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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.: 00134498

PROTOCOL NO.: A5091025

PROTOCOL TITLE: Phase 3, Multi-Site, Double-Blind, Randomized, Forced Titration, Parallel Group Evaluation Of The Efficacy, Safety, And Tolerability Of Fixed Combination Torcetrapib (CP 529,414)/Atorvastatin Administered Orally, Once Daily (QD) For Eighteen Weeks, Compared With Atorvastatin Alone, In Subjects With Fredrickson Type IV Hypertriglyceridemia

Study Center(s): 3 centers in Canada and 20 centers in the United States

Study Initiation and Completion Dates: First Subject Visit: 21 February 2005
Last Subject Visit: 20 November 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 once daily (QD) administrations of torcetrapib/atorvastatin (T/A; 60/20 mg, 60/40 mg, 60/80 mg) in raising levels of high density lipoprotein cholesterol (HDL-C) and lowering levels of non-HDL-C in subjects with Fredrickson Type IV Hypertriglyceridemia, when compared to atorvastatin alone (20 mg, 40 mg, 80 mg, QD).

METHODS

Study Design: This was a multi-center, double-blind, parallel group, forced titration study of fixed combination T/A in male and female subjects aged ≥ 18 years with Fredrickson Type IV Hypertriglyceridemia. After initial screening (Week -6), eligible subjects entered a 6-week washout/dietary lead-in and screening period during which subjects 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, lipid levels were assessed and low density lipoprotein cholesterol (LDL-C) target goals were determined. At Week 0, subjects were randomized to receive 1 of the following for 18 weeks of double-blind treatment: T/A 60/20 mg QD (Weeks 0-6), followed by 60/40 mg QD (Weeks 6-12) and then 60/80 mg QD (Weeks 12-18); or atorvastatin: 20 mg QD (Weeks 0-6), followed by 40 mg QD (Weeks 6-12) and then 80 mg QD (Weeks 12-18). Subjects unable to tolerate dose increases were discontinued from the study.

Number of Subjects (Planned and Analyzed): It was planned to randomize 160 subjects, in order to have 136 subjects complete the study (68 subjects per treatment arm). Subsequently, 690 subjects were screened for enrolment in the study and 169 subjects were randomized and treated: 81 subjects were randomized to receive T/A and 88 subjects were randomized to receive atorvastatin. The randomization was stratified with respect to presence/absence of Type 2 diabetes mellitus (Type 2 DM) at baseline to achieve a 1:1 balance. All 169 treated subjects were evaluated for safety. In the T/A and atorvastatin treatment groups, respectively, 76 and 83 subjects were evaluated for efficacy over Weeks 0-6 (full analysis set; FAS), 72 and 79 subjects were evaluated over Weeks 6-10, and 64 and 76 subjects were evaluated over Weeks 12-18.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years or older with Fredrickson Type IV Hypertriglyceridemia, who were candidates for TLC and drug therapy according to the NCEP ATP-III guidelines, were screened for study participation. In accordance with the aim of the stratified randomization, approximately half of the subjects were non diabetic and half had type 2 DM.

Study Treatment: During the 18-week double-blind treatment period, study drug was taken QD with water, immediately after the morning meal, except on the morning of clinic visits, when study drug was taken with water after the clinic visit procedures were completed and after eating. Subjects were instructed to take 2 or 3 tablets QD; 1 tablet of T/A or its matching placebo, and 1 (for 20 or 40 mg dose) or 2 (for 80 mg dose) tablets of atorvastatin or its matching placebo. No down titration was permitted. If subjects were unable to tolerate dose increases, they were discontinued from the study.

Efficacy Evaluations: The primary efficacy endpoints were the percent changes in HDL-C and non-HDL-C from baseline to Week 6. A lipid profile which included HDL-C and non-HDL-C was obtained at each study visit.

Safety Evaluations: Safety was assessed using routine clinical laboratory evaluations (urinalysis and hematology at Weeks 0 and 18, and chemistry also at Weeks -2, -1, 6 and 12). Vital signs were monitored at every visit and physical examinations were performed at Weeks 0 and 18. Serum pregnancy testing was carried out at Weeks -2 and 18.

Electrocardiograms (ECGs) were performed at Weeks 0 and 18. Subjects were monitored for adverse events (AEs) from Weeks -2 to 18. Week 18 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 non-HDL-C from baseline to Week 6.

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 (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 and diabetic status and included baseline value as a covariate. Treatment differences and corresponding 95% confidence intervals (CIs) were based on least squares (LS) means from the linear model. A 2-step inference procedure was used in which statistical significance was required during the first step (HDL-C) before testing for the second (non-HDL-C). Hypothesis testing was 2-sided with a 5% error rate (ie, $p = 0.05$ significance level).

RESULTS

Subject Disposition and Demography: Of the 690 subjects screened for enrolment in the study, 169 subjects were randomized and treated: 81 subjects received T/A and 88 subjects received atorvastatin (Table S1). The majority of subjects completed the study: 66 (81.5%) in the T/A treatment group and 76 (86.4%) in the atorvastatin treatment group. A total of 15 subjects (18.5%) in the T/A treatment group and 12 subjects (13.6%) in the atorvastatin treatment group discontinued from the study. The most common reason for withdrawal from the T/A treatment group was AEs (9 of 15 subjects), and from the atorvastatin treatment was other reasons (5 of 12 subjects; 3 were lost to follow-up and 2 were attending a center which was subsequently closed). Demographic characteristics were similar across treatment groups. A majority of subjects were white (79.3%), between the ages of 45 and 64 years (59.2%) and male (77.5%).

Table S1. Subject Evaluation Groups and Disposition

		Number of Subjects (n, %)	
		T/A ^a	A ^b
Screened	n=690		
Assigned to Treatment	n=169		
Treated		81	88
Completed		66 (81.5)	76 (86.4)
Discontinued		15 (18.5)	12 (13.6)
Evaluated for Efficacy (FAS ^c)			
Full Analysis, Wk 0-6		76 (93.8)	83 (94.3)
Full Analysis, Wk 6-12		72 (88.9)	79 (89.8)
Full Analysis, Wk 12-18		64 (79.0)	76 (86.4)
Evaluated for Safety			
Adverse Events		81 (100.0)	88 (100.0)
Laboratory Tests		80 (98.8)	87 (98.9)

T/A=torcetrapib/atorvastatin, A=atorvastatin

^a T/A forced titration 60/20 mg QD (Weeks 0–6), 60/40 mg QD (Weeks 6–12) and 60/80 mg QD (Weeks 12-18)

^b Atorvastatin forced titration 20 mg QD (Weeks 0–6), 40 mg QD (Weeks 6–12) and 80 mg QD (Weeks 12-18)

^c 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 statistically significant changes in the primary lipid endpoint of HDL-C, and non-statistically significant changes in non-HDL-C at Week 6, when compared to treatment with atorvastatin. The LS mean percent increase from baseline to Week 6 in HDL-C for T/A 60/20 mg-treated subjects compared with those subjects who received atorvastatin 20 mg only, resulted in an LS mean treatment difference of 44.1% (95% CI: [37.1, 51.2]; $p < 0.0001$). Statistically significant increases in levels of HDL-C from baseline when compared to atorvastatin were measured during the forced titration at Weeks 12 and 18 ($p < 0.0001$ at other doses). The LS mean percent decrease from baseline to Week 6 in non-HDL-C for T/A 60/20 mg-treated subjects compared with subjects who received atorvastatin 20 mg resulted in an LS mean treatment difference of 2.4% (95% CI: [-6.4, 1.5]; $p = 0.2281$). Comparable non significant decreases in levels of non-HDL-C from baseline comparing T/A to atorvastatin alone were measured at Weeks 12 and 18.

Safety Results:

Adverse Events: Of the 169 subjects who were evaluated for safety, 50 (61.7%) of the T/A-treated subjects and 57 (64.8%) of atorvastatin-treated subjects reported at least 1 treatment-emergent AE. Twenty-five subjects (30.9%) who received T/A reported at least 1 treatment-related AE, compared with 16 subjects (18.2%) who received atorvastatin. Treatment-emergent AEs occurring in $\geq 3\%$ of subjects in either treatment group 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=81		A N=88	
	All Causalities	Treatment- Related	All Causalities	Treatment- Related
Number (%) of Subjects With Adverse Events	50 (61.7)	25 (30.9)	57 (64.8)	16 (18.2)
Gastrointestinal Disorders	18 (22.2)	6 (7.4)	14 (15.9)	5 (5.7)
Gastrointestinal Motility and Defecation Conditions	10 (12.3)	4 (4.9)	6 (6.8)	2 (2.3)
Constipation	5 (6.2)	1 (1.2)	3 (3.4)	0
Diarrhea	4 (4.9)	2 (2.5)	3 (3.4)	2 (2.3)
Gastrointestinal Signs and Symptoms	5 (6.2)	1 (1.2)	8 (9.1)	4 (4.5)
Nausea	2 (2.5)	0	4 (4.5)	2 (2.3)
General Disorders and Administration Site Conditions	9 (11.1)	5 (6.2)	5 (5.7)	2 (2.3)
General System Disorders NEC	8 (9.9)	4 (4.9)	3 (3.4)	2 (2.3)
Fatigue	4 (4.9)	3 (3.7)	2 (2.3)	1 (1.1)
Edema peripheral	3 (3.7)	1 (1.2)	0	0
Infections and Infestations	17 (21.0)	0	19 (21.6)	0
Infections – Pathogen Class Unspecified	17 (21.0)	0	15 (17.0)	0
Nasopharyngitis	4 (4.9)	0	6 (6.8)	0
Injury, Poisoning and Procedural Complications	5 (6.2)	0	2 (2.3)	0
Injuries NEC	4 (4.9)	0	2 (2.3)	0
Investigations	7 (8.6)	4 (4.9)	10 (11.4)	3 (3.4)
Cardiac and Vascular Investigations (Excl Enzyme Tests)	6 (7.4)	4 (4.9)	1 (1.1)	0
Blood Pressure Increased	5 (6.2)	3 (3.7)	1 (1.1)	0
Hepatobiliary Investigations	0	0	3 (3.4)	2 (2.3)
Metabolic, Nutritional and Blood Gas Investigations	0	0	3 (3.4)	0
Metabolism and Nutrition Disorders	2 (2.5)	1 (1.2)	5 (5.7)	1 (1.1)
Glucose Metabolism Disorders (Incl Diabetes Mellitus)	0	0	3 (3.4)	0
Musculoskeletal and Connective Tissue Disorders	15 (18.5)	4 (4.9)	14 (15.9)	4 (4.5)
Joint Disorders	4 (4.9)	2 (2.5)	3 (3.4)	0
Arthralgia	4 (4.9)	2 (2.5)	3 (3.4)	0
Muscle Disorders	7 (8.6)	5 (6.2)	5 (5.7)	2 (2.3)
Myalgia	3 (3.7)	2 (2.5)	4 (4.5)	2 (2.3)
Musculoskeletal and Connective Tissue Disorders NEC	9 (11.1)	1 (1.2)	6 (6.8)	3 (3.4)
Musculoskeletal Pain	2 (2.5)	0	3 (3.4)	2 (2.3)
Pain In Extremity	3 (3.7)	0	3 (3.4)	1 (1.1)
Tendon, Ligament and Cartilage Disorders	1 (1.2)	0	3 (3.4)	0
Nervous System Disorders	13 (16.0)	6 (7.4)	9 (10.2)	0
Headaches	5 (6.2)	2 (2.5)	3 (3.4)	0
Headache	5 (6.2)	2 (2.5)	2 (2.3)	0
Neurological Disorders NEC	7 (8.6)	4 (4.9)	4 (4.5)	0
Dizziness	4 (4.9)	1 (1.2)	2 (2.3)	0
Psychiatric Disorders	5 (6.2)	1 (1.2)	4 (4.5)	0
Respiratory, Thoracic and Mediastinal Disorders	3 (3.7)	0	8 (9.1)	1 (1.1)
Respiratory Disorders NEC	4 (4.9)	0	4 (4.5)	1 (1.1)
Upper Respiratory Tract Disorders (Excl Infections)	1 (1.2)	0	4 (4.5)	0
Skin and Subcutaneous Tissue Disorders	7 (8.6)	2 (2.5)	7 (8.0)	1 (1.1)
Epidermal and Dermal Conditions	5 (6.2)	1 (1.2)	7 (8.0)	1 (1.1)
Rash	5 (6.2)	1 (1.2)	1 (1.1)	0
Vascular Disorders	12 (14.8)	7 (8.6)	2 (2.3)	2 (2.3)
Vascular Hypertensive Disorders	9 (11.1)	5 (6.2)	1 (1.1)	1 (1.1)
Hypertension	9 (11.1)	5 (6.2)	1 (1.1)	1 (1.1)

T/A=torcetrapib/atorvastatin, A=atorvastatin, 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 $\geq 3\%$ of subjects in either treatment group

^b MedDRA (v9.1) Preferred Term included only when AE (all causalities) occurred in $\geq 3\%$ of subjects in either treatment group

The SOCs most affected with all causality AEs were (in decreasing order in the T/A treatment group): Gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders and vascular disorders. By preferred term, the most frequently reported AEs in the T/A treatment group were hypertension (11.1%), rash, headache and blood pressure increased (6.2% each). The most frequently reported AEs in the atorvastatin treatment group were nasopharyngitis (6.8%), nausea and myalgia (6.8% each). Hypertension (6.2%), blood pressure increased and fatigue (3.7% each) were the most frequently reported treatment-related AEs in the T/A treatment group. In the atorvastatin treatment group, the most frequently reported treatment-related AEs were diarrhea, nausea and myalgia (2.3% each).

Permanent Discontinuations Due to Adverse Events: The number of subjects who discontinued due to any AE was higher in the T/A than atorvastatin treatment group whether all causality (9 and 3 subjects, respectively) or treatment related (9 and 2 subjects, 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	44/M	Muscle spasms ^a , Headache ^a , Hot flush ^a
	23/M	Abdominal pain upper ^a
	64/M	Blood pressure increased ^a , Headache ^a , Flushing ^a
	61/F	Blood pressure increased ^a
	47/M	Fatigue ^a , Arthralgia ^a , Muscular weakness ^a , Musculoskeletal stiffness ^a , Myalgia ^a
	60/M	Diarrhea ^a
	62/M	Pruritus ^a , Rash ^a , Urticaria ^a
	42/F	Abdominal pain ^a , Myalgia ^a
	45/M	Burning sensation ^a , Constipation, Dizziness
A	52/M	Constipation, Arthralgia
	51/M	Pain in extremity ^a
	64/F	Abdominal distension ^a , Asthenia ^a , Weight decreased ^a , Hot flush ^a , Nasal congestion

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

^a Considered treatment-related (investigator causality)

The most frequently reported all causality AEs leading to discontinuation in the T/A treatment group were myalgia, blood pressure increased and headache (2 subjects each). The majority of AEs leading to discontinuation from the study were considered treatment-related. None were considered serious.

Serious Adverse Events: Two subjects in the T/A treatment group experienced a serious adverse event (SAE), both considered by the investigator not related to study drug. A 63-year-old male subject experienced an SAE of stenosis of the left bypass graft whilst receiving T/A 60/40 mg. A 62-year-old male subject experienced an SAE of lower gastrointestinal bleed whilst receiving T/A 60/80 mg. Both subjects recovered. There were no deaths reported during the course of the study.

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

Blood Pressure: Mean systolic blood pressure (SBP) increased from baseline to Weeks 6, 12 and 18 in the T/A treatment group (4.6 mmHg, 4.5 mmHg, and 6.3 mmHg, respectively). In the atorvastatin treatment group, mean SBP decreased from baseline to Week 6 (1.2 mmHg) and Week 12 (1.6 mmHg), and increased slightly at Week 18 (0.3 mmHg). Treatment differences between T/A and atorvastatin were therefore 5.7 mmHg (95% CI: [2.72, 8.70]) at Week 6, 6.1 mmHg (95% CI: [2.35, 9.74]) at Week 12 and 6.0 mmHg (95% CI: [1.98, 10.03]) at Week 18.

CONCLUSION(S): This Phase 3, multi-center, double-blind, randomized, parallel group study comparing the efficacy of forced titration T/A with forced titration atorvastatin (both administered QD for 18 weeks) in subjects with Fredrickson Type IV Hypertriglyceridemia yielded the following conclusions:

- Treatment with T/A 60/20 mg resulted in statistically significant increases in HDL-C from baseline at Week 6 when compared to atorvastatin 20 mg only-treatment ($p < 0.0001$ for difference between treatment groups).
- Treatment with T/A 60/20 mg compared to atorvastatin 20 mg only-treatment failed to reach statistical significance for change from baseline in non-HDL-C at Week 6 ($p > 0.05$ for the difference between treatment groups).
- The number of subjects with all causality treatment-emergent AEs was similar in the T/A treatment group compared to the atorvastatin treatment group (61.7% and 64.8%, respectively) and higher in the T/A treatment group than in the atorvastatin treatment group for treatment-related AEs (30.9% and 18.2%, respectively). The number of discontinuations due to AEs was greater for the T/A treatment group (9 subjects) compared to the atorvastatin treatment group (3 subjects). Two subjects in the T/A treatment group experienced SAEs, neither of which were considered by the investigator as treatment-related. There were no deaths reported during the course of the study.
- Mean SBP increased from baseline to Weeks 6, 12 and 18 in the T/A treatment group (4.6 mmHg, 4.5 mmHg, and 6.3 mmHg, respectively), for treatment differences versus

atorvastatin of 5.7 mmHg (95% CI: [2.72, 8.70]) at Week 6, 6.1 mmHg (95% CI: [2.35, 9.74]) at Week 12, and 6.0 mmHg (95% CI: [1.98, 10.03]) at Week 18.