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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.: 00136981

PROTOCOL NO.: A5091003

PROTOCOL TITLE: Phase 3, Multi-Center, Double-Blind, Randomized, Parallel Group, Carotid B-Mode Ultrasound Evaluation of the Anti-Atherosclerotic Efficacy, Safety, and Tolerability, of Fixed Combination CP-529,414/Atorvastatin, Administered Orally, Once Daily (QD) for 24 Months, Compared With Maximally Tolerated Atorvastatin Therapy Alone, in Subjects With Heterozygous Familial Hypercholesterolemia

Study Center(s): 37 centers: Czech Republic, 2 centers; Finland, 2 centers; France, 2 centers; Italy, 2 centers; The Netherlands 13 centers; Canada, 5 centers; United States, 8 centers; and South Africa, 3 centers.

Study Initiation and Completion Dates: First Subject Visit: 19 December 2003
Last Subject Visit: 22 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 efficacy objective was to demonstrate that fixed combination torcetrapib/atorvastatin (T/A; 60 mg/20, 40, or 80 mg) treatment slows the progression of atherosclerosis, measured by the annualized rate (mm/year) of change in maximum carotid intima-media thickness (IMT), when compared to atorvastatin alone (20, 40 or 80 mg), in subjects with Heterozygous Familial Hypercholesterolemia (HeFH) following 24 months of treatment.

METHODS

Study Design: This was a multi-center, double-blind, randomized, parallel group study of fixed combination T/A in male and female subjects between 18 and 70 years of age with HeFH. After initial screening during which subjects were assessed and received therapeutic lifestyle change (TLC) counseling according to National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP-III) clinical guidelines, eligible subjects entered a 4 to 12 week run-in period consisting of up to 4 visits (starting 2 weeks after screening, then every 4 weeks; Visits 2, 3, 4, and 5). During the run-in period, atorvastatin (20, 40, or 80 mg) was titrated to a target LDL-C level according to the subject's cardiovascular risk based on NCEP-ATP III guidelines, or to the maximally tolerated atorvastatin dose (not to exceed 80 mg QD). Subjects who had already reached the target LDL-C value, or were receiving atorvastatin 80 mg QD, continued to receive atorvastatin at the same dose. Subjects who were receiving another statin were prescribed an equivalent atorvastatin dose. Subjects who were not previously receiving a statin were prescribed atorvastatin 20 mg. Once target LDL-C levels were reached, or subjects were receiving their maximally tolerated atorvastatin dose (not to exceed 80 mg QD), atorvastatin dose was maintained for approximately 2 weeks, until subjects were randomized (Week 0; Visit 6) to 1 of 2 treatment groups for 24 months (atorvastatin dose was established during the run-in period): fixed combination T/A at doses of 60/20, 60/40 or 60/80 mg, or atorvastatin alone at doses of 20, 40 or 80 mg. Post-randomization visits occurred every 3 months (Months 1, 3, 6, 9, 12, 15, 18, 21 and 24, respectively).

Number of Subjects (Planned and Analyzed): It was planned to randomize approximately 760 subjects, 380 subjects per treatment arm. Subsequently, 1118 subjects were screened for enrolment in the study and 904 subjects were randomized and treated: 450 subjects were randomized to receive fixed combination T/A, of whom 423 were evaluated for efficacy and 454 subjects were randomized to receive atorvastatin alone, of whom 427 were evaluated for efficacy. All 904 treated subjects were evaluated for safety.

Diagnosis and Main Criteria for Inclusion: Men and women between 18 and 70 years of age with HeFH, were screened for study participation.

Study Treatment: Tablets were taken QD, with water, immediately after the morning meal, except on the morning of clinic visits, when study medication was taken (with food) after the visit procedures were completed. During the run-in period, atorvastatin alone was taken as one 20 or 40 mg tablet, or two 40 mg tablets for up to 12 weeks. During the double-blind treatment period, fixed combination T/A was taken as 2 tablets of torcetrapib 30 mg combined with atorvastatin 10, 20, or 40 mg, and placebo matching atorvastatin; and atorvastatin alone was taken as one 20 or 40 mg tablet or two 40 mg tablets QD, and placebo matching T/A, for 24 months.

Efficacy Evaluations: The primary efficacy endpoint was the annualized rate (mm/year) of change in the maximum carotid IMT for 12 carotid segments (defined by the side of the carotid arteries [left and right], the wall [near and far], and the sites [internal, bifurcation, and

common]) measured over 24 months for fixed combination T/A, compared to atorvastatin alone. Two baseline B-mode ultrasounds were done within 14 days prior to the randomization visit and within 7 days of each other. B-mode ultrasounds were done every 6 months (Visits 9, 11, and 13, with a ± 14 day visit window). And 2 B-mode ultrasounds were done at the end of the study within 14 days prior to the end of study visit or at the early termination (ET), and within 7 days of each other.

Safety Evaluations: Safety was assessed using routine clinical laboratory evaluations (hematology and urinalysis panels at screening, Week 0 and Month 24, and chemistry at every visit). Lipid safety monitoring was performed at Months 6, 12 and 18. Vital signs were monitored at every visit, and physical examinations were performed at screening, Week 0 and Month 24. Urine pregnancy testing was carried out at screening and end of study, and in Canada also at randomization, and at 3, 12, 18 and 24 months). Electrocardiograms (ECGs) were performed at screening, Week 0 and Month 24. Subjects were monitored for adverse events (AEs) at every visit. Month 24 safety assessments were carried out at early termination if this took place.

Statistical Methods: The primary efficacy endpoint was the annualized rate (mm/year) of change in the maximum carotid IMT for 12 carotid segments measured over 24 months.

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 carotid IMT. Missing data were not imputed.

The primary efficacy endpoint was analyzed by Analysis of Covariance (ANCOVA) using a longitudinal model fit by mixed linear models (SAS PROC MIXED). The longitudinal model included fixed effects for treatment, geographic region (North America, Europe, South Africa), atorvastatin dose at baseline, carotid segment (12 levels), time, and time by treatment interaction. Random effects included subject-specific intercept and slope terms that represent individual deviations from the overall treatment-specific regression line. Time was a continuous variable representing years. The treatment effect was measured by the magnitude of the term for time by treatment interaction. The null hypothesis tested whether the annualized rate of change for fixed combination T/A was different from that for atorvastatin alone. Hypothesis testing was 2-sided with a 5% error rate (ie, $p = 0.05$ significance level).

RESULTS

Subject Disposition and Demography: Of the 1118 subjects screened for enrolment in the study, 904 were randomized and treated: 450 subjects received fixed combination T/A and 454 subjects received atorvastatin alone (Table S1). Three hundred and eighty-seven subjects (86.0%) in the T/A treatment group and 391 subjects (86.1%) in the atorvastatin treatment group completed the study. The same number of subjects discontinued from each treatment group: 63 subjects (14.0%) in the T/A treatment group and 63 subjects (13.9%) in the atorvastatin treatment group. The most common reasons for withdrawal within the T/A and atorvastatin treatment groups were AEs: (8.7% and 6.4%, respectively). Demographic

characteristics were similar between treatment groups. The majority of subjects were white (88.1%), between the ages of 18 and 64 years (95.0%), and male (49.3%).

Table S1. Subject Evaluation Groups and Disposition

		Number of Subjects (n, %)	
		T/A	A
Screened	1118		
Assigned to Study Treatment	904		
Treated		450	454
Completed		387 (86.0)	391 (86.1)
Discontinued		63 (14.0)	63 (13.9)
Evaluated for Efficacy			
Full Analysis Set		423 (94.0)	427 (94.1)
Evaluated for Safety		450 (100.0)	454 (100.0)

T/A=torcetrapib/atorvastatin, A=atorvastatin alone

Efficacy Results: Treatment with fixed combination T/A (60/20, 40 or 80 mg) did not result in a statistically significant difference in the annualized rate of change from baseline in maximum carotid IMT after 24 months when compared to treatment with atorvastatin (20, 40, or 80 mg) alone. The treatment difference for the annualized rate of change measured from baseline to Month 24 in carotid IMT for the T/A treatment group, compared to that of the atorvastatin alone treatment group, was -0.0006 mm/year (95% CI: [-0.0084, 0.0072]).

Safety Results:

Adverse Events: Of the 904 subjects who were evaluated for safety, 386 (85.8%) of the fixed combination T/A-treated subjects and 385 (84.8%) of the atorvastatin alone-treated subjects reported at least 1 treatment-emergent AE. One hundred and eighty-six subjects (41.3%) in the T/A treatment group and 157 subjects (34.6%) in the atorvastatin treatment group had treatment-related AEs. Forty subjects (8.9%) in the T/A treatment group and 27 subjects (5.9%) in the atorvastatin treatment group were discontinued from the study due to treatment-emergent AEs.

Treatment-emergent AEs occurring in $\geq 5\%$ 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=450		A N=454	
	All Causalities	Treatment- Related	All Causalities	Treatment- Related
Number (%) of Subjects With Adverse Events	386 (85.8)	186 (41.3)	385 (84.8)	157 (34.6)
Cardiac Disorders	32 (7.1)	3 (0.7)	21 (4.6)	0
Gastrointestinal Disorders	131 (29.1)	65 (14.4)	109 (24.0)	50 (11.0)
Gastrointestinal Motility and Defecation Conditions	46 (10.2)	29 (6.4)	32 (7.0)	18 (4.0)
Diarrhea	22 (4.9)	17 (3.8)	23 (5.1)	14 (3.1)
Gastrointestinal Signs and Symptoms	82 (18.2)	47 (10.4)	79 (17.4)	40 (8.8)
General Disorders and Administration Site Conditions	59 (13.1)	23 (5.1)	57 (12.6)	23 (5.1)
General System Disorders NEC	55 (12.2)	22 (4.9)	52 (11.5)	21 (4.6)
Chest pain	17 (3.8)	3 (0.7)	23 (5.1)	5 (1.1)
Infections and Infestations	227 (50.4)	4 (0.9)	215 (47.4)	8 (1.8)
Infections – Pathogen Class Unspecified	187 (41.6)	2 (0.4)	163 (35.9)	6 (1.3)
Nasopharyngitis	53 (11.8)	0	49 (10.8)	2 (0.4)
Upper Respiratory Tract Infection	24 (5.3)	0	28 (6.2)	0
Viral Infectious Disorders	94 (20.9)	1 (0.2)	85 (18.7)	2 (0.4)
Influenza	78 (17.3)	1 (0.2)	72 (15.9)	1 (0.2)
Injury, Poisoning and Procedural Complications	60 (13.3)	2 (0.4)	55 (12.1)	2 (0.4)
Injuries NEC	34 (7.6)	2 (0.4)	37 (8.1)	2 (0.4)
Investigations	49 (10.9)	19 (4.2)	44 (9.7)	21 (4.6)
Cardiac and Vascular Investigations (excluding enzyme tests)	33 (7.3)	11 (2.4)	16 (3.5)	4 (0.9)
Musculoskeletal and Connective Tissue Disorders	156 (34.7)	46 (10.2)	145 (31.9)	52 (11.5)
Joint Disorders	46 (10.2)	8 (1.8)	46 (10.1)	6 (1.3)
Arthralgia	28 (6.2)	7 (1.6)	30 (6.6)	6 (1.3)
Muscle Disorders	45 (10.0)	27 (6.0)	58 (12.8)	37 (8.1)
Myalgia	35 (7.8)	22 (4.9)	35 (7.7)	28 (6.2)
Musculoskeletal and Connective Tissue Disorders NEC	89 (19.8)	18 (4.0)	71 (15.6)	14 (3.1)
Back Pain	39 (8.7)	4 (0.9)	32 (7.0)	4 (0.9)
Pain in Extremity	23 (5.1)	8 (1.8)	13 (2.9)	3 (0.7)
Nervous System Disorders	107 (23.8)	44 (9.8)	94 (20.7)	36 (7.9)
Headaches	63 (14.0)	24 (5.3)	52 (11.5)	20 (4.4)
Headache	51 (11.3)	20 (4.4)	45 (9.9)	18 (4.0)
Neurological Disorders NEC	39 (8.7)	21 (4.7)	44 (9.7)	16 (3.5)
Dizziness	23 (5.1)	9 (2.0)	17 (3.7)	9 (2.0)
Psychiatric Disorders	32 (7.1)	5 (1.1)	26 (5.7)	7 (1.5)
Reproductive System and Breast Disorders	22 (4.9)	5 (1.1)	27 (5.9)	9 (2.0)
Respiratory, Thoracic and Medistinal Disorders	57 (12.7)	7 (1.6)	36 (7.9)	3 (0.7)
Respiratory Disorders NEC	46 (10.2)	5 (1.1)	22 (4.8)	3 (0.7)
Cough	26 (5.8)	3 (0.7)	7 (1.5)	0
Skin and Subcutaneous Tissue Disorders	44 (9.8)	12 (2.7)	37 (8.1)	13 (2.9)
Epidermal and Dermal Conditions	31 (6.9)	7 (1.6)	21 (4.6)	7 (1.5)
Vascular Disorders	65 (14.4)	38 (8.4)	38 (8.4)	15 (3.3)
Vascular Hypertensive Disorders	40 (8.9)	28 (6.2)	17 (3.7)	8 (1.8)
Hypertension	40 (8.9)	28 (6.2)	16 (3.5)	8 (1.8)

T/A=torcetrapib/atorvastatin, A=atorvastatin alone, 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 $\geq 5\%$ of subjects in either treatment group

^b MedDRA (v9.0) Preferred Term included only when AE (all causalities) occurred in $\geq 5\%$ of subjects in either treatment group

The incidence of treatment-emergent AEs (all causalities) was generally similar between treatment groups, with infections and infestations, musculoskeletal and connective tissue disorders, gastrointestinal disorders and nervous system disorders most commonly reported. The most frequently reported AEs in the fixed combination T/A and atorvastatin alone treatment groups were viral infectious disorders (20.9% and 18.7%, respectively), gastrointestinal signs and symptoms (18.2% and 17.4%, respectively) and influenza (17.3% and 15.9%, respectively). The most frequently reported treatment-related AE was gastrointestinal signs and symptoms for both T/A and atorvastatin-treated subjects (10.4% and 8.8%, respectively).

Permanent Discontinuations Due to Adverse Events: The number of subjects who discontinued due to any treatment-emergent AE (all causalities) was higher in the fixed combination T/A treatment group (40; 8.9%), compared to atorvastatin alone (27; 5.9%). The most common all causality AEs resulting in discontinuation in the T/A treatment were myalgia (7 subjects, 1.6%), blood pressure increased, dizziness, headache, diarrhea and hypertension (3 subjects each, 0.7%). The most common all causality AEs resulting in discontinuation in the atorvastatin treatment were myalgia (5 subjects, 1.1%), abdominal pain (4 subjects, 0.9%), and headache and aspartate aminotransferase increased/alanine aminotransferase increased (3 subjects each, 0.7%). Subjects who discontinued from the study due to 1 or more treatment-emergent AEs are listed by treatment 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)
TA	M/70	Blood pressure increased ^a
	M/40	Arterial stenosis ^c , Chest pain ^c , Electrocardiogram change ^c
	F/54	Arthralgia ^a , Myalgia ^a ,
	M/38	Fatigue ^a
	F/54	Blood pressure increased ^a
	F/23	Abdominal pain ^{a, c}
	F/42	Chills, Dizziness, Headache, Hypoesthesia oral
	M/41	Diarrhea ^a , Dyspepsia ^a , Dysuria ^a
	M/62	Ankle fracture ^{b, c}
	F/64	Dyspepsia ^a , Myalgia ^a
	F/59	Influenza like illness
	F/23	Pregnancy
	F/54	Influenza like illness ^a
	F/61	Dyspnea ^c , Lung adenocarcinoma ^c
	F/39	Musculoskeletal stiffness ^a , Paraesthesia ^{a, b}
	M/43	Headache
	F/57	Pain ^a
	F/41	Nausea ^a , Dizziness ^a
	F/47	Dermatitis allergic ^{a, b}
	F/57	Myalgia ^a
	M/41	Dizziness
	F/36	Flatulence ^{a, b}
	F/43	Diarrhea ^{a, b} , Flatulence ^a
	F/45	Depression ^{a, b}
	M/48	Arthralgia ^a , Diarrhea ^a , Myalgia ^a
	M/51	Myalgia ^a
	F/58	Headache ^a , Nausea ^a
	M/55	Atrial fibrillation ^c
	M/56	Blood pressure increased ^a
	F/27	Pregnancy
	M/53	Myalgia ^b
	M/48	Hypertension ^{a, b, c} Hypokalemia ^{b, c}
	M/45	Chest pain ^c
	F/58	Brain neoplasm ^{a, c} ,
	F/29	Flushes ^a , Muscle spasm ^a
	F/61	Liver function test abnormal ^{a, c}
M/51	Angina pectoris	
M/64	Hypertension ^a	
M/66	Hypertension ^a	
F/36	Myalgia ^{a, b}	
A	F/70	Anxiety ^a , Headache ^a , Insomnia ^a , Neck pain ^a , Myalgia ^{a, b} , Visual acuity reduced ^a
	M/44	Abdominal pain
	M/63	Lung cancer metastatic ^c , Metastases to central nervous system ^c
	F/47	Myalgia ^a
	F/47	Myalgia ^{a, b}
	F/68	Alanine aminotransferase increased ^a , Aspartate aminotransferase increased ^a
	F/62	Abdominal pain upper ^a , Diarrhea ^a , Malaise ^{a, b}
	F/47	Dyspepsia ^a
F/62	Anorexia ^a , Dyspepsia ^a , Abdominal pain ^a	

F/59	Bone Pain ^a , Pain in extremity ^a
F/45	Fatigue ^{a, b}
F/43	Arthralgia ^a , Exercise tolerance decreased ^a , Myalgia ^{a, b}
F/53	Pemphigus ^a
F/34	Colitis ulcerative ^b
F/42	Cutaneous lupus erythematosus ^{a, c}
M/67	Aspartate aminotransferase increased ^{a, b} , Hepatitis B ^a
F/68	Headache, Hypertension ^a
F/33	Dizziness ^a , Fatigue ^a
F/44	Abdominal pain upper, Diarrhea, Nausea
F/40	Angina pectoris
M/33	Hereditary spherocytosis
M/37	Urticaria ^a
M/47	Nausea ^a , Vomiting ^a
F/55	Arthralgia ^{a, b} , Headache ^a
M/36	Aspartate aminotransferase increased ^a , Alanine aminotransferase increased ^{a, b}
F/51	Productive cough
F/60	Hot flush ^a , Hyperchlorhydria ^a , Myalgia ^a

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

^a Considered treatment-related (investigator causality)

^b Multiple episodes of AE reported

^c AE considered serious

In the fixed combination T/A treatment group, 27 of 40 subject discontinuations due to AEs were considered treatment related by the investigator, compared to 21 of 27 in the atorvastatin alone treatment group.

Serious Adverse Events: Serious adverse events (SAEs) were reported up to 28 days after the last dose of study drug. 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 (MedDRA Term)
T/A	M/40	Chest pain ^c , Electrocardiogram change ^c , Arterial stenosis ^c
	M/65	Coronary artery disease
	F/63	Carotid artery stenosis
	M/50	Convulsions
	M/43	Invertebral disc protrusion
	M/61	Inguinal Hernia, Hernia
	M/66	Cerebrovascular accident
	M/51	Chest discomfort
	F/46	Chest pain, Viral infection, Vertigo
	M/56	Pancreatic carcinoma metastatic ^a
	F/23	Abdominal pain ^{a, c}
	M/47	Muscle hemorrhage, Musculoskeletal pain,
	F/65	Back pain
	F/51	Metrorrhagia
	M/48	Arteriosclerosis coronary artery, Coronary artery bypass
	M/62	Ankle fracture ^c
	F/61	Ovarian cyst
	F/36	Gastroesophageal reflux disease, Breast mass
	F/53	Joint injury
	M/55	Ventricular tachycardia, Myocardial ischemia
	M/54	Angina unstable, Hiatus hernia, Myocardial ischemia
	M/31	Angina unstable
	F/60	Angina pectoris
	F/63	Coronary artery disease, Atelectasis
	F/61	Lung adenocarcinoma ^c , Dyspnoea ^c
	M/54	Bronchpneumonia
	M/34	Angina unstable, Cluster headache, Vomiting, Dehydration
	F/38	Dizziness
	F/23	Primary atypical pneumonia
	F/49	Abdominal pain
	M/42	Myocardial infarction
	M/21	Overdose ^c
	F/43	Carbon monoxide poisoning
	M/46	Humerus fracture
	F/44	Myocardial infarction
	M/44	Gastritis
	F/58	Large cell carcinoma of the respiratory tract stage unspecified
	M/53	Chest pain
	M/47	Clavicle fracture
	M/55	Transient ischemic attack, Atrial fibrillation ^c , Myocardial ischemia
	M/51	Phlebitis
	F/27	Pregnancy ^c
	M/54	Finger amputation ^f , Musculoskeletal pain
	F/40	Abdominal pain upper, Diarrhea ^a , Hyperthermia, Fibroma, Nerve compression, Pelvic pain
	M/48	Hypertension ^{c, a, e} , Hypokalemia ^{a, c} , Glucose tolerance impaired
	M/45	Chest pain ^c
	F/58	Brain neoplasm ^{a, c}
	F/61	Liver function test abnormal ^{a, c}
	M/44	Myocardial infarction
	F/57	Schizophrenia paranoid type
	M/52	Chest pain, Benign prostatic hyperplasia

	F/26	Arthralgia
	F/43	Chest pain
	M/59	Transient ischemic attack
	F/61	Diverticulitis, Intestinal resection
	F/45	Hip surgery
A	M/55	Back pain
	M/48	Angina pectoris
	M/63	Lung cancer metastatic ^c , Metastases to central nervous system
	F/57	Periarthritis, Rotator cuff syndrome, Angina unstable
	F/35	Abortion spontaneous ^c
	F/19	Abortion spontaneous
	M/66	Suicide attempt
	M/64	Rotator cuff syndrome
	M/31	Facial bones fracture
	M/47	Angina unstable, Myocardial infarction, Non-Hodgkin's lymphoma, Coronary artery disease, Angina pectoris, Atrial fibrillation, Congestive cardiac failure
	M/48	Nephrolithiasis, Arrhythmia
	M/44	Appendicitis
	M/37	Transient ischemic attack
	F/49	Cholelithiasis, Ovarian cyst
	F/50	Abdominal hernia
	M/54	Cerebrovascular accident, Carotid artery stenosis, Hematoma, Myocardial infarction, Syncope, Headache, Angina pectoris, Angina unstable
	F/66	Duodenitis
	M/35	Angina unstable, Tendon rupture
	M/62	Benign prostatic hyperplasia
	M/36	Chest pain
	F/21	Ectopic pregnancy
	M/65	Prostate cancer
	F/45	Drug abuser
	F/42	Bile duct stone, Cutaneous lupus erythematosus ^{a, c}
	M/53	Prostate cancer
	M/54	Coronary artery stenosis
	M/38	Localized infection
	M/37	Ligament rupture
	F/54	Exophthalmus
	M/26	Small intestinal obstruction
	M/36	Inguinal hernia repair
	M/42	Coronary artery insufficiency
	M/56	Vitrectomy
	M/34	Chest pain
	F/57	Somnolence
	M/60	Cerebrovascular accident
	F/49	Diverticulum
	M/52	Glomus tumor
	F/43	Tibia fracture, Bone graft

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

^a Considered treatment-related (investigatory causality)

^b Multiple events

^c Led to withdrawal from the study (drug permanently discontinued)

One death occurred during the atorvastatin run-in period (multi-organ failure, septicemia and arrhythmia). Four deaths occurred during the double-blind treatment period; 2 in the fixed combination T/A treatment group (metastatic pancreatic carcinoma; adenocarcinoma), and 2 in the atorvastatin alone treatment group (pulmonary carcinoma/brain metastases; coronary artery disease progression). The case of metastatic pancreatic carcinoma was the only death considered by the investigator as related to the study drug.

Ninety-five subjects experienced treatment-emergent SAEs: 56 (12.4%) fixed combination T/A- and 39 (8.6%) atorvastatin alone-treated subjects. The most common SAEs in the T/A treatment group were chest pain (7 subjects), myocardial infarction and myocardial ischemia (3 subjects each). The most common SAEs in the atorvastatin treatment group were angina pectoris, unstable angina and myocardial infarction (3 subjects each). Treatment-related SAEs were reported in 7 subjects (1.6%) in the T/A treatment group and 1 subject (0.2%) in the atorvastatin treatment group.

Nine T/A-treated subjects (2.0%) and 3 atorvastatin-treated subjects (0.7%) experienced SAEs that led to discontinuation from the study. Five of these were considered by the investigator related to treatment: Acute infectious ileitis, hypokalemia, cerebellum tumor, and liver test elevation (T/A); lupus erythematosus cutaneous (atorvastatin).

Clinical Laboratory Tests: In general, laboratory abnormalities were infrequent and similar between the T/A and atorvastatin alone treatment groups.

Blood Pressure: Mean systolic blood pressure (SBP) increased from baseline to Month 24 in the fixed combination T/A and atorvastatin alone treatment groups (5.52 mmHg and 2.37 mmHg, respectively), for a treatment difference of 3.15 mmHg (95% CI: [1.66, 4.64]).

CONCLUSION(S): This Phase 3, multi-center, double-blind, randomized, parallel group study of fixed combination T/A in male and female subjects between 18 and 70 years of age with HeFH did not demonstrate a statistically significant difference in the annualized rate of change from baseline in maximum carotid IMT after 24 months when compared to treatment with atorvastatin alone. The treatment difference for the annualized rate of change measured from baseline to Month 24 in carotid IMT for the T/A treatment group, compared to that of the atorvastatin alone treatment group, measured -0.0006 mm/year (95% CI: [-0.0084, 0.0072]).

The incidence of treatment-emergent AEs (all causalities) was generally similar between treatment groups; 386 (85.8%) of the fixed combination T/A-treated subjects and 385 (84.8%) of the atorvastatin alone-treated subjects reported at least 1 treatment-emergent AE. In the fixed combination T/A treatment group, 27 of 40 subject discontinuations due to AEs were considered treatment related by the investigator, compared to 21 of 27 in the atorvastatin alone treatment group. One death occurred during the run-in period (multi-organ failure, septicemia and arrhythmia), and 4 deaths occurred during the double-blind treatment period; 2 in the T/A treatment group (metastatic pancreatic carcinoma; adenocarcinoma), and 2 in the atorvastatin alone treatment group (pulmonary carcinoma/brain metastases; coronary artery disease progression). The case of metastatic pancreatic carcinoma was the only death considered by the investigator related to the study drug. Treatment-related SAEs were

reported in 7 subjects (1.6%) in the T/A treatment group and 1 subject (0.2%) in the atorvastatin treatment group. Nine T/A-treated subjects (2.0%) and 3 atorvastatin-treated subjects (0.7%) experienced SAEs that led to discontinuation from the study; considered by the investigator related to treatment for 4 subjects and 1 subject, respectively.

Mean systolic blood pressure (SBP) increased from baseline to Month 24 in the fixed combination T/A and atorvastatin alone treatment groups (5.52 mmHg and 2.37 mmHg, respectively), for a treatment difference of 3.15 mmHg (95% CI: [1.66, 4.64]).

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