2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Choline fenofibrate (ABT-335)	**Volume:**	
Name of Active Ingredient: ABT-335, A-7770335.115	**Page:**	
Title of Study: A Multicenter, Randomized, Double-Blind, Prospective Study Comparing the Safety and Efficacy of Fenofibric Acid and Atorvastatin Calcium Combination Therapy to Fenofibric Acid and Atorvastatin Calcium Monotherapy in Subjects with Mixed Dyslipidemia		
Coordinating Investigator: Anne Carol Goldberg, MD, FACP		
Study Sites: Multicenter; 117 study sites in the United States, Canada, and Puerto Rico screened subjects, with 101 of these sites randomizing subjects.		
Publications: None		
Studied Period (Years): Date First Subject Dosed: 22 March 2006 Date Last Subject Completed Dosing: 08 February 2007	**Phase of Development:** 3	
Objectives: The objective of this study was to evaluate and compare the effects of once daily ABT-335 monotherapy and atorvastatin calcium (atorvastatin) monotherapy with ABT-335 and atorvastatin combination therapy on coronary heart disease (CHD) lipid risk factors in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb).		
Methodology: This Phase 3, multicenter, randomized, double-blind, prospective study was designed to compare the effects of once daily treatment with ABT-335 in combination with two doses of atorvastatin to ABT-335 monotherapy and atorvastatin monotherapy on the primary lipid parameters associated with increased risk of CHD in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb). Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio to one of the six treatment groups as follows: 135 mg ABT-335 monotherapy, 20 mg atorvastatin monotherapy, ABT-335 in combination with 20 mg atorvastatin, 40 mg atorvastatin monotherapy, ABT-335 in combination with 40 mg atorvastatin, and 80 mg atorvastatin monotherapy. The planned duration of the study was approximately 22 weeks, consisting of a 42-day diet run-in/hypolipidemic washout period (Screening Period), a 12-week Treatment Period, and a 30-day Safety Follow-up Period. During the Treatment Period, subjects took study drug orally once daily, recorded missed doses as well as adverse events and use of concomitant medications in a subject diary, and returned to the study site for two Interim Visits at approximately Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 3 days), and a Week 12 Final/Discontinuation Visit (Day 85 or earlier for premature discontinuation ± 3 days). After one or two Screening Visits, subjects were randomized at the Baseline Visit and dispensed study drug. At the Baseline and Interim Visits, physical examination was performed (full physical at baseline with symptom-directed exam if indicated at the Interim Visits);		

Methodology (Continued):

electrocardiogram (ECG, at Baseline and Final Visits); vital signs were measured; routine hematology, serum chemistry and urinalysis were performed in all subjects, with serum pregnancy tests in females of childbearing potential; samples were collected for measurements of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides (TG), very-low-density lipoprotein cholesterol (VLDL-C), high sensitivity C-reactive protein (hsCRP), and apolipoprotein B (ApoB); study drug and subject diaries were dispensed; subject diaries were reviewed (at Interim Visits); diet compliance, adverse events and use of concomitant medications were assessed; study drug was accounted for and a new study drug kit was dispensed. Nuclear Magnetic Resonance (NMR) samples for LipoProfile® (Baseline and Final Visits) were obtained at a subset of sites.

At the Week 12 Final/Discontinuation Visit (Day 85 or earlier for premature discontinuation ± 3 days), procedures that had been performed at the Interim Visits were repeated (except study drug and subject diaries were not dispensed); in addition, an ECG was performed and blood samples were obtained for measurement of apolipoprotein AI (ApoAI), apolipoprotein CIII (ApoCIII), adiponectin, and lipoprotein-associated phospholipase A2 (LpPLA2). Subjects who completed the Treatment Period of the study at the Week 12 Final/Discontinuation Visit were eligible to participate in an open-label safety extension study (M05-758). Subjects who declined participation in the extension study were contacted a minimum of 30 calendar days after the Week 12 Final/Discontinuation Visit; at this Safety Follow-up call, adverse events and use of any concomitant medications were assessed, and subjects were asked about any positive pregnancy test results or pregnancy confirmation in the subject or partner.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 560 subjects (102 subjects in each of the following treatment groups: ABT-335 monotherapy, 20 mg atorvastatin monotherapy, ABT-335 in combination with 20 mg atorvastatin, 40 mg atorvastatin monotherapy, and ABT-335 in combination with 40 mg atorvastatin, and 51 subjects to 80 mg atorvastatin monotherapy).

Enrolled in Treatment Period: 613 subjects were randomized with 609 subjects treated:

ABT-335 monotherapy (N = 112)
20 mg atorvastatin monotherapy (N = 113)

ABT-335 in combination with 20 mg atorvastatin (N = 110)
40 mg atorvastatin monotherapy (N = 109)

ABT-335 in combination with 40 mg atorvastatin (N = 110)
80 mg atorvastatin monotherapy (N = 55)

Diagnosis and Main Criteria for Inclusion:

Male and female subjects ≥ 18 years of age with mixed dyslipidemia (Frederickson Type IIb), with the following screening values: TG ≥ 150 mg/dL (≥ 1.69 mmol/L), HDL-C < 40 mg/dL (< 1.02 mmol/L) for men and < 50 mg/dL (< 1.28 mmol/L) for women, and LDL-C ≥ 130 mg/dL (≥ 3.35 mmol/L). In addition, subjects must have been willing to observe the diet recommend by the American Heart Association entitled "An Eating Plan for Healthy Americans: Our American Heart Association Diet."

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Test Product: ABT-335 (equivalent to 135 mg fenofibric acid) capsule, once daily, orally

ABT-335 (135 mg) capsule and atorvastatin calcium (equivalent to 20 mg atorvastatin) capsule, once daily, orally

ABT-335 (135 mg) capsule and atorvastatin calcium (equivalent to 40 mg atorvastatin) capsule, once daily, orally

For the respective lot number, please refer to the table below.

Study Drug	Dosage Form	Bulk Lot No.	Finishing Lot No.
ABT-335	135 mg capsule (blinded)	05-002450	06-004758
		05-002449	06-006299
		05-002450	06-006466
ABT-335 placebo	matching 135 mg placebo capsule (blinded)	05-003032	06-004758
		05-003032	06-006299
		05-003032	06-006466
Atorvastatin calcium	20 mg capsule (blinded)	05-003735	06-004758
		05-003735	06-006299
		06-007092	06-006466
Atorvastatin calcium	40 mg capsule (blinded)	05-003743	06-004758
		05-003743	06-006299
		06-007093	06-006466
Atorvastatin calcium placebo	matching 20 mg or 40 mg placebo capsule (blinded)	06-003750	06-004758
		06-003750	06-006299
		06-006961	06-006466

Duration of Treatment: 12 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Atorvastatin (20 mg), once daily, orally

Atorvastatin (40 mg), once daily, orally

Atorvastatin (80 mg), once daily, orally, given as two atorvastatin 40 mg capsules

For the respective lot numbers, please refer to the table above.

Criteria for Evaluation

Efficacy:

The primary efficacy variables were percent changes from baseline to 12 weeks post-baseline (Final Visit) in:

1. HDL-C (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy).
2. Triglycerides (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy).
3. LDL-C (combination therapy with each dose of atorvastatin vs. ABT-335 monotherapy).

All three comparisons must have demonstrated superiority of the combination therapy to the appropriate monotherapy in order to declare the combination therapy successful for a particular atorvastatin combination dose. The study was declared successful when the superiority of the combination was demonstrated for all three primary comparisons for at least one atorvastatin dose.

Criteria of Evaluation

Efficacy (Continued):

The ranked secondary efficacy variables were percent changes from baseline to 12 weeks post-baseline (Final Visit) in:

1. Non-HDL-C (combination therapy with each dose of atorvastatin vs. ABT-335 monotherapy)
2. Non-HDL-C (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)
3. VLDL-C (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)
4. Total-Cholesterol (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)
5. Apolipoprotein B (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)
6. hsCRP (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)

The secondary endpoints were tested in a fixed sequence separately for each combination therapy group that was statistically significantly superior to the appropriate monotherapy for each of the three primary endpoints. The secondary endpoints were tested in order at the alpha = 0.05 level until one endpoint failed to reach statistical significance. If the secondary endpoints were tested for both combination therapy groups, comparisons for one combination therapy group could continue down the fixed sequence of endpoints, even if comparisons for the other combination therapy group were stopped due to failure to reach statistical significance for an endpoint.

Additional efficacy parameters measured were ApoAI, ApoCIII, adiponectin, and LpPLA2 as well as parameters derived by the NMR LipoProfile® test (including but not limited to VLDL, LDL, and HDL total and subclass particle concentration and VLDL, LDL, and HDL mean particle size). All additional efficacy parameters were considered exploratory efficacy variables.

Safety: Safety assessments included adverse events, physical examination, laboratory parameters, vital signs, and ECGs.

Statistical Methods

Efficacy:

For the primary and secondary efficacy variables, the Baseline and Final Visit values were summarized with the mean for each treatment group. The within-group percent changes from baseline were summarized for each treatment group with the mean, standard error and range, and the between-group differences were summarized with the mean and standard error. The percent changes from baseline were compared between the combination therapy groups and each corresponding monotherapy group using contrast statements within an analysis of covariance (ANCOVA) with baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as a covariate and with effects for treatment group, diabetic status (diabetic, non-diabetic), screening TG (≤ 250 mg/dL [≤ 2.8 mmol/L], > 250 mg/dL [> 2.8 mmol/L]), and the interaction of diabetic status by screening TG. Data from all treatment groups were included when performing the ANCOVA. The interactions of treatment by diabetic status and treatment by screening TG were tested. However, these interaction terms were not included in the model that supported the primary inferences.

Statistical Methods

Efficacy (Continued):

All three primary efficacy comparisons must have demonstrated superiority of the combination therapy to the appropriate monotherapy in order to declare the combination therapy successful for a particular atorvastatin dose. Hence, no multiple comparisons adjustment was necessary for the three comparisons within a dose level.

The study was declared successful if superiority of the combination therapy group to the appropriate monotherapy group was demonstrated for all three primary comparisons for *at least* one atorvastatin dose. Hence, adjustments for multiple comparisons were performed using the Hochberg method in order to adjust for treatment group comparisons being performed for two atorvastatin doses.

The secondary endpoints were tested in a fixed sequence, separately for each combination therapy group that was statistically significantly superior for each of the three primary endpoint comparisons.

Efficacy data for the 80 mg atorvastatin calcium monotherapy group were summarized with descriptive statistics. No formal statistical comparisons were made between this treatment group and the other treatment groups in the study.

Safety:

Frequencies and percentages of subjects with treatment-emergent adverse events were calculated for each treatment group for all events, for events by organ class and preferred terms, by severity, by relationship, for events that led to death, for serious adverse events, and for events that led to discontinuation. Percentages for "any event" and for each preferred term were compared between the combination therapy groups and each corresponding monotherapy group using Fisher's exact tests.

For laboratory and vital sign parameters, mean changes and potentially clinically significant values were presented and compared between the combination therapy groups and each corresponding monotherapy group. In addition for each laboratory parameter, shifts from baseline according to the normal range were provided. For ECG, a shift table presenting results at baseline and the Final Visit was presented.

Safety data for the 80 mg atorvastatin monotherapy group were summarized with descriptive statistics; however, no formal statistical comparisons were made between this treatment group and the other treatment groups in the study.

Summary/Conclusions

Of the 609 treated subjects, 311 (51.1%) were female and 298 (48.9%) were male; 91.8% of subjects were White. Mean age was 55 years. The majority (60.6%) of subjects were between 40 and 60 years of age; 8.2% were younger than 40 years and 31.2% were older than 60 years. In addition to hyperlipidemia, common medical history conditions included hypertension (53.2%), eye disease/disorder (32.2%), gastroesophageal reflux disease (28.7%), drug allergies/reactions (28.2%), osteoarthritis (26.8%), diabetes mellitus (25.0%), depression (21.3%), and obesity (20.7%).

Of 609 treated subjects, 518 (85.1%) completed the study and 91 (14.9%) prematurely discontinued study drug. Overall, the most common reasons for prematurely discontinuing study drug were adverse event (9.0%) and withdrawal of consent (3.4%).

Efficacy Results:

For the primary efficacy comparisons, statistically significant greater mean percent increases from baseline in HDL-C and decreases from baseline in TG and LDL-C were observed for both combination therapy groups compared to the corresponding monotherapy groups. As shown below, ABT-335 in combination with 20 mg and 40 mg atorvastatin, compared to 20 mg and 40 mg atorvastatin monotherapy, respectively, resulted in significantly greater mean percent increases in HDL-C and significantly greater mean percent decreases in TG. ABT-335 in combination with 20 mg and 40 mg atorvastatin, compared to ABT-335 monotherapy, resulted in a significantly greater mean percent decrease in LDL-C. Based on the significant results for all three primary comparisons (HDL-C, TG, LDL-C), each combination therapy group was declared superior to the corresponding monotherapy group. Results of sensitivity analyses, including a worst-case analysis, were generally consistent with results of the primary analysis, although some comparisons between ABT-335 in combination with 40 mg atorvastatin and 40 mg atorvastatin monotherapy were not statistically significant for TG. Differences observed in the primary analyses at Week 12 were apparent by Week 4 and were sustained throughout the duration of treatment.

Primary Endpoints	ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	p-value	40 mg atorva	ABT-335 + 40 mg atorva	p-value	80 mg atorva
HDL-C								
BL mean	38.3	38.7	38.7		38.4	38.0		37.6
Mean % Δ	19.8%	5.6%	13.9%	0.003[a]	5.2%	12.5%	0.010[a]	6.1%
TG								
BL mean	289.7	267.4	264.3		278.7	282.5		303.6
Mean % Δ	-27.7%	-3.0%	-43.8%	< 0.001[a]	-21.3%	-40.0%	0.032[a]	-28.2%
LDL-C								
BL mean	166.0	157.3	159.9		160.4	158.4		162.7
Mean % Δ	-3.5%	-37.5%	-33.8%	< 0.001[b]	-39.8%	-35.5%	< 0.001[b]	-46.0%

a. Combination therapy vs. atorvastatin monotherapy

b. Combination therapy vs. ABT-335 monotherapy

Results of the analysis of secondary endpoints are shown below. ABT-335 in combination with both 20 mg and 40 mg atorvastatin resulted in significantly greater mean percent decreases in non-HDL-C compared to ABT-335 monotherapy. Compared to atorvastatin monotherapy, ABT-335 in combination with 20 mg atorvastatin demonstrated a significantly greater mean percent decrease in non-HDL-C compared to 20 mg atorvastatin monotherapy, while results were similar between ABT-335 in combination with 40 mg atorvastatin and 40 mg atorvastatin monotherapy. Compared to the corresponding atorvastatin monotherapy groups, greater mean percent decreases in VLDL-C were observed with ABT-335 in combination with 20 mg atorvastatin and ABT-335 in combination with 40 mg atorvastatin. No differences were observed between combination therapy and monotherapy in total-C. ABT-335 in combination with 20 mg atorvastatin resulted in greater mean percent decreases in

Efficacy Results (Continued):

ApoB compared to 20 mg atorvastatin monotherapy; the mean percent decrease in ApoB with ABT-335 in combination with 40 mg atorvastatin was similar to that of 40 mg atorvastatin monotherapy. Nonparametric analysis of hsCRP demonstrated that median percent decreases in hsCRP were similar between each dose of combination therapy and the corresponding atorvastatin monotherapy and both doses of combination therapy demonstrated significantly larger median percent decreases in hsCRP than ABT-335 monotherapy. Because of the prespecified ranking of secondary comparisons, statistical significance could not be claimed for the positive results on VLDL-C with ABT-335 in combination with 40 mg atorvastatin, or on ApoB with ABT-335 in combination with 20 mg atorvastatin.

Secondary Endpoints	ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	p-value	40 mg atorva	ABT-335 + 40 mg atorva	p-value	80 mg atorva
Non-HDL-C								
BL mean	229.6	215.0	220.0	< 0.001[a]	222.3	219.8	< 0.001[a]	228.9
Mean % Δ	-14.8%	-35.7%	-40.8%	0.026[b]	-41.7%	-42.5%	0.737[b]	-45.2%
VLDL-C								
BL mean	67.0	59.5	59.2		65.2	61.8		68.4
Mean % Δ	-36.5%	-26.2%	-48.3%	< 0.001[b]	-35.6%	-53.5%	< 0.001[b]	-38.9%
Total-C								
BL mean	269.4	255.9	256.6		261.7	259.3		265.5
Mean % Δ	-10.1%	-29.6%	-32.8%	0.072[b]	-33.8%	-34.6%	0.688[b]	-38.2%
ApoB								
BL mean	149.1	144.1	145.5		146.0	145.7		149.3
Mean % Δ	-12.4%	-32.9%	-37.0%	0.046[b]	-35.3%	-37.1%	0.383[b]	-40.3%
hsCRP[c]								
BL median	0.26	0.21	0.25		0.38	0.26		0.31
Median % Δ	-12.4%	-29.6%	-26.2%	0.993[b,c]	-30.3%	-42.9%	0.074[b,c]	-31.9%

a. Combination therapy vs. ABT-335 monotherapy.
b. Combination therapy vs. atorvastatin monotherapy.
c. Post hoc nonparametric analysis.

The benefits of combination therapy as demonstrated by the primary and secondary efficacy analyses were supported by results of several exploratory efficacy analyses. As shown below, both doses of combination therapy resulted in greater mean percent decreases in ApoCIII compared to corresponding atorvastatin monotherapy. ABT-335 in combination with 20 mg atorvastatin resulted in a greater mean increase in ApoAI than 20 mg atorvastatin monotherapy. No consistent pattern was seen for adiponectin. For LpPLA2, a mean percent increase was observed in the ABT-335 monotherapy group with mean percent decreases in the atorvastatin monotherapy and combination therapy groups; a greater mean percent decrease was observed with 40 mg atorvastatin monotherapy compared to the corresponding combination.

Efficacy Results (Continued):

Exploratory Endpoints	ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	p-value	40 mg atorva	ABT-335 +40 mg atorva	p-value	80 mg atorva
ApoAI								
BL mean	139.9	142.0	140.2	0.057[a]	140.8	143.0	< 0.001[a]	141.1
Mean % Δ	11.3%	2.0%	7.0%	0.022[b]	2.3%	1.9%	0.837[b]	2.0%
ApoCIII								
BL mean	19.5	18.4	18.5	0.004[a]	19.0	19.3	0.004[a]	19.5
Mean % Δ	-25.6%	-14.7%	-35.4%	< 0.001[b]	-16.9%	-35.6%	< 0.001[b]	-22.2%
Adiponectin								
BL mean	6029.4	5943.7	6288.0	0.109[a]	6817.1	4951.0	0.520[a]	5839.4
Mean % Δ	-0.4%	7.0%	-8.7%	0.002[b]	-0.4%	-3.8%	0.517[b]	6.7%
LpPLA2								
BL mean	265.8	255.1	251.0	< 0.001[a]	288.3	267.5	< 0.001[a]	266.0
Mean % Δ	20.7%	-8.6%	-2.0%	0.056[b]	-11.9%	-3.3%	0.014[b]	-12.1%

a. Combination therapy vs. ABT-335 monotherapy.

b. Combination therapy vs. atorvastatin monotherapy.

Both doses of combination therapy had positive effects on additional measures of atherogenicity. In general, combination therapy resulted in favorable effects on all lipid ratios reflecting atherogenic vs. non-atherogenic lipid particles, including the ratios of total-C to HDL-C, non-HDL-C to HDL-C, and ApoB to ApoAI, as well as TG to HDL-C. For both doses of combination therapy, greater improvements in ratios were noted compared to ABT-335 monotherapy and improvements were similar to or more favorable than those for atorvastatin monotherapy.

These observations were reinforced by favorable effects of combination therapy on LDL-P, VLDL-P and VLDL-TG, emerging measures of atherogenicity. Mean percent decreases in LDL-P were similar between ABT-335 in combination with 20 mg and 20 mg atorvastatin monotherapy (-35.9% vs. -37.4%) but were lower with ABT-335 in combination with 40 mg atorvastatin than with 40 mg atorvastatin monotherapy (-36.9% vs. -41.9%). In contrast, compared to the corresponding atorvastatin monotherapy, greater mean percent decreases were observed with both ABT-335 in combination with 20 mg and 40 mg atorvastatin on VLDL-P (-51.7% vs. -23.0% and -50.7% vs. -32.1%, respectively) and VLDL-TG (-53.7% vs. -2.1% and -52.0% vs. -25.2%, respectively). In addition, greater mean percent increases in LDL particle size were observed with combination therapy than with atorvastatin monotherapy, and combination therapy resulted in a shift from a more atherogenic, small LDL (pattern B) to a less atherogenic, large LDL (pattern A) that was not observed in either atorvastatin monotherapy group.

Efficacy Results (Continued):

Across all risk categories, higher proportions of subjects in the 20 mg and 40 mg atorvastatin monotherapy groups than in the ABT-335 in combination with 20 mg and 40 mg groups achieved National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) goals for LDL-C (80.8% vs. 72.2% and 84.2% vs. 71.9%, respectively), while similar proportions of subjects in the monotherapy and combination therapy groups achieved NCEP ATP III non-HDL-C goals (76.0% vs. 74.5% and 72.9% vs. 76.6%). A higher proportion of subjects in the 20 mg atorvastatin monotherapy group than in the ABT-335 in combination with 20 mg atorvastatin group achieved NCEP ATP III goals for both LDL-C and non-HDL-C (72.1% vs. 62.9%), with similar proportions of subjects in the 40 mg atorvastatin monotherapy and ABT-335 in combination with 40 mg atorvastatin groups (71.6% vs. 71.3%) achieving both goals.

Across subgroups stratified by diabetic status, gender, baseline HDL-C level, baseline TG level, and baseline LDL-C level, greater mean percent changes in HDL-C, TG, and LDL-C were generally observed in the combination therapy groups than in the corresponding monotherapy groups. The treatment effect of both doses of combination therapy was similar in diabetic and non-diabetic subjects. No consistent pattern was observed for the treatment effect of combination therapy or atorvastatin monotherapy in males and females.

Compared to corresponding atorvastatin monotherapy, ABT-335 in combination with 20 mg and 40 mg atorvastatin resulted in a greater mean percent change in:

- TG among subjects with baseline TG levels > 200 mg/dL (-54.7% and -49.5%, respectively) than among those with baseline levels ≤ 200 mg/dL (-30.7% and -36.2%, respectively).
- LDL-C among subjects with baseline LDL-C > 160 mg/dL (-42.3% and -44.5%, respectively) than among those with baseline LDL-C ≤ 160 mg/dL (-27.2% and -27.6%, respectively).

Notably, in the subgroup with baseline LDL-C > 160 mg/dL, mean percent decreases in LDL-C were similar between each combination therapy and the corresponding atorvastatin monotherapy. For ABT-335 in combination with 20 mg atorvastatin and 20 mg atorvastatin monotherapy, mean percent decreases in LDL-C were -42.3% and -44.4%, respectively; for ABT-335 in combination with 40 mg atorvastatin and 40 mg atorvastatin monotherapy, mean percent decreases in LDL-C were -44.5% and -44.8%, respectively.

ABT-335 in combination with 40 mg atorvastatin resulted in a greater treatment effect on HDL-C among subjects with baseline HDL-C levels ≤ 37 mg/dL (19.7%) than among those with baseline levels > 37 mg/dL (6.2%); mean percent increase in HDL-C was similar in the two subgroups stratified by baseline HDL-C for subjects treated with ABT-335 in combination with 20 mg atorvastatin (14.6% vs. 12.4%).

The treatment response to ABT-335 monotherapy was greater in females than males for all three primary efficacy comparisons. Similar treatment effects were observed for combination therapy and atorvastatin monotherapy, with two exceptions. For ABT-335 in combination with 40 mg atorvastatin compared to 40 mg atorvastatin monotherapy, a greater mean percent decrease was observed among females than males in TG (-43.2% vs. -34.1%) and LDL-C (-40.0% vs. -31.4%).

Safety Results:

All treatments were generally well tolerated. The adverse event profiles of the monotherapy comparators were consistent with the known or expected safety profiles. In addition, the safety profiles were similar between the two doses of combination therapy, with no indication of additional adverse effects of the ABT-335 in combination with 40 mg atorvastatin relative to the ABT-335 combination with 20 mg atorvastatin.

The overall incidence of treatment-emergent adverse events was generally similar across treatment groups. One or more adverse events were reported by 63.4% of subjects receiving ABT-335 monotherapy, 54.0% of subjects receiving 20 mg atorvastatin monotherapy, 62.7% of subjects receiving ABT-335 in combination with 20 mg atorvastatin, 71.6% of subjects receiving 40 mg atorvastatin monotherapy, 64.5% of subjects receiving ABT-335 in combination with 40 mg atorvastatin, and 67.3% of subjects receiving 80 mg atorvastatin monotherapy. Overall, the most frequently reported treatment-emergent adverse events were headache, diarrhea, nausea, myalgia, nasopharyngitis, upper respiratory tract infection, back pain, arthralgia, muscle spasms, and pain in extremity.

The incidence of specific events was generally similar across treatment groups. Statistically significant differences were observed between the ABT-335 in combination with 20 mg atorvastatin and 20 mg atorvastatin monotherapy groups in the adverse events of alanine aminotransferase (ALT) increased (5.5% and 0%, respectively) and aspartate aminotransferase (AST) increased (5.5% and 0%, respectively). A statistically significant difference was observed between the ABT-335 in combination with 40 mg atorvastatin and 40 mg atorvastatin monotherapy groups in the adverse event, oedema peripheral (0% and 6.4%, respectively). Most adverse events were mild or moderate in intensity.

One or more possibly or probably treatment-related adverse events were reported by 12.5% of the ABT-335 monotherapy group; 20.0% and 22.7% of the ABT-335 in combination with 20 mg and 40 mg atorvastatin groups, respectively; and 6.2%, 18.3%, and 21.8% of the 20 mg, 40 mg, and 80 mg atorvastatin monotherapy groups, respectively. Statistically significant differences were observed between ABT-335 in combination with 20 mg atorvastatin and 20 mg atorvastatin monotherapy in the overall incidence of treatment-related adverse events (20.0% and 6.2%, respectively) and the incidence of treatment-related events of ALT increased (4.5% and 0%, respectively) and AST increased (4.5% and 0%, respectively). Across treatment groups, the most frequently reported possibly or probably treatment-related adverse events were myalgia, diarrhea, and nausea.

No subjects died during the conduct of the study. A total of 12 subjects had treatment-emergent serious adverse events: three subjects receiving ABT-335 monotherapy; two subjects each receiving 20 mg atorvastatin monotherapy, 40 mg atorvastatin monotherapy, ABT-335 in combination with 40 mg atorvastatin, and 80 mg atorvastatin monotherapy; and one subject receiving ABT-335 in combination with 20 mg atorvastatin. No serious adverse event was reported by more than one subject.

Safety Results (Continued):

A total of 55 subjects had adverse events that led to discontinuation from the study. Adverse events that led to discontinuation from the study were reported by 7.1% of the ABT-335 monotherapy group; 10.9% and 12.7% of the ABT-335 in combination with 20 mg and 40 mg atorvastatin groups, respectively; and 2.7%, 11.0%, and 10.9% of the 20 mg, 40 mg, and 80 mg atorvastatin monotherapy groups, respectively. A statistically significant difference in the overall incidence of adverse events that led to discontinuation from the study was observed between the ABT-335 in combination with 20 mg atorvastatin and 20 mg atorvastatin monotherapy groups (10.9% and 2.7%, respectively). Overall, the most common adverse events that led to discontinuation were myalgia (nine subjects), nausea (eight subjects), ALT and/or AST increased (seven subjects), and hepatic enzyme increased (six subjects). Higher proportions of subjects in the ABT-335 in combination with 20 mg atorvastatin group discontinued due to ALT increased (3.6%) or AST increased (2.7%) than in the other groups (0% to 1.8%) but, in six of seven subjects, the magnitude of the increase did not meet the criterion for a potentially clinically significant elevation. Hepatic enzyme increased and liver function test abnormal were reasons for discontinuation in the combination therapy groups, with one subject in the 40 mg atorvastatin monotherapy group discontinuing due to the adverse event of hepatic enzyme increased.

Adverse events and laboratory evaluations of special interest included those related to muscle events, renal events, and hepatic events. No cases of rhabdomyolysis were reported. Myalgia was reported in lower proportions of subjects in the combination therapy groups than in the corresponding atorvastatin monotherapy groups (1.8% vs. 4.4% for 20 mg atorvastatin and 4.5% vs. 7.3% for 40 mg atorvastatin. The incidence of myalgia was 2.7% in the ABT-335 monotherapy group and 5.5% in the 80 mg atorvastatin monotherapy group. Nine subjects discontinued study drug due to myalgia, with a higher proportion of discontinuations due to myalgia in the 40 mg atorvastatin monotherapy (2.8%) than in the other groups (0% to 1.8%). One subject each receiving 40 mg and 80 mg atorvastatin monotherapy discontinued study drug due to severe myalgia. Seven subjects (four on ABT-335 in combination with 20 mg atorvastatin, one on 40 mg atorvastatin monotherapy, and two on 80 mg atorvastatin monotherapy) experienced an adverse event of blood creatine phosphokinase (CPK) increased.

No subject receiving ABT-335 monotherapy or combination therapy had a post-baseline CPK > 5 × ULN. Only one subject (20 mg atorvastatin monotherapy) had a CPK > 5 × ULN post-baseline.

Renal events were infrequently reported in all treatment groups and no new safety signals were identified with combination therapy. Events of blood creatinine increased were reported for three subjects on combination therapy and events of creatinine renal clearance decreased were reported for seven subjects (five on combination therapy and one each on ABT-335 and 80 mg atorvastatin monotherapy). No subjects discontinued due to increases in serum creatinine or decreases in calculated creatinine clearance.

ABT-335 monotherapy and combination therapy resulted in greater mean increases from baseline in creatinine and greater mean decreases from baseline in calculated creatinine clearance compared to atorvastatin monotherapy. A total of four subjects had creatinine values > 2.0 mg/dL at any visit (one each on ABT-335 in combination with 20 mg atorvastatin and 80 mg atorvastatin monotherapy and two on ABT-335 in combination with 40 mg atorvastatin); two of these subjects also had creatinine values that increased at least 100% from baseline. Only one subject (ABT-335 in combination with 40 mg atorvastatin) had a calculated creatinine clearance value of < 30 mL/min reported during the study.

Safety Results (Continued):

Compared to the corresponding atorvastatin monotherapy group, the incidence of hepatic events was higher in the ABT-335 in combination with 20 mg (10% vs. 0%, $p < 0.001$) and 40 mg (7.3% vs. 0.9%, $p = 0.035$) groups. In addition, incidence of hepatic events was higher in the ABT-335 in combination with 20 mg atorvastatin group than in the ABT-335 monotherapy group (10% vs. 2.7%, $p = 0.029$). Statistically significant differences were observed between ABT-335 in combination with 20 mg atorvastatin and 20 mg atorvastatin monotherapy in the events of AST increased and ALT increased (5.5% and 0.0%, respectively; $p = 0.013$ for both comparisons).

Seven subjects (one each on ABT-335 monotherapy, ABT-335 in combination with 40 mg atorvastatin, and 80 mg atorvastatin monotherapy; four on ABT-335 in combination with 20 mg atorvastatin) discontinued study drug due to an event of ALT increased and/or AST increased. Of these, four subjects had ALT and/or AST values > 5 × ULN on any occasion and/or > 3 × ULN on two consecutive occasions. Three subjects (two on ABT-335 in combination with 40 mg atorvastatin and one on ABT-335 in combination with 20 mg atorvastatin) discontinued study drug due to the event of liver function test abnormal, one of whom had an ALT > 3 × ULN on two consecutive occasions. Six subjects (three subjects on ABT-335 in combination with 40 mg atorvastatin, two subjects on ABT-335 in combination with 20 mg atorvastatin, and one 40 mg atorvastatin monotherapy) discontinued study drug due to the event of hepatic enzyme increased. Of these, three subjects had ALT and/or AST values > 5 × ULN on any occasion and/or > 3 × ULN on two consecutive occasions.

No subject had an increase in ALT or AST > 10 × ULN or an AST value > 5 × ULN. Seven subjects (four on ABT-335 in combination with 20 mg atorvastatin, two on ABT-335 in combination with 40 mg atorvastatin, and one on 80 mg atorvastatin monotherapy) had post-baseline increases in ALT > 5 × ULN on any single occasion; six of the seven subjects prematurely discontinued study drug due to events of ALT and/or AST increased or hepatic enzyme increased. Two subjects in each combination therapy group and one subject in the 80 mg atorvastatin monotherapy group had increases in ALT to > 3 × ULN on two consecutive visits; one additional subject in each combination therapy group had increases in both ALT and AST to > 3 × ULN on two consecutive visits; all of these subjects prematurely discontinued study drug due to events of ALT and/or AST increased, hepatic enzyme increased, or liver function test abnormal.

Minor mean increases and decreases from baseline in hematology and chemistry parameters were observed in all treatment groups, none of which were clinically meaningful. The majority of subjects had hematology and chemistry values that were within normal range both at baseline and following study drug administration.

Minor mean increases and decreases from baseline in vital sign parameters were observed in all treatment groups, none of which were clinically meaningful. All subjects had ECG results throughout the study that were either normal or abnormal but not clinically significant.

Conclusions:

Both doses of combination therapy were demonstrated to be superior to corresponding monotherapy. For the primary endpoints, ABT-335 in combination with both atorvastatin doses resulted in significantly greater increases in HDL-C and decreases in TG compared to statin monotherapy and significantly greater decreases in LDL-C compared to ABT-335 monotherapy. Results of sensitivity analyses, including a worst-case analysis, were generally consistent with the primary analysis. All primary efficacy analyses, as well as most secondary and exploratory efficacy analyses, demonstrated the efficacy of combination therapy with ABT-335 and 20 mg or 40 mg atorvastatin in reducing CHD lipid risk factors in subjects with mixed dyslipidemia.

ABT-335, administered as monotherapy or as part of combination therapy with atorvastatin, was generally safe and well tolerated in this population of adults with mixed dyslipidemia. Adverse events and laboratory abnormalities were similar between the two doses of combination therapy, with no indication of additional adverse effects with the moderate dose combination relative to the low dose combination. No unexpected hepatic, renal, or muscular safety signals were observed.

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