Finally the following table illustrates the overall mean percent change at each assessment in the primary efficacy parameters for the *Initial Statin Monotherapy* and *Initial ABT-335 Monotherapy* analysis sets.

Table 6.1.5.J. Percent Change from Baseline to Each Time Point in HDL-C, TG, and LDL-C (Initial Statin Monotherapy and Initial ABT-335 Monotherapy Analysis Sets)

Weeks on Open-Label Combination Therapy	HDL-C		TG		LDL-C	
	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy
4 Weeks	(N=875)	(N=320)	(N=875)	(N=321)	(N=868)	(N=318)
BL mean	41.2	44.7	190.0	171.3	94.0	148.1
Visit mean	44.5	45.6	143.8	130.4	94.3	93.6
Mean % Δ	8.7%	3.2%	-21.6%	-17.3%	3.2%	-36.3%
8 Weeks	(N=819)	(N=310)	(N=819)	(N=310)	(N=815)	(N=309)
BL mean	41.3	44.6	195.4	169.5	94.4	149.1
Visit mean	44.7	44.9	139.8	137.7	98.5	95.4
Mean % Δ	8.8%	1.1%	-22.6%	-12.6%	3.2%	-35.7%
12 Weeks	(N=812)	(N=308)	(N=812)	(N=308)	(N=810)	(N=308)
BL mean	41.2	44.5	196.4	172.0	94.3	148.3
Visit mean	44.4	44.5	139.2	137.2	98.1	98.9
Mean % Δ	8.4%	1.0%	-23.7%	-13.8%	7.0%	-34.1%
16 Weeks	(N=777)	(N=291)	(N=777)	(N=291)	(N=775)	(N=291)
BL mean	41.3	44.6	194.2	169.9	94.2	148.6
Visit mean	43.0	45.8	133.9	137.4	95.8	95.2
Mean % Δ	0.8%	2.9%	-25.6%	-15.8%	4.5%	-33.3%
20 Weeks	(N=736)	(N=276)	(N=736)	(N=276)	(N=734)	(N=276)
BL mean	41.1	44.6	198.5	170.3	93.8	147.2
Visit mean	45.8	45.6	135.4	139.9	94.5	93.7
Mean % Δ	12.4%	3.3%	-25.6%	-15.9%	4.0%	-35.8%
28 Weeks	(N=542)	(N=206)	(N=543)	(N=205)	(N=543)	(N=205)
BL mean	41.6	44.6	193.6	168.5	92.1	146.9
Visit mean	47.2	48.4	133.2	129.4	92.5	87.4
Mean % Δ	14.0%	5.3%	-25.3%	-17.9%	2.7%	-39.9%
52 Weeks	(N=222)	(N=81)	(N=222)	(N=81)	(N=222)	(N=81)
BL mean	42.5	44.9	192.6	163.2	92.0	152.5
Visit mean	48.7	47.6	133.9	130.6	90.4	94.0
Mean % Δ	14.2%	6.8%	-28.7%	-15.9%	0.4%	-37.6%

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: For all lipid parameters, subjects initially treated with ABT-335 monotherapy demonstrated beneficial changes upon addition of a moderate-dose statin. As expected, those initially treated with a statin as monotherapy (any dose) demonstrated improvements in HDL-C and TG, but had mean increases from 0.4% to 7% in LDL-C.

Overall

Comparisons across Studies

The differences in the magnitude of treatment effect of the primary lipid parameters that were seen across studies reflect the efficacy differences in the studied statins. The greatest treatment effect for all the lipid parameters was generally observed in the rosuvastatin study (M05-748). For HDL-C, mean percent increases were generally similar in Study M05-748 (rosuvastatin) and Study M05-749 (simvastatin) but were lower in Study M05-750 (atorvastatin). For LDL-C, mean percent decreases were generally similar in Study M05-748 and Study M05-750 but were lower in Study M05-749. For TG, mean percent decreases with the moderate-dose statin combination were similar in all three studies but were lower with the low-dose statin

combination in Study M05-749 than in the low-dose statin combination in Study M05-748 and Study M05-750.

Table 6.1.5.K. 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%

Controlled Analyses Set

The following table describes the changes overall when the primary efficacy results from the three controlled trials are combined.

Table 6.1.5.L. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C (Controlled Studies Analysis Set)

	ABT-335 (N=498)	Low-dose statin (N=493)	ABT-335 + Low-dose statin (N=498)	p-value	Moderate-dose statin (N=491)	ABT-335 + Moderate-dose statin (N=489)	p-value	High-dose statin (N=245)
HDL-C	(N=420)	(N=455)	(N=423)		(N=430)	(N=422)		(N=217)
BL mean	38.4	38.4	38.2		38.4	38.1		38.0
Final mean	44.3	40.7	44.8		41.1	44.3		40.6
Mean % Δ	16.3%	7.4%	18.1%	< 0.001[a]	8.7%	17.5%	< 0.001[a]	7.9%
TG	(N=459)	(N=477)	(N=470)		(N=472)	(N=462)		(N=235)
BL mean	280.7	286.1	282.1		287.9	286.1		282.5
Final mean	177.3	217.6	146.7		202.5	147.5		186.1
Mean % Δ	-31.0%	-16.8%	-43.9%	< 0.001[a]	-23.7%	-42.0%	< 0.001[a]	-28.1%
LDL-C	(N=427)	(N=463)	(N=436)		(N=439)	(N=434)		(N=225)
BL mean	158.4	153.8	155.7		158.0	156.4		156.1
Final mean	146.1	100.6	101.9		91.6	99.1		81.7
Mean % Δ	-5.1%	-33.9%	-33.1%	< 0.001[b]	-40.6%	-34.6%	< 0.001[b]	-47.1%

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

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

Comment: These data reinforce the inappropriateness of ABT-335 monotherapy for treatment of lipid disorders requiring LDL-lowering for cardiovascular benefit. 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 changes.

Supplementary Analyses

This reviewer constructed descriptive tables of clinically relevant categorical endpoints achieved on the last (week 12) study visit for the primary variables LDL-C, HDL-C, and TG. Additionally, the sponsor provided an assessment of the proportion of subjects meeting NCEP ATP III goals. These categorical analyses are presented in the Exploratory Analyses subsection.

Sensitivity Analyses

In order to assess the impact of missing data on the efficacy results, the sponsor performed the following sensitivity analyses in which all randomized subjects were included in the analyses of the primary efficacy endpoints in each double-blind study: use of multiple imputations, LOCF and zero change imputed, zero change imputed, median value imputed, and a "worst-case" analysis. 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). For the "worst-case" analysis, 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). In all three studies, results were consistent with the primary efficacy results, such that statistically significant differences were observed between each combination therapy group and the corresponding monotherapy group for all comparisons of the primary efficacy variables. Greater percent increases in HDL-C and greater percent decreases in TG and LDL-C were observed in the combination therapy groups than in the corresponding monotherapy groups. The following table presents the worst-case analysis for the Controlled Studies Analysis Set:

Table 6.1.5.M. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C - Worst-Case Analysis (Controlled Studies Analysis Set - All Randomized Subjects)

Treatment Group	N	BL Mean	Final Mean	Mean % Δ	p-value
HDL-C (mg/dL)					
Low-dose statin	499	38.4	41.5	9.2%	< 0.001[a]
ABT-335 + low-dose statin	491	38.4	44.3	16.0%	
Moderate-dose statin	495	38.3	41.8	10.4%	< 0.001[a]
ABT-335 + moderate-dose statin	491	38.4	44.3	15.8%	
TG (mg/dL)					
Low-dose statin	499	283.6	208.1	-21.1%	< 0.001[a]
ABT-335 + low-dose statin	491	281.0	158.5	-40.8%	
Moderate-dose statin	495	280.6	198.3	-26.1%	< 0.001[a]
ABT-335 + moderate-dose statin	491	280.5	156.1	-40.7%	
LDL-C (mg/dL)					
ABT-335	492	159.6	138.2	-10.7%	< 0.001[b]
ABT-335 + low-dose statin	491	153.9	111.0	-27.7%	
ABT-335	492	158.6	137.8	-11.0	< 0.001[b]
ABT-335 + moderate-dose statin	491	156.5	108.6	-29.1	

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

6.1.6 Secondary endpoints

Secondary Endpoints and Statistical Considerations

The secondary efficacy endpoints were ranked and tested in a fixed sequence, separately for each combination therapy group. For ABT-335 in combination with each dose of statin, statistical significance could not be claimed for a lower ranked endpoint if an endpoint above it did not achieve statistical significance. The ranked comparisons were:

- ABT-335 in combination with each dose of statin vs. ABT-335 monotherapy:
  1. Non-HDL-C

- ABT-335 in combination with each dose of statin vs. statin monotherapy at the corresponding dose:
  2. Non-HDL-C
  3. VLDL-C
  4. Total-C
  5. ApoB
  6. hsCRP

Results

In all three studies, both doses of combination therapy resulted in greater mean percent decreases in non-HDL-C compared to ABT-335 monotherapy. Compared to the corresponding low-dose

statin monotherapy, ABT-335 in combination with each low-dose statin resulted in greater mean percent decreases in non-HDL-C, VLDL-C, and ApoB in all three studies. High-dose statin monotherapy was associated with the greatest non-HDL-C, Total-C, and ApoB lowering. As with the primary endpoints, although the individual statins imparted different mean percent changes in these parameters based on the statin's potency (rosuvastatin > atorvastatin > simvastatin), the impact of adding ABT-335 to each statin was similar. The results from each controlled trial are presented in Tables 6.1.6.A, 6.1.6.B, and 6.1.6.C.

Study M05-748

Table 6.1.6.A. Mean Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, ApoB, and hsCRP, Study M05-748

	ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	p-value	20 mg rosuva	ABT-335 + 20 mg rosuva	p-value	40 mg rosuva
Non-HDL-C								
BL mean	218.7	218.7	217.7		220.9	220.8		219.0
Final mean	176.5	130.9	119.9	< 0.001[a]	118.6	118.5	< 0.001[a]	105.9
Mean % Δ	-18.5%	-39.8%	-44.7%	< 0.001[b]	-45.8%	-45.3%	0.704[b]	-51.5%
VLDL-C								
BL mean	63.3	69.8	66.9		70.5	67.9		68.1
Final mean	35.7	38.2	26.5		36.5	27.0		31.0
Mean % Δ	-31.9%	-41.0%	-55.8%	< 0.001[b]	-42.1%	-50.6%	0.038[b]	-49.1%
Total-C								
BL mean	256.2	258.2	257.9		260.0	258.3		258.1
Final mean	220.2	173.3	167.8		161.7	164.0		147.0
Mean % Δ	-13.5%	-32.5%	-34.4%	0.080[b]	-37.3%	-35.7%	0.138[b]	-42.7%
ApoB								
BL mean	143.1	145.5	144.7		146.1	145.6		145.4
Final mean	119.7	94.8	87.6		87.0	86.8		79.2
Mean % Δ	-16.2%	-34.1%	-39.2%	< 0.001[b]	-39.6%	-39.2%	0.729[b]	-45.0%
hsCRP								
BL mean	0.50	0.44	0.52		0.49	0.50		0.47
Final mean	0.46	0.35	0.41		0.35	0.32		0.34
Mean % Δ	46.0%	2.6%	6.5%	0.862[b]	-0.7%	-11.6%	0.632[b]	4.8%

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

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

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

Study M05-749

Table 6.1.6.B. Mean Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, ApoB, and hsCRP, 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
Non-HDL-C								
BL mean	223.9	217.4	223.6		225.5	213.8		213.9
Final mean	183.7	163.6	151.3	< 0.001[a]	143.3	138.5	< 0.001[a]	128.9
Mean % Δ	-17.3%	-24.6%	-30.7%	0.001[b]	-35.9%	-35.0%	0.654[b]	-40.0%
VLDL-C								
BL mean	67.2	64.3	68.2		64.4	59.9		59.4
Final mean	38.3	45.3	34.1		36.8	26.5		36.6
Mean % Δ	-36.9%	-19.2%	-38.9%	< 0.001[b]	-35.7%	-51.1%	0.005[b]	-38.0%
Total-C								
BL mean	292.6	284.9	291.5		293.3	282.8		282.4
Final mean	227.8	209.7	194.8		192.8	184.7		169.4
Mean % Δ	-12.4%	-19.8%	-23.9%	0.012[b]	-30.0%	-27.1%	0.074[b]	-33.6%
ApoB								
BL mean	150.0	144.3	149.4		149.8	142.7		143.8
Final mean	121.7	110.7	102.9		98.7	98.2		89.2
Mean % Δ	-17.0%	-22.9%	-29.5%	0.001[b]	-32.7%	-31.2%	0.445[b]	-38.0%
hsCRP								
BL mean	0.61	0.56	0.62		0.57	0.87		0.55
Final mean	0.80	0.51	0.40		0.48	0.40		0.41
Mean % Δ	229.1%	54.3%	26.7%	0.672[b]	14.1%	17.0%	0.937[b]	5.6%

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

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

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

Study M05-750

Table 6.1.6.C. Mean Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, ApoB, and hsCRP, 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
Non-HDL-C								
BL mean	220.6	215.0	220.0		222.3	219.8		228.9
Final mean	188.4	138.0	129.1	< 0.001[a]	128.9	126.2	< 0.001[a]	122.4
Mean % Δ	-14.8%	-35.7%	-40.8%	0.020[b]	-40.7%	-42.5%	0.737[b]	-45.2%
VLDL-C								
BL mean	67.0	59.5	59.2		65.2	61.8		68.4
Final mean	36.6	39.2	26.8		37.4	26.4		36.4
Mean % Δ	-38.5%	-26.2%	-48.3%	< 0.001[b]	-35.8%	-53.5%	< 0.001[b]	-38.9%
Total-C								
BL mean	289.4	255.9	258.6		261.7	259.3		265.5
Final mean	235.6	179.8	172.1		172.1	169.0		161.5
Mean % Δ	-18.1%	-29.6%	-32.8%	0.072[b]	-33.8%	-34.6%	0.686[b]	-38.2%
ApoB								
BL mean	149.1	144.1	145.5		146.0	145.7		149.3
Final mean	127.7	96.5	90.8		93.5	91.6		87.8
Mean % Δ	-12.4%	-32.9%	-37.0%	0.048[b]	-35.3%	-37.1%	0.389[b]	-40.3%
hsCRP								
BL mean	0.45	0.45	0.48		0.53	0.48		0.43
Final mean	0.38	0.29	0.41		0.48	0.31		0.27
Mean % Δ	20.7%	36.2%	13.1%	0.491[b]	28.1%	-5.2%	0.462[b]	-22.8%

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

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

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

Study M05-758

Among subjects initially treated with statin monotherapy, the change to combination therapy with ABT-335 and the moderate-dose statin resulted in incremental mean percent decreases in non-HDL-C (-6.6%), VLDL-C (-21.5%), total-C (-1.8%), and ApoB (-10.6%), all of which were sustained throughout open-label treatment.

Among subjects initially treated with ABT-335 monotherapy, the change to combination therapy with ABT-335 and the moderate-dose statin resulted in incremental mean percent decreases in non-HDL-C (-38.1%), VLDL-C (-16.6%), total-C (-29.7%), and ApoB (-36.1%), all of which were sustained throughout open-label treatment.

A summary of the overall mean percent change at each assessment in non-HDL-C, VLDL-C, total-C, ApoB, and hsCRP (median percent change) for the *Initial Statin Monotherapy* and *Initial ABT-335 Monotherapy* analysis sets is presented in Table 6.1.6.D.

Table 6.1.6.D. Percent Change from Baseline to Each Time Point in Non-HDL-C, VLDL-C, Total-C, ApoB, and hsCRP (Initial Statin Monotherapy and Initial ABT-335 Monotherapy Analysis Sets)

Weeks on Open-Label Combination Therapy	Non-HDL-C		VLDL-C		Total-C		ApoB		hsCRP[a]	
	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy
4 Weeks	(N=679)	(N=320)	(N=655)	(N=319)	(N=679)	(N=321)	(N=672)	(N=315)	(N=679)	(N=319)
BL mean	131.4	133.4	37.5	35.5	172.5	228.2	98.4	122.9	0.3	0.4
Visit mean	122.4	128.7	28.1	25.5	166.8	164.4	87.3	85.5	0.3	0.4
Mean % Δ	-4.9%	-34.8%	-11.0%	-11.7%	-1.9%	-27.5%	-5.3%	-28.8%	-14.0%	-20.1%
8 Weeks	(N=619)	(N=320)	(N=613)	(N=308)	(N=619)	(N=310)	(N=617)	(N=305)	(N=619)	(N=310)
BL mean	131.3	133.9	37.1	34.9	173.5	228.7	98.1	123.4	0.3	0.4
Visit mean	128.2	121.7	26.8	26.3	167.8	168.1	86.2	85.3	0.3	0.3
Mean % Δ	-3.9%	-33.4%	-14.7%	-6.4%	-1.2%	-26.7%	-5.9%	-30.4%	-26.9%	-24.3%
12 Weeks	(N=613)	(N=308)	(N=598)	(N=300)	(N=613)	(N=308)	(N=610)	(N=300)	(N=598)	(N=300)
BL mean	131.3	133.9	37.3	35.6	173.6	228.3	98.5	123.2	0.3	0.4
Visit mean	123.6	122.4	25.5	25.6	167.8	168.9	83.4	84.6	0.3	0.3
Mean % Δ	-3.8%	-32.8%	-19.8%	-12.5%	-1.2%	-26.3%	-7.2%	-30.8%	-11.4%	-21.1%
16 Weeks	(N=777)	(N=391)	(N=775)	(N=389)	(N=777)	(N=391)	-	-	-	-
BL mean	130.8	133.8	36.8	35.2	171.9	228.3				
Visit mean	121.3	121.1	25.7	26.5	168.1	168.6				
Mean % Δ	-1.0%	-33.3%	-16.7%	-8.9%	-1.9%	-26.5%				

a. For hsCRP, % changes represent median percent changes.
Baseline represents the last value prior to the first dose of combination therapy in Study M05-758.
All weeks represent the open-label study, M05-758.

Weeks on Open-Label Combination Therapy	Non-HDL-C		VLDL-C		Total-C		ApoB		hsCRP[a]	
	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy	Initial Statin Monotherapy	Initial ABT-335 Monotherapy
28 Weeks	(N=734)	(N=278)	(N=733)	(N=274)	(N=734)	(N=278)	(N=732)	(N=274)	(N=733)	(N=279)
BL mean	130.7	132.3	37.3	35.1	171.7	226.8	98.1	122.4	0.3	0.4
Visit mean	119.6	118.7	25.1	23.3	165.3	165.3	81.7	81.3	0.3	0.4
Mean % Δ	-6.1%	-33.7%	-31.2%	-11.9%	-1.2%	-26.9%	-10.9%	-32.9%	-22.6%	-26.5%
40 Weeks	(N=648)	(N=250)	(N=642)	(N=250)	(N=648)	(N=252)	(N=642)	(N=247)	(N=641)	(N=247)
BL mean	128.7	131.3	34.8	34.7	170.2	225.8	98.0	123.4	0.3	0.3
Visit mean	117.9	119.9	24.3	23.3	164.9	167.2	81.9	77.8	0.3	0.3
Mean % Δ	-6.6%	-38.1%	-31.5%	-14.6%	-1.8%	-28.7%	-10.6%	-36.1%	12.8%	-27.0%
52 Weeks	(N=522)	(N=203)	(N=522)	(N=203)	(N=522)	(N=203)	(N=520)	(N=201)	(N=521)	(N=201)
BL mean	128.1	130.1	34.5	33.3	170.7	221.0	96.3	120.7	0.3	0.3
Visit mean	117.5	118.4	23.2	24.4	168.7	169.9	81.8	82.2	0.2	0.2
Mean % Δ	-8.0%	-35.5%	-32.1%	-8.6%	-2.8%	-27.5%	-13.8%	-34.4%	-19.3%	-18.8%

a. For hsCRP, % changes represent median percent changes.
Baseline represents the last value prior to the first dose of combination therapy in Study M05-758.
All weeks represent the open-label study, M05-758.

Comments: Because the initial statin monotherapy group includes subjects who were initially randomized to all doses of statins, some of the benefit in this analysis set could be attributed to a subset of subjects increasing the statin dose from the low-dose in the initial 12 weeks to the moderate-dose combination in the extension portion of the trial. There was also a subset of subjects, albeit smaller, who were initally randomized to a high dose of statin and subsequently had the dose reduced when switched to the moderate-dose combination in the extension trial. The initial moderate-dose statin monotherapy group (Table 6.1.6.E, below) is more informative in determining lipid changes when ABT-335 is added to a statin.

Table 6.1.6.E. Percent Change from Baseline of M05-758 to Each Time Point in Non-HDL-C, VLDL-C, Total-C, ApoB, and hsCRP (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	Non-HDL-C		VLDL-C		Total-C		ApoB		hsCRP[a]	
	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	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=228)	(N=227)	(N=225)	(N=225)	(N=228)	(N=227)	(N=226)	(N=226)	(N=221)	(N=217)
BL mean	130.3	129.6	36.9	37.2	173.3	170.7	91.8	92.1	0.4	0.4
Visit mean	123.6	123.0	34.8	34.2	165.8	167.1	84.2	87.6	0.3	0.3
Mean % Δ	-5.0%	-5.7%	-5.4%	-12.0%	-4.4%	-1.9%	-8.1%	-5.0%	-2.9%	-14.7%
8 Weeks	(N=213)	(N=209)	(N=211)	(N=213)	(N=213)	(N=209)	(N=210)	(N=210)	(N=212)	(N=204)
BL mean	129.9	128.8	37.0	36.7	174.0	170.2	91.6	91.5	0.4	0.4
Visit mean	118.2	123.2	34.5	37.1	164.2	167.4	84.3	84.2	0.3	0.3
Mean % Δ	-6.6%	-2.1%	-10.9%	-11.7%	-5.8%	-0.1%	-7.6%	-6.5%	-14.8%	-23.0%
12 Weeks	(N=211)	(N=207)	(N=210)	(N=212)	(N=211)	(N=207)	(N=209)	(N=211)	(N=210)	(N=203)
BL mean	129.8	128.8	37.1	37.2	173.9	170.8	91.7	92.0	0.4	0.4
Visit mean	123.5	123.4	35.0	35.6	165.2	169.0	83.2	86.4	0.3	0.3
Mean % Δ	-4.1%	-3.5%	-10.9%	-19.3%	-4.8%	0.3%	-8.6%	-5.8%	-13.9%	-13.7%
16 Weeks	(N=204)	(N=202)	(N=203)	(N=205)	(N=204)	(N=202)	NA	NA	NA	NA
BL mean	130.1	128.8	36.9	36.4	173.9	170.1				
Visit mean	118.8	122.6	35.0	35.6	164.2	167.0				
Mean % Δ	-7.3%	-2.6%	33.7%	-12.2%	-1.4%	-0.2%				

Weeks on Open-Label Combination Therapy	Non-HDL-C		VLDL-C		Total-C		ApoB		hsCRP	
	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	Initial Combination at Low Statin Dose	Initial Moderate-Dose Statin Monotherapy	Initial Combination at Low Statin Dose	Initial Moderate-Dose Statin Monotherapy
28 Weeks	(N=204)	(N=204)	(N=202)	(N=203)	(N=204)	(N=205)	(N=203)	(N=202)	(N=203)	(N=195)
BL mean	128.7	128.2	36.9	36.9	173.7	169.5	91.4	91.5	0.4	0.4
Visit mean	117.5	122.1	34.4	34.9	163.7	169.2	80.8	82.2	0.3	0.3
Mean % Δ	-7.2%	-4.9%	-18.3%	-21.5%	-4.8%	-0.9%	-11.4%	-8.8%	-14.7%	-18.9%
40 Weeks	(N=212)	(N=210)	(N=212)	(N=210)	(N=212)	(N=210)	(N=210)	(N=210)	(N=210)	(N=202)
BL mean	124.1	123.8	34.6	35.1	171.2	167.5	90.8	91.4	0.3	0.4
Visit mean	115.1	117.3	33.4	35.1	162.1	168.5	78.7	81.5	0.3	0.4
Mean % Δ	-7.6%	-5.2%	-21.2%	-18.8%	-4.5%	-1.1%	-11.3%	-9.0%	-16.5%	-11.5%
52 Weeks	(N=187)	(N=187)	(N=186)	(N=187)	(N=187)	(N=187)	(N=186)	(N=187)	(N=186)	(N=187)
BL mean	121.2	125.7	33.9	35.0	167.0	169.3	88.9	94.3	0.3	0.4
Visit mean	109.7	118.1	33.7	35.2	157.7	162.9	77.1	82.5	0.2	0.3
Mean % Δ	-9.6%	-5.9%	10.6%	-16.7%	-5.0%	-3.1%	-13.3%	-12.6%	-14.6%	-23.3%

a. For hsCRP, % changes represent median percent changes.
Baseline represents the last value prior to the first dose of combination therapy with the moderate statin dose in Study M05-758.
All weeks represent the open-label study, M05-758.

Comment: Mean decreases were seen in the secondary endpoints in the initial moderate-dose statin group, although lowering of non-HDL-C was relatively modest: -1.5% at 12 weeks. This is likely because non-HDL-C reflects changes in LDL-C, which increases in some patients with the addition of ABT-335, in addition to reflecting changes in TG. The sponsor explains that the mean percent increases seen in VLDL-C in the Initial Combination at Low Statin Dose analysis set (reflecting an increase in the statin dose component of the combination) were influenced by a small number of subjects with large outlying percent increases. Median percent decreases from baseline in VLDL-C were generally observed after four weeks of open-label treatment, ranging from –5.7% to -9.3% from eight weeks to 40 weeks. ApoB decreases were similar in the initial combination at low statin dose and initial moderate-dose statin monotherapy groups.

Overall

The integrated results were consistent with secondary efficacy results from each of the three controlled studies. A summary of mean percent change from baseline to the final value in the secondary efficacy parameters is presented in Table 6.1.6.E.

Table 6.1.6.F. Mean Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, ApoB, and hsCRP (Controlled Studies Analysis Set)

Primary Endpoints	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + low-dose statin (N=490)	p-value	Moderate-dose statin (N=491)	ABT-335 + moderate-dose statin (N=489)	p-value	High-dose statin (N=245)
Non-HDL-C	(N=420)	(N=454)	(N=422)		(N=431)	(N=420)		(N=217)
BL mean	222.5	217.6	219.9		222.4	218.9		220.2
Final mean	181.4	140.9	129.7	<0.001[a]	127.0	125.7	<0.001[a]	115.5
Mean % Δ	-17.3%	-34.9%	-40.4%	<0.001[b]	-42.4%	-42.0%	0.710[b]	-47.3%
VLDL-C	(N=449)	(N=463)	(N=455)		(N=458)	(N=449)		(N=232)
BL mean	65.0	66.0	65.5		67.8	64.5		66.1
Final mean	36.1	40.2	28.4		36.7	26.8		33.6
Mean % Δ	-34.2%	-32.1%	-50.0%	<0.001[b]	-38.9%	-51.2%	<0.001[b]	-42.1%
Total-C	(N=459)	(N=477)	(N=469)		(N=472)	(N=462)		(N=235)
BL mean	260.9	257.0	258.6		261.3	257.3		258.5
Final mean	225.8	182.4	175.4		169.2	170.3		155.8
Mean % Δ	-12.4%	-28.7%	-31.5%	0.001[b]	-34.7%	-33.3%	0.093[b]	-39.5%
ApoB	(N=455)	(N=470)	(N=465)		(N=468)	(N=455)		(N=229)
BL mean	146.2	145.0	146.1		147.1	145.0		146.0
Final mean	122.1	99.1	92.0		91.6	90.7		83.6
Mean % Δ	-15.6%	-31.1%	-36.3%	<0.001[b]	-36.9%	-36.7%	0.817[b]	-42.4%
hsCRP	(N=457)	(N=471)	(N=467)		(N=470)	(N=457)		(N=231)
BL mean	0.52	0.47	0.53		0.58	0.59		0.48
Final mean	0.53	0.37	0.41		0.40	0.33		0.34
Mean % Δ	87.4%	24.0%	13.0%	0.003[b]	7.8%	-2.7%	0.622[b]	0.1%

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

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

The following is a summary of the ranked secondary efficacy analyses:

Table 6.1.6.G. Summary of Analyses of Ranked Secondary Efficacy Variables (Controlled Studies Analysis Set)

		Combination Therapy Treatment Group			
		ABT-335 + low dose statin		ABT-335 + moderate dose statin	
Variable	Comparison	p-value	Statistically Significant	p-value	Statistically Significant
Non-HDL-C	ABT-335 combination vs. ABT-335 monotherapy	< 0.001	X	< 0.001	X
Non-HDL-C	ABT-335 combination vs. statin monotherapy	< 0.001	X	0.710	
VLDL-C	ABT-335 combination vs. statin monotherapy	< 0.001	X	< 0.001	
Total-C	ABT-335 combination vs. statin monotherapy	< 0.001	X	0.093	
ApoB	ABT-335 combination vs. statin monotherapy	< 0.001	X	0.817	
hsCRP	ABT-335 combination vs. statin monotherapy	0.603		0.622	

The analysis of mean percent change in hsCRP is difficult to interpret due to the highly skewed distribution of values, with one or more subjects in each treatment group demonstrating an increase > 1000%. Therefore, the sponsor conducted a post hoc nonparametric analysis to compare treatment groups. Both combination therapy groups demonstrated significantly larger median percent decreases in hsCRP than the corresponding rosuvastatin monotherapy group. The median percent change from baseline to the Final Visit in hsCRP in the individual controlled studies and the Controlled Studies Analysis Set, is presented in Tables 6.1.6.H and 6.1.6.I, respectively.

Table 6.1.6.H. Median Percent Change from Baseline to Final Value in hsCRP in Studies M05-748, M05-749, and M05-750

M05-748 hsCRP (mg/dL)	ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	p-value[a]	20 mg rosuva	ABT-335 + 20 mg rosuva	p-value[a]	40 mg rosuva
	(N=241)	(N=240)	(N=252)		(N=254)	(N=248)		(N=125)
BL median	0.28	0.27	0.35		0.27	0.31		0.29
Median % Δ	-12.1%	-22.9%	-39.8%	0.013	-29.9%	-40.8%	0.010	-33.1%
M05-749 hsCRP (mg/dL)	ABT-335	20 mg simva	ABT-335 + 20 mg simva	p-value[a]	40 mg simva	ABT-335 +40 mg simva	p-value[a]	80 mg simva
	(N=112)	(N=113)	(N=111)		(N=112)	(N=110)		(N=54)
BL median	0.35	0.28	0.31		0.28	0.27		0.24
Median % Δ	-15.8%	-11.4%	-26.8%	0.057	-14.8%	-32.1%	0.141	-18.8%
M05-750 hsCRP (mg/dL)	ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	p-value[a]	40 mg atorva	ABT-335 +40 mg atorva	p-value[a]	80 mg atorva
	(N=104)	(N=109)	(N=104)		(N=104)	(N=101)		(N=52)
BL median	0.26	0.21	0.25		0.28	0.26		0.31
Median % Δ	-12.4%	-28.6%	-26.2%	0.993	-30.3%	-42.8%	0.074	-31.9%

Note: P-value from a van Elteren's test with screening TG level and diabetic status as strata.

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

Table 6.1.6.I. Median Percent Change from Baseline to Final Value in hsCRP (Controlled Studies Analysis Set)

hsCRP (mg/dL)	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + Low statin (N=490)	p-value[a]	Moderate-dose statin (N=491)	ABT-335 + Moderate statin (N=489)	p-value[a]	High-dose statin (N=245)
	(N=457)	(N=471)	(N=467)		(N=470)	(N=457)		(N=231)
BL Median	0.29	0.27	0.31		0.29	0.30		0.30
Median % Δ	-13.1%	-20.9%	-31.2%	0.009	-27.7%	-37.3%	< 0.001	-28.4%

Note: P-value from a van Elteren's test with screening TG level and diabetic status as strata

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

Comment: It is unclear if the outliers skewing the mean results are artifactual or real; regardless, this reviewer found the sponsor's updated analysis using the median percent change to be helpful – the results appear to be a more meaningful description of the CRP data. It is reassuring that the combination is nearly the ABT-335 and statin monotherapies' results combined.

Exploratory Analyses

Blood draws for exploratory parameters were conducted at baseline and on the Week 12 Final/Discontinuation Visit: apoAI, apoCIII, adiponectin, and LpPLA2. The results of the exploratory efficacy analyses were generally consistent in each of the three double-blind studies. In each study, mean percent increases from baseline were observed in apoAI and mean percent decreases from baseline were observed in ApoCIII and LpPLA2 throughout the treatment period. Increases in apoAI and decreases in LpPLA2 were greatest in Study M05-748 (rosuvastatin), while decreases in apoCIII were greatest in Study M05-750 (atorvastatin). A summary of the mean percent change from baseline to final value in the exploratory efficacy parameters with

ABT-335 in combination with low-dose statins and moderate-dose statins is presented for each double-blind study in Table 6.1.6.J (M05-748), Table 6.1.6.K (M05-749), and Table 6.1.6.L (M05-750), and for all the studies pooled (Table 6.1.6.M).

Table 6.1.6.J. Mean Percent Change from Baseline to the Final Value in ApoAI, ApoCIII, Adiponectin, and LpPLA2 in Study M05-748

	ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	p-value	20 mg rosuva	ABT-335 + 20 mg rosuva	p-value	40 mg rosuva
ApoAI								
BL mean	142.9	140.8	140.1		141.4	141.6		142.7
Final mean	154.8	149.9	155.9	0.249[a]	150.9	155.4	0.428[a]	148.5
Mean % Δ	9.9%	7.4%	11.7%	0.004[b]	8.3%	11.1%	0.055[b]	5.7%
ApoCIII								
BL mean	17.9	18.9	19.0		19.0	18.6		17.8
Final mean	13.3	16.2	12.7	0.014[a]	16.0	12.5	0.362[a]	14.6
Mean % Δ	-23.5%	-11.0%	-30.8%	< 0.001[b]	-12.1%	-26.2%	< 0.001[b]	-14.7%
Adiponectin								
BL mean	5870.2	6219.4	6022.5		5930.6	6158.7		5886.5
Final mean	5693.4	5840.0	5349.6	0.925[a]	5420.7	5328.2	0.165[a]	5105.3
Mean % Δ	1.6%	0.8%	1.1%	0.956[b]	-1.4%	-5.7%	0.411[b]	-11.7%
LpPLA2								
BL mean	288.7	264.9	266.6		277.5	273.3		279.8
Final mean	284.0	222.0	243.7	< 0.001[a]	231.2	239.2	< 0.001[a]	209.1
Mean % Δ	4.2%	-13.6%	-7.4%	0.007[b]	-13.7%	-9.9%	0.095[b]	-22.1%

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

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

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

Table 6.1.6.K. Mean Percent Change from Baseline to the Final Value in ApoAI, ApoCIII, Adiponectin, and LpPLA2 in Study M05-749

	ABT-335	ABT-335 + 20 mg simva			ABT-335 + 40 mg simva			80 mg simva
		20 mg simva	+ 20 mg simva	p-value	40 mg simva	40 mg simva	p-value	
ApoAI								
BL mean	142.3	144.6	141.4		148.9	142.3		143.6
Final mean	140.8	145.4	150.3	0.345[a]	146.6	153.2	0.157[a]	143.9
Mean % Δ	5.8%	1.8%	7.1%	0.010[b]	4.1%	8.7%	0.024[b]	1.2%
ApoCIII								
BL mean	18.7	18.9	19.4		18.7	17.8		18.3
Final mean	13.7	16.2	12.8	0.190[a]	15.1	12.2	0.061[a]	15.0
Mean % Δ	-25.4%	-10.9%	-20.6%	< 0.001[b]	-16.3%	-31.4%	< 0.001[b]	-16.7%
Adiponectin								
BL mean	5784.4	5338.6	5760.5		5627.2	4984.6		6360.8
Final mean	5542.8	5470.8	5704.0	0.783[a]	5854.1	4762.5	0.828[a]	5670.8
Mean % Δ	3.6%	8.2%	2.2%	0.256[b]	9.5%	2.5%	0.193[b]	-1.7%
LpPLA2								
BL mean	269.8	271.1	266.3		281.7	259.3		271.6
Final mean	279.3	238.2	258.0	0.044[a]	237.0	250.7	0.022[a]	227.7
Mean % Δ	6.0%	-9.3%	-1.4%	0.029[b]	-12.1%	-2.5%	0.010[b]	-13.7%

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

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

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

Table 6.1.6.L. Mean Percent Change from Baseline to the Final Value in ApoAI, ApoCIII, Adiponectin, and LpPLA2 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
ApoAI								
BL mean	139.9	142.0	140.2		140.8	143.0		141.1
Final mean	154.8	143.3	149.4	0.057[a]	142.3	144.7	<0.001[a]	143.2
Mean % Δ	11.3%	2.8%	7.0%	0.022[b]	2.3%	1.9%	0.837[b]	2.8%
ApoCIII								
BL mean	19.5	18.4	18.5		19.0	19.3		19.5
Final mean	13.8	15.1	11.5	0.004[a]	15.2	11.8	0.004[a]	14.8
Mean % Δ	-25.6%	-14.7%	-35.4%	<0.001[b]	-16.9%	-35.6%	<0.001[b]	-22.2%
Adiponectin								
BL mean	6029.4	5943.7	6288.0		6817.1	4951.9		5839.4
Final mean	5610.1	5970.6	5578.3	0.108[a]	6192.3	4562.9	0.520[a]	5896.2
Mean % Δ	-0.4%	7.0%	-8.7%	0.002[b]	-0.4%	-3.8%	0.517[b]	6.7%
LpPLA2								
BL mean	265.8	255.1	251.0		288.3	267.5		266.0
Final mean	303.7	231.8	241.9	<0.001[a]	232.8	248.1	<0.001[a]	224.1
Mean % Δ	20.7%	-8.6%	-2.0%	0.056[b]	-11.9%	-3.3%	0.014[b]	-12.1%

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

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

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

Table 6.1.6.M. Mean Percent Change from Baseline to the Final Value in ApoAI, ApoCIII, Adiponectin, and LpPLA2 (Controlled Studies Analysis Set)

Exploratory Endpoints	ABT-335	Low-dose statin	ABT-335 + Low-dose statin	p-value	Moderate-dose statin	ABT-335 + Moderate-dose statin	p-value	High-dose statin
ApoAI	(N=402)	(N=430)	(N=406)		(N=428)	(N=408)		(N=206)
BL mean	142.1	142.0	140.5		141.3	142.1		142.6
Final mean	153.4	147.2	152.1	0.077[a]	148.0	152.4	0.045[a]	148.2
Mean % Δ	9.1%	4.6%	8.5%	<0.001[b]	5.9%	8.5%	0.015[b]	3.7%
ApoCIII	(N=209)	(N=328)	(N=206)		(N=310)	(N=207)		(N=147)
BL mean	18.5	18.8	19.0		19.0	18.6		18.4
Final mean	13.6	16.0	12.5	<0.001[a]	15.6	12.2	0.006[a]	14.8
Mean % Δ	-24.6%	-12.0%	-31.8%	<0.001[b]	-14.4%	-29.6%	<0.001[b]	-17.2%
Adiponectin	(N=389)	(N=401)	(N=382)		(N=378)	(N=388)		(N=192)
BL mean	5888.7	5987.8	6041.4		6200.7	5888.5		5888.8
Final mean	5638.4	5788.1	5493.7	0.463[a]	5698.9	5881.6	0.120[a]	5498.5
Mean % Δ	1.6%	3.0%	-0.8%	0.151[b]	1.4%	-3.5%	0.137[b]	-4.9%
LpPLA2	(N=309)	(N=322)	(N=309)		(N=311)	(N=311)		(N=153)
BL mean	270.5	264.9	262.3		281.2	257.5		273.4
Final mean	288.4	229.7	247.8	<0.001[a]	233.3	245.0	<0.001[a]	218.9
Mean % Δ	9.3%	-10.5%	-4.0%	<0.001[b]	-12.5%	-6.2%	<0.001[b]	-16.0%

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

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

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

Comments: The directional mean percent change with these exploratory variables is not always consistent with the baseline vs. visit mean; this may be because of drop-outs or lack of sample. Overall, the ABT-335 groups (monotherapy and combination therapy) increase

ApoAI (associated with HDL-C), decrease ApoCIII (associated with VLDL-C and TG metabolism), and increase LpPLA2 (a marker of inflammation). These studies were not designed to test these hypotheses, however, and it is unclear which is most important for prediction of risk or benefit of treatment. Therefore, the clinical significance of the adverse mean change with ABT-335 treatment on LpPLA2, for example, is unknown.

At selected sites in each double-blind study, samples were collected for NMR LipoProfile® testing, which quantifies the number of atherogenic particles. According to the sponsor, low-density lipoprotein particle number (LDL-P) and very-low-density lipoprotein particle number (VLDL-P) are the most representative measures of atherogenicity and potential predictors of cardiovascular risk. Research has demonstrated that large, more buoyant LDL particles are less atherogenic than small LDL particles[12,13,14,15,16,17].

Comment: Several of the references on this topic (provided by the sponsor) indicate that the predictive value of LDL particle size is diminished when taking into account other lipid findings. For example, Blake[12] found that the predictive value of LDL particle concentration (NMR) was not substantively different from that of TC:HDL-C ratio and was less than that of CRP. El Harchaoui[13] noted that while in individuals with moderately elevated LDL-C, LDL-P was related to CAD on top of Framingham Heart Score as well as after adjusting for LDL-C, but the additional value of LDL-P was comparable to non-HDL-C, and it was abolished after adjusting for TG and HDL-C.

In all three double-blind, controlled studies, greater mean percent increases in LDL particle size were observed in the ABT-335 monotherapy group and both combination therapy groups than in the statin monotherapy groups. Because the conclusions are similar in the three studies, only the results of the controlled studies combined are presented below.

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12 Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation. 2002;106:1930-1937.

13 El Harchaoui K, van der Steeg WA, Stroes ES, Kuivenhoven JA, Otvos JD, Wareham NJ, et al. Value of low-density lipoprotein particle number and size as predictors of coronary artery disease in apparently healthy men and women. J Am College Cardio. 2007;49:547-553.

14 Otvos JD, Collins D, Freedman DS, Shalaurova I, Schaefer EJ, McNamara JR, et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation. 2006;113:1556-1563.

15 Kuller L, Arnold A, Tracy R, Otvos J, Burke G, Psaty B, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. Arterioscler Thromb Vasc Biol. 2002;22:1175-1180.

16 Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC, et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2002;192:211-217.

17 Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) Trial. Am J Cardiol. 2002;90:89-94.

Table 6.1.6.N. Mean Percent Change from Baseline to the Final Value in LDL Particle Number, VLDL Particle Number, VLDL Triglycerides, and LDL Particle Size Using NMR (Controlled Studies Analysis Set – Subset of Randomized Subjects)

	ABT-335	Low-dose statin	ABT-335 + Low statin	p-value	Moderate-dose statin	ABT-335 + Moderate statin	p-value	High-dose statin
LDL-P	(N=155)	(N=153)	(N=146)		(N=170)	(N=154)		(N=62)
BL mean	2062.6	2012.2	2057.8		2023.1	2019.1		2000.1
Final mean	1724.3	1272.7	1284.6	<0.001[a]	1160.6	1205.2	<0.001[a]	1104.2
Mean % Δ	-14.2%	-36.4%	-38.1%	0.800[b]	-41.8%	-38.9%	0.810[b]	-48.1%
VLDL-P	(N=155)	(N=153)	(N=146)		(N=170)	(N=154)		(N=62)
BL mean	140.4	142.8	147.1		144.3	142.7		141.8
Final mean	94.8	103.9	69.3	<0.001[a]	93.9	69.3	<0.001[a]	92.7
Mean % Δ	-34.2%	-25.8%	-50.5%	<0.001[b]	-33.3%	-50.4%	<0.001[b]	-33.9%
VLDL-TG	(N=154)	(N=153)	(N=146)		(N=169)	(N=153)		(N=62)
BL mean	225.9	225.2	219.6		222.8	217.6		232.5
Final mean	129.7	173.8	93.9	0.006[a]	158.6	98.5	0.021[a]	142.6
Mean % Δ	-41.3%	-18.9%	-53.9%	<0.001[b]	-28.6%	-52.3%	<0.001[b]	-31.7%
LDL Size	(N=154)	(N=153)	(N=146)		(N=169)	(N=153)		(N=62)
BL mean	20.0	19.9	19.8		19.9	19.9		19.8
Final mean	20.5	20.1	20.5	0.426	20.1	20.5	0.548[a]	20.2
Mean % Δ	2.9%	0.9%	3.2%	<0.001[b]	1.0%	2.7%	<0.001[b]	1.5%

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

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

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

The sponsor conducted analyses evaluating the proportion of subjects meeting National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III goals for LDL-C and non-HDL-C. Across all risk categories in all three double-blind, controlled studies, higher proportions of subjects in each statin monotherapy group than in the corresponding combination therapy group achieved NCEP ATP III goals for LDL-C. In general, higher or similar proportions of subjects in each combination therapy group as in the corresponding statin monotherapy group achieved NCEP ATP III non-HDL-C goals and goals for both LDL-C and non-HDL-C. In Study M05-750, a higher proportion of subjects in the 20 mg atorvastatin monotherapy group than in the ABT-335 in combination with 20 mg atorvastatin group achieved NCEP ATP III goals for both LDL-C and non-HDL-C, with similar proportions of subjects in the 40 mg atorvastatin monotherapy and ABT-335 in combination with 40 mg atorvastatin groups achieving both goals. These findings are presented in Table 6.1.6.O. This reviewer supplemented these analyses with an exploratory evaluation of the achievement of clinically meaningful categorical targets for LDL-C, HDL-C, TG, and non-HDL-C. The results follow in descriptive tables below.

Table 6.1.6.O. Number and Percentage of Subjects Meeting National Cholesterol Education Program Adult Treatment Panel Guideline LDL-C and Non-HDL-C Goals at the Final Visit in Studies M05-748, M05-749, and M05-750

Goal	Subjects at Goal at Final Visit n/N (%)					
M05-748	ABT-335	10 mg rosuva	ABT-335 + 10 mg rosuva	20 mg rosuva	ABT-335 + 20 mg rosuva	40 mg rosuva
LDL-C	58/223 (26.0)	216/244 (88.5)	195/232 (84.1)	218/241 (90.5)	189/231 (81.8)	110/120 (91.7)
non-HDL-C	69/226 (30.5)	185/246 (75.2)	201/237 (84.8)	198/246 (80.5)	191/235 (81.3)	105/121 (86.8)
LDL-C and non-HDL-C	49/223 (22.0)	186/243 (74.1)	186/232 (80.2)	190/241 (78.8)	179/231 (77.5)	103/120 (85.8)
M05-749	ABT-335	20 mg simva	ABT-335 + 20 mg simva	40 mg simva	ABT-335 + 40 mg simva	80 mg simva
LDL-C	33/107 (30.8)	70/116 (60.3)	62/109 (56.9)	76/106 (71.7)	70/109 (64.2)	44/55 (80.0)
non-HDL-C	34/108 (31.5)	50/116 (43.1)	59/109 (54.1)	64/106 (60.4)	72/109 (66.1)	40/55 (72.7)
LDL-C and non-HDL-C	30/107 (28.0)	48/116 (41.4)	52/109 (47.7)	61/106 (57.5)	66/109 (60.6)	39/55 (70.9)
M05-750	ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	40 mg atorva	ABT-335 + 40 mg atorva	80 mg atorva
LDL-C	24/97 (24.7)	84/104 (80.8)	70/97 (72.2)	80/95 (84.2)	69/96 (71.9)	44/50 (88.0)
non-HDL-C	23/98 (23.2)	79/104 (76.0)	73/98 (74.5)	70/96 (72.9)	72/94 (76.6)	40/50 (80.0)
LDL-C and non-HDL-C	16/97 (16.5)	75/104 (72.1)	61/97 (62.9)	68/95 (71.6)	67/94 (71.3)	40/50 (80.0)

n/N = number of subjects meeting goal/total number of subjects in treatment group with data

Comment: In most cases, a higher proportion of subjects achieved goal with the next highest dose statin monotherapy than the preceding combination therapy, suggesting that it may be preferable in some cases to maximize statin therapy prior to adding ABT-335 in order to achieve NCEP goals. This is somewhat speculation, however, because the study was not conducted to answer that specific question. Furthermore, because non-HDL-C encompasses LDL-C, it is not reflecting beneficial changes to TG, a target when adding fibrate to statin therapy. These findings are consistent with this reviewer's categorical summaries, below.[18] The comparatively low proportion of subjects meeting LDL-C and non-HDL-C goals with ABT-335 monotherapy is noted (16.5-28%).

Table 6.1.6.P. Categorical results for LDL-C at 12 weeks, Study M05-748

	N	LDL ≤ 130 mg/dL n (%)	LDL ≤ 100 mg/dL n (%)	LDL ≤ 70 mg/dL n (%)
ABT-335	223	69 (30.9)	10 (4.5)	3 (1.4)
ABT-335 and Rosuvastatin 10 mg	231	207 (89.6)	140 (60.6)	28 (12.1)
ABT-335 and Rosuvastatin 20 mg	230	205 (89.1)	158 (68.7)	43 (18.7)
Rosuvastatin 10 mg	243	220 (90.5)	157 (64.6)	29 (11.9)
Rosuvastatin 20 mg	238	224 (94.1)	187 (78.6)	71 (29.8)
Rosuvastatin 40 mg	120	115 (95.8)	101 (84.2)	58 (48.3)

18 Note: These results are based on this reviewer's exploration of the datasets, and should not be interpreted to be rigorous analyses.

Table 6.1.6.Q. Categorical results for LDL-C at 12 weeks, Study M05-749

	N	LDL ≤ 130 mg/dL n (%)	LDL ≤ 100 mg/dL n (%)	LDL ≤ 70 mg/dL n (%)
ABT-335	107	33 (30.8)	8 (7.5)	0 (0)
ABT-335 and Simvastatin 20 mg	109	79 (72.5)	34 (31.2)	8 (7.3)
ABT-335 and Simvastatin 40 mg	108	85 (78.7)	37 (34.3)	2 (1.9)
Simvastatin 20 mg	116	78 (67.2)	34 (29.3)	4 (3.5)
Simvastatin 40 mg	106	87 (82.1)	50 (47.2)	6 (5.7)
Simvastatin 80 mg	55	48 (87.3)	37 (67.3)	8 (14.6)

Table 6.1.6.R. Categorical results for LDL-C at 12 weeks, Study M05-750

	N	LDL ≤ 130 mg/dL n (%)	LDL ≤ 100 mg/dL n (%)	LDL ≤ 70 mg/dL n (%)
ABT-335	97	20 (20.6)	1 (1.0)	0 (0)
ABT-335 and Atorvastatin 20 mg	97	81 (83.5)	46 (47.4)	7 (7.2)
ABT-335 and Atorvastatin 40 mg	96	83 (86.5)	55 (57.3)	7 (7.3)
Atorvastatin 20 mg	104	93 (89.4)	58 (55.8)	9 (8.7)
Atorvastatin 40 mg	95	85 (89.5)	59 (62.1)	14 (14.7)
Atorvastatin 80 mg	50	46 (92.0)	38 (76.0)	12 (24.0)

Table 6.1.6.S. Categorical results for HDL-C at 12 weeks, Study M05-748

	N	HDL > 50 mg/dL n (%)
ABT-335	220	58 (26.4)
ABT-335 and Rosuvastatin 10 mg	224	63 (28.1)
ABT-335 and Rosuvastatin 20 mg	225	57 (25.3)
Rosuvastatin 10 mg	239	29 (12.1)
Rosuvastatin 20 mg	236	28 (11.9)
Rosuvastatin 40 mg	115	10 (8.7)

Table 6.1.6.T. Categorical results for HDL-C at 12 weeks, Study M05-749

	N	HDL > 50 mg/dL n (%)
ABT-335	107	24 (22.4)
ABT-335 and Simvastatin 20 mg	105	28 (26.7)
ABT-335 and Simvastatin 40 mg	106	27 (25.5)
Simvastatin 20 mg	114	12 (10.5)
Simvastatin 40 mg	102	13 (12.8)
Simvastatin 80 mg	52	9 (17.3)

Table 6.1.6.U. Categorical results for HDL-C at 12 weeks, Study M05-750

	N	HDL > 50 mg/dL n (%)
ABT-335	93	25 (26.9)
ABT-335 and Atorvastatin 20 mg	95	26 (27.4)
ABT-335 and Atorvastatin 40 mg	91	22 (24.2)
Atorvastatin 20 mg	102	10 (9.8)
Atorvastatin 40 mg	92	9 (9.8)
Atorvastatin 80 mg	50	6 (12.0)

Table 6.1.6.V. Categorical results for TG at 12 weeks, Study M05-748

	N	TG ≤ 150 mg/dL n (%)
ABT-335	242	128 (52.9)
ABT-335 and Rosuvastatin 10 mg	252	179 (71.0)
ABT-335 and Rosuvastatin 20 mg	249	169 (67.9)
Rosuvastatin 10 mg	252	89 (35.3)
Rosuvastatin 20 mg	255	90 (35.3)
Rosuvastatin 40 mg	127	61 (48.0)

Table 6.1.6.W. Categorical results for TG at 12 weeks, Study M05-749

	N	TG ≤ 150 mg/dL n (%)
ABT-335	113	51 (45.1)
ABT-335 and Simvastatin 20 mg	113	66 (58.4)
ABT-335 and Simvastatin 40 mg	111	75 (67.6)
Simvastatin 20 mg	116	26 (22.4)
Simvastatin 40 mg	112	40 (35.7)
Simvastatin 80 mg	56	19 (33.9)

Table 6.1.6.X. Categorical results for TG at 12 weeks, Study M05-750

	N	TG ≤ 150 mg/dL n (%)
ABT-335	104	47 (45.2)
ABT-335 and Atorvastatin 20 mg	105	81 (77.1)
ABT-335 and Atorvastatin 40 mg	102	66 (64.7)
Atorvastatin 20 mg	109	38 (34.9)
Atorvastatin 40 mg	105	46 (43.8)
Atorvastatin 80 mg	52	21 (40.4)

Table 6.1.6.Y. Categorical results for non-HDL-C at 12 weeks, Study M05-748

	N	Non-HDL ≤ 160 mg/dL n (%)	Non-HDL ≤ 130 mg/dL n (%)	Non-HDL ≤ 100 mg/dL n (%)
ABT-335	220	77 (35.0)	21 (9.6)	1 (0.5)
ABT-335 and Rosuvastatin 10 mg	224	200 (89.3)	155 (69.2)	59 (26.3)
ABT-335 and Rosuvastatin 20 mg	225	195 (86.7)	167 (74.2)	67 (29.8)
Rosuvastatin 10 mg	238	190 (79.8)	128 (53.8)	31 (13.0)
Rosuvastatin 20 mg	236	210 (89.0)	166 (70.3)	66 (28.0)
Rosuvastatin 40 mg	115	104 (90.4)	90 (78.3)	62 (53.9)

Table 6.1.6.Z. Categorical results for non-HDL-C at 12 weeks, Study M05-749

	N	Non-HDL ≤ 160 mg/dL n (%)	Non-HDL ≤ 130 mg/dL n (%)	Non-HDL ≤ 100 mg/dL n (%)
ABT-335	107	34 (31.8)	10 (9.4)	0 (0)
ABT-335 and Simvastatin 20 mg	104	69 (66.4)	34 (32.7)	9 (8.7)
ABT-335 and Simvastatin 40 mg	104	82 (78.9)	44 (42.3)	7 (6.7)
Simvastatin 20 mg	114	58 (50.9)	23 (20.2)	1 (0.9)
Simvastatin 40 mg	103	75 (72.8)	40 (38.8)	8 (7.8)
Simvastatin 80 mg	52	44 (84.6)	31 (59.6)	11 (21.2)

Table 6.1.6.AA. Categorical results for non-HDL-C at 12 weeks, Study M05-750

	N	Non-HDL ≤ 160 mg/dL n (%)	Non-HDL ≤ 130 mg/dL n (%)	Non-HDL ≤ 100 mg/dL n (%)
ABT-335	93	18 (19.4)	3 (3.2)	0 (0)
ABT-335 and Atorvastatin 20 mg	95	79 (83.2)	55 (57.9)	17 (17.9)
ABT-335 and Atorvastatin 40 mg	91	75 (82.4)	56 (61.5)	24 (26.4)
Atorvastatin 20 mg	102	83 (81.4)	46 (45.1)	7 (6.9)
Atorvastatin 40 mg	92	76 (82.6)	51 (55.4)	11 (12.0)
Atorvastatin 80 mg	50	41 (82.0)	32 (64.0)	12 (24.0)

The final exploratory analysis conducted by the sponsor is of lipid parameter ratios, which in epidemiological studies have been found to correlate with cardiovascular risk. In particular, two large studies (AMORIS[19] and INTERHEART[20]) have shown a strong direct relation between a high apoB and apoAI ratio and an increased risk of fatal MI and acute MI, respectively.[21] However, an analysis of data from the Framingham study[22] demonstrated that total cholesterol:HDL-C ratio, LDL-C:HDL-C ratio, and apo B:apo A-I ratio were all positively

19 Walldius G, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001;358:2026-2033.
20 Yusuf S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-952.
21 Walldius G and Jungner I. Rationale for using apolipoprotein B and apolipoprotein A-I as indicators of cardiac risk and as targets for lipid-lowering therapy. Eur Heart J 2005. 26(3):210-2.
22 Ingelsson E, et al. Clinical Utility of Different Lipid Measures for Prediction of Coronary Heart Disease in Men and Women. JAMA 2007. 298(7):776-85.

associated with CHD risk of approximately the same magnitude and statistical significance as non-HDL-C in that cohort.

Table 6.1.6.BB. Mean Percent Change from Baseline to the Final Value between Combination Therapy and the Corresponding Monotherapy Group in Ratios of the Lipid Parameters (Controlled Studies Analysis Set)

Exploratory Endpoints	ABT-335 (N=[illegible])	Low-dose statin (N=[illegible])	ABT-335 + low statin (N=[illegible])	p-value	Moderate-dose statin (N=[illegible])	ABT-335 + moderate statin (N=[illegible])	p-value	High-dose statin (N=[illegible])
Total-C to HDL-C	(N=420)	(N=455)	(N=422)		(N=430)	(N=422)		(N=217)
BL mean	7.0	6.9	6.9		7.0	7.0		7.0
Final mean	5.4	4.7	4.1	<0.001[a]	4.2	4.1	<0.001[a]	4.0
Mean % Δ	-21.4%	-31.2%	-39.7%	<0.001[b]	-38.3%	-40.1	0.181[b]	-42.1%
LDL-C to HDL-C	(N=414)	(N=451)	(N=417)		(N=421)	(N=416)		(N=216)
BL mean	4.2	4.1	4.2		4.2	4.2		4.2
Final mean	3.5	2.6	2.4	<0.001[a]	2.3	2.4	<0.001[a]	2.1
Mean % Δ	-15.5%	-36.4%	-46.6%	0.007[b]	-43.5%	-40.8%	0.007[b]	-49.1%
Non-HDL-C to HDL-C	(N=420)	(N=454)	(N=422)		(N=430)	(N=420)		(N=217)
BL mean	6.0	5.9	5.9		6.0	6.0		6.0
Final mean	4.4	3.7	3.1	<0.001[a]	3.2	3.1	<0.001[a]	3.0
Mean % Δ	-25.0%	-36.5%	-46.6%	<0.001[b]	-45.0%	-47.1%	0.108[b]	-49.4%
ApoB to ApoAI	(N=402)	(N=439)	(N=409)		(N=420)	(N=408)		(N=205)
BL mean	1.0	1.0	1.1		1.1	1.0		1.0
Final mean	0.8	0.7	0.6	<0.001[a]	0.6	0.6	<0.001[a]	0.6
Mean % Δ	-20.3%	-33.2%	-40.1%	<0.001[b]	-39.9%	-38.9%	0.494[b]	-43.4%
TG to HDL-C	(N=420)	(N=455)	(N=423)		(N=430)	(N=422)	0.080[a]	(N=217)
BL mean	7.8	7.9	7.8		8.0	8.0		7.9
Final mean	4.6	6.0	3.7	0.004[a]	3.1	3.8	<	3.0
Mean % Δ	-34.3%	-13.3%	-48.0%	<0.001[b]	-25.7%	-45.9%	0.001[b]	-28.7%

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

Comment: These ratios reflect what is seen with the individual lipid and lipoprotein parameters. The moderate-dose combination therapy was notably not different than moderate-dose statin monotherapy in the apoB:apoAI ratio, an apparent predictor of MI independent of LDL-C[21] (although this is somewhat controversial).

6.1.7 Subpopulations

Baseline TG

Based on an ANCOVA with the corresponding baseline value as the covariate and with effects on primary endpoints for treatment group, baseline TG level and the treatment group by baseline TG level interaction, a statistically significant treatment by baseline TG level interaction was observed for mean percent change in LDL-C ($p = 0.012$). No statistically significant interactions by baseline TG level were observed for mean percent change in the secondary efficacy parameters.

In the integrated study population, approximately 32% of subjects had baseline TG levels ≤ 200 mg/dL and 68% of subjects had baseline TG levels > 200 mg/dL. For subjects with baseline TG ≤ 200 mg/dL and subjects with baseline TG > 200 mg/dL, results were consistent with the

overall efficacy results, with greater mean percent increases in HDL-C and decreases in TG and LDL-C observed in both combination therapy groups than in the corresponding monotherapy groups for all three primary comparisons; that is, for HDL-C and TG: combination vs. monotherapy statin and for LDL-C: combination vs. ABT-335 monotherapy.

ABT-335 in combination with low-dose statins and moderate-dose statins resulted in a greater treatment effect on TG among subjects with baseline TG levels > 200 mg/dL (-51.3% and -49.9%, respectively) than among subjects with baseline TG levels ≤ 200 mg/dL (-28.5% and -28.7%, respectively). Both doses of combination therapy also resulted in a greater treatment effect on HDL-C among subjects with baseline TG levels> 200 mg/dL (19.9% and 19.0%, respectively) than those with TG levels ≤ 200 mg/dL (14.3% each). Conversely, ABT-335 in combination with low-dose statins and moderate-dose statins resulted in a greater treatment effect on LDL-C among subjects with baseline TG levels ≤ 200 mg/dL (-39.4% and -40.9%, respectively) than among subjects with TG levels > 200 mg/dL (-30.2% and -31.9%, respectively).

Comment: LDL-lowering with ABT-335 in subjects with BL TG > 200 mg/dL was negligible (-1.9%). Furthermore, TG lowering in this group was similar to the high dose statin (-38.2% and -38.8%, respectively). HDL-raising was greater in the ABT-335 groups as compared to any of the statin monotherapy groups. Findings in the individual studies were similar (data not shown).

Table 6.1.7.A. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C by Baseline TG (Controlled Studies Analysis Set)

		ABT-335	Low-dose statin	ABT-335 + low statin	p-value	Moderate-dose statin	ABT-335 + moderate statin	p-value	High-dose statin
Baseline TG ≤ 200 mg/dL									
HDL-C		(N=147)	(N=147)	(N=139)		(N=133)	(N=136)		(N=70)
	BL mean	39.8	40.8	38.8		40.2	40.1		41.3
	Mean % Δ	12.4%	5.2%	14.3%	< 0.001[a]	5.3%	14.3%	< 0.001[a]	6.3%
TG		(N=156)	(N=149)	(N=156)		(N=145)	(N=150)		(N=75)
	BL mean	162.9	160.9	168.2		163.0	158.7		162.1
	Mean % Δ	-18.4%	-2.9%	-28.5%	< 0.001[a]	-4.2%	-28.7%	< 0.001[a]	-7.5%
LDL-C		(N=148)	(N=147)	(N=141)		(N=132)	(N=137)		(N=73)
	BL mean	169.0	162.4	162.6		167.7	164.6		168.0
	Mean % Δ	-12.1%	-37.8%	-39.4%	< 0.001[b]	-43.0%	-40.9%	< 0.001[b]	-47.7%
Baseline TG > 200 mg/dL									
HDL-C		(N=273)	(N=308)	(N=284)		(N=297)	(N=286)		(N=147)
	BL mean	37.9	37.4	38.1		37.8	37.4		36.6
	Mean % Δ	18.1%	8.3%	19.9%	< 0.001[a]	18.1%	19.9%	< 0.001[a]	8.5%
TG		(N=303)	(N=328)	(N=314)		(N=327)	(N=312)		(N=160)
	BL mean	323.4	325.9	322.4		327.9	333.5		320.6
	Mean % Δ	-38.2%	-24.2%	-51.3%	< 0.001[a]	-33.3%	-49.9%	< 0.001[a]	-38.8%
LDL-C		(N=279)	(N=316)	(N=205)		(N=307)	(N=297)		(N=152)
	BL mean	153.9	150.9	153.4		154.7	153.5		151.6
	Mean % Δ	-1.9%	-32.2%	-30.2%	< 0.001[b]	-30.7%	-31.9%	< 0.001[b]	-47.1%

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

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

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

The Tricor (fenofibrate) label describes the effects of LDL-C in patients with Fredrickson Types IV and V hyperlipidemia; specifically, that there is a mean increase in LDL-C in patients with TG 500-1500 with Tricor treatment. This reviewer conducted an analysis of LDL-C and TG change with a baseline TG cutoff of 500 mg/dL[18]:

Table 6.1.7.B. LDL-C and TG Percent Change by Baseline TG Cutoff of 500 mg/dL

	ABT-335	Low-dose statin	ABT-335 + low-dose statin	Moderate-dose statin	ABT-335 + moderate-dose statin	High-dose statin
BL TG < 500						
N	394	433	405	405	433	212
LDL % change (SD)	-7.1 (19.0)	-33.0 (18.0)	-33.3 (19.0)	-41.0 (16.2)	-33.0 (18.0)	-46.8 (15.8)
N	424	444	438	435	424	220
TG % change (SD)	-29.9 (30.4)	-15.7 (69.4)	-43.8 (25.3)	-23.7 (31.8)	-41.3 (28.1)	-27.6 (32.1)
BL TG ≥ 500						
N	33	30	32	34	37	13
LDL % change (SD)	+26.5 (47.7)	-20.4 (26.3)	-11.6 (29.7)	-26.1 (29.5)	-9.7 (39.1)	-30.3 (19.7)
N	35	33	32	37	38	15
TG % change (SD)	-52.9 (24.1)	-44.4 (31.5)	-55.1 (31.5)	-37.6 (52.4)	-61.8 (23.3)	-46.7 (17.6)

Comment: The primary goal of fibrate therapy in patients with baseline TG ≥ 500 mg/dL is prevention of pancreatitis,[23] therefore, in certain patients the LDL-C is of secondary importance. Adding statin to the lipid regimen in these patients does improve LDL-C (decrease of 10-12%), although not as much as monotherapy statin would. Clearly, ABT-335 is very effective for TG-lowering in this subset as monotherapy, and particularly in combination with moderate-dose statin. Interestingly, TG-lowering with ABT-335 was only slightly better than high-dose statin in the subset of subjects with the highest baseline TG. Monotherapy with ABT-335 seems to be a less advantageous option than in combination with a statin, even in the group with TG ≥ 500 mg/dL. Patients with TG > 200 mg/dL (as described in Table 6.1.8.A), get the most benefit from combination therapy in triglycerides (50-51% with combination therapy vs. a maximum decrease of 38-39% with ABT-335 or the highest dose of statin monotherapy).

Baseline LDL-C

In order to get efficacy results that could be compared with the fenofibrate label, a subgroup of baseline LDL-C > 160 mg/dL was evaluated. The results are demonstrated in Table 6.1.7.C.

23 Executive Summary of the Third Report of the National Cholesterol Education Program, (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285 (19):2486-97.

Table 6.1.7.C. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C by Baseline LDL-C (Controlled Studies Analysis Set)

		ABT-335	Low-dose statin	ABT-335 + low statin	p-value	Moderate-dose statin	ABT-335 + moderate statin	p-value	High-dose statin
Baseline LDL-C ≤ 100 mg/dL									
HDL-C	BL mean	(N=220) 37.6	(N=202) 37.2	(N=262) 36.8		(N=240) 37.2	(N=230) 37.2		(N=120) 36.8
	Mean % Δ	17.7%	7.7%	17.8%	< 0.001[a]	8.3%	17.7%	< 0.001[a]	7.4%
TG	BL mean	(N=240) 301.1	(N=300) 308.5	(N=287) 302.9		(N=270) 310.0	(N=262) 302.4		(N=130) 291.4
	Mean % Δ	-32.3%	-16.7%	-45.3%	< 0.001[a]	-27.2%	-42.5%	< 0.001[a]	-38.8%
LDL-C	BL mean	(N=232) 134.9	(N=286) 134.4	(N=270) 134.1		(N=251) 135.6	(N=244) 134.1		(N=132) 135.5
	Mean % Δ	1.2%	-29.2%	-28.2%	< 0.001[b]	-37.7%	-27.7%	< 0.001[b]	-42.9%
Baseline LDL-C > 100 mg/dL									
HDL-C	BL mean	(N=191) 39.5	(N=162) 40.5	(N=161) 40.6		(N=179) 40.4	(N=181) 39.5		(N=89) 39.8
	Mean % Δ	14.6%	7.3%	18.9%	< 0.001[a]	9.1%	17.3%	< 0.001[a]	8.7%
TG	BL mean	(N=211) 254.1	(N=173) 260.9	(N=182) 248.2		(N=199) 250.6	(N=196) 248.3		(N=96) 265.2
	Mean % Δ	-28.7%	-17.2%	-42.6%	< 0.001[a]	-18.2%	-41.6%	< 0.001[a]	-24.1%
LDL-C	BL mean	(N=195) 187.9	(N=167) 188.4	(N=168) 192.6		(N=188) 189.5	(N=190) 186.6		(N=93) 187.2
	Mean % Δ	-13.3%	-40.1%	-40.7%	< 0.001[b]	-44.6%	-43.9%	< 0.001[b]	-50.9%

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

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

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

Comment: LDL-C efficacy with all groups, but particularly with ABT-335 monotherapy, was better in the subgroup of subjects with LDL-C > 160 mg/dL. The percent change of -13.5% is still less than the ~ -20% in Fredrickson's Type IIb subjects described in the fenofibrate label; although there was no placebo group in these studies. LDL-lowering with ABT-335 monotherapy is greatest when TG are taken into account; i.e., a Fredrickson's Type IIa profile of LDL-C > 160 and TG ≤ 200 mg/dL: mean change = -16% (reviewer's analysis). The studies supporting original approval of Tricor defined Type IIa as LDL > 160 mg/dL and TG ≤ 150 mg/dL, a group that was excluded (by TG) in the studies supporting this NDA. Additionally, it is unknown how undescribed baseline and other mitigating factors such as diet may have played a role in the LDL-lowering discrepancy. It should be noted that the FIELD study[6] studied patients with diabetes and a lower baseline LDL-C (~118 mg/dL); fenofibrate demonstrated a decrease of 12% at 4 months and 1 year in LDL-C. A published study[24] of patients with diabetes (baseline LDL-C ~135 mg/dL) evaluating inflammatory and lipid markers with treatment with fenofibrate, simvastatin, and the combination, demonstrated a % LDL-C change of -5.6 in the fenofibrate group, similar to the ABT-335 group in the controlled studies.

The combination groups demonstrated LDL-lowering similar to the statin monotherapy groups in the subset of patients with higher baseline LDL-C. However, the highest dose of

24 Muhlestein JB, et al. The Reduction of Inflammatory Biomarkers by Statin, Fibrate, and Combination Therapy Among Diabetic Patients With Mixed Dyslipidemia: The DIACOR (Diabetes and Combined Lipid Therapy Regimen) Study. J Am Coll Cardiol 2006;48:396-401.

statin demonstrated the greatest LDL-lowering in either subset. Labeling should reinforce the notion that maximizing statins for lipid goals is advised prior to considering adding on ABT-335.

Sex

The integrated study population included 1393 (51.6%) females and 1305 (48.4%) males. The sponsor concludes that for both females and males, results were consistent with the overall efficacy results, and in general, greater mean percent changes were observed in the primary efficacy variables among females than among males.

Table 6.1.7.D. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C by Gender (Controlled Studies Analysis Set)

		ABT-335	Low-dose statin	ABT-335 + low-dose statin	p-value	Moderate-dose statin	ABT-335 + moderate-dose statin	p-value	High-dose statin
Males									
HDL-C	BL mean	(N=187) 34.8	(N=240) 35.3	(N=197) 34.5		(N=221) 35.0	(N=208) 34.5		(N=108) 34.5
	Mean % Δ	12.9%	7.3%	15.3%	<0.001[a]	9.8%	13.3%	0.040[a]	6.8%
TG	BL mean	(N=203) 295.7	(N=251) 298.9	(N=218) 283.6		(N=238) 297.0	(N=229) 298.8		(N=117) 304.1
	Mean % Δ	-25.2%	-13.5%	-42.0%	<0.001[a]	-21.9%	-39.8%	<0.001[a]	-31.4%
LDL-C	BL mean	(N=103) 154.4	(N=244) 148.2	(N=207) 149.6		(N=223) 152.7	(N=216) 151.0		(N=111) 146.3
	Mean % Δ	2.3%	-31.8%	-28.6%	<0.001[b]	-38.4%	-38.1%	<0.001[b]	-47.2%
Females									
HDL-C	BL mean	(N=233) 41.1	(N=215) 41.6	(N=226) 41.2		(N=200) 41.2	(N=214) 41.4		(N=100) 41.0
	Mean % Δ	18.3%	8.1%	19.9%	<0.001[a]	7.9%	21.1%	<0.001[a]	8.7%
TG	BL mean	(N=256) 280.2	(N=228) 275.5	(N=252) 281.6		(N=234) 279.2	(N=233) 282.2		(N=118) 282.2
	Mean % Δ	-35.7%	-20.2%	-45.5%	<0.001[a]	-23.9%	-44.2%	<0.001[a]	-24.6%
LDL-C	BL mean	(N=234) 161.3	(N=218) 150.9	(N=229) 161.0		(N=210) 163.3	(N=218) 161.4		(N=114) 165.8
	Mean % Δ	-11.1%	-35.8%	-37.2%	<0.001[b]	-42.3%	-38.0%	<0.001[b]	-47.2%

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

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

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

Comment: Efficacy overall is somewhat better in females than males, but this is particularly noted in the groups treated with ABT-335. Females in these controlled studies had higher baseline LDL-C and lower baseline TG.

Age

The integrated study population included 2207 (81.8%) subjects < 65 years of age and 491 (18.2%) subjects ≥ 65 years of age. Results by age group were consistent with the overall primary efficacy results. In general, greater mean percent changes were observed in the primary efficacy variables among subjects ≥ 65 years of age than subjects < 65 years of age.

Table 6.1.7.E. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C by Age (Controlled Studies Analysis Set)

		ABT-335	Low-dose statin	ABT-335 + low statin	p-value	Moderate-dose statin	ABT-335 + moderate statin	p-value	High-dose statin
< 65 Years of Age									
		(N=344)	(N=309)	(N=342)		(N=334)	(N=338)		(N=171)
HDL-C	BL mean	38.0	38.4	37.6		38.3	37.7		37.6
	Mean % Δ	15.9%	7.6%	17.3%	< 0.001[a]	8.6%	16.8%	< 0.001[a]	7.9%
		(N=377)	(N=403)	(N=378)		(N=392)	(N=387)		(N=180)
TG	BL mean	281.3	281.5	285.6		287.3	287.5		283.6
	Mean % Δ	-28.8%	-15.1%	-41.6%	< 0.001[a]	-22.3%	-39.7%	< 0.001[a]	-26.7%
		(N=350)	(N=398)	(N=354)		(N=362)	(N=350)		(N=177)
LDL-C	BL mean	159.2	153.6	153.8		157.1	154.9		155.2
	Mean % Δ	-3.9%	-32.6%	-31.3%	< 0.001[b]	-39.6%	-33.1%	< 0.001[b]	-45.7%
≥ 65 Years of Age									
		(N=76)	(N=66)	(N=81)		(N=76)	(N=84)		(N=46)
HDL-C	BL mean	40.0	38.2	40.6		38.2	38.7		38.3
	Mean % Δ	17.5%	6.6%	21.3%	< 0.001[a]	8.1%	19.8%	< 0.001[a]	7.2%
		(N=82)	(N=74)	(N=92)		(N=88)	(N=93)		(N=49)
TG	BL mean	277.0	308.8	288.1		288.1	279.8		269.7
	Mean % Δ	-38.7%	-22.5%	-51.0%	< 0.001[a]	-27.9%	-48.9%	< 0.001[a]	-30.7%
		(N=77)	(N=73)	(N=82)		(N=77)	(N=84)		(N=48)
LDL-C	BL mean	154.5	153.4	163.2		161.9	161.7		150.3
	Mean % Δ	-9.7%	-30.8%	-38.9%	< 0.001[b]	-44.2%	-48.0%	< 0.001[b]	-51.4%

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

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

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

Race

The integrated study population included 2497 (92.6%) subjects who were White, 126 (4.7%) subjects who were Black, and 75 (2.8%) who were of other races (e.g., Asian, multiracial, or American Indian/Alaska native).

Comment: This reviewer agrees that too few subjects were Black and of other races to make meaningful conclusions regarding treatment effects in these races, although Black subjects treated with ABT-335 appeared to have less of a TG-lowering as compared to the other race groups (-32.2%, White; -8.3%, Black; -21.2%, Other).

Ethnicity

In the integrated study population, 267 (9.9%) subjects were Hispanic and 2431 (90.1%) subjects were non-Hispanic. For both Hispanic subjects and non-Hispanic subjects, greater mean percent increases in HDL-C and decreases in TG and LDL-C were observed in both combination therapy groups than in the corresponding monotherapy groups for all three primary comparisons. Although too few subjects were Hispanic to make meaningful conclusions regarding treatment effects in this ethnic group, efficacy results were consistent with the overall results, without any clear pattern of reduced or greater treatment effect for either Hispanic or non-Hispanic subjects.

Diabetic Status

In the integrated study population, approximately 22% were diabetic and 78% were non-diabetic. Results by diabetic status were consistent with the overall efficacy results for all three primary comparisons. In general, the treatment effect of both doses of combination therapy was similar among diabetics and non-diabetics.

Table 6.1.7.F. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C by Diabetic Status as Reported in Medical History (Controlled Studies Analysis Set)

		ABT-335	ABT-335 + low-dose statin	ABT-335 + low statin	p-value	ABT-335 + moderate-dose statin	ABT-335 + moderate statin	p-value	ABT-335 + high-dose statin
Diabetic									
		(N=93)	(N=98)	(N=90)		(N=95)	(N=93)		(N=45)
HDL-C	BL mean	38.0	38.0	38.4		38.5	38.6		38.3
	Mean % Δ	13.6%	4.1%	16.8%	<0.001[a]	8.8%	16.2%	0.012[a]	7.7%
		(N=102)	(N=102)	(N=103)		(N=105)	(N=103)		(N=50)
TG	BL mean	293.0	292.6	299.0		294.4	283.6		250.0
	Mean % Δ	-32.1%	-5.6%	-44.2%	<0.001[a]	-24.3%	-43.9%	0.022[a]	-34.1%
		(N=97)	(N=100)	(N=97)		(N=99)	(N=96)		(N=48)
LDL-C	BL mean	150.8	153.2	149.5		154.2	150.9		150.4
	Mean % Δ	-5.3%	-37.5%	-34.0%	<0.001[b]	-41.3%	-32.6%	<0.001[b]	-30.2%
Non-Diabetic									
		(N=327)	(N=330)	(N=327)		(N=335)	(N=329)		(N=172)
HDL-C	BL mean	38.5	39.4	38.1		38.4	38.0		37.8
	Mean % Δ	17.2%	9.0%	19.3%	<0.001[a]	9.4%	18.3%	<0.001[a]	8.8%
		(N=357)	(N=375)	(N=367)		(N=388)	(N=358)		(N=185)
TG	BL mean	272.8	279.7	272.4		281.4	282.2		286.4
	Mean % Δ	-32.0%	-20.9%	-45.2%	<0.001[a]	-24.7%	-42.9%	<0.001[a]	-27.3%
		(N=338)	(N=363)	(N=339)		(N=360)	(N=338)		(N=177)
LDL-C	BL mean	150.3	155.2	150.8		160.4	157.6		156.8
	Mean % Δ	-3.7%	-31.5%	-31.5%	<0.001[b]	-38.9%	-33.7%	<0.001[b]	-44.7%

Note: P-value from an ANCOVA with corresponding baseline lipid value as the covariate and effects for treatment group and screening TG level

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

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

Comment: It is noted that subjects with and without diabetes had similar baseline lipids in these studies, which is probably more likely to impact ABT-335 efficacy, than diabetes per se.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The data for ABT-335 in this application only describe the 135 mg dose, and therefore, clinical information relevant to dosing recommendations was that of the statins, for which a low dose (rosuvastatin 10 mg, simvastatin 20 mg, and atorvastatin 20 mg) and a mid dose (rosuvastatin 20 mg, simvastatin 40 mg, and atorvastatin 40 mg) were combined with ABT-335. The following table, repeated from Section 6.1.5, suggests that the low-and mid-dose statins in comparison with ABT-335 resulted in similar primary lipid changes, although formal comparisons were not conducted.

Table 6.1.8.A. 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%

Comment: These data suggest that the lowest dose statin needed to achieve goal lipid concentrations should be used in combination with ABT-335, because on average there was not much added benefit with use of the higher dose statin combination, at least for the three primary lipid parameters. It is unfortunate that ABT-335 was not studied in combination with high-dose statin.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy is best described by the M05-758 extension trial, the results of which were discussed in detail in the subsections above.

Mean lipid values after 52 weeks of treatment (12 weeks of double-blind treatment in Studies M05-748, M05-749, and M05-750 and 40 weeks of open-label treatment in Study M05-758) were similar. Mean final values for LDL-C ranged from 87 to 94 mg/dL, those for HDL-C ranged from 46 to 48 mg/dL, those for TG ranged from 129 to 138 mg/dL, those for non-HDL-C ranged from 111 to 121 mg/dL, and those for ApoB ranged from 78 to 83 mg/dL.

The sponsor provided the following figures, which display mean values of HDL-C, TG, LDL-C, non-HDL-C, and ApoB in the various analysis sets after 12 weeks of treatment and after 52 weeks of treatment; the mean baseline value is indicated by the reference line.

Figure 6.1.9.A. Mean Values for HDL-C after 12 Weeks of Double-blind Treatment and after 52 Total Weeks of Treatment

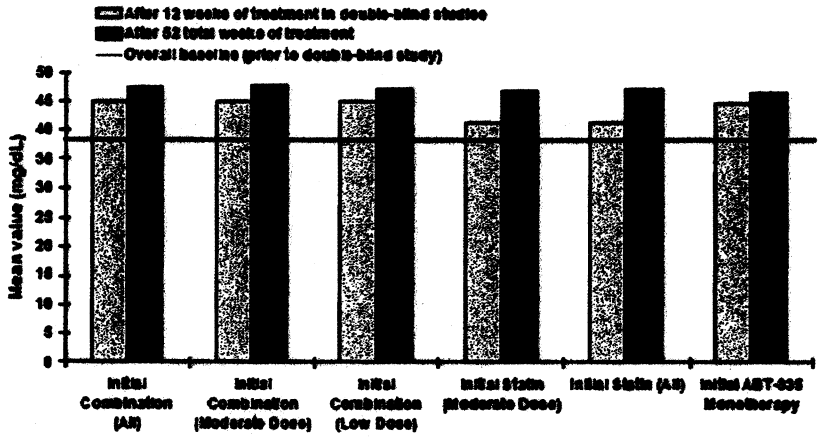

Figure 6.1.9.B. Mean Values for HDL-C after 12 Weeks of Double-blind Treatment and after 52 Total Weeks of Treatment

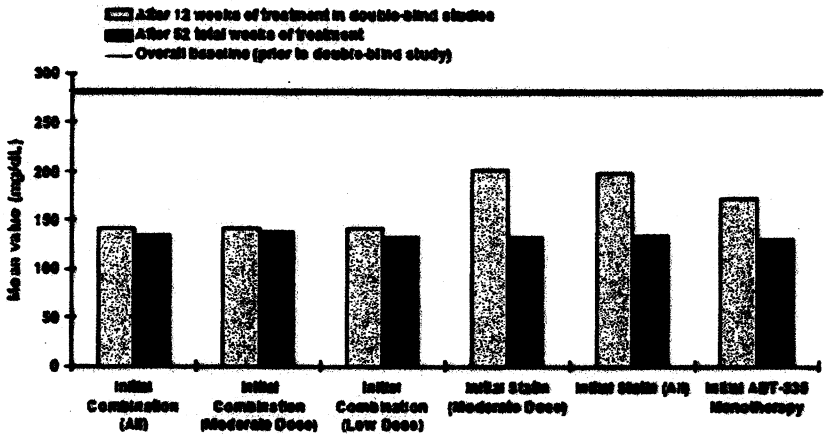

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Figure 6.1.9.C. Mean Values for LDL-C after 12 Weeks of Double-blind Treatment and after 52 Total Weeks of Treatment

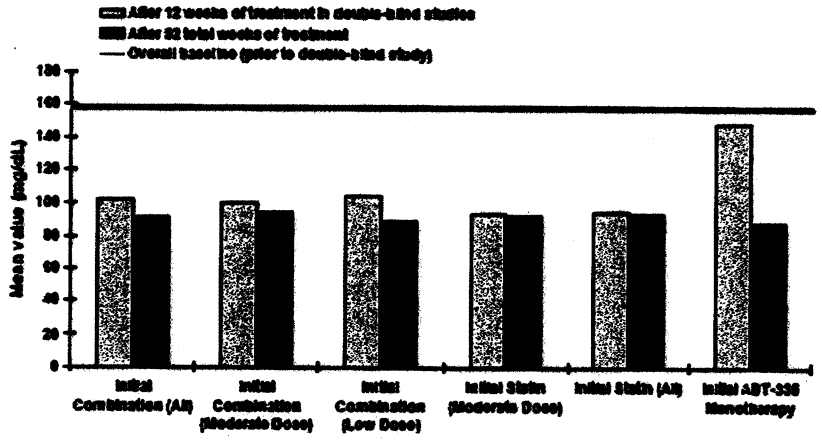
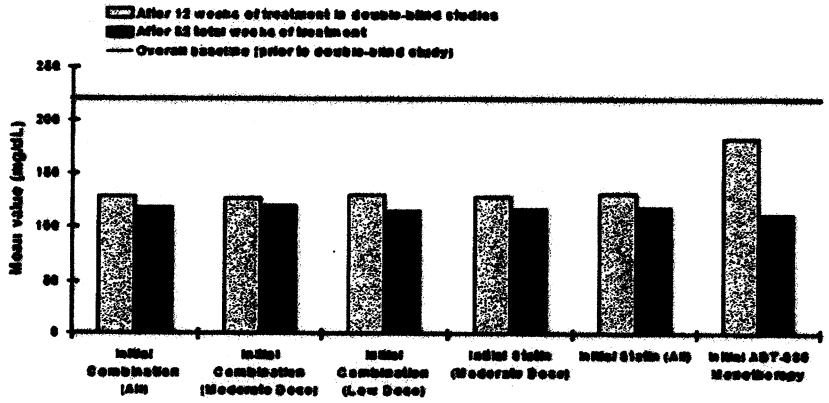


Figure 6.1.9.D. Mean Values for Non-HDL-C after 12 Weeks of Double-blind Treatment and after 52 Total Weeks of Treatment



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