

**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.

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

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** None

**NCT NO.:** 00139061

**PROTOCOL NO.:** A5091034

**PROTOCOL TITLE:** Phase 3 Multi-Center, Double-Blind, Randomized, Parallel Group, Forced Titration Study of the Efficacy, Safety, and Tolerability of Torcetrapib/Atorvastatin Compared to Fenofibrate in Subjects with Fredrickson Type IIb Dyslipidemia (Mixed Hyperlipidemia)

**Study Center(s):** 27 centers in France

**Study Initiation and Completion Dates:** First Subject Visit: 31 March 2005  
Last Subject Visit: 24 May 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 the study was to assess the high density lipoprotein cholesterol (HDL-C) elevating and non-HDL-C lowering efficacy of fixed combination torcetrapib/atorvastatin (T/A) 60 mg/10 mg compared to that of fenofibrate (F) 200 mg at Week 12 in subjects with Fredrickson Type IIb dyslipidemia (mixed hyperlipidemia).

The secondary objectives were to:

- assess the HDL-C elevating and non-HDL-C lowering efficacy of fixed combination T/A 60 mg/20 mg, 60 mg/40 mg, and 60 mg/80 mg compared to that of fenofibrate 200 mg at Weeks 18, 24 and 30/end of study (EOS) respectively;

- assess the safety and tolerability of fixed combination T/A 60 mg/10 mg, 60 mg/20 mg, 60 mg/40 mg, and 60 mg/80 mg compared to that of fenofibrate 200 mg at Weeks 12, 18, 24 and 30/EOS;
- compare the incidence of subjects meeting their National Cholesterol Education Program Adult Treatment Panel (NCEP ATP-III) low density lipoprotein cholesterol (LDL-C) and non-HDL-C goals on T/A versus fenofibrate alone at Weeks 12, 18, 24 and 30/EOS;
- evaluate the changes in other lipids, apolipoproteins, and other markers of coronary heart disease (CHD) risk.

## METHODS

**Study Design:** This was a multi-center, double-blind, randomized, parallel group study of forced titration T/A compared to fixed-dose fenofibrate in male and female subjects  $\geq 18$  years of age with Fredrickson Type IIb dyslipidemia. After initial screening, eligible subjects entered a 6-week screening period consisting of 3 visits (Weeks -6, -2 and -1), during which subjects underwent a washout of all lipid-regulating medication and received therapeutic lifestyle change (TLC) counseling according to NCEP-ATP-III clinical guidelines. Following washout and TLC counseling, lipid levels were assessed and each subject's 10 year CHD risk was calculated; LDL-C and non-HDL-C target goals were also determined. At Week 0, subjects were randomized to receive 1 of the following for 30 weeks of double-blind treatment: (a) T/A at doses of 60/10 mg QD (Weeks 0-12); 60/20 mg QD (Weeks 12-18); 60/40 mg QD (Weeks 18-24); 60/80 mg QD (Weeks 24-30); or (b) fenofibrate: fixed dose of 200 mg QD for the entire 30 week double-blind treatment period. Subjects unable to tolerate T/A dose increases were discontinued from the study. Post-randomization study visits were scheduled for Weeks 4, 12, 18, 24 and 30.

**Number of Subjects (Planned and Analyzed):** It was planned to randomize approximately 128 subjects in the study, 64 subjects per treatment arm. Subsequently, 312 subjects were screened for enrolment in the study and 147 subjects were randomized and treated: 74 subjects were randomized to receive T/A and 73 subjects were randomized to receive fenofibrate. All 147 subjects were evaluated for safety. In the T/A and fenofibrate treatment groups, respectively, 74 and 72 subjects were evaluated for efficacy over Weeks 0-12 (full analysis set; FAS), 68 and 66 subjects were evaluated over Weeks 12-18, 66 and 64 subjects were evaluated over Weeks 18-24, and 59 and 61 subjects were evaluated over Weeks 24-30.

**Diagnosis and Main Criteria for Inclusion:** Men and women 18 years of age or older with Fredrickson Type IIb dyslipidemia meeting CHD risk assessment lipid eligibility criteria, were screened for study participation.

**Study Treatment:** During the 30-week double-blind treatment period, subjects were instructed to take 1 tablet and 1 capsule once daily (QD), immediately after the morning meal, except on the morning of clinic visits, when study medication was to be taken (with food) after the clinic visit procedures were completed. Tablets contained T/A at a dose of 60/10 mg (Weeks 0-12), 60/20 mg (Weeks 12-18), 60/40 mg (Weeks 18-24), or 60/80 mg, or were a matching placebo for T/A; and capsules either contained fenofibrate at a dose of

200 mg, or were a matching placebo for fenofibrate. No down titration of T/A was permitted. If subjects were unable to tolerate dose increases, they were discontinued from the study.

**Efficacy Evaluations:** The primary endpoints were mean percent change in HDL-C and non-HDL-C from baseline to Week 12. A lipid profile (total cholesterol [TC], HDL-C, LDL-C, non-HDL-C, and triglycerides [TG]) was obtained at screening and all subsequent visits through Week 30 or early termination (ET).

**Safety Evaluations:** Safety was assessed using routine clinical laboratory assessments (chemistry and basic lipid profile at all visits from Weeks -2 to 30 or ET, hematology and urinalysis at Weeks -1 and 30 or ET). Vital signs were monitored at every visit, and physical examinations were performed at Weeks 0 and 30 or ET. Urine pregnancy testing and electrocardiograms (ECGs) were performed at Weeks -1 and 30 or ET. Subjects were monitored for adverse events (AEs) from Weeks -2 to 30 or ET.

**Statistical Methods:** The primary efficacy endpoints were the percent changes in HDL-C and non-HDL-C from baseline to Week 12. Secondary lipid endpoints included nominal change from baseline in HDL-C and LDL-C, and percent change and nominal change in TG and TC.

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 non-HDL-C. Standard last observation carried forward methodology was employed to handle missing values.

The primary efficacy endpoints were analyzed by Analysis of Covariance using linear models fit by ordinary least squares (LS) (SAS PROC MIXED). The linear model included treatment and corresponding baseline lipids as main effects. Treatment differences and corresponding 95% confidence intervals (CIs) were based on LS means from the linear model. Hypothesis testing was 2-sided with a 5% type I error rate (ie,  $p = 0.05$  significance level). The Bonferroni method was used to adjust the significance level for multiple comparisons.

The proportion of subjects meeting their individual NCEP goal at the end of study was computed for each treatment group.

## RESULTS

**Subject Disposition and Demography:** Of the 312 subjects screened for enrolment in the study, 147 subjects were randomized and treated: 74 subjects received T/A and 73 subjects received fenofibrate (Table S1). Sixty-five (87.8%) subjects in the T/A group and 67 (91.8%) subjects in the fenofibrate group completed the study. A total of 9 subjects (12.2%) in the T/A treatment group and 6 subjects (8.2%) in the fenofibrate treatment group discontinued from the study. The most common reason for withdrawal within the T/A and fenofibrate treatment group was AEs (9.5% and 4.1%, respectively). Demographic characteristics were similar between treatment groups. A majority of all subjects were male

(70.7%) and between the ages of 45 and 64 years (51.0%). Race/ethnicity information was not collected for subjects screened in this study.

**Table S1. Subject Evaluation Groups and Disposition**

		Number of Subjects (n, %)	
		T/A <sup>a</sup>	F
Screened	312		
Randomized	147		
Assigned to Treatment		74	73
Treated		74	73
Completed		65 (87.8)	67 (91.8)
Discontinued		9 (12.2)	6 (8.2)
Evaluated for Efficacy (FAS <sup>b</sup> )			
Full Analysis, Wk 0-12		74 (100.0)	72 (98.6)
Full Analysis, Wk 12-18		68 (91.9)	66 (90.4)
Full Analysis, Wk 18-24		66 (89.2)	64 (87.7)
Full Analysis, Wk 24-30		59 (79.7)	61 (83.6)
Evaluated for Safety		74 (100.0)	73 (100.0)

T/A=torcetrapib/atorvastatin, F=fenofibrate, FAS=full analysis set.

<sup>a</sup> T/A forced titration 60/10 mg QD (Weeks 0–12), 60/20 mg QD (Weeks 12–18), 60/40 mg QD (Weeks 18-24), and 60/80 mg QD (Weeks 24–30).

<sup>b</sup> FAS=Full Analysis Set (Observed Cases); table entries reflect the number of subjects who had a HDL-C measurement within the visit window

**Efficacy Results:** Treatment with T/A fixed combination resulted in significantly significant changes in the primary lipid endpoints of HDL-C and non-HDL-C at Week 12 when compared to treatment with fenofibrate ( $p < 0.0001$  for differences between treatment groups). The LS mean percent increase from baseline to Week 12 in HDL-C was 66.9% for T/A-treated subjects, compared with 10.3% for fenofibrate-treated subjects. The LS mean percent decrease from baseline in non-HDL-C at Week 12 was 45.0% for T/A-treated subjects compared with 11.4% in subjects who received fenofibrate.

Using Hochberg’s procedure, treatment with T/A resulted in statistically significant decreases in LDL-C and the LDL-C/HDL-C ratio at Week 12 and Week 30/EOS, compared with fenofibrate ( $p < 0.0001$  for differences between treatment groups for both parameters).

More T/A-treated subjects obtained their NCEP ATP-III non-HDL goal compared with fenofibrate-treated subjects at Week 12 (91.2% and 40.6%, respectively) and at Week 30 (94.9% and 52.5%, respectively) ( $p < 0.0001$  for differences between treatment groups at each timepoint). Similar results were observed for subjects reaching their NCEP ATP-III LDL goal: 94.1% for the T/A group compared to 46.4% in the fenofibrate group at Week 12, and 94.9% for the T/A group compared to 60.7% for the fenofibrate group at Week 30 ( $p < 0.0001$  for differences between treatment groups at each timepoint).

**Safety Results:**

Adverse Events: Of the 147 subjects who were evaluated for safety, 42 (56.8%) of the T/A-treated subjects and 37 (50.7%) of the fenofibrate-treated subjects reported at least

1 treatment-emergent AE. Nineteen subjects (25.7%) in the T/A treatment group and 12 subjects (16.4%) in the fenofibrate treatment group had treatment-related AEs. Seven subjects (9.5%) in the T/A treatment group and 4 subjects (5.5%) in the fenofibrate treatment group were discontinued from the study due to AEs.

Treatment-emergent AEs 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 <sup>a</sup> / High-Level Group Term <sup>a</sup> / MedDRA Preferred Term <sup>b</sup>	T/A N=74		F N=73	
	All Causalities	Treatment- Related	All Causalities	Treatment- Related
Number (%) of Subjects with Adverse Events	42 (56.8)	19 (25.7)	37 (50.7)	12 (16.4)
<b>Ear and Labyrinth Disorders</b>	1 (1.4)	0	4 (5.5)	1 (1.4)
<b>Gastrointestinal Disorders</b>	10 (13.5)	7 (9.5)	9 (12.3)	5 (6.8)
Gastrointestinal Motility and Defaecation Conditions	2 (2.7)	1 (1.4)	4 (5.5)	2 (2.7)
<b>General Disorders and Administration Site Conditions</b>	6 (8.1)	3 (4.1)	1 (1.4)	1 (1.4)
<b>Infections and Infestations</b>	21 (28.4)	1 (1.4)	21 (28.8)	0
Infections – Pathogen Class Unspecified	16 (21.6)	1 (1.4)	20 (27.4)	0
Bronchitis	5 (6.8)	0	7 (9.6)	0
Nasopharyngitis	6 (8.1)	0	6 (8.2)	0
<b>Injury, Poisoning and Procedural Complications</b>	6 (8.1)	1 (1.4)	4 (5.5)	0
<b>Musculoskeletal and Connective Tissue Disorders</b>	11 (14.9)	8 (10.8)	8 (11.0)	1 (1.4)
Joint Disorders	4 (5.4)	4 (5.4)	3 (4.1)	0
Musculoskeletal and Connective Tissue Disorders NEC	5 (6.8)	2 (2.7)	4 (5.5)	1 (1.4)
Back Pain	4 (5.4)	1 (1.4)	0	0
<b>Nervous System Disorders</b>	3 (4.1)	3 (4.1)	6 (8.2)	1 (1.4)
<b>Psychiatric Disorders</b>	4 (5.4)	3 (4.1)	2 (2.7)	1 (1.4)
<b>Skin and Subcutaneous Tissue Disorders</b>	5 (6.8)	1 (1.4)	3 (4.1)	0
Epidermal and Dermal Conditions	4 (5.4)	1 (1.4)	3 (4.1)	0
<b>Vascular Disorders</b>	3 (4.1)	3 (4.1)	5 (6.8)	2 (2.7)

T/A=torcetrapib/atorvastatin, F=fenofibrate, MedDRA=Medical Dictionary for Regulatory Affairs, NEC=Not Elsewhere Classified.

<sup>a</sup> Includes only System Organ Classes and High Level Group term where AEs (all causalities) occurred in  $\geq 5\%$  of subjects in either treatment group.

<sup>b</sup> MedDRA (v9.1) Preferred Term included only when AE (all causalities) occurred in  $\geq 5\%$  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, musculoskeletal and connective tissue disorders, and gastrointestinal disorders. The frequency of AEs within each SOC listed above was higher in T/A-treated subjects, with the exception of infections and infestations, for which a similar percentage of T/A-treated and fenofibrate-treated subjects reported AEs.

By preferred term, the most frequent all causality AEs reported (at least 5% of subjects in either treatment group) were nasopharyngitis, bronchitis and back pain. No treatment-related AEs were reported by at least 2% of subjects in either the T/A or E/S treatment group. The most commonly reported treatment-related AE was arthralgia, which was reported by 3 T/A-treated subjects (4.1%) and no fenofibrate-treated subjects.

Permanent Discontinuations Due to Adverse Events: The number of subjects who discontinued due to any AE was higher in the T/A than fenofibrate treatment group whether all causality (9.5% and 5.5%, respectively) or treatment-related (9.5% and 4.1%, respectively).

Subjects who discontinued from the study due to treatment-emergent AEs are listed by treatment group and subject age at screening/gender in Table S3.

**Table S3. Subjects Discontinued From the Study Due to Treatment-Emergent Adverse Events**

Treatment	Subject Age/Gender	Adverse Event (MedDRA Preferred Term)
T/A	50/M	Feeling hot <sup>a</sup> , Pain in extremity <sup>a</sup>
	32/F	Abdominal pain lower <sup>a</sup>
	60/M	Intestinal function disorder <sup>a</sup> , Asthenia <sup>a</sup> , Muscular weakness <sup>a</sup>
	62/F	Myalgia <sup>a</sup>
	57/F	Anorexia <sup>a</sup> , Insomnia <sup>a</sup>
	49/M	Blood pressure increased <sup>a</sup>
	66/M	Blood pressure increased <sup>a</sup>
F	54/M	Alanine aminotransferase increased <sup>a</sup>
	25/F	Weight increased <sup>a</sup>
	51/F	Facial palsy
	56/F	Diarrhoea <sup>a</sup>

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

<sup>a</sup> Considered treatment-related (investigator causality)

The most common all causality AEs (MedDRA preferred term) resulting in discontinuation in the T/A group was blood pressure increased (2 subjects). With the exception of 1 event of facial palsy in the fenofibrate treatment group, all of these AEs were considered treatment-related by the investigator.

Serious Adverse Events: Serious adverse events (SAEs) were reported up to 28 days after the last dose of study drug. Six randomized subjects experienced SAEs: 3 T/A- and 3 fenofibrate-treated subjects. Serious adverse events are summarized by treatment group and subject age at screening/gender in Table S4.

**Table S4. Subjects With Serious Adverse Events**

Treatment	Subject Age/Gender	Adverse Event (Investigator Term)
T/A	67/F	Cystocele
	45/M	Neurinoma <sup>a</sup>
	59/M	Heart attack <sup>b</sup>
F	52/F	Suicide attempt <sup>a</sup>
	58/M	Superinfected varicose ulcer
	51/F	Facial paralysis <sup>c</sup>

T/A=torcetrapib/atorvastatin, F=fenofibrate, F=female, M=male

<sup>a</sup> Led to temporary withdrawal from study (drug temporarily discontinued)

<sup>b</sup> Occurred post-therapy (treatment period completed)

<sup>c</sup> Led to withdrawal from study (drug permanently discontinued)

No SAEs were considered treatment-related.

There were no deaths reported during the course of this study. No subjects experienced an SAE that was considered by the investigator to be related to study medication. One fenofibrate-treated subject experienced an SAE (facial palsy [investigator term: facial paralysis]) that led to discontinuation from the study.

**Clinical Laboratory Tests:** In general, laboratory abnormalities were infrequent and comparable between the T/A and fenofibrate treatment groups.

**Blood Pressure:** Mean systolic blood pressure (SBP) increased from baseline in both treatment groups. The LS mean difference in change from baseline in SBP between the T/A and fenofibrate treatment groups was 2.2 mmHg at Week 12 and 5.1 mmHg at Week 30. By Week 30, more subjects in the T/A than fenofibrate treatment group received antihypertensive therapy (16.2% and 8.2%, respectively), experienced a treatment emergent AE related to blood pressure (5.4% and 2.7%, respectively), or experienced a treatment emergent AE related to blood pressure resulting in discontinuation (2.7% and 0%, respectively). By Week 30, the same number of subjects in the T/A and fenofibrate treatment groups experienced a treatment emergent AE of hypertension (2.7%), or experienced a treatment emergent AE of hypertension and SBP >140 or diastolic blood pressure >90 mmHg.

**CONCLUSION(S):** This Phase 3, multi-center, double-blind, randomized, parallel group study comparing the efficacy of forced titration T/A with a fixed dose of fenofibrate (both administered QD for 30 weeks) in subjects with Fredrickson Type IIb dyslipidemia (mixed hyperlipidemia) yielded the following conclusions:

- Treatment with T/A resulted in statistically significant elevations in the primary lipid endpoint of HDL-C and statistically significant reductions in non-HDL-C at Week 12 when compared to treatment with fenofibrate (p <0.0001 for difference between treatment groups).

- The non-HDL-C reduction observed in the T/A treatment group was associated with statistically significant changes from baseline at Weeks 12 and 30 in LDL-C and LDL-C/HDL-C ratio.
- The number of subjects in the T/A treatment group reaching their NCEP ATP-III non-HDL and NCEP ATP-III LDL goal was greater at all timepoints compared to subjects treated with fenofibrate; the difference was statistically significant.
- The number of subjects with all causality treatment-emergent AEs and the number of discontinuations were numerically higher in the T/A treatment group compared to the fenofibrate treatment group. The frequency of SAEs was the same in both treatment groups. There were no treatment-related SAEs for either treatment group.
- Mean SBP increased from baseline to Week 12 and Week 30 in both treatment groups. The mean increase in SBP was 2.2 mmHg greater in T/A-treated subjects at Week 12, and 5.1 mmHg greater at Week 30.