Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients

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Background High-density lipoprotein cholesterol (HDL-C) levels are inversely associated with cardiovascular risk. Cholesteryl ester transfer protein inhibition is one strategy for increasing HDL-C. This study evaluated the lipid-altering efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy or coadministered with atorvastatin in patients with dyslipidemia.

Methods A total of 589 patients with primary hypercholesterolemia or mixed hyperlipidemia (53.8% of the study population had low HDL-C) were randomized equally to one of 10 groups: 5 groups received background statin therapy of atorvastatin 20 mg and 5 did not, and each of these was randomized to placebo, anacetrapib 10, 40, 150, and 300 mg once daily for 8 weeks. An equal proportion of patients had triglycerides >150 mg/dL in each group.

Results For placebo and anacetrapib monotherapy (10, 40, 150, and 300 mg), least squares mean percent changes from baseline to week 8 for low-density lipoprotein cholesterol (LDL-C) were 2%, –16%, –27%, –40%, and –39%, respectively, and for HDL-C were 4%, 44%, 86%, 139%, and 133%, respectively ($P < .001$ vs placebo for all doses). Coadministration of anacetrapib with atorvastatin produced significant incremental LDL-C reductions and similar HDL-C increases versus atorvastatin monotherapy. For both anacetrapib monotherapy and coadministration with atorvastatin, the LDL-C reductions were similar in patients with baseline triglyceride levels greater than and less than or equal to the median. Anacetrapib was well tolerated, and the incidence of adverse events was similar for placebo and all active treatment groups. There were no increases in systolic or diastolic blood pressure in any treatment arm.

Conclusions Anacetrapib, as monotherapy or coadministered with atorvastatin, produced significant reductions in LDL-C and increases in HDL-C; the net result of treatment with anacetrapib + atorvastatin was ~70% lowering of LDL-C and more than doubling of HDL-C. Anacetrapib was generally well tolerated with no discernable effect on blood pressure. (Am Heart J 2009;157:352-60.e2.)

A high residual risk of cardiovascular events remains despite the use of statins, underscoring the need for agents that yield additional low-density lipoprotein cholesterol (LDL-C) lowering while producing beneficial effects on other targets that may impact the dyslipidemic state, such as high-density lipoprotein-cholesterol (HDL-C). Cholesteryl ester transfer protein (CETP) is a plasma protein that catalyzes the exchange of cholesteryl esters and triglycerides (TG) between HDL and the atherogenic apolipoprotein (apo) B–containing lipoproteins, especially very low density lipoprotein.[1] Reduction in CETP activity resulting from genetic mutations or pharmacologic inhibition has been associated with reductions in cholesterol within the apo B-containing particles and cholesterol enrichment of HDL.[2,3] The magnitude of lipoprotein changes is substantial relative to existing therapies, particularly for HDL-C.[4]

Torcetrapib, a CETP inhibitor, has been shown to produce substantial increases in HDL-C and modest reductions in LDL-C.[5-10] However, treatment with torcetrapib is associated with an increase in blood pressure, an

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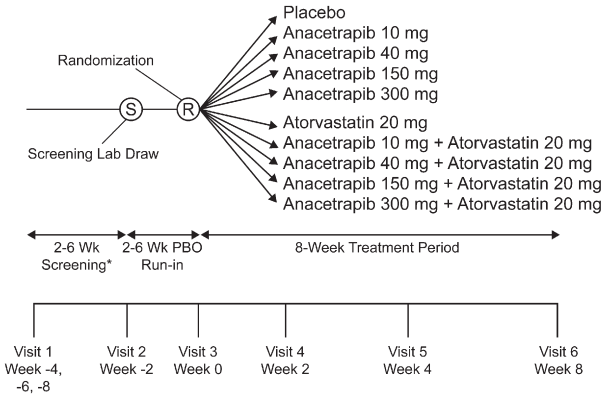
Figure 1



*Visit 1 to Visit 2 period was 6 weeks if the patient needed to wash out from the fibrate therapy or 4 weeks if the patient needed to wash out from all other lipid-lowering therapy; patients not requiring a wash out had 2 weeks between Visits 1 and 2.

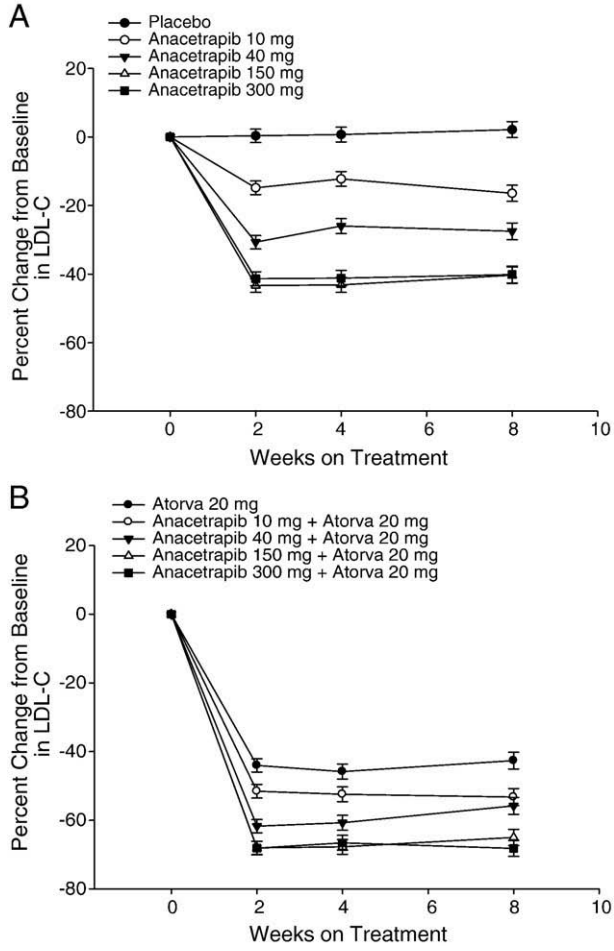
Study design.

Table I. Baseline patient demographics and efficacy parameters

Parameter	Overall population
Men, n (%)	252 (42.8)
Mean age, y (±SD)	56.4 (9.6)
Race, n (%)	
White	493 (83.7)
Black	53 (9.0)
Other	43 (7.3)
Mean BMI, kg/m^2 (±SD)	30.2 (5.9)
Mean LDL-C, mg/dL (±SD)	141.1 (22.0)
Mean apo B, mg/dL (±SD)	142.5 (23.8)
Mean LDL-C/apo B, mg/dL (±SD)	1.0 (0.12)
Mean HDL-C, mg/dL (±SD)	50.5 (12.6)
Mean apo A-I, mg/dL (±SD)	168.9 (27.7)
Mean HDL-C/apo A-I, mg/dL (±SD)	0.3 (0.04)
Mean TC, mg/dL (±SD)	225.3 (28.1)
Median TGs, mg/dL (±SD)	153.5 (87.0)
Mean LDL-C/HDL-C, mg/dL (±SD)	3.0 (0.8)
Mean apo E, mg/dL (±SD)	4.7 (1.6)
Mean Lp(a), mg/dL (±SD)	22.6 (27.4)
Median CRP, mg/L (±SD)	2.2 (3.3)
Mean SBP/DBP, mmHg	120.2/76.1
Mean Na, mEq/L (±SD)	139.7 (2.0)
Mean Cl, mEq/L (±SD)	103.1 (2.3)
Mean K, mEq/L (±SD)	4.3 (0.4)
Diabetes mellitus, n (%)	26 (4)
Hypertension, n (%)	223 (37.9)

BMI, Body mass index; *SBP/DBP*, systolic blood pressure/diastolic blood pressure.

Figure 2

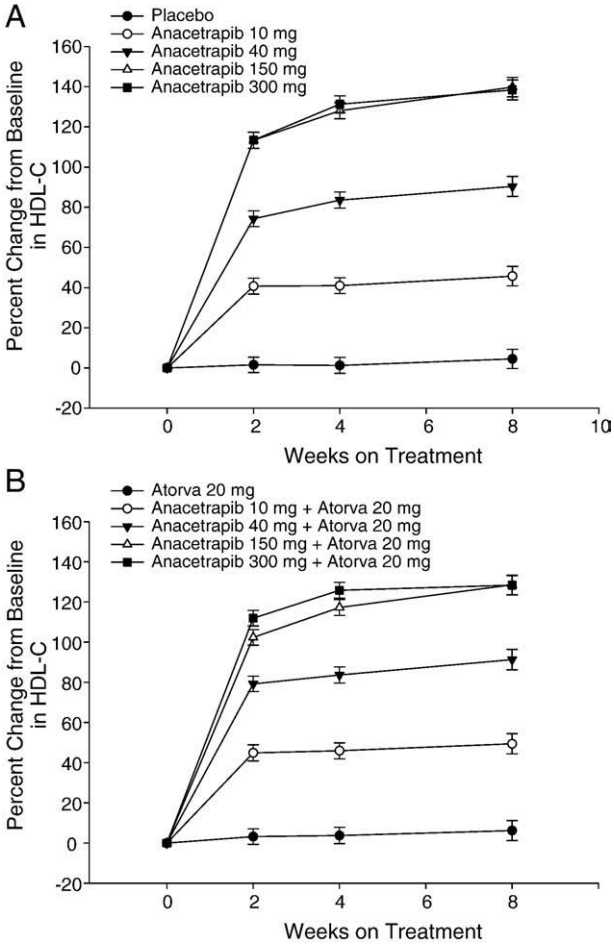


Changes from baseline in LDL-C over time: **A**, anacetrapib monotherapy versus placebo and **B**, anacetrapib + atorvastatin 20 versus atorvastatin 20 mg.

effect that has not been reported with other CETP inhibitors in development.[11,12] A clinical outcomes study of torcetrapib in high-risk patients, ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events), was stopped early owing to an excess in cardiovascular events in patients treated with the combination of torcetrapib and atorvastatin versus atorvastatin alone.[7] Subsequently, 3 studies have reported that torcetrapib did not reduce (nor increase) the atherosclerotic burden assessed in the coronary arteries (by intravascular ultrasonography) and in the carotid arteries (by ultrasonography of intima-media thickness).[8-10]

Anacetrapib is an orally active, potent, selective CETP inhibitor. In preclinical models, anacetrapib consistently increased HDL-C concentrations with no observed effects on blood pressure or heart rate and was well tolerated.[11] Preliminary studies in healthy subjects showed that single and multiple doses of anacetrapib for 2 weeks produced CETP inhibition and favorable HDL-C, LDL-C, and apolipoprotein effects, and were generally well tolerated without an effect on blood pressure.[11] The present study examines the efficacy, safety, and tolerability of anacetrapib

Figure 3



Changes from baseline in HDL-C over time: **A**, anacetrapib monotherapy versus placebo and **B**, anacetrapib + atorvastatin 20 versus atorvastatin 20 mg.

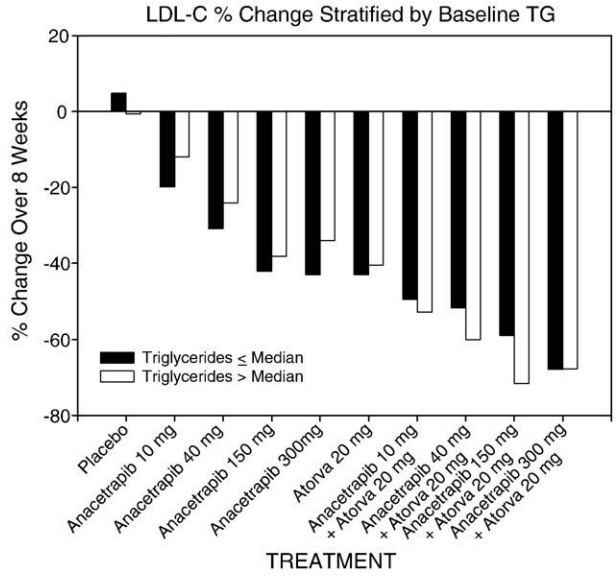
in patients with primary hypercholesterolemia or mixed hyperlipidemia.

Methods

Study design

This was a multicenter (61 centers), randomized, double-blind, placebo-controlled, parallel-group dose-ranging study to assess the efficacy, safety, and tolerability of anacetrapib, administered as monotherapy or with atorvastatin 20 mg (Pfizer Pharmaceuticals, Ltd, New York, NY), in patients with primary hypercholesterolemia or mixed hyperlipidemia. After screening and placebo run-in, eligible patients were randomized via an interactive voice response system equally to one of 10 groups: 5 groups received background statin therapy of atorvastatin 20 mg and 5 did not, and each of these was randomized to placebo, anacetrapib 10, 40, 150, and 300 mg once daily for 8 weeks (Figure 1).

Figure 4



Changes from baseline in LDL-C for patients with triglycerides above and below the median.

Patients

Adults, aged 18 to 75 years, with LDL-C values ranging from 100 to 190 mg/dL, 100 to 160 mg/dL for moderate-risk patients (10-year coronary heart disease [CHD] risk of 10%-20%, as designated by the National Cholesterol Education Program ATP III criteria), or 100 to 130 mg/dL for diabetic patients, were included. Patients were stratified such that each treatment arm included an equal proportion with TG >150 mg/dL.

Patients with a history of CHD, symptomatic carotid artery disease, uncontrolled cardiac arrhythmias, hypertension (>160/90 mm Hg), or uncontrolled diabetes (HbA_{1c} >8.0%) were excluded. Women of childbearing potential or who were pregnant or lactating were excluded. Concomitant therapy with cardiovascular medications, warfarin, antiobesity drugs, potent inhibitors/inducers of CYP3A4, cyclical hormones, systemic corticosteroids, systemic anabolic agents, psyllium/fiber-based laxatives, investigational drugs, and over-the-counter medications known to affect serum lipids was prohibited.

The protocol was approved by the institutional review board or independent ethics committee at each site, and the study was conducted in compliance with the Declaration of Helsinki. Patients provided written informed consent before initiation of any study procedure.

Efficacy assessments

Efficacy end points included percent change from baseline in LDL-C (primary) and HDL-C; total cholesterol (TC); non–HDL-C; TG; and apo B, A-I, and E (secondary) with anacetrapib monotherapy versus placebo, and anacetrapib + atorvastatin 20 mg versus atorvastatin 20 mg. Additional analyses included percent change from baseline in lipoprotein (Lp) (a), C-reactive protein (CRP), sodium (Na), potassium (K), and chloride (Cl) in anacetrapib monotherapy

Table II. Percent change (95% CI) in efficacy parameters after 8 weeks of treatment

		Anacetrapib (mg/d)			
Lipid parameter	**Placebo**	**10**	**40**	**150**	**300**
n	*58*	*59*	*58*	*57*	*57*
Apo B	2.2 (–1.3 to 5.7)	–13.2 (–16.7 to –9.7)	–19.7 (–23.2 to –16.2)	–29.3 (–32.9 to –25.8)	–29.6 (–33.2 to –26.0)
LDL-C/apo B	–0.8 (–4.5 to 2.9)	–5.0 (–8.7 to –1.4)	–10.7 (–14.4 to –7.1)	–18.2 (–22.0 to –14.5)	–17.3 (–21.1 to –13.5)
Apo A-I	2.4 (–1.7 to 6.5)	16.7 (12.6 to 20.8)	31.9 (27.8 to 36.0)	47.1 (42.9 to 51.3)	43.1 (38.8 to 47.4)
HDL-C/apo A-I	2.2 (–2.5 to 6.9)	21.7 (17.1 to 26.4)	39 (34.3 to 43.6)	59.9 (55.2 to 64.7)	64.2 (59.3 to 69.0)
TC	1.5 (–1.6 to 4.6)	–1.5 (–4.6 to 1.5)	1.5 (–1.6 to 4.6)	3.5 (0.4 to 6.6)	3.9 (0.8 to 7.0)
TG*	–2.5 (–9.2 to 4.2)	–11.0 (–17.6 to –4.5)	–10.7 (–17.8 to –3.7)	–11.4 (–19.1 to –3.7)	–5.1 (–13.9 to 3.6)
LDL-C/HDL-C	–1.2 (–5.6 to 3.3)	–39.4 (–43.8 to –35.0)	–57.8 (–62.3 to –53.4)	–73.8 (–78.3 to –69.3)	–70.8 (–75.3 to –66.3)
CRP*	–9.9 (–25.4 to 5.6)	0.0 (–15.1 to 15.1)	–1.3 (–20.3 to 17.8)	11.1 (–5.8 to 28.0)	0.0 (–10.7 to 10.7)
Na	–0.1 (–0.6 to 0.3)	0.3 (–0.1 to 0.8)	0.2 (–0.3 to 0.7)	–0.1 (–0.5 to 0.4)	0.4 (–0.1 to 0.9)
Cl	–0.6 (–1.1 to –0.1)	–0.1 (–0.5 to 0.4)	–0.1 (–0.6 to 0.4)	–0.6 (–1.1 to –0.2)	–0.1 (–0.6 to 0.4)
K	0.1 (–0.0 to 0.1)	0.1 (–0.0 to 0.2)	0.1 (–0.0 to 0.2)	–0.0 (–0.1 to 0.1)	–0.1 (–0.1 to 0.0)
Aldosterone					

Values are mean, unless otherwise noted. * Median.

versus placebo and anacetrapib + atorvastatin 20 mg versus atorvastatin 20 mg. Median percent change from baseline in aldosterone levels was analyzed post hoc from archived serum samples from 4 representative treatment arms: anacetrapib (40, 150, 300 mg) + atorvastatin 20 mg versus atorvastatin 20 mg.

Analytical methods

Lipid and apolipoprotein determinations and other study-specific tests, including CRP, were performed by a centralized laboratory certified by the Centers for Disease Control (Pharmaceutical Product Development, Inc, Highland Heights, KY). Plasma cholesterol and TGs were quantified by a standardized enzymatic assay. Low-density lipoprotein cholesterol was calculated using the Friedewald equation: LDL-C = Total C − (HDL-C + TG/5).[13] HDL-C was measured by separating HDL from LDL and very low density lipoprotein by heparin-manganese Cl precipitation. C-Reactive protein was measured by high-sensitivity immunonephelometry (Dade Behring, Deerfield, IL), as described previously.[14] Lipoprotein(a) was measured using the Poly-chem chemistry analyzer (Polymedco, Cortlandt Manor, NY), and apolipoproteins A-I, B, and E were measured using the BN nephelometer (Dade Behring). Plasma measurements of Na, Cl, and K, and aldosterone were taken at week 0 (baseline) and week 8.

Safety assessments

Clinical evaluation included physical examination and measurement of vital signs, laboratory evaluations, electrocardiograms, and adverse event (AE) assessments. Blood pressure was measured with an automated blood pressure device (BpTRU BPM-100, VSM, MedTech, Coquitlam, British, Columbia, Canada). Patients remained seated for 5 minutes before blood pressure readings were recorded; sitting systolic and diastolic blood pressures were determined as the average of 5 replicate measurements taken 2 minutes apart; overall, 6 blood pressure measurements were taken, with the first reading excluded from the average calculation.

Statistical analyses

Percent changes from baseline in LDL-C and HDL-C were analyzed using an analysis-of-covariance model, with terms for treatment, baseline TG stratum, and baseline LDL-C. Comparisons of individual doses (10, 40, 150, and 300 mg) of anacetrapib monotherapy versus placebo were performed using a step-down trend test.

The exploratory analysis of electrolyte parameters (Na, Cl, and K) was similar to the analysis of the primary end point. Percent change from baseline in aldosterone was analyzed using a 1-way analysis of variance model applied to Tukey's normalized ranks, with a term for treatment. The between-treatment group differences in medians were assessed based on Hodges-Lehman estimates, with the corresponding distribution-free 95% CI based on Wilcoxon's rank sum test. Safety and tolerability were assessed by clinical and/or statistical review of all safety parameters, including AEs, laboratory values, vital signs, and ECG data.

Results

Baseline demographics and efficacy variables

Baseline demographic characteristics and efficacy variables of the randomized patients (n = 589) were similar across the 10 treatment groups (Table I; expanded Table I in Appendix A, available online). Overall, 53.8% of patients had low HDL-C levels (≤44 mg/dL in men and ≤54 mg/dL in women). The median baseline LDL-C for the overall population was 140.1 mg/dL. Median baseline aldosterone levels were 7.5, 0.0, and 8.8 ng/dL in the anacetrapib 40-, 150-, and 300-mg + atorvastatin 20-mg groups, respectively, and 2.5 ng/dL in the atorvastatin 20-mg group.

Efficacy parameters

Anacetrapib monotherapy: LDL-C and HDL-C. At week 8, all anacetrapib monotherapy doses produced significantly greater LDL-C reductions and HDL-C increases than placebo (Figures 2, *A* and 3, *A*). For both

	Atorvastatin 20 (mg/d) + anacetrapib (mg/d)			
Atorvastatin 20	**10**	**40**	**150**	**300**
58	58	59	58	58
−34.2 (−37.8 to −30.7)	−40.2 (−43.7 to −36.7)	−42.2 (−45.7 to −38.7)	−47.2 (−50.7 to −43.6)	−48.7 (−52.2 to −45.2)
−12.3 (−16.1 to −8.6)	−23 (−26.7 to −19.3)	−26.8 (−30.4 to −23.1)	−36.5 (−40.3 to −32.8)	−40.3 (−44.0 to −36.6)
0.1 (−4.0 to 4.3)	15.6 (11.4 to 19.7)	28.9 (24.8 to 33.0)	42.2 (38.1 to 46.4)	39.5 (35.3 to 43.6)
6.5 (1.8 to 11.2)	28.0 (23.3 to 32.7)	45.9 (41.2 to 50.6)	59.7 (55.0 to 64.5)	61.8 (57.1 to 66.5)
−27.7 (−30.8 to −24.6)	−24.3 (−27.4 to −21.2)	−20.0 (−23.1 to −16.9)	−18.1 (−21.2 to −15.0)	−19.5 (−22.6 to −16.4)
−25.8 (−34.8 to −16.7)	−23.0 (−31.9 to −14.0)	−28.8 (−37.4 to −20.1)	−25.9 (−32.6 to −19.2)	−27.2 (−33.4 to −20.9)
−44.5 (−48.9 to −40.0)	−63.5 (−67.9 to −59.0)	−72.8 (−77.2 to −68.4)	−82.1 (−86.6 to −77.6)	−84.1 (−88.5 to −79.6)
−30.9 (−43.8 to −17.9)	−17.4 (−28.0 to −6.8)	−21.8 (−32.9 to −10.7)	−25.6 (−37.4 to −13.8)	−14.3 (−31.0 to 2.5)
1.0 (0.5 to 1.4)	1.0 (0.6 to 1.5)	0.8 (0.3 to 1.3)	0.6 (0.2 to 1.1)	0.8 (0.4 to 1.3)
0.6 (0.1 to 1.1)	0.3 (−0.2 to 0.8)	0.1 (−0.4 to 0.6)	0.1 (−0.4 to 0.6)	−0.2 (−0.7 to 0.3)
−0.0 (0.1 to 0.0)	−0.0 (−0.1 to 0.1)	−0.0 (−0.1 to 0.1)	0.0 (−0.1 to 0.1)	−0.1 (−0.1 to 0.0)
2.5 (−7.6 to 12.7)		7.5 (1.1 to 13.9)	0.0 (−7.1 to 7.1)	8.8 (−1.7 to 19.4)

parameters, there were statistically significant incremental changes among the anacetrapib 10-, 40-, and 150-mg doses; no differences in lipid-altering response resulted from increasing the anacetrapib dose from 150 to 300 mg. For all doses, maximal LDL-C lowering was attained by week 2 (Figure 2, *A*). The observed decreases in LDL-C were accompanied by significant decreases in apo B, signaling a reduction in the concentration of circulating LDL particles. Similarly, the observed increases in HDL-C were accompanied by significant increases in the levels of apo A-I.

Coadministration of anacetrapib and atorvastatin: LDL-C and HDL-C. With coadministration, all anacetrapib doses produced significantly greater LDL-C reductions than atorvastatin monotherapy at week 8 (Figure 2, *B*). As with monotherapy, there were statistically significant incremental decreases in LDL-C among the individual doses of anacetrapib 10, 40, and 150 mg; however, no difference in LDL-C-lowering response resulted from increasing the anacetrapib dose from 150 to 300 mg. The dose-dependent increases in HDL-C with coadministered anacetrapib were significantly larger than those produced by atorvastatin monotherapy and similar to the increases in HDL-C observed with anacetrapib monotherapy (Figure 3, *B*).

Subgroup analyses of the effect of anacetrapib. The enhanced LDL-C-lowering efficacy of anacetrapib (pooled across doses), either as monotherapy or coadministration with atorvastatin, was consistent across subgroups based on age (≤ or >65 years), gender, and baseline LDL-C level (≤ or > median). The dose-dependent reductions in LDL-C were observed in patients with TG above and below the median value (153.5 mg/dL), although the magnitude of the reduction was slightly lower in patients with TG above the median (Figure 4) and slightly greater in patients receiving anacetrapib and atorvastatin. The HDL-C–increasing efficacy of anacetrapib (pooled across doses), either as monotherapy or coadministration with atorvastatin, was consistent across subgroups based on age (≤ or >65 years), gender, baseline HDL-C (≤ or > median), and baseline TG (≤ or > median).

Effects on other efficacy parameters. There were no consistent dose-dependent effects of anacetrapib, as monotherapy or when coadministered with atorvastatin, on TC or TG (Table II). Increasing doses of anacetrapib increased concentrations of apo E (up to 40% increases compared with baseline) (Figure 5, *A*). At week 8, all anacetrapib monotherapy and coadministration doses produced significantly greater reductions in Lp(a) relative to placebo (up to 50%) and atorvastatin, respectively (Figure 5, *B*).

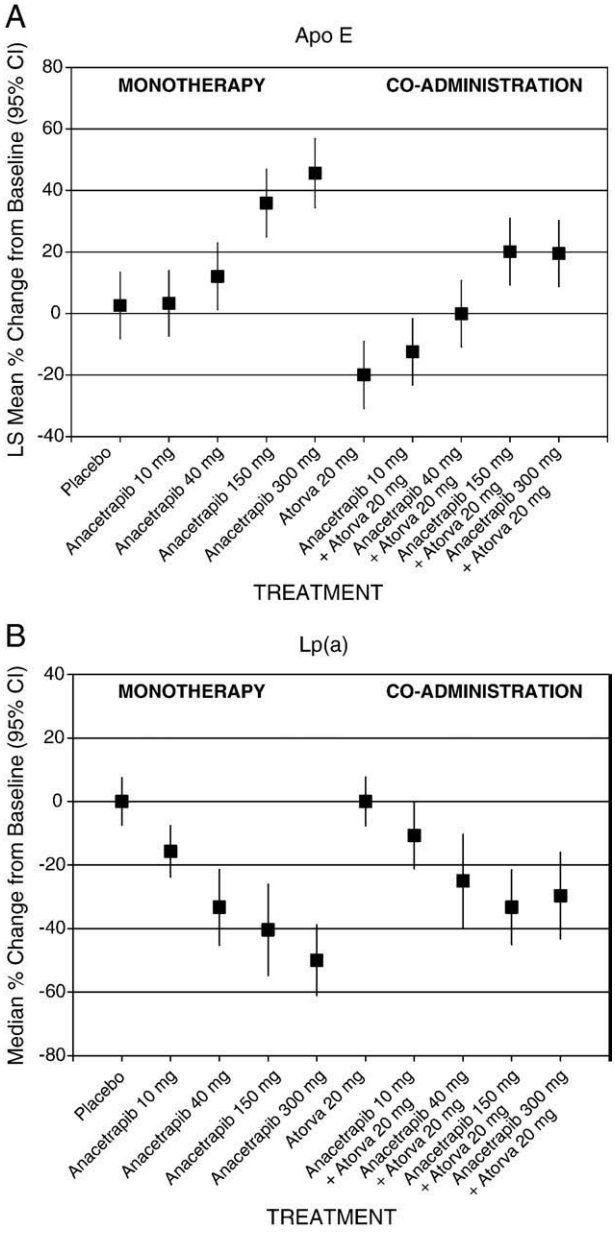
Treatment with anacetrapib as monotherapy had no significant effects on CRP (Table II). As expected, atorvastatin 20 mg was associated with a 30.9% reduction in CRP. The reduction in CRP observed with atorvastatin alone appeared to be somewhat attenuated when anacetrapib was coadministered with atorvastatin.

There were no consistent dose-dependent effects of anacetrapib monotherapy or coadministration with atorvastatin on Na, Cl, or K (Table II). There was no statistically significant difference in aldosterone levels between any of the anacetrapib doses in coadministration with atorvastatin versus atorvastatin alone, and no dose-response relationship was observed across the 3 anacetrapib doses (40, 150, and 300 mg) + atorvastatin (Table II).

Safety and tolerability

Anacetrapib monotherapy and coadministration with atorvastatin were generally well tolerated (see Appendix A, Table II, available online). The incidences for all AE categories were similar across pooled treatment groups, and no dose-response

Figure 5



Changes from baseline in **A**, apo E and **B**, Lp(a).

relationships were observed. Most treatment-related AEs were mild or moderate, with constipation, diarrhea, dyspepsia, and myalgia being most common. There were no treatment-related serious AEs or deaths. Treatment-related discontinuations were rare, and no patient discontinued owing to serious treatment-related AEs.

Four patients experienced serious AEs during the study. According to the investigators' blinded assessments, none were considered to be related to treatment. Laboratory test abnormalities showed sparse and non–dose-related incidences of clinically important elevations in alanine aminotransferase, aspartate aminotransferase, and creatine kinase. There were no hepatitis-related AEs or rhabdomyolysis.

After 8 weeks of treatment, there was no discernible effect of anacetrapib on either systolic or diastolic blood pressure (Table III; Figure 6). The proportions of patients with isolated >15-mm Hg increases in systolic blood pressure were similar across the placebo (22.4%), atorvastatin (12.1%), pooled anacetrapib monotherapy (18.3%), and pooled anacetrapib + atorvastatin (15.0%) treatment arms. No patient discontinued from the study owing to elevated systolic or diastolic blood pressure.

Discussion

Anacetrapib, a potent CETP inhibitor, was associated with substantial and significant dose-dependent decreases in LDL-C and increases in HDL-C, with no demonstrable increase in blood pressure. The maximal pharmacodynamic lipid effect resulted in decreases in LDL-C and apo B of ~40% and ~30%, respectively, and increases in HDL-C and apo A-I of 139% and 47%, respectively. At the top doses of anacetrapib (150 and 300 mg), the maximal reductions in LDL-C and apo B were similar to those with atorvastatin 20 mg. Moreover, incremental reductions in LDL-C were observed when anacetrapib was coadministered with atorvastatin 20 mg. The net result of treatment with anacetrapib + atorvastatin was ~70% lowering of LDL-C and more than doubling of HDL-C in patients with dyslipidemia. The favorable lipid-altering effects observed with anacetrapib were similar across subgroups of patients based on age, gender, and baseline lipid values.

Apolipoprotein E

Anacetrapib, alone or coadministered with atorvastatin, was associated with dose-related increases in apo E versus the control group (placebo for anacetrapib monotherapy and atorvastatin 20 mg for coadministered anacetrapib and atorvastatin). Both LDL and HDL particles contain apo E. Reductions in apo E associated with statins (and observed in this study with atorvastatin monotherapy) are believed to be related to a reduction in apo E on LDL particles. Given the ~40% reduction in LDL-C with anacetrapib, the observed increase in apo E observed with anacetrapib is likely due to an increase in apo E on HDL particles.

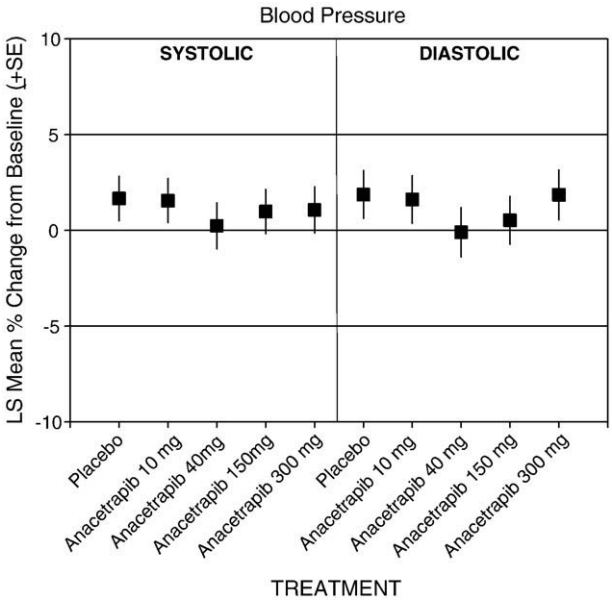
Lipoprotein(a)

Anacetrapib was associated with a clear, dose-dependent reduction in Lp(a). Up to 50% reductions in Lp(a) were observed at the highest anacetrapib doses. Although the physiologic function of Lp(a) is unknown, several studies suggest an association

Table III. Least squares mean changes from baseline (95% CI) in blood pressure after 8 weeks of treatment

	Placebo	Anacetrapib (mg/d) 10	40	150	300	Atorvastatin 20	Atorvastatin 20 (mg/d) + anacetrapib (mg/d) 10	40	150	300
n	56	57	53	56	52	53	52	53	57	58
Systolic										
	1.5 (–1.3 to 4.3)	1.2 (–1.5 to 4.0)	–0.1 (–2.9 to 2.8)	0.4 (–2.3 to 3.2)	0.7 (–2.2 to 3.6)	–0.9 (–3.7 to 2.0)	0.4 (–2.5 to 3.2)	–0.8 (–3.7 to 2.0)	0.4 (–2.3 to 3.1)	–0.6 (–3.3 to 2.1)
Diastolic										
	1.0 (–0.9 to 2.8)	0.9 (–0.9 to 2.7)	–0.3 (–2.2 to 1.6)	0.1 (–1.8 to 1.9)	1.1 (–0.8 to 3.0)	–1.6 (–3.5 to 0.3)	–0.6 (–2.5 to 1.3)	–2.0 (–3.8 to –0.1)	–0.6 (–2.4 to 1.2)	–0.3 (–2.1 to 1.5)

Figure 6



Changes from baseline in systolic and diastolic blood pressure at week 8 with anacetrapib monotherapy versus placebo.

between higher plasma levels of Lp(a) and an increased risk of atherosclerosis and vascular events.[15,16]

C-Reactive protein

Anacetrapib monotherapy did not have a consistent effect on CRP, whereas a ~30% reduction in CRP was observed with atorvastatin alone, consistent with published reports.[17] Baseline CRP values were relatively low in this study, owing to the exclusion of patients with CHD or CHD-equivalent disease. However, most LDL-C–lowering therapies have been associated with a reduction in CRP.[17] Thus, the lack of effect of anacetrapib on CRP in this study is intriguing, considering that the observed reductions in LDL-C with anacetrapib are similar to (or even greater than) those observed with other pharmacologic agents that lower LDL-C and reduce CRP. A clinical benefit specifically attributable to lowering CRP levels with any pharmacologic intervention (independent of reductions in other risk factors such as LDL-C) has not been demonstrated.

Comparison with other CETP inhibitors

Anacetrapib appears to be a more potent inhibitor of CETP associated with larger changes in LDL-C and HDL-C compared with other CETP inhibitors.[5,6] The lipid effects of the top 2 doses of anacetrapib (150 and 300 mg) were nearly identical despite an increase in plasma concentration of the drug (data not shown), suggesting a maximal pharmacodynamic effect of the inhibition of CETP. Although no formal head-to-head studies of different CETP inhibitors have been conducted, looking across studies, there appears to be an association between the degree of CETP inhibition, the decrease in LDL-C, and the increase in HDL-C. Low-density lipoprotein cholesterol reductions have been observed with greater inhibition of CETP (and corresponding greater increases in HDL-C). Increases in HDL-C are seen with modest inhibition of CETP without an effect on LDL-C. The lack of a reduction in LDL-C in the clinical studies of JTT-705 and torcetrapib is likely related to a lesser degree of CETP inhibition owing to a lower potency relative of anacetrapib and/or to limitations on the maximal tolerated dose by off-target toxicity.[5,6,12]

Anacetrapib was associated with similar decreases in LDL-C in patients with TG levels above and below the median. Conversely, with torcetrapib, reductions in LDL-C were only observed in patients with TGs below the median (<2.0 mmol/L).[5,6] In patients with TGs above the median, torcetrapib did not reduce LDL-C despite increasing HDL-C. The reason for the different LDL-C results between torcetrapib and anacetrapib in patients with elevated TGs is unclear.

The most striking difference between torcetrapib and anacetrapib pertains to their effects on blood pressure. Owing to the well-documented increases in blood pressure experienced in the torcetrapib program,[5-10] the current study placed increased scrutiny on both the measurement and analysis of blood pressure to precisely characterize even modest potential increases in blood pressure. Given the level of precision with which blood pressure was measured, the data demonstrate that anacetrapib had no effect on blood pressure, despite having achieved greater CETP inhibition than torcetrapib (based on lipid responses). Similarly, no documented effects on blood pressure have been reported in phase I studies with anacetrapib[11] or in studies with JTT-705.[12]

The precise mechanism by which torcetrapib raises blood pressure is not known; however, the effect is compound specific and unrelated to the mechanism of CETP inhibition.[18] We recently demonstrated that torcetrapib causes an acute increase in plasma aldosterone and corticosterone levels in rats and that torcetrapib releases aldosterone via a direct action on rat adrenocortical cells.[18] In ILLUMINATE, increases in plasma aldosterone were observed in the group of patients treated with torcetrapib.[7] Moreover, patients treated with torcetrapib had reductions in K and increases in Na and bicarbonate, which are consistent with a pharmacodynamic effect of aldosterone excess.[7] In the present study, increasing doses of anacetrapib had no effect on aldosterone, Na, K, or bicarbonate compared with the control group.

Implications and future directions

The potential therapeutic benefit of CETP inhibition remains a charged controversy fueled by the interplay of several factors: the magnitude of the unmet medical need, the potential for this class of drugs to dramatically improve the lipid profile, the ILLUMINATE results, and ongoing debate over the functionality of lipoprotein particles that occur in the setting of CETP inhibition. The unmet medical need is underscored by the number of patients with cardiovascular events despite the significant improvements in outcomes with LDL-C–lowering therapy. Low HDL-C is a well-documented risk factor for the development of cardiovascular events; however, data supporting the clinical benefit attributable to pharmacologic interventions that increase HDL-C are limited to studies with niacin.[19,20] Although recent data demonstrate that HDL particles from patients with CETP deficiency or those treated with torcetrapib have a normal or even enhanced ability to efflux cholesterol from cholesterol-loaded macrophages,[21] uncertainty remains regarding the functionality of large HDL particles described in patients with CETP deficiency. Moreover, the abnormal distribution of apo B–containing lipoproteins reported in patients with CETP deficiency has raised questions regarding the functionality of LDL particles. Although most in vivo studies of atherosclerosis in animal models suggest that a number of CETP inhibitors (including torcetrapib) improve atherosclerosis, the applicability of these animal models is unclear owing to differences in lipoprotein composition and potential differences in the toxicity of these compounds across species.[22-25] Finally, epidemiologic data on the prevalence of atherosclerosis in patients with CETP deficiency are limited and conflicting.[3]

The unexpected results from the ILLUMINATE study[7] (as well as the imaging studies with torcetrapib[8-10]) and the associated discontinuation of the torcetrapib program have further heightened the controversy surrounding the clinical benefit of CETP inhibitors. The definitive assessment of the potential clinical benefits associated with inhibiting CETP will require studies of a compound that does not have the off-target toxicity that was observed with torcetrapib. The present study demonstrates that anacetrapib, a potent CETP inhibitor that is well tolerated, and without a pressor effect, is a compound that would enable the elucidation of this important clinical and scientific question.

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Appendix A

Table I. Baseline patient demographics and efficacy parameters

		Anacetrapib (mg/d)					Atorvastatin 20 (mg/d) + Anacetrapib (mg/d)			
Parameter	**Placebo**	**10**	**40**	**150**	**300**	**Atorvastatin 20**	**10**	**40**	**150**	**300**
n	59	59	59	59	59	59	58	59	59	59
Men, n (%)	29 (49.2)	32 (54.2)	20 (33.9)	29 (49.2)	25 (42.4)	20 (33.9)	23 (39.7)	27 (45.8)	26 (44.1)	21 (35.6)
Age, y (±SD)	55.0 (8.6)	57.1 (8.8)	55.9 (9.2)	58.2 (8.7)	56.3 (9.4)	56.7 (9.0)	54.9 (11.8)	57.4 (8.9)	55.7 (10.9)	56.3 (10.2)
Race, n (%)										
White	48 (81.4)	47 (79.7)	48 (81.4)	53 (89.8)	49 (83.1)	47 (79.7)	48 (82.8)	52 (88.1)	51 (86.4)	50 (84.7)
Black	5 (8.5)	6 (10.2)	6 (10.2)	3 (5.1)	7 (11.9)	5 (8.5)	8 (13.8)	2 (3.4)	5 (8.5)	6 (10.2)
Other	6 (10.2)	6 (10.2)	5 (8.5)	3 (5.1)	3 (5.1)	7 (11.9)	2 (3.4)	5 (8.5)	3 (5.1)	3 (5.1)
BMI, kg/m^2	31.0	30.8	29.3	30.2	30.7	29.6	30.8	29.0	30.5	29.9
LDL-C, mg/dL	139.3 (22.4)	141.9 (24.3)	142.8 (22.1)	139.3 (16.9)	142.7 (22.2)	140.8 (20.9)	142.1 (23.5)	145.6 (22.5)	139.7 (25.1)	137.1 (19.9)
Apo B, mg/dL	138.7 (22.7)	145.8 (24.8)	142.1 (23.9)	140.9 (20.4)	141.4 (25.2)	143.7 (21.1)	142.1 (23.7)	148 (27)	140.4 (27.3)	142.1 (20.8)
LDL-C/ apo B, mg/dL	1.0 (0.17)	1.0 (0.11)	1.0 (0.11)	1.0 (0.1)	1.0 (0.14)	1.0 (0.11)	1.0 (0.11)	1.0 (0.13)	1.0 (0.1)	1.0 (0.12)
HDL-C, mg/dL	51.6 (13.3)	49.7 (13.4)	51.4 (11.8)	49.8 (10.1)	50.0 (10.0)	50.8 (14.9)	52.3 (14.4)	51.5 (12.2)	49.1 (12.0)	49.0 (13.1)
Apo A-I, mg/dL	169.7 (24.3)	167.5 (29.4)	170.7 (26.6)	168.4 (24.0)	167.6 (23.2)	171.6 (34.1)	172 (34.3)	171.1 (24.8)	163.4 (26.0)	166.9 (28.3)
HDL-C/ apo A-I, mg/dL	0.3 (0.05)	0.3 (0.04)	0.3 (0.04)	0.3 (0.03)	0.3 (0.04)	0.3 (0.04)	0.3 (0.04)	0.3 (0.03)	0.3 (0.04)	0.3 (0.04)
TC, mg/dL	223.5 (29.6)	224 (27.1)	226.3 (27.6)	223.0 (24.0)	225.6 (29.9)	226.2 (27.8)	227.0 (28.5)	231.7 (29.7)	222.8 (30.4)	222.4 (26.4)
TGs, mg/dL*	145.0 (78.6)	155.0 (60.0)	156.5 (103.7)	146.0 (92.1)	147.0 (86.5)	162.5 (84.2)	156.0 (75.8)	156.5 (111.6)	146.5 (79.1)	157.5 (115.3)
LDL-C/ HDL-C, mg/dL	2.8 (0.7)	3.0 (0.8)	2.9 (0.8)	2.9 (0.7)	2.9 (0.6)	2.9 (0.8)	2.9 (0.8)	3.0 (0.8)	3.0 (1.0)	3.0 (0.9)
Apo E, mg/dL	4.5 (1.1)	4.6 (1.4)	4.5 (1.2)	4.4 (1.3)	5.3 (2.9)	4.6 (1.1)	4.7 (1.4)	4.9 (1.5)	4.6 (1.4)	4.9 (1.5)
Lp(a), mg/dL	24.9 (33.3)	23.6 (26.4)	19.1 (22.1)	19.9 (25.6)	23.2 (30.2)	24.5 (27.4)	20.9 (24.4)	24.6 (30.7)	23 (25.9)	22.5 (27.9)
CRP mg/L*	2.4 (4.1)	2.8 (4.6)	2.1 (3.4)	1.5 (3.3)	2.0 (3.1)	2.1 (3.1)	2.4 (2.7)	2.2 (2.4)	1.9 (3.3)	2.7 (6.2)
SBP/DBP, mm Hg	120/77.4	123.6/77.6	117.2/74.8	120/74.7	120.5/76.9	118.5/76.1	120.4/76.6	122.2/75.4	118.7/74.5	120.7/76.9
Na, mEq/L	139.6	139.8	140.0	139.7	139.7	139.6	140.1	139.5	140.0	139.8
Cl, mEq/L	103.1	102.9	103.3	103.1	103.1	103.3	103.5	103.2	103.1	103.2
K, mEq/L	4.3	4.2	4.2	4.2	4.3	4.3	4.4	4.2	4.3	4.1
Diabetes mellitus, n (%)	2 (3.4)	2 (3.4)	2 (3.4)	2 (3.4)	3 (5.1)	4 (6.8)	4 (6.8)	2 (3.4)	3 (5.1)	2 (3.4)
Hypertension, n (%)	24 (40.7)	27 (45.8)	24 (40.7)	26 (44.1)	18 (30.5)	17 (28.8)	21 (36.2)	19 (32.2)	20 (33.9)	27 (45.8)

BMI, Body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure. Values are mean (±SD), unless otherwise noted. * Median.

Table II. Summary of adverse experiences (AEs)

		Anacetrapib (mg/d)					Atorvastatin 20 (mg/d) + anacetrapib (mg/d)			
	Placebo	**10**	**40**	**150**	**300**	**Atorvastatin 20**	**10**	**40**	**150**	**300**
Clinical AEs	25 (42.4)	31 (52.5)	25 (42.4)	16 (27.1)	29 (49.2)	27 (45.8)	27 (46.6)	23 (39.0)	22 (37.3)	30 (50.8)
Treatment-related clinical AE	11 (18.6)	15 (25.4)	8 (13.6)	5 (8.5)	4 (6.8)	8 (13.6)	11 (19.0)	10 (16.9)	10 (16.9)	9 (15.3)
Serious clinical AE	2 (3.4)	0	1 (1.7)	0	0	0	0	0	0	1 (1.7)
Discontinuations due to clinical AE	2 (3.4)	4 (6.8)	2 (3.4)	1 (1.7)	3 (5.1)	1 (1.7)	3 (5.2)	3 (5.1)	2 (3.4)	2 (3.4)
Discontinuations due to treatment-related clinical AE	0	3 (5.1)	2 (3.4)	1 (1.7)	2 (3.4)	1 (1.7)	2 (3.4)	3 (5.1)	2 (3.4)	0
Individual AE of interest										
ALT and/or AST $\geq 3 \times$ ULN	0	0	1	0	0	0	0	0	0	0
CK $\geq 10 \times$ ULN	0	0	1	0	0	0	1	1	0	0

Values are n (%).