Efficacy and Safety of ABT-335 (Fenofibric Acid) in Combination With Atorvastatin in Patients With Mixed Dyslipidemia

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In patients with mixed dyslipidemia characterized by increased triglycerides (TG), decreased high-density lipoprotein (HDL) cholesterol, and increased low-density lipoprotein (LDL) cholesterol, monotherapy with lipid-altering drugs often fails to achieve all lipid targets. This multicenter, double-blind, active-controlled study evaluated ABT-335 (fenofibric acid) in combination with 2 doses of atorvastatin in patients with mixed dyslipidemia. A total of 613 patients with LDL cholesterol ≥130 mg/dl, TG ≥150 mg/dl, and HDL cholesterol <40 mg/dl for men and <50 mg/dl for women were randomly assigned to ABT-335 (135 mg), atorvastatin (20, 40, or 80 mg), or combination therapy (ABT-335 + atorvastatin 20 or 40 mg) and treated for 12 weeks. Combination therapy with ABT-335 + atorvastatin 20 mg resulted in significantly greater improvements in TG (−45.6% vs −16.5%) and HDL cholesterol (14.0% vs 6.3%) compared with atorvastatin 20 mg and LDL cholesterol (−33.7% vs −3.4%) compared with ABT-335. Similarly, significantly greater improvements were observed with ABT-335 + atorvastatin 40 mg in TG (−42.1% vs −23.2%) and HDL cholesterol (12.6% vs 5.3%) compared with atorvastatin 40 mg and LDL cholesterol (−35.4% vs −3.4%) compared with ABT-335 monotherapy. Combination therapy also improved multiple secondary variables. Combination therapy was generally well tolerated with a safety profile consistent with those of ABT-335 and atorvastatin monotherapies. No rhabdomyolysis was reported. In conclusion, ABT-335 + atorvastatin combination therapy resulted in more effective control of multiple lipid parameters than either monotherapy and may be an appropriate therapy for patients with mixed dyslipidemia. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:515–522)

Mixed dyslipidemia, also referred to as atherogenic dyslipidemia, is a common lipid abnormality characterized by increased triglycerides (TG), decreased high-density lipoprotein (HDL) cholesterol, and increased low-density lipoprotein (LDL) cholesterol with an increased proportion of small dense LDL cholesterol particles. Patients with mixed dyslipidemia are at higher risk of coronary heart disease than patients with increased LDL cholesterol alone.[1–5] A rational therapeutic approach to treating patients with mixed dyslipidemia is to combine a statin with an agent that simultaneously improves TG and HDL cholesterol.[6–12] The currently marketed fenofibrate is an ester of fenofibric acid and requires enzymatic cleavage to form fenofibric acid, the active metabolite. ABT-335 is a newly developed choline salt formulation of fenofibric acid. In contrast to fenofibrate, ABT-335 does not require first-pass hepatic metabolism to become active because it dissociates to form the free fenofibric acid within the gastrointestinal tract, which is rapidly absorbed throughout the gastrointestinal tract. This phase 3, randomized, active-controlled, double-blind study evaluated the effects of ABT-335 in combination with atorvastatin on abnormal lipid parameters in patients with mixed dyslipidemia.

Methods

Men and women ≥18 years of age with mixed dyslipidemia characterized by fasting TG ≥150 mg/dl, HDL cholesterol <40 mg/dl for men and <50 mg/dl for women, and LDL cholesterol ≥130 mg/dl after a lipid therapy washout period were eligible for inclusion in the study. Patients agreed to adhere to an American Heart Association diet[13] and discontinue lipid-altering medications. Patients were excluded from the study if they were pregnant; had evidence of unstable coronary heart disease, type 1 diabetes mellitus, history of diabetic ketoacidosis, unstable type 2 diabetes mellitus with hemoglobin A1c >8.5%, or history of diagnosed myopathy; or used prohibited medications. Additional details about patient criteria and study visits were described in a separate article.[14] Patients provided written

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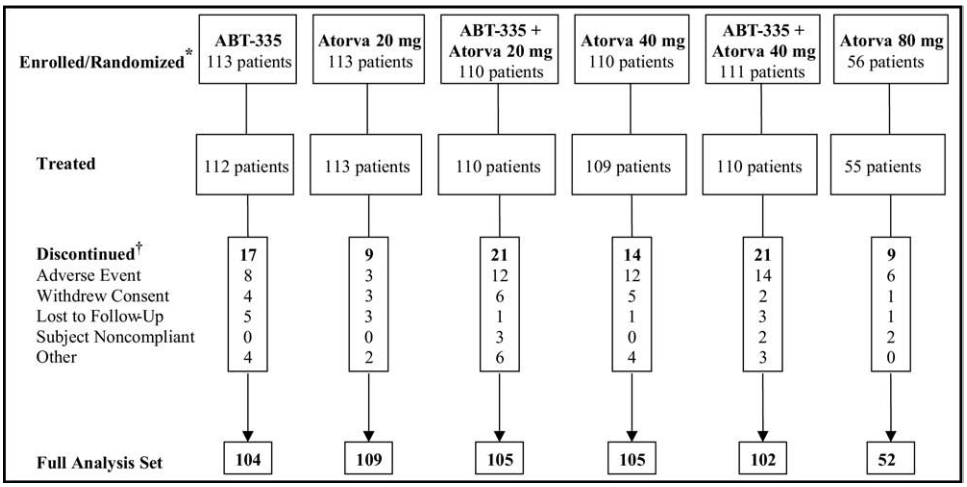

Figure 1. Participant flow. The number of patients randomly assigned, treated, discontinued, and analyzed are shown. The full analysis set is composed of all patients included in the analysis of ≥1 of the 3 primary variables. [a]All randomly assigned patients who received ≥1 dose of study drug. Discontinued patients may have been counted >1 time. [b]Other reasons for discontinuation included difficulty attending scheduled visits, issues with study medication, and investigator/sponsor decision. Atorva = atorvastatin.

informed consent before study-specific procedures, and ethics committees or institutional review boards at each participating institution approved the study protocol and monitored Good Clinical Practice and International Conference on Harmonization guidelines.[15] The study was conducted from March 2006 to February 2007.

This phase 3, multicenter, double-blind, active-controlled study evaluated the effect of ABT-335 + atorvastatin 20 or 40 mg compared with monotherapy on the primary end points of TG, HDL cholesterol, and LDL cholesterol. Patients were randomly assigned in a 2:2:2:2:2:1 ratio to ABT-335 (135 mg), atorvastatin 20 mg, ABT-335 + atorvastatin 20 mg, atorvastatin 40 mg, ABT-335 + atorvastatin 40 mg, or atorvastatin 80 mg, respectively. ABT-335 is an investigational new drug manufactured by Abbott, North Chicago, Illinois, and atorvastatin is manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland.

The study duration was approximately 22 weeks, with a 6-week diet run-in period (during which patients underwent wash out of any previous lipid-lowering medications), a 12-week treatment period, and a 30-day safety follow-up period. Study drug kits (separate pills for each medication) were dispensed at the treatment period baseline and interim visits (at 4-week intervals). Patients were instructed to take the first dose after randomization at the research site and take subsequent doses of study drug in a consistent manner, irrespective of food intake. Adherence to therapy was assessed using pill count. Fasting (≥12 hours) blood samples and urine samples were collected at each study visit. Laboratory analyses were performed by Covance Central Laboratory Services, Indianapolis, Indiana. Patients, site research personnel, and sponsor personnel were blinded to each patient's treatment regimen and laboratory efficacy parameters during the entire study.

The planned sample size of 561 patients was based on the primary variables (TG, HDL cholesterol, and LDL cholesterol) and non–HDL cholesterol. For each atorvastatin dose (20 and 40 mg), this sample size provided 99% and >99% power to detect an increase of 13% in HDL cholesterol and a decrease of 20% in TG, respectively, relative to atorvastatin monotherapy and >99% power to detect a decrease of 31% for LDL cholesterol relative to ABT-335 monotherapy. Overall power to show superiority of both combination doses was 99%. For each atorvastatin dose (20 and 40 mg), this sample size also provided 95% power to detect a decrease of 7.5% in non–HDL cholesterol relative to atorvastatin monotherapy. Overall power to show superiority of both combination doses with respect to non–HDL cholesterol was 90%. Loss to follow-up of 10% was assumed.

For each efficacy variable, the full analysis set included all randomly assigned patients who had both a baseline value and ≥1 postbaseline value. Mean baseline and final-visit values were summarized for each primary and secondary efficacy variable for each treatment group. The last observation carried forward was used to impute values for patients missing a postbaseline value; however, the baseline value was not carried forward. For the primary efficacy analysis of TG and HDL cholesterol, ABT-335 + atorvastatin 20 mg and 40 mg were compared with atorvastatin 20 mg and 40 mg, respectively. For the primary efficacy analysis of LDL cholesterol, ABT-335 + atorvastatin 20 mg and 40 mg were compared with ABT-335 monotherapy. All statistical comparisons were performed separately for each dose of combination therapy. Comparisons of mean percentages of change from baseline between the combination treatment groups and each corresponding monotherapy group were performed using contrast statements within an analysis of covariance with the baseline value of the specific lipid as a covariate and effects for treatment group, diabetic status, screening TG levels, and the interaction of diabetic status by screening TG levels. ABT-335 in combination with the specific atorvastatin dose (20 or 40 mg) was considered successful only if a statistically significant difference was shown for each of the 3 primary efficacy comparisons. Thus, for the 3 comparisons within a dose level, no multiple-comparisons adjustment was required.

Table 1
Demographics and baseline characteristics

	ABT-335 (n = 112)	Atorvastatin 20 mg (n = 113)	ABT-335 + Atorvastatin 20 mg (n = 110)	Atorvastatin 40 mg (n = 109)	ABT-335 + Atorvastatin 40 mg (n = 110)	Atorvastatin 80 mg (n = 55)
Sex						
Women	57 (50.9%)	48 (42.5%)	56 (50.9%)	60 (55.0%)	61 (55.5%)	29 (52.7%)
Men	55 (49.1%)	65 (57.5%)	54 (49.1%)	49 (45.0%)	49 (44.5%)	26 (47.3%)
Race/ethnicity						
White	109 (97.3%)	101 (89.4%)	102 (92.7%)	101 (92.7%)	98 (89.1%)	48 (87.3%)
Black	2 (1.8%)	6 (5.3%)	4 (3.6%)	2 (1.8%)	7 (6.4%)	3 (5.5%)
Indian/Alaskan	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Asian	0 (0%)	4 (3.5%)	4 (3.6%)	4 (3.7%)	3 (2.7%)	2 (3.6%)
Other	0 (0%)	2 (1.8%)	0 (0%)	0 (0%)	1 (0.9%)	1 (1.8%)
Multiracial	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)	0 (0%)	1 (1.8%)
Hispanic	10 (8.9%)	10 (8.8%)	12 (10.9%)	7 (6.4%)	7 (6.4%)	5 (9.1%)
Age (yrs)						
Mean	54.0 ± 10.7	53.7 ± 11.6	56.2 ± 10.2	56.3 ± 10.4	54.9 ± 11.9	55.4 ± 10.7
Minimum, Maximum	25, 79	25, 80	25, 82	34, 78	18, 80	30, 78
Mean weight (kg)						
Women	85.4 ± 19.5	88.5 ± 22.4	87.2 ± 18.3	85.6 ± 19.0	83.9 ± 18.5	88.1 ± 21.3
Men	98.9 ± 20.4	94.5 ± 14.4	96.9 ± 15.4	98.4 ± 16.2	97.8 ± 12.8	96.0 ± 14.5
Waist circumference (cm)						
Women	100.7 ± 13.8	101.4 ± 12.9	103.7 ± 15.4	101.0 ± 14.8	101.1 ± 15.4	100.5 ± 15.0
Men	106.9 ± 18.0	103.2 ± 10.5	104.7 ± 11.2	107.9 ± 15.8	107.6 ± 12.3	105.4 ± 12.6
Tobacco use						
Tobacco user	20 (17.9%)	16 (14.2%)	25 (22.7%)	16 (14.7%)	18 (16.4%)	8 (14.5%)
Former	39 (34.8%)	37 (32.7%)	27 (24.5%)	29 (26.6%)	42 (38.2%)	17 (30.9%)
Never	53 (47.3%)	60 (53.1%)	58 (52.7%)	64 (58.7%)	50 (45.5%)	30 (54.5%)
Preexisting conditions						
Type 2 diabetes mellitus*	26 (23.2%)	27 (23.9%)	28 (25.5%)	28 (25.7%)	29 (26.4%)	14 (25.5%)
Hypertension*	52 (46.4%)	58 (51.3%)	63 (57.3%)	62 (56.9%)	56 (50.9%)	33 (60.0%)
Obesity*	25 (22.3%)	14 (12.4%)	24 (21.8%)	29 (26.6%)	25 (22.7%)	9 (16.4%)
Metabolic syndrome†	73 (65.2%)	68 (60.2%)	75 (68.2%)	77 (70.6%)	72 (65.5%)	40 (72.7%)

Data for all randomly assigned patients who received ≥1 dose of study drug. Values expressed are mean ± SD or number (percent).
* Based on reported medical history.
† Determined according to National Cholesterol Education Program Adult Treatment Panel III definition.[16]

Comparisons of secondary variables were performed separately and independently for each combination treatment group that had shown superiority for each of the 3 primary efficacy variables. Secondary efficacy variables were tested in the rank order of non–HDL cholesterol comparing ABT-335 + atorvastatin versus ABT-335 monotherapy, non–HDL cholesterol comparing ABT-335 + atorvastatin versus atorvastatin monotherapy, very LDL (VLDL) cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein (each evaluated ABT-335 + atorvastatin compared with atorvastatin monotherapy). Testing was performed in a prespecified fixed sequence at the $\alpha = 0.05$ level until 1 variable failed to achieve statistical significance.

One patient in the atorvastatin 20-mg monotherapy group had an extreme outlying value in change from baseline to final value in TG (1,264%) and HDL cholesterol (−56%). Because mean and SE values were model-based, these outlying values affected all treatment group comparisons. Therefore, post hoc analysis of the primary end points was performed excluding this patient. Results were consistent with the primary analysis for all primary end point comparisons. Results for the primary lipid parameters presented in this report excluded this subject. Distribution of high-sensitivity C-reactive protein values was highly skewed. Thus, post hoc nonparametric analysis (van Elteren's test) was used to compare treatment groups. Data were analyzed using SAS, version 8.2 (SAS Institute Inc., Cary, North Carolina).

The safety analysis set included all patients who received ≥1 dose of study drug. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities and summarized by treatment group. Collection of treatment-emergent AEs began with the first dose of study drug. Treatment-emergent AEs starting through 30 days after the discontinuation of study drug were included in the analyses.

Results

A total of 613 patients were randomly assigned and 609 received ≥1 dose of study drug at 101 investigative sites across the United States (including Puerto Rico) and Canada (Figure 1). A total of 518 treated patients (85.1%) completed the study. Baseline demographic and disease characteristics were similar among treatment groups (Table 1).

ABT-335 + atorvastatin 20 mg resulted in significantly higher mean percentages of change in TG (−45.6% vs −16.5%, $p < 0.001$) and HDL cholesterol (14.0% vs 6.3%, $p = 0.005$) compared with atorvastatin 20-mg monotherapy

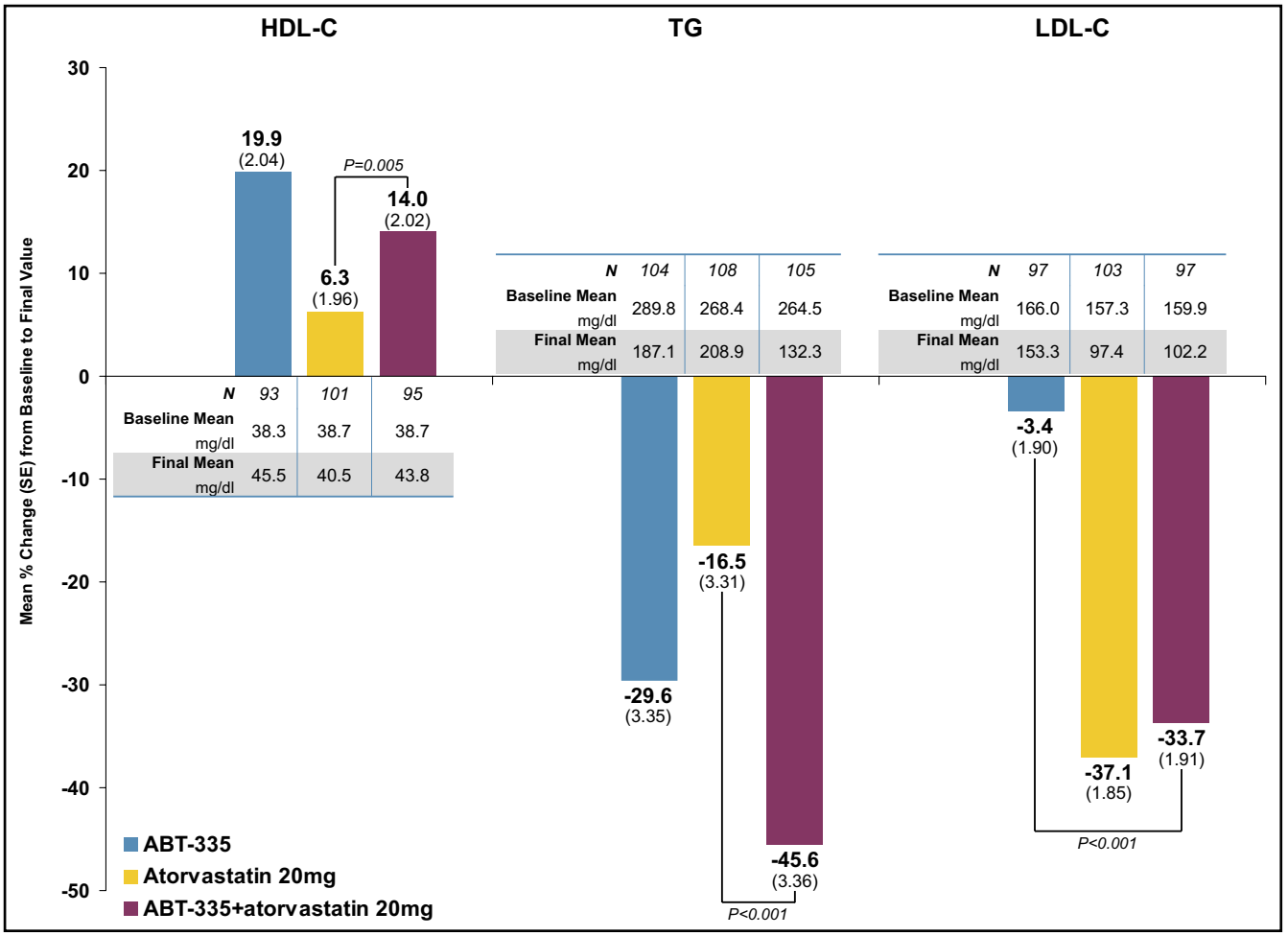

Figure 2. Mean percentage of change (SE), baseline, and final values for primary efficacy variables (HDL cholesterol [HDL-C], triglycerides [TG], and LDL cholesterol [LDL-C]) in the ABT-335, atorvastatin 20-mg, and ABT-335 + atorvastatin 20-mg treatment groups.

and resulted in significantly higher percentages of decrease in LDL cholesterol compared with ABT-335 monotherapy (−33.7% vs −3.4%, p <0.001; Figure 2). ABT-335 + atorvastatin 40 mg resulted in significantly higher mean percentages of change in TG (−42.1% vs −23.2%, p <0.001) and HDL cholesterol (12.6% vs 5.3%, p = 0.010) compared with atorvastatin 40 mg monotherapy and resulted in significantly higher mean percentages of decrease in LDL cholesterol versus ABT-335 monotherapy (−35.4% vs −3.4%, p <0.001; Figure 3). Monotherapy with atorvastatin 80 mg resulted in a 6.2% increase in HDL cholesterol, 30.4% decrease in TG, and 46.0% decrease in LDL cholesterol.

Table 2 lists percentages of change in ranked secondary variables. Treatment with ABT-335 + atorvastatin 20 mg resulted in significantly higher mean percentages of decrease in non–HDL cholesterol compared with ABT-335 (p <0.001) and atorvastatin 20-mg monotherapies (p = 0.026) and in VLDL cholesterol compared with atorvastatin 20-mg monotherapy (p <0.001). More improvement in apolipoprotein B was observed with ABT-335 + atorvastatin 20-mg combination therapy compared with atorvastatin 20-mg monotherapy (nominal p = 0.046). Treatment with ABT-335 + atorvastatin 40 mg resulted in a significantly higher mean percentage of decrease in non–HDL cholesterol compared with ABT-335 monotherapy (p <0.001) and a higher decrease in VLDL cholesterol compared with atorvastatin 40-mg monotherapy (nominal p <0.001). Improvements in other secondary variables, such as total cholesterol and high-sensitivity C-reactive protein, were similar between combination therapy and atorvastatin monotherapy.

Although some subjects discontinued the study drug because of AEs, treatments were otherwise generally well tolerated. Safety profiles with combination therapy were similar to those for both monotherapies, and incidences of AEs were similar between the 2 doses of combination therapy. A summary of AEs occurring in each treatment group is listed in Table 3. The overall incidence of treatment-related AEs (p = 0.003) and increased alanine and aspartate aminotransferases (p = 0.028) were significantly higher in the ABT-335 + atorvastatin 20-mg group versus the atorvastatin 20-mg group, but similar to the ABT-335 monotherapy group. The overall incidence of treatment-related AEs was similar between the ABT-335 + atorvastatin 40-mg group and the atorvastatin 40-mg and ABT-335 monotherapy groups. The most frequently reported treatment-related AEs across all treatment groups were myalgia, diarrhea, and nausea. Twelve patients had serious AEs, with

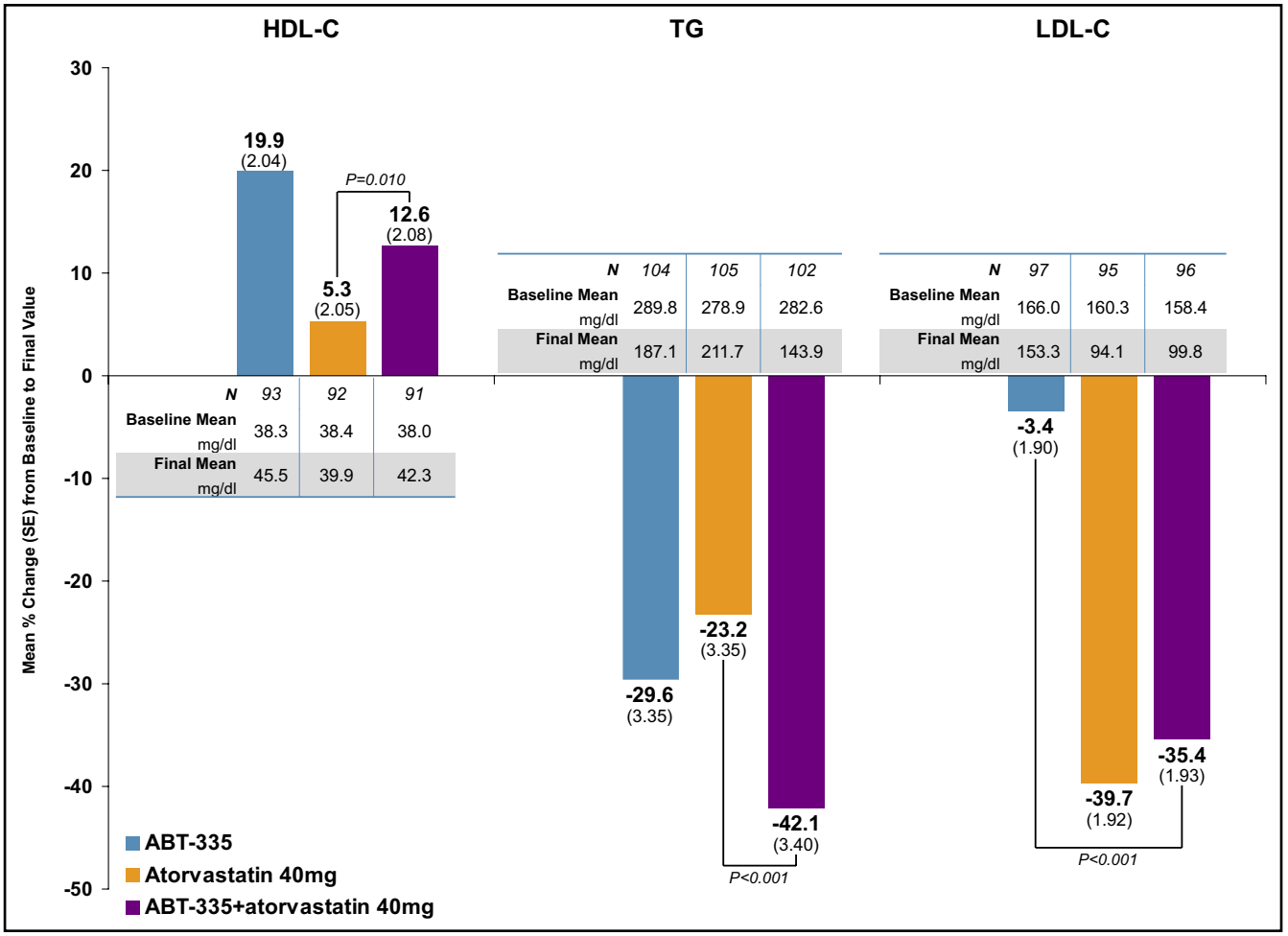

Figure 3. Mean percentage of change (SE), baseline, and final values for primary efficacy variables (HDL cholesterol [HDL-C], triglyceride [TG], and LDL cholesterol [LDL-C]) in the ABT-335, atorvastatin 40-mg, and ABT-335 + atorvastatin 40-mg treatment groups.

similar incidences between the combination-therapy groups and each corresponding monotherapy (Table 3). Only 1 patient receiving ABT-335 + atorvastatin 40 mg had serious AEs (cholecystitis and cholelithiasis) determined by the investigator to be possibly related to study medication.

Of 609 treated patients, 91 (14.9%) prematurely discontinued treatment. Fifty-five patients experienced AEs that led to discontinuation (Figure 1; Table 3). A statistically significant difference ($p = 0.016$) in incidence of AEs leading to discontinuation was observed between the ABT-335 + atorvastatin 20-mg combination therapy and atorvastatin 20-mg monotherapy groups. Higher proportions of patients in the ABT-335 + 20-mg atorvastatin group discontinued therapy because of increased alanine (3.6%) or aspartate aminotransferases (2.7%) than in the other groups (0% to 1.8%). However, in each of these instances, the increase in alanine or aspartate aminotransferase showed resolution on subsequent testing.

Table 4 lists increases in laboratory parameters pertaining to muscle, hepatic, or renal function and related AEs. In general, these events were rare. The incidence of myalgia ranged from 1.8% (ABT-335 + atorvastatin 20-mg group) to 7.3% (atorvastatin 40-mg group), and no case of rhabdomyolysis was reported. Postbaseline increases in alanine aminotransferase >5 times the upper limit of normal were reported in 7 patients, and all patients discontinued treatment. None of the alanine and/or aspartate aminotransferase increases were accompanied by increases in total bilirubin higher than the upper limit of normal. Although 4 patients had creatinine >2.0 mg/dl (Table 4), only 1 patient (atorvastatin 80 mg) discontinued treatment because of increased creatinine levels. For patients with increased muscle-, hepatic-, or renal-related laboratory values and related AEs listed in Table 4 who continued treatment, blood chemistry variables were monitored until resolution to clinically acceptable levels.

Discussion

This study showed that ABT-335 (fenofibric acid) + atorvastatin 20 and 40 mg resulted in effective control of multiple lipid parameters in patients with mixed dyslipidemia, greater than that achieved with either monotherapy alone. Both combination-therapy dose groups (ABT-335 + atorvastatin 20 and 40 mg) resulted in significantly higher improvements in HDL cholesterol and TG compared with the corresponding atorvastatin monotherapy dose and significantly higher improvements in LDL cholesterol com-

Table 2
Percentages of change from baseline for non–HDL cholesterol, VLDL cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein

Lipid Parameters	ABT-335	Atorvastatin 20 mg	ABT-335 + Atorvastatin 20 mg	p Value
Non-HDL cholesterol (mg/dl)	n = 93	n = 102	n = 95	
Baseline mean	229.6	215.0	220.0	
Final mean	189.4	138.0	129.1	<0.001*
Change (%)	−14.8 ± 1.71%	−35.7 ± 1.64%	−40.8 ± 1.69%	0.026†
VLDL cholesterol (mg/dl)	n = 104	n = 107	n = 103	
Baseline mean	67.0	59.5	59.2	
Final mean	36.6	39.2	26.8	
Change (%)	−36.5 ± 3.66%	−26.2 ± 3.63%	−48.3 ± 3.72%	<0.001†
Total cholesterol (mg/dl)	n = 104	n = 109	n = 105	
Baseline mean	269.4	255.9	256.6	
Final mean	235.6	179.8	172.1	
Change (%)	−10.1 ± 1.32%	−29.6 ± 1.29%	−32.8 ± 1.32%	0.072†
Apolipoprotein B (mg/dl)	n = 104	n = 109	n = 104	
Baseline mean	149.1	144.1	145.5	
Final mean	127.7	96.5	90.8	
Change (%)	−12.4 ± 1.49%	−32.9 ± 1.46%	−37.0 ± 1.49%	0.046†
High-sensitivity C-reactive protein (mg/dl)‡	n = 104	n = 109	n = 104	
Baseline median	0.26	0.21	0.25	
Median change (%)	−12.4%	−29.6%	−26.2%	0.993†

	ABT-335	Atorvastatin 40 mg	ABT-335 + Atorvastatin 40 mg	p Value	Atorvastatin 80 mg§
Non-HDL cholesterol (mg/dl)	n = 93	n = 92	n = 91		n = 50
Baseline mean	229.6	222.3	219.8		228.9
Final mean	189.4	128.9	126.2		122.4
Change (%)	−14.8 ± 1.71%	−41.7 ± 1.72%	−42.5 ± 1.74%	<0.001* 0.737†	−45.2 ± 2.30%
VLDL cholesterol (mg/dl)	n = 104	n = 105	n = 101		n = 52
Baseline mean	67.0	65.2	61.8		68.4
Final mean	36.6	37.4	26.4		36.4
Change (%)	−36.5 ± 3.66%	−35.6 ± 3.66%	−53.5 ± 3.74%	<0.001†	−38.9 ± 5.13%
Total cholesterol (mg/dl)	n = 104	n = 105	n = 102		n = 52
Baseline mean	269.4	261.7	259.3		265.5
Final mean	235.6	172.1	169.0		161.5
Change (%)	−10.1 ± 1.32%	−33.8 ± 1.31%	−34.6 ± 1.33%	0.688†	−38.2 ± 1.84%
Apolipoprotein B (mg/dl)	n = 104	n = 104	n = 101		n = 52
Baseline mean	149.1	146.0	145.7		149.3
Final mean	127.7	93.5	91.6		87.8
Change (%)	−12.4 ± 1.49%	−35.3 ± 1.50%	−37.1 ± 1.52%	0.383†	−40.3 ± 2.08%
High-sensitivity C-reactive protein (mg/dl)	n = 104	n = 104	n = 101		n = 52
Baseline median	0.26	0.38	0.26		0.31
Median change (%)	−12.4%	−30.3%	−42.9%	0.074†	−31.9%

Values expressed as percent or mean ± SE unless noted otherwise.
* ABT-335/atorvastatin combination therapy versus ABT-335 monotherapy.
† ABT-335/atorvastatin combination therapy versus corresponding atorvastatin monotherapy.
‡ A post hoc nonparametric analysis (van Elteren's test) was performed for the high-sensitivity C-reactive protein comparison.
§ No statistical comparisons were performed with the atorvastatin 80-mg monotherapy group.

pared with ABT-335 monotherapy. Treatment with ABT-335 + atorvastatin 20 and 40 mg resulted in final mean TG (132.3 and 143.9 mg/dl, respectively), HDL cholesterol (43.8 and 42.3 mg/dl), and LDL cholesterol (102.2 and 99.8 mg/dl) that met or approached treatment guideline targets for high-risk patients.[16–18] Improvements in secondary efficacy variables further showed the advantages of ABT-335 + atorvastatin combination therapy because greater improvements in non–HDL cholesterol, VLDL cholesterol, and apolipoprotein B were observed with 1 or both combination therapy doses compared with the corresponding monotherapies.

This study observed smaller, but statistically similar, decreases in LDL cholesterol with ABT-335 + atorvastatin 20 or 40 mg (resulting in final mean values of 102.2 and 99.8 mg/dl, respectively) compared with atorvastatin 20- (final mean 97.4 mg/dl) or 40-mg (final mean 94.1 mg/dl) monotherapy. This finding was observed previously in smaller clinical studies using a fibrate in combination with statins.[10,19] However, the decreases in LDL cholesterol observed with ABT-335 +

Table 3
Patients with adverse events (AEs)

	ABT-335 (n = 112)	Atorvastatin 20 mg (n = 113)	ABT-335 + Atorvastatin 20 mg (n = 110)	Atorvastatin 40 mg (n = 109)	ABT-335 + Atorvastatin 40 mg (n = 110)	Atorvastatin 80 mg (n = 55)
Any AEs	71 (63.4%)	61 (54.0%)	69 (62.7%)	78 (71.6%)	71 (64.5%)	37 (67.3%)
Treatment-related AEs	14 (12.5%)	7 (6.2%)	22 (20.0%)*	20 (18.3%)	25 (22.7%)	12 (21.8%)
Discontinued because of AEs	8 (7.1%)	3 (2.7%)	12 (10.9%)*	12 (11.0%)	14 (12.7%)	6 (10.9%)
Serious AEs	3 (2.7%)	2 (1.8%)	1 (0.9%)	2 (1.8%)	2 (1.8%)	2 (3.6%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

* A p value ≤0.05 versus atorvastatin 20 mg.

Table 4
Clinical laboratory measurements and incidence of specific adverse events

Postbaseline Increase Criteria	ABT-335 (n = 112)	Atorvastatin 20 mg (n = 113)	ABT-335 + Atorvastatin 20 mg (n = 110)	Atorvastatin 40 mg (n = 109)	ABT-335 + Atorvastatin 40 mg (n = 110)	Atorvastatin 80 mg (n = 55)
Muscle related						
Mean change in creatine kinase* (U/L)	−2.3 ± 75.47	12.4 ± 139.20	14.6 ± 74.51	4.8 ± 48.40	−5.9 ± 145.11	13.9 ± 88.19
Creatine kinase > 5 × ULN	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Creatine kinase > 10 × ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Incidence of myalgia	3 (2.7%)	5 (4.4%)	2 (1.8%)	8 (7.3%)	5 (4.5%)	3 (5.5%)
Incidence of rhabdomyolysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hepatic function						
Mean change in ALT* (U/L)	4.4 ± 13.61	5.1 ± 13.75	5.2 ± 20.29	0.1 ± 24.11	7.0 ± 23.50	7.5 ± 13.24
Mean change in AST* (U/L)	2.7 ± 7.48	2.0 ± 8.27	3.8 ± 11.59	−0.2 ± 9.92	3.8 ± 12.46	2.8 ± 6.12
ALT > 5 × ULN	0 (0%)	0 (0%)	4 (3.6%)	0 (0%)	2 (1.8%)	1 (1.8%)
ALT and/or AST > 3 × ULN on 2 consecutive visits	0 (0%)	0 (0%)	3 (2.7%)	0 (0%)	3 (2.7%)	1 (1.8%)
Concomitant bilirubin >ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal function						
Mean change in creatinine* (mg/dl)	0.12 ± 0.129	0.01 ± 0.094	0.15 ± 0.147	0 ± 0.089	0.11 ± 0.166	0.02 ± 0.116
Creatinine >2.0 mg/dl any visit	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.8%)	1 (1.8%)
Creatinine increased ≥50% and > ULN	1 (0.9%)	0 (0%)	2 (1.8%)	0 (0%)	4 (3.6%)	1 (1.8%)

Values expressed as mean ± SD or number (percent).
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
* Change from baseline to final value.

atorvastatin 20 and 40 mg represented significant clinically relevant decreases of >33% in mean LDL cholesterol and were accompanied by significantly higher improvements in HDL cholesterol and TG compared with the corresponding atorvastatin 20- and 40-mg monotherapy. The simultaneous achievement of optimal mean TG and HDL cholesterol levels showed the advantage of combination therapy in patients with mixed dyslipidemia.

Larger decreases in LDL cholesterol have been observed with atorvastatin 20-mg (−42.6%), 40-mg (−47.8%), and 80-mg (−51.1%) monotherapy in studies of patients with hypercholesterolemia.[20] LDL cholesterol response is typically dependent on baseline lipids; in particular, the LDL cholesterol response is directly related to baseline LDL cholesterol and inversely related to baseline TG. The mixed dyslipidemic patient population included in this study had relatively low pretreatment mean LDL cholesterol (161.1 mg/dl) and high mean TG (276.6 mg/dl). In the subgroup of patients with baseline LDL cholesterol >160 mg/dl (n = 241; mean baseline LDL cholesterol range 187.4 to 197.8mg/dl), atorvastatin 20- and 40-mg monotherapy resulted in mean percentages of decrease in LDL cholesterol of −44.4% and −44.8%,

respectively, which was similar ($p > 0.05$ for each) to those achieved with ABT-335 + atorvastatin 20 and 40 mg (−42.3% and −44.5%) and consistent with results observed with atorvastatin monotherapy in hypercholesterolemic populations.

No death occurred during this study, and the combination of ABT-335 + atorvastatin was generally well tolerated, with a safety profile consistent with those of the individual monotherapy components. The primary safety concern of combining fibrates with statins for the management of mixed dyslipidemia is the potential for increased muscle-related AEs, in particular, the risk of rhabdomyolysis. Although myalgia was the most common AE in patients treated with combination therapy, the incidence was similar to the atorvastatin or ABT-335 monotherapy arms, and there was no case of rhabdomyolysis. These data suggest that the short-term risk of significant muscle-related AEs with the combination of ABT-335 + atorvastatin is low and no higher than with atorvastatin or ABT-335 monotherapy. Importantly, these safety results suggest that patients treated with atorvastatin 20 or 40 mg who need the additional benefit of TG lowering and HDL cholesterol increasing may add ABT-335 without increasing these risks.

Limitations of this study included the absence of a placebo arm and the short duration of the study. Also, exclusion criteria at randomization limited extrapolation of these results beyond the population studied. Ongoing studies are evaluating the long-term safety and efficacy of this combination. Nonetheless, the present study, along with 2 other related studies evaluating ABT-335 in combination with either simvastatin or rosuvastatin, provided valuable information about the benefits of combining a fibrate, ABT-335, with a statin in patients with mixed dyslipidemia.

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