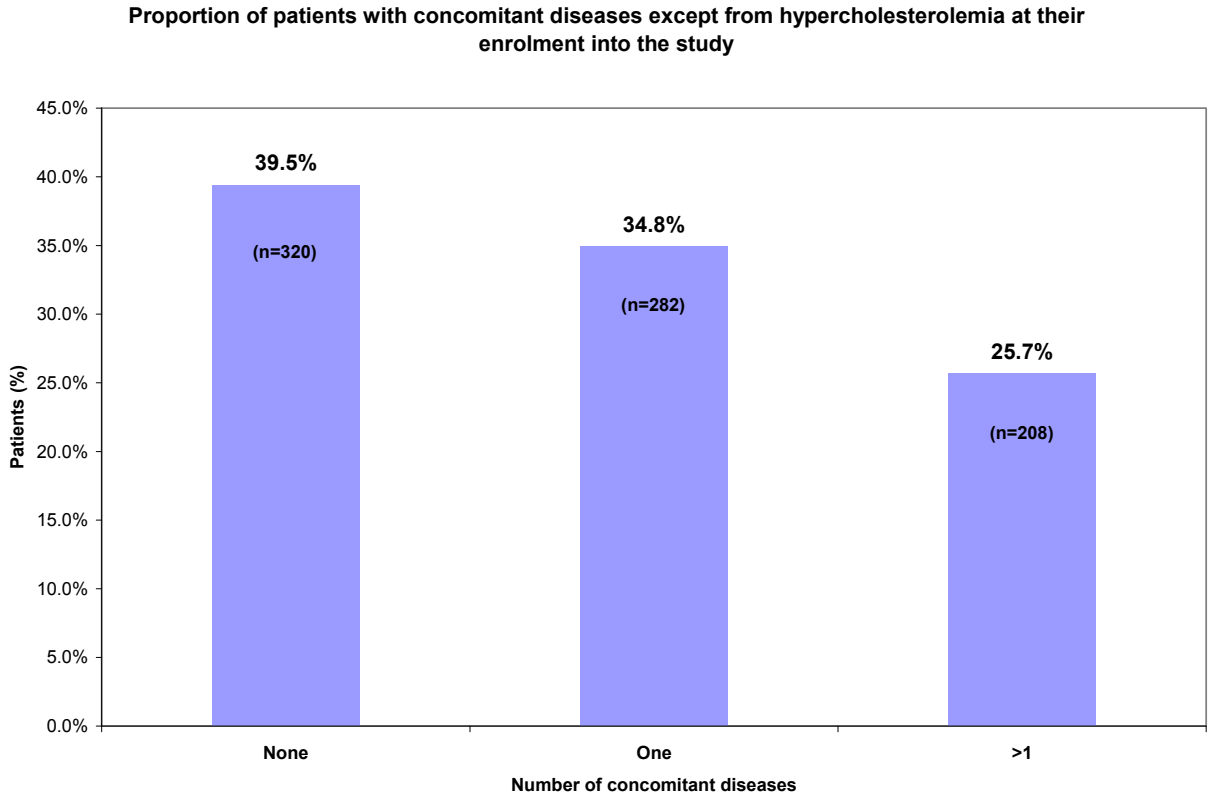
Table 6 Alcohol consumption

Alcohol Consumption	n	%
Yes	186	23.0%
No	621	76.7%
Missing	3	0.4%

6.6 Medical history and concomitant diseases

39.5% of the patients didn't suffer from any other disease except of hypercholesterolemia, while 490/810 (60.5%) reported at least one concomitant disease according to their medical history [Figure 2].

Figure 2 Proportion of patients with concomitant diseases



Tables 7, 8, 9 and 10 present in detail all concomitant diseases of study participants, based on their medical history and categorized by organ system.

The majority of concomitant diseases recorded, were falling within the categories of cardiovascular (39.6%), endocrine-metabolic (19.3%), and musculoskeletal disorders (10.2%).

Table 7 Medical history and list of concomitant diseases (a)

Medical History and Concomitant Diseases	n	%
Cardiovascular Diseases	**321**	**39.6%**
Arterial Hypertension	194	24.0%
Coronary Artery Disease	94	11.6%
Cardiac arrhythmia	12	1.5%
Valvular Heart Disease	12	1.5%
Congestive Heart Failure	3	0.4%
Abdominal Aortic Aneurysm	2	0.2%
Cardiac Conduction Disease	1	0.1%
Fallot's Tetralogy	1	0.1%
Pericarditis	1	0.1%
Prinzmetal's Angina	1	0.1%
Atherosclerotic Cerebrovascular Disease	**13**	**1.6%**
Cerebrovascular Accident	11	1.4%
Carotic Artery Stenosis	2	0.2%
Respiratory Disease	**45**	**5.6%**
COPD	32	4.0%
Bronchial Asthma	9	1.1%
Bronchitis	3	0.4%
Bronchopneumonia	1	0.1%
Liver-Kidney-Pancreas Disease	**20**	**2.5%**
Fatty Liver Infiltration	4	0.5%
Hepatitis B	3	0.4%
Pancreatitis	3	0.4%
Renal Lithiasis	3	0.4%
Chronic Renal Failure	2	0.2%
Australia-Antigen Positive	1	0.1%
Chololithiasis	1	0.1%
Polycystic Kidney Disease	1	0.1%
Pyelonephritis	1	0.1%
Steatohepatitis	1	0.1%
Skin Disease	**18**	**2.2%**
Psoriasis	5	0.6%
Eczematous Dermatitis	3	0.4%
Psoriatic Arthritis	2	0.2%
Scleroderma	2	0.2%
Acne	1	0.1%
Atopic Dermatitis	1	0.1%
Nail Mycosis	1	0.1%
Pemphigus	1	0.1%
Pityriasis Versicolor	1	0.1%
Xanthelasma	1	0.1%

Table 8 Medical history and list of concomitant diseases-continued (b)

Medical History and Concomitant Diseases	n	%
Gastrointestinal Disease	**76**	**9.4%**
Gastroesophageal Reflux Disease	23	2.8%
Gastritis	21	2.6%
Duodenal Ulcer	12	1.5%
Esophagitis	4	0.5%
Irritable Bowel Syndrome	4	0.5%
Peptic Ulcer	4	0.5%
Colitis	2	0.2%
Colorectal Polyps	2	0.2%
Diaphragmatic Hernia	2	0.2%
Gastric Neurosis	1	0.1%
Gastrorrhagia	1	0.1%
Genitourinary Disease	**25**	**3.1%**
Benign Prostate Hyperplasia	16	2.0%
Urinary Tract Infection	6	0.7%
Prostatitis	1	0.1%
Reccurent Cystitis	1	0.1%
Erectile Dysfunction	1	0.1%
Endocrine-Metabolic Disease	**156**	**19.3%**
Diabetes Mellitus Type II	94	11.6%
Hypothyroidism	29	3.6%
Diabetes Mellitus Type I	5	0.6%
Thyroid Nodule	5	0.6%
Goiter	4	0.5%
Impaired Glucose Tolerance	4	0.5%
Hyperthyroidism	3	0.4%
Nodular Goiter	3	0.4%
Thyroidectomy	3	0.4%
Thyroidopathy	2	0.2%
Dysthyroid Ophthalmopathy	1	0.1%
Hashimoto's thyroiditis	1	0.1%
Latent Autoimmune Diabetes	1	0.1%
Hyperuricemia	1	0.1%

Table 9 Medical history and list of concomitant diseases -continued (c)

Medical History and Concomitant Diseases	n	%
Blood and Immune System Disease	**12**	**1.5%**
Anemia	8	1.0%
Leukopenia	2	0.2%
Chronic Myelogenous Leukemia	1	0.1%
Idiopathic Thrombopenia	1	0.1%
Neoplasmatic Disease	**10**	**1.2%**
Breast Cancer	4	0.5%
Colorectal Cancer	2	0.2%
Melanoma	1	0.1%
Prostate Cancer	1	0.1%
Head and Neck Carcinomas	2	0.2%
Psychiatric - Neurological Disease	**31**	**3.8%**
Depression	18	2.2%
Anxiety Disorder	5	0.6%
Vertigo	3	0.4%
Psychotic Syndrome	2	0.2%
Autonomic Nervous System Disorder	1	0.1%
Lower Extremity Neuropathy	1	0.1%
Poliomyelitis	1	0.1%

Table 10 Medical history and list of concomitant diseases -continued (d)

Medical History and Concomitant Diseases	n	%
Musculoskeletal Disorders	**83**	**10.2%**
Osteoporosis	23	2.8%
Low Back Pain	10	1.2%
Osteoarthritis	9	1.1%
Tendonitis	6	0.7%
Spondyloarthropathy	4	0.5%
Discopathy	3	0.4%
Osteopenia	3	0.4%
Sciatica	3	0.4%
Arthritis	2	0.2%
Cervical Syndrome	2	0.2%
Neck Pain	2	0.2%
Low Back and Leg Pain	2	0.2%
Uric Arthritis	2	0.2%
Arthralgias	1	0.1%
Arthropathy	1	0.1%
Carpal Tunnel Syndrome	1	0.1%
Injury of the Right Upper Extremity	1	0.1%
Lumbar Stenosis	1	0.1%
Myelopathy	1	0.1%
Retrogressive Spondylopathy	1	0.1%
Rheumatoid Arthritis	1	0.1%
Surgically Operated Hernia of Intervertebral Disc	1	0.1%
Surgically Operated Talipes Varus	1	0.1%
Finger Amputation	1	0.1%
Myalgias	1	0.1%
Peripheral Vascular Disease	**3**	**0.4%**
Chronic Obstructive Arteriopathy	2	0.2%
Lower Extremity Angiopathy	1	0.1%
Other	**10**	**1.2%**
Sleep Apnea Hypopnea Syndrome	2	0.2%
Hysterectomy	2	0.2%
Prostatectomy	2	0.2%
Chronic Venous Insufficiency of the Lower Extremities	1	0.1%
Gastric Ring	1	0.1%
Hypovitaminosis D3	1	0.1%
Thoracotomy (sphenoidal hamartoma resection)	1	0.1%

6.7 Presence of cardiovascular risk factors

Table 11 depicts the proportion of patients with cardiovascular (CV) risk factors.

Table 11 Proportion of patients with cardiovascular risk factors

Presence of CV Risk Factors	Statistic	Study Population (n=810)
History of Coronary Artery Disease		
Yes	n(%)	94 (11.6%)
No	n(%)	716 (88.4%)
History of Peripheral Artery Disease		
Yes	n(%)	3 (0.4%)
No	n(%)	807 (99.6%)
History of Cerebrovascular Disease		
Yes	n(%)	13 (1.6%)
No	n(%)	797 (98.4%)
Family History of Coronary Artery Disease		
Yes	n(%)	1 (0.1%)
No	n(%)	0 (0%)
Current Smoker		
Yes	n(%)	251 (31.0%)
No	n(%)	559 (69.0%)
Diabetes Mellitus		
Yes	n(%)	100 (12.3%)
No	n(%)	710 (87.7%)
Arterial Hypertension		
Yes	n(%)	194 (24.0%)
No	n(%)	616 (76.0%)
Low HDL-C level (<40mg/dL)		
Yes	n(%)	289 (35.7%)
No	n(%)	521 (64.3%)

6.8 Subjects' Risk Category According to 2003 TJETF Guidelines

In order to assess whether a patient had reached the LDL-C goal recommended by the TJETF guidelines, the risk category to which the patient was belonging was determined, as described in Table 12.

Table 12 2003 European risk categories and target goals (Third Joint Task Force)

Subject characteristics	European risk category	LDL-C goal
Atherosclerotic disease, or Type 2 diabetes, or TC ≥8 mmol/L (320 mg/dL), or LDL-C ≥6 mmol/L (240 mg/dL), or SBP ≥180 mmHg, or DBP ≥110 mmHg	High (1)	<100 mg/dL (2.5 mmol/L)
10-year risk of fatal CV disease ≥5%, and TC<5 mmol/L (190 mg/dL) and LDL-C <3 mmol/L (115 mg/dL)	High (2)	<100 mg/dL (2.5 mmol/L)
10-year risk of fatal CV disease ≥5%, and TC≥5 mmol/L (190 mg/dL) or LDL-C ≥3 mmol/L (115 mg/dL)	High (3)	<115 mg/dL (3.0 mmol/L)
10-year risk of fatal CV disease <5%	Other	<115 mg/dL (3.0 mmol/L)

The distribution of patients' European risk category based on TJETF guidelines, is described in Table 13. Based on this classification, for 33.8% of the participating patients the recommended LDL-C treatment goal was < 100mg/dL, and for the remaining 66.2% the LDL-C target was < 115mg/dL.

Table 13 Distribution of patients by risk category according to the TJETF guidelines

European Risk Category	n	%
High(1)	274	33.8%
High (2)	0	0.0%
High (3)	93	11.5%
Other	443	54.7%

6.9 Time since diagnosis of hypercholesterolemia

The mean time since diagnosis of hypercholesterolemia was 3.2 years, with minimum time of less than 1 year and maximum time of 46 years, respectively [Table 14].

Table 14 Summary statistics for the time since diagnosis of hypercholesterolemia of subjects participated in the study

Summary Statistics	Mean	Std Dev	Median	Minimum	Maximum	n
Time since diagnosis of hypercholesterolemia (in years)	3.2	4.7	1.0	0.0	46.0	790

6.10 Type of hypercholesterolemia

The distribution of patients per type of hypercholesterolemia based in three different classifications (Fredrickson classification, primary versus secondary, and familial versus non-familial) is presented in Table 15. Of the 609 (75.2%) patients with known type of hypercholesterolemia, 91.3% had type IIa or IIb hypercholesterolemia according to Fredrickson classification.

Table 15 Distribution of patients according to the type of hypercholesterolemia

Classification of Hypercholesterolemia	n	%
Fredrickson Classification		
Type I	44	5.4%
Type IIa	274	33.8%
Type IIb	282	34.8%
Type IV	9	1.1%
Unknown	201	24.8%
Primary vs Secondary		
Primary	264	32.6%
Secondary	36	4.4%
Unknown	510	63.0%
Familial vs Non-familial		
Familial	84	10.4%
Non-Familial	42	5.2%
Unknown	678	83.7%
Missing	6	0.7%

6.11 Lipid-lowering medications taken prior to Crestor® treatment commencement

Statins were the most frequently reported medication that study participants were taken prior to Crestor® treatment commencement [Table 16].

Table 16 Lipid-lowering medication prior to Crestor® treatment commencement

Lipid-lowering therapy prior to Crestor® treatment commencement	n	%
Statins	**163**	**20.1%**
Atorvastatin	67	8.3%
Lovastatin	3	0.4%
Pravastatin	28	3.5%
Fluvastatin	11	1.4%
Simvastatin	53	6.5%
Other	1	0.1%
Cholesterol Absorption Inhibitors	**8**	**1.0%**
Ezetimibe	8	1.0%
Cholesterol Absorption Inhibitors/Statin	**4**	**0.5%**
Ezetimibe+Simvastatin (INEGY)	4	0.5%
Fibrates	**4**	**0.5%**
Fenofibrate	2	0.2%
Gemfibrozil	1	0.1%
Other	1	0.1%
Omega-3 Fatty Acids	**12**	**1.5%**

6.12 Patient's lipidemic and biochemical profile prior to Crestor® treatment commencement

Table 17 presents summary statistics for patients' lipidemic and biochemical profile as evaluated at baseline (prior to Crestor® therapy initiation).

Table 17 Summary statistics of patients' lipidemic and biochemical profile at Visit 1

Lipidemic/biochemical profile - Visit 1	Mean	Std Deviation	Median	Min	Max	n
Total Cholesterol (TC)	273.5	41.2	273.0	120.0	520	810
HCL-C	46.1	13.2	42.0	21.0	98	807
LDL-C	183.4	38.6	181.0	59.4	460	803
Triglycerides	178.7	79.9	170.0	55.0	770	810
AST (SGOT)	25.0	8.2	24.0	7.0	56	725
ALT (SGPT)	26.7	10.1	26.0	7.0	82	724
Creatine Kinase (CK)	104.8	50.0	98.0	16.0	426	477

6.13 Recommended dosage of Crestor® at treatment commencement

The recommended initial dose of Crestor® at therapy commencement for the majority of the participating patients (89.6%) was 10mg - 20 mg [Table 18] and the mean dose was 14.7 mg/day (SD:7.7) [Table 24].

Table 18 Crestor® Dosage at treatment commencement

Total daily dose of Crestor® at treatment commencement	n	%
5 mg	38	4.7%
10 mg	456	56.3%
20 mg	270	33.3%
40 mg	45	5.6%
Missing	1	0.1%

6.14 Compliance with Crestor® treatment at Visit 1

Patients' compliance with Crestor® is presented in Table 19. 91.3% of the subjects reported good to very good compliance with therapy, as assessed at Visit 1.

Table 19 Compliance with Crestor® treatment at Visit 1

Compliance with Crestor® Therapy at Visit 1	n	%
Very good *(the patient was receiving the medication every day)*	586	72.3%
Good *(the patient was receiving the medication regularly)*	154	19.0%
Moderate *(the patient was receiving the medication irregularly)*	30	3.7%
Poor *(the patient was not receiving the medication most of the days)*	5	0.6%
Very poor *(the patient didn't receive the medication almost at all)*	3	0.4%
Missing data	32	4.0%

7 EFFICACY RESULTS

7.1 Analysis of primary efficacy variables

- ***Percentage change in LDL-C levels from baseline to Week 12 (Visit 2)***

The mean decrease in LDL-C levels at Week 12 compared to baseline was 32.3%. This represents a statistically significant change (<0.0001). Table 20 presents all summary statistics for the percentage changes observed in patients' lipidemic profile from baseline to Week 12. All percentage changes in mean values of lipid parameters were statistically significant (p<0.0001).

Table 20 Percentage change in lipid and biochemical values from baseline to Week 12

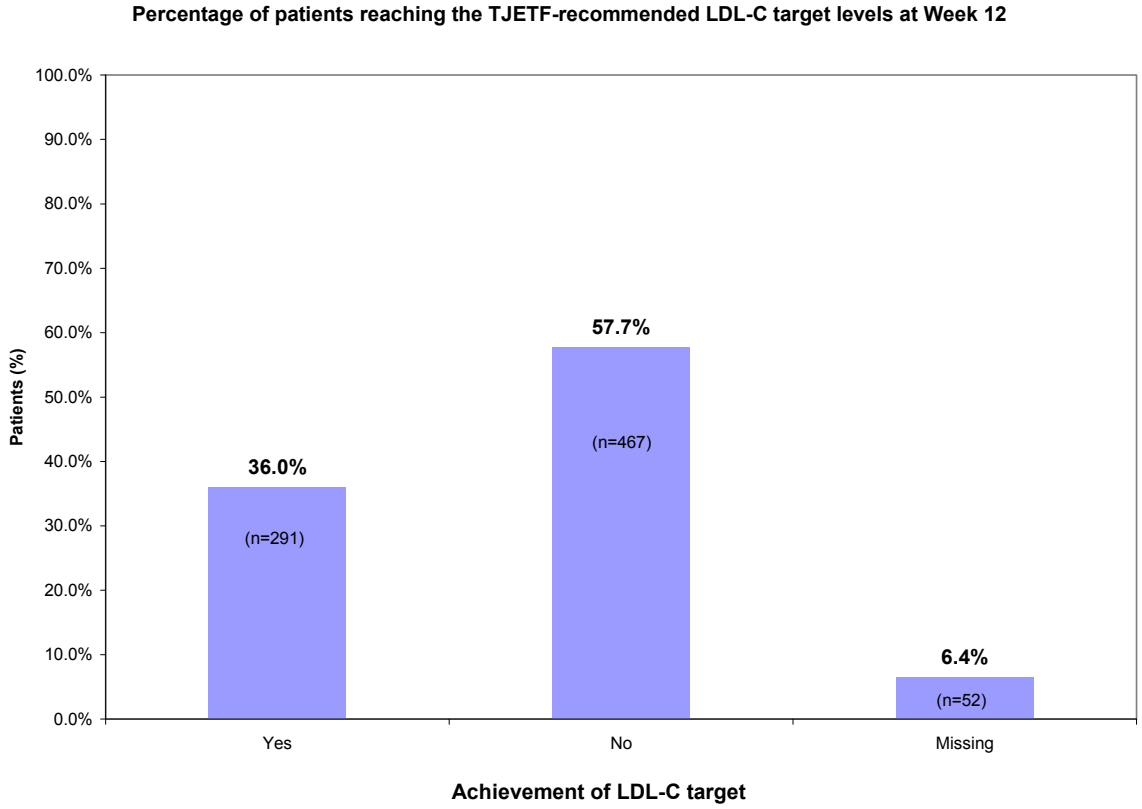
Percentage change from baseline to Visit 2	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
Total Cholesterol (TC)	-27.7	12.1	-27.6	-61.6	42.4	773	<0.0001*
HDL-C	6.5	18.0	5.6	-58.0	124.3	761	<0.0001*
LDL-C	-32.3	17.1	-32.0	-78.1	29.6	751	<0.0001*
Triglycerides (TG)	-16.5	25.5	-18.8	-80.0	123.0	764	<0.0001*

* Statistical Significant at α=0.05

- ***Percentage of patients reaching the TJETF-recommended LDL-C target levels at Week 12***

At Week 12, 36.0% (n=291) of the study participants reached their TJETF-recommended LDL-C target [Figure 3].

Figure 3 Percentage of patients reaching the TJETF-recommended LDL-C target levels at Week 12



- ***Identification of factors associated with potential failure to attain LDL-C goals after 12 Weeks of therapy***

Table 21 present the frequency of patients attaining the TJETF-recommended LDL-C target levels according to baseline characteristics. Correlation between the number of patients who failed to achieve their LDL-C target levels and the baseline characteristics, such as age group, BMI, gender and risk category were evaluated using the chi-square test. Regarding the three different classifications of hypercholesterolemia no statistical test was performed, as the majority of cases were not classified (their type of hypercholesterolemia was recorded as unknown), resulting in many missing data. The same applied for the type of therapy (monotherapy versus combination), where the majority of study participants were treated with Crestor® monotherapy. Therefore, only descriptive results are presented for these factors. Only risk category was statistically significantly related to LDL-C target achievement ($p<0.05$), whereas age, BMI and gender did not seem to be significantly correlated with LDL-C goal attainment. It should be stressed out that these results are only indicative of the correlation between the risk category and

the LDL-C achievement, since further analyses with more covariates should be used in order to draw more generalized and safe conclusions, which are beyond the purpose of this study.

Table 21 Patients attaining the TJETF-recommended LDL-C goal according to baseline characteristics at Visit 2

Visit 2 (Week 12)	Patients on LDL-C target		Patients not on LDL-C target		Total	p value
	n	%	n	%		
Overall	**291**	**35.9%**	**467**	**57.7%**	**810**	
Age						
<40	12	37.5%	20	62.5%	32	0.7789
40-54	86	36.6%	149	63.4%	235	
55-69	139	40.4%	205	59.6%	344	
≥70	54	36.7%	93	63.3%	147	
Missing					52	
Gender						
Male	150	37.5%	250	62.5%	400	0.5941
Female	141	39.4%	217	60.6%	358	
Missing					52	
BMI						
Normal weight (<25)	49	40.2%	73	59.8%	122	0.8196
Overweight (25-29)	162	38.8%	256	61.2%	418	
Obese (≥30)	80	36.9%	137	63.1%	217	
Missing					53	
Type of hypercholesterolemia						
Type I	16	41.0%	23	59.0%	39	NA
Type IIa	99	37.8%	163	62.2%	262	
Type IIb	90	34.5%	171	65.5%	261	
Type IV	2	28.6%	5	71.4%	7	
Unknown	84	44.4%	105	55.6%	189	
Missing					52	
Primary	99	40.1%	148	59.9%	247	NA
Secondary	20	64.5%	11	35.5%	31	
Unknown	172	35.8%	308	64.2%	480	
Missing					52	
Familial	27	35.5%	49	64.5%	76	NA
Non-Familial	20	54.1%	17	45.9%	37	
Unknown	243	37.9%	399	62.1%	642	
Missing					55	
Risk category						
High (1)	80	30.7%	181	69.3%	261	0.0055*
High (2)	-	-	-	-	-	
High (3)	35	39.8%	53	60.2%	88	
Other	176	43.0%	233	57.0%	409	
Missing					52	
Type of Therapy						
Crestor monotherapy	289	38.9%	453	61.1%	742	NA
Combination therapy	2	12.5%	14	87.5%	16	
Missing					52	

* Statistical significant at α=0.05

7.2 Analysis of secondary efficacy variables

- ***Percentage change in LDL-C levels from Week 12 to Week 24 of the study and from the period prior to rosuvastatin therapy initiation (baseline values) to Week 24 of the study***

Mean LDL-C levels were statistically reduced by 6.7% from Week 12 to Week 24 [Table 22] and by 38.2% from baseline to Week 24 [Table 23]. Both reductions reached statistical significance.

Table 22 Percentage change in lipids values from Week 12 to Week 24

Percentage change from Visit 2 to Visit 3	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
Total Cholesterol (TC)	-5.2	13.3	-5.3	-49.8	89.4	743	<0.0001*
HDL-C	3.1	12.1	2.2	-55.3	93.0	732	<0.0001*
LDL-C	-6.7	20.0	-6.5	-71.1	132.0	725	<0.0001*
Triglycerides (TG)	-2.1	28.7	-5.3	-84.6	261.6	730	<0.0001*

* Statistical Significant at α=0.05

Table 23 Percentage change in lipids values from baseline to Week 24

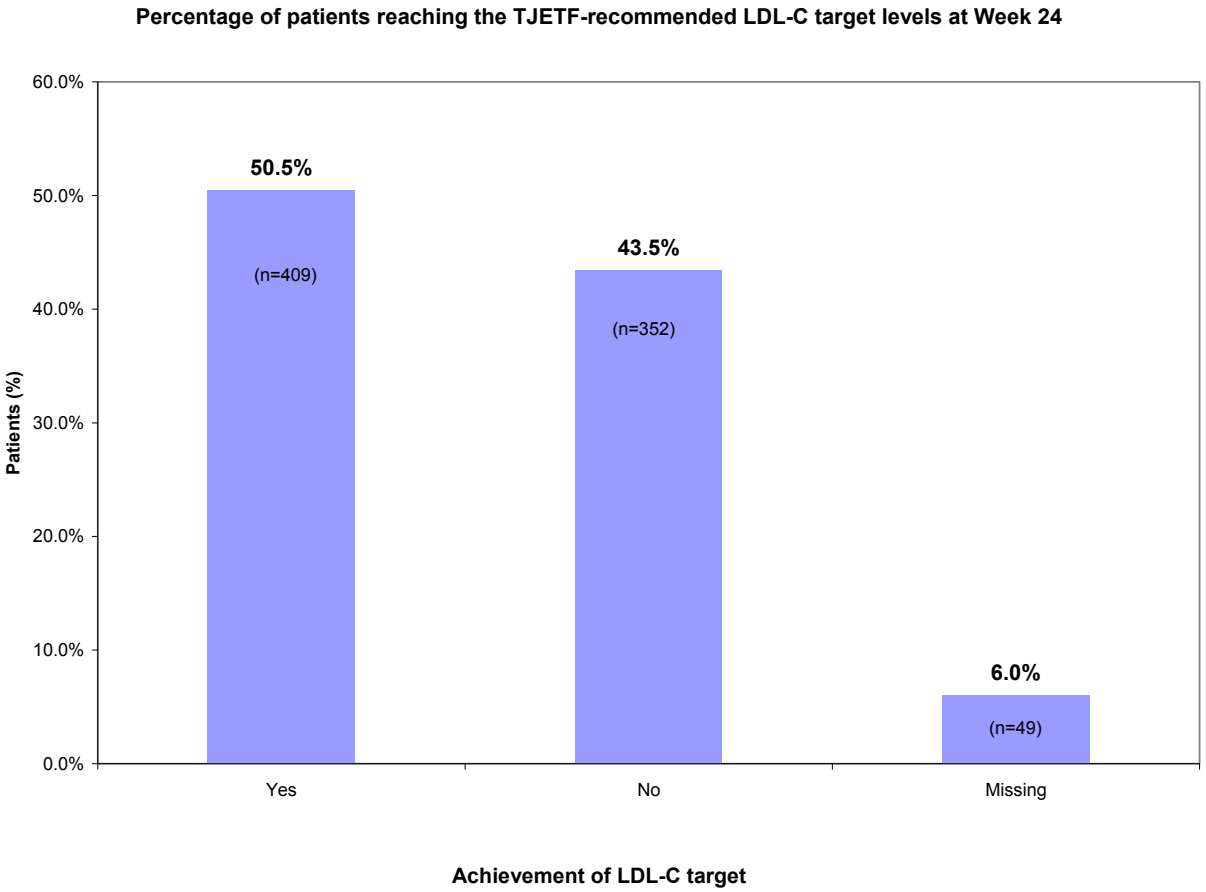
Percentage change from baseline to Visit 3	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
Total Cholesterol (TC)	-32.2	10.8	-32.8	-64.3	21.2	769	<0.0001*
HDL-C	9.4	21.4	7.6	-56.8	120.0	762	<0.0001*
LDL-C	-38.2	16.6	-39.3	-88.6	30.0	754	<0.0001*
Triglycerides (TG)	-20.4	28.7	-22.7	-92.6	179.7	760	<0.0001*

* Statistical Significant at α=0.05

- ***Percentage of patients reaching their LDL-C goal (as defined by the EAS guidelines) at Week 24***

At week 24, approximately half of all patients participated in study, achieved the TJETF recommended LDL-C target levels [Figure 4].

Figure 4 Percentage of patients reaching the TJETF –recommended LDL-C target levels at Week 24



- ***Percentage change in HDL-C, total cholesterol (TC) and fasting triglycerides (TG) levels from the period prior to rosuvastatin therapy initiation (baseline values) to Week 12 of the study***

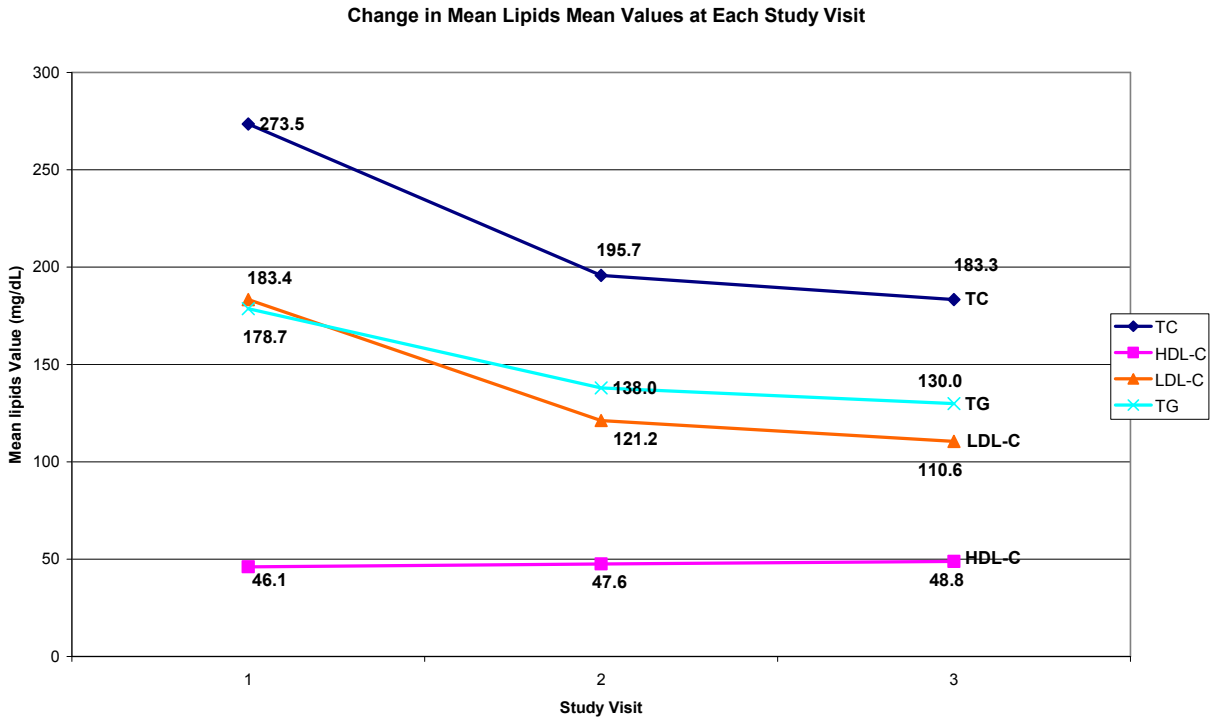
Both mean total cholesterol (TC) and triglycerides (TG) levels decreased significantly by 27.7% and 16.5% respectively ($p<0.0001$) [Table 20] from baseline to Week 12. Furthermore, a statistically significant increase of 6.5% in the mean HDL-C levels was observed ($p<0.0001$) [Table 20].

- ***Percentage change in HDL-C, total cholesterol (TC) and fasting triglycerides (TG) levels from Week 12 to Week 24 of the study and from the period prior to rosuvastatin therapy initiation (baseline values - historical data) to Week 24 of the study***

Similarly, the percentage reduction in TC and TG levels between Week 12 and Week 24 was statistically significant (-5.2% and -2.1% respectively) [Table 22]. Mean HDL-C levels increased at Week 24 compared to Week 12 by 3.1% reaching statistical significance (p<0.0001) [Table 22]. Percentage changes in the lipid values were also statistically significant (p<0.0001) between baseline and Week 24 (TC: -32.2%; TG: -20.4%; HDL-C: +9.4%) [Table 23].

Figure 5 depicts the change observed in study participants' lipidemic profile between study visits.

Figure 5 Patients' lipidemic profile change over the study period



The dose titration schedule followed until the achievement of LDL-C target levels, in real life clinical practice

Table 24 Mean total daily dosage of Crestor® across all study visits

Mean Total Daily Dosage of Crestor®	Mean	Std Devation	Median	Min	Max	n
Visit1	14.6	7.7	10.0	5.0	40.0	810
Visit 2	15.1	8.2	10.0	5.0	40.0	810
Visit 3	15.1	8.0	10.0	5.0	40.0	810

Table 25 Summary statistics for the mean daily dosage of Crestor® at Visit 2 and Visit 3 according to LDL-C target achievement

Mean Total Daily Dosage of Crestor®		Mean	Std Devation	Median	Min	Max	n
Visit 2	Patients not reaching LDL-C target	16.3	8.9	10.0	5.0	40.0	467
	Patients reaching LDL C target	13.1	6.2	10.0	5.0	40.0	291
Visit 3	Patients not reaching LDL-C target	15.5	8.4	10.0	5.0	40.0	352
	Patients reaching LDL C target	15.1	7.9	10.0	5.0	40.0	409

Table 26 Change in Crestor® Dosage at Visit 2 compared to Baseline

Change in Crestor® Dosage at Visit 2 compared to Visit 1	Patients reaching LDL-C target at Week 12 (n=291)		Patients not reaching LDL-C target at Week 12 (n=467)	
	n	%	n	%
Crestor® Dosage Reduction	9	3.1%	9	1.9%
No Change in Crestor® Dosage	279	95.9%	419	89.7%
Crestor® Dosage Increase	3	1.0%	39	8.4%

Table 27 Change in Crestor® Dosage at Visit 3 compared to Visit 2

Change in Crestor® Dosage at Visit 3 compared to Visit 2	Patients reaching LDL-C target at Week 24 (n=409)		Patients not reaching LDL-C target at Week 24 (n=352)	
	n	%	n	%
Crestor® Dosage Reduction	2	0.5%	7	2.0%
No Change in Crestor® Dosage	406	99.3%	334	94.9%
Crestor® Dosage Increase	1	0.2%	11	3.1%

Tables 28 and 29 present the concomitant lipid lowering medication administered with Crestor®, as recorded at Visit 2 and Visit 3, respectively.

Table 28 Co-administered lipid lowering medication at Visit 2

Concomitant lipid-lowering medication at Visit 2	n	%
Cholesterol Absorption Inhibitors	**4**	**0.5%**
Ezetimibe	4	0.5%
Fibrates	**1**	**0.1%**
Fenofibrate	1	0.1%
Omega-3 Fatty Acids	**12**	**1.5%**

Table 29 Co-administered lipid lowering medication at Visit 3

Concomitant lipid-lowering medication at Visit 3	n	%
Cholesterol Absorption Inhibitors	**6**	**0.7%**
Ezetimibe	6	0.7%
Omega-3 Fatty Acids	**7**	**0.9%**

- ***Compliance with Crestor® treatment throughout the study***

Compliance with Crestor®, as evaluated at Week 12 and Week 24, is presented in Table 30. Approximately 93% of patients reported good to very good compliance with study treatment in both Visits 2 and 3.

Table 30 Compliance with Crestor® Treatment at Visit 2 and Visit 3

Compliance with Crestor® Therapy	Visit 2 (Week 12)		Visit 3 (Week 24)	
	n	%	n	%
Very good *(the patient was receiving the medication every day)*	575	71.0%	583	72.0%
Good *(the patient was receiving the medication regularly)*	176	21.7%	170	21.0%
Moderate *(the patient was receiving the medication irregularly)*	28	3.5%	27	3.3%
Poor *(the patient was not receiving the medication most of the days)*	3	0.4%	6	0.7%
Very Poor *(the patient didn't receive the medication almost at all)*	0	0.0%	1	0.1%

- ***Identification of factors associated with potential failure to attain LDL-C goals after 24 weeks of treatment***

Similarly to Visit 2, at Visit 3 (Week 24 of study), only risk category was found to be statistically significant related to LDL-C target achievement ($p<0.05$) [Table 31].

Table 31 Patients attaining the TJETF-recommended LDL-C goal according to baseline characteristics at Visit 3

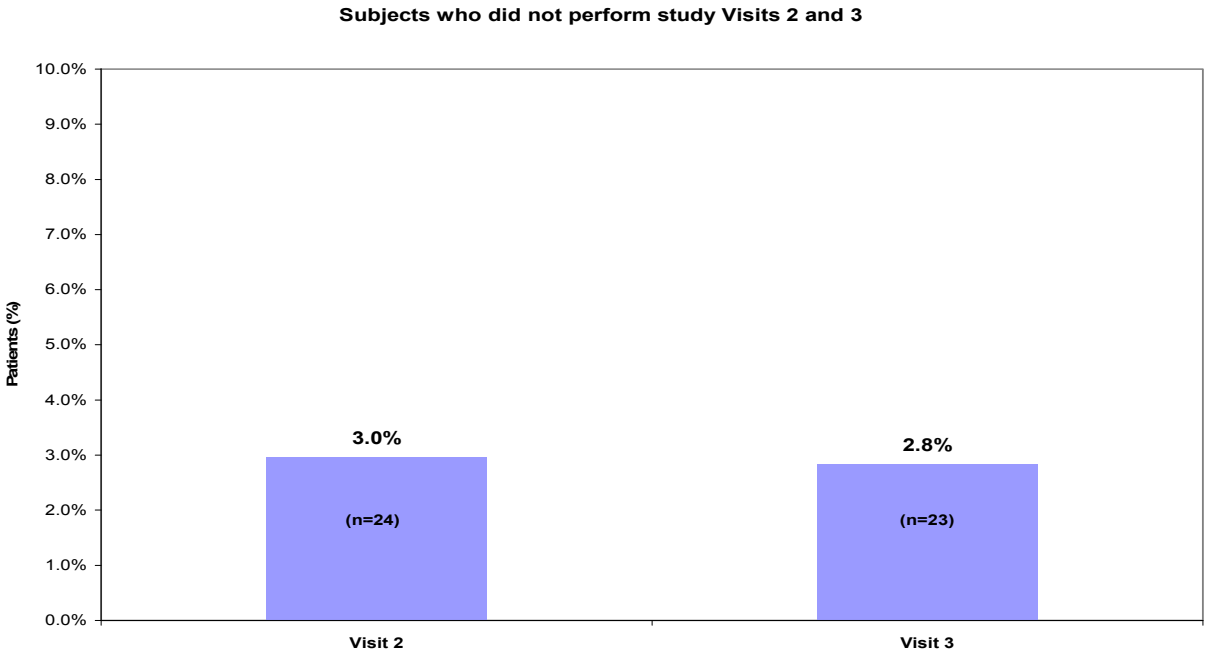
Visit 3 (Week 24)	Patients on LDL-C target		Patients not on LDL-C target		Total	p value
	n	%	n	%		
Overall	**409**	**50.5%**	**352**	**43.5%**	**810**	
Age						
<40	16	51.6%	15	48.4%	31	0.2002
40-54	111	48.3%	119	51.7%	230	
55-69	200	57.3%	149	42.7%	349	
≥70	82	54.3%	69	45.7%	151	
Missing					49	
Gender						
Male	214	53.8%	184	46.2%	398	0.9890
Female	195	53.7%	168	46.3%	363	
Missing					49	
BMI						
Normal weight (<25)	68	55.3%	55	44.7%	123	0.6713
Overweight (25-29)	221	52.2%	202	47.8%	423	
Obese (≥30)	119	55.6%	95	44.4%	214	
Missing					50	
Type of hypercholesterolemia						
Type I	17	41.5%	24	58.5%	41	NA
Type Iia	139	55.2%	113	44.8%	252	
Type Iib	137	50.6%	134	49.4%	271	
Type IV	4	66.7%	2	33.3%	6	
Unknown	112	58.6%	79	41.4%	191	
Missing					49	
Primary	129	52.2%	118	47.8%	247	NA
Secondary	26	86.7%	4	13.3%	30	
Unknown	254	52.5%	230	47.5%	484	
Missing					49	
Familial	39	53.4%	34	46.6%	73	NA
Non-Familial	30	83.3%	6	16.7%	36	
Unknown	336	52.0%	310	48.0%	646	
Missing					55	
Risk category						
High (1)	111	43.2%	146	56.8%	257	0.0001*
High (2)	-	-	-	-	-	
High (3)	49	56.3%	38	43.7%	87	
Other	249	59.7%	168	40.3%	417	
Missing					49	
Type of Therapy						
Crestor monotherapy	405	54.1%	344	45.9%	749	NA
Combination therapy	4	33.3%	8	66.7%	12	
Missing					49	

* Statistical significant at α=0.05

7.3 Subjects who discontinued prematurely their participation to the study and reasons for therapy withdrawal

24 patients did not perform Visit 2 of the study. Only 9 of them dropped out (performed neither Visit 2 nor Visit 3), while the remaining 15 continued to Visit 3. Overall, Visit 3 was not performed by 23 subjects (including the nine subjects who did not attend Visit 2) [Figure 6]. In total 787 (97.2%) of the patients completed the study.

Figure 6 Number of subjects who discontinued prematurely study participation per visit



The proportion of patients who did not perform each study visit, as well as the reasons for this are presented in Tables 32 and 33.

Table 32 Reasons for not performing study Visit 2

Reasons for not performing Visit 2	n	%
Personal reasons	10	1.2%
Lost to follow-up	11	1.4%
Adverse event	2	0.2%
Non compliance	1	0.1%

Table 33 Reasons for not performing study Visit 3

Reasons for not performing Visit 3	n	%
Lost to follow-up	18 (8)	2.2%
Adverse event	3 (1)	0.4%
Personal reasons	2	0.2%

*Number in parentheses refer to the number of patients not performing either Visit 2

7.4 Post hoc analysis of the population with no protocol violation/deviation.

A secondary post hoc analysis of the primary efficacy variables (see section 6.2) was performed in the study population with no protocol violation/deviation regarding eligibility criteria [Table 34 & 35].

Table 34 Percentage change in LDL-C values for the study population with no protocol violation/deviation

Percentage change from baseline to Visit 2	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
LDL-C	-31.6	17.6	-31.1	-78.1	29.6	579	<0.0001*

* Statistical Significant at α=0.05

Percentage change from baseline to Visit 3	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
LDL-C	-37.6	17.1	-38.3	-88.6	30.0	579	<0.0001*

* Statistical Significant at α=0.05

Percentage change from Visit 2 to Visit 3	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
LDL-C	-6.5	21.0	-6.4	-70.1	132.0	556	<0.0001*

* Statistical Significant at α=0.05

Table 35 Acievement of TJETF-recommended LDL-C target levels for the study population with no protocol violation deviation

Patients on LDL-C Target		
Visit 2		
On Target	222	35.5%
Not on Target	361	57.8%
Missing	42	6.7%
Visit 3		
On Target	313	50.1%
Not on Target	270	43.2%
Missing	42	6.7%

8 EVALUATION OF SAFETY DATA

8.1 Adverse events

Overall 31 (3.8%) subjects reported at least one (1) AE during the conduct of the study. The total number of AEs reported was 39.

8.1.1 Classification of adverse event by frequency rate

The reported AEs classified according to their incidence rate are presented in Table 36. AEs associated with abnormal laboratory findings and gastrointestinal disorders were the most frequently reported by the study population.

Table 36 Classification of AE with relation to their frequency rate

Classification of AE Frequency	n	%
Very common (≥1/10)		
None	-	-
Common (≥1/100 - <1/10)		
Laboratory abnormalities	11	1.4%
Gastrointestinal disorders	10	1.2%
Musculoskeletal and connective tissue disorders	8	1.0%
Uncommon (≥1/1.000 - <1/100)		
Infections and infestations	3	0.4%
Hepatobiliary disorders	2	0.2%
Skin and subcutaneous tissue disorders	2	0.2%
Respiratory, thoracic and mediastinal disorders	1	0.1%
Nervous system disorders	1	0.1%
Blood and lymphatic system disorders	1	0.1%

8.1.2 Classification of adverse events by system organ class and preferred term

The description of AEs as well as their frequency rates are presented in Table 37.

Table 37 List of AE reported by system organ

Adverse Event Description	n	%
Laboratory abnormalities	**11**	**1.4%**
Elevated CPK (≤ 1.8 x ULN)	6	0.7%
Elevated liver enzymes	3	0.4%
Elevated SGPT (1.2 x ULN)	1	0.1%
Elevated GAMMA-GT	1	0.1%
Gastrointestinal disorders	**10**	**1.2%**
Nausea	2	0.2%
Vomiting	2	0.2%
Diarrhea	2	0.2%
Flatulence	2	0.2%
Abdomnal pain	1	0.1%
Epigastric discomfort	1	0.1%
Musculoskeletal and connective tissue disorders	**8**	**1.0%**
Myalgia	2	0.2%
Cramps	2	0.2%
Musculosceletal pain	2	0.2%
Pain in calves	1	0.1%
Lower extrimity myalgia	1	0.1%
Infections and infestations	**3**	**0.4%**
Respiratory tract infection	2	0.2%
Herpes zoster	1	0.1%
Hepatobiliary disorders	**2**	**0.2%**
Acute cholecystitis	1	0.1%
Pancreatitis	1	0.1%
Skin and subcutaneous tissue disorders	**2**	**0.2%**
Urticaria	1	0.1%
Lower extrimity edema	1	0.1%
Respiratory, thoracic and mediastinal disorders	**1**	**0.1%**
COPD exacerbation	1	0.1%
Nervous system disorders	**1**	**0.1%**
Dry mouth	1	0.1%
Blood and lymphatic system disorders	**1**	**0.1%**
Anemia	1	0.1%
Total number of AEs observed	**39**	

In tables 38 to 41, the classification of AEs according to their causal relationship to Crestor®, seriousness, severity and outcome, as assessed and recorded by the investigators, are presented. As it is apparent, 53.8% of the reported AEs had probable to certain causal relationship to Crestor® and 92.3% of total AEs were of mild to moderate severity. Of the AEs reported with

known outcome, 96.6% were fully resolved (73.7% of all AEs observed). Additionally, no AE was characterized as serious.

Table 38 Number of AEs according to their causal relationship with Crestor®

Causal relationship with Crestor	Number of AEs	%
Certain	7	17.9
Probable	14	35.9
Possible	5	12.8
None	13	33.3

Table 39 Number of AEs according to their seriousness

Seriousness	Number of AEs	%
Not serious	39	100
Serious	0	0

Table 40 Number of AEs according to their severity

Severity (intensity)	Number of AE	%
Mild	21	53.8
Moderate	15	38.5
Severe	3	7.7

Table 41 Number of AEs according to the outcome

Outcome of AEs	Number of AEs	%
Full recovery	28	73.7
Partial recovery	1	2.6
Permanent damage	0	0.0
Death	0	0.0
Unknown	10	26.3

8.2 Serious adverse events

No serious adverse events were reported during the present study.

8.3 Treatment discontinuation due to AE

Only 3 (0.4%) patients discontinued Crestor® therapy due to AE occurrence. None of the reported AEs was serious and all of them resulted in full recovery. Table 42 presents in detail the AE that resulted in therapy discontinuation.

Table 42 Treatment discontinuation due to AE occurrence

Description of AE	Visit of discontinuation	Causal relationship with Crestor®	Severity	Seriousness	Outcome
Pain in calves/cramps	Visit 2	Certain	Moderate	Non serious	Full Recovery
Elevated CPK	Visit 3	Probable	Mild	Non serious	Full Recovery
Urticaria	Visit 3	Probable	Mild	Non serious	Full Recovery

9 APPENDIX A –SUPPLEMENTARY FIGURES AND TABLES

Figure 7 Mean change in biochemical parameters between study visits

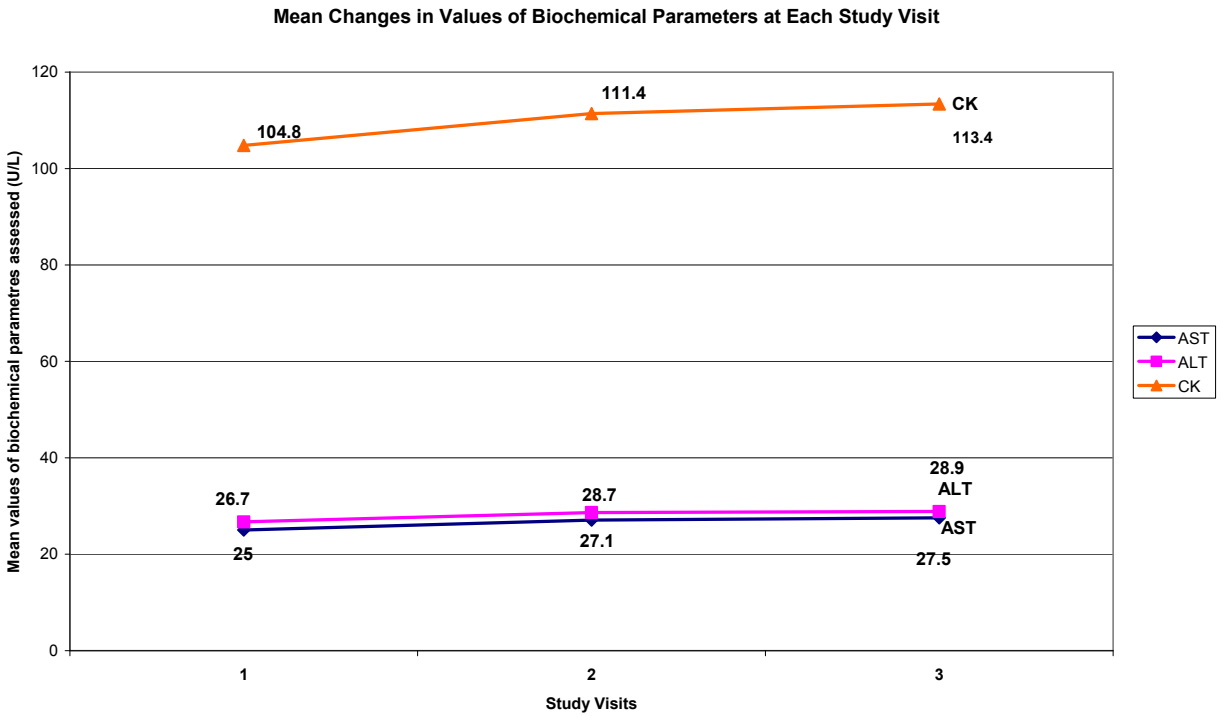


Table 43 Patients' lipidemic/biochemical profile – Visit 2

Lipidemic/biochemical profile Visit 2	Mean	Std Deviation	Median	Min	Max	N
Total Cholesterol (TC)	195.7	33.1	195.0	114.0	340	773
HCL-C	47.6	10.9	45.0	23.0	92	763
LDL-C	121.2	30.3	120.0	42.0	256	758
Triglycerides (TG)	138.0	46.2	135.0	42.0	367	764
AST (SGOT)	27.1	9.0	25.0	10.0	91	695
ALT (SGPT)	28.7	10.1	28.0	8.0	96	695
Creatine Kinase (CK)	111.4	50.3	103.0	14.0	488	585

Table 44 Patients' lipidemic/biochemical profile – Visit 3

Lipidemic/biochemical profile Visit 3	Mean	Std Deviation	Median	Min	Max	N
Total Cholesterol (TC)	183.3	26.4	180.0	97.0	311	769
HCL-C	48.8	10.4	47.0	23.0	95	764
LDL-C	110.6	27.1	109.0	19.0	210	761
Triglycerides (TG)	130.0	46.3	130.0	20.0	716	760
AST (SGOT)	27.5	9.8	26.0	10.0	106	689
ALT (SGPT)	28.9	10.1	28.0	8.0	80	688
Creatine Kinase (CK)	113.4	53.1	105.0	10.0	643	602

Table 45 Change in patients' lipidemic/biochemical profile from baseline to Visit 2

Percentage change from baseline to Visit 2	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
Total Cholesterol (TC)	-27.7	12.1	-27.6	-61.6	42.4	773	<0.0001*
HDL-C	6.5	18.0	5.6	-58.0	124.3	761	<0.0001*
LDL-C	-32.3	17.1	-32.0	-78.1	29.6	751	<0.0001*
Triglycerides (TG)	-16.5	25.5	-18.8	-80.0	123.0	764	<0.0001*
AST (SGOT)	12.5	34.7	5.9	-73.3	237.0	653	<0.0001*
ALT (SGPT)	14.2	44.0	5.3	-79.7	362.5	654	<0.0001*
Creatine Kinase (CK)	17.5	48.2	6.7	-90.1	333.3	417	<0.0001*

* Statistical Significant at α=0.05

Table 46 Change in patients' lipidemic/biochemical profile from baseline to Visit 3

Percentage change from baseline to Visit 3	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
Total Cholesterol (TC)	-32.2	10.8	-32.8	-64.3	21.2	769	<0.0001*
HDL-C	9.4	21.4	7.6	-56.8	120.0	762	<0.0001*
LDL-C	-38.2	16.6	-39.3	-88.6	30.0	754	<0.0001*
Triglycerides (TG)	-20.4	28.7	-22.7	-92.6	179.7	760	<0.0001*
AST (SGOT)	16.4	41.5	9.1	-73.3	341.7	640	<0.0001*
ALT (SGPT)	16.8	44.6	9.1	-70.3	277.8	639	<0.0001*
Creatine Kinase (CK)	20.8	59.6	5.8	-87.5	411.1	414	<0.0001*

* Statistical Significant at α=0.05

Table 47 Change in patients' lipidemic/biochemical profile from Visit 2 to Visit 3

Percentage change from Visit 2 to Visit 3	Mean (%)	Std Deviation	Median (%)	Min (%)	Max (%)	N	p value
Total Cholesterol (TC)	-5.2	13.3	-5.3	-49.8	89.4	743	<0.0001*
HDL-C	3.1	12.1	2.2	-55.3	93.0	732	<0.0001*
LDL-C	-6.7	20.0	-6.5	-71.1	132.0	725	<0.0001*
Triglycerides (TG)	-2.1	28.7	-5.3	-84.6	261.6	730	<0.0001*
AST (SGOT)	5.7	28.5	3.4	-82.4	307.7	636	0.0056*
ALT (SGPT)	5.8	31.0	2.5	-88.5	218.2	635	0.1462
Creatine Kinase (CK)	9.8	62.8	2.3	-86.4	1107.1	527	0.0936

* Statistical Significant at α=0.05