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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.: 00134264

PROTOCOL NO.: A5091043

PROTOCOL TITLE: Phase 3 Multi-Center, Double-Blind, Randomized, Parallel Group Evaluation Of The Fixed Combination Torcetrapib/Atorvastatin, Administered Orally, Once Daily (QD), Compared With Atorvastatin Alone, On The Occurrence Of Major Cardiovascular Events In Subjects With Coronary Heart Disease Or Risk Equivalents (ILLUMINATE).

Study Center(s): 260 centers: United States 111 centers, Australia 25 centers, the Netherlands 26 centers, Spain 26 centers, Sweden 26 centers, the United Kingdom 25 centers and Canada 21 centers.

Study Initiation and Completion Dates: First Subject Visit: 14 July 2004
Last Subject Visit: 29 April 2007

The A5091043 study (also known as the **I**nvestigation of **L**ipid **L**evel Management to **U**nderstand its I**M**pact **IN AT**herosclerotic **E**vents or ILLUMINATE) was ongoing at the time of termination of the torcetrapib program on 02 December 2006, and so was not completed, but terminated early. Clinical investigators were instructed to contact all subjects randomized into the trial to stop taking study medication immediately and to complete end of study procedures. The last subject last visit occurred in April 2007 due to a potential lost-to-follow-up subject being located. The subject was in the atorvastatin treatment group.

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 A5091043 (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.

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Study Objective(s): The primary objective was to demonstrate whether the fixed combination torcetrapib/atorvastatin (T/A) could incrementally reduce the risk for future occurrence of major cardiovascular disease events (MCVE), when compared to atorvastatin alone, in subjects with coronary heart disease (CHD) or risk equivalents.

METHODS

Study Design: This was a multi-center, double-blind, randomized, parallel group study of the fixed combination T/A versus atorvastatin alone, in male and female subjects aged 45 to 75 years, with prior CHD, peripheral vascular disease (PVD), symptomatic carotid artery disease, or type 2 diabetes.

The original protocol was amended on 28 November 2006, a change that had not yet received institutional review board or ethics committee approval at the time of the trial's termination. The amendment included the addition of hospitalization for unstable angina to the primary endpoint (MCVE) to increase the number of events and thus increase the statistical power to reject the null hypothesis. The methods and results described are based on the amended protocol.

After initial screening, eligible subjects entered a 4 to 10-week atorvastatin only run-in period, during which subjects had therapeutic lifestyle change counseling and received atorvastatin titrated to the target low density lipoprotein cholesterol (LDL-C) value of <100 mg/dL (2.6 mmol/L). A variability tolerance of +15 mg/dL (0.4 mmol/L) was allowed. Subjects who were previously treated with statins were immediately switched to atorvastatin at a milligram strength expected to provide LDL-C lowering equivalent to their prior statin therapy. Once target LDL-C value was reached subjects were randomized to 1 of 2 treatment regimens: fixed combination T/A at doses of 60/10, 60/20, 60/40, or 60/80 mg, once daily (QD) and concurrent placebo atorvastatin; or atorvastatin alone (10, 20, 40, or 80 mg) QD, and concurrent placebo fixed combination T/A. For both treatment arms, the dose of active atorvastatin was the same as that used to reach target LDL-C during the run-in period. Subjects who failed to reach their target LDL-C goal at the maximum dose of atorvastatin (80 mg) were not eligible for randomization. Post-randomization study visits occurred at Months 1, 3, 6, 9 and 12. Thereafter, subjects were seen twice-yearly until study completion, which was scheduled to occur when 1820 primary endpoints were accrued or when subjects had been followed for a mean of 4.5 years, whichever was later. Subjects were not to be withdrawn from double-blind study drug or follow up if they experienced a nonfatal clinical endpoint.

Number of Subjects (Planned and Analyzed): It was planned to randomize approximately 13000 subjects in the study, 6500 subjects per treatment arm, to yield 551 primary outcomes in the atorvastatin-only group (8.48%) and 433 in the group receiving both atorvastatin and torcetrapib (6.66%) after an average of 4.5 years of follow-up (ie. an absolute reduction of 1.82 percentage points or a relative reduction of 21% in the cumulative incidence). Subsequently, 19014 subjects were screened for enrollment in the study and 16960 subjects were enrolled in the atorvastatin run-in period. A total of 15067 subjects were randomized: 7533 were randomized to receive T/A and 7528 were treated; 7534 subjects were randomized

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to receive atorvastatin and 7526 were treated. Data for the primary efficacy analyses were censored on 02 December 2006 (study termination), at which time 6520 subjects were ongoing in the T/A treatment group and 6695 subjects were ongoing in the atorvastatin treatment group. All 15067 randomized subjects were evaluated for safety.

Diagnosis and Main Criteria for Inclusion: Men and women aged 45 to 75 years, inclusive, who were at high risk for CVD events (prior CHD, PVD, symptomatic carotid artery disease, or type 2 diabetes) and who were eligible for statin treatment, were screened for study participation.

Study Treatment: During the atorvastatin run-in period, subjects were instructed to take 1 (for 10, 20, 40 mg doses) or 2 tablets (for 80 mg dose) 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 and after eating. During the double-blind treatment period, subjects randomized to T/A were instructed to take 2 or 3 tablets QD; 1 tablet of T/A or its matching placebo, and 1 (for 10, 20, 40 mg doses) or 2 tablets (for 80 mg dose) of atorvastatin or its matching placebo. Study medication was to be taken in the same manner as during the run-in period. Atorvastatin was supplied as 10 mg, 20 mg or 40 mg tablets. T/A was supplied as tablets containing 60 mg of torcetrapib combined with atorvastatin at a dose of 10, 20, 40, or 80 mg.

Efficacy Evaluations: The primary efficacy endpoint was the time to first MCVE, defined as death from CHD, nonfatal myocardial infarction (MI) (excluding procedure-related MI), stroke (fatal and nonfatal), or hospitalization for unstable angina. The fourth component of MCVE, hospitalization for unstable angina, was included in the primary composite endpoint in a protocol amendment prior to termination of the trial. The original protocol was amended with Steering Committee approval just prior to the trial's early termination but the amendment had not yet been approved by IRBs or submitted to the appropriate Regulatory Agencies. The amendment included the addition of hospitalization for unstable angina to the primary endpoint composite which is used in this report.

Safety Evaluations: Safety was assessed using routine clinical laboratory assessments (hematology and urinalysis at screening and randomization [Month 0] and Months 12, 24, 36, 48 and 60, and chemistry at screening, during the atorvastatin run-in period, at randomization, and at Months 1, 3 and 6). Vital signs were monitored at every visit. Physical examinations and electrocardiograms (ECGs) were performed at randomization and Months 12, 24, 36, 48 and 60. Subjects were monitored for adverse events (AEs) throughout the treatment period. Safety evaluations planned for the end of the study were performed at early termination if this occurred.

Statistical Methods: The primary efficacy endpoint was the time to first MCVE.

The primary efficacy analysis population was the Intent to Treat population which included all randomized subjects. All data were censored for the primary analyses on 02 December 2006, when the study was terminated by the sponsor. Events occurring after that date, in the period between study termination and the end of data collection, were captured either at a

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final visit following study drug discontinuation or as a result of instructions to subjects to report serious adverse events (SAEs).

The primary efficacy endpoint was analyzed using the log-rank test. The time to the first occurrence of an MCVE for each treatment group was summarized by Kaplan-Meier curves. Hypothesis testing was 2-sided with a 5% error rate (ie, p = 0.05 significance level). The hazard ratio and its 95% confidence intervals were computed. No adjustments were made for multiple comparisons.

The prespecified safety monitoring boundary (a p-value <0.01, unadjusted for multiple comparisons) was based on a log-rank test for death from any cause. An efficacy-monitoring boundary (to be implemented after approximately 50% of the expected number of events had occurred in the primary outcome) was prespecified, but the requisite event count was never reached.

RESULTS

Subject Disposition and Demography: Of the 19014 subjects screened for enrollment in the study, 16960 subjects were enrolled in the atorvastatin run-in period and 15067 subjects were randomized to double-blind treatment. Of the 7533 subjects who were randomized to receive T/A, 7528 were treated and of the 7534 subjects randomized to receive atorvastatin, 7526 were treated (Table S1). Early discontinuation of treatment (ie, before study termination on 02 December 2006) occurred in 1008 subjects (13.4%) in the T/A treatment group and in 831 subjects (11.0%) in the atorvastatin treatment group, therefore 6520 subjects (86.6%) in the T/A treatment group and 6695 subjects (89.0%) in the atorvastatin treatment group were discontinued due to study termination. At the end of the study (02 December 2006) follow-up was 99.7% complete, and the median follow-up in each treatment group was 550 days.

The most common reasons for early discontinuation (before study termination) within the T/A and atorvastatin treatment groups were nonfatal AEs (9.3% and 5.7%, respectively) and withdrawal of consent (1.7% and 2.1%, respectively). Demographic characteristics were similar between treatment groups. A majority of all subjects were male (77.8%) and white (93.2%). The average age was 61.3 years in both treatment groups.

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Table S1. Subject Evaluation Groups and Disposition

	n	Number of Subjects, n (%)	
		T/A	Atorvastatin
Screened	19014		
Enrolled in Run-In Period (Atorvastatin Only)	16960		
Randomized to Double-Blind Treatment	15067		
Assigned to Treatment		7533	7534
Treated		7528	7526
Discontinued before Study Termination[a]		1008 (13.4)	831 (11.0)
Discontinued at Study Termination[a]		6520 (86.6)	6695 (89.0)
Evaluated for Efficacy (ITT)		7533 (100.0)	7534 (100.0)
Evaluated for Safety		7533 (100.0)	7534 (100.0)

T/A=torcetrapib/atorvastatin, ITT=Intent to Treat
[a] Early termination of study on 02 December 2006

Efficacy Results:

At the time of the 30 November 2006 Periodic Report prepared for the independent DSMB, data analyzed showed an imbalance in death due to any cause (T/A: 82/7533 (1.09%), atorvastatin: 51/7534 (0.68%); p = 0.007) which exceeded the pre-specified safety-monitoring boundary (p <0.01) with a log-rank test p-value of 0.007 and a hazard ratio of 1.61 (95% CI: [1.14, 2.28]). Based on these data, the DSMB recommended termination of the study.

Subsequent to the halting of the study, data acquisition continued and all efficacy data were censored on 02 December 2006. Four hundred and sixty-four subjects (6.2%) experienced a primary endpoint MCVE in the T/A treatment group, compared with 373 subjects (5.0%) in the atorvastatin only treatment group; for a hazard ratio of 1.25 (95% CI: [1.09 to 1.44]; p = 0.001). There were 38 MCVEs reported in each treatment group which occurred after the termination of the study with 14 deaths in the T/A group and 20 deaths in the atorvastatin only group.

Safety Results:

Adverse Events: Adverse events were reported by 86.6% of subjects in the T/A treatment group and 83.3% of subjects in the atorvastatin treatment group.

The most commonly reported AEs are summarized by MedDRA preferred term and treatment group in Table S2.

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Table S2. Most Commonly Reported Adverse Events

MedDRA Preferred Term	Number of Subjects, n (%)	
	T/A N=7533	Atorvastatin N=7534
Hypertension	1411 (18.7)	564 (7.5)
Upper Respiratory Tract Infection	555 (7.4)	582 (7.7)
Nasopharyngitis	528 (7.0)	524 (7.0)
Arthalgia	453 (6.0)	486 (6.5)
Myalgia	417 (5.5)	491 (6.5)
Edema Peripheral	467 (6.2)	353 (4.7)
Back Pain	451 (6.0)	431 (5.7)
Angina Pectoris	451 (6.0)	360 (4.8)
Headache	412 (5.5)	296 (3.9)
Pain in Extremity	394 (5.2)	387 (5.1)
Influenza	347 (4.6)	303 (4.0)
Fatigue	339 (4.5)	359 (4.8)
Dizziness	342 (4.5)	339 (4.5)
Cough	323 (4.3)	305 (4.1)
Diarrhea	315 (4.2)	292 (3.9)
Dyspnea	313 (4.2)	243 (3.2)
Urinary Tract Infection	268 (3.6)	260 (3.5)
Bronchitis	265 (3.5)	262 (3.5)
Musculoskeletal Pain	247 (3.3)	255 (3.4)
Sinusitis	236 (3.1)	223 (3.0)

MedDRA=Medical Dictionary for Regulatory Affairs (version 8.0), T/A=torcetrapib/atorvastatin

The most commonly reported AEs in both the T/A and atorvastatin treatment groups were hypertension (18.7% and 7.5%, respectively), upper respiratory tract infection (7.4% and 7.7%, respectively) and nasopharyngitis (7.0% in both). Adverse events that were reported more commonly (i.e., > 1%) in the T/A treatment group than in the atorvastatin treatment group included hypertension, edema peripheral, angina pectoris, headache and dyspnea.

Permanent Discontinuations Due to Adverse Events: The number of subjects who discontinued treatment before study termination, due to any nonfatal AE, was higher in the T/A than atorvastatin treatment group (698 subjects [9.3%] and 432 subjects [5.7%], respectively). The higher rates of discontinuation in the T/A treatment group were associated mainly with a higher frequency of hypertension, nonspecific gastrointestinal symptoms, and headache.

Serious Adverse Events: Serious adverse events (SAEs) with onset occurring after randomization and up to 02 December 2006, were reported by 16.4% of T/A-treated subjects and by 15.0% of atorvastatin-treated subjects.

The most commonly reported treatment-emergent SAEs are summarized by preferred term and treatment group in Table S3.

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Table S3. Most Commonly Reported Treatment-Emergent[a] Serious Adverse Events

MedDRA Preferred Term	Number of Subjects, n (%)	
	T/A N=7533	Atorvastatin N=7534
Chest Pain	165 (2.19)	126 (1.67)
Osteoarthritis	48 (0.64)	39 (0.52)
Angina Unstable	48 (0.64)	36 (0.48)
Pneumonia	46 (0.61)	34 (0.45)
Angina Pectoris	42 (0.56)	33 (0.44)
Atrial Fibrillation	41 (0.54)	48 (0.64)
Fall	38 (0.50)	36 (0.48)
Prostate Cancer	28 (0.37)	30 (0.40)
Chronic Obstructive Pulmonary Disease	27 (0.36)	25 (0.33)
Syncope	26 (0.35)	22 (0.29)
Gastrointestinal Hemorrhage	25 (0.33)	15 (0.20)
Anemia	25 (0.33)	14 (0.19)
Congestive Cardiac Failure	24 (0.32)	16 (0.21)
Noncardiac Chest Pain	22 (0.29)	27 (0.36)
Cellulitis	22 (0.29)	17 (0.23)
Abdominal Pain	11 (0.15)	18 (0.24)
Cholelithiasis	12 (0.16)	17 (0.23)
Dyspnea	13 (0.17)	16 (0.21)
Urinary Tract Infection	13 (0.17)	14 (0.19)

MedDRA=Medical Dictionary for Regulatory Affairs (version 8.0), T/A=torcetrapib/atorvastatin
[a] Onset occurred after randomization and prior to 02 December 2006

The most commonly reported treatment-emergent SAE (onset before study termination) in both treatment groups was chest pain, which was reported by 165 subjects (2.19%) in the T/A treatment group and 126 subjects (1.67%) in the atorvastatin treatment group. All other SAEs were reported by less than 1% of subjects in either treatment group.

At study termination there were 93 deaths from all causes in the T/A treatment group and 59 deaths from all causes in the atorvastatin treatment group, for a hazard ratio of 1.58 in the T/A group (95% CI: [1.14 to 2.19]; p = 0.006). Causes of death are listed in Table S4 by treatment group and adjudicated event.

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Table S4. Causes of Death[a]

Adjudicated Event Category	Number of Subjects	
	T/A N=7533	Atorvastatin N=7534
Any Event	93	59
Any Cardiovascular Cause	49	35
Sudden Death	26	25
Fatal Myocardial Infarction	8	6
Fatal Stroke:		
Hemorrhagic	4	0
Ischemic	2	0
Embolic	0	0
Not Classified	0	0
Fatal Heart Failure	2	1
Other Vascular-Related Cause	1	2
Fatal Myocardial infarction (Procedure-Related)	2	0
Other Cardiac-Related Cause	4	1
Any Noncardiovascular Cause	40	20
Cancer	24	14
Infection	9	0
Trauma	3	3
Suicide or Homicide	0	1
Other Cause	4	2
Reason Unknown	4	4

T/A=torcetrapib/atorvastatin
[a] Data were censored on 02 December 2006, the date of study termination

In the T/A treatment group, as compared with the atorvastatin treatment group, there was an imbalance in the number of deaths from both cardiovascular causes (49 and 35 subjects, respectively) and noncardiovascular causes (40 and 20 subjects, respectively). For death from noncardiovascular causes, more subjects in the T/A treatment group than in the atorvastatin treatment group had adjudicated causes of death from cancer (24 and 14 subjects, respectively) and infection (9 and 0 subjects, respectively).

Clinical Laboratory Tests: At Month 12, there was a mean decrease from baseline in serum potassium for the T/A treatment group (-0.08 mmol/L) compared with a mean increase for the atorvastatin treatment group (0.06 mmol/L; $p<0.001$). For both treatment groups there were mean increases from baseline in serum sodium (T/A: 1.39 mmol/L; atorvastatin: 0.78 mmol/L [$p<0.001$]) and bicarbonate (T/A: 2.28 mmol/L; atorvastatin: 1.93 mmol/L [$p<0.001$]).

Blood Pressure: The mean increase in systolic blood pressure from baseline to Month 12 was 5.4 mmHg in the T/A treatment and 0.9 mmHg in the atorvastatin treatment group ($p<0.001$).

CONCLUSION(S): This prematurely terminated Phase 3, multi-center, double-blind, randomized, parallel group study demonstrated an increased risk of mortality and morbidity of unknown mechanism, with T/A treatment compared to atorvastatin only treatment, in subjects with prior CHD, PVD, symptomatic carotid artery disease, or type 2 diabetes. There

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was a significant increase in the risk of MCVEs in the T/A treatment group compared with the atorvastatin treatment group, with a hazard ratio of 1.25 (95% CI: [1.09 to 1.44]; p = 0.001).

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