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**PROPRIETARY DRUG NAME/INN:** Not Applicable/Torcetrapib and atorvastatin calcium

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:**

**NCT #:** 00134485

**PROTOCOL NO.:** A5091026

**PROTOCOL TITLE:** Phase 3, Multi-Center, Double-Blind, Randomized, Parallel Group Study of the Efficacy, Safety, and Tolerability of Fixed Combination Torcetrapib (CP-529,414)/Atorvastatin Administered Orally, Once Daily (QD) for Six Months, Compared With Maximally Tolerated Atorvastatin Therapy Alone, in Subjects With Heterozygous Familial Hypercholesterolemia

**Study Center(s):** Australia, 6 centers; Canada, 4 centers; Denmark, 2 centers; France, 4 centers; Iceland, 1 center; Norway, 2 centers; South Africa, 4 centers; Sweden, 4 centers; and United States, 11 centers.

**Study Initiation and Completion Dates:** First Subject Visit: 07 March 2005  
Last Subject Visit: 03 March 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 demonstrate the efficacy of fixed combination Torcetrapib/Atorvastatin (T/A) in lowering low density lipoprotein cholesterol (LDL-C), raising levels of high density lipoprotein cholesterol (HDL-C) and favorably altering the levels of other lipid parameters and biomarkers, when compared to atorvastatin alone, in subjects with heterozygous familial hypercholesterolemia (HeFH).

- Additional objectives included assessing the safety and tolerability of T/A, in subjects with HeFH.

## METHODS

**Study Design:** This was a multi-center, double-blind, randomized, parallel group study of fixed combination T/A in male and female subjects  $\geq 18$  years of age with HeFH. After initial screening, eligible subjects entered a 6 to 14-week run-in phase which consisted of up to 4 visits (every 4 weeks), during which their once daily (QD) atorvastatin dose (20, 40, or 80 mg) was titrated to a target LDL-C level according to the subject's cardiovascular risk based on the NCEP-ATP III guidelines, or to their maximally tolerated atorvastatin dose (maximal atorvastatin daily dose was 80 mg). Subjects not receiving a statin prior to study entry were prescribed atorvastatin 20 mg daily. Subjects continued on that atorvastatin dose for an additional 2 weeks before being randomized to receive one of the following for 24 weeks of double-blind treatment: (A) fixed combination T/A (60 mg torcetrapib combined with 20, 40, or 80 mg atorvastatin) QD and concurrent placebo atorvastatin or (B) atorvastatin (20, 40, or 80 mg) QD and concurrent placebo-fixed combination. For both treatment arms, the dose of active atorvastatin was established during the run-in period as specified above.

**Number of Subjects (planned and analyzed):** The protocol called for screening of approximately 420 potential subjects in order to randomize 356 subjects. Subsequently, 519 subjects were screened for enrollment in the study, and 437 were randomized and treated (221 subjects were randomized to receive T/A of which 218 were evaluated for efficacy, and 216 subjects received atorvastatin alone, of which 213 were evaluated for efficacy; all 437 subjects were evaluated for safety).

**Diagnosis and Main Criteria for Inclusion:** Men and women 18 years of age or older who were diagnosed with HeFH were screened for study participation. The subject's lipid profile at the time of diagnosis must have met one of the lipid eligibility criteria as set forth by the protocol.

**Study Treatment: Run-in Period:** During the run-in period (Visits 2, 3, 4, and 5), the atorvastatin dose was titrated to a target LDL-C level according to the subject's cardiovascular risk based on the NCEP-ATP III guidelines, or to the maximally tolerated atorvastatin dose (not to exceed 80 mg daily). Atorvastatin was to be taken orally, once a day, with water, immediately after the morning meal at a dose of 20, 40, or 80 mg daily (1 or 2 tablets a day), except on the morning of clinic visits, when study medication was to be taken following blood sampling for clinical laboratory measurements. Once the target LDL-C level was reached, the subject was maintained on that atorvastatin dose for approximately 2 weeks, until they returned for the randomization visit (Visit 6). Additional details regarding the titration to the target atorvastatin dose during the run-in period are located in Appendix 1 of the study protocol (see Appendix A1 of this report).

**Treatment Period:** After randomization and during the treatment period (Visits 6, 7, and 8), subjects were instructed to take 2 or 3 tablets a day, with water, immediately after the morning meal, except on the morning of clinic visits, when study medication was to be taken

following blood sampling for laboratory studies and ECGs, when applicable. Subjects were randomized to receive one of the following double-blind treatments for 24 weeks:

- Fixed combination torcetrapib (60 mg)/atorvastatin (20, 40, or 80 mg) QD and concurrent placebo atorvastatin; OR
- Atorvastatin (20, 40, or 80 mg) QD and concurrent placebo-fixed combination.

**Efficacy Evaluations:** The primary endpoints were mean percent change in HDL-C and LDL-C plasma levels from Baseline to Week 24. A lipid profile (total cholesterol, HDL-C, LDL-C, and triglycerides [TG]) was performed at screening, the run-in visit at which the subject reached the LDL-C target or the maximally tolerated atorvastatin dose, Visit 6 (randomization), and all subsequent visits through Visit 9 (Week 24) or early termination (ET). Fasting blood samples for special lipid studies were also obtained at Visits 6 and 9 or ET. Special lipid studies included HDL subclasses (HDL2-C, HDL3-C), apolipoproteins [Apo A-I, Apo B-100, lipoprotein (a)]; remnant lipoprotein cholesterol (RLP-C); and lipoprotein particle subclass composition and size by Nuclear Magnetic Resonance (NMR) (HDL, LDL, and very low density lipoprotein [VLDL] subclass composition and size, mean particle size, and calculated lipids). The inflammatory biomarker high sensitivity-C-reactive protein (hs-CRP) was assessed at Visit 6 (randomization) and Visit 9 (Week 24) or ET.

**Safety Evaluations:** Safety was assessed using routine clinical laboratory evaluations (hematology, chemistry, and urinalysis), 12-lead ECG and vital sign measurements, physical examination, and by monitoring adverse events (AEs) and serious adverse events (SAEs) throughout the study. Clinically significant physical examination findings were recorded as AEs. Lipid safety profiles (LDL-C and TG values, monitored by the central laboratory) were performed at Visits 7 and 8. Liver function and creatine kinase (CK)/symptomatic myopathy monitoring were also performed starting at Visit 3. Vital signs (blood pressure [BP] and heart rate [HR]) were measured in triplicate at each visit. Elevations in BP were carefully managed as outlined in the study protocol.

**Statistical Methods:** The primary efficacy analysis population was the full analysis set (FAS). Analysis of covariance (ANCOVA) using linear models fit by ordinary least squares was applied to analyze the change in all laboratory efficacy endpoints. The linear model included terms for baseline value, baseline atorvastatin dose, geographic region (North America, Europe, South Africa, and Australia) and treatment group. The treatment differences between T/A and atorvastatin alone were estimated using least squares (LS) means from the linear model. All testing was 2-sided and conducted with a 5% type I error rate. Ninety-five percent confidence intervals (CIs) of the treatment differences were also provided.

Percent changes in HDL-C and LDL-C from baseline to Week 24 were the primary endpoints. The 2 null hypotheses tested whether the mean percent change in HDL-C or LDL-C levels from baseline to the end of the study for the T/A combination was not different from the atorvastatin alone treatment. The overall type I error rate was controlled by testing the hypotheses in the fixed order: HDL-C first and LDL-C second. The second hypothesis was tested only if the first hypothesis was rejected.

The secondary endpoints were divided into 2 sets: Key secondary endpoints and supporting secondary endpoints. For key secondary endpoints, 2 families of endpoints were identified: Apo A-associated and Apo B-associated. If any of the primary hypotheses was statistically significant, the 2 families of key secondary hypotheses were tested separately at a family-wise type I error rate at 0.05 (2-sided), using Hochberg's procedure to test the difference between the 2 treatment groups. If any one of the members in the first family of hypotheses was significant, Hochberg's procedure was used again to test the second family of hypotheses. A treatment effect was significant only if the direction of the difference was in favor of a T/A effect.

## RESULTS

**Subject Disposition and Demography:** Of the 519 subjects screened for enrollment in the study, 437 were randomized and treated (221 subjects were randomized to receive T/A, and 216 subjects received atorvastatin alone) (Table S1). Of the 437 subjects who were treated, 398 (91%) completed the study and 39 (9%) withdrew prematurely. The most common reason for withdrawal within each treatment group was AEs: 18 (of 28) T/A-treated subjects and 6 (of 11) atorvastatin only-treated subjects withdrew due to AEs. A majority of all subjects were white (90%), between the ages of 45 and 64 years (52%), and male (60%).

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

	Number of Subjects (n, %)	
	T/A	A
Screened	519	
Assigned to Study Treatment	221	216
Treated	221	216
Completed	193 (87.3)	205 (94.9)
Discontinued	28 (12.7)	11 (5.1)
Assessed for Safety:		
Adverse Events	221 (100.0)	216 (100.0)
Laboratory Tests	221 (100.0)	214 (99.1)
Evaluated for Efficacy (FAS) <sup>a</sup> :	218 (98.6)	213 (98.6)
Baseline	218	213
Week 4	211	209
Week 12	206	208
Week 24	193	202

A = Atorvastatin; FAS = Full Analysis Set (Observed Cases); T/A = Torcetrapib/Atorvastatin.

<sup>a</sup> Table entries for baseline through Week 24 reflect the number of subjects who had an HDL-C measurement within the visit window.

**Efficacy Results:** Treatment with T/A resulted in statistically significant changes from baseline in the primary lipid endpoints of HDL-C and LDL-C at Week 24 when compared to treatment with atorvastatin alone ( $p < 0.0001$  for difference between treatment groups). The difference in the mean percent increase from baseline in HDL-C at Week 24 among T/A-treated subjects was +56.6% when compared with atorvastatin alone. The difference in the mean percent change from baseline in LDL-C at Week 24 among T/A-treated versus atorvastatin only-treated subjects was -27.1%. Statistically significant changes in HDL-C and LDL-C from baseline, in favor of treatment with T/A, were also observed at Weeks 4 and 12.

Using Hochberg's procedure, treatment with T/A also showed mean incremental changes from baseline over treatment with atorvastatin alone as shown by statistically significant differences in the following key secondary efficacy parameters at Week 24.

The Apo A-associated family of lipoproteins had increases in Apo A-I, HDL2-C, HDL3-C, and HDL size [NMR] and decreases in LDL-C/HDL-C and total cholesterol/HDL-C ratios ( $p < 0.0001$  for the difference between treatment groups for all parameters).

The Apo B-associated family of lipoproteins had decreases in Apo B-100, non-HDL-C, total LDL, total small LDL particle number and intermediate-density lipoprotein (IDL) particle number by NMR and an increase in LDL size by NMR ( $p < 0.0001$  for the difference between treatment groups for all parameters).

Treatment with T/A therapy also showed decreases from baseline in the following supporting secondary endpoints at Week 24, as compared to atorvastatin alone: Apo B-100/Apo A-I and non-HDL-C/HDL-C ratios ( $p < 0.0001$  for both), and TGs ( $p = 0.0072$ ), lipoprotein (a) ( $p < 0.0001$ ), and RLP-C levels ( $p < 0.0001$ ). There was no significant difference between treatment groups in mean nominal change from baseline in hs-CRP levels or mean hs-CRP levels based on logarithmic transformation at Week 24.

Complete statistical output, including summary statistics, for total, large, medium, and small VLDL particles, additional supporting secondary endpoints, is on file with the sponsor.

**Safety Results:** Of the 437 subjects who were evaluated for safety, 145 (66%) of the T/A-treated subjects and 108 (50%) of atorvastatin only-treated subjects reported at least 1 treatment-emergent AE. The incidence of treatment-related AEs was higher in the T/A treatment group (73 subjects, 33%) as compared with subjects who received atorvastatin alone (36 subjects, 17%). The number of subjects who discontinued due to any treatment-emergent AE (all causality) was also higher in the T/A treatment group (17 [8%] T/A-treated subjects as compared with 4 [2%] atorvastatin only-treated subjects).

Treatment-emergent adverse events by system organ class and treatment group are summarized in the following table.

**Table S2. Treatment-Emergent Adverse Events by System Organ Class and Treatment Group (Safety Analysis Set)**

System Organ Class <sup>a</sup> / High-Level Group Term <sup>a</sup> / MedDRA Preferred Term <sup>b</sup>	T/A N = 221		A N = 216	
	All Causalities	Treatment- Related	All Causalities	Treatment- Related
Number (%) of Subjects With Adverse Events	145 (65.6)	73 (33.0)	108 (50.0)	36 (16.7)
<b>Gastrointestinal Disorders</b>	34 (15.4)	18 (8.1)	20 (9.3)	6 (2.8)
Gastrointestinal motility and defaecation conditions	14 (6.3)	7 (3.2)	3 (1.4)	1 (0.5)
Gastrointestinal signs and symptoms	17 (7.7)	11 (5.0)	11 (5.1)	4 (1.9)
<b>General Disorders and Administration Site Conditions</b>	8 (3.6)	2 (0.9)	16 (7.4)	6 (2.8)
General system disorders NEC	5 (2.3)	0	13 (6.0)	5 (2.3)
<b>Infections and Infestations</b>	53 (24.0)	0	40 (18.5)	0
Infections – pathogen class unspecified	51 (23.1)	0	31 (14.4)	0
Viral infections disorders	7 (3.2)	0	11 (5.1)	0
<b>Investigations</b>	17 (7.7)	8 (3.6)	10 (4.6)	2 (0.9)
Cardiac and vascular investigations (excluding enzyme tests)	11 (5.0)	4 (1.8)	1 (0.5)	0
<b>Musculoskeletal and Connective Tissue Disorders</b>	38 (17.2)	18 (8.1)	27 (12.5)	12 (5.6)
Joint disorders				
Arthralgia	16 (7.2)	8 (3.6)	13 (6.0)	5 (2.3)
Muscle Disorders	11 (5.0)	7 (3.2)	9 (4.2)	5 (2.3)
Myalgia	13 (5.9)	7 (3.2)	13 (6.0)	8 (3.7)
Musculoskeletal and connective tissue disorders NEC	10 (4.5)	6 (2.7)	11 (5.1)	7 (3.2)
disorders NEC	15 (6.8)	4 (1.8)	6 (2.8)	3 (1.4)
<b>Nervous System Disorders</b>	26 (11.8)	15 (6.8)	12 (5.6)	6 (2.8)
Headache <sup>c</sup>	12 (5.4)	7 (3.2)	3 (1.4)	1 (0.5)
Headache	11 (5.0)	7 (3.2)	3 (1.4)	1 (0.5)
Neurological disorders NEC	12 (5.4)	7 (3.2)	8 (3.7)	4 (1.9)
<b>Vascular Disorders</b>	25 (11.3)	16 (7.2)	7 (3.2)	5 (2.3)
Vascular hypertensive disorders	21 (9.5)	14 (6.3)	5 (2.3)	5 (2.3)
Hypertension	21 (9.5)	14 (6.3)	5 (2.3)	5 (2.3)

T/A = torcetrapib/atorvastatin; A = Atorvastatin; NEC = Not Elsewhere Classified

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

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

<sup>c</sup> Higher Level Group term “Headache” includes AEs that coded to both of the following terms: Headache and Migraine. Note: The above table includes data up to 42 days after last dose of study drug.

The system organ classes most affected with AEs were (in decreasing order): Infections and infestations, musculoskeletal and connective tissue disorders, gastrointestinal disorders, nervous system, and vascular disorders. The frequency of AEs within each system organ class listed above was higher in T/A-treated subjects: AEs within nervous system and vascular disorders were of the greatest imbalance. Within the category of nervous system, the majority of imbalance was attributed to AEs of mild to moderate headache; within the category of vascular disorders, the imbalance was primarily exclusive to reported episodes of mild to moderate hypertension.

By preferred term, the most frequent AEs reported in either treatment group (by decreasing frequency) included hypertension, myalgia, arthralgia, and headache. The incidence of AEs

related to laboratory abnormalities involving elevated LFTs, CK, and/or musculoskeletal-related laboratory parameters was similar between treatment groups.

Subjects who discontinued from the study due to one or more treatment-emergent adverse event are listed by treatment group and subject age at screening/gender in the following table.

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

Treatment	Subject Age/Gender	Adverse Event (MedDRA Preferred Term)
T/A	55/F	Gastroesophageal reflux disease <sup>a</sup> , back pain <sup>a</sup> , osteoarthritis
	38/M	Suprapubic pain, dysuria
	53/M	Hypertension <sup>a</sup>
	48/F	Breast pain <sup>a</sup>
	59/F	Postoperative wound infection
	48/M	Myalgia <sup>a</sup>
	62/F	Dyspepsia <sup>a,b</sup> , gastroesophageal reflux disease <sup>a,b</sup>
	53/M	Renal pain <sup>b</sup>
	42/F	Dyspepsia <sup>a</sup> , nausea <sup>a,b</sup>
	48/F	Constipation <sup>a</sup>
	37/F	Myalgia <sup>a</sup>
	64/M	Hypertension <sup>a</sup>
	69/F	Aortic valve incompetence, blood pressure increased <sup>a</sup>
	49/F	Arthralgia <sup>a</sup>
	42/M	Arthralgia <sup>a</sup>
44/M	Hepatic enzyme increased <sup>a</sup>	
24/F	Arthralgia <sup>a</sup> , back pain <sup>a</sup>	
Atorvastatin Only	76/F	Drug hypersensitivity <sup>a</sup>
	20/F	Chest discomfort <sup>a</sup>
	46/M	Myalgia <sup>a,b</sup>
	48/M	Nausea <sup>a</sup>

T/A = Torcetrapib/atorvastatin; A = Atorvastatin; F = female; M = male

<sup>a</sup> Treatment-related

<sup>b</sup> Multiple episodes of AE reported

Twenty-one subjects discontinued from the study due to AEs: 14 of 17 T/A-treated and all (4 of 4) atorvastatin only-treated subjects discontinued from the study due to AEs that were considered related to study medication by the investigator.

SAEs are summarized by treatment group and age at screening/gender in the following table.

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

Treatment Group	Age/ Gender	Adverse Event (Investigator Term)
T/A	43/M	Angina pectoris
T/A	77/F	Gastric ulcer, gastric erosions
T/A	72/M	Osteoarthritis right hip
T/A	59/F	Acute myocardial infarction, sternotomy wound sepsis <sup>a</sup>
T/A	22/F	Spontaneous abortion <sup>c, d</sup>
T/A	50/M	Worsening of nephrolithiasis <sup>b</sup>
T/A	70/F	Hypertensive episode
T/A	69/F	Blood pressure elevation <sup>a, d</sup> , aortic valve dysfunction <sup>a</sup>
T/A	59/F	Unstable angina, transient ischemic attack, left carotid stenosis
A	58/F	Fall, fracture left wrist
A	76/F	Drug hypersensitivity <sup>a, d</sup>
A	55/M	Torn right Achilles tendon; deep vein thrombosis
A	48/F	Fracture left humerus, accidental fall
A	21/M	Acute appendicitis, hyperthermia, right colon colitis, iodine anaphylactic reaction
A	57/M	Upper digestive hemorrhage, bleeding gastric polyps, anemia

T/A = Torcetrapib/atorvastatin; A = Atorvastatin

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

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

<sup>c</sup> Occurred post-therapy (drug previously discontinued)

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

There were no deaths reported during the course of the study. Serious adverse events (SAEs) were reported up to 28 days after the last dose of study medication. Eight T/A, and 6 atorvastatin only-treated subjects reported SAEs during the course of the study. One additional T/A-treated subject experienced an SAE during the post-therapy phase that was unrelated to study drug. Three subjects had SAEs that were considered treatment related (2 T/A, 1 atorvastatin only). These included 1 T/A-treated (60/20 mg) subject who experienced a SAE of spontaneous abortion, 1 T/A-treated (60/80 mg) subject that experienced a SAE of blood pressure increased, and 1 atorvastatin (80 mg) only-treated subject who experienced a SAE of drug hypersensitivity. The first of these 3 subjects completed the study while the other 2 subjects discontinued treatment due to their SAE.

Among all SAEs, there were 3 subjects with investigator-reported cardiovascular events of angina pectoris, acute myocardial infarction, unstable angina, transient ischemic attack, and left carotid stenosis. These events were adjudicated by an independent committee and further analyzed at the summary level within the context of the larger torcetrapib/atorvastatin program.

The only other notable SAEs involved 2 subjects who experienced SAEs during the atorvastatin run-in phase of the study. One subject experienced a SAE of pancreatitis and the other subject experienced a SAE of adenocarcinoma of the prostate. Both of these SAEs were considered unrelated to study drug by the investigator.

In general, laboratory abnormalities were infrequent and comparable in both treatment groups. The incidence of AEs due to laboratory abnormalities due to elevated LFTs, CK, and/or musculoskeletal-related laboratory parameters was similar between treatment groups.

A mean increase in systolic blood pressure (SBP) was noted in both treatment groups over the course of the study. Although the mean increase in SBP was 2 mm Hg greater in T/A-treated subjects (at Week 24), the difference between treatment groups was not statistically significant.

**CONCLUSION(S):** This Phase 3, multi-center, double-blind, randomized, parallel-group study comparing the efficacy of fixed combination T/A with a maximally tolerated dose of atorvastatin (administered for 24 weeks) demonstrates that treatment with T/A results in statistically significant changes in the lipid profile of subjects with HeFH, as supported by the following conclusions:

- Treatment with T/A resulted in statistically significant changes in the primary lipid endpoints of HDL-C and LDL-C at Week 24 when compared to treatment with atorvastatin alone ( $p < 0.0001$  for difference between treatment groups). The effect of T/A on both HDL-C and LDL-C was evident by Weeks 4 and 12.
- The HDL-C increase observed in the T/A treatment group was associated with statistically significant changes in the following Apo A-associated key secondary parameters: increased in Apo A-I, HDL2-C, HDL3-C, and HDL size (NMR); and decreased LDL-C/HDL-C and total cholesterol/HDL-C ratios.
- The LDL-C decrease observed in the T/A treatment group was accompanied by significant changes in other atherogenic parameters, including: decreased Apo B-100, non-HDL-C, total LDL, total small LDL and IDL particle number (NMR), TGs, lipoprotein (a), RLP-C, and an increase in LDL size (NMR).
- The number of subjects with all causality and treatment-related AEs was higher in the T/A treatment group, the frequency of treatment-related SAEs was low and comparable in both treatment groups. Overall, discontinuation due to study drug-related AEs was relatively uncommon and there were no deaths during the course of the study.
- An increase in mean SBP from baseline to Week 24 was seen in both treatment groups over the course of the study. Although the mean increase in SBP was 2 mm Hg greater in T/A-treated subjects (at Week 24), the difference between treatment groups was not statistically significant. Overall, 12 of the 221 T/A-treated subjects (5.4%) met the SBP  $\geq +15$  mm Hg criteria: 7 of the 12 subjects were treated with anti-hypertensive therapy and of these, 3 returned to within 5 mm Hg of their baseline SBP. Consistent with these observations, T/A-treated subjects had a higher percentage of subjects requiring anti-hypertensive therapy by Week 24, a greater number of blood-pressure associated AEs, and a higher rate of discontinuation due to BP-associated AEs.