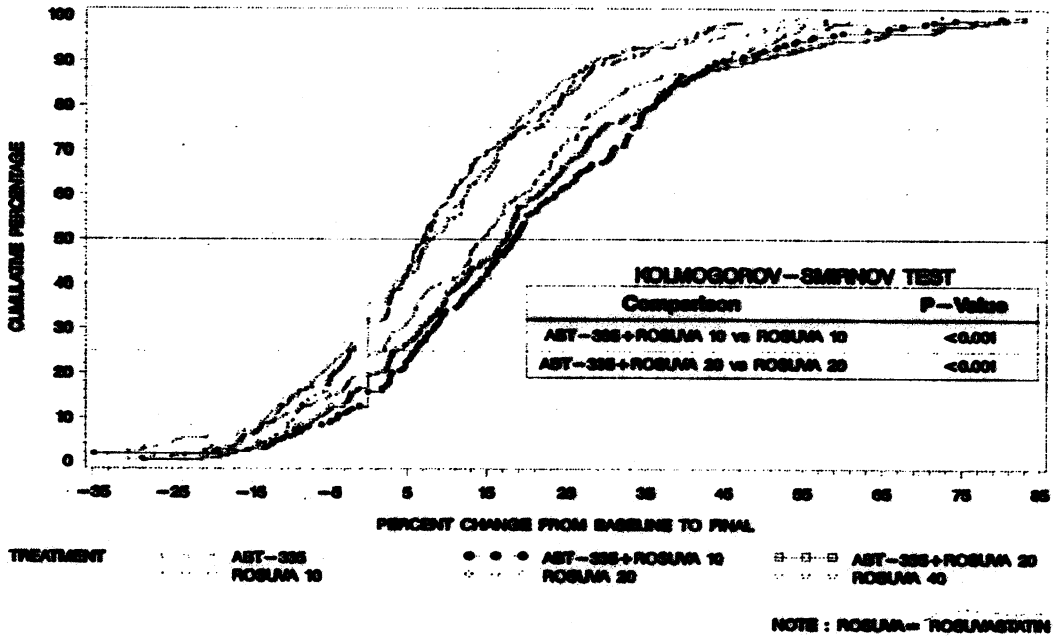
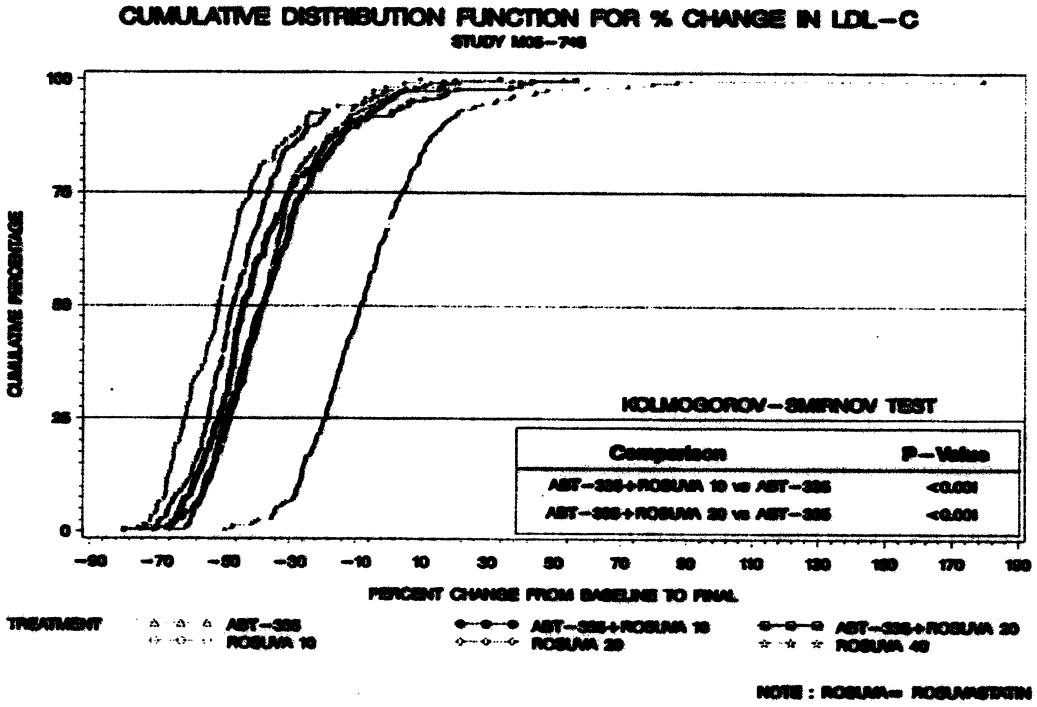
CUMULATIVE DISTRIBUTION FUNCTION FOR % CHANGE IN HDL–C

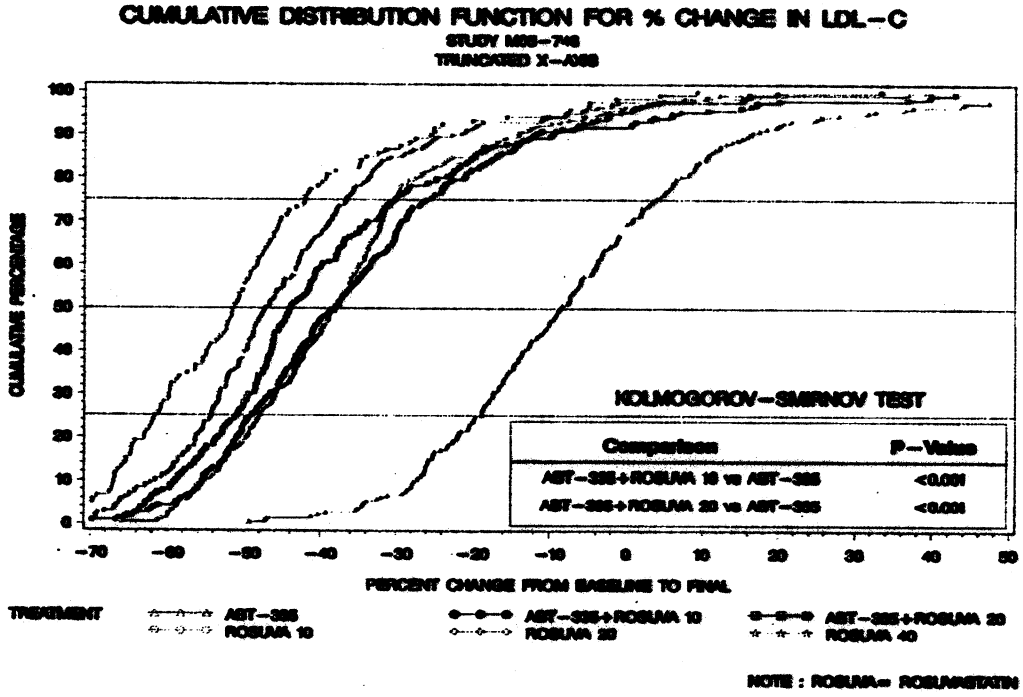
STUDY M06–748

TRUNCATED X–A06



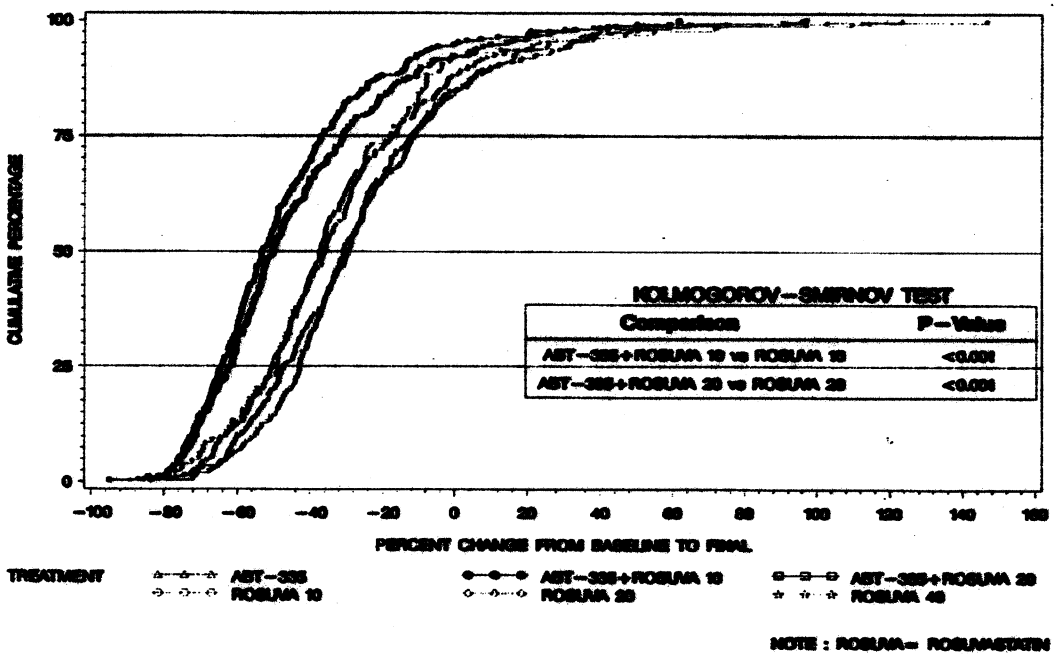
NOTE : ROSUVA= ROSUVASTATIN



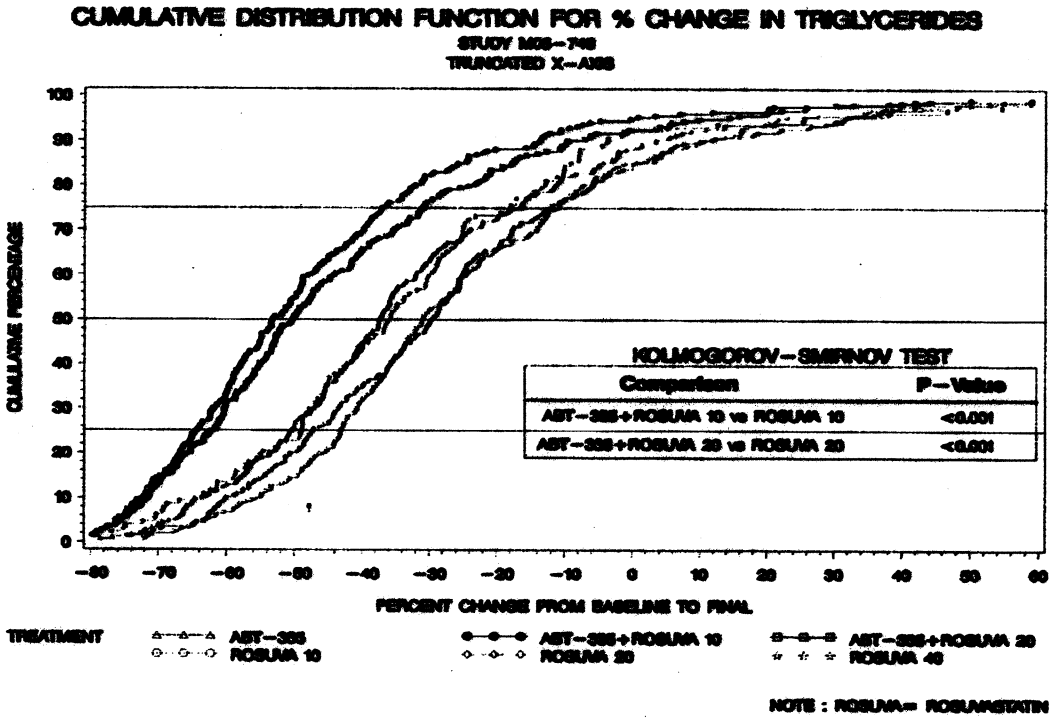


CUMULATIVE DISTRIBUTION FUNCTION FOR % CHANGE IN TRIGLYCERIDES

STUDY M05-740



NOTE : ROSUVA= ROSUVASTATIN



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

Study M05-749

Study Design and Endpoints (All three studies with three different statins were similar)

This was a Phase 3, multicenter, randomized, double-blind, prospective, comparative study in mixed dyslipidemic adults (Fredrickson Type IIb) designed to assess the safety and efficacy once daily treatment with ABT-335 in combination with two doses of simvastatin to ABT-335 monotherapy and simvastatin monotherapy on the primary lipid parameters associated with

increased risk of CHD in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb). Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio to 1 of the 6 treatment regimens as follows: 135 mg ABT-335 monotherapy, 20 mg simvastatin monotherapy, ABT-335 in combination with 20 mg simvastatin, 40 mg simvastatin monotherapy, ABT-335 in combination with 40 mg simvastatin, and 80 mg simvastatin monotherapy.

Study procedures were about the same as in Study 148 (previous one).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 560 subjects (102 subjects each to 135 mg ABT-335 monotherapy, 135 mg ABT-335 and 20 mg simvastatin, 135 mg ABT-335 and 40 mg simvastatin, 20 mg simvastatin monotherapy, and 40 mg simvastatin monotherapy, and 51 subjects in 80 mg simvastatin monotherapy)

Enrolled in Treatment Period: 657 subjects were randomized with 650 subjects treated:

ABT-335 monotherapy (N=119)
20 mg simvastatin monotherapy (N=119)
ABT-335 in combination with 20 mg simvastatin (N=119)
40 mg simvastatin monotherapy (N=116)
ABT-335 in combination with 40 mg simvastatin (N=118)
80 mg simvastatin monotherapy (N=59)

Efficacy Variables:

The primary efficacy variables were percent changes from baseline to 12 weeks post-baseline (Final Visit) in:
1. HDL-C (combination therapy with each dose of simvastatin vs. corresponding simvastatin monotherapy)
2. Triglycerides (combination therapy with each dose of simvastatin vs. corresponding simvastatin monotherapy)
3. LDL-C (combination therapy with each dose of simvastatin vs. ABT-335 monotherapy)

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

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

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

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

Additional efficacy parameters measured were Lp-PLA2, adiponectin, apolipoprotein AI, and apolipoprotein C-III. In addition, the following parameters derived by the NMR LipoProfile test were also considered exploratory: VLDL, LDL, and HDL total and subclass particle concentration; VLDL, LDL, and HDL mean particle size; and calculated lipid estimates of TG, VLDL, and HDL. All additional efficacy parameters measured during the conduct of the study were considered exploratory efficacy variables.

Patient Disposition

A total of 657 subjects were randomized and 650 were treated with at least one dose of study drug (Table 14.1__1.1). Of the treated subjects, 555 (85.4%) completed the study and 95 (14.6%) prematurely discontinued study drug. Overall, the most common reasons for prematurely discontinuing study drug were adverse event (7.8%) and withdrawal of consent (5.1%); 2.3% of subjects were lost to follow-up and 1.1% of subjects were discontinued due to noncompliance (Table 14.1__1.2). "Other" reasons for withdrawal, specified in Appendix 16.2__1.1, including relocation, difficulty attending scheduled visits, and difficulty swallowing capsules, were cited by 4.2% of subjects.

Disposition of Subjects

	ABT-335	20 mg simva	ABT-335 + 20 mg simva	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	113	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)

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.
Cross Reference: Table 14.1__1.1 and Table 14.1__1.2 and Appendix 16.2__1.1

One hundred forty-eight (148) investigative sites screened subjects, with 121 of these sites randomizing subjects. The majority of sites (112/122; 92.6%) enrolled and treated fewer than 12 subjects (Table 14.1__1.1). Nine sites had at least 12 randomized subjects (Table 14.2__1.12).

Subject disposition was also summarized by baseline calculated creatinine clearance level (Table 14.1__1.3.1 and Table 14.1__1.3.2) and baseline eGFR level (Table 14.1__1.4.1 and Table 14.1__1.4.2). Three of 18 (16.7%) subjects with baseline calculated creatinine clearance < 60 mL/min and four of 29 (13.8%) subjects with baseline eGFR < 60 mL/min/1.73m^2 prematurely discontinued the study.

Demographic and Baseline Characteristics

No statistically significant differences were observed among treatment groups in categorical demographic characteristics (Table 14.1__2.1). Of the 650 randomized and treated subjects, 332 (51.1%) were female and 318 (48.9%) were male; 93.8% of all subjects were White, 2.8% were Black, 2.0% were Asian, 0.9% were of other races, and 0.5% were American Indian/Alaska natives. Hispanics comprised 10.8% of the study population. The majority (64.5%) of subjects

were between 40 and 60 years of age; 8.6% were younger than 40 years and 26.9% were older than 60 years. A total of 99 subjects (15.2%) were 65 years of age and older. A summary of categorical demographic variables is presented in Table below.

Demographic Characteristics (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=116)	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.

Cross Reference: Table 14.1__2.1 and Table 14.1__2.3 and Appendix 16.2__4.1.1 and Appendix 16.2__4.3

A summary of quantitative demographic variables is presented in Table below. No statistically significant differences were observed among treatment groups in age (p = 0.427), weight (p =

0.886), or waist circumference (p = 0.774) (Table 14.1__2.2). Mean age was 54.4 years. Mean weight was 90.2 kg overall, 84.2 kg among females, and 96.3 kg among males. Mean waist circumference was 102.1 cm overall, 99.3 cm among females and 105.1 cm among males.

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

	Treatment Group n (%)						
Demographic Characteristic	ABT-335	20 mg simva	ABT-335 + 20 mg simva	40 mg simva	ABT-335 + 40 mg simva	80 mg simva	p-value[a]
Age (years)	(N=119)	(N=119)	(N=119)	(N=116)	(N=118)	(N=59)	0.427
Mean (SD)	53.9 (11.65)	54.3 (9.78)	55.9 (9.89)	53.7 (9.36)	53.7 (11.02)	55.8 (10.32)	
Median	55.0	54.0	57.0	53.0	53.0	55.0	
Min, max	24, 79	30, 79	25, 82	33, 77	27, 74	30, 80	
Weight (kg)							0.886[b]
Females	(N=68)	(N=56)	(N=59)	(N=61)	(N=57)	(N=31)	
Mean (SD)	81.7 (19.18)	83.6 (20.48)	85.7 (18.45)	82.1 (17.26)	87.4 (19.02)	86.7 (21.28)	
Median	77.1	80.5	81.2	78.9	84.4	85.7	
Min, max	43.1, 144.2	54.4, 143.0	58.5, 155.1	45.8, 139.7	48.5, 136.5	57.2, 132.9	
Males	(N=51)	(N=63)	(N=60)	(N=55)	(N=61)	(N=28)	
Mean (SD)	98.3 (21.37)	94.2 (19.97)	95.9 (17.02)	98.6 (19.25)	95.3 (17.72)	96.2 (12.43)	
Median	92.0	88.9	98.0	97.1	94.3	95.4	
Min, max	70.3, 165.6	64.0, 151.5	56.7, 140.2	59.0, 150.1	65.8, 156.9	73.0, 121.6	
Waist circumference (cm)							0.774[b]
Females	(N=68)	(N=55)	(N=59)	(N=61)	(N=57)	(N=30)	
Mean (SD)	97.0 (12.77)	98.1 (15.63)	100.7 (14.29)	98.6 (12.08)	100.9 (13.79)	102.0 (14.20)	
Median	96.5	94.0	101.0	96.5	99.1	100.3	
Min, max	67.3, 124.5	71.1, 139.0	72.4, 138.4	76.2, 140.5	66.0, 131.0	68.6, 138.4	
Demographic Characteristic	ABT-335	20 mg simva	ABT-335 + 20 mg simva	40 mg simva	ABT-335 + 40 mg simva	80 mg simva	p-value[a]
Waist circumference (cm) (continued)							
Males	(N=48)	(N=61)	(N=59)	(N=52)	(N=60)	(N=27)	
Mean (SD)	105.9 (16.06)	104.1 (14.30)	104.7 (11.90)	106.9 (14.23)	104.3 (13.65)	105.0 (11.07)	
Median	103.5	101.6	104.1	104.1	101.6	104.1	
Min, max	76.2, 148.6	81.3, 139.7	71.1, 137.2	84.5, 142.2	81.3, 143.5	87.0, 135.0	

simva = simvastatin; SD = standard deviation; Min, max = minimum, maximum

a. p-value for differences among treatment groups from one-way ANOVA.

b. p-value for differences among the groups for all subjects, not by gender.

Cross Reference: Table 14.1__2.2 and Appendix 16.2__4.1.1

At baseline, no statistically significant differences were observed among treatment groups in mean values for the primary lipid parameters (Table 14.1__5.1). The subject population had a low mean baseline level of HDL-C (38.3 mg/dL) and high mean baseline levels of TG (281.0 mg/dL) and LDL-C (158.2 mg/dL). A summary of the primary lipid parameters at baseline is presented by treatment group in Table below.

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

	Treatment Group n (%)						
Lipid Parameter (mg/dL)	ABT-335	20 mg simva	ABT-335 + 20 mg simva	40 mg simva	ABT-335 + 40 mg simva	80 mg simva	p-value[a]
HDL-C	(N=118)	(N=117)	(N=114)	(N=111)	(N=114)	(N=56)	0.735
Mean (SD)	38.4 (6.95)	38.3 (6.31)	37.5 (7.16)	38.5 (7.36)	38.5 (8.22)	39.4 (6.77)	
Median	38.0	38.0	36.0	37.0	36.8	38.5	
Min, max	22.0, 60.0	25.0, 57.0	23.0, 56.0	22.0, 60.0	23.0, 71.0	29.0, 62.0	
TG	(N=119)	(N=119)	(N=119)	(N=116)	(N=118)	(N=59)	0.416
Mean (SD)	300.2 (195.29)	280.3 (131.02)	292.1 (160.61)	290.5 (167.07)	272.7 (125.77)	258.1 (132.11)	
Median	246.0	254.9	246.0	247.5	256.5	220.0	
Min, max	95.0, 1700.0	93.0, 1050.0	104.0, 964.0	75.0, 1250.0	92.0, 1112.0	99.0, 810.0	
LDL-C	(N=119)	(N=119)	(N=119)	(N=116)	(N=117)	(N=59)	0.715
Mean (SD)	159.2 (34.74)	153.9 (38.63)	156.7 (43.01)	160.6 (35.09)	157.1 (31.51)	153.8 (30.51)	
Median	158.0	149.8	148.6	156.5	154.0	150.0	
Min, max	74.0, 258.0	80.0, 325.0	78.0, 324.3	69.0, 266.0	61.0, 266.0	105.0, 255.0	

simva = simvastatin; SD = standard deviation; Min, max = minimum, maximum

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

Cross Reference: Table 14.1__5.1 and Appendix 16.2__4.11.1 and Appendix 16.2__4.11.2

At baseline, no statistically significant differences were observed among groups in mean values for the secondary lipid parameters (Table 14.1__5.1) or exploratory variables.Mean values were 220.3 mg/dL for non-HDL-C, 63.5 mg/dL for VLDL-C, 258.8 mg/dL for total-C, and 146.3 mg/dL for ApoB; median values for hsCRP ranged from 0.24 to 0.35 mg/dL across treatment groups.

Statistical Methodologies

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

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

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

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

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

Results and Conclusions

Data Sets Analyzed

Of the 650 treated subjects, 621 subjects had both a baseline value and at least one post-baseline value for at least one of the three primary endpoints and were included in the Full Analysis Set. Subjects who were excluded from the primary analysis of HDL-C, LDL-C, and TG are listed in Appendix 16.2__3. The most common reason for exclusion from the primary analysis was that the subject did not have eligible Final Visit values for the primary lipid parameters.

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

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

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

		ABT-335	20 mg simva	ABT-335 + 20 mg simva	p-value
HDL-C (mg/dL)		(N=107)	(N=114)	(N=105)	
	Baseline Mean	38.2	38.4	37.2	
	Mean % Δ (SE)	16.2% (1.85)	7.2% (1.80)	17.8% (1.86)	< 0.001[a]
TG (mg/dL)		(N=113)	(N=116)	(N=113)	
	Baseline Mean	300.9	281.2	295.6	
	Mean % Δ (SE)	-31.7% (2.74)	-14.2% (2.71)	-37.4% (2.75)	< 0.001[a]
LDL-C (mg/dL)		(N=107)	(N=116)	(N=109)	
	Baseline Mean	156.5	153.2	157.9	
	Mean % Δ (SE)	-4.0% (1.96)	-22.4% (1.90)	-24.0% (1.94)	< 0.001[b]

simva = simvastatin; Δ= change; SE = standard error

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

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

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

Cross Reference: Table 14.2__1.1.1, Appendix 16.2__6.1.1, Appendix 16.2__6.1.2, and Appendix 16.2__6.3

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

ABT-335 in combination with 20 mg simvastatin resulted in a significantly greater mean percent increase in HDL-C (17.8% vs. 7.2%, $p < 0.001$) and a significantly greater mean percent decrease in TG (-37.4% vs. -14.2%, $p < 0.001$) compared to 20 mg simvastatin monotherapy. ABT-335 in combination with 20 mg simvastatin resulted in a significantly greater mean percent decrease in LDL-C (-24.0% vs. -4.0%, $p < 0.001$) compared to ABT-335 monotherapy. A summary of baseline means, mean percent changes from baseline to the Final Visit, and p-values for between-group comparisons of mean percent change in HDL-C, TG, and LDL-C is presented for the ABT-335 and 20 mg simvastatin monotherapy groups and the ABT-335 in combination with 20 mg simvastatin group in Table above.

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

		ABT-335	40 mg simva	ABT-335 + 40 mg simva	p-value	80 mg simva
HDL-C (mg/dL)		(N=107)	(N=102)	(N=106)		(N=52)
	Baseline Mean	38.2	38.5	38.5		39.5
	Mean % Δ (SE)	16.2% (1.85)	8.5% (1.89)	18.9% (1.86)	< 0.001[a]	6.8% (2.61)
TG (mg/dL)		(N=113)	(N=112)	(N=111)		(N=56)
	Baseline Mean	300.9	284.4	274.1		257.4
	Mean % Δ (SE)	-31.7% (2.74)	-22.4% (2.76)	-42.7% (2.77)	< 0.001[a]	-20.2% (3.82)
LDL-C (mg/dL)		(N=107)	(N=106)	(N=108)		(N=55)
	Baseline Mean	156.5	163.3	155.9		155.4
	Mean % Δ (SE)	-4.0% (1.96)	-31.7% (1.98)	-25.3% (1.96)	< 0.001[b]	-40.8% (2.69)

simva = simvastatin; Δ = change; SE = standard error

Note: p-value from 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 + 40 mg simvastatin vs. 40 mg simvastatin monotherapy.

b. ABT-335 + 40 mg simvastatin vs. ABT-335 monotherapy.

Cross Reference: Table 14.2__1.1.1, Appendix 16.2__6.1.1, Appendix 16.2__6.1.2, and Appendix 16.2__6.3

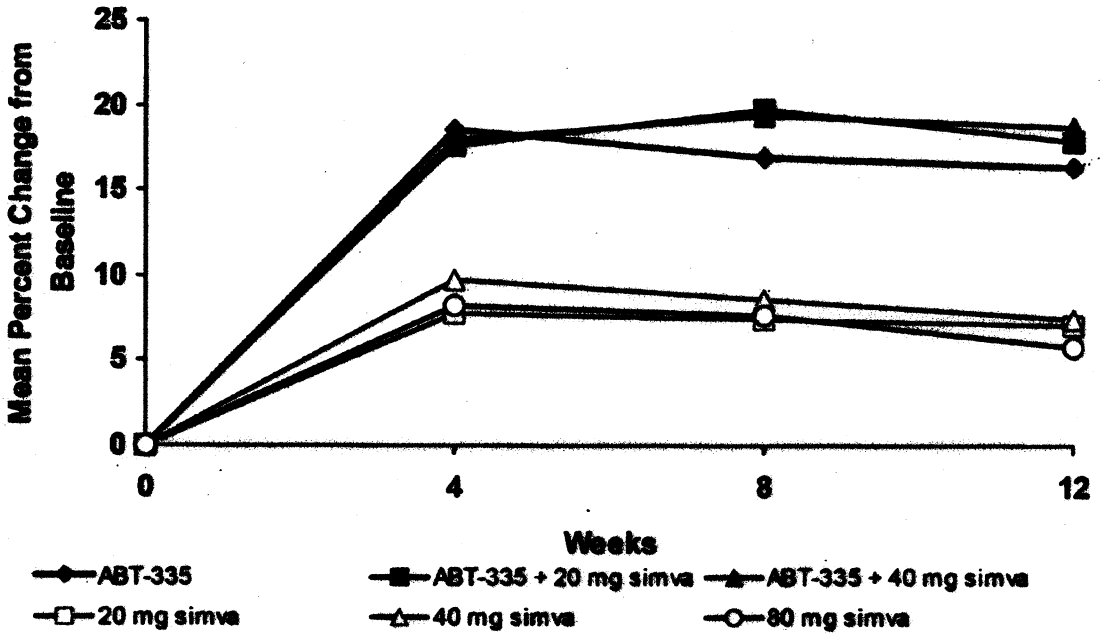
ABT-335 in combination with 40 mg simvastatin resulted in a significantly greater mean percent increase in HDL-C (18.9% vs. 8.5%, $p < 0.001$) and a significantly greater mean percent decrease in TG (-42.7% vs. -22.4%, $p < 0.001$) compared to 40 mg simvastatin monotherapy. ABT-335 in combination with 40 mg simvastatin resulted in a significantly greater mean percent

decrease in LDL-C (-25.3% vs. -4.0%, $p < 0.001$) compared to ABT-335 monotherapy. A summary of baseline means, mean percent change from baseline to the Final Visit, and p-values for between-group comparisons of mean percent change in HDL-C, TG, and LDL-C is presented for the 40 mg simvastatin monotherapy, ABT-335 in combination with 40 mg simvastatin, and 80 mg simvastatin monotherapy groups in Table above.

Although not a primary comparison for LDL-C, a smaller mean percent decrease in LDL-C was observed with ABT-335 in combination with 40 mg simvastatin than in the 40 mg simvastatin monotherapy (-25.3% vs. -31.7%, $p = 0.017$).

Note: This reviewer's analyses and the many sensitivity analyses provided (Section 14.2 of the Study Report) did not raise any concern about the sponsor's claims.

Mean Percent Change from Baseline in HDL-C Over Time

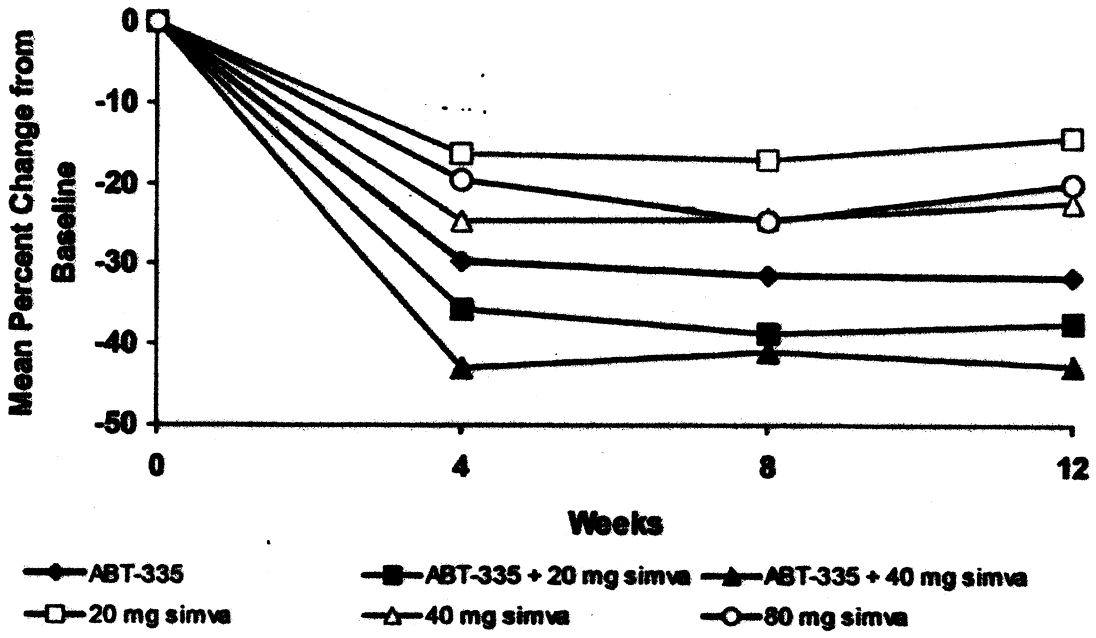


simva = simvastatin

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

Cross Reference: Table 14.2__3.1

Mean Percent Change from Baseline in TG Over Time

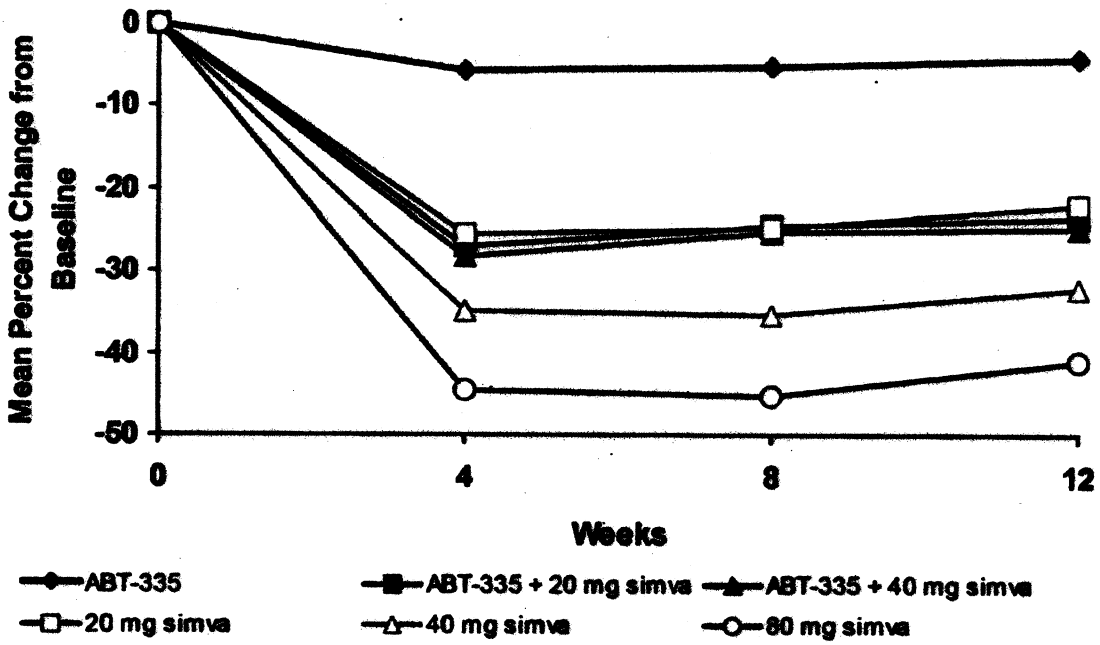


simva = simvastatin

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

Cross Reference: Table 14.2__3.1

Mean Percent Change from Baseline in LDL-C Over Time



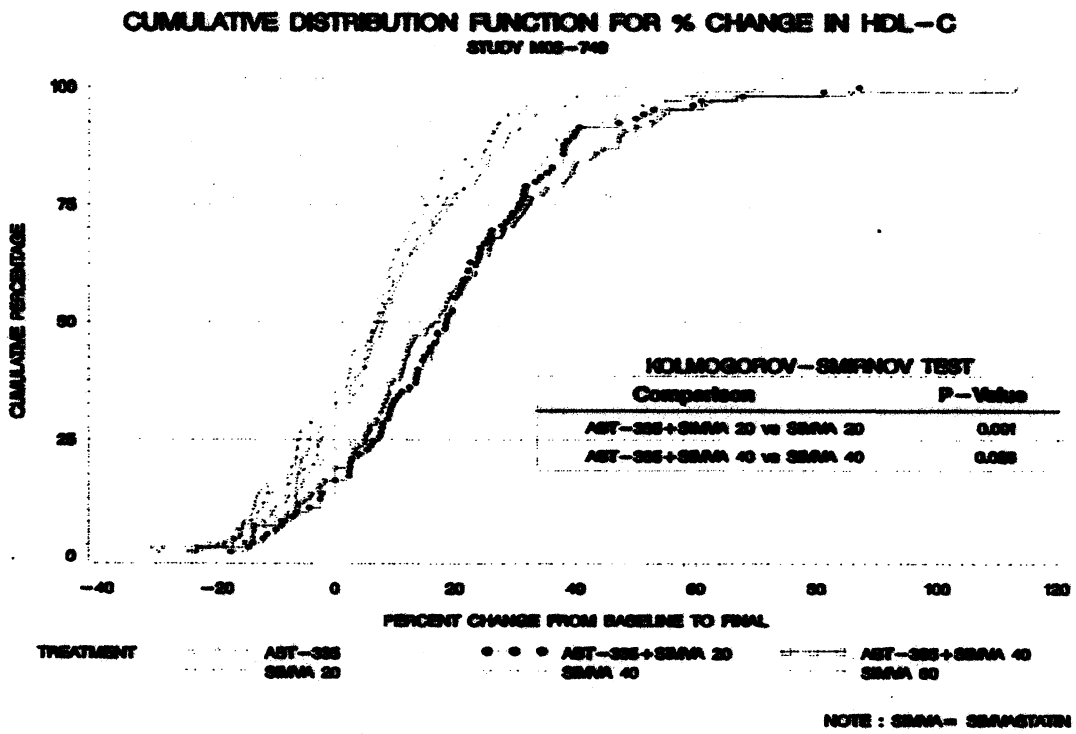
simva = simvastatin

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

Cross Reference: Table 14.2__3.1

§ Graphs of the cumulative distribution functions by treatment groups for the primary efficacy variables (%change in HDL-C, LDL-C, Triglycerides from baseline to endpoint) is provided below. From this, the percent of patients (y-axis value) with a value of %change in the efficacy variable from baseline to endpoint, smaller than or equal to a value on the x-axis, can be read. For example (2nd graph is enlarged), fifty percent patients in each treatment arm had a percent change in HDL-C from baseline to endpoint of less than 18.62, 18.60, 17.50, 8.14, 8.82, 7.14, respectively, for the ABT-335, ABT-335+SIMVA 20, ABT-335+SIMVA 40, SIMVA 20, a SIMVA 40, and SIMVA 80.

TTT

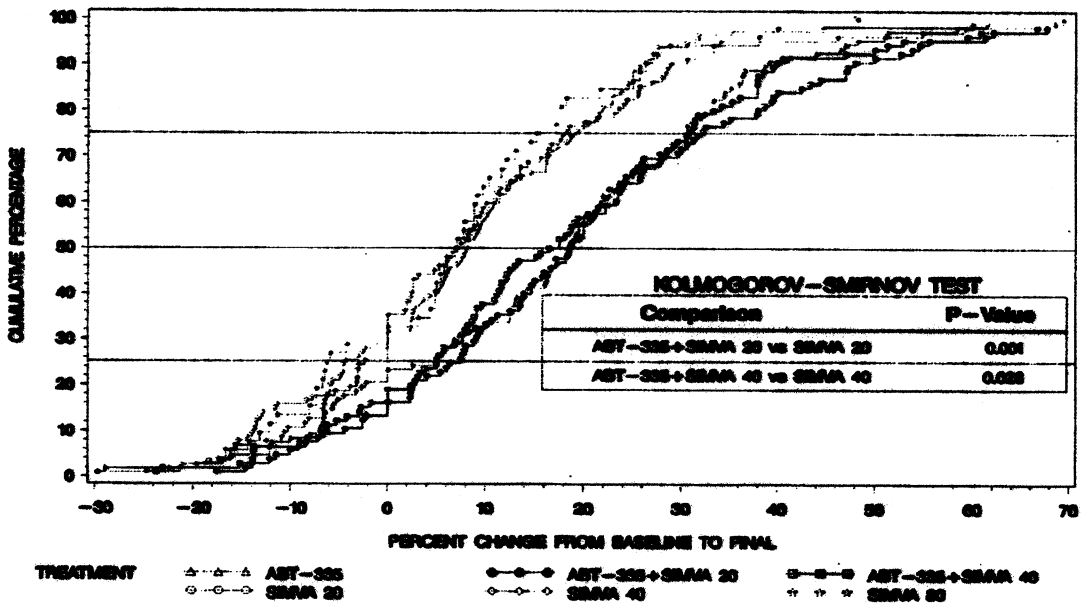


The second figure for each of HDL-C, LDL-C, and Triglycerides is meant for better visualization with truncated X-axis.

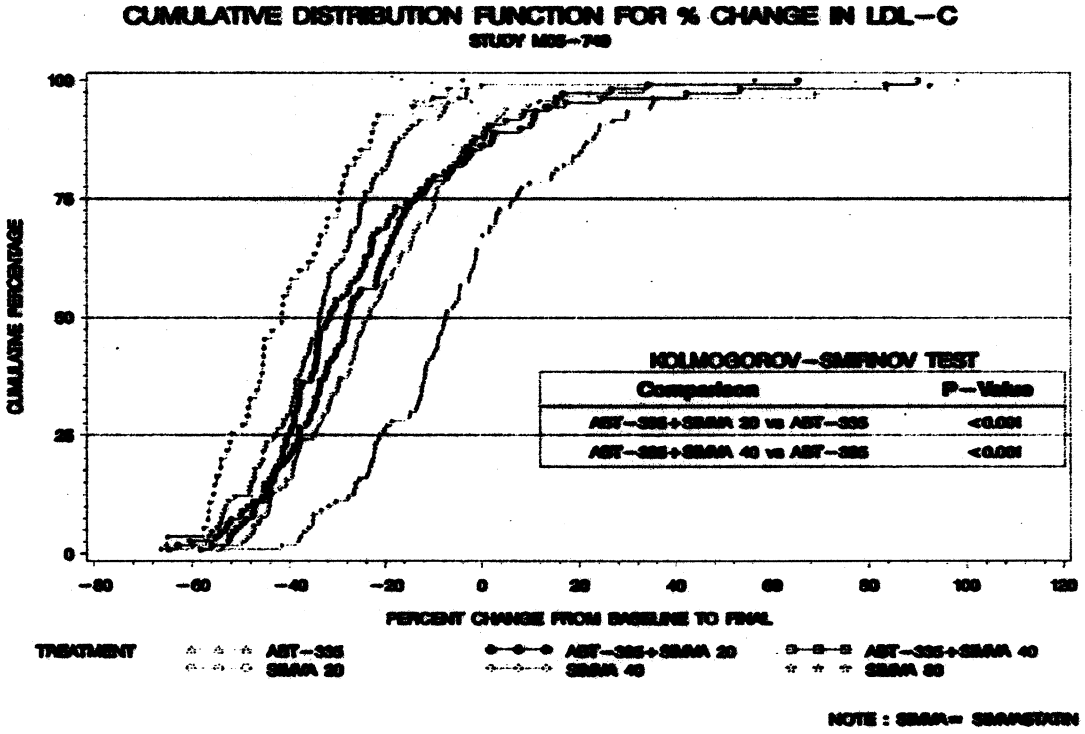
CUMULATIVE DISTRIBUTION FUNCTION FOR % CHANGE IN HDL-C

STUDY M05-749

TRUNCATED X-A05B



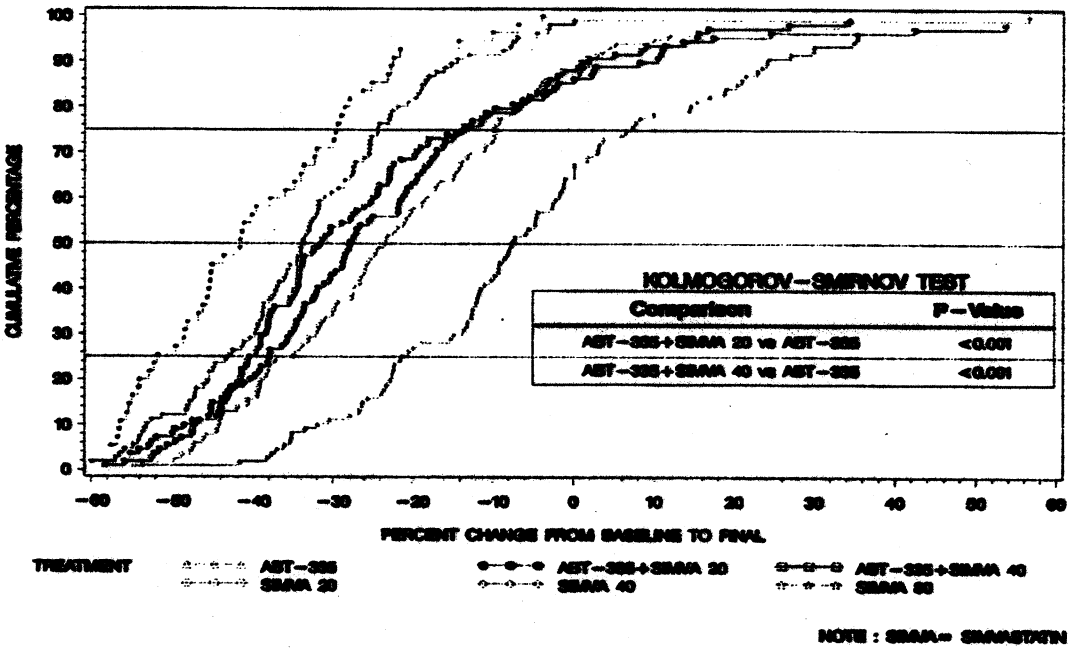
NOTE : SIMVA= SIMVASTATIN



CUMULATIVE DISTRIBUTION FUNCTION FOR % CHANGE IN LDL–C

STUDY MDS–748

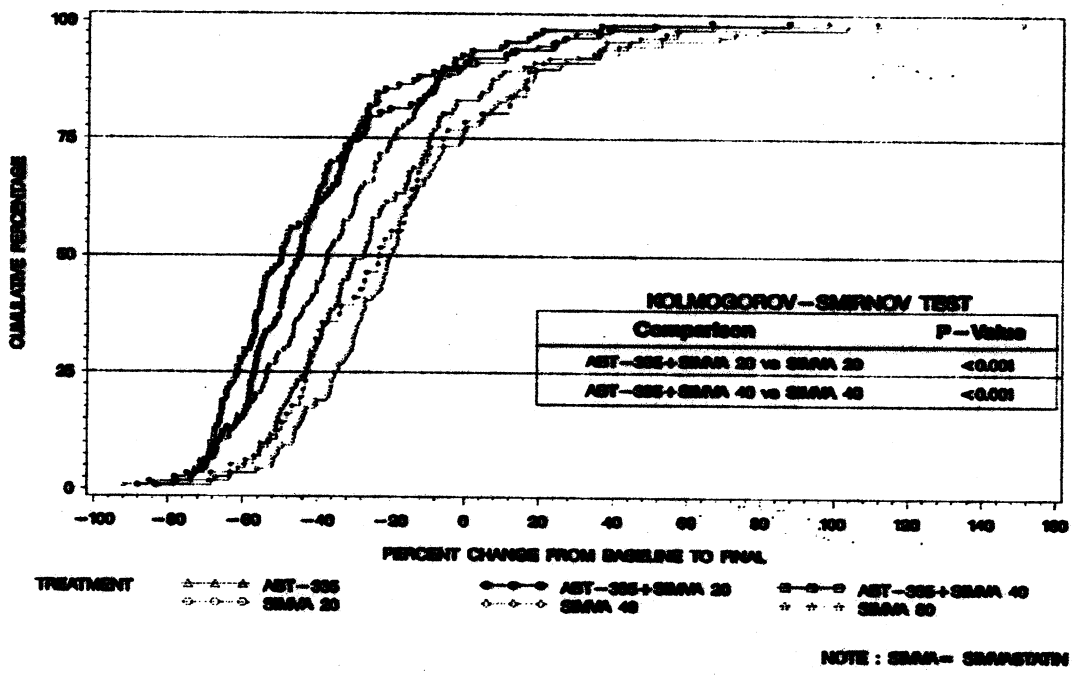
TRUNCATED X–AXIS



NOTE : SIMVA= SIMVASTATIN

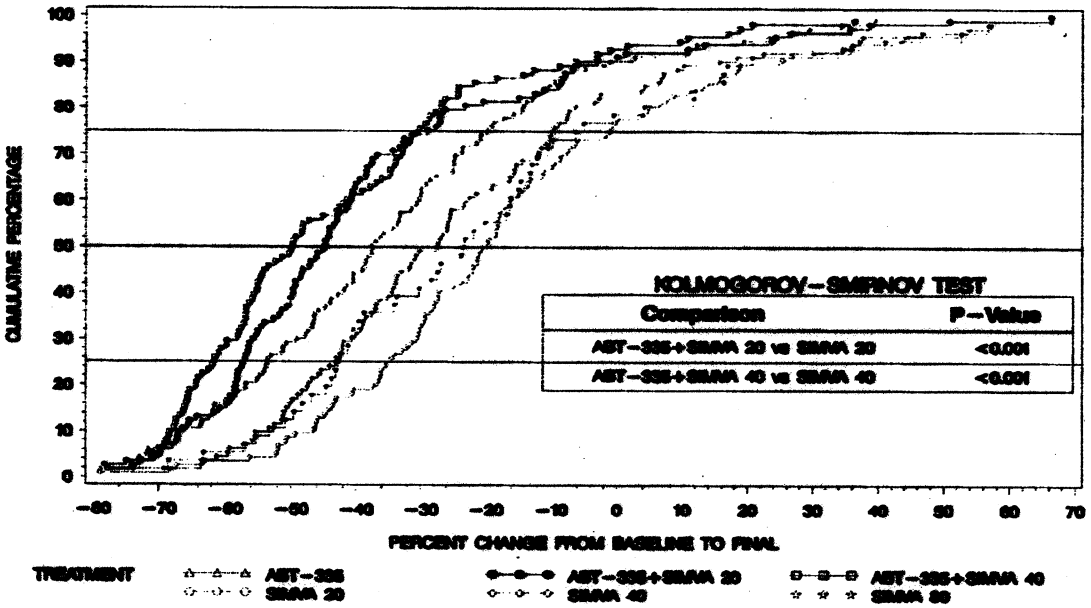
CUMULATIVE DISTRIBUTION FUNCTION FOR % CHANGE IN TRIGLYCERIDES

STUDY MIS—749



NOTE : SIMVA= SIMVASTATIN

CUMULATIVE DISTRIBUTION FUNCTION FOR % CHANGE IN TRIGLYCERIDES
STUDY M05-749
TRUNCATED X-AXIS



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

Study M05-750

Study Design and Endpoints (All three studies with three different statins were similar)

This Phase 3, multicenter, randomized, double-blind, prospective study was designed to compare the effects of once daily treatment with ABT-335 in combination with two doses of atorvastatin to ABT-335 monotherapy and atorvastatin monotherapy on the primary lipid parameters associated with increased risk of CHD in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb). Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio to one of

the six treatment groups as follows: 135 mg ABT-335 monotherapy, 20 mg atorvastatin monotherapy, ABT-335 in combination with 20 mg atorvastatin, 40 mg atorvastatin monotherapy, ABT-335 in combination with 40 mg atorvastatin, and 80 mg atorvastatin monotherapy.

Study procedures were about the same as in Study 148.

Number of Subjects (Planned and Analyzed):

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

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

ABT-335 monotherapy (N = 112)
20 mg atorvastatin monotherapy (N = 113)
ABT-335 in combination with 20 mg atorvastatin (N = 110)
40 mg atorvastatin monotherapy (N = 109)
ABT-335 in combination with 40 mg atorvastatin (N = 110)
80 mg atorvastatin monotherapy (N = 55)

Efficacy:

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

1. HDL-C (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy).

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

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

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

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

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

3. VLDL-C (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)

4. Total-Cholesterol (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)

5. Apolipoprotein B (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)

6. hsCRP (combination therapy with each dose of atorvastatin vs. corresponding atorvastatin monotherapy)

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

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

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

Patient Disposition

A total of 613 subjects were randomized and 609 were treated with at least one dose of study drug (Table 14.1__1.1). Of the 609 treated subjects, 518 (85.1%) completed the study and 91 (14.9%) prematurely discontinued study drug. Overall, the most common reasons for prematurely discontinuing study drug were adverse event (9.0%) and withdrawal of consent (3.4%); 2.3% of subjects were lost to follow-up and 1.1% of subjects were discontinued due to noncompliance. "Other" reasons for withdrawal specified in Appendix 16.2__1.1, including

difficulty attending scheduled visits, issues with study medication, and Investigator/Sponsor decision, were cited by 3.1% of subjects.

The overall discontinuation rate in both combination therapy groups (19.1%) was slightly higher than in the ABT-335 (15.2%), 40 mg atorvastatin (12.8%), and 80 mg atorvastatin (16.4%) monotherapy groups; the discontinuation rate in the 20 mg atorvastatin monotherapy group was 8.0%. The incidence of discontinuation due to adverse events was lowest in the 20 mg atorvastatin (2.7%) and ABT-335 (7.1%) monotherapy groups and similar in the combination and higher dose atorvastatin groups (10.9% to 12.7%). A summary of subject disposition by treatment group is presented in Table 6.

Disposition of Subjects

	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.

Cross Reference: Table 14.1__1.1, Table 14.1__1.2 and Appendix 16.2__.1.1

One hundred seventeen (117) investigative sites screened subjects, with 101 of these sites randomizing subjects. The majority of sites (89/101; 88.1%) enrolled fewer than 12 subjects (Table 14.1__1.1). Twelve sites had at least 12 randomized subjects.

Subject disposition was also summarized by baseline calculated creatinine clearance (Table 14.1__1.3.1 and Table 14.1__1.3.2) and baseline eGFR level (Table 14.1__1.4.1 and Table 14.1__1.4.2). Only one of 16 subjects (6.3%) with calculated creatinine clearance < 60 mL/min and four of 39 subjects (10.3%) with eGFR < 60 mL/min/1.73m2 prematurely discontinued the study. Disposition for the larger subgroups was generally similar to the overall subject disposition.

Demographic and Baseline Characteristics

No statistically significant differences were observed among the treatment groups in categorical demographic characteristics (Table 14.1__2.1). Of the 609 randomized and treated subjects, 311 (51.1%) were female and 298 (48.9%) were male; 91.8% of all subjects were White, 3.9% were Black, 2.8% were Asian, 0.7% were of other races, 0.5% were multiracial, and 0.3% were American Indian/Alaska natives. Hispanics comprised 8.4% of the study population. The majority (60.6%) of subjects were between 40 and 60 years of age; 8.2% were younger than 40 years and 31.2% were older than 60 years. A total of 119 subjects (19.5%) were 65 years of age and older. A summary of categorical demographic variables is presented in Table below.

Demographic Characteristics (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.

Cross Reference: Table 14.1__2.1, Table 14.1__2.3, Appendix 16.2__4.1.1, and Appendix 16.2__4.3

No statistically significant differences were observed among the treatment groups in quantitative demographic characteristics (Table 14.1__2.2). Mean age was 55 years. Mean weight was 91.5 kg overall, 86.2 kg among females, and 97.1 kg among males. Mean waist circumference was 103.6 cm overall, 101.5 cm among females, and 105.8 cm among males. A summary of quantitative demographic variables is presented in Table below.

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

Demographic Characteristic	Treatment Group n (%) ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	40 mg atorva	ABT-335 + 40 mg atorva	80 mg atorva	p-value[a]
Age (years)	(N=112)	(N=113)	(N=110)	(N=109)	(N=110)	(N=55)	0.368
Mean (SD)	54.0 (10.70)	53.7 (11.60)	56.2 (10.21)	56.3 (10.44)	54.9 (11.89)	55.4 (10.70)	
Median	55.0	53.0	57.0	57.0	55.0	55.0	
Min, max	25.0, 79.0	25.0, 80.0	25.0, 82.0	34.0, 78.0	18.0, 80.0	30.0, 78.0	
Weight (kg)							0.975[b]
Females	(N=57)	(N=48)	(N=56)	(N=60)	(N=61)	(N=29)	
Mean (SD)	85.4 (19.54)	88.5 (22.44)	87.2 (18.32)	85.6 (19.01)	83.9 (18.54)	88.1 (21.26)	
Median	83.9	86.7	83.0	83.5	81.6	88.5	
Min, max	48.5, 140.2	50.8, 156.5	59.9, 133.8	57.2, 121.6	53.1, 136.1	58.5, 162.8	
Males	(N=55)	(N=65)	(N=54)	(N=49)	(N=49)	(N=26)	
Mean (SD)	98.9 (20.35)	94.5 (14.41)	96.9 (15.35)	98.4 (16.19)	97.8 (12.84)	96.0 (14.50)	
Median	98.0	94.3	96.7	97.5	96.2	94.0	
Min, max	57.2, 170.6	69.4, 125.6	68.5, 130.2	72.6, 142.0	73.0, 128.4	74.8, 137.9	
Waist circumference (cm)							0.936[b]
Females	(N=57)	(N=47)	(N=56)	(N=60)	(N=59)	(N=28)	
Mean (SD)	100.7 (13.79)	101.4 (12.86)	103.7 (15.37)	101.0 (14.75)	101.1 (15.44)	100.5 (15.02)	
Median	99.1	100.5	101.6	99.0	99.1	98.5	
Min, max	72.0, 142.2	73.7, 135.0	74.0, 139.0	71.1, 135.3	75.4, 143.0	76.2, 137.2	
Males	(N=55)	(N=65)	(N=52)	(N=49)	(N=49)	(N=25)	
Mean (SD)	106.9 (18.04)	103.2 (10.48)	104.7 (11.15)	107.9 (15.83)	107.6 (12.31)	105.4 (12.61)	
Median	104.1	102.9	103.3	104.1	106.0	106.5	
Min, max	78.0, 203.2	83.8, 130.8	87.0, 137.5	88.5, 178.5	83.8, 138.4	84.0, 143.0	

atorva = atorvastatin; SD = standard deviation; Min, max = minimum, maximum

a. p-value for differences among treatment groups from one-way ANOVA.

b. p-value for differences among the groups for all subjects, not by gender.

Cross Reference: Table 14.1__2.2 and Appendix 16.2__4.1.1

At baseline, no statistically significant differences were observed among groups in mean values for the primary lipid parameters (Table 14.1__5.1). The subject population had a low mean baseline level of HDL-C (38.4 mg/dL) and high mean baseline levels of TG (276.6 mg/dL) and LDL-C (161.1 mg/dL). A summary of the primary lipid parameters at baseline is presented by treatment group in Table below.

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

	Treatment Group n (%)						
Lipid Parameter (mg/dL)	ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	40 mg atorva	ABT-335 + 40 mg atorva	80 mg atorva	p-value[a]
HDL-C	(N=106)	(N=111)	(N=107)	(N=104)	(N=105)	(N=54)	0.934
Mean (SD)	38.4 (6.92)	38.9 (7.14)	38.5 (6.94)	38.5 (7.83)	38.3 (7.01)	37.6 (6.77)	
Median	38.0	38.0	39.0	38.0	38.0	36.0	
Min, max	19.0, 58.0	23.0, 58.0	22.0, 60.0	21.0, 61.0	22.0, 55.0	27.0, 53.0	
TG	(N=112)	(N=113)	(N=110)	(N=109)	(N=110)	(N=55)	0.454
Mean (SD)	290.2 (145.15)	266.4 (156.18)	264.4 (139.01)	279.3 (134.71)	286.6 (181.51)	298.4 (154.96)	
Median	237.5	233.0	215.5	233.0	224.5	254.0	
Min, max	116.0, 866.0	76.0, 1192.0	116.0, 1182.0	72.0, 812.0	44.0, 1234.0	98.0, 1140.0	
LDL-C	(N=112)	(N=113)	(N=110)	(N=109)	(N=110)	(N=55)	0.671
Mean (SD)	164.9 (37.92)	158.1 (35.38)	159.6 (36.35)	158.9 (36.43)	159.0 (32.15)	163.7 (34.98)	
Median	157.5	156.0	155.0	155.0	154.0	157.0	
Min, max	68.0, 296.0	74.0, 263.0	79.0, 274.0	66.0, 261.0	82.0, 250.0	105.0, 278.0	

atorva = atorvastatin; SD = standard deviation; Min, max = minimum, maximum

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

Cross Reference: Table 14.1__5.1, Appendix 16.2__4.11.1 and Appendix 16.2__4.11.2

At baseline, no statistically significant differences were observed among groups in mean values for the secondary lipid parameters (Table 14.1__5.1). Mean values were 222.9 mg/dL for non-

HDL-C, 63.0 mg/dL for VLDL-C, 261.5 mg/dL for total-C, and 147.1 mg/dL for ApoB (Table 14.1__5.1); median value for hsCRP ranged from 0.21 to 0.37 mg/dL across treatment groups (Table 14.1__5.1).

For the exploratory lipid parameters, a statistically significant difference was observed among groups at baseline in mean values for LpPLA2 ($p = 0.034$); mean values ranged from 247.8 ng/mL in the ABT-335 in combination with 20 mg atorvastatin group to 280.3 ng/mL in the 40 mg atorvastatin group (Table 14.1__5.1), with an overall mean of 261.8 ng/mL. This difference was not expected to affect efficacy results. For the other exploratory lipid parameters, mean values were 141.6 mg/dL for ApoAI, 18.2 mg/dL for ApoCIII, and 5591.1 ng/mL for adiponectin.

Results of additional lipid testing at baseline using NMR (LipoProfile®) methodology are presented in Table 14.1__5.2. Statistically significant differences were observed among treatment groups at baseline for the distribution of mean total VLDL particle concentration ($p < 0.001$), VLDL size ($p = 0.040$), total TG concentration ($p = 0.014$), large HDL concentration ($p = 0.031$), medium VLDL concentration ($p = 0.002$), and VLDL triglycerides ($p = 0.016$).

Statistical Methodologies

Statistical Methods

Efficacy:

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

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

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

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

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

Results and Conclusions

Data Sets Analyzed

Of the 609 treated subjects, 577 subjects had both a baseline value and at least one post-baseline value for at least one of the three primary endpoints and were included in the Full Analysis Set (Table 6). Subjects who were excluded from the primary analysis of HDL-C, LDL-C, and TG are listed in Appendix 16.2__3. The most common reason for exclusion from the primary analysis was that the subject did not have eligible Final Visit values for the primary lipid parameters.

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

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

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

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

Primary Variable		ABT-335	20 mg atorva	ABT-335 + 20 mg atorva	p-value
		(N=93)	(N=102)	(N=95)	
HDL-C (mg/dL)	Baseline mean	38.3	38.7	38.7	
	Final mean	45.5	40.3	43.8	
	Mean % Δ (SE)	19.8% (2.05)	5.6% (1.96)	13.9% (2.04)	0.003[a]
		(N=104)	(N=109)	(N=105)	
TG (mg/dL)	Baseline mean	289.7	267.4	264.3	
	Final mean	191.5	243.4	137.2	
	Mean % Δ (SE)	-27.7% (6.32)	-3.0% (6.20)	-43.8% (6.32)	< 0.001[a]
		(N=97)	(N=104)	(N=97)	
LDL-C (mg/dL)	Baseline mean	166.0	157.3	159.9	
	Final mean	153.2	96.8	102.1	
	Mean % Δ (SE)	-3.5% (1.90)	-37.5% (1.85)	-33.8% (1.91)	< 0.001[b]

atorva = atorvastatin; Δ = change; SE = standard error

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

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

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

Cross Reference: Table 14.2__1.1.1, Appendix 16.2__6.1.1, Appendix 16.2__6.1.2, and Appendix 16.2__6.3

ABT-335 in combination with 20 mg atorvastatin resulted in a significantly greater mean percent increase in HDL-C (13.9% vs. 5.6%, p = 0.003) and a significantly greater mean percent decrease in TG (-43.8% vs. -3.0%, p < 0.001) compared to 20 mg atorvastatin monotherapy. ABT-335 in combination with 20 mg atorvastatin resulted in a significantly greater mean percent decrease in LDL-C (-33.8% vs. -3.5%, p < 0.001) compared to ABT-335 monotherapy. A summary of baseline means, mean percent change from baseline to the Final Visit, and p-values for between-group comparisons of mean percent change in HDL-C, TG, and LDL-C is presented for the ABT-335 and 20 mg atorvastatin monotherapy groups and the ABT-335 in combination with 20 mg atorvastatin group in Table above.

Although not a primary comparison for HDL-C, a smaller mean percent increase in HDL-C was observed with ABT-335 in combination with 20 mg atorvastatin than in the 20 mg atorvastatin monotherapy group (13.9% vs. 19.8%, p = 0.003).

ABT-335 in combination with 40 mg atorvastatin resulted in a significantly greater mean percent increase in HDL-C (12.5% vs. 5.2%, p = 0.010) and a significantly greater mean percent decrease in TG (-40.0% vs. -21.3%, p = 0.032) compared to 40 mg atorvastatin monotherapy. ABT-335 in combination with 40 mg atorvastatin resulted in a significantly greater mean percent decrease in LDL-C (-35.5% vs. -3.5%, p < 0.001) compared to ABT-335 monotherapy. A summary of baseline means, mean percent change from baseline to the Final Visit, and p-values for between-group comparisons of mean percent change in HDL-C, TG, and LDL-C is presented for the ABT-335 and 40 mg atorvastatin monotherapy groups and the ABT-335 in combination with 40 mg atorvastatin group in Table below.

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

Primary Variable		ABT-335	40 mg atorva	ABT-335 + 40 mg atorva	p-value	80 mg atorva
		(N=93)	(N=92)	(N=91)		(N=50)
HDL-C (mg/dL)	Baseline mean	38.3	38.4	38.0		37.6
	Final mean	45.5	39.8	42.3		39.9
	Mean % Δ (SE)	19.8% (2.05)	5.2% (2.07)	12.5% (2.10)	0.010[a]	6.1% (2.77)
		(N=104)	(N=105)	(N=102)		(N=52)
TG (mg/dL)	Baseline mean	289.7	278.7	282.5		303.6
	Final mean	191.5	216.5	149.0		197.2
	Mean % Δ (SE)	-27.7% (6.32)	-21.3% (6.32)	-40.0% (6.41)	0.032[a]	-28.2% (8.85)
		(N=97)	(N=95)	(N=96)		(N=50)
LDL-C (mg/dL)	Baseline mean	166.0	160.4	158.4		162.7
	Final mean	153.2	94.0	99.7		85.8
	Mean % Δ (SE)	-3.5% (1.90)	-39.8% (1.93)	-35.5% (1.94)	< 0.001[b]	-46.0% (2.62)

atorva = atorvastatin; SE = standard error

Note: p-value from 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 + 40 mg atorvastatin vs. 40 mg atorvastatin monotherapy.

b. ABT-335 + 40 mg atorvastatin vs. ABT-335 monotherapy.

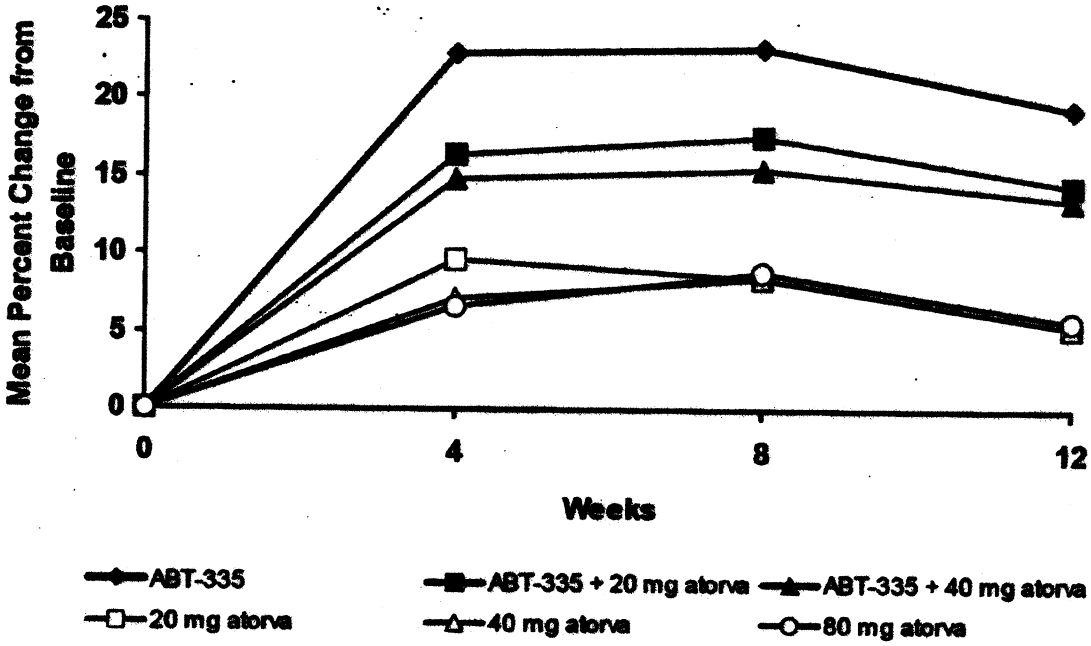
Cross Reference: Table 14.2__1.1.1 and Appendix 16.2__6.1.1, Appendix 16.2__6.1.2, and Appendix 16.2__6.3

Although not a primary comparison for HDL-C, a smaller mean percent increase in HDL-C was observed with ABT-335 in combination with 40 mg atorvastatin than in the 40 mg atorvastatin monotherapy group (12.5% vs. 19.8%, p = 0.010).

One subject in the 20 mg atorvastatin monotherapy group (#32024) had an extreme outlying value in change from baseline to final value in TG (1264%), as well as an outlying value in change from baseline to final in HDL-C (-56%) (Table 14.2__1.1.1). Since the means and standard errors are model-based, these outlying values affected the mean and standard errors of all six treatment groups and therefore affected all treatment group comparisons. Therefore, a post hoc analysis of the primary endpoints was performed excluding Subject #32024; the results were consistent with the primary analysis for all the primary efficacy endpoint comparisons. The mean percent changes in the primary efficacy variables, excluding Subject #32024, are presented in Table 16 and Table 17 (*Note: This reviewer has looked at those tables*).

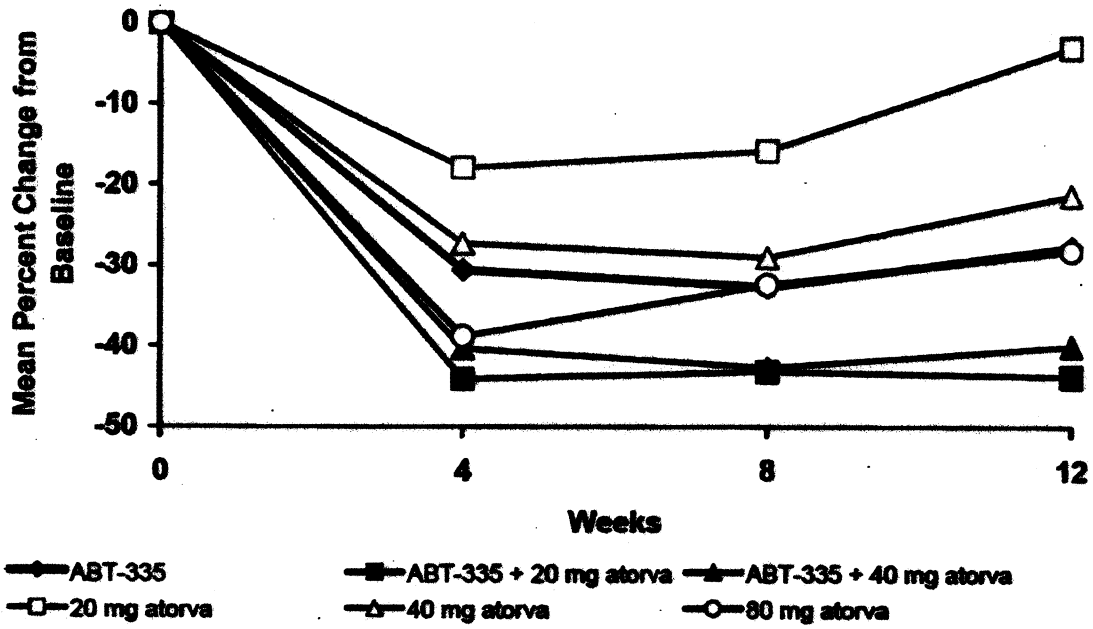
Similar to the overall analysis, in the analysis excluding Subject #32024, ABT-335 in combination with 20 mg atorvastatin, compared to 20 mg atorvastatin monotherapy, resulted in a significantly greater mean percent increase in HDL-C (14.0% vs. 6.3%, $p = 0.005$) and a significantly greater mean percent decrease in TG (-45.6% vs. -16.5%, $p < 0.001$). ABT-335 in combination with 20 mg atorvastatin resulted in a significantly greater mean percent decrease in LDL-C (-33.7% vs. -3.4%, $p < 0.001$) compared to ABT-335 monotherapy.

Mean Percent Change from Baseline in HDL-C Over Time



atorva = atorvastatin
Note: Analyses were performed using LOCF. At each visit, differences in mean percent change in HDL-C between each combination therapy group and the corresponding atorvastatin monotherapy group were statistically significant ($p = 0.05$).
Cross Reference: Table 14.2__3.1

Mean Percent Change from Baseline in TG Over Time

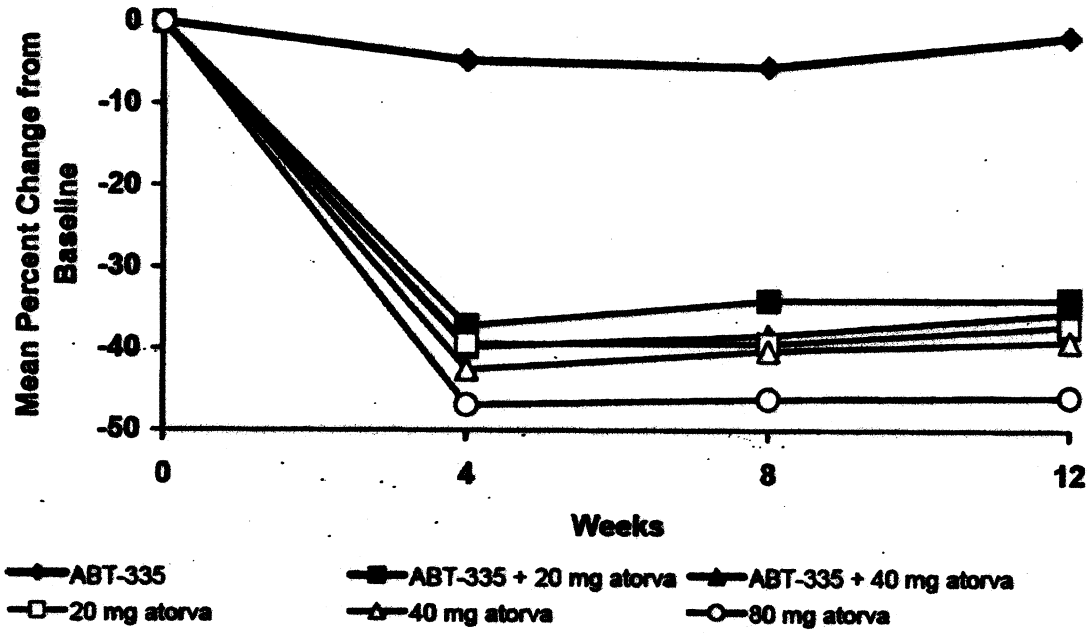


atorva = atorvastatin

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

Cross Reference: Table 14.2__3.1

Mean Percent Change from Baseline in LDL-C Over Time



atorva = atorvastatin

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

Cross Reference: Table 14.2__3.1

§ Graphs of the cumulative distribution functions by treatment groups for the primary efficacy variables (%change in HDL-C, LDL-C, Triglycerides from baseline to endpoint) is provided below. From this, the percent of patients (y-axis value) with a value of %change in the efficacy variable from baseline to endpoint, smaller than or equal to a value on the x-axis, can be read.