CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-224

STATISTICAL REVIEW(S)

10/10/08

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22224/N_000
Drug Name:	Trilipix (Choline fenofibrate capsules)
Intended Indication(s):	Dyslipidemia (primary hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia)
Applicant:	Abbott Laboratories
Submission Date(s):	Submitted 12-07-07
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Keywords: Clinical studies, NDA review, interaction

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1. EXECUTIVE SUMMARY

Efficacy and safety of ABT-335 have been assessed in three double-blind, controlled Phase 3 studies (M05-748, M05-749, and M05-750) and one long-term, open-label extension study (M05-758). The three double-blind studies had similar designs, differing primarily in the statin used for combination therapy/monotherapy, some excluded concomitant medications, and the number of subjects. All were multicenter, randomized, double-blind, prospective, comparative studies in mixed dyslipidemic adults (Fredrickson Type IIb) conducted at sites in the United States, Canada, and Puerto Rico. All studies assessed the efficacy and safety of once daily treatment with ABT-335 (equivalent to 135 mg fenofibric acid) in combination with either a low or a moderate dose of a statin compared to ABT-335 monotherapy and statin monotherapy on the primary lipid parameters associated with increased risk of CHD in a population of subjects with mixed dyslipidemia. The statins in the three Phase 3 studies were rosuvastatin calcium (equivalent to 10 mg, 20 mg, and 40 mg rosuvastatin) in Study M05-748, simvastatin (20 mg, 40 mg, and 80 mg) in Study M05-749, and atorvastatin calcium (equivalent to 20 mg, 40 mg, and 80 mg atorvastatin) in Study M05-750. The numbers of patients treated were, respectively, 1439, 650, and 609.

A list of abbreviation and definition of terms has been provided in the sNDA and is reproduced in this document as Appendix I.

Note: New Drug Application is abbreviated by NDA. Tables and Figures presented in this document are referenced by "below" or "above". Those referenced with an extended numbering system are in the NDA Study Report.

1.1 Conclusions and Recommendations

The three studies have provided significant p-values for the pre-planned primary comparisons:
. TG: statin in combination with ABT-335 vs. statin monotherapy (low or medium dose of statin).
. HDL-C: statin in combination with ABT-335 vs.statin monotherapy(low or medium dose of statin) .
. Direct LDL-C: rosuvastatin calcium in combination with ABT-335 vs. ABT-335 monotherapy.

There was a statistically significant quantitative treatment by gender interaction; there was no lack of benefit in any subgroups. The significant gender-by-treatment interaction for HDL ($p<.001$) reflects that fact that, comparing combination therapy to statin monotherapy (measuring the additional benefit of ABT-335 on HDL), females had significantly greater HDL increases than did males. For LDL and non-HDL, in each treatment arm, females did better (that is, greater LDL and non-HDL lowering) than males. However, when we look at the superiority of

the combination to ABT-335 monotherapy, this superiority (of the combination to monotherapy) is bigger for males than for females (in the cases of LDL and non-HDL).

Labeling

Because of the fixed-sequence rule of multiple comparisons pre-specified by the sponsor, the medium dose combination is superior to ABT-335 monotherapy only with respect to Non HDL-C. Nothing else can be claimed for the medium dose combination with respect to pre-specified secondary efficacy variables.

The pre-specified comparisons for the low dose combination produced significant p-values with respect to all pre-specified secondary efficacy variables.

§ Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C with Combination Therapy in Studies M05-748, M05-749, and M05-750

	M05-748		M05-749		M05-750	
	ABT-335 + 10 mg rosuva	ABT-335 + 20 mg rosuva	ABT-335 + 20 mg simva	ABT-335 + 40 mg simva	ABT-335 + 20 mg atorva	ABT-335 + 40 mg atorva
HDL-C						
Mean % Δ	20.3%	19.0%	17.8%	18.9%	13.9%	12.5%
TG						
Mean % Δ	-47.1%	-42.9%	-37.4%	-42.7%	-43.8%	-40.0%
LDL-C						
Mean % Δ	-37.2%	-38.8%	-24.0%	-25.3%	-33.8%	-35.5%

1.2 Brief Overview of Clinical Studies

Tabular Listing of Clinical Studies:

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M05-748	5.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and rosuvastatin monotherapy with ABT-335 and rosuvastatin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 10 mg rosuvastatin, 20 mg rosuvastatin, 40 mg rosuvastatin, 135 mg ABT-335 + 10 mg rosuvastatin or ABT-335 + 20 mg rosuvastatin	1445	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full
Phase 3 Efficacy and Safety	M05-749	5.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and simvastatin monotherapy with ABT-335 and simvastatin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 20 mg simvastatin, 40 mg simvastatin, 80 mg simvastatin, 135 mg ABT-335 + 20 mg simvastatin or ABT-335 + 40 mg simvastatin	657	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full
Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M05-750	5.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and rosuvastatin monotherapy with ABT-335 and rosuvastatin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 20 mg atorvastatin, 40 mg atorvastatin, 80 mg atorvastatin, 135 mg ABT-335 + 20 mg atorvastatin or ABT-335 + 40 mg atorvastatin	613	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full
Phase 3 Efficacy and Safety	M05-758	5.3.5.2	Long Term Safety and Efficacy	Open-label	Once daily oral doses of: 135 mg ABT-335 + statin (20 mg atorvastatin or 40 mg simvastatin or 40 mg rosuvastatin)	1911	Patients with mixed dyslipidemia (Fredrickson Type IIb)	52 weeks	Ongoing; interim report with 9/1/2009 data cut-off utilized for the NDA submission

Planned enrollment in Study M05-748 was approximately 1,250 subjects at approximately 250 sites; planned enrollment in Study M05-749 and Study M05-750 was approximately 560 subjects at approximately 115 sites in each study. Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio (planned number of subjects for the first five treatment groups was double the planned

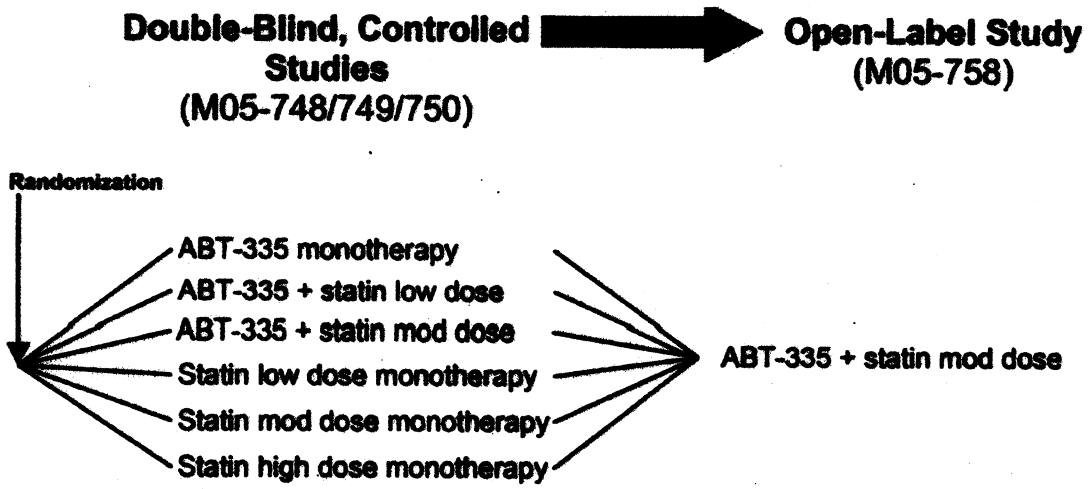
number of subjects for the high-dose statin monotherapy group) to one of the six once daily treatment regimens, as shown in Table below.

M05-748	M05-749	M05-750
135 mg ABT-335 monotherapy	135 mg ABT-335 monotherapy	135 mg ABT-335 monotherapy
10 mg rosuvastatin monotherapy	20 mg simvastatin monotherapy	20 mg atorvastatin monotherapy
135 mg ABT-335 in combination with 10 mg rosuvastatin	135 mg ABT-335 in combination with 20 mg simvastatin	135 mg ABT-335 in combination with 20 mg atorvastatin
20 mg rosuvastatin monotherapy	40 mg simvastatin monotherapy	40 mg atorvastatin monotherapy
135 mg ABT-335 in combination with 20 mg rosuvastatin	135 mg ABT-335 in combination with 40 mg simvastatin	135 mg ABT-335 in combination with 40 mg atorvastatin
40 mg rosuvastatin monotherapy	80 mg simvastatin monotherapy	80 mg atorvastatin monotherapy

The planned duration of each double-blind 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 (only if not entering the open-label safety extension study). Subjects who completed the Treatment Period of each double-blind study were eligible to participate in a one-year, open-label safety extension study (M05-758).

Subjects entered the open-label safety extension (M05-758) after completing one of the three double-blind, controlled studies (M05-748, M05-749, or M05-750); subjects who prematurely terminated from the efficacy trials were ineligible to participate in Study M05-758. The first visit of the safety extension study (Baseline Visit) corresponded to the Final Visit of the preceding double-blind, controlled study. If a subject chose not to enroll into the open-label safety extension study at the last visit of the double-blind study, the subject was allowed to subsequently enroll into the open-label safety extension study up to seven days after the Final Visit of the preceding study.

Subject Enrollment into Study M05-758



1.3 Statistical Issues and Findings

This reviewer's analyses and the many analyses of the sponsor have provided significant p-values for the pre-planned primary comparisons:

. TG: statin in combination with ABT-335 vs. statin monotherapy (low or medium dose of statin).
. HDL-C: statin in combination with ABT-335 vs.statin monotherapy(low or medium dose of statin) .
. Direct LDL-C: rosuvastatin calcium in combination with ABT-335 vs. ABT-335 monotherapy.

There was a statistically significant quantitative treatment by gender interaction; there was no lack of benefit in any subgroups. The significant gender-by-treatment interaction for HDL ($p<.001$) reflects that fact that, comparing combination therapy to statin monotherapy (measuring the additional benefit of ABT-335 on HDL), females had significantly greater HDL increases than did males. For LDL and non-HDL, in each treatment arm, females did better (that is, greater LDL and non-HDL lowering) than males. However, when we look at the superiority of the combination to ABT-335 monotherapy, this superiority (of the combination to monotherapy) is bigger for males than for females (in the cases of LDL and non-HDL).

The beneficial treatment effect of combination therapy was generally greater in subjects ≥ 65 years of age than in subjects < 65 years of age. Combination therapy resulted in even greater mean percent decreases in TG among subjects with baseline TG > 200 mg/dL than among subjects with baseline TG ≤ 200 mg/dL and in even greater mean percent decreases in LDL-C

among subjects with baseline LDL-C > 160 mg/dL than among subjects with baseline LDL-C ≤160 mg/dL.

Some non-crucial observations:

This reviewer's nonparametric analyses for Study 749, produced non-significant p-values for HDL-C at Week 4 for medium dose comparison.

There was a similar lack of robustness for the low dose comparison at earlier weeks for HDL-C in Study 750.

2. INTRODUCTION

2.1 Overview

PROPOSED INDICATIONS AND USAGE

Co-administration Therapy with Statins for the Treatment of Mixed/Atherogenic Dyslipidemia

Co-administration therapy with TRADE NAME and HMG-CoA reductase inhibitors (statins) is indicated as adjunctive therapy to diet for the reduction of elevated triglycerides, LDL-C, non-HDL-C, VLDL-C, Apo B, and Total-C, and to increase HDL-C in adult patients with mixed/atherogenic dyslipidemia (Fredrickson Type IIb) when combination therapy is appropriate.

Treatment of Primary Hypercholesterolemia or Mixed Dyslipidemia

TRADE NAME is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, triglycerides, and Apo B, and to increase HDL-C in adults with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb).

Treatment of Hypertriglyceridemia

TRADE NAME is indicated as adjunctive therapy to diet for treatment of adults with hypertriglyceridemia (Fredrickson Types IV and V). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention. Markedly elevated

levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRADE NAME therapy on reducing this risk has not been adequately studied.

Tabular Listing of Clinical Studies

Study ID/ No. of Centers/ Locations/ Duration	Study Dates/ Study Status/ Total Enrollment	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Treated/ Completed	Gender M/F Median Age (Range)	Key Eligibility Criteria	Primary Endpoints
M05-748/ 205 sites/ US, Canada, Puerto Rico/ 22 weeks (12 weeks of treatment)	21 Mar 2006 to 14 Dec 2006/ completed/ 1445 randomized; 1439 treated	Randomized, double-blind, prospective, comparative	Once daily oral doses of: 135 mg ABT-335 10 mg rosuvastatin 135 mg ABT-335 + 10 mg rosuva 20 mg rosuvastatin 135 mg ABT-335 + 20 mg rosuva 40 mg rosuvastatin	To evaluate and compare the effects of once daily ABT-335 monotherapy and rosuvastatin monotherapy with ABT-335 and rosuvastatin combination therapy on CHD lipid risk factors in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb)	ABT-335: 250 / 208 10 mg rosuva: 261 / 237 ABT-335 + 10 mg rosuva: 261 / 220 20 mg rosuva: 266 / 243 ABT-335 + 20 mg rosuva: 261 / 220 40 mg rosuva: 131 / 115	689M/750F 55.0 years (20-83 years)	Males & females ≥ 18 years old, with mixed dyslipidemia (Frederickson Type IIb), screening TG ≥ 150 mg/dL, HDL-C < 40 mg/dL for men and < 50 mg/dL for women, and LDL-C ≥ 130 mg/dL, willing to follow AHA diet; subjects of Asian ancestry were excluded	Mean percent change from baseline to Final Visit in HDL-C and TG (combination therapy vs. rosuvastatin monotherapy) and in LDL-C (combination therapy vs. ABT-335 monotherapy)

atorva = atorvastatin; CHD = coronary heart disease; M = male(s); F = female(s); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; rosuva = rosuvastatin; simva = simvastatin; TG = triglycerides

Study ID/ No. of Centers/ Locations/ Duration	Study Dates/ Study Status/ Total Enrollment	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Treated/ Completed	Gender M/F Median Age (Range)	Key Eligibility Criteria	Primary Endpoints
M05-749/ 121 sites/ US, Canada, Puerto Rico/ 22 weeks (12 weeks of treatment)	27 Mar 2006 to 05 Mar 2007/ completed/ 657 randomized; 650 treated	Randomized, double-blind, prospective, comparative	Once daily oral doses of: 135 mg ABT-335 20 mg simvastatin 135 mg ABT-335 + 20 mg simva 40 mg simvastatin 135 mg ABT-335 + 40 mg simva 80 mg simvastatin	To evaluate and compare the effects of once daily ABT-335 monotherapy and simvastatin monotherapy with ABT-335 and simvastatin combination therapy on CHD lipid risk factors in subjects with mixed dyslipidemia (Fredrickson Type IIb)	ABT-335: 119 / 98 20 mg simva: 119 / 105 ABT-335 + 20 mg simva: 119 / 103 40 mg simva: 116 / 99 ABT-335 + 40 mg simva: 118 / 102 80 mg simva: 50 / 48	318M/332F 55 years (24-82 years)	Males & females ≥ 18 years old, with mixed dyslipidemia (Fredrickson Type IIb), screening TG ≥ 150 mg/dL, HDL-C < 40 mg/dL for men and < 50 mg/dL for women, and LDL-C ≥ 130 mg/dL, willing to follow AHA diet; subjects taking macrolide/ lincolide antibiotics, azole antifungals, HIV protease inhibitors, nefazodone, danazol, amiodarone, verapamil, or > one quart daily of grapefruit juice were excluded	Mean percent change from baseline to Final Visit in HDL-C and TG (combination therapy vs. simvastatin monotherapy) and in LDL-C (combination therapy vs. ABT-335 monotherapy)

atorva = atorvastatin; CHD = coronary heart disease; M = male(s); F = female(s); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; rosuva = rosuvastatin; simva = simvastatin; TG = triglycerides

Study ID/ No. of Centers/ Locations/ Duration	Study Dates/ Study Status/ Total Enrollment	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Treated/ Completed	Gender M/F Median Age (Range)	Key Eligibility Criteria	Primary Endpoints
M05-750/ 101 sites/ US, Canada, Puerto Rico/ 22 weeks (12 weeks of treatment)	22 Mar 2006 to 08 Feb 2007/ completed/ 613 randomized: 609 treated	Randomized, double-blind, prospective, comparative	Once daily oral doses of: 135 mg ABT-335 20 mg atorvastatin 135 mg ABT-335 + 20 mg atorva 40 mg atorvastatin 135 mg ABT-335 + 40 mg atorva 80 mg atorvastatin	To evaluate and compare the effects of once daily ABT-335 monotherapy and atorvastatin monotherapy with ABT-335 and atorvastatin combination therapy on CHD lipid risk factors in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb)	ABT-335: 112 / 95 20 mg atorva: 113 / 104 ABT-335 + 20 mg atorva: 110 / 89 40 mg atorva: 109 / 95 ABT-335 + 40 mg atorva: 110 / 89 80 mg atorva: 55 / 46	298M/311F 55.0 years (18-82 years)	Males & females ≥ 18 years old, with mixed dyslipidemia (Fredrickson Type IIb), screening TG ≥ 150 mg/dL, HDL-C < 40 mg/dL for men and < 50 mg/dL for women, and LDL-C ≥ 130 mg/dL, willing to follow AHA diet; subjects taking macrolide or ketolide antibiotics or azole antifungals were excluded	Mean percent change from baseline to Final Visit in HDL-C and TG (combination therapy vs. atorvastatin monotherapy) and in LDL-C (combination therapy vs. ABT-335 monotherapy)

atorva = atorvastatin; CHD = coronary heart disease; M = male(s); F = female(s); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; rosuva = rosuvastatin; simva = simvastatin; TG = triglycerides

Study ID/ No. of Centers/ Locations/ Duration	Study Dates/ Study Status/ Total Enrollment	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Treated/ Completed	Gender M/F Median Age (Range)	Key Eligibility Criteria	Primary Endpoints
M05-758/ 380 sites/ US, Canada, Puerto Rico/ 52 weeks of treatment	Ongoing 1911 enrolled; 1895 treated	Open-label, multicenter, prospective	Once daily oral doses of: 135 mg ABT-335 + 20 mg rosuva 135 mg ABT-335 + 40 mg simva 135 mg ABT-335 + 40 mg atorva	To assess the long-term safety and efficacy of (open-label) 135 mg ABT-335 in combination with (open-label) 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin in subjects with mixed dyslipidemia (Fredrickson Type IIb)	135 mg ABT-335 + 20 mg rosuva 1029/ongoing 135 mg ABT-335 + 40 mg simva 432/ongoing 135 mg ABT-335 + 40 mg atorva 434/ongoing	388M/521F 55.0 years (20-83 years) 210M/216F 54.0 years (24-82 years) 221M/213F 55.0 years (18-80 years)	Subject successfully completed M05-748, M05-749, or M05-750 and agreed to enroll in M05-758	Mean percent change from baseline to Final Visit in HDL-C and TG (combination therapy vs. statin monotherapy) and in LDL-C (combination therapy vs. ABT-335 monotherapy)

atorva = atorvastatin; CHD = coronary heart disease; M = male(s); F = female(s); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; rosuva = rosuvastatin; simva = simvastatin; TG = triglycerides

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Planned enrollment in Study M05-748 was approximately 1,250 subjects at approximately 250 sites; planned enrollment in Study M05-749 and Study M05-750 was approximately 560 subjects at approximately 115 sites in each study. Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio (planned number of subjects for the first five treatment groups was double the planned

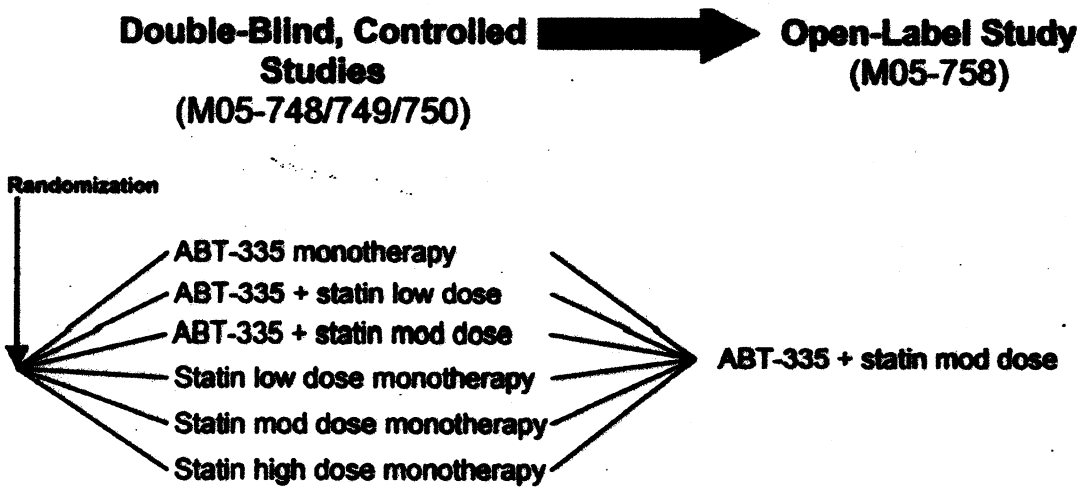
number of subjects for the high-dose statin monotherapy group) to one of the six once daily treatment regimens, as shown in Table below.

M05-748	M05-749	M05-750
135 mg ABT-335 monotherapy	135 mg ABT-335 monotherapy	135 mg ABT-335 monotherapy
10 mg rosuvastatin monotherapy	20 mg simvastatin monotherapy	20 mg atorvastatin monotherapy
135 mg ABT-335 in combination with 10 mg rosuvastatin	135 mg ABT-335 in combination with 20 mg simvastatin	135 mg ABT-335 in combination with 20 mg atorvastatin
20 mg rosuvastatin monotherapy	40 mg simvastatin monotherapy	40 mg atorvastatin monotherapy
135 mg ABT-335 in combination with 20 mg rosuvastatin	135 mg ABT-335 in combination with 40 mg simvastatin	135 mg ABT-335 in combination with 40 mg atorvastatin
40 mg rosuvastatin monotherapy	80 mg simvastatin monotherapy	80 mg atorvastatin monotherapy

The planned duration of each double-blind 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 (only if not entering the open-label safety extension study). Subjects who completed the Treatment Period of each double-blind study were eligible to participate in a one-year, open-label safety extension study (M05-758).

Subjects entered the open-label safety extension (M05-758) after completing one of the three double-blind, controlled studies (M05-748, M05-749, or M05-750); subjects who prematurely terminated from the efficacy trials were ineligible to participate in Study M05-758. The first visit of the safety extension study (Baseline Visit) corresponded to the Final Visit of the preceding double-blind, controlled study. If a subject chose not to enroll into the open-label safety extension study at the last visit of the double-blind study, the subject was allowed to subsequently enroll into the open-label safety extension study up to seven days after the Final Visit of the preceding study.

Subject Enrollment into Study M05-758



The open-label safety extension study, Study M05-758, was designed to assess the safety and efficacy of once daily 135 mg ABT-335 in combination with either 20 mg rosuvastatin once daily, 40 mg simvastatin once daily, or 40 mg atorvastatin once daily. As presented in Figure 1, all subjects received ABT-335 in combination with moderate dose statin, regardless of the treatment received in the double-blind, controlled study; the statin taken by subjects was the same as that used in the double-blind, controlled study in which they were enrolled. That is, subjects entering from Study M05-748 received ABT-335 in combination with rosuvastatin, subjects entering from Study M05-749 received ABT-335 in combination with simvastatin, and subjects entering from Study M05-750 received ABT-335 in combination with atorvastatin. The planned duration of the long-term safety study was 52 weeks (12 months) of therapy with a 1-month Safety Follow-up Period. Interim visits occurred every four weeks for the first 16 weeks and then every 12 weeks for the remainder of the Treatment Period.

Abbott has developed an oral formulation of ABT-335, the choline salt of fenofibric acid (choline fenofibrate), for the treatment of dyslipidemia. Fenofibric acid is the active metabolite of fenofibrate, the active ingredient in currently marketed TriCor® tablets (NDA 21-656). Choline fenofibrate capsules are intended for oral use, and consist of gelatin capsule shells filled with enteric-coated minitablets. Two strengths of choline fenofibrate capsules have been developed and are proposed for commercial distribution: a 135 mg capsule, and a 45 mg capsule.

Pharmacological Class / Mode of Action

Numerous clinical studies have demonstrated that the administration of fenofibrate produces reductions in total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-C), and elevations in high-density lipoprotein cholesterol (HDL-C). However, because fenofibrate is rapidly converted to fenofibric acid in vivo, it is fenofibric acid, not fenofibrate, that is found circulating in plasma and is responsible for the clinical effect. Fenofibric acid is the active moiety of choline fenofibrate.

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained by activation of peroxisome proliferators activated receptor a(PPARa). Through this mechanism, fenofibric acid increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apolipoprotein CIII (an inhibitor of lipoprotein lipase activity). This results in a decrease in serum TG and an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to larger, more buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARa also induces an increase in the synthesis of HDL-C and apolipoproteins AI and AII.

Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C in Study M05-748

	ABT-335	ABT-335 + 10 mg rosuva	ABT-335 + 10 mg rosuva	p-value	ABT-335 + 20 mg rosuva	ABT-335 + 20 mg rosuva	p-value	40 mg rosuva
HDL-C								
BL mean	38.5	38.2	38.5		38.5	38.0		37.4
Final mean	43.9	41.0	45.7		41.6	44.9		40.6
Mean % Δ	15.0%	8.5%	20.3%	< 0.001[a]	10.3%	19.0%	< 0.001[a]	9.3%
TG								
BL mean	267.4	295.9	282.8		292.8	292.9		284.5
Final mean	167.9	202.6	141.6		196.1	145.9		177.1
Mean % Δ	-32.6%	-24.4%	-47.1%	< 0.001[a]	-25.6%	-42.9%	< 0.001[a]	-32.1%
LDL-C								
BL mean	155.8	152.2	152.7		154.4	155.5		153.5
Final mean	142.3	93.8	94.8		83.1	91.8		74.6
Mean % Δ	-6.5%	-38.0%	-37.2%	< 0.001[b]	-45.0%	-38.8%	< 0.001[b]	-50.6%

a. ABT-335 in combination with statin vs. corresponding statin monotherapy

b. ABT-335 in combination with statin vs. ABT-335 monotherapy

Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C in Study M05-749

	ABT-335	20 mg simva	ABT-335 + 20 mg simva	p-value	40 mg simva	ABT-335 + 40 mg simva	p-value	80 mg simva
HDL-C								
BL mean	38.2	38.4	37.2		38.5	38.5		39.5
Final mean	44.1	40.8	43.9		41.3	45.0		41.5
Mean % Δ	16.2%	7.2%	17.8%	< 0.001[a]	8.5%	18.9%	< 0.001[a]	6.8%
TG								
BL mean	300.9	281.2	295.6		284.4	274.1		257.4
Final mean	181.4	223.1	164.4		202.3	147.0		192.9
Mean % Δ	-31.7%	-14.2%	-37.4%	< 0.001[a]	-22.4%	-42.7%	< 0.001[a]	-20.2%
LDL-C								
BL mean	156.5	153.2	157.9		163.3	155.9		155.4
Final mean	147.1	117.5	116.6		108.1	113.3		92.7
Mean % Δ	-4.0%	-22.4%	-24.0%	< 0.001[b]	-31.7%	-25.3%	< 0.001[b]	-40.8%

a. ABT-335 in combination with statin vs. corresponding statin monotherapy

b. ABT-335 in combination with statin vs. ABT-335 monotherapy

Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C in Study M05-750

	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
Final mean	45.5	40.3	43.8		39.8	42.3		39.9
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
Final mean	191.5	243.4	137.2		216.5	149.0		197.2
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
Final mean	153.2	96.8	102.1		94.0	99.7		85.8
Mean % Δ	-3.5%	-37.5%	-33.8%	< 0.001[b]	-39.8%	-35.5%	< 0.001[b]	-46.0%

a. ABT-335 in combination with statin vs. corresponding statin monotherapy

b. ABT-335 in combination with statin vs. ABT-335 monotherapy

Sponsor's Efficacy Conclusions:

". ABT-335 in combination with statins resulted in comprehensive clinically meaningful improvements in all three primary lipid parameters that are independently associated with

CHD risk – high LDL-C, high TG, and low HDL-C - and that occur simultaneously in patients with mixed dyslipidemia.

. ABT-335 in combination with low-dose statins and moderate-dose statins resulted in statistically significant improvements in all three primary lipid parameters compared to the appropriate monotherapy in all three double-blind, controlled studies; all studies demonstrated the superiority of combination therapy over monotherapy based on the prespecified primary analyses.

. Compared to statin monotherapy, combination therapy resulted in a more comprehensive improvement in multiple lipid parameters, including HDL-C, TG, non-HDL-C, VLDL-C, total-C, and ApoB, demonstrating a positive impact on overall atherogenicity.

. After 12 weeks of treatment with ABT-335 in combination with both low-dose statins and moderate-dose statins, lipid levels were at or within recommended optimal treatment targets for patients at high risk for CHD.

. After 12 weeks of treatment, levels for LDL-C and secondary efficacy parameters were generally lower following treatment with ABT-335 in combination with moderate-dose statins than with ABT-335 in combination with low-dose statins, although the differences were modest. In addition, subjects initially on the low-dose statin combination in the double-blind controlled studies who changed to the moderate-dose combination in the long-term extension study had clinically meaningful improvements in LDL-C, non-HDL-C, and ApoB, consistent with expected results when the statin dose was doubled.

. In subjects initially treated with monotherapy in the double-blind, controlled studies, incremental or clinically meaningful improvements in most lipid parameters were observed that were maintained throughout treatment in the long-term extension study.

. In subjects initially treated with moderate-dose statin monotherapy, switching to ABT-335 in combination with moderate-dose statin resulted in incremental clinically meaningful improvements in HDL-C, TG, VLDL-C, and ApoB, with a minimal, non-clinically significant increase in LDL-C (from 91 to 92 mg/dL) after 40 weeks of open-label combination therapy.

. In subjects initially treated with ABT-335 monotherapy, adding a moderate-dose statin resulted in incremental clinically meaningful improvements in LDL-C, TG, non-HDL-C, VLDL-C, total-C, and ApoB, and a modest increase in HDL-C.

. Improvements in lipid parameters with combination therapy were observed within 4 weeks and were sustained throughout the course of a treatment.

. Efficacy results were consistent across the three double-blind, controlled studies, the integrated analyses, and the long-term analyses, demonstrating the clinical benefits of ABT-335 in combination with statins in subjects with mixed dyslipidemia."

2.2 Data Sources

Location of the NDA in EDR (electronic documents room):
\\CDSESUB1\EVSPROD\NDA022224

STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The subsections for each study in this Section are: **Study Design and Endpoints; Patient Disposition, Demographic and Baseline Characteristics; Statistical Methodologies; Results and Conclusions** under each study heading.

Study M05-748

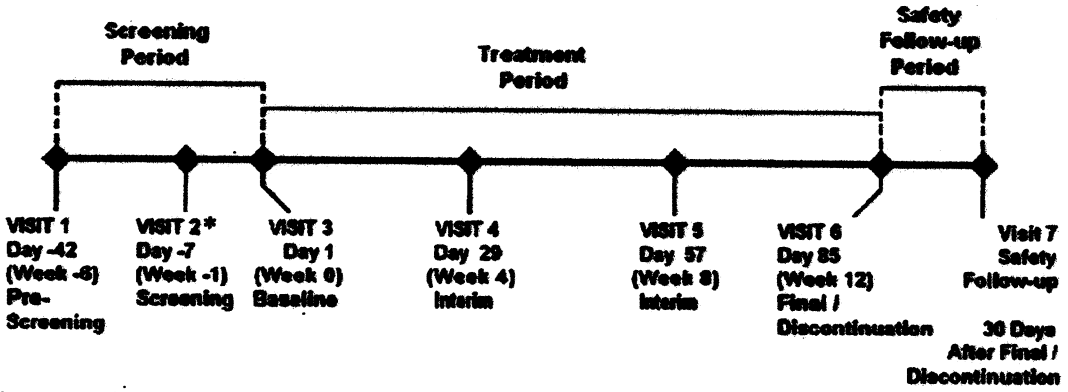
Study Design and Endpoints

This was a Phase 3, multicenter, randomized, double-blind, prospective, comparative study designed to assess the safety and efficacy of once daily treatment with ABT-335 in combination with one of two doses (10 mg or 20 mg) of rosuvastatin compared to ABT-335 monotherapy and rosuvastatin monotherapy on the primary lipid parameters associated with increased risk of CHD in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb). Approximately 1,250 subjects were planned to be randomized at approximately 250 investigative sites across the United States, Canada, and Puerto Rico; however, due to multiple sites enrolling at the same time and the design of the study, it was recognized that the study could over-enroll by up to 200 subjects. Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio (planned number of subjects was 228 for the first five treatment groups and 114 for the last treatment group) to one of the six once daily treatment regimens defined as follows:

. 135 mg ABT-335 monotherapy . 10 mg rosuvastatin monotherapy . 135 mg ABT-335 and 10 mg rosuvastatin . 20 mg rosuvastatin monotherapy . 135 mg ABT-335 and 20 mg rosuvastatin . 40 mg rosuvastatin 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. Subjects who completed the Treatment Period of the study were allowed to participate in an open-label safety extension study (M05-758).

Study Design Schematic:



* An optional second Screening Visit (Visit 2.1) may have been performed for subjects who were within 30% of the laboratory cut-off criteria for a specific laboratory parameter(s).

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); 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 (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 that 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.

Primary Variables

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

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

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

Secondary Variables

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

1. Non-HDL-C (Combination therapy with each dose of rosuvastatin vs. ABT-335 monotherapy)

2. Non-HDL-C (Combination therapy with each dose of rosuvastatin vs. corresponding rosuvastatin monotherapy)

3. VLDL-C (Combination therapy with each dose of rosuvastatin vs. corresponding rosuvastatin monotherapy)

4. Total-C (Combination therapy with each dose of rosuvastatin vs. corresponding rosuvastatin monotherapy)

5. ApoB (Combination therapy with each dose of rosuvastatin vs. corresponding rosuvastatin monotherapy)

6. hsCRP (Combination therapy with each dose of rosuvastatin vs. corresponding rosuvastatin 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 group were stopped due to failure to reach statistical significance for an endpoint.

Patient Disposition

A total of 1445 subjects were randomized and 1439 were treated with at least one dose of study drug (Submission Table 14.1__1.1). Of the treated subjects, 1243 (86.4%) completed the study and 196 (13.6%) prematurely discontinued study drug. Overall, the most common reasons for prematurely discontinuing study drug were adverse event (7.7%) and withdrawal of consent (4.7%); 1.7% of subjects were lost to follow-up and 0.4% of subjects were discontinued due to noncompliance (Submission Table 14.1__1.2). "Other" reasons for withdrawal, specified in Submission Appendix 16.2__1.1, including relocation, difficulty attending scheduled visits, and difficulty swallowing capsules, were cited by 4.0% of subjects.

The discontinuation rate in both combination therapy groups was 15.7% and in the ABT-335 monotherapy group was 19.7%. The incidence of discontinuation due to adverse events was higher in the ABT-335 monotherapy and combination groups (10.8% and 9.6%, respectively) than in the rosuvastatin monotherapy groups (3.8% to 7.6%). A summary of subject disposition by treatment group is presented in Table below.

Patient Disposition

	ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	20 mg rosuva	ABT-335 + 20 mg rosuva	40 mg rosuva	Total
All Randomized Subjects	260	265	261	266	262	131	1445
All Treated Subjects	259	261	261	266	261	131	1439
Full Analysis Set[a]	242	252	252	255	249	127	1377
Safety Analysis Set	259	261	261	266	261	131	1439
	Treatment Group n (%)						
Completed Study	208 (80.3)	237 (90.8)	220 (84.3)	243 (91.4)	220 (84.3)	115 (87.8)	1243 (86.4)
Prematurely Terminated[b]	51 (19.7)	24 (9.2)	41 (15.7)	23 (8.6)	41 (15.7)	16 (12.2)	196 (13.6)
Adverse event	28 (10.8)	10 (3.8)	25 (9.6)	13 (4.9)	25 (9.6)	10 (7.6)	111 (7.7)
Withdrew consent	18 (6.9)	10 (3.8)	16 (6.1)	9 (3.4)	11 (4.2)	4 (3.1)	68 (4.7)
Lost to follow-up	8 (3.1)	3 (1.1)	4 (1.5)	4 (1.5)	4 (1.5)	1 (0.8)	24 (1.7)
Noncompliance	2 (0.8)	2 (0.8)	1 (0.4)	1 (0.4)	0	0	6 (0.4)
Other	15 (5.8)	11 (4.2)	9 (3.4)	7 (2.6)	12 (4.6)	4 (3.1)	58 (4.0)

rosuva = rosuvastatin

a. Included all subjects included in the analysis of at least one of the three primary endpoints.
b. Subjects may have provided more than one reason for discontinuation and were counted under each provided reason; therefore, the sum of the reasons is greater than the overall number of discontinuations.

Two hundred twenty-four (224) investigative sites screened subjects, with 205 of these sites randomizing subjects. The majority of sites (174/205; 84.9%) enrolled and treated fewer than 12 subjects (submission Table 14.1__1.1). Thirty-two sites had at least 12 randomized subjects (Submission Table 14.2__1.12).

Subject disposition was also summarized by baseline creatinine clearance (Submission Table 14.1__1.3.1 and Table 14.1__1.3.2) and baseline eGFR level (Submission Table 14.1__1.4.1 and Table 14.1__1.4.2). Six of 57 subjects (10.5%) with calculated creatinine clearance < 60 mL/min and 11 of 108 subjects (10.2%) with eGFR < 60 mL/min/1.73m^2 prematurely discontinued the study.

Demographic and Baseline Characteristics

Of the 1439 randomized and treated subjects, 750 (52.1%) were female and 689 (47.9%) were male; 92.3% of all subjects were White, 5.8% were Black, 0.8% were multiracial, 0.6% were of other races, 0.4% were American Indian/Alaska natives, and one (< 0.1%) subject was Asian (submission Table 14.1__2.1). Hispanics comprised 10.1% of the study population. The majority

(61.5%) of subjects was between 40 and 60 years of age; 8.1% were younger than 40 years and 30.4% were older than 60 years. A total of 273 subjects (19.0%) were 65 years of age and older. A statistically significant difference was observed among treatment groups in the distribution of gender (p = 0.048). The majority of subjects in the ABT-335 monotherapy group and ABT-335 in combination with 10 mg rosuvastatin group were females (58.7% and 56.7%, respectively) while the majority of subjects in the 20 mg rosuvastatin monotherapy group were males (53.4%); the distribution by gender was equal in the remaining three treatment groups. Sensitivity analysis adjusting for gender indicated that this difference did not affect the interpretation of the study results (Submission Table 14.2__1.16). A summary of categorical demographic variables is presented in Table below.

Demographic and Baseline Characteristics - Categorical Variables (All Randomized Subjects Who Received at Least One Dose of Study Drug)

	Treatment Group n (%)						
Demographic Characteristic	ABT-335 (N=259)	10 mg rosuva (N=261)	ABT-335 + 10 mg rosuva (N=261)	20 mg rosuva (N=266)	ABT-335 + 20 mg rosuva (N=261)	40 mg rosuva (N=131)	p-value[a]
Gender							0.048*
Female	152 (58.7)	130 (49.8)	148 (56.7)	124 (46.6)	131 (50.2)	65 (49.6)	
Male	107 (41.3)	131 (50.2)	113 (43.3)	142 (53.4)	130 (49.8)	66 (50.4)	
Race							0.234
White	236 (91.1)	249 (95.4)	236 (90.4)	245 (92.1)	238 (91.2)	124 (94.7)	
Black	15 (5.8)	8 (3.1)	21 (8.0)	18 (6.8)	15 (5.7)	7 (5.3)	
Indian/Alaskan	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	0	
Asian	1 (0.4)	0	0	0	0	0	
Other	3 (1.2)	0	2 (0.8)	1 (0.4)	2 (0.8)	0	
Multiracial	3 (1.2)	2 (0.8)	1 (0.4)	1 (0.4)	5 (1.9)	0	
Ethnicity							0.862
Hispanic	28 (10.8)	30 (11.5)	28 (10.7)	25 (9.4)	25 (9.6)	10 (7.6)	
No ethnicity	231 (89.2)	231 (88.5)	233 (89.3)	241 (90.6)	236 (90.4)	121 (92.4)	
Age Group (years)							0.218
< 40	16 (6.2)	26 (10.0)	26 (10.0)	18 (6.8)	25 (9.6)	6 (4.6)	
40 to 60	165 (63.7)	170 (65.1)	147 (56.3)	167 (62.8)	152 (58.2)	84 (64.1)	
> 60	78 (30.1)	65 (24.9)	88 (33.7)	81 (30.5)	84 (32.2)	41 (31.3)	
Age Group (years)							0.218
< 65	209 (80.7)	222 (85.1)	206 (78.9)	217 (81.6)	209 (80.1)	103 (78.6)	
≥ 65	50 (19.3)	39 (14.9)	55 (21.1)	49 (18.4)	52 (19.9)	28 (21.4)	
Tobacco Use							0.842
User	58 (22.4)	52 (19.9)	57 (21.8)	62 (23.3)	58 (22.2)	34 (26.0)	
Ex-User	64 (24.7)	72 (27.6)	80 (30.7)	82 (30.8)	68 (26.1)	38 (29.0)	
Non-User	137 (52.9)	137 (52.5)	124 (47.5)	122 (45.9)	135 (51.7)	59 (45.0)	
Alcohol Use[b]							0.465
Drinker	135 (52.1)	117 (45.0)	127 (48.7)	128 (48.1)	139 (53.3)	66 (50.4)	
Ex-Drinker	25 (9.7)	16 (6.2)	23 (8.8)	15 (5.6)	11 (4.2)	16 (12.2)	
Non-Drinker	99 (38.2)	127 (48.8)	111 (42.5)	123 (46.2)	111 (42.5)	49 (37.4)	

rosuva = rosuvastatin; Indian/Alaskan = American Indian/Alaska native

a. P-value for differences among treatment groups from Chi-square test. Non-white races were combined for analysis of race; ex-user and non-users were combined for analysis of tobacco use; ex-drinker and non-drinkers were combined for analysis of alcohol use.

b. Alcohol use was missing for one subject in the 10 mg rosuvastatin monotherapy group (N=260).

* = statistically significant at the p = 0.05 level.

Mean age was 55 years. Mean weight was 92.0 kg overall, 85.7 kg among females, and 98.8 kg among males. Mean waist circumference was 102.8 cm overall, 99.9 cm among females and 105.9 cm among males. There was a statistically significant difference in Height (p=.037) among the treatment groups, although the means varied between 168.0 cm and 170.8 cm only. A summary of quantitative demographic variables is presented in Table below.

	Treatment Group n (%)					
Demographic Characteristic	ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	20 mg rosuva	ABT-335 + 20 mg rosuva	40 mg rosuva
Age (years)	(N=259)	(N=261)	(N=261)	(N=266)	(N=261)	(N=131)
Mean (SD)	55.6 (10.81)	53.6 (10.51)	55.6 (11.53)	55.5 (10.52)	54.4 (11.21)	56.3 (10.13)
Median	56.0	55.0	56.0	56.0	55.0	56.0
Min, max	20, 82	20, 80	26, 83	23, 83	21, 82	30, 79
Weight (kg)						
Females	(N=152)	(N=130)	(N=148)	(N=124)	(N=131)	(N=65)
Mean (SD)	85.6 (17.92)	86.0 (17.30)	83.2 (17.58)	87.2 (20.98)	86.7 (20.69)	85.9 (18.98)
Median	83.1	83.1	81.0	85.5	82.6	84.0
Min, max	42.9, 139.3	54.4, 160.6	50.8, 135.2	54.0, 171.0	52.2, 153.8	57.2, 157.4
Males	(N=107)	(N=131)	(N=113)	(N=142)	(N=130)	(N=66)
Mean (SD)	101.0 (22.15)	101.2 (21.17)	96.4 (21.17)	97.0 (16.12)	98.4 (20.50)	99.3 (16.46)
Median	100.2	98.4	92.1	95.7	95.3	100.1
Min, max	56.7, 186.4	63.1, 170.1	64.4, 185.1	62.6, 152.9	67.1, 199.6	69.9, 156.0
Waist circumference (cm)						
Females	(N=150)	(N=128)	(N=148)	(N=122)	(N=128)	(N=64)
Mean (SD)	100.6 (13.81)	99.1 (13.18)	99.1 (14.65)	99.4 (16.03)	100.8 (15.67)	100.8 (13.75)
Median	99.1	97.1	96.5	96.5	99.1	99.1
Min, max	67.3, 139.7	73.7, 144.8	67.3, 157.9	42.0, 138.4	63.5, 154.9	78.7, 147.3
Males	(N=107)	(N=128)	(N=112)	(N=142)	(N=129)	(N=65)
Mean (SD)	107.7 (15.10)	107.2 (15.19)	104.6 (15.33)	104.4 (11.29)	105.3 (14.91)	106.7 (11.85)
Median	106.5	104.1	101.6	101.9	102.9	106.0
Min, max	73.7, 160.0	81.3, 149.9	81.3, 166.5	81.3, 147.3	83.8, 162.6	86.4, 144.8

rosuva = rosuvastatin; SD = standard deviation; Min, max = minimum, maximum

Primary Lipid Parameters at Baseline (All Randomized Subjects Who Received at Least One Dose of Study Drug)

Lipid Parameter (mg/dL)	Treatment Group n (%)						
	ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	20 mg rosuva	ABT-335 + 20 mg rosuva	40 mg rosuva	p-value[a]
HDL-C	(N=253)	(N=253)	(N=246)	(N=255)	(N=248)	(N=124)	0.522
Mean (SD)	38.8 (6.73)	38.3 (7.09)	38.6 (7.22)	38.4 (6.98)	38.1 (7.01)	37.4 (6.96)	
Median	38.0	38.0	37.0	38.0	38.0	37.0	
Min, max	22.8, 60	18.5, 60	23, 62	12, 61	18.1, 57	26, 59	
TG	(N=259)	(N=261)	(N=261)	(N=266)	(N=261)	(N=131)	0.215
Mean (SD)	267.6 (152.72)	293.0 (156.22)	282.7 (144.59)	293.8 (170.67)	293.6 (164.95)	282.4 (141.38)	
Median	232.0	259.0	235.0	249.5	247.0	248.7	
Min, max	55, 1442	64, 1282	73, 1236	88, 1704	88, 1238	95, 1006	
LDL-C	(N=259)	(N=260)	(N=260)	(N=263)	(N=260)	(N=131)	0.872
Mean (SD)	155.3 (34.36)	152.1 (31.45)	154.1 (34.57)	153.8 (32.79)	155.5 (38.16)	153.2 (32.61)	
Median	158.0	150.3	149.0	153.0	154.0	153.0	
Min, max	47.9, 266	85, 275	65, 279	76.4, 254	61.5, 350	80, 263	

rosuva = rosuvastatin; SD = standard deviation; Min, max = minimum, maximum

a. From ANOVA with effects for treatment group, diabetic status, screening TG, and the interaction of diabetic status by screening TG level.

At baseline, no statistically significant differences were observed among groups in mean values for the secondary lipid parameters (Submission Table 14.1__5.1). Mean values were 220 mg/dL for non-HDL-C, 68 mg/dL for VLDL-C, 259 mg/dL for total-C, and 146 mg/dL for ApoB; median value for hsCRP ranged from 0.27 to 0.35 mg/dL across treatment groups.

At baseline, no statistically significant differences were observed among groups in mean values for the additional lipid parameters (Table 14.1__5.1). Mean values were 143 mg/dL for ApoAI, 19 mg/dL for ApoCIII, 5695 ng/dL for adiponectin, and 275 ng/dL for LpPLA2.

Statistical Methodologies

The sponsor states that changes made via protocol amendments and a data handling memo as well as changes made post-blind break are incorporated into the following:

> "Datasets for Analysis
>
> Full Analysis Set
>
> The primary efficacy analysis set was the set of all randomized subjects who had both a baseline value and at least one post-baseline value. Last observation carried forward (LOCF) was used to impute values for subjects missing a post-baseline visit value. The baseline value was not carried forward.
>
> The Baseline value for a given variable was defined as the last value for that variable obtained prior to the initiation of study drug.
>
> Efficacy assessments performed more than three days after the final dose of study drug were excluded from analyses.
>
> Efficacy
>
> The primary analysis of the primary, secondary and additional efficacy parameters included effects in the model for screening TG level [≤250 mg/dL (≤ 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)] and diabetic status (diabetic, non-diabetic). The values for each of these factors were based on the values given at the Baseline Visit for randomization and recorded on the Randomization Stratification section of the CRF.
>
> Primary Efficacy Variables
>
> Primary Analyses
>
> The primary analysis of the primary efficacy endpoints, TG, HDL-C and direct LDL-C, were performed using the full analysis set as defined previously.
>
> A change in the laboratory procedures for the HDL-C assay at the central laboratory occurred on 28 August 2006. Therefore, for the primary analyses of percent change from Baseline to the Final Visit (Week 12) in HDL-C and LDL-C, measurements with an HDL-C assay date prior to 28 August 2006 were excluded. As a result of this change in HDL-C assay, all samples assayed prior to 28 August 2006 were reassayed; the reassayed HDL-C value for those samples, as well as the recalculated LDL-C values, were included in the primary analyses. Subjects without a repeated analysis value for HDL-C available (due to lack of sample) and as a result who were missing either the Baseline and/or post-Baseline measurements (i.e., available value(s) had an HDL-C assay date prior to 28 August 2006) were not included in the primary analyses of these two endpoints. These subjects were included in sensitivity analyses of HDL-C and LDL-C performed to assess the impact of missing data.
>
> For each rosuvastatin calcium dose given in combination with ABT-335 (i.e., 10 mg and 20 mg), there were three primary comparisons.

. TG: rosuvastatin calcium in combination with ABT-335 vs. rosuvastatin calcium monotherapy. . HDL-C: rosuvastatin calcium in combination with ABT-335 vs. rosuvastatin calcium monotherapy. . Direct LDL-C: rosuvastatin calcium in combination with ABT-335 vs. ABT-335 monotherapy.

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

The study was to be declared successful if superiority of the combination arm was demonstrated for all three primary comparisons for at least one rosuvastatin calcium dose. Hence, adjustments for multiple comparisons were performed using the Hochberg Method in order to adjust for treatment group comparisons being performed for two rosuvastatin calcium doses. When performing the Hochberg method, the maximum of the three p-values for the primary comparisons for each dose level was used. If both p-values (i.e., the maximum p-value for each dose level) were significant at the $\alpha = 0.05$ level then all hypotheses were rejected (i.e., the combination therapy arm was declared significantly superior to the monotherapy arms for both rosuvastatin calcium doses). Otherwise, if the p-value for any of the three primary efficacy variables was not significant at the $a = 0.05$ level for one of the rosuvastatin calcium doses then the remaining rosuvastatin calcium dose was considered at the alpha level of 0.025 for all three efficacy variables.

The Final Visit (Week 12) TG, HDL-C and direct LDL-C values were summarized for each treatment group with the mean. The within-group percent changes from Baseline to the Final Visit 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. Two-sided 95% percent confidence intervals were calculated for the differences in mean percent change from baseline between the combination therapy arms and the corresponding monotherapy arms. The Baseline mean was also calculated. The percent changes from baseline were compared between the combination therapy arms and each corresponding monotherapy arm using contrast statements within an 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 was 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 supports the primary inferences. The primary treatment group comparisons were performed using the model specified above with the main effects for treatment group, diabetic status and screening TG and the interaction of diabetic status by screening TG.

Sensitivity Analyses to Address Missing Data

The primary analysis of the primary efficacy variables were performed using the Full Analysis Set as defined previously. However, in order to assess the impact of missing data on the results, the following sensitivity analyses were performed in which all randomized subjects were included in the analyses. The imputation methods outlined below applied to all randomized subjects missing the baseline

and/or post-baseline value, including those subjects missing HDL-C and LDL-C measurements with an assay date on or after August 28, 2006.

1. Multiple imputation methods were used to impute percent changes from baseline for subjects with the baseline value and/or the Final Visit (Week 12) value missing. The PROC MI statement in SAS was used to impute values for percent change from baseline. The VAR statement of the MI procedure included the following variables in the following order: percent change from baseline, baseline lipid value (lipid parameter corresponding to the outcome variable being modeled), screening triglyceride level [= 250 mg/dL (= 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)], diabetic status (diabetic, non-diabetic) and five indicator variables for treatment group. Imputations were done using the Markov Chain Monte Carlo method. Five imputed datasets (default number of imputations for MI procedure) were created. An analysis of covariance with baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as the covariate and effects for screening triglyceride level [= 250 mg/dL (= 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)], diabetic status (diabetic, non-diabetic), the interaction of diabetic status by screening TG and treatment group (as five indicator variables using the appropriate reference group) was then performed using each of these imputed datasets. The results were combined using PROC MIANALYZE to obtain treatment group differences and corresponding p-values for the primary endpoints.

2. 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.

3. A zero change from baseline was imputed for all randomized subjects who were missing a Final Visit value or a Baseline value (regardless of whether the subjects had an Interim Visit value).

4. If a subject has a Baseline value but was missing a Final Visit value, the following method was used to impute a value for the Final Visit. Subjects with a Final Visit value were divided into strata based on diabetic status (diabetic, non-diabetic) and screening TG value [= 250 mg/dL (= 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)]. The median of the Final Visit values was then calculated within each stratum. These values were imputed for all subjects within a stratum who were missing a Final Visit value.

If a subject had a Final Visit value but was missing the Baseline value, the following method was used to impute a value for Baseline. Subjects with a Baseline value were divided into strata based on diabetic status (diabetic, non-diabetic) and screening TG value [= 250 mg/dL (= 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)]. The median of the Baseline values was then calculated within each stratum. These values were imputed for all subjects within a stratum who were missing a Baseline value.

If a subject was missing both the Baseline and Final Visit values, the following method was used to impute a value for the percent change from Baseline to the Final Visit. Subjects with both a Baseline and Final Visit value were divided into strata based on diabetic status (diabetic, non-diabetic) and screening TG value [= 250 mg/dL (= 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)]. The median of the percent change from Baseline values was then calculated within each of the strata. These values were imputed for all subjects within a stratum who were missing both a Baseline and Final Visit value.

5. As an exploratory analysis, a "worst case" analysis was performed in which subjects in the monotherapy comparator arms with missing values had "good" values imputed and subjects in the combination therapy arms with missing data had "bad" values imputed. When performing the "worst case" analysis, the mean percent change of the combination arm was imputed for subjects with missing values in the corresponding monotherapy comparator arm and vice versa.

Additional Supportive Analyses

As supportive data, the results for subgroups based on diabetic status and screening TG (i.e., diabetic and screening TG = 250 mg/dL (= 2.8 mmol/L), diabetic and screening TG > 250 mg/dL (> 2.8 mmol/L), non-diabetic and screening TG = 250 mg/dL (= 2.8 mmol/L), non-diabetic and screening TG > 250 mg/dL (> 2.8 mmol/L), diabetic, non-diabetic, TG = 250 mg/dL (= 2.8 mmol/L), and TG > 250 mg/dL (> 2.8 mmol/L) were presented.

As a supportive analysis of percent changes from Baseline to the Final Visit in the primary endpoints, a CMH mean score test using diabetic status (diabetic, non-diabetic) and screening TG [= 250 mg/dL (= 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)] as the stratification factors and using modified ridit scores (i.e., van Elteren test) was performed to compare treatment groups.

The log of the ratio of the Final Visit and Baseline Visit values were analyzed for each primary endpoint using an ANCOVA with baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as the 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.

An additional supportive analysis of percent change from baseline to the Final Visit in the primary endpoints was performed without including the baseline value as a covariate. That is, an ANOVA was performed 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.

An analysis was performed of the absolute change from baseline to the Final Visit in the primary endpoints using an ANCOVA with baseline lipid value (i.e., 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.

To evaluate the change in the primary lipid parameters over the study, a repeated measures analysis was performed using the PROC MIXED statement in SAS. The model included baseline lipid value (i.e., lipid parameter corresponding to the outcome variable being modeled) as a covariate and factors for treatment group, visit, the interaction between visit and 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. An unstructured covariance matrix was used.

A sensitivity analysis was performed for HDL-C and LDL-C in which values with an assay date prior to 28 August 2006 were included if no measurement with an

assay date on or after 28 August 2006 was available. For this analysis, an ANCOVA was performed with baseline lipid value (i.e., 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.

Since a statistically significant difference among treatment groups was observed for gender, a sensitivity analysis was performed of percent change from baseline to the Final Visit in the primary endpoints in which gender was included as a factor in the model in addition to the factors and covariate in the primary model.

Shift tables for changes from the Baseline to the Final Visit according to the normal range were provided for TG, HDL-C and direct LDL-C.

The primary efficacy endpoints were summarized for each investigative site with 12 or more randomized subjects.

A sensitivity analysis of the primary endpoints was performed in which subjects from investigator site 33087 were excluded.

Secondary efficacy Variables

The secondary endpoints were tested in fixed sequence separately for each combination therapy arm since both combination therapy arms were statistically significantly superior for each of the three primary endpoint comparisons. That is, for each combination arm, the secondary endpoints were tested in order at the a = 0.05 level until one endpoint failed to reach statistical significance. Comparisons for one combination therapy arm continued down the fixed sequence of endpoints even if comparisons for the other combination arm stopped due to failure to reach statistical significance for an endpoint.

The Final Visit (Week 12) values were summarized for each treatment group with the mean. The within-group changes from Baseline to the Final Visit 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. Two-sided 95% percent confidence intervals were calculated for the differences in mean percent change from baseline between the combination therapy arms and the corresponding monotherapy arms. The Baseline mean was also calculated. The percent changes from baseline were compared between the combination therapy arms and each corresponding monotherapy arm using contrast statements within an 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 supports the primary inferences. The primary treatment group comparisons were performed using the model specified above with main effects for treatment group, diabetic status and screening TG and the interaction of diabetic status by screening TG.

As supportive data, the results for subgroups based on diabetic status and screening TG (i.e., diabetic and screening TG = 250 mg/dL (= 2.8 mmol/L), diabetic and screening TG > 250 mg/dL (> 2.8 mmol/L), non-diabetic and screening TG = 250 mg/dL (= 2.8 mmol/L), non-diabetic and screening TG > 250 mg/dL (> 2.8 mmol/L), diabetic, non-diabetic, TG = 250 mg/dL (= 2.8 mmol/L), and TG > 250 mg/dL (> 2.8 mmol/L) were presented.

Due to the skewness of the hsCRP data, a CMH mean score test using diabetic status (diabetic, non-diabetic) and screening TG [≤250 mg/dL (≤ 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)] as the stratification factors and using modified ridit scores (i.e., van Elteren test) was performed as a sensitivity analysis to compare treatment groups with respect to percent changes in hsCRP from baseline to the Final Visit.

For the primary analysis of percent change from Baseline to the Final Visit (Week 12) in non-HDL-C, measurements with an HDL-C assay date prior to 28 August 2006 were excluded. The recalculated non-HDL-C values occurring as a result of the reassaying of samples for HDL-C were included in analyses. Subjects without a recalculated value for non-HDL-C available (due to lack of sample) and as a result who were missing either the Baseline and/or post-Baseline measurements (i.e., available value(s) had an HDL-C assay date prior to 28 August 2006) were not included in the primary analysis of non-HDL-C.

Subgroup Analyses

Several subgroups were explored with respect to efficacy parameters.

Percent changes from baseline to the Final Visit in the primary and secondary efficacy endpoints were summarized for subgroups based on the following parameters.

. Baseline HDL-C and diabetic status (as indicated on medical history): HDL-C = 37 mg/dL and diabetic, HDL-C = 37 mg/dL and non-diabetic, HDL-C > 37 mg/dL and diabetic, and HDL-C > 37 mg/dL and non-diabetic
. Baseline LDL-C (= 160 mg/dL, > 160 mg/dL)
. Baseline triglycerides (= 200 mg/dL, > 200 mg/dL)
. Baseline HDL-C (= 37 mg/dL, > 37 mg/dL)
. Gender
. Diabetic status (diabetic, non-diabetic as indicated on medical history)
. Baseline creatinine clearance level (< 60 ml/min, = 60 ml/min)
. Baseline eGFR (< 60 ml/min/1.73m2, = 60 ml/min/1.73m2)

Estimated GFR was calculated as follows:

eGFR (ml/min/1.73m2) = 186 × (serum creatinine in mg/dL)-1.154 × (age)-0.203 × (0.742 if female) × (1.210 if African-American)

An ANCOVA with baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as the covariate and with effects for treatment group, subgroup parameter and the interaction between treatment group and subgroup parameter was used to test for a difference in treatment effect across subgroups. If a subgroup has at least five subjects per treatment group (combination therapy groups and corresponding monotherapy groups) then the combination therapy groups were compared to each corresponding monotherapy group within the subgroup using an ANCOVA with baseline lipid value (lipid parameter

corresponding to the outcome variable being modeled) as a covariate and with effects for treatment group and screening TG [= 250 mg/dL (= 2.8 mmol/L), > 250 mg/dL (> 2.8 mmol/L)]. For subgroups based on diabetic status, an effect for diabetic status and the interaction of diabetic status by screening TG were not included in the model."

Results and Conclusions

Of the 1439 treated subjects, 1377 subjects had both a baseline value and at least one post-baseline value for at least one of the three primary endpoints and were included in the Full Analysis Set (Table 6). Subjects who were excluded from the primary analysis of HDL-C, TG, and LDL-C are listed in Appendix 16.2__3. The most common reason for exclusion from the primary analysis was that the subject did not have eligible Final Visit values for the primary lipid parameters.

Efficacy Results

The primary efficacy endpoints were mean percent changes from baseline to final value in HDL-C, TG, and LDL-C in the Full Analysis Set. There were three primary comparisons of the primary efficacy variables:

. For HDL-C and TG, ABT-335 in combination with each dose of rosuvastatin was compared with the corresponding dose rosuvastatin monotherapy.
. For LDL-C, ABT-335 in combination with each dose of rosuvastatin was compared with ABT-335 monotherapy.

Mean percent increases from baseline in HDL-C and mean percent decreases from baseline in TG and LDL-C were observed in all six treatment groups at the Final Visit. For all three primary comparisons, statistically significant differences were observed between each combination therapy and the corresponding monotherapy (Table 14.2__1.1.1).

ABT-335 in combination with 10 mg rosuvastatin resulted in a significantly greater mean percent increase in HDL-C (20.3% vs. 8.5%, $p < 0.001$) and a significantly greater mean percent decrease in TG (-47.1% vs. -24.4%, $p < 0.001$) compared to 10 mg rosuvastatin monotherapy. ABT-335 in combination with 10 mg rosuvastatin resulted in a significantly greater mean percent decrease in LDL-C (-37.2% vs. -6.5%, $p < 0.001$) compared to ABT-335 monotherapy.

A summary of baseline means, mean percent change from baseline to the Final Visit, and p-values for between-group comparisons of mean percent change in HDL-C, TG, and LDL-C is presented for the ABT-335 monotherapy, 10 mg rosuvastatin monotherapy, and ABT-335 in combination with 10 mg rosuvastatin groups in Table 14.

Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C - Part 1 (Full Analysis Set)

		ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	p-value
		(N=220)	(N=239)	(N=224)	
HDL-C (mg/dL)	Baseline mean	38.5	38.2	38.5	
	Final mean	43.9	41.0	45.7	
	Mean % Δ (SE)	15.0% (1.37)	8.5% (1.32)	20.3% (1.36)	< 0.001[a]
		(N=242)	(N=252)	(N=252)	
TG (mg/dL)	Baseline mean	267.4	295.9	282.8	
	Final mean	167.9	202.6	141.6	
	Mean % Δ (SE)	-32.6% (1.84)	-24.4% (1.81)	-47.1% (1.81)	< 0.001[a]
		(N=223)	(N=243)	(N=231)	
LDL-C (mg/dL)	Baseline mean	155.8	152.2	152.7	
	Final mean	142.3	93.8	94.8	
	Mean % Δ (SE)	-6.5% (1.22)	-38.0% (1.18)	-37.2% (1.21)	< 0.001[b]

rosuva = rosuvastatin; Δ= change; SE = standard error

Note: P-value from an ANCOVA with corresponding baseline lipid value as the covariate, and with effects for treatment group, diabetic status, screening TG level, and interaction of diabetic status by screening TG level.

a. ABT-335 + 10 mg rosuvastatin vs. 10 mg rosuvastatin monotherapy.

b. ABT-335 + 10 mg rosuvastatin vs. ABT-335 monotherapy.

ABT-335 in combination with 20 mg rosuvastatin resulted in a significantly greater mean percent increase in HDL-C (19.0% vs. 10.3%, $p < 0.001$) and a significantly greater mean percent decrease in TG (-42.9% vs. -25.6%, $p < 0.001$) compared to 20 mg rosuvastatin monotherapy. ABT-335 in combination with 20 mg rosuvastatin resulted in a significantly greater mean percent decrease in LDL-C (-38.8% vs. -6.5%, $p < 0.001$) compared to ABT-335 monotherapy. A summary of baseline means, mean percent change from baseline to the Final Visit, and p-values for between-group comparisons of mean percent change in HDL-C, TG, and LDL-C is presented for the ABT-335

Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C - Part 2 (Full Analysis Set)

		ABT-335	20 mg rosuva	ABT-335 + 20 mg rosuva	p-value	40 mg rosuva
		(N=220)	(N=236)	(N=225)		(N=115)
HDL-C (mg/dL)	Baseline mean	38.5	38.5	38.0		37.4
	Final mean	43.9	41.6	44.9		40.6
	Mean % Δ (SE)	15.0% (1.37)	10.3% (1.32)	19.0% (1.35)	< 0.001[a]	9.3% (1.85)
		(N=242)	(N=255)	(N=249)		(N=127)
TG (mg/dL)	Baseline mean	267.4	292.8	292.9		284.5
	Final mean	167.9	196.1	145.9		177.1
	Mean % Δ (SE)	-32.6% (1.84)	-25.6% (1.80)	-42.9% (1.82)	< 0.001[a]	-32.1% (2.48)
		(N=223)	(N=238)	(N=230)		(N=120)
LDL-C (mg/dL)	Baseline mean	155.8	154.4	155.5		153.5
	Final mean	142.3	83.1	91.8		74.6
	Mean % Δ (SE)	-6.5% (1.22)	-45.0% (1.19)	-38.8% (1.21)	< 0.001[b]	-50.6% (1.64)

rosuva = rosuvastatin; Δ = change; SE = standard error

Note: P-value from an ANCOVA with corresponding baseline lipid value as the covariate, and with effects for treatment group, diabetic status, screening TG level, and interaction of diabetic status by screening TG level.

a. ABT-335 + 20 mg rosuvastatin vs. 20 mg rosuvastatin monotherapy.

b. ABT-335 + 20 mg rosuvastatin vs. ABT-335 monotherapy.

Although not a primary comparison for LDL-C, a smaller mean percent decrease in LDL-C was observed with ABT-335 in combination with 20 mg rosuvastatin than in the 20 mg rosuvastatin monotherapy group (-38.8% vs. -45.0%, $p < 0.001$).

Sensitivity Analyses

Missing Data

In order to assess the impact of missing data on the efficacy results, a variety of sensitivity analyses were performed in which all randomized subjects were included in the analyses. These sensitivity analyses included use of multiple imputations (Table 14.2__1.2), LOCF and zero change imputed (Table 14.2__1.3), zero change imputed (Table 14.2__1.4), and median value imputed (Table 14.2__1.5). For the "LOCF and zero change imputed" analysis, interim visit values were carried forward for subjects who were missing the Final Visit value and then a zero

change was imputed for any remaining randomized subjects without a Final Visit value and for subjects without a baseline value. For the "zero change imputed" analysis, a zero change from baseline was imputed for all randomized subjects missing a Final Visit value or a baseline value (regardless of whether the subjects had an Interim Visit value). Finally, a "worst-case" analysis was performed in which subjects in the monotherapy groups with missing data had "good" values imputed (mean value of combination therapy group) and subjects in the combination therapy groups with missing data had "bad" values imputed (mean value of relevant monotherapy group) (Table 14.2__1.15). In all five sensitivity analyses, statistically significant differences were observed between both combination therapy groups and the corresponding monotherapy groups for all of the three primary comparisons for the primary efficacy variables. Greater mean percent increases in HDL-C and greater mean percent decreases in TG and LDL-C were observed in the combination therapy groups than in the corresponding monotherapy groups.

A summary of the worst-case analysis comparisons between combination therapy and monotherapy is presented in Table below.

Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C - Worst-Case Analysis (All Randomized Subjects)

		ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	p-value
		NA	(N=265)	(N=261)	
HDL-C (mg/dL)	Baseline mean		38.3	38.7	
	Final mean		41.8	45.2	
	Mean % Δ (SE)		10.0% (1.22)	18.0% (1.23)	< 0.001[a]
		NA	(N=265)	(N=261)	
TG (mg/dL)	Baseline mean		292.4	282.6	
	Final mean		192.9	149.9	
	Mean % Δ (SE)		-27.8% (1.75)	-45.0% (1.77)	< 0.001[a]
		(N=260)	NA	(N=261)	
LDL-C (mg/dL)	Baseline mean	155.4		153.9	
	Final mean	132.9		105.2	
	Mean % Δ (SE)	-13.0% (1.24)		-30.8% (1.24)	< 0.001[b]
		ABT-335	20 mg rosuva	ABT-335 + 20 mg rosuva	p-value
		NA	(N=266)	(N=262)	
HDL-C (mg/dL)	Baseline mean		38.4	38.4	
	Final mean		42.1	44.8	
	Mean % Δ (SE)		11.7% (1.21)	18.1% (1.23)	< 0.001[a]
		NA	(N=266)	(N=262)	
TG (mg/dL)	Baseline mean		293.7	293.5	
	Final mean		193.4	152.9	
	Mean % Δ (SE)		-27.6% (1.74)	-41.5% (1.75)	< 0.001[a]
		(N=260)	NA	(N=262)	
LDL-C (mg/dL)	Baseline mean	155.4		155.4	
	Final mean	132.1		101.4	
	Mean % Δ (SE)	-13.4% (1.25)		-32.8% (1.25)	< 0.001[b]

rosuva = rosuvastatin; Δ = change; SE = standard error;
NA = not applicable: imputations were dependent on the treatment group comparison being performed.
Note: P-value from an ANCOVA with corresponding baseline lipid value as the covariate, and with effects for treatment group, diabetic status, screening TG level and interaction of diabetic status by screening TG level.

a. ABT-335 + 10 mg or 20 mg rosuvastatin vs. 10 mg or 20 mg rosuvastatin monotherapy.
b. ABT-335 + 10 mg or 20 mg rosuvastatin vs. ABT-335 monotherapy.

Analyses Including Values with an Assay Date Prior to 28 August 2006

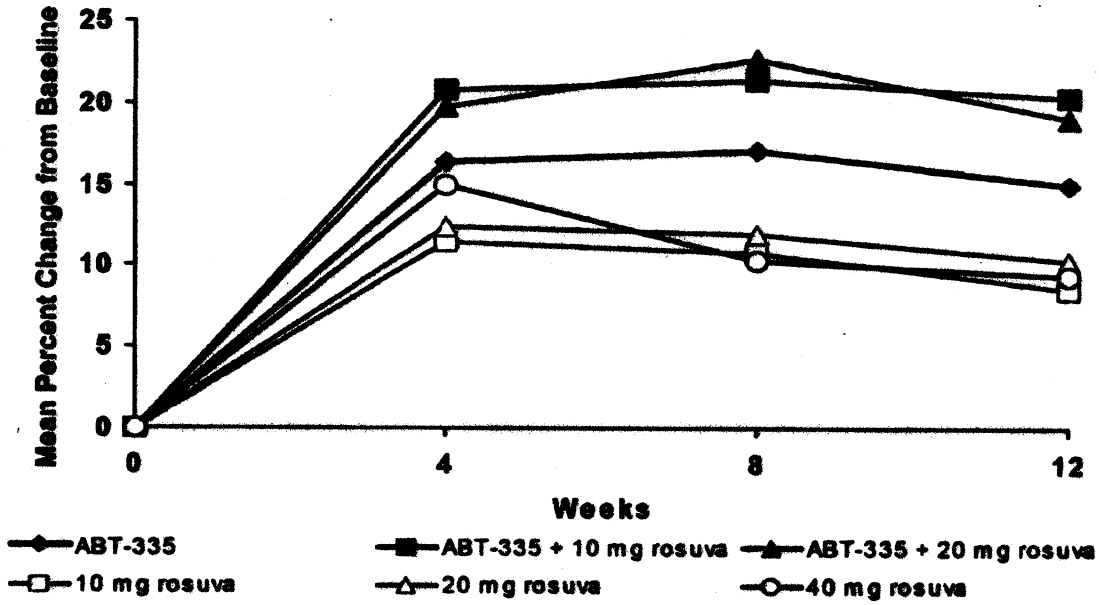
A change in the central laboratory procedures for the HDL-C assay occurred on 28 August 2006. All samples assayed prior to 28 August 2006 were reassayed and the reassayed HDL-C values for those samples, as well as the recalculated LDL-C and non-HDL-C values, were included in the primary analyses. Subjects without an available repeated assay value for HDL-C were excluded in the primary analyses of these three endpoints (Table 14.2__3.2) but were included in an additional analysis of HDL-C and LDL-C (Table 14.2__3.1). When subjects without an available repeated assay value for HDL-C were included, results were similar to the primary analysis.

Additional Supportive Analyses

For each primary endpoint, the following additional supportive analyses were performed: a nonparametric test of percent change from baseline to the Final Visit (Table 14.2__1.7), a repeated measures analysis (Table 14.2__1.13), log of the ratio of the Final Visit and Baseline Visit values using an ANCOVA with the baseline value as the covariate (Table 14.2__1.8), mean percent change from baseline to the Final Visit without including the baseline value as a covariate using ANOVA (Table 14.2__1.9), and the absolute change from baseline to the Final Visit using an ANCOVA (Table 14.2__1.10). All primary comparisons between combination therapy and monotherapy were statistically significant in each of these analyses.

The primary efficacy endpoints were assessed at Weeks 4, 8, and 12 (Table 14.2__3.1 and Table 14.2__3.2). Differences observed in the primary analyses at Week 12 were apparent by Week 4 and were sustained throughout the duration of treatment. At Weeks 4, 8 and 12, statistically significant differences were observed between the combination therapy and rosuvastatin monotherapy groups in mean percent change from baseline in HDL-C and TG, and between the combination therapy and ABT-335 monotherapy groups in mean percent change from baseline in LDL-C. Mean percent change from baseline to Weeks 4, 8, and 12 is displayed in Figure 4 (HDL-C), Figure 5 (TG), and Figure 6 (LDL-C).

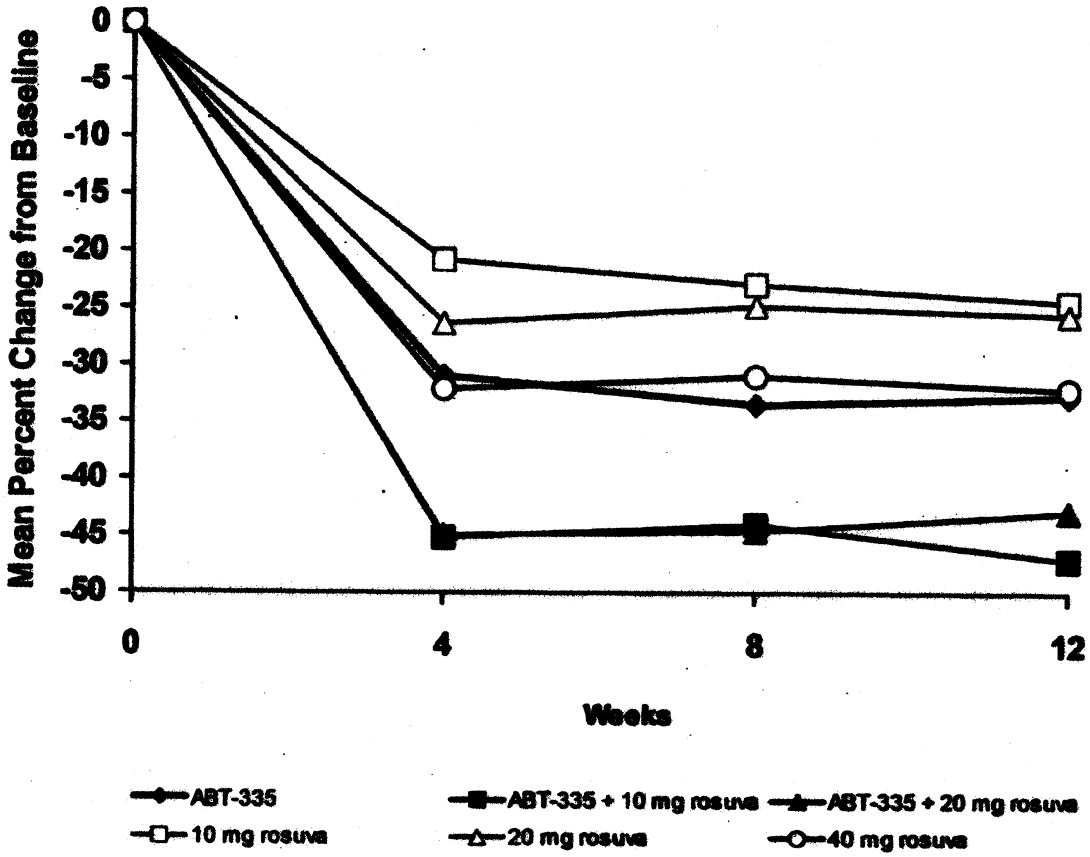
Mean Percent Change from Baseline in HDL-C Over Time



rosuva = rosuvastatin

Note: Analyses were performed using LOCF. At each visit, differences in mean percent change in HDL-C between each combination therapy group and the corresponding rosuvastatin monotherapy group were statistically significant ($p \leq 0.05$).

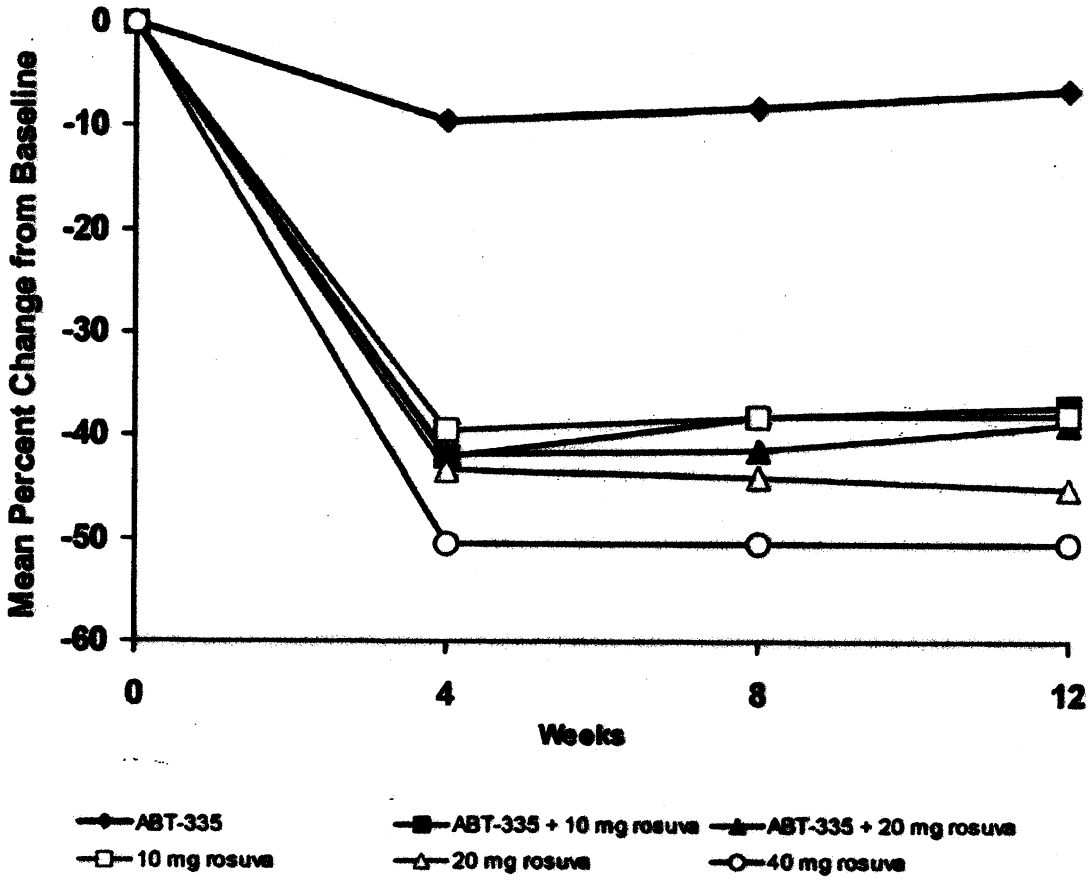
Mean Percent Change from Baseline in TG Over Time



rosuva = rosuvastatin

Note: Analyses were performed using LOCF. At each visit, differences in mean percent change in TG between each combination therapy group and the corresponding rosuvastatin monotherapy group were statistically significant ($p \leq 0.05$).

Mean Percent Change from Baseline in LDL-C Over Time



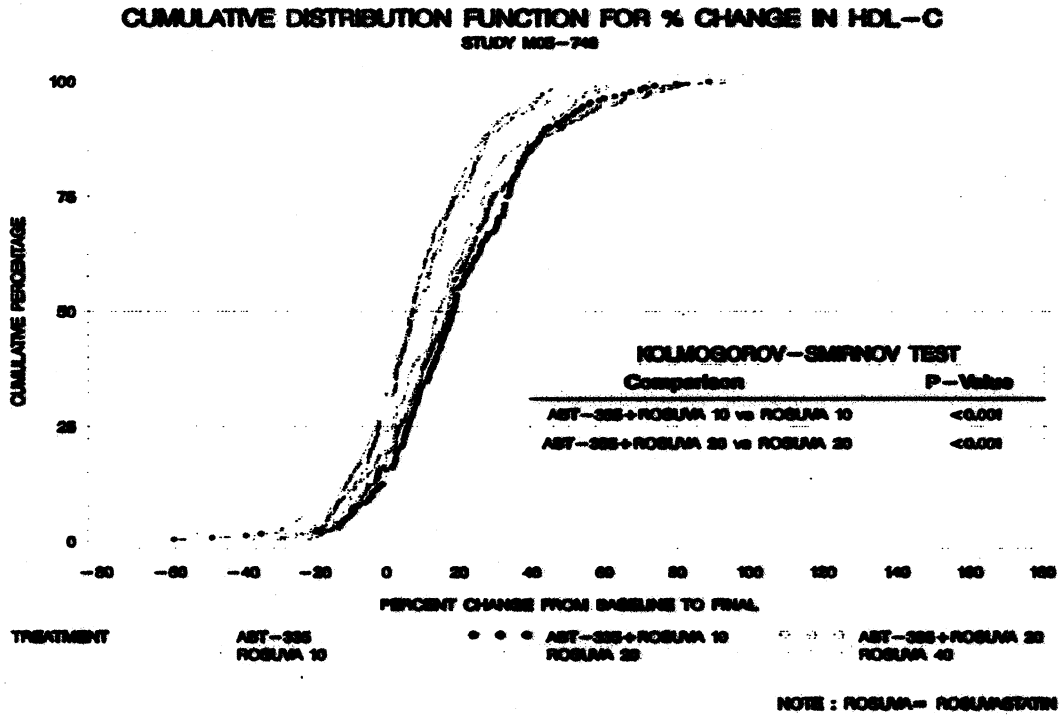
rosuva = rosuvastatin

Note: Analyses were performed using LOCF. At each visit, differences in mean percent change in LDL-C between each combination therapy group and the ABT-335 monotherapy group were statistically significant ($p \leq 0.05$).

§ Graphs of the cumulative distribution functions by treatment groups for the primary efficacy variables (%change in HDL-C, LDL-C, Triglycerides from baseline to endpoint) is provided below. From this, the percent of patients (y-axis value) with a value of %change in the efficacy variable from baseline to endpoint, smaller than or equal to a value on the x-axis, can be read. For example (2nd graph is enlarged), fifty percent patients in each treatment arm had a percent change in HDL-C from baseline to endpoint of less than 14.56, 17.95, 18.03, 8.57, 8.11, 7.65,

respectively, for the ABT-335, ABT-335+ROSUVA 10, ABT-335+ROSUVA 20, ROSUVA 10, ROSUVA 20, and ROSUVA 40.

TTT



The second figure for each of HDL-C, LDL-C, and Triglycerides is meant for better visualization with truncated X-axis