2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Fenofibric acid (ABT-335, Trilipix™)	**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 ABT-335 in Combination with Atorvastatin and Ezetimibe to Atorvastatin in Combination with Ezetimibe in Subjects with Combined (Atherogenic) Dyslipidemia

Coordinating Investigator: Peter Jones, MD, FACP

Study Sites: Multicenter, 117 sites in the United States screened subjects, with 107 of these sites randomizing subjects.

Publications: None

Studied Period (Years): First Subject First Visit: 12 February 2008 Last Subject Last Visit: 09 October 2008	**Phase of Development:** 3

Objectives: The objective of this study was to evaluate the safety and efficacy of once-daily ABT-335 135 mg when given in combination with ezetimibe 10 mg and atorvastatin 40 mg compared with ezetimibe 10 mg in combination with atorvastatin 40 mg in a population of subjects with combined (atherogenic) dyslipidemia.

Methodology: This Phase 3, multicenter, randomized, double-blind, prospective study was designed to assess the safety and efficacy of once-daily ABT-335 135 mg coadministered with atorvastatin 40 mg and ezetimibe 10 mg treatment compared to atorvastatin 40mg and ezetimibe 10 mg treatment. Subjects were randomized in a double-blind, 1:1 ratio to 1 of 2 treatment regimens, either ABT-335 or placebo. All subjects, regardless of randomized treatment, received atorvastatin and ezetimibe.

The planned duration of the study was approximately 16 weeks, consisting of a 4-week (28-day) diet/lipid-modifying drug washout period (Screening Period) and a 12-week (84-day) Treatment Period. During the Treatment Period, subjects self-administered each study drug orally once daily. Subjects returned to the study site for Interim Visits at Week 4 (Day 29 ± 3 days) and Week 8 (Day 57 ± 3 days), and a Week 12 Final/Discontinuation Visit (Day 85 ± 3 days or earlier for premature discontinuation). During the Safety Follow-up Period, subjects were responsible for notifying the site within 30 days after the last dose of study drug if an adverse event occurred or if pregnancy occurred in the subject or partner.

Methodology (Continued): After 1 or 2 Screening Visits, subjects were randomized to 1 of 2 treatment regimens at the Baseline Visit, and study drug was dispensed. All subjects received an open-label study drug kit (atorvastatin and ezetimibe) and a blinded study bottle (ABT-335 or placebo) and were instructed on when and how to self-administer the study drug. At the Baseline, Interim, and Final Visits, physical examinations were performed (full physical at baseline with symptom-directed exam if indicated at the Interim and Final/Discontinuation Visits), vital signs were measured, routine hematology, serum chemistry, and urinalysis were performed, study drug use was accounted for, new blinded study drug dispensed, dietary compliance, adverse events, pregnancy status, and use of concomitant medications was assessed. Blood samples were collected at Baseline, each Interim Visit, and the Final/Discontinuation Visit for measurements of the primary efficacy parameters of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), secondary parameters of very low-density lipoprotein cholesterol (VLDL-C), non-high-density lipoprotein cholesterol (non–HDL-C), and high sensitivity C-reactive protein (hsCRP), and additional efficacy parameters of low-density lipoprotein cholesterol (LDL-C), and total cholesterol (total-C). At Baseline and Final/Discontinuation Visits, electrocardiogram (ECG) findings were evaluated and blood samples were collected for measurements of apolipoprotein A1 (apoA1), apolipoprotein C3 (apoC3), apolipoprotein B (apoB), exploratory efficacy parameters of nuclear magnetic resonance (NMR) LipoProfile® testing (lipid particle number and size).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 460 subjects (230 subjects in each treatment group)

Randomized: 543 subjects (272 subjects randomized to ABT-335 coadministered with atorvastatin and ezetimibe and 271 subjects randomized to atorvastatin and ezetimibe)

Treated: 542 subjects (272 subjects randomized to ABT-335 coadministered with atorvastatin and ezetimibe and 270 subjects randomized to atorvastatin and ezetimibe)

Diagnosis and Main Criteria for Inclusion: Male and female subjects ≥ 18 years of age with mixed (atherogenic) dyslipidemia, with the following lipid screening values: TG ≥ 150 mg/dL and < 400 mg/dL, HDL-C < 40 mg/dL for males and, < 50 mg/dL for females, and LDL-C ≥ 130 mg/dL. In addition, subjects were willing to observe the diet recommended by the American Heart Association titled "Making Healthy Food and Lifestyle Choices."

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

- ABT-335 (equivalent to 135 mg fenofibric acid) capsules, coadministered with atorvastatin calcium 40 mg tablets and ezetimibe 10 mg tablets, each administered orally, once daily
- ABT-335 placebo capsules, coadministered with atorvastatin calcium 40 mg tablets and ezetimibe 10 mg tablets, each administered orally, once daily

Study Drug	Dosage Form	Lot Number	Finishing Number
ABT-335	135 mg capsule (blinded)	07-012900	08-015526, 08-017665
ABT-335 placebo	matching capsule	06-009790	08-015526, 08-017665
Atorvastatin calcium	40 mg tablet	07-014854, 08-017716	08-014949, 08-017659
Ezetimibe	10 mg tablet	07-014855, 08-017715	08-014949, 08-017659

Duration of Treatment: 12 weeks

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

Atorvastatin calcium (40 mg), administered orally, once daily
Ezetimibe (10 mg), administered orally, once daily
For the respective lot numbers please refer to the table above.

Criteria for Evaluation:

Efficacy: The primary efficacy variables were percent change from baseline to Final Visit in:

1. HDL-C: ABT-335 coadministered with atorvastatin and ezetimibe versus atorvastatin and ezetimibe
2. TG: ABT-335 coadministered with atorvastatin and ezetimibe versus atorvastatin and ezetimibe

The ranked secondary efficacy variables were percent changes from baseline to Final Visit in:

1. apoA1
2. VLDL-C
3. apoC3
4. non–HDL-C
5. apoB
6. hsCRP

Percent changes from baseline to Final Visit in the primary and secondary efficacy variables were summarized and compared between treatment groups by baseline LDL-C (≤ 160 mg/dL, > 160 mg/dL).

Additional efficacy parameters included LDL-C, total-C, NMR LipoProfile parameters, NCEP ATP III LDL-C and non–HDL-C goal attainment, and lipid ratios of TG/HDL-C, non–HDL-C/HDL-C, total-C/HDL-C, and apoB/apoA1.

Safety: Safety assessments included adverse events, physical examinations, chemistry, hematology, and urinalysis laboratory parameters, vital signs, and ECGs.

Statistical Methods

Efficacy: The primary analysis was an analysis of percent change from baseline to Final Visit. For HDL-C, the percent changes from baseline were compared between the 2 treatment arms 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 an effect for treatment group. Model-based 2-sided 95% confidence intervals for the difference between treatment groups were calculated.

For the primary endpoint of TG, a test of normality of the percent changes from baseline to the Final Visit was performed. If the test indicated that the percent changes form baseline were not normally distributed, then the primary comparison between treatment groups of percent changes from baseline to the Final Visit in TG would be performed by using a Wilcoxon rank-sum test. The baseline, Final Visit, and percent change from baseline values would also be summarized with the univariate mean, standard deviation, median midrange, minimum and maximum. If the test for normality indicated that the percent changes from baseline were normally distributed, then an ANCOVA would be used to analyze the percent changes as previously described for HDL-C. Comparisons for both primary endpoints must have demonstrated superiority of ABT-335 coadministered with atorvastatin and ezetimibe therapy to that of atorvastatin and ezetimibe therapy in order to declare ABT-335 coadministered with atorvastatin and ezetimibe therapy successful.

To assess the effect of missing data on the primary efficacy variables, 3 sensitivity analyses were performed. Interim Visit values were carried forward for subjects who were missing the Final Visit value and then a zero change from baseline was imputed for any remaining randomized subjects without a Final Visit value and for subjects without a baseline value. A zero change from baseline was imputed for all randomized subjects who were missing a Final Visit value or a baseline value. Lastly, a worst-case analysis was performed in which the mean percent change of the ABT-335 coadministered with atorvastatin and ezetimibe arm was imputed for subjects with missing values in the atorvastatin and ezetimibe arm and vice versa.

The secondary endpoints were ranked and tested in a fixed sequence. If superiority of ABT-335 coadministered with atorvastatin and ezetimibe therapy was demonstrated for both primary endpoints, the secondary endpoints were tested in order at the alpha = 0.05 level until 1 endpoint failed to reach statistical significance. For all secondary efficacy laboratory parameters other than hsCRP, the percent changes from baseline were analyzed with an ANCOVA with baseline efficacy laboratory values (i.e., efficacy laboratory parameter corresponding to the outcome variable being modeled) as the covariate and with an effect for treatment group. A nonparametric analysis of the percent changes from baseline to Final Visit was performed for hsCRP, comparing treatment groups by using a Wilcoxon rank-sum test.

Safety: Frequencies and percentages of subjects with treatment-emergent adverse events were calculated for each treatment group for all events, for events by system organ class and preferred term, by severity, by relationship, for events that led to death, for serious adverse events, for events that led to study drug discontinuation, and for adverse events of special interest. Percentages for any event and for events by system organ class and by preferred term were compared between treatment groups by using Fisher's exact test. Comparisons were performed for all treatment-emergent events, possibly or probably related events, and adverse events of special interest.

Statistical Methods (Continued):

Safety: For laboratory and vital sign parameters, mean changes from baseline and percentages of subjects with potentially clinically significant values (PCS) were presented and compared between treatment groups. Shift tables for changes from baseline according to the normal range were provided for each laboratory parameter.

Summary/Conclusion: A total of 543 subjects were randomized and 542 subjects received at least 1 dose of study drug (Safety Analysis Set). The Full Analysis set included 524 subjects, 262 subjects from each treatment group, who had a baseline value and at least 1 postbaseline value for at least 1 of 2 primary efficacy variables (HDL-C and TG). The majority of subjects treated in this study were female (55.0%), white (89.3%), and younger than 65 years of age (79.9%). In addition to mixed dyslipidemia, 62.5% of subjects met the criteria for metabolic syndrome, 54.2% of subjects had a history of hypertension, 21.4% of subjects were diabetic, and 19.2% of subjects were reported to have obesity. A total of 40.8% of subjects took 6 or more concomitant medications.

Of 542 treated subjects, 486 subjects completed the study and 56 subjects prematurely discontinued study drug. The most common reasons for premature discontinuation were adverse event (6.1%) and lost to follow-up (2.6%).

Efficacy Results: Statistically significant differences between treatment groups from baseline to Final Visit were observed for the primary efficacy comparisons of HDL-C and TG. As shown below, treatment with ABT-335 coadministered with atorvastatin and ezetimibe resulted in a significantly greater mean percent increase in HDL-C compared to the increase observed with atorvastatin and ezetimibe treatment. In addition, treatment with ABT-335 coadministered with atorvastatin and ezetimibe resulted in a significantly greater median percent decrease in TG compared to atorvastatin and ezetimibe treatment. Treatment with ABT-335 coadministered with atorvastatin and ezetimibe had a superior effect on the primary endpoints of HDL-C and TG. Mean percent increases in HDL-C and median percent decreases in TG levels were observed at Week 4 and were sustained throughout the 12-week Treatment Period. Results of the sensitivity analyses, including a worst-case analysis, were consistent with the results of the primary analysis.

Efficacy Results (Continued):			
Lipid Parameter (mg/dL)	**Atorvastatin/Ezetimibe N = 262**	**ABT-335 /Atorvastatin/Ezetimibe N = 262**	***P* value**
HDL-C			
Baseline mean	40.7	38.9	
Final Visit mean	41.8	43.8	
Mean % Δ	4.2	13.0	< 0.001
Triglycerides			
Baseline median	217.0	225.5	
Final Visit Median	136.0	96.0	
Median % Δ	–39.7	–57.3	< 0.001
Statistically significant differences between treatment groups from baseline to Final Visit were observed for the secondary endpoints. Treatment with ABT-335 coadministered with atorvastatin and ezetimibe resulted in statistically significantly greater improvements in apoA1, VLDL-C, apoC3, non–HDL-C, and apoB. Nonparametric analysis of hsCRP demonstrated that median decreases in hsCRP were also statistically significantly greater following treatment with ABT-335 coadministered with atorvastatin and ezetimibe compared to atorvastatin and ezetimibe treatment. Furthermore, mean percent decreases in VLDL-C and non–HDL-C, and median percent decreases in hsCRP levels were observed at Week 4, and were sustained throughout the 12-week Treatment Period. Therefore, treatment with ABT-335 coadministered with atorvastatin and ezetimibe had a superior effect on secondary endpoints. Results of the secondary analyses are shown below.			

Efficacy Results (Continued):			
Lipid Parameter (mg/dL)	**Atorvastatin/Ezetimibe**	**ABT-335 /Atorvastatin/Ezetimibe**	***P* value**
apoA1	N = 239	N = 248	
Baseline mean	132.1	128.6	
Final visit mean	129.5	130.7	
Mean % Δ	–1.3	1.8	0.004
VLDL-C	N = 262	N = 261	
Baseline mean	52.4	55.1	
Final visit mean	27.5	20.3	
Mean % Δ	–41.1	–57.8	< 0.001
apoC3	N = 242	N = 249	
Baseline mean	16.1	16.5	
Final visit mean	11.8	9.2	
Mean % Δ	–25.3	–42.5	< 0.001
non–HDL-C	N = 262	N = 262	
Baseline mean	205.4	208.1	
Final visit mean	99.6	90.6	
Mean % Δ	–51.0	–55.6	< 0.001
apoB	N = 239	N = 248	
Baseline mean	131.3	131.4	
Final visit mean	72.0	66.0	
Mean % Δ	–44.7	–49.1	< 0.001
hsCRP	N = 262	N = 261	
Baseline median	0.34	0.29	
Final visit median	0.19	0.14	
Median % Δ	–40.3	–52.1	< 0.001

Efficacy Results (Continued):

Both treatment regimens resulted in clinically significant decreases in LDL-C, 52.9% for subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe and 52.0 % for subjects treated with atorvastatin and ezetimibe. A statistically significant difference between treatment groups in percent change from baseline to Final Visit in total-C was observed at Week 12, favoring subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe. Mean percent decreases in LDL-C and total-C were observed at Week 4 and were sustained throughout the 12-week Treatment Period.

The benefits of ABT-335 coadministered with atorvastatin and ezetimibe therapy are supported by analyses of the ratios of atherogenic to non-atherogenic particles. Statistically significant greater decreases in the ratios of TG/HDL-C, apoB/apo A1, total-C/HDL-C, and non–HDL-C/HDL-C were observed after treatment with ABT-335 coadministered with atorvastatin and ezetimibe.

The positive effects of therapy with ABT-335 coadministered with atorvastatin and ezetimibe were reinforced by favorable effects on HDL particle number (HDL-P) and VLDL particle number (VLDL-P). In contrast, treatment with atorvastatin and ezetimibe resulted in statistically significantly greater decreases in LDL-P. A statistically significant difference in mean percent change in HDL particle size was observed between treatment groups; a slight decrease was observed in subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe versus an increase in subjects treated with atorvastatin and ezetimibe. In addition, the percentage of subjects with the number of LDL particles that shifted from small (more atherogenic) to large (less atherogenic) increased with both treatments from baseline to Final Visit.

The majority of subjects in both treatment groups achieved the NCEP ATP III LDL-C and non–HDL-C goals. Overall a slightly greater percentage of subjects in the ABT-335 coadministered with atorvastatin and ezetimibe treatment group achieved the LDL-C and non–HDL-C goals, with greater differences between treatment groups observed in the high-risk (subjects with coronary heart disease or risk equivalents) and moderate-risk (≥ 2 risk factors) categories. Within the low-risk (0 to 1 risk factor) category, similar or slightly smaller percentages of subjects achieved the LDL-C and non–HDL-C goals in the ABT-335 coadministered with atorvastatin and ezetimibe treatment group.

When comparisons between treatment groups were performed within subgroups by baseline LDL-C concentration (≤ 160 mg/dL or > 160 mg/dL), statistically significantly greater improvements in HDL-C and TG from baseline to Final Visit were observed with ABT-335 coadministered with atorvastatin and ezetimibe treatment in both subgroups. Regardless of LDL-C subgroup, statistically significantly greater mean percent decreases in VLDL-C, apoC3, and non–HDL-C and median percent decreases in hsCRP were observed in subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe. For apoA1, within the baseline LDL-C ≤ 160 mg/dL subgroup, the mean percent change from baseline was statistically significantly different between treatment groups with a mean percent increase observed for subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe. For apoB, within the baseline LDL-C > 160 mg/dL subgroup, a statistically significantly greater mean percent decrease was observed with ABT-335 coadministered with atorvastatin and ezetimibe.

Safety Results:

All treatments were generally well tolerated. The adverse event profiles of the treatment groups were consistent with the known or expected safety profiles of each individual drug. The overall incidence of treatment-emergent adverse events was 50.7% in both treatment groups. Overall, the most frequently reported adverse events (≥ 3.0% in either treatment group) were muscle spasms, myalgia, arthralgia, fatigue, diarrhea, headache, and nausea. There were no statistically significant differences in adverse events between treatment groups in the incidence of any specific adverse event preferred term.

Most adverse events were mild or moderate in intensity. Severe events were reported in a total of 26 subjects: 12 subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe and 14 subjects treated with atorvastatin and ezetimibe. One or more possibly or probably treatment-related adverse events were reported for 19.1% of subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe and 16.7% of subjects treated with atorvastatin and ezetimibe. There were no statistically significant differences between treatment groups in the incidence of possibly or probably treatment-related adverse events.

Treatment-emergent serious adverse events were reported in 8 subjects: 3 subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe and 5 subjects treated with atorvastatin and ezetimibe. There were no deaths in this study.

A total of 33 subjects had 1 or more adverse events that led to discontinuation: 16 subjects from the ABT-335 coadministered with atorvastatin and ezetimibe group and 17 subjects from the atorvastatin and ezetimibe group. Myalgia was the most common adverse event that led to discontinuation, reported for 7 subjects.

Adverse events of special interest included muscle events, renal events, and hepatic events. No cases of rhabdomyolysis were reported. Moreover, no new safety signals were identified in either treatment group. Adverse events of special interest were reported for 48 subjects: 26 subjects (9.6%) treated with ABT-335 coadministered with atorvastatin and ezetimibe and 22 subjects (8.1%) treated with atorvastatin and ezetimibe. Of these adverse events of special interest, there were 29 subjects with reported muscle-related adverse events, 7 subjects with reported renal-related adverse events, and 17 subjects with reported hepatic-related adverse events. Myalgia was the most commonly reported adverse event of special interest reported for 17 subjects, 7 subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe and 10 subjects treated with atorvastatin and ezetimibe. There were no statistically significant differences between treatment groups for adverse events of special interest.

Sixteen subjects met the postbaseline criteria for having 1 or more PCS laboratory values. The most common parameter to meet PCS criteria was ALT (≥ 200 U/L) noted in 6 subjects (4 subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe and 2 subjects treated with atorvastatin and ezetimibe). Two subjects with an increase in ALT that were treated with ABT-335 coadministered with atorvastatin and ezetimibe also had an increase in AST. Potentially clinically significant increases in blood CK were reported in 3 subjects. All elevated values occurred on posttreatment Day 1.

Safety Results (Continued):

One subject in the atorvastatin and ezetimibe treatment group had a postbaseline CK value > 10 × ULN that occurred 1 day after the last dose of study drug. Three subjects had a postbaseline CK value > 5 × ULN: 1 subject treated with ABT-335 coadministered with atorvastatin and ezetimibe and 2 subjects treated with atorvastatin and ezetimibe. All elevated values occurred on posttreatment Day 1. No subject with elevations in CK > 5 × or 10 × ULN prematurely discontinued the study.

Three subjects had postbaseline creatinine values that were either > 2.0 mg/dL or increased ≥ 100% from baseline values. Two subjects had elevations in creatinine > 2.0 mg/dL during the study that occurred after they prematurely discontinued treatment following an adverse event other than creatinine increased. Both subjects prematurely discontinued treatment. Two subjects had a creatinine value that increased ≥ 100% from baseline during the Treatment Period, including 1 subject with a creatinine value > 2.0mg/dL. Postbaseline creatinine values remained elevated from baseline for 2 subjects.

No subject had postbaseline ALT or AST levels > 10 × ULN. Six subjects had ALT and/or AST > 5 × ULN. With the exception of 1 subject, these subjects were treated with ABT-335 coadministered with atorvastatin and ezetimibe. In 5 of the 6 subjects, ALT and/or AST > 5 × ULN improved by the time of final measurement. The remaining subject did not have any additional ALT or AST measurements after the ALT value > 5 × ULN was obtained. Two subjects with ALT and/or AST > 5 × ULN prematurely discontinued treatment.

Minor mean increases and decreases from baseline in hematology, chemistry, and urinalysis parameters were observed in both treatment groups at each visit. The majority of subjects had hematology, chemistry, and urinalysis parameters 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 both treatment groups, none of which were clinically meaningful. Potentially clinically significant blood pressure values were observed postbaseline in 2 subjects treated with atorvastatin and ezetimibe for both systolic blood pressure and diastolic blood pressure. Potentially clinically significant low pulse rates were also reported for 2 subjects treated with ABT-335 coadministered with atorvastatin and ezetimibe and 6 subjects treated with atorvastatin and ezetimibe.

There were 3 subjects with clinically significant ECG findings, 1 in a subject who withdrew before treatment began, 1 in a subject who was lost to follow-up within the first 15 days of study drug treatment, and 1 in a subject who completed the study.

Conclusions: Treatment with 135 mg coadministered with atorvastatin 40 mg and ezetimibe 10 mg demonstrated efficacy that was superior to corresponding treatment with atorvastatin 40 mg and ezetimibe 10 mg. For the primary efficacy endpoints, statistically significant differences between treatment groups from baseline to Final Visit were observed for the primary efficacy comparisons, HDL-C and TG. Mean percent increases in HDL-C and median percent decreases in TG levels were observed at Week 4, and were sustained throughout the 12-week Treatment Period. In addition, 3 sensitivity analyses, demonstrated statistically significantly greater improvements in HDL-C and TG in the ABT-335 coadministered with atorvastatin and ezetimibe treatment group. Statistically significant differences between treatment groups from baseline to Final Visit were also observed for the secondary endpoints of apoA1, VLDL-C, apoC3, non–HDL-C, apoB, and hsCRP and many exploratory efficacy endpoints.

ABT-335 coadministered with atorvastatin and ezetimibe was generally well tolerated in the study population of adults with mixed dyslipidemia. Adverse events and laboratory abnormalities were similar between treatment groups. No unexpected muscle, renal, or hepatic safety signals were observed. No reported events of rhabdomyolysis were identified.