PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions for atorvastatin (Lipitor®) should be made based on the approved package insert. Torcetrapib is not a marketed drug and its clinical development was discontinued.
For publications based on this study, see associated bibliography.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Torcetrapib/Atorvastatin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: None

NCT NO.: 00138762

PROTOCOL NO.: A5091018

PROTOCOL TITLE: A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Parallel Group, Multi-Center Study of the Efficacy, Safety, and Tolerability of Fixed Combination Torcetrapib/Atorvastatin Administered Orally, Once Daily for 6 Months, Compared to Atorvastatin Alone or Placebo, in Subjects with Mixed Dyslipidemia (Frederickson Types IIa and IIb)

Study Center(s): 162 centers in Belgium, Germany, Mexico, Norway, South Korea, Sweden, United Kingdom, and the United States

Study Initiation and Completion Dates: First Subject Visit: 01 July 2004
Last Subject Visit: 31 July 2006

Phase of Development: Phase 3

Note: All clinical development of torcetrapib was halted on 02 December 2006, after the independent Data and Safety Monitoring Board monitoring the Phase 3 ILLUMINATE morbidity and mortality study for torcetrapib/atorvastatin recommended terminating the study because of a statistically significant imbalance in all cause mortality between subjects receiving torcetrapib/atorvastatin and those receiving atorvastatin alone. Full details of the cause of this imbalance have yet to be determined.

Study Objective(s): The primary objective of this study was to evaluate the low density lipoprotein cholesterol (LDL-C) lowering and high density lipoprotein cholesterol (HDL-C) elevating efficacy of torcetrapib 60 mg administered in a fixed combination with atorvastatin 10 to 80 mg/day, compared to atorvastatin alone or placebo, in subjects with Fredrickson Type IIa or IIb dyslipidemia. The LDL-C lowering and HDL-C elevating efficacy of the fixed combination torcetrapib/atorvastatin (T/A) were compared to (1) all atorvastatin doses combined, (2) each of 4 atorvastatin dose levels alones, and (3) placebo.

METHODS

Study Design: This was a multi-center, double-blind, placebo-controlled, randomized, parallel group study of fixed combination T/A in male and female subjects aged ≥18 years with Fredrickson IIa or IIb dyslipidemia. After initial screening (Week -7), eligible subjects entered a 4-week screening and washout period consisting of 2 screening visits (Week -7 to Week -4) during which subjects underwent a washout of all lipid-regulating medication and received therapeutic lifestyle change (TLC) counseling according to National Cholesterol Education Program Adult Treatment Panel (NCEP ATP-III) clinical guidelines. Following washout and TLC counseling, subjects entered a 3-week qualifying period consisting of 2 qualifying visits (Weeks -3 and -2), during which LDL-C and triglyceride (TG) levels were assessed to determine lipid eligibility and the dyslipidemia stratum to which they would be assigned. At Week 0 (Visit 4) subjects were stratified into either Fredrickson Type IIa or IIb dyslipidemia groups on the basis of their TG levels and were randomized to 1 of 9 treatments groups: fixed combination T/A at doses of 60/10, 60/20, 60/40 or 60/80 mg/mg, or atorvastatin alone at doses of 10, 20, 40 or 80 mg, or placebo, once daily (QD) for 6 months. Post-randomization visits occurred at Weeks 2, 4, 13 and 26.

Number of Subjects (Planned and Analyzed): It was planned to randomize approximately 3816 subjects, 212 subjects per treatment arm. Subsequently, 10385 subjects were screened for enrolment in the study and 3872 subjects were randomized and treated: 1759 subjects were randomized to receive T/A (884 and 916 subjects with Fredrickson Type IIa and IIb, respectively), of whom 1731 were evaluated for efficacy; 1692 subjects were randomized to receive atorvastatin (821 and 871 subjects with Fredrickson Type IIa and IIb, respectively), of whom 1671 were evaluated for efficacy; and 421 subjects were randomized to receive placebo (208 and 213 subjects with Fredrickson Type IIa and IIb, respectively), of whom 418 were evaluated for efficacy. All but 2 of the 3872 treated subjects (ie, 3870 subjects) were evaluated for safety; 2 subjects in the atorvastatin treatment group were not evaluated for safety because they were missing postbaseline data.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years or older with Fredrickson Type IIa or IIb dyslipidemia, whose lipid profile at the time of diagnosis met 1 of the lipid eligibility criteria as set forth by the protocol, were screened for study participation.

Study Treatment: During the 6-month, double-blind treatment period, subjects were instructed to take 1 tablet QD, with water, immediately after the morning meal, except on the morning of clinic visits, when study medication was to be taken after the clinic visit procedures were completed. T/A was supplied as tablets containing 60 mg torcetrapib combined with 1 of the following doses of atorvastatin: 10 mg, 20 mg, 40 mg or 80 mg; each had a matching placebo tablet. Atorvastatin was supplied as tablets containing 10 mg, 20 mg, or 40 mg, and each had a matching placebo tablet. Atorvastatin 80 mg and matching placebo were administered as 2 tablets of 40 mg atorvastatin (or matching placebo).

Efficacy Evaluations: The primary endpoints were mean percent changes in HDL-C and LDL-C plasma levels from baseline to Week 26. A lipid profile which included HDL-C and LDL-C was obtained at each study visit.

Safety Evaluations: Safety was assessed using routine clinical laboratory evaluations (urinalysis at Weeks -7, 0 and 26, hematology also at Week 4, and chemistry also at Weeks 2 and 13). Vital signs were monitored at every visit and physical examinations were performed at Weeks 0 and 26. Urine pregnancy testing was carried out at Weeks –2 and 26. Electrocardiograms (ECGs) were performed at Weeks -3 and 26. Subjects were monitored for adverse events (AEs) from Weeks -3 to 26. Week 26 safety evaluations were carried out at early termination if this took place.

Statistical Methods: The primary efficacy endpoints were the percent changes in HDL-C and LDL-C from baseline to Week 26.

The primary efficacy analysis population was the full analysis set (FAS), which included all randomized subjects who received at least 1 dose of study drug and had both a baseline and at least 1 valid post-baseline measurement for both HDL-C and LDL-C. Standard last observation carried forward (LOCF) methodology was employed to handle missing values.

The primary efficacy endpoints were analyzed by Analysis of Covariance (ANCOVA) using linear models fit by ordinary least squares (SAS PROC MIXED). The linear model included terms for treatment, Fredrickson dyslipidemia strata and corresponding baseline lipid measures as covariates. Treatment differences and corresponding 95% confidence intervals (CIs) were based on least squares (LS) means from the linear model. A step-wise hypothesis testing procedure was used, involving (1) individual T/A dose versus placebo comparisons, (2) marginal mean comparisons (ie, all doses combined), and (3) individual dose-to-dose comparisons for T/A versus atorvastatin. Within each step, hypothesis testing was 2-sided with a 5% error rate (ie, p = 0.05 significance level) and applied to each f the 2 primary endpoints in a fixed order: HDL-C followed by LDL-C.

Analogous methodology was applied within each of the (Fredrickson) strata separately using a linear model which did not include a term for (Fredrickson) strata.

RESULTS

Subject Disposition and Demography: Of the 10385 subjects screened for enrolment in the study, 3872 subjects were randomized and treated: 1759 subjects received T/A, 1692 subjects received atorvastatin and 421 subjects received placebo (Table S1). The majority of subjects completed the study: 1460 (83.0%) in the T/A treatment group, 1459 (86.2%) in the atorvastatin treatment group and 360 (85.5%) in the placebo treatment group. A total of 299 subjects (17.0%) in the T/A treatment group, 233 subjects (13.8%) in the atorvastatin treatment group and 61 subjects (14.5%) in the placebo treatment group discontinued from the study. The most common reason for withdrawal within each treatment group in the combined dyslipidemia strata was AEs: 196 (11.1%) T/A-treated subjects, 131 (7.7%) atorvastatin-treated subjects, and 30 (7.1%) placebo-treated subjects discontinued due to AEs. Demographic characteristics were similar across treatment groups. There was approximately the same number of males and females in each treatment group. A majority of subjects were white (85.1%) and between the ages of 45 and 64 years (64.6%).

Table S1. Subject Evaluation Groups and Disposition

		Number of Subjects (n, %)		
		T/A	A	Placebo
Screened	10385			
Assigned to Treatment	3872			
Treated		1759	1692	421
Completed		1460 (83.0)	1459 (86.2)	360 (85.5)
Discontinued		299 (17.0)	233 (13.8)	61 (14.5)
Evaluated for Efficacy				
Full Analysis Set (LOCF)		1731 (98.4)	1671 (98.8)	418 (99.3)
Evaluated for Safety				
Adverse Events		1759 (100.0)	1690 (99.9)	421 (100.0)
Laboratory Data		1749 (99.4)	1685 (99.6)	420 (99.8)

T/A=torcetrapib/atorvastatin, A=atorvastatin, LOCF=last observation carried forward

Efficacy Results: Treatment with T/A fixed combination resulted in statistically significant changes in the primary lipid endpoints of HDL-C and LDL-C at Week 26 when compared to treatment with placebo or atorvastatin. For the combined dyslipidemia strata, the measure of the LS mean percent increases from baseline to Week 26 in HDL-C for T/A compared to placebo was 61.66% (95% CI: [59.11, 64.21]) $p< 0.0001$ and for T/A compared to atorvastatin alone (all doses combined) was 58.76 (95% CI: [57.16, 60.37]) $p< 0.0001$. For the combined dyslipidemia strata, the measure of the LS mean percent decreases from baseline to Week 26 in LDL-C for T/A compared to placebo was 54.20% (95% CI: [55.93, 52.46]) $p< 0.0001$ and for T/A compared to atorvastatin alone (all doses combined) was 11.19 (95% CI: [12.28, 10.10]) $p< 0.0001$. Comparable changes in HDL-C and LDL-C were noted for T/A for comparisons by atorvastatin dose and within dyslipidemia strata.

Safety Results:

Adverse Events: Of the 3870 subjects who were evaluated for safety, 1189 (67.6%) of the T/A-treated subjects, 1061 (62.7%) of atorvastatin-treated subjects, and 272 (64.6%) of the placebo-treated subjects reported at least 1 treatment-emergent AE. Five hundred and thirty-eight subjects (30.6%) who received T/A reported at least 1 treatment-related AE, compared with 408 subjects (24.1%) who received atorvastatin and 98 subjects (23.3%) who received placebo. Treatment-emergent AEs occurring in ≥5% of subjects in any treatment group (combined dyslipidemia strata) are summarized by system organ class (SOC), treatment group and investigator's assessment of relationship to treatment in Table S2.

Table S2. Treatment Emergent Adverse Events by System Organ Class and Treatment Group

System Organ Class[a]/ High-Level Group Term[a]/ MedDRA Preferred Term[b]	T/A N=1759		A N=1692		Placebo N=421	
	A/C	T/R	A/C	T/R	A/C	T/R
Number (%) of Subjects With Adverse Events	1189 (67.6)	538 (30.6)	1061 (62.7)	408 (24.1)	272 (64.6)	98 (23.3)
Gastrointestinal Disorders	409 (23.3)	252 (14.3)	300 (17.7)	173 (10.2)	74 (17.6)	42 (10.0)
Gastrointestinal Motility and Defecation Conditions	177 (10.1)	111 (6.3)	113 (6.7)	65 (3.8)	31 (7.4)	17 (4.0)
Diarrhea	93 (5.3)	52 (3.0)	55 (3.3)	27 (1.6)	19 (4.5)	11 (2.6)
Gastrointestinal Signs and Symptoms	253 (14.4)	164 (9.3)	192 (11.3)	117 (6.9)	54 (12.8)	31 (7.4)
General Disorders and Administration Site Conditions	143 (8.1)	59 (3.4)	116 (6.9)	49 (2.9)	32 (7.6)	19 (4.5)
General System Disorders NEC	131 (7.4)	56 (3.2)	107 (6.3)	50 (3.0)	30 (7.1)	19 (4.5)
Infections and Infestations	439 (25.0)	8 (0.5)	404 (23.9)	1 (0.1)	104 (24.7)	2 (0.5)
Infections – Pathogen Class Unspecified	375 (21.3)	7 (0.4)	361 (21.3)	1 (0.1)	96 (22.8)	1 (0.2)
Nasopharyngitis	103 (5.9)	0	92 (5.4)	0	24 (5.7)	0
Upper Respiratory Tract Infection	92 (5.2)	2 (0.1)	80 (4.7)	1 (0.1)	21 (5.0)	0
Injury, Poisoning and Procedural Complications	84 (4.8)	1 (0.1)	80 (4.7)	1 (0.1)	24 (5.7)	1 (0.2)
Investigations	118 (6.7)	70 (4.0)	99 (5.9)	58 (3.4)	20 (4.8)	12 (2.9)
Musculoskeletal and Connective Tissue Disorders	329 (18.7)	108 (6.1)	310 (18.3)	111 (6.6)	70 (16.6)	26 (6.2)
Joint Disorders	103 (5.9)	22 (1.3)	85 (5.0)	22 (1.3)	21 (5.0)	6 (1.4)
Muscle Disorders	115 (6.5)	68 (3.9)	122 (7.2)	78 (4.6)	27 (6.4)	17 (4.0)
Musculoskeletal and Connective Tissue Disorders NEC	130 (7.4)	28 (1.6)	117 (6.9)	26 (1.5)	27 (6.4)	6 (1.4)
Nervous System Disorders	199 (11.3)	83 (4.7)	197 (11.6)	80 (4.7)	43 (10.2)	17 (4.0)
Headaches	103 (5.9)	47 (2.7)	98 (5.8)	42 (2.5)	21 (5.0)	8 (1.9)
Headache	89 (5.1)	46 (2.6)	85 (5.0)	39 (2.3)	19 (4.5)	8 (1.9)
Neurological Disorders NEC	87 (4.9)	42 (2.4)	97 (5.9)	47 (2.8)	19 (4.5)	10 (2.4)
Respiratory, Thoracic and Mediastinal Disorders	90 (5.1)	14 (0.8)	93 (5.5)	7 (0.4)	36 (8.6)	3 (0.7)
Respiratory Disorders NEC	66 (3.8)	12 (0.7)	59 (3.5)	5 (0.3)	21 (5.0)	3 (0.7)
Skin and Subcutaneous Tissue Disorders	99 (5.6)	30 (1.7)	101 (6.0)	30 (1.8)	12 (2.9)	2 (0.5)
Vascular Disorders	116 (6.6)	68 (3.9)	37 (2.2)	16 (0.9)	8 (1.9)	3 (0.7)

T/A=torcetrapib/atorvastatin, A=atorvastatin, A/C=All Causalities, T/R=Treatment-Related, MedDRA=Medical Dictionary for Regulatory Affairs, NEC=Not Elsewhere Classified.

[a] Includes only System Organ Classes and High Level Group Terms where AEs (all causalities) occurred in ≥5% of subjects in either treatment group

[b] MedDRA (v9.0) Preferred Term included only when AE (all causalities) occurred in ≥5% of subjects in either treatment group

The SOCs most affected with all causality AEs were (in decreasing order in the T/A treatment group): Infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, and nervous system disorders. By preferred term, the most frequently reported AEs in any treatment group included nasopharyngitis, diarrhea, upper respiratory infection, and headache. Diarrhea and headache were the most frequently

reported treatment-related AEs in the T/A treatment group. The incidence of all causality and treatment-related AEs was consistent across dyslipidemia strata.

Permanent Discontinuations Due to Adverse Events: One hundred and ninety-six subjects (11.1%) in the T/A treatment group, 131 subjects (7.7%) in the atorvastatin treatment group and 30 subjects (7.1%) in the placebo group were discontinued from the study due to all causality AEs. One hundred and fifty-nine (9.0%) of the T/A-treated subjects, 104 (6.1%) of the atorvastatin-treated subjects, and 24 (5.7%) of the placebo-treated subjects were discontinued due to AEs that were considered treatment-related.

Adverse events which resulted in discontinuation of ≥10 subjects in any treatment group are summarized by treatment and subject age at screening/gender in Table S3.

Table S3. Summary of Treatment-Emergent Adverse Events Resulting in Discontinuation in At Least Ten Subjects in any Treatment Group

Treatment	Adverse Event (MedDRA Preferred Term)	Subject Age/Gender
TA	Myalgia	55/F[a], 70/F[a], 62/M[a], 64/M[a], 57/M[a], 53/F[a], 60/F[a], 63/M[a], 67/F[a], 46/F[a], 50/M[a], 50/M[a], 50/F, 36/M, 56/F[a], 65/F[a], 54/F[a], 65/F[a], 57/F[a], 65/F[a]
	Nausea	49/M[a], 65/F[a], 41/F[a], 46/M[a], 65/M[a], 41/F[a], 59/F[a], 46/M[a], 50/F[a], 66/F[a], 62/F[a], 54/M[a], 42/M[a], 54/F[a], 82/F[a], 63/F[a], 57/F[a], 70/M[a], 74/F[a]
	Hypertension / Systolic Hypertension	61/F[a], 63/M[a], 65/F[a], 56/F[a], 63/F[a], 66/F[a], 77/M[a], 71/M[a], 62/M[a], 65/M[a], 76/M[a], 64/F[a], 63/F[a], 54/M[a], 81/F[a]
	Headache	41/F[a], 55/F[a], 68/F[a], 44/M[a], 61/M[a], 50/F[a], 30/M[a], 56/M[a], 60/F[a], 60/M[a], 65/F[a], 82/F[a], 39/F
	Fatigue	60/F[a], 56/F[a], 57/F[a], 42/M[a], 55/M[a], 67/F[a], 64/F[a], 60/M[a], 65/F[a], 70/F[a], 73/F[a]
	Blood Pressure Increased	59/F[a], 82/F[a], 61/F[a], 69/F[a b], 65/M[a], 56/F[a], 57/F[a], 63/F[a], 65/M[a], 71/F[a], 68/F[a]
	Abdominal Pain/Upper	61/M, 45/M[a], 59/F[a], 74/F[a], 75/M[a], 56/F[a], 74/F[a], 41/F[a], 62/F[a], 47/F[a], 60/M[a]
	Arthralgia	32/M[a], 57/F[a], 46/F[a], 70/F[a]
A	Myalgia	73/F[a], 29/M[a], 33/M[a], 60/F[a], 50/F[a], 57/F[a], 62/F[a], 62/F[a], 53/M[a], 59/F[a], 62/F[a], 59/F[a], 57/M[a], 66/M[a], 56/M[a], 69/M[a], 56/F[a], 56/F[a]
	Nausea	46/M, 55/F[a], 61/M[a], 45/F[a], 44/F[a], 65/F[a]
	Hypertension / Systolic Hypertension	68/M[a], 51/M[a]
	Headache	57/F, 55/F[a], 62/F[a], 60/M[a], 56/F, 58/F, 67/F, 45/F[a], 48/F[a], 53/M[a], 44/F[a], 65/F[a], 45/F[a]
	Fatigue	73/F[a], 53/M[a], 74/F[a], 55/M[a], 67/F, 50/F[a], 53/M[a], 56/F[a]
	Blood Pressure Increased	53/F[a]
	Abdominal Pain/Upper	74/F, 55/F, 41/F[a], 64/F[a], 61/F[a], 63/F[a], 58/M[a]
	Arthralgia	62/F[a], 56/F[a], 32/F, 69/M[a], 33/M[a], 72/F[a], 53/M[a], 66/F[a], 64/F[a], 64/F[a]
Placebo	Myalgia	57/M[a], 57/F[a], 50/M[a], 67/F[a]
	Nausea	56/F, 70/F[a]
	Hypertension / Systolic Hypertension	None
	Headache	46/M[a], 44/M[a], 58/M[a]
	Fatigue	59/M[a], 42/M[a]
	Blood Pressure Increased	46/M[a], 49/F[a]
	Abdominal Pain/Upper	56/F, 50/M[a]
	Arthralgia	57/F[a]

T/A=torcetrapib/atorvastatin, A=atorvastatin, F=female, M=male, MedDRA= Medical Dictionary for Regulatory Affairs

[a] Adverse event considered treatment-related (investigator causality)

[b] Adverse event considered serious

The most frequently reported all causality AEs leading to discontinuation in the T/A treatment group were myalgia (20 subjects), nausea (19 subjects), hypertension (15 subjects) and headache (13 subjects). In the atorvastatin treatment group, myalgia (18 subjects), headache (13 subjects) and arthralgia (10 subjects) were most often reported. Myalgia (4 subjects) was most commonly reported by placebo-treated subjects. All events of myalgia were considered treatment-related.

Serious Adverse Events: Serious adverse events (SAEs) were reported up to 28 days after the last dose of study drug.

A total of 53 (3.0%) T/A-treated subjects, 26 (1.6%) atorvastatin-treated subjects, and 4 (1.0%) placebo-treated subjects reported SAEs during the course of the study. For 5 of the 53 T/A-treated subjects, the SAEs were reported during the post-therapy phase after having completed the study. Three T/A-treated subjects experienced SAEs that were considered treatment-related (1 subject each with elevated liver function tests; rhabdomyolysis; and elevated blood alkaline phosphatase, alanine aminotransferase and bilirubin); no treatment-related SAEs were reported for subjects in the atorvastatin or placebo treatment groups. In total, 23 subjects (18 T/A-treated, 4 atorvastatin-treated and 1 placebo-treated) had SAEs which led to permanent discontinuation.

Serious adverse events reported by >1 subject in any treatment group are summarized by treatment group and subject age at screening/gender in Table S4.

Table S4. Subjects With Serious Adverse Events Reported by More Than One Subject in Any Treatment Group

Adverse Event (MedDRA Preferred Term)	Number of Subjects		
	T/A N=1759	A N=1692	Placebo N=421
Acute Myocardial Infarction	2[a]	0	0
Angina Unstable	1	2[a]	0
Coronary Artery Disease	3[a c]	0	0
Myocardial Infarction	4[b d]	1	1[d]
Chest Pain	4[a]	1[a]	0
Non-Cardiac Chest Pain	2[a]	0	0
Drug Exposure During Pregnancy	1[a]	1	0
Fall	2[c]	1	0
Breast Cancer	2[a]	0	0
Depression	0	2[c]	0
Hypertension	2[a c]	1	0

T/A=torcetrapib/atorvastatin, A=atorvastatin
[a] Led to permanent discontinuation for 1 subject
[b] Led to permanent discontinuation for 2 subjects
[c] Led to temporary discontinuation of study drug for 1 subject
[d] Resulted in nondrug-related death in 1 subject

Three deaths were reported during the course of the study: 1 subject was receiving T/A 60/80 mg, 1 subject was receiving T/A 60/20 mg, and 1 subject was receiving placebo. Two of these deaths were within 60 days of the last dose of study drug, and 1 death occurred 62 days after the last dose of study drug. None of the deaths was considered by the investigator to be related to study treatment.

A 60-year-old white male with Type IIb dyslipidemia died due to a myocardial infarction on Day 96, 62 days after receiving his last dose of T/A 60/80 mg.

A 77-year-old white female with Type IIa dyslipidemia randomized to the T/A 60/20 mg treatment group, experienced a spontaneous cerebral hemorrhage on Day 67. Study drug was discontinued on the same day but the subject subsequently died on Day 80 (13 days after last treatment).

A 63-year-old white male with Type IIb dyslipidemia randomized to the placebo treatment group, developed fatigue and backache on Day 37 and the emergency services were called. The subject was found dead; cause of death was suspected myocardial infarction.

Clinical Laboratory Tests: In general, laboratory abnormalities were infrequent and comparable across treatment groups.

Blood Pressure: Mean systolic blood pressure (SBP) increased from baseline to Week 26 in the T/A (4.6 mmHg), atorvastatin (0.3 mmHg) and placebo (0.9 mmHg) treatment groups. The change in SBP from baseline to Week 26 for T/A measured 4.4 mmHg (95% CI: [3.7, 5.1]) and 3.8 mmHg (95% CI: [2.7, 4.9]) versus atorvastatin and placebo, respectively.

CONCLUSION(S): This Phase 3, multi-center, double-blind, randomized, parallel group study comparing the efficacy of fixed doses of T/A 60/10 mg, 60/20 mg, 60/40 mg, and 60/80 mg with placebo and the corresponding atorvastatin dose (administered for 26 weeks) demonstrated that treatment with every T/A combination resulted in statistically significant changes in the lipid profile of subjects with Fredrickson Type IIa or Type IIb dyslipidemia.

- For the primary endpoints, treatment with every T/A combination dose resulted in statistically significant increases in HDL-C and statistically significant decreases in LDL-C at Week 26 compared with the placebo and atorvastatin alone for atorvastatin doses combined and at each individual atorvastatin dose.

- The number of subjects with all causality and treatment-related AEs was higher in the T/A treatment group than in the atorvastatin and placebo treatment groups. More subjects discontinued from the T/A treatment group due to treatment-related AEs (159 subjects, 9.0%) than atorvastatin-treated subjects (104 subjects, 6.1%) or placebo-treated subjects (24 subjects, 5.7%). A total of 53 (3.0%) T/A-treated subjects, 26 (1.6%) atorvastatin-treated subjects, and 4 (1.0%) placebo-treated subjects reported SAEs during the course of the study. For 5 of 53 T/A-treated subjects, the SAEs were reported during the post-therapy phase after having completed the study. Three T/A-treated subjects experienced SAEs that were considered treatment-related; no treatment-related SAEs were reported for subjects in the atorvastatin or placebo treatment groups. In total, 23 subjects (18 T/A-treated, 4 atorvastatin-treated and 1 placebo-treated) had SAEs which led to permanent discontinuation. Three deaths were reported during the course of the study: myocardial infarction in 1 subject receiving T/A 60/80 mg, spontaneous cerebral hemorrhage in 1 subject receiving T/A 60/20 mg, and suspected myocardial infarction in 1 subject receiving placebo. None of the deaths was considered by the investigator to be related to study treatment.

- Mean SBP increased from baseline to Week 26 in the T/A (4.6 mmHg), atorvastatin (0.3 mmHg) and placebo (0.9 mmHg) treatment groups. The change in SBP from

baseline to Week 26 for T/A measured 4.4 mmHg (95% CI: [3.7, 5.1]) and 3.8 mmHg (95% CI: [2.7, 4.9]) versus atorvastatin and placebo, respectively.