- TG level ≥ 150 mg/dL (≥ 1.69 mmol/L), and
- HDL-C < 40 mg/dL (< 1.02 mmol/L) for males and < 50 mg/dL (< 1.28 mmol/L) for females, and
- LDL-C ≥ 130 mg/dL (≥ 3.35 mmol/L).

4. Subject has, in the opinion of the investigator, a life expectancy greater than 6 months at the Pre-screening Visit.
5. If female, the result of a serum pregnancy test performed at the Screening Visit is negative.
6. If female, subject is either not of childbearing potential, defined as postmenopausal for at least one year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or is of childbearing potential and must agree to practice one of the following methods of birth control for the duration of the study:
   - total abstinence from sexual intercourse (minimum one complete menstrual cycle);
   - a vasectomized partner;
   - hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration;
   - intrauterine device (IUD); or
   - double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams).
7. Subject is not breastfeeding at the Pre-screening Visit.
8. Subject must be willing to observe the diet recommended by the American Heart Association entitled "An Eating Plan for Healthy Americans: Our American Heart Association Diet."
9. Subject must be willing to participate in the study and to complete all follow-up assessments.

Exclusion Criteria

1. Subject has a history of an allergic reaction or significant hypersensitivity to fenofibrate, fenofibric acid, rosuvastatin calcium or to any inactive materials contained in the study drug formulations.
2. Subject has been previously enrolled in this study.
3. Subject has used any investigational drug within 42 days of the Baseline Visit.
4. Subject is of Asian ancestry (having Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin).
5. Subject has any of the following diabetic conditions:
   - Type I diabetes mellitus, or
   - A history of diabetic ketoacidosis, or
   - Uncontrolled type II diabetes mellitus (defined as hemoglobin A_{1c} of > 8.5%).
6. Subject has a history of pancreatitis or gallbladder disease. Subjects with gallbladder disease who have previously undergone a cholecystectomy will be allowed to enroll.
7. Subject has a history of gastric or duodenal ulcer within 3 months of the Pre-screening Visit.
8. Subject has a significant history of oncologic, hematologic, gastrointestinal, hepatic, renal or a neurological disorder (cerebrovascular disease, degenerative disease) that would limit study evaluation or participation.
9. Subject has evidence of unstable cardiovascular disease:
   - Myocardial infarction, coronary bypass surgery, or angioplasty within 12 months of the Pre-screening Visit.

- Severe peripheral artery disease as evidenced by intermittent claudication within 3 months of the Pre-screening Visit.
- Unstable angina pectoris or uncontrolled cardiac arrhythmias within 3 months of the Pre-screening Visit.
- Congestive heart failure (CHF) as defined by the New York Heart Association (NYHA) – Class III or IV.

10. Subject has a history of diagnosed hereditary or acquired myopathy.
11. Subject has received a solid organ transplant.
12. Subject is known to be HIV positive.
13. Subject has a history of mental instability, recreational drug or alcohol abuse or subject has been treated for severe psychiatric illness, which, in the opinion of the investigator, may interfere with optimal participation in the study.
14. Subject has initiated, discontinued or changed dosage of hormone replacement therapy, including estrogen, progesterone, testosterone and/or thyroid hormone supplementation therapy, within eight weeks of the Pre-screening Visit.
15. Subject received coumarin anticoagulants, cyclosporine, nicotinic acid, bile acid binding resins, HMG-CoA reductase inhibitors (statins), fibric acid derivatives, ezetimibe, sibutramine, orlistat, oral corticosteroids, oral garlic supplements, fish oil, plant stanols or other agents/supplements specifically to alter lipid levels within six weeks of enrollment (Baseline Visit).
16. Screening Laboratory analyses show any of the following abnormal laboratory results:
    - ALT/SGPT or AST/SGOT > 1.5 X Upper Limit of Normal (ULN)
    - Creatine phosphokinase (CPK) level > 3 X ULN.
    - Calculated creatinine clearance < 50 mL/min (0.83 mL/s).
    - Thyroid Stimulating Hormone (TSH) level that is outside the central laboratory reference range.
17. Subject is unwilling or unable to consent to enter the study.
18. Subject is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason.

Comment: Patients with diabetes in this study are relatively well-controlled, with the upper limit of HbA1c 8.5%; this somewhat limits the generalizability to the type 2 diabetes population.

Treatment Phase

At the Day 1/Baseline Visit (Visit 3, Day 1), subjects who met the enrollment criteria were randomized into the study. Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio to one of the six once daily treatment regimens (ABT-335 monotherapy, low-dose statin, low-dose statin + ABT-335, moderate-dose statin, moderate-dose statin + ABT-335, and high-dose statin, respectively). Subjects continued to follow the AHA diet.

To ensure the randomized dosing regimen assignment for all subjects remained intact throughout the Treatment Phase, lipid parameters were blinded for all visits after the Baseline Visit. The site, subject, and sponsor personnel remained blinded to the lipid parameter results for the remainder of the study conduct following the Baseline Visit.

The central laboratory reported potentially clinical concerning lipid parameters directly to a Designated Safety Medical Monitor (who did not participate in the Fenofibric Acid Program) for safety review and follow-up with the investigational site, if needed. The Abbott Project Medical Monitor remained blinded throughout the conduct of the study, except in the event where it was necessary to break the blind due to a medical emergency of an enrolled subject.

Subjects returned to the study site for two Interim Visits and one Final/Discontinuation Visit as outlined in Figure 6.1.2.A. The first and second Interim Visits occurred on Day 29 (± 3 days) and Day 57 (± 3 days), respecively. The Final/Discontinuation Visit occurred on Day 85 (± 3 days). Subjects continued to take study drug on the day of the Final/Discontinuation Visit. Study procedures are outlined in Table 6.1.2.A. At the Final/Discontinuation Visit, enrolled subjects who completed the treatment phase were eligible to participate in the open-label safety extension study. Subjects who prematurely discontinued from the study should have returned for a Final/Discontinuation Visit.

Table 6.1.2.A. Schedule of Assessments, Controlled Studies

Procedures	Visit 1 Pre-screening (-2 - -42 Days)	Visit 2 Screening (-5 - 7 Days)	Visit 2.1 Optional Screening Day[a]	Visit 3 Baseline (Day 1)	Visit 4 First Interim (Day 29)	Visit 5 Second Interim (Day 57)	Visit 6 Final/ Discontinuation (Day 85)	Safety F/U Call (10 Days After Last Dose Study Drug)[b]
Informed Consent	X							
Discontinuation of Previous Lipid Lowering Therapy	X							
Dietary Instruction/Diet Compliance Assessment	X	X	X	X	X	X	X	
Inclusion/Exclusion Assessment[c]	X	X		X				
Medical History[d]	X	X		X				
Prior/Concomitant Drug Assessment[e]	X	X		X	X	X	X	X
Vital Signs/Weight/Height/Waist Circumference	X	X	X	X[f]	X	X	X	
ECG				X			X	
Pre-screen Lipid Labs (FG, Total-C, HDL-C, LDL-C Preferred)	X							
Urinalysis		X		X	X	X	X	
Routine Hematology		X		X	X	X	X	
$HgbA_{1c}$		X	X					
Coagulation		X						
Total-C, Direct LDL-C, HDL-C, non HDL-C, TG, VLDL-C[g]		X	X	X	X	X	X	

Procedures	Visit 1 Pre-screening (2 - 42 Days)	Visit 2 Screening (≤ - 7 Days)	Visit 2.1 Optional Screening Day[a]	Visit 3 Baseline (Day 1)	Visit 4 First Interim (Day 29)	Visit 5 Second Interim (Day 57)	Visit 6 Final/ Discontinuation (Day 85)	Safety F/U Call (30 Days After Last Dose Study Drug)[b]
TSH		X	X					
Clinical Chemistry[c]		X	X	X	X	X	X	
Calculated Creatinine Clearance		X	X	X	X	X	X	
Serum Pregnancy		X		X	X	X	X	
hsCRP and apoB				X	X	X	X	
apoA-I, apoC-III, Adiponectin, Lp-PLA2				X			X	
Archive sample (whole blood)[h]				X				
IVRS Calls	X	X	X	X	X	X	X	X
Randomization				X				
Physical Examination[i]				X	X	X	X	
Adverse Event Assessment[j]		X	X	X	X	X	X	X
Dispense Study Drug				X	X	X		
Study Drug Accountability					X	X	X	
Dispense Subject Diary				X	X	X		
Subject Diary Assessment					X	X	X	
Assessment of Pregnancy Status of Subject/Subject's Partner		X		X	X	X	X	X

a. An optional second screening visit may be necessary for subjects who are within 30% of the lab criteria (Section 5.2.1 and 5.2.2) for a specific parameter(s).
b. Subjects who complete the Treatment Phase of this study will be eligible to participate in an open-label safety extension study. A 30-day Safety Follow-up call will not be conducted for these subjects.
c. Subjects will be assessed for study inclusion and exclusion criteria throughout the Screening Phase. Only subjects meeting inclusion/exclusion criteria at the Baseline Visit will be enrolled.
d. The subject's medical history will be reviewed throughout the Screening Phase for meeting inclusion/exclusion criteria. A thorough medical history will be collected at the Baseline Visit.
e. The subject's prior and concomitant medications will be reviewed throughout the Screening Phase for meeting inclusion/exclusion criteria. A thorough review of the subject's concomitant medications will be made at each subsequent visit including the Safety Follow-up contact.
f. Height and waist circumference measurements will be collected at the Baseline Visit only.
g. Subject must fast (water is permitted) for at least twelve (12) hours prior to the sample collection.
h. Archive sample may be used for pharmacogenetic (DNA) testing and/or potential emerging cardiac markers, provided the site's IRB/IEC has approved this testing and the subject has given voluntary consent separate from the main protocol.
i. A complete physical examination will be performed at the Baseline Visit. A symptom directed physical examination will be performed at all other study visits.
j. Serious adverse events will be collected and recorded on the appropriate CRF from the time that the informed consent is signed. Non-serious adverse events will be recorded in source and collected on the appropriate CRF from the start of study drug administration until 30 days following discontinuation of study drug administration.

Safety Follow-Up Phase

During the Safety Follow-up Phase, subjects were to be contacted a minimum of 30 calendar days after their Final/Discontinuation Visit for an assessment of adverse events, pregnancy, and concomitant medications. Subjects who elected to participate in the open-label safety extension study following the completion of the Treatment Phase were not contacted for a 30-day Safety Follow-up.

Open-Label Extension

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.

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. The planned

duration of the long-term safety study was 52 weeks of therapy with a one-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 for laboratory testing and follow-up assessment.

Subjects who prematurely discontinue from the study should have returned for a Final/Discontinuation Visit, which occurred on the day of study drug discontinuation, but no later than 3 days after the final dose of study drug. In the 30 days following the last dose of study drug, subjects are responsible for notifying the site of any adverse events or pregnancy.

A schematic of the study timeline is shown in Figure 6.1.2.B.

Figure 6.1.2.B. Schematic of Study Timeline, Study M05-758

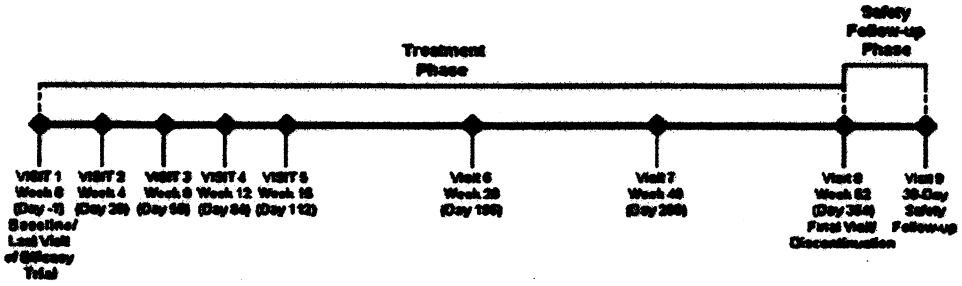

Table 6.1.2.B. Schedule of Assessments, Study M05-758

Procedures	Visit 1 Baseline	Visit 2 Week 4 (+/-3 days)	Visit 3 Week 8 (+/-3 days)	Visit 4 Week 12 (+/-3 days)	Visit 5 Week 16 (+/-3 days)	Visit 6 Week 28 (+/-7 days)	Visit 7 Week 40 (+/- 7 days)	Visit 8 Week 52 Final/ Discontinuation (+/-7 days)	Safety Follow-up Phone (30 Days After Last Dose Study Drug)
Informed Consent	X								
Diet Compliance Assessment	X[a]	X	X	X	X	X	X	X	
Inclusion/Exclusion Assessment[b]	X								
Medical History[b]	X								
Prior/Concomitant Drug Assessment	X[a]	X	X	X	X	X	X	X	X[d]
Vital Signs/Weight	X[a]	X	X	X	X	X	X	X	
ECG	X[a]							X	
Urinalysis	X[a]	X	X	X	X	X	X	X	
Routine Hematology	X[a]	X	X	X	X	X	X	X	
Total-C, Direct LDL-C, HDL-C, non HDL-C, TG, direct VLDL-C[c]	X[a]	X	X	X	X	X	X	X	
Clinical Chemistry[c]	X[a]	X	X	X	X	X	X	X	
Calculated Creatinine Clearance	X[a]	X	X	X	X	X	X	X	
Serum Pregnancy	X[a]	X	X	X	X	X	X	X	

Procedures	Visit 1 Baseline	Visit 2 Week 4 (+/-3 days)	Visit 3 Week 8 (+/-3 days)	Visit 4 Week 12 (+/-3 days)	Visit 5 Week 16 (+/-3 days)	Visit 6 Week 28 (+/-7 days)	Visit 7 Week 40 (+/- 7 days)	Visit 8 Week 52 Final/ Discontinuation (+/-7 days)	Safety Follow-up Phone (30 Days After Last Dose Study Drug)
hsCRP, apoB	X[f]	X	X	X		X	X	X	
apoA-I, apoC-III, Adiponectin, Lp-PLA2	X[f]			X		X	X	X	
Physical Examination[d]	X[f]	X	X	X	X	X	X	X	
Adverse Event Assessment[e]	X[f]	X	X	X	X	X	X	X	X
Dispense Study Drug	X			X	X	X	X		
IVRS Call	X	X	X	X	X	X	X	X	
Study Drug Accountability				X	X	X	X	X	
Dispense Subject Diary	X	X	X	X	X	X	X		
Subject Diary Assessment		X	X	X	X	X	X	X	
Assessment of Pregnancy Status of Subject/Subject's Partner	X	X	X	X	X	X	X	X	X

a. Only subjects meeting inclusion/exclusion criteria at the Baseline Visit will be enrolled.

b. Medical History will be updated from the medical history recorded during the subject's previous efficacy study.

c. Subject must fast (water is permitted) for at least twelve (12) hours prior to the sample collection.

d. A symptom directed physical examination will be performed at study visits.

e. Ongoing adverse events from the efficacy trial will be followed until conclusion in this open-label safety extension study. Adverse events ongoing as of the start of study drug in M05-758 and adverse events starting on or after the start of study drug in M05-758 will be collected in this open-label safety extension study.

f. These assessments will be performed as part of the Final Visit in one of the efficacy studies (M05-748, M05-749 or M05-750). The Final Visit assessment from the efficacy study remains valid as a baseline in the event the subject exercises the option to defer deciding on enrollment into M05-758 for a maximum of 7 days.

g. Occurs when the subject contacts the site during the Safety Follow-up Phase to report an adverse event.

6.1.3 Demographics and Baseline Characteristics

Of the 2698 randomized and treated subjects, 1393 (51.6%) were female and 1305 (48.4%) were male. In both study M05-748 and M05-749, a greater proportion of subjects in the ABT-335 groups were female; this is reflected in the pooled demographic data as seen in Table 6.1.3.A.

A total of 92.6% of all subjects were White, 4.7% were Black, and 2.8% were of other races. Hispanics comprised 9.9% of the study population. The majority of subjects (81.8%) were younger than 65 years of age; 18.2% were ≥ 65 years of age.

A statistically significant difference was observed among treatment groups in mean age. Mean age overall was 54.9 years, and ranged from 53.8 years in the low-dose statin monotherapy group to 56.0 years in the high-dose statin monotherapy group ($p = 0.021$). The proportion of subjects < 65 years of age was similar between groups, however (range: 75.6-85.0%).

Most (87.5%) subjects weighed ≥ 70 kg at baseline. Mean weight was 91.4 kg overall, 85.5 kg among females, and 97.8 kg among males. Mean waist circumference was 102.8 cm overall, 100.1 cm among females and 105.7 cm among males. No statistically significant difference was observed among treatment groups in weight or waist circumference overall or by gender.

The following table summarized demographic and baseline characteristics for the Controlled Studies Analysis Set; the tables that follow are demographic summaries for the individual studies.

Table 6.1.3.A. Demographic and Baseline Characteristics – Categorical Variables (Controlled Studies Analysis Set)

Demographic Characteristic	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + Low statin (N=490)	Moderate-dose statin (N=491)	ABT-335 + Moderate statin (N=489)	High-dose statin (N=245)
Sex						
Female	277 (56.5)	234 (47.5)	263 (53.7)	245 (49.9)	249 (50.9)	125 (51.0)
Male	213 (43.5)	259 (52.5)	227 (46.3)	246 (50.1)	240 (49.1)	120 (49.0)
Race						
White	461 (94.1)	460 (93.3)	446 (91.0)	458 (93.3)	445 (91.0)	227 (92.7)
Black	18 (3.7)	19 (3.9)	29 (5.9)	22 (4.5)	27 (5.5)	11 (4.5)
Other	11 (2.2)	14 (2.8)	15 (3.1)	11 (2.2)	17 (3.5)	7 (2.9)
Ethnicity						
Hispanic	51 (10.4)	51 (10.3)	51 (10.4)	48 (9.8)	45 (9.2)	21 (8.6)
No ethnicity	439 (89.6)	442 (89.7)	439 (89.6)	443 (90.2)	444 (90.8)	224 (91.4)
Age Group (years)						
< 65	402 (82.0)	419 (85.0)	394 (80.4)	408 (83.1)	389 (79.6)	195 (79.6)
≥ 65	88 (18.0)	74 (15.0)	96 (19.6)	83 (16.9)	100 (20.4)	50 (20.4)
Body Weight (kg)						
< 70	68 (13.9)	55 (11.2)	70 (14.3)	59 (12.0)	56 (11.5)	30 (12.2)
≥ 70	422 (86.1)	438 (88.8)	420 (85.7)	432 (88.0)	433 (88.5)	215 (87.8)
Tobacco Use						
User	108 (22.0)	92 (18.7)	106 (21.6)	103 (21.0)	95 (19.4)	60 (24.5)
Ex-User	135 (27.6)	152 (30.8)	142 (29.0)	152 (31.0)	149 (30.5)	72 (29.4)
Non-User	247 (50.4)	249 (50.5)	242 (49.4)	236 (48.1)	245 (50.1)	113 (46.1)
Alcohol Use[a]						
Drinker	257 (52.4)	254 (51.6)	245 (50.0)	248 (50.5)	258 (52.8)	126 (51.4)
Ex-Drinker	38 (7.8)	33 (6.7)	41 (8.4)	31 (6.3)	31 (6.3)	28 (11.4)
Non-Drinker	195 (39.8)	205 (41.7)	204 (41.6)	212 (43.2)	200 (40.9)	91 (37.1)

a. Alcohol use was missing for one subject in the low-dose monotherapy group (N=492)

In the demographic evaluations for the individual controlled studies, two instances of p value < 0.1 was noted: in study M05-748, a discrepancy in sex distribution was noted between groups (p=0.048) and in study M05-749, a discrepancy in one of the categorical age groupings (< 40, 40-60, > 60) was noted between groups (p=0.092).

Table 6.1.3.B. 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=269)	10 mg resava (N=261)	ABT-335 + 10 mg resava (N=261)	20 mg resava (N=266)	ABT-335 + 20 mg resava (N=268)	40 mg resava (N=131)	p-value[a]
Gender							0.048*
Female	152 (56.7)	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)	

resava = resveratrol; 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 resveratrol monotherapy group (N=260).

* = statistically significant at the p = 0.05 level.

Study M05-749, Demographics

Table 6.1.3.C. 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=119)	20 mg simva (N=119)	ABT-335 + 20 mg simva (N=119)	40 mg simva (N=119)	ABT-335 + 40 mg simva (N=118)	80 mg simva (N=59)	p-value[a]
Gender							0.677
Female	68 (57.1)	56 (47.1)	59 (49.6)	61 (52.6)	57 (48.3)	31 (52.5)	
Male	51 (42.9)	63 (52.9)	60 (50.4)	55 (47.4)	61 (51.7)	28 (47.5)	
Race							0.217
White	116 (97.5)	110 (92.4)	108 (90.8)	112 (96.6)	109 (92.4)	55 (93.2)	
Black	1 (0.8)	5 (4.2)	4 (3.4)	2 (1.7)	5 (4.2)	1 (1.7)	
Indian/Alaskan	0	0	1 (0.8)	2 (1.7)	0	0	
Asian	1 (0.8)	4 (3.4)	4 (3.4)	0	3 (2.5)	1 (1.7)	
Other	1 (0.8)	0	2 (1.7)	0	1 (0.8)	2 (3.4)	
Ethnicity							0.887
Hispanic	13 (10.9)	11 (9.2)	11 (9.2)	16 (13.8)	13 (11.0)	6 (10.2)	
No ethnicity	106 (89.1)	108 (90.8)	108 (90.8)	100 (86.2)	105 (89.0)	53 (89.8)	
Age Group (years)							0.092
< 40	15 (12.6)	10 (8.4)	4 (3.4)	9 (7.8)	15 (12.7)	3 (5.1)	
40 to 60	71 (59.7)	79 (66.4)	88 (73.9)	78 (67.2)	69 (58.5)	34 (57.6)	
> 60	33 (27.7)	30 (25.2)	27 (22.7)	29 (25.0)	34 (28.8)	22 (37.3)	
Age Group (years)							0.426
< 65	98 (82.4)	104 (87.4)	101 (84.9)	104 (89.7)	96 (81.4)	48 (81.4)	
≥ 65	21 (17.6)	15 (12.6)	18 (15.1)	12 (10.3)	22 (18.6)	11 (18.6)	
Tobacco Use							0.334
User	29 (24.4)	24 (20.2)	24 (20.2)	25 (21.6)	19 (16.1)	18 (30.5)	
Ex-User	33 (27.7)	43 (36.1)	35 (29.4)	41 (35.3)	39 (33.1)	17 (28.8)	
Non-User	57 (47.9)	52 (43.7)	60 (50.4)	50 (43.1)	60 (50.8)	24 (40.7)	
Alcohol Use							0.516
Drinker	59 (49.6)	71 (59.7)	61 (51.3)	66 (56.9)	62 (52.5)	28 (47.5)	
Ex-Drinker	8 (6.7)	10 (8.4)	10 (8.4)	10 (8.6)	9 (7.6)	8 (13.6)	
Non-Drinker	52 (43.7)	38 (31.9)	48 (40.3)	40 (34.5)	47 (39.8)	23 (39.0)	

simva = simvastatin; 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.

Study M05-750, Demographics

Table 6.1.3.D. 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=112)	20 mg atorva (N=113)	ABT-335 + 20 mg atorva (N=110)	40 mg atorva (N=109)	ABT-335 + 40 mg atorva (N=110)	80 mg atorva (N=55)	p-value[a]
Gender							0.424
Female	57 (50.9)	48 (42.5)	56 (50.9)	60 (55.0)	61 (55.5)	29 (52.7)	
Male	55 (49.1)	65 (57.5)	54 (49.1)	49 (45.0)	49 (44.5)	26 (47.3)	
Race							0.145
White	109 (97.3)	101 (89.4)	102 (92.7)	101 (92.7)	98 (89.1)	48 (87.3)	
Black	2 (1.8)	6 (5.3)	4 (3.6)	2 (1.8)	7 (6.4)	3 (5.5)	
Indian/Alaskan	1 (0.9)	0	0	0	1 (0.9)	0	
Asian	0	4 (3.5)	4 (3.6)	4 (3.7)	3 (2.7)	2 (3.6)	
Other	0	2 (1.8)	0	0	1 (0.9)	1 (1.8)	
Multiracial	0	0	0	2 (1.8)	0	1 (1.8)	
Ethnicity							0.827
Hispanic	10 (8.9)	10 (8.8)	12 (10.9)	7 (6.4)	7 (6.4)	5 (9.1)	
No ethnicity	102 (91.1)	103 (91.2)	98 (89.1)	102 (93.6)	103 (93.6)	50 (90.9)	
Age Group (years)							0.322
< 40	11 (9.8)	13 (11.5)	3 (2.7)	8 (7.3)	11 (10.0)	4 (7.3)	
40 to 60	73 (65.2)	69 (61.1)	71 (64.5)	60 (55.0)	64 (58.2)	32 (58.2)	
> 60	28 (25.0)	31 (27.4)	36 (32.7)	41 (37.6)	35 (31.8)	19 (34.5)	
Age Group (years)							0.709
< 65	95 (84.8)	93 (82.3)	87 (79.1)	87 (79.8)	84 (76.4)	44 (80.0)	
≥ 65	17 (15.2)	20 (17.7)	23 (20.9)	22 (20.2)	26 (23.6)	11 (20.0)	
Tobacco Use							0.556
User	20 (17.9)	16 (14.2)	25 (22.7)	16 (14.7)	18 (16.4)	8 (14.5)	
Ex-User	39 (34.8)	37 (32.7)	27 (24.5)	29 (26.6)	42 (38.2)	17 (30.9)	
Non-User	53 (47.3)	60 (53.1)	58 (52.7)	64 (58.7)	50 (45.5)	30 (54.5)	
Alcohol Use							0.732
Drinker	63 (56.3)	66 (58.4)	57 (51.8)	54 (49.5)	57 (51.8)	32 (58.2)	
Ex-Drinker	5 (4.5)	7 (6.2)	8 (7.3)	6 (5.5)	11 (10.0)	4 (7.3)	
Non-Drinker	44 (39.3)	40 (35.4)	45 (40.9)	49 (45.0)	42 (38.2)	19 (34.5)	

atorva = atorvastatin; 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-users and non-users were combined for analysis of tobacco use; ex-drinkers and non-drinkers were combined for analysis of alcohol use.

Overall, Baseline Lipid Parameters

At baseline, the study population overall had low mean HDL-C (38.4 mg/dL) and high mean TG (282.2 mg/dL) and LDL-C (157.3 mg/dL). A summary of the primary lipid parameters at baseline is presented by treatment group in Table 6.1.3.E.

Table 6.1.3.E. Primary Lipid Parameters at Baseline (Controlled Studies Analysis Set)

Lipid Parameter (mg/dL)	Treatment Group n (%)						p-value[a]
	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + low statin (N=490)	Moderate-dose statin (N=491)	ABT-335 + moderate statin (N=489)	High-dose statin (N=245)	
HDL-C	(N=477)	(N=481)	(N=467)	(N=470)	(N=467)	(N=234)	0.876
Mean	38.6	38.4	38.3	38.4	38.3	37.9	
Median	38.0	38.0	37.0	37.9	38.0	37.0	
Min, max	19.0, 60.0	18.5, 60.0	22.0, 62.0	12.0, 61.0	18.1, 71.0	26.0, 62.0	
TG	(N=490)	(N=493)	(N=490)	(N=491)	(N=489)	(N=245)	0.875
Mean	280.9	284.1	281.2	290.0	287.2	280.4	
Median	236.5	248.7	233.3	247.0	245.0	248.0	
Min, max	55.0, 1700.0	64.0, 1282.0	73.0, 1236.0	72.0, 1704.0	44.0, 1238.0	95.0, 1140.0	
LDL-C	(N=490)	(N=492)	(N=489)	(N=488)	(N=487)	(N=245)	0.497
Mean	158.6	154.0	156.1	156.7	156.8	155.8	
Median	158.0	151.0	151.0	154.0	154.0	155.0	
Min, max	47.9, 296.0	74.0, 325.0	65.0, 324.3	66.0, 266.0	61.0, 350.0	80.0, 278.0	

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

Mean values overall for the secondary efficacy parameters were 220.8 mg/dL for non-HDL-C, 65.6 mg/dL for VLDL-C, 259.6 mg/dL for total-C, and 146.4 mg/dL for apoB; mean value for hsCRP was 0.48 mg/dL, with a median value of 0.29 mg/dL (none of the baseline secondary parameters were statistically different between groups).

A statistically significant difference was observed among treatment groups at baseline in the distribution of values for LpPLA2. The overall mean was 271.7 ng/mL and ranged from 264.7 ng/mL in the ABT-335 in combination with low-dose statin group to 278.7 ng/mL in the moderate-dose statin monotherapy group ($p = 0.046$). Mean values for the other exploratory efficacy parameters were 142.4 mg/dL for ApoAI, 18.4 mg/dL for ApoCIII, and 5611.6 ng/dL for adiponectin.

Overall, Metabolic and Medical Conditions at Baseline

Almost two-thirds (65%) of the study population met the criteria for metabolic syndrome defined as the presence at baseline of three or more of the following criteria:

- Abdominal obesity as measured by waist circumference: > 102 cm (men) and > 88 cm (women)
- TG ≥ 150 mg/dL
- HDL-C < 40 mg/dL (men) and < 50 mg/dL (women)
- Blood pressure ≥ 130/≥ 85 mmHg
- Fasting glucose ≥ 110 mg/dL

Subjects were categorized into the following three Framingham risk categories as defined in the Third Report of the National Cholesterol Education (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

- High (CHD or CHD risk equivalents)
- Moderate (multiple [2+] risk factors)
- Low (zero to one risk factor)

Overall, 35.4% were classified as having high risk, 43.9% were classified as having moderate risk, and 20.8% were classified as having low risk.

Table 6.1.3.F. Demographic and Baseline Characteristics - Metabolic Syndrome and Framingham Risk Category (Controlled Studies Analysis Set)

	Treatment Group n (%)						
Demographic Characteristic	ABT-335 (N=[illegible])	Low-dose statin (N=[illegible])	ABT-335 + Low-dose statin (N=[illegible])	Moderate-dose statin (N=[illegible])	ABT-335 + Moderate-dose statin (N=[illegible])	High-dose statin (N=[illegible])	p-value[a]
Metabolic Syndrome							0.232
Absent	163 (33.3)	189 (38.3)	164 (33.5)	162 (33.0)	179 (36.6)	75 (30.5)	
Present	327 (66.7)	304 (61.7)	326 (66.5)	329 (67.0)	310 (63.4)	170 (69.1)	
Framingham Risk Category							0.182
High	170 (34.7)	159 (32.3)	170 (34.7)	181 (36.9)	178 (36.4)	90 (36.2)	
Moderate	207 (42.2)	215 (43.6)	235 (48.0)	208 (42.4)	215 (44.0)	106 (43.3)	
Low	113 (23.1)	119 (24.1)	85 (17.3)	104 (21.2)	96 (19.6)	43 (17.6)	

a. P-value for differences among treatment groups from Chi-square test.

All but one subject (> 99.9%) cited a history of hyperlipidemia. One subject without hyperlipidemia was randomized into Study M05-748 in error, and was discontinued after 16 days of treatment. Other common medical history conditions overall included hypertension (53.8%), eye disease/disorder (33.1%), GERD (29.9%), osteoarthritis (29.0%), drug allergies/reactions (28.0%), depression (24.9%), obesity (22.6%), and diabetes mellitus (21.7%). In addition, 6.9% of subjects reported a history of coronary artery disease and 3.7% reported a history of myocardial infarction. A summary of medical conditions reported by ≥ 10.0% of subjects in any treatment group (excluding "other" conditions) is presented by treatment group in Table 6.1.3.G.

Table 6.1.3.G. Medical Conditions Reported at Baseline by at Least 10.0% of Subjects in any Treatment Group (Controlled Studies Analysis Set)

	Treatment Group n (%)					
Body System Condition/diagnosis	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + Low-dose statin (N=490)	Moderate-dose statin (N=491)	ABT-335 + Moderate-dose statin (N=489)	High-dose statin (N=245)
Cardiovascular						
Hypertension	264 (53.9)	260 (52.7)	278 (56.7)	254 (51.7)	264 (54.0)	132 (53.9)
Eye/Ear/Nose/Throat						
Eye disease/disorder	145 (29.6)	178 (36.1)	159 (32.4)	162 (33.0)	169 (34.6)	79 (32.2)
Hearing disorder	37 (7.6)	54 (11.0)	50 (10.2)	53 (10.8)	49 (10.0)	31 (12.7)
Gastrointestinal						
GERD	140 (28.6)	146 (29.6)	152 (31.0)	141 (28.7)	149 (30.5)	80 (32.7)
Metabolic						
Diabetes mellitus	105 (21.4)	105 (21.3)	106 (21.6)	107 (21.8)	110 (22.5)	53 (21.6)
Hyperlipidemia	490 (100)	492 (99.8)	490 (100)	491 (100)	489 (100)	245 (100)
Hypothyroidism	48 (9.8)	43 (8.7)	50 (10.2)	42 (8.6)	60 (12.3)	18 (7.3)
Obesity	117 (23.9)	97 (19.7)	109 (22.2)	108 (22.0)	115 (23.5)	64 (26.1)
Musculoskeletal						
Degenerative disc disease	52 (10.6)	42 (8.5)	53 (10.8)	56 (11.4)	43 (8.8)	24 (9.8)
Osteoarthritis	137 (28.0)	126 (25.6)	139 (28.4)	148 (30.1)	158 (32.3)	74 (30.2)
Neurologic and Psychiatric System						
Depression	126 (25.7)	109 (22.1)	130 (26.5)	123 (25.1)	120 (24.5)	64 (26.1)
Migraine headache	69 (14.1)	58 (11.8)	51 (10.4)	70 (14.3)	72 (14.7)	23 (9.4)
Pulmonary						
Asthma	40 (8.2)	41 (8.3)	45 (9.2)	47 (9.6)	51 (10.4)	24 (9.8)
Whole Body						
Drug allergies/reactions	138 (28.2)	139 (28.4)	150 (30.6)	145 (29.5)	140 (28.6)	53 (21.6)

GERD = gastroesophageal reflux disease

6.1.4 Patient Disposition

Overall, the majority of subjects completed each of the controlled studies; reasons for discontinuation from each of the individual studies are presented in tables that follow. The majority of subjects that completed the individual controlled studies went on to participate in the open-label extension study (M05-758).

Table 6.1.4.A. Patient Disposition, Controlled Studies

	ABT-335	Low-dose statin	ABT-335 + Low-dose statin	Moderate-dose statin	ABT-335 + Moderate-dose statin	High-dose statin	Total
Treated in M05-748	259	261	261	266	261	131	1439
Completed	208	237	220	243	220	115	1243
Discontinued	52	28	41	23	42	16	202
Enrolled in M05-758 (% completed 748)	172 (82.7%)	200 (84.4%)	189 (85.9%)	208 (85.6%)	180 (81.8%)	93 (80.9%)	1042 (83.8%)
Treated in M05-749	119	119	119	116	118	59	650
Completed	98	105	103	99	102	48	555
Discontinued	21	16	17	20	16	12	102
Enrolled in M05-758 (% completed 749)	83 (84.7%)	83 (79.0%)	78 (75.7%)	79 (79.8%)	77 (75.5%)	33 (68.8%)	433 (78.0%)
Treated in M05-750	112	113	110	109	110	55	609
Completed	95	104	89	95	89	46	518
Discontinued	18	9	21	15	22	10	95
Enrolled in M05-758 (% completed 750)	77 (81.0%)	90 (86.5%)	78 (87.6%)	81 (85.3%)	75 (84.3%)	35 (76.0%)	436 (84.2%)
Treated in M05-758	329	369	343	364	330	160	1895

Study M05-748

A total of 1445 subjects were randomized and 1439 were treated with at least one dose of study drug. Of the treated subjects, 1243 (86.4%) completed the study and 196 (13.6%) prematurely discontinued study drug. Table 6.1.4.B presents the reasons for discontinuation by treatment group.

Table 6.1.4.B. Reason for Discontinuation – Study M05-748

	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.

Study M05-749

A total of 657 subjects were randomized and 650 were treated with at least one dose of study drug. Of the treated subjects, 555 (85.4%) completed the study and 95 (14.6%) prematurely discontinued study drug. Table 6.1.4.C presents the reasons for discontinuation by treatment group.

Table 6.1.4.C. Reason for Discontinuation – Study M05-749

	ABT-335	ABT-335 + 20 mg simva	ABT-335 + 20 mg simva	ABT-335 + 40 mg simva	ABT-335 + 40 mg simva	80 mg simva	Total
All Randomized Subjects	119	121	120	119	118	60	657
All Treated Subjects	119	119	119	116	118	59	650
Full Analysis Set[a]	113	116	115	112	111	56	621
Safety Analysis Set	119	119	119	116	118	59	650
	Treatment Group n (%)						
Completed Study	98 (82.4)	105 (88.2)	103 (86.6)	99 (85.3)	102 (86.4)	48 (81.4)	555 (85.4)
Prematurely Terminated[b]	21 (17.6)	14 (11.8)	16 (13.4)	17 (14.7)	16 (13.6)	11 (18.6)	95 (14.6)
Adverse event	13 (10.9)	8 (6.7)	8 (6.7)	11 (9.5)	7 (5.9)	4 (6.8)	51 (7.8)
Withdrew consent	3 (2.5)	5 (4.2)	7 (5.9)	5 (4.3)	8 (6.8)	5 (8.5)	33 (5.1)
Lost to follow-up	2 (1.7)	4 (3.4)	2 (1.7)	4 (3.4)	1 (0.8)	2 (3.4)	15 (2.3)
Noncompliance	1 (0.8)	1 (0.8)	2 (1.7)	1 (0.9)	1 (0.8)	1 (1.7)	7 (1.1)
Other	4 (3.4)	3 (2.5)	4 (3.4)	4 (3.4)	7 (5.9)	5 (8.5)	27 (4.2)

simva = simvastatin

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.

Study M05-750

A total of 613 subjects were randomized and 609 were treated with at least one dose of study drug. Of the 609 treated subjects, 518 (85.1%) completed the study and 91 (14.9%) prematurely discontinued study drug. Table 6.1.4.D presents the reasons for discontinuation by treatment group.

Table 6.1.4.D. Disposition of Subjects – Study M05-750

	ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	40 mg atorva	ABT-335 + 40 mg atorva	80 mg atorva	Total
All Randomized Subjects	113	113	110	110	111	56	613
All Treated Subjects	112	113	110	109	110	55	609
Full Analysis Set[a]	104	109	105	105	102	52	577
Safety Analysis Set	112	113	110	109	110	55	609
	Treatment Group n (%)						
Completed Study	95 (84.8)	104 (92.0)	89 (80.9)	95 (87.2)	89 (80.9)	46 (83.6)	518 (85.1)
Prematurely Terminated[b]	17 (15.2)	9 (8.0)	21 (19.1)	14 (12.8)	21 (19.1)	9 (16.4)	91 (14.9)
Adverse event	8 (7.1)	3 (2.7)	12 (10.9)	12 (11.0)	14 (12.7)	6 (10.9)	55 (9.0)
Withdrew consent	4 (3.6)	3 (2.7)	6 (5.5)	5 (4.6)	2 (1.8)	1 (1.8)	21 (3.4)
Lost to follow-up	5 (4.5)	3 (2.7)	1 (0.9)	1 (0.9)	3 (2.7)	1 (1.8)	14 (2.3)
Noncompliance	0	0	3 (2.7)	0	2 (1.8)	2 (3.6)	7 (1.1)
Other	4 (3.6)	2 (1.8)	6 (5.5)	4 (3.7)	3 (2.7)	0	19 (3.1)

atorva = atorvastatin

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.

Study M05-758

Because this open-label extension study is ongoing, the data are provided from an interim analysis with a data lock of September 1, 2007. A total of 1911 subjects were enrolled and 1895 subjects received at least one dose of ABT-335 in combination with moderate-dose statin. Of the 1895 treated subjects, 468 (24.7%) completed treatment, 337 (17.8%) prematurely discontinued, and 1090 (57.5%) were ongoing as of September 1, 2007 (Table 6.1.4.E).

Table 6.1.4.E. Summary of Subject Final Status and Reasons for Discontinuation

	Treatment Group n (%)			
	ABT-335 + 20 mg rosuva (N=1029)	ABT-335 + 40 mg simva (N=432)	ABT-335 + 40 mg atorva (N=413)	Total (N=1898)
Total Completed	306 (29.7)	56 (13.0)	106 (24.4)	468 (24.7)
Total Discontinued	192 (18.7)	73 (16.9)	72 (16.6)	337 (17.8)
Adverse event	92 (8.9)	32 (7.4)	39 (9.0)	163 (8.6)
Withdrew consent	54 (5.2)	20 (4.6)	12 (2.8)	86 (4.5)
Lost to follow-up	32 (3.1)	7 (1.6)	10 (2.3)	49 (2.6)
Subject noncompliant	7 (0.7)	3 (0.7)	3 (0.7)	13 (0.7)
Other	73 (7.1)	32 (7.4)	20 (4.6)	125 (6.6)
Total Ongoing (01Sep2007)	531 (51.6)	303 (70.1)	256 (59.0)	1090 (57.5)

Note: Includes data from Study M05-758.

Note: Subjects who discontinued study drug are counted under each reason given for discontinuation. Therefore, the sum of the counts for the reasons may be greater than the overall number of discontinuations.

6.1.5 Analysis of the Primary Endpoints

Primary Efficacy Endpoints

- HDL-C: ABT-335 in combination with each dose of statin vs. statin monotherapy at the corresponding dose.
- TG: ABT-335 in combination with each dose of statin vs. statin monotherapy at the corresponding dose.
- LDL-C: ABT-335 in combination with each dose of statin vs. ABT-335 monotherapy.

Statistical Considerations

The mean baseline and Final Visit (Week 12) values were summarized for each treatment group. The mean within-group percent changes from baseline were summarized for each treatment group with the standard error and range and the mean between-group differences were summarized with the standard error.

The percent changes from baseline were compared between the combination therapy arms and each corresponding monotherapy arm using ANCOVA with the corresponding baseline lipid value as a covariate and with effects for treatment group, diabetic status (diabetic, non-diabetic) screening TG ($\leq$ 250 mg/dL, > 250 mg/dL) and the interaction of diabetic status by screening TG. Data from all six treatment groups were included when performing the ANCOVA.

Efficacy data for the high-dose statin monotherapy arm were summarized with descriptive statistics. No formal statistical comparisons were made between this treatment arm and the other treatment groups in the study.

The number and percentage of subjects meeting National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Guideline LDL-C and non-HDL-C goals at Week 12 were summarized for each treatment group.

LOCF was used to impute values for subjects missing a post-baseline visit value. In order to assess the impact of missing data on the results, several sensitivity analyses were performed for HDL-C, TG, and direct LDL-C in which all randomized subjects were included in the analyses. These sensitivity analyses included LOCF and zero change imputed, zero change imputed, and a "worst-case" analysis, 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).

Efficacy data for the open-label extension study, M05-758, were descriptive. Baseline was the last value prior to the first dose of combination therapy with the moderate statin dose in Study M05-758. Prior to the baseline values, subjects in the *Initial Statin Monotherapy* analysis set had completed 12 weeks of treatment with either 10 mg, 20 mg, or 40 mg rosuvastatin; 20 mg, 40 mg, or 80 mg simvastatin; or 20 mg, 40 mg, or 80 mg atorvastatin. Subjects in the *Initial ABT-335 Monotherapy* analysis set had completed 12 weeks of treatment with 135 mg ABT-335.

Assay Change

A change in the laboratory procedures for the HDL-C assay at the central laboratory occurred on August 28, 2006. Therefore, for the primary analyses of percent change from baseline to the Final Visit (Week 12) in HDL-C, direct LDL-C and non-HDL-C, measurements with an HDL-C assay date prior to August 28, 2006 were excluded. HDL-C was reassayed for those samples, and recalculated LDL-C and non-HDL-C 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 August 28, 2006) were not included in the primary analyses of these three endpoints.

A sensitivity analysis of percent changes from baseline to the Final Visit was performed for HDL-C, LDL-C and non-HDL-C in which values with an HDL-C assay date prior to August 28, 2006 were included if no HDL-C measurement on or after that date was available.

Protocol Changes

The following statistical changes were made after breaking the blind:

<u>Study M05-748</u>

- Additional summaries of demographics and concomitant medications to further characterize the study population.
- Additional details were added to further explain the calculation of study drug duration and compliance.
- Ninety-five percent confidence intervals were added for the primary and secondary efficacy variables to further characterize the treatment effect.

- The interactions of the randomization stratification factors (diabetic status and screening TG) by treatment group were not a main focus of the analyses of the study and thus testing of these interactions was limited to the primary and secondary efficacy variables.
- Since there was a significant difference among treatment groups in gender, an additional analysis of the primary endpoints was performed including gender as a factor in the model.

Study M05-749

- Additional summaries of demographics and concomitant medications to further characterize the study population.
- Additional details were added to further explain the calculation of study drug duration and compliance.
- Ninety-five percent confidence intervals were added for the primary and secondary efficacy variables to further characterize the treatment effect.
- The interactions of the randomization stratification factors (diabetic status and screening TG) by treatment group were not a main focus of the analyses of the study and thus testing of these interactions was limited to the primary and secondary efficacy variables.
- Summary of shifts in LDL size and a summary of changes in lipid ratios were added to further characterize the efficacy variables.
- To further characterize the safety details additional analyses were added.

Study M05-750

- Additional summaries of demographics and concomitant medications to further characterize the study population.
- Additional details were added to further explain the calculation of study drug duration and compliance.
- Ninety-five percent confidence intervals were added for the primary and secondary efficacy variables to further characterize the treatment effect.
- The interactions of the randomization stratification factors (diabetic status and screening TG) by treatment group were not a main focus of the analyses of the study and thus testing of these interactions was limited to the primary and secondary efficacy variables.
- Since there was a significant difference among treatment groups in gender, an additional analysis of the primary endpoints was performed including gender as a factor in the model.

Protocol Deviations

Study M05-748

All but nine subjects satisfied all the inclusion criteria. Forty-nine subjects from 42 discrete sites met an exclusion criterion. The following subjects (Table 6.1.5.A) were noted to have violated entry criteria during the study.

Table 6.1.5.A. Subjects Not Meeting Entry Criteria, Study M05-748

Criterion #	Inclusion/Exclusion Criterion Description	Subjects Not Meeting Criterion
Inclusion #3 (8 subjects)	Subject had the following fasting parameter results after a ≥ 12-hour fasting period, measured at the Screening Visit[s] (prior to Baseline): TG level ≥ 150 mg/dL; HDL-C < 40 mg/dL for men and < 50 mg/dL for women; and LDL-C ≥ 130 mg/dL	#14001, #14221, #13177, #12105, #13195, #13234, #13126, #13028
Inclusion #5 (1 subject)	Female subjects of childbearing potential (defined as not surgically sterile or postmenopausal) had a negative pregnancy test at the Screening Visit	#13179 (no pregnancy test at the Screening Visit; all subsequent pregnancy tests were negative)
Exclusion #4[a] (1 subject)	Subject was of Asian ancestry	#13475
Exclusion #5 (7 subjects)	Type I diabetes mellitus, or history of diabetic ketoacidosis, or uncontrolled Type II diabetes mellitus	#14093, #12065, #11057, #13323, #14153, #13227, #13375
Exclusion #6 (6 subjects)	History of pancreatitis or gall bladder disease	#14280, #11076, #13065, #14484, #13515, #12080
Exclusion #8 (9 subjects)	History of oncologic, hematologic, gastrointestinal, hepatic, renal, or a neurological disorder that would have limited study evaluation or participation	#14231, #12148, #14104, #14275, #14276, #14383, #13501, #14268, #13289
Exclusion #9 (1 subject)	Evidence of unstable cardiovascular disease	#13351
Exclusion #14 (4 subjects)	Initiated, discontinued, or changed dosage of hormone replacement therapy, including estrogen, progesterone, testosterone, and/or thyroid hormone supplementation therapy, within eight weeks of the Prescreening Visit	#14263, #13567, #13124, #13419
Exclusion #15 (6 subjects)	Received coumarin anticoagulants, cyclosporine, nicotinic acid, bile acid-binding resins, or any agents to alter lipid levels (e.g., statins, fibric acid derivatives, fish oil) within six weeks of enrollment	#14001, #14202, #13073, #13125, #11025, #14499
Exclusion #16 (17 subjects)	Abnormal screening laboratory results: ALT or AST > 1.5 × ULN, CPK level > 3 × ULN, calculated creatinine clearance < 50 mL/min, or TSH level outside central laboratory reference range	#13323, #11094, #14079, #14111, #13418, #13315, #13314, #14171, #13006, #13510, #12019, #13389, #14095, #13285, #14515, #14357, #14229

Protocol deviations during the study included receipt of the wrong treatment or incorrect dose, or use of an excluded medication. Fifty-seven subjects received the wrong treatment or incorrect dose. Five subjects received one study drug kit of the wrong treatment group during the study. Forty-one subjects received an excluded concomitant medication. The most commonly used excluded medication was oral prednisone/prednisolone. Two subjects (#13379 and #14164) both received the wrong treatment or incorrect dose and used an excluded medication.

The randomization schedule was stratified by diabetic status and screening TG level. These stratification factors were included in analyses of the efficacy parameters. Twenty-nine subjects were assigned to the wrong strata at the time of randomization. That is, the diabetic status and/or screening TG level given at the time of randomization did not match the medical history and/or laboratory data, respectively. Sixteen subjects were randomized according to the incorrect diabetic status and 14 subjects were randomized according to the incorrect screening TG level. One of these subjects (#13566) was mismatched on both factors.

Table 6.1.5.B. Summary of Subjects Incorrectly Stratified by Diabetic Status and/or Screening TG Level

Randomization Strata	Subjects Incorrectly Stratified
Diabetic stratum but no history of diabetes	#11042
Non-diabetic stratum but history of diabetes	#13218, #13228, #13294, #13383, #14385, #13405, #13566, #14068, #14077, #14181, #14188, #14367, #14376, #14413, #14550
Screening TG stratum ≤ 250 but screening value > 250 mg/dL	#13040, #13095, #13177, #13260, #13443, #13566
Screening TG stratum > 250 but screening value ≤ 250 mg/dL	#12091, #12135, #14054, #14284, #14344, #14471
No screening TG value	#13004, #14221

Due to the small percentage of subjects incorrectly stratified at the time of randomization, subjects were analyzed according to the randomization strata. No additional efficacy analyses were performed correcting for these mismatches.

Comment: This reviewer tallied the treatment groups of these subjects who were incorrectly stratified and found fairly equal subject distribution among groups (ABT-335 = 5, ABT-335 + rosuva 10 mg = 4, ABT-335 + rosuva 20 mg = 5, rosuva 10 mg = 3, rosuva 20 mg = 6, rosuva 40 mg = 5, and one subject [#13004] did not receive study drug).

Study M05-749

All but six subjects satisfied all the inclusion criteria. Thirty-three subjects from 31 discrete sites met an exclusion criterion. The following subjects (Table 6.1.5.C) were noted to have violated entry criteria during the study.

Table 6.1.5.C. Subjects Not Meeting Entry Criteria, Study M05-749

Criterion #	Inclusion/Exclusion Criterion Description	Subjects Not Meeting Criterion
Inclusion #3 (2 subjects)	Subject had the following fasting parameter results after a ≥ 12-hour fasting period, measured at the Screening Visit[s] (prior to Baseline): TG level ≥ 150 mg/dL; HDL-C < 40 mg/dL for men and < 50 mg/dL for women; and LDL-C ≥ 130 mg/dL	#22010, #21061
Inclusion #5 (4 subjects)	Female subjects of childbearing potential (defined as not surgically sterile or postmenopausal) had a negative pregnancy test at the Screening Visit.	#24108, #24214, #24191, #23255 (no pregnancy test at Screening Visit; all subsequent pregnancy tests were negative)
Exclusion #3 (1 subject)	Used an investigational drug within 42 days of the Baseline Visit.	#24047
Exclusion #4 (1 subject)	Type I diabetes mellitus, history of diabetic ketoacidosis, or uncontrolled type II diabetes mellitus (defined as hemoglobin A_{1c} of > 8.5%).	#22034
Exclusion #5 (5 subjects)	History of pancreatitis or gall bladder disease. Subjects with gall bladder disease who had previously undergone a cholecystectomy were allowed to enroll.	#23169, #23148, #22026, #23139, #24140
Exclusion #6 (1 subject)	History of gastric or duodenal ulcer within three months of the Prescreening Visit.	#24023
Exclusion #7 (2 subjects)	Significant history of oncologic, hematologic, gastrointestinal, hepatic, renal, or a neurological disorder (cerebrovascular disease, degenerative disease) that would have limited study evaluation or participation.	#24136, #23192
Exclusion #8 (3 subjects)	Evidence of unstable cardiovascular disease.	#22064, #22050, #24023
Exclusion #13 (2 subjects)	Initiated, discontinued, or changed dosage of hormone replacement therapy, including estrogen, progesterone, testosterone, and/or thyroid hormone supplementation therapy, within eight weeks of the Prescreening Visit.	#24040, #24112

Seven subjects received the wrong treatment or incorrect dose. Two subjects received one study drug kit of the wrong treatment group on a single occasion. Thirty-five subjects received an excluded concomitant medication. The most commonly used excluded medication was oral prednisone/prednisolone. Six subjects developed withdrawal criteria during the study and were not withdrawn.

Twenty-one subjects were assigned to the wrong diabetic status and screening TG level strata prior to randomization. Ten subjects were randomized according to the incorrect diabetic status and eleven subjects were randomized according to the incorrect screening TG level. Due to the small percentage of subjects incorrectly stratified at the time of randomization, subjects were analyzed according to the randomization strata.

Study M05-750

All but four subjects satisfied all the inclusion criteria. Ten subjects from nine discrete sites met an exclusion criterion. The following subjects (Table 6.1.5.D) were noted to have violated entry criteria during the study.

Table 6.1.5.D. Subjects Not Meeting Entry Criteria, Study M05-750

Criterion #	Inclusion/Exclusion Criterion Description	Subjects Not Meeting Entry Criterion
Inclusion #3 (3 subjects)	Subject had the following fasting parameter results after a ≥ 12-hour fasting period, measured at the Screening Visit[s] (prior to Baseline): HDL-C < 40 mg/dL for men and < 50 mg/dL for women, TG level ≥ 150 mg/dL, and LDL-C ≥ 130 mg/dL.	#33163, #33003, #33044
Inclusion #5 (1 subject)	Female subjects of childbearing potential (defined as not surgically sterile or postmenopausal) had a negative pregnancy test at the Screening Visit	#31052 (no pregnancy test at screening visit; all subsequent pregnancy tests were negative)
Exclusion #1 (1 subject)	Subject had a history of an allergic reaction or significant hypersensitivity to fenofibrate, ABT-335, anoveranib, or any inactive materials contained in the study drug formulations	#34135
Exclusion #4 (2 subjects)	Subject had type I diabetes mellitus, history of diabetic ketoacidosis, or uncontrolled type II diabetes mellitus	#31009, #31015
Exclusion #7 (1 subject)	Subject had a significant history of oncologic, hematologic, gastrointestinal, hepatic, renal, or a neurological disorder (cerebrovascular disease, degenerative disease) that would have limited study evaluation or participation	#31003
Exclusion #14 (3 subjects)	Subjects received nicotinic acid, bile acid binding resins, HMG-CoA reductase inhibitors (statins), fibric acid derivatives, ezetimibe, sibutramine, orlistat, oral corticosteroids, oral garlic supplements, fish oil, plant stanols, or other agents/supplements used specifically to alter lipid levels or received coumarin anticoagulants, macrolide or ketolide antibiotics, azole antifungals, or cyclosporine within six weeks of enrollment	#32043, #33137, #33067
Exclusion #15 (3 subjects)	Screening laboratory analyses showed any of the following abnormal laboratory results: ALT/SGPT or AST/SGOT > 1.5 × upper limit of normal (ULN), CPK level > 3 × ULN, calculated creatinine clearance < 50 mL/min (< 0.83 mL/s), or TSH level outside the central laboratory reference range	#33095, #32002, #32071

Fourteen subjects received the wrong treatment or incorrect dose. One subject was dispensed the wrong study drug kit on a single occasion. Twenty-two subjects received an excluded concomitant medication. The most commonly used excluded medications were antibiotics and prednisone/prednisolone.

Twenty subjects were incorrectly stratified by diabetic status and/or screening TG level at the time of randomization. Fifteen subjects were randomized according to the incorrect diabetic status and six subjects were randomized according to the incorrect screening TG level. One of these subjects (#33069) was mismatched on both factors. Due to the small percentage of

subjects incorrectly stratified at the time of randomization, subjects were analyzed according to the randomization strata.

Results

In each study, ABT-335 in combination with both low and moderate statin doses resulted in significantly greater increases in HDL-C and decreases in TG compared to statin monotherapy and significantly greater decreases in LDL-C compared to ABT-335 monotherapy.

Study M05-748

All of the primary efficacy analyses were highly statistically significant.

Table 6.1.5.E. 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

Comments: LDL-lowering appears to be less robust with ABT-335 monotherapy than is seen with fenofibrate in Tricor and other fenofibrate labels. Some of the diminished response is likely due to the inclusion of subjects with very high TG or low LDL-C (see Section 6.1.7). Nevertheless, without a placebo group, the true treatment effect is unknown. It may be that dietary changes were less emphasized in this trial than in trials past, or these subjects had already made beneficial lifestyle changes prior to enrollment. It appears that fenofibrate LDL-lowering efficacy varies among various (more current) clinical trials; this is discussed further in Section 6.1.7.

These findings do not reflect changes that would occur if the study was designed to evaluate the addition of ABT-335 on the various lipid parameters to already maximal (or optimal for LDL-lowering) statin therapy.

Statistical analyses were also conducted on the comparisons not formally analyzed as primary efficacy comparisons:

- Combination therapy vs. monotherapy ABT-335 for HDL-C and TG
- Combination therapy vs. monotherapy statin for LDL-C

The TG and HDL-C comparisons were statistically significant in favor of the combination vs. ABT-335 monotherapy. However, with respect to mean percent LDL-C change, there was no statistically significant difference between rosuvastatin 10 mg monotherapy and combination therapy (-38.0% vs -37.2%, p=0.620) and, in fact, 20 mg rosuvastatin monotherapy was *superior* to the combination therapy for LDL-lowering (-38.8% vs. -45.0%, $p < 0.001$).

Comments: Consistent with this finding, the overall data (see Table 6.1.5.E, below) suggest that there is some attenuation of the LDL-C decrease with the addition of ABT-335 to the moderate dose of statin. This reviewer conducted additional analyses to determine if there was a subgroup (i.e., baseline high TG, low HDL-C, or low LDL-C) that would predict who might be at risk from having an adverse LDL-C effect with the combination therapy as compared to statin monotherapy. Individuals with very high TG have been identified as a subgroup likely to have an increase in LDL-C with fenofibrate[11], and this is demonstrated when comparing subjects with baseline TG ≤ 200 mg/dL vs. > 200 mg/dL. However, removing subgroups of patients with very high TG (≥ 500 mg/dL, ≥ 1000 mg/dL) did not affect efficacy conclusions, likely due to the relatively small numbers. Section 6.1.7 has more detail on subgroups.

The sponsor described this phenomenon as follows: PPAR-α activation leads to an increase in lipoprotein lipase activity, which accelerates the conversion of very low-density lipoprotein (VLDL) to LDL via intermediate-density lipoprotein (IDL). As a result, the increase in LDL-C liberated from VLDL-C mitigates the magnitude of LDL-C reduction, especially in patients with high TG and only moderately elevated LDL-C, such as those with mixed dyslipidemia studied in the ABT-335 development program.

These results should be presented in the in the Clinical Studies section of Trilipix labeling. Individuals on statins for LDL-lowering who are to be started on add-on ABT-335 therapy for high TG and/or low HDL-C should have LDL-C carefully monitored for any significant worsening. This is discussed further with the results of the open-label extension study, M05-758.

No statistical analysis was conducted evaluating the highest dose of rosuvastatin (40 mg); therefore, these findings are considered descriptive. Mean change in HDL-C was 9.3%, TG was -32.1%, and LDL-C was -50.6%.

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11 Tricor PI, NDA 21-656

Comment: The following observations are this reviewer's interpretation of the data that includes the highest dose of rosuvastatin:

1. **Rosuvastatin 40 mg increased mean HDL-C less than ABT-335 monotherapy.**
2. **Triglyceride lowering at the highest dose of rosuvastatin is comparable to that of ABT-335 monotherapy.**
3. **The addition of ABT-335 to low- to moderate-dose rosuvastatin provides greater TG lowering (43-47%) than high-dose rosuvastatin.**
4. **LDL-lowering with rosuvastatin 40 mg was greater than any of the other groups, including ABT-335 added to moderate-dose rosuvastatin.**

Although the study was not designed to test this question specifically, if a patient is on moderate dose rosuvastatin and needs further LDL-C lowering, it might make sense to increase the rosuvastatin dose rather than add ABT-335. This is consistent with the recommended use of a statin as first-line therapy to reduce CV outcomes based on CV outcome trial data for this class. How high TG or low HDL-C should be managed once LDL-C is at goal is up to the discretion of the physician; fibrates are a viable option based on NCEP ATPIII guidelines.[1] However, based on these data, incrementally increasing rosuvastatin to meet goals might be an option as well. High-dose statin results should be included in the Clinical Studies section of labeling.

Study M05-749

All of the primary efficacy analyses were highly statistically significant.

Table 6.1.5.F. 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	156.9		156.4
Final mean	147.1	117.5	116.6		108.1	113.3		92.7
Mean % Δ	-4.0%	-22.4%	-24.9%	< 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

In contrast to the findings from the rosuvastatin study (M05-748), there was no significant difference between ABT-335 and combination therapy (both doses) for HDL-C changes or for ABT-335 monotherapy and the low-dose combination therapy for TG changes. Furthermore, combination therapy did not offer any significant benefit for LDL-lowering when compared to

simvastatin monotherapy, and as with rosuvastatin, was associated with a significantly lesser LDL-lowering effect than the moderate-dose statin monotherapy.

Study M05-750

All of the primary efficacy analyses were highly statistically significant.

Table 6.1.5.G. 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	98.8	102.1		94.0	98.7		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

A novel finding was seen in this atorvastatin study in contrast to the other controlled studies: a greater mean percent increase in HDL-C was observed with the ABT-335 monotherapy group vs. the low-dose combination therapy (19.8% vs. 13.9%, p = 0.003) and vs. the moderate-dose combination therapy group (19.8% vs. 12.5%, p = 0.010). The combination therapy was not significantly different in LDL-lowering than either of the respective atorvastatin monotherapies.

Comment: The ABT-335 group had a higher increase in HDL-C in this study (~19%) than in the other two studies (~15-16%) and the increase of HDL-C with atorvastatin was less than with statins in the other two studies.

Study M05-758

Of particular interest, given the findings of attenuated LDL-C decrease with combination therapy compared with moderate-dose statin monotherapy, was the initial moderate-dose statin analysis set. This analysis evaluated the lipid changes in the group that was initially treated with moderate-dose statin prior to switching to the combination therapy in the open-label portion of the study.

Comment: This analysis set is the closest to providing information about lipid changes that might occur in a real-world setting where a patient who achieves LDL-C goals but is not at TG/non-HDL-C target despite statin therapy would be provided add-on ABT-335.

However, the study was not designed to provide combination therapy to those that would qualify for combination therapy based on NCEP targets. One advantage to this study design is that subjects were not discontinued per protocol for lipid rescue; therefore, the benefit of the combination is not falsely overstated.

Table 6.1.5.H. Percent Change from Baseline of Study M05-758 to Each Time Point in HDL-C, TG, and LDL-C (Initial Combination Therapy at the Low Statin Dose and Initial Statin Monotherapy at the Moderate Statin Dose Analysis Sets)

Weeks on Open-Label Combination Therapy	HDL-C		TG		LDL-C	
	Initial Combination at Low Statin Dose	Initial Moderate-Dose Statin Monotherapy	Initial Combination at Low Statin Dose	Initial Moderate-Dose Statin Monotherapy	Initial Combination at Low Statin Dose	Initial Moderate-Dose Statin Monotherapy
4 Weeks	(N=328)	(N=357)	(N=328)	(N=357)	(N=328)	(N=354)
BL mean	45.1	41.1	140.1	201.1	102.8	92.5
Visit mean	45.0	44.1	136.6	148.4	93.6	95.0
Mean % Δ	0.5%	7.8%	3.9%	-19.8%	-7.3%	5.2%
8 Weeks	(N=313)	(N=335)	(N=313)	(N=335)	(N=313)	(N=334)
BL mean	45.1	41.3	140.4	194.5	100.0	92.6
Visit mean	45.0	44.2	133.4	148.9	94.8	96.3
Mean % Δ	0.9%	7.7%	1.8%	-20.2%	-6.3%	7.2%
12 Weeks	(N=311)	(N=337)	(N=311)	(N=337)	(N=311)	(N=336)
BL mean	45.1	41.1	140.0	196.4	100.0	92.8
Visit mean	44.8	43.7	132.7	148.6	95.6	100.0
Mean % Δ	0.1%	6.8%	0.0%	-22.2%	-6.2%	10.4%
16 Weeks	(N=304)	(N=322)	(N=304)	(N=322)	(N=301)	(N=323)
BL mean	45.3	41.1	138.8	193.1	100.2	92.9
Visit mean	45.4	44.5	130.3	136.9	93.7	96.1
Mean % Δ	1.4%	8.9%	1.3%	-22.8%	-7.9%	6.1%
20 Weeks	(N=284)	(N=304)	(N=284)	(N=305)	(N=280)	(N=304)
BL mean	45.0	41.1	138.8	195.1	101.8	91.6
Visit mean	46.2	45.3	130.2	136.8	93.1	95.2
Mean % Δ	3.0%	10.9%	1.0%	-23.0%	-7.0%	6.3%
28 Weeks	(N=212)	(N=230)	(N=212)	(N=230)	(N=211)	(N=230)
BL mean	45.2	41.7	139.4	195.8	98.8	90.7
Visit mean	47.0	46.7	132.8	132.0	88.4	92.2
Mean % Δ	4.9%	12.6%	3.7%	-21.7%	-8.7%	3.2%
32 Weeks	(N=87)	(N=87)	(N=87)	(N=87)	(N=88)	(N=87)
BL mean	45.9	42.6	130.8	182.6	94.9	90.9
Visit mean	48.0	48.6	133.7	133.4	83.7	90.9
Mean % Δ	4.7%	10.6%	2.6%	-20.1%	-10.9%	2.9%

Baseline represents the last value prior to the first dose of combination therapy in the open-label study.
All weeks represent the open-label study.

Comment: As discussed in comments of the controlled studies results in which the moderate-dose combination was found to be significantly adverse with respect to LDL-C, it is of considerable importance that the LDL-C efficacy is diminished in the subgroup of subjects originally randomized to moderate-dose statin monotherapy who are continued in the extension and treated with OL combination therapy (up to an increase of 10% at 12 weeks). There is clearly a subgroup of subjects, not obviously identified in this dataset, whose LDL-C responds adversely to ABT-335. As noted previously, these subjects were not selected for enrollment in the OL trial based on the need for further TG/non-HDL-lowering, so it will be important to monitor lipids carefully after starting combination therapy.

The following table illustrates the persistence of effects: these are the primary efficacy variable changes in the open label trial in the subset of subjects who were randomized to any and the moderate-dose combination therapy during the 12-week controlled trials.

Table 6.1.5.I. Percent Change from Baseline to Each Time Point in HDL-C, TG, and LDL-C (Initial Combination Therapy and Initial Combination Therapy at the Moderate Statin Dose Analysis Sets)

	HDL-C		TG		LDL-C	
	Initial Combination Therapy	Initial Combination at Moderate Statin Dose	Initial Combination Therapy	Initial Combination at Moderate Statin Dose	Initial Combination Therapy	Initial Combination at Moderate Statin Dose
Week 4	(N=822)	(N=457)	(N=822)	(N=457)	(N=810)	(N=454)
BL mean	38.7	38.7	284.9	284.0	133.7	133.6
Visit mean	45.6	45.3	143.3	139.9	96.9	93.5
Mean % Δ	18.6%	18.1%	-44.9%	-44.9%	-35.7%	-38.2%
Week 8	(N=804)	(N=436)	(N=804)	(N=436)	(N=800)	(N=436)
BL mean	38.6	38.6	283.1	288.1	133.9	133.6
Visit mean	46.1	45.9	142.4	140.0	99.7	97.6
Mean % Δ	20.2%	20.1%	-44.7%	-45.9%	-33.8%	-34.8%
Week 12	(N=812)	(N=405)	(N=812)	(N=405)	(N=808)	(N=405)
BL mean	38.5	38.5	284.9	289.1	133.5	133.6
Visit mean	45.0	45.0	141.4	141.0	104.7	99.8
Mean % Δ	17.9%	17.9%	-45.7%	-45.5%	-32.2%	-33.2%
Week 16	(N=633)	(N=313)	(N=633)	(N=313)	(N=627)	(N=310)
BL mean	38.5	38.4	288.6	297.6	133.1	134.4
Visit mean	45.2	45.3	140.8	145.5	96.1	98.7
Mean % Δ	18.2%	19.2%	-46.6%	-45.2%	-35.7%	-33.4%
Week 20	(N=608)	(N=298)	(N=608)	(N=298)	(N=608)	(N=298)
BL mean	38.5	38.4	288.4	298.5	134.9	133.4
Visit mean	45.1	45.2	136.4	138.7	96.9	98.9
Mean % Δ	18.8%	18.9%	-47.3%	-46.9%	-35.2%	-32.8%
Week 24	(N=605)	(N=297)	(N=605)	(N=297)	(N=605)	(N=297)
BL mean	38.5	38.3	288.5	298.9	134.8	133.5
Visit mean	44.8	44.7	133.4	137.7	97.4	98.5
Mean % Δ	17.9%	17.9%	-48.1%	-47.4%	-35.1%	-32.8%
Week 28	(N=600)	(N=293)	(N=600)	(N=293)	(N=602)	(N=292)
BL mean	38.4	38.2	289.6	298.7	134.4	133.1
Visit mean	45.0	44.8	135.0	137.9	98.5	96.9
Mean % Δ	18.1%	18.3%	-48.1%	-47.2%	-36.2%	-34.3%

	HDL-C		TG		LDL-C	
	Initial Combination Therapy	Initial Combination at Moderate Statin Dose	Initial Combination Therapy	Initial Combination at Moderate Statin Dose	Initial Combination Therapy	Initial Combination at Moderate Statin Dose
Week 40	(N=573)	(N=283)	(N=573)	(N=283)	(N=572)	(N=283)
BL mean	38.3	38.2	290.4	298.7	134.1	132.8
Visit mean	46.1	46.1	134.2	137.7	94.4	96.0
Mean % Δ	21.1%	21.9%	-48.7%	-48.3%	-30.8%	-34.9%
Week 52	(N=428)	(N=214)	(N=428)	(N=214)	(N=427)	(N=214)
BL mean	38.5	38.5	294.4	301.3	132.5	132.7
Visit mean	47.3	47.6	133.5	138.3	96.7	93.7
Mean % Δ	24.0%	23.5%	-47.6%	-47.2%	-30.2%	-30.7%
Week 64	(N=165)	(N=78)	(N=165)	(N=78)	(N=164)	(N=78)
BL mean	39.1	39.8	288.3	297.0	140.5	140.3
Visit mean	46.2	46.5	130.8	127.6	85.3	87.1
Mean % Δ	24.3%	23.0%	-47.8%	-49.0%	-41.0%	-38.4%

Comment: It is reassuring that the mean LDL-C remained below 100 mg/dL and the mean TG remained below 150 mg/dL throughout the 12-month trial in both analysis sets.