2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-335	**Volume:**	
Name of Active Ingredient: ABT-335, A-7770335.115	**Page:**	

Title of Study: A Multicenter, Randomized, Double-Blind, Prospective Study Comparing the Safety and Efficacy of ABT-335 and Simvastatin Combination Therapy to ABT-335 and Simvastatin Monotherapy in Subjects with Mixed Dyslipidemia

Coordinating Investigator: Syed Mohiuddin, MD [redacted]

Study Sites: Multicenter; 148 study sites in the United States, Canada, and Puerto Rico screened subjects, with 121 of these sites randomizing subjects redacted information 10Jun2014

Publications: None

Studied Period (Years): Date First Subject Dosed: 27 March 2006 Date Last Subject Completed Dosing: 05 March 2007	**Phase of Development:** 3

Objectives: The objective of this study was to evaluate and compare the effects of once daily ABT-335 monotherapy and simvastatin monotherapy with ABT-335 and simvastatin combination therapy on coronary heart disease (CHD) lipid risk factors in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb).

Methodology:

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.

The planned duration of the study was approximately 22 weeks, consisting of 42-day diet run-in/hypolipidemic washout period (Screening Period), a 12-week Treatment Period, and a 30-day Safety Follow-up Period. During the Treatment Period, subjects took study drug orally once daily, recorded missed doses as well as adverse events and use of concomitant medications in a subject diary, and returned to the study site for 2 Interim Visits at approximately Week 4 (Day 29 ± 3 days) and Week 8 (Day 57 ± 3 days) and a Week 12 Final/Discontinuation Visit (Day 85 or earlier for premature discontinuation ± 3 days). After one or two Screening Visits, subjects were randomized at the Baseline Visit and dispensed study drug. At the Baseline and Interim Visits, physical examination was performed (full physical at baseline with symptom-directed exam if indicated at the Interim Visits);

Methodology (Continued):

electrocardiogram (ECG, at baseline and final visits) vital signs were measured; routine hematology, serum chemistry and urinalysis were performed in all subjects, with serum pregnancy tests in females of childbearing potential; samples were collected for measurements of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides (TG), very-low-density lipoprotein cholesterol (VLDL-C), high sensitivity C-reactive protein (hsCRP), and apolipoprotein B (ApoB); study drug and subject diaries were dispensed; subject diaries were reviewed (at Interim Visits); diet compliance, adverse events and use of concomitant medications were assessed; study drug was accounted for and a new study drug kit was dispensed. Nuclear Magnetic Resonance (NMR) samples for LipoProfile® (Baseline and Final Visits) were obtained at a subset of sites.

At the Week 12 Final/Discontinuation Visit (Day 85 or earlier for premature discontinuation ± 3 days), procedures that had been performed at the Interim Visits were repeated (except study drug and subject diaries were not dispensed); in addition, an ECG was performed and blood samples were obtained for measurement of apolipoprotein AI (ApoAI), apolipoprotein CIII (ApoCIII), adiponectin, and lipoprotein-associated phospholipase A2 (LpPLA2). Subjects who completed the Treatment Period of the study at the Week 12 Final/Discontinuation Visit were eligible to participate in an open-label safety extension study (M05-758). Subjects who declined participation in the extension study were contacted a minimum of 30 calendar days after the Week 12 Final/Discontinuation Visit; at this Safety Follow-up call, adverse events and use of any concomitant medications were assessed, and subjects were asked about any positive pregnancy test results or pregnancy confirmation in the subject or partner.

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)

Diagnosis and Main Criteria for Inclusion:

Male and female subjects ≥ 18 years of age with mixed dyslipidemia (Frederickson Type IIb), with the following screening values: TG ≥ 150 mg/dL (≥ 1.69 mmol/L), HDL-C < 40 mg/dL (< 1.02 mmol/L) for men and < 50 mg/dL (< 1.28 mmol/L) for women, and LDL-C ≥ 130 mg/dL (≥ 3.35 mmol/L). In addition, subjects must have been willing to observe the diet recommend by the American Heart Association entitled "An Eating Plan for Healthy Americans: Our American Heart Association Diet."

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

Test product: ABT-335 (equivalent to 135 mg fenofibric acid) capsule, once daily, orally

ABT-335 (135 mg) capsule and simvastatin (equivalent to 20 mg simvastatin) capsule, once daily, orally;

ABT-335 (135 mg) capsule and simvastatin (equivalent to 40 mg simvastatin) capsule, once daily, orally

For the respective lot number, please refer to the table below.			
Study Drug	**Dosage Form**	**Bulk Lot #**	**Finishing Lot #**
ABT-335	135 mg capsule (blinded)	05-002449 05-002449 05-002450	06-004355 06-005984 06-006030
Study Drug	**Dosage Form**	**Bulk Lot #**	**Finishing Lot #**
ABT-335 placebo	matching 135 mg placebo capsule (blinded)	05-003032 05-003032 05-003032	06-004355 06-005984 06-006030
Simvastatin	20 mg capsule (blinded)	05-003747 05-003747 06-007289	06-004355 06-005984 06-006030
Simvastatin	40 mg capsule (blinded)	05-003746 05-003746 06-007293	06-004355 06-005984 06-006030
Simvastatin placebo	matching 20 mg or 40 mg placebo capsule (blinded)	06-003750 06-003750 06-006961	06-004355 06-005984 06-006030

Duration of Treatment: 12 weeks

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

Simvastatin (20 mg), once daily, orally
Simvastatin (40 mg), once daily, orally
Simvastatin (80 mg), once daily, orally, given as two simvastatin 40 mg capsules

For the respective lot numbers, please refer to the table above.

Criteria for Evaluation

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 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)

Criteria for Evaluation

Efficacy (Continued):

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.

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

Statistical Methods

Efficacy:

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.

Statistical Methods

Efficacy (Continued):

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.

Safety:

Frequencies and percentages of subjects with treatment-emergent adverse events were calculated for each treatment group for all events, for events by organ class and preferred terms, by severity, by relationship, for events that led to death, for serious adverse events, and for events that led to discontinuation. Percentages for "any event" and for each preferred term were compared between the combination therapy groups and each corresponding monotherapy group using Fisher's exact tests.

For laboratory and vital sign parameters, mean changes and potentially clinically significant values were presented and compared between the combination therapy groups and each corresponding monotherapy group. In addition for each laboratory parameter, shifts from baseline according to the normal range were provided. For ECGs, a shift table presenting results at baseline and the Final Visit was presented.

Safety data for the 80 mg simvastatin monotherapy group were summarized with descriptive statistics; however, no formal statistical comparisons were made between this treatment group and the other treatment groups in the study.

Summary/Conclusions

Of the 650 treated subjects, 332 (51.1%) were female and 318 (48.9%) were male; 93.8% of subjects were White. Mean age was 54.4 years. 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. In addition to hyperlipidemia, common medical history conditions included hypertension (53.8%), eye disease/disorder (34.5%), osteoarthritis (29.7%), gastroesophageal reflux disease (29.1%), drug allergies/reactions (26.3%), obesity (25.8%), depression (25.7%), and diabetes mellitus (22.9%).

Of 650 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%).

Efficacy Results:

For the primary efficacy comparisons, statistically significant greater mean percent increases from baseline in HDL-C and decreases from baseline in TG and LDL-C were observed for both combination therapy groups compared to the corresponding monotherapy groups. As shown below, ABT-335 in combination with 20 mg and 40 mg simvastatin, compared to 20 mg and 40 mg simvastatin monotherapy, respectively, resulted in significantly greater mean percent increases in HDL-C and significantly greater mean percent decreases in TG. ABT-335 in combination with 20 mg and 40 mg simvastatin, compared to ABT-335 monotherapy, resulted in a significantly greater mean percent decrease in LDL-C. Based on the significant results for all three primary comparisons (HDL-C, TG, LDL-C), each combination therapy group was declared superior to the corresponding monotherapy group. Results of all sensitivity analyses, including a worst-case analysis, were consistent with results of the primary analysis. Differences observed in the primary analyses at Week 12 were apparent by Week 4 and were sustained throughout the duration of treatment.

Primary Endpoints	ABT-335	20 mg simva	ABT-335 + 20 mg simva	p-value	40 mg simva	ABT-335 + 40 mg simva	p-value	80 mg simva
HDL-C								
BL mean	38.2	38.4	37.2		38.5	38.5		39.5
Mean % Δ	16.2%	7.2%	17.8%	< 0.001[a]	8.5%	18.9%	< 0.001[a]	6.8%
TG								
BL mean	300.9	281.2	295.6		284.4	274.1		257.4
Mean % Δ	-31.7%	-14.2%	-37.4%	< 0.001[a]	-22.4%	-42.7%	< 0.001[a]	-20.2%
LDL-C								
BL mean	156.5	153.2	157.9		163.3	155.9		155.4
Mean % Δ	-4.0%	-22.4%	-24.0%	< 0.001[b]	-31.7%	-25.3%	< 0.001[b]	-40.8%

a. Combination therapy vs. simvastatin monotherapy.
b. Combination therapy vs. ABT-335 monotherapy.

Results of the analysis of secondary endpoints are shown below. ABT-335 in combination with both 20 mg and 40 mg simvastatin resulted in significantly greater mean percent decreases in non-HDL-C compared to ABT-335 monotherapy. ABT-335 in combination with 20 mg simvastatin demonstrated a significantly greater mean percent decrease in non-HDL-C compared to 20 mg simvastatin monotherapy, while results were similar between ABT-335 in combination with 40 mg simvastatin and 40 mg simvastatin monotherapy. Compared to the corresponding simvastatin monotherapy groups, greater mean percent decreases in VLDL-C were observed with ABT-335 in combination with 20 mg and 40 mg simvastatin. ABT-335 in combination with 20 mg simvastatin resulted in greater mean percent decreases in ApoB and total-C compared to 20 mg simvastatin monotherapy; the mean percent decreases in ApoB and total-C with ABT-335 in combination with 40 mg simvastatin were similar to that of 40 mg simvastatin monotherapy. Median percent decreases in hsCRP were similar between each dose of combination therapy and the corresponding simvastatin monotherapy, based on nonparametric analysis. Because of the prespecified ranking of secondary comparisons, statistical significance could not be claimed for the positive results on VLDL-C with ABT-335 in combination with 40 mg simvastatin.

Secondary Endpoints	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	< 0.001[a]	225.5	213.8	< 0.001[a]	213.9
Mean % Δ	-17.3%	-24.4%	-30.7%	0.001[b]	-35.9%	-35.0%	0.654[b]	-40.6%
VLDL-C								
BL mean	67.2	64.3	68.2		64.4	59.9		59.4
Mean % Δ	-36.9%	-19.2%	-38.9%	< 0.001[b]	-35.7%	-51.1%	0.005[b]	-30.0%
Total-C								
BL mean	262.6	254.9	261.5		263.3	252.8		252.4
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
Mean % Δ	-17.6%	-22.9%	-29.5%	0.001[b]	-32.7%	-31.2%	0.445[b]	-38.9%
hsCRP[c]								
BL median	0.35	0.28	0.31		0.28	0.27		0.24
Median % Δ	-15.8%	-11.4%	-26.8%	0.057[bc]	-14.8%	-32.1%	0.141[bc]	-19.8%

a. Combination therapy vs. ABT-335 monotherapy.
b. Combination therapy vs. simvastatin monotherapy.
c. Post hoc nonparametric analysis.

Efficacy Results (Continued):

The benefits of combination therapy as demonstrated by the primary and secondary efficacy analyses were supported by results of several exploratory efficacy analyses. As shown below, both doses of combination therapy had positive effects on ApoAI and ApoCIII, with greater mean percent increases in ApoAI and greater mean percent decreases in ApoCIII, compared to corresponding simvastatin monotherapy. Minor mean percent increases were seen in the ABT-335 monotherapy and combination therapy groups for adiponectin; no consistent pattern was observed in the simvastatin monotherapy groups. For LpPLA2, a mean percent increase was observed in the ABT-335 monotherapy group with mean percent decreases in the simvastatin monotherapy and combination therapy groups. Greater mean decreases were observed with 20 mg simvastatin monotherapy compared to ABT-335 in combination with 20 mg simvastatin (-9.3% vs. -1.4%, p = 0.029) and with 40 mg simvastatin monotherapy compared to ABT-335 in combination with 40 mg simvastatin (-12.1% vs. -2.5%, p = 0.010).

Exploratory Endpoints	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
ApoAI								
BL mean	142.3	144.6	141.4	0.545[a]	140.9	142.3	0.157[a]	143.6
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	0.190[a]	18.7	17.8	0.061[a]	18.3
Mean % Δ	-25.4%	-10.9%	-29.6%	< 0.001[b]	-16.3%	-31.4%	< 0.001[b]	-16.7%
Adiponectin								
BL mean	5784.4	5338.6	5769.5	0.783[a]	5627.2	4904.6	0.828[a]	6360.8
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	0.044[a]	281.7	259.3	0.022[a]	271.6
Mean % Δ	6.0%	-9.3%	-1.4%	0.029[b]	-12.1%	-2.5%	0.010[b]	-13.7%

a. Combination therapy vs. ABT-335 monotherapy.
b. Combination therapy vs. simvastatin monotherapy.

Both doses of combination therapy had positive effects on additional measures of atherogenicity that are potential predictors of cardiovascular risk. In general, combination therapy resulted in favorable effects on all lipid ratios reflecting atherogenic vs. non-atherogenic lipid particles, including the ratios of total LDL-C to HDL-C, total-C to HDL-C, non-HDL-C to HDL-C, and ApoB to ApoAI, as well as TG to HDL-C. For ABT-335 in combination with 20 mg simvastatin, the results were superior to both ABT-335 monotherapy and simvastatin monotherapy; for ABT-335 in combination with 40 mg simvastatin, results were superior to ABT-335 monotherapy and were similar to those for 40 mg simvastatin monotherapy.

These observations were reinforced by favorable effects of ABT-335 in combination with 20 mg and 40 mg simvastatin on LDL-P, VLDL-P and VLDL-TG, additional emerging indicators of atherogenicity. Mean percent decreases in LDL-P were similar between ABT-335 in combination with 20 mg and 20 mg simvastatin monotherapy (-19.7% vs. -21.3%) and were lower with ABT-335 in combination with 40 mg simvastatin than with 40 mg simvastatin monotherapy (-31.1% vs. -30.4%). Compared to the corresponding simvastatin monotherapy, greater mean percent decreases were observed with both ABT-335 in combination with 20 mg and 40 mg simvastatin on VLDL-P (-35.7% vs. -7.5% and -53.6% vs. -24.4%, respectively) and VLDL-TG (-36.6% vs. -2.6% and -58.9% vs. -15.8%, respectively). In

Efficacy Results (Continued):

addition, greater mean percent increases in LDL particle size were observed with combination therapy than with simvastatin monotherapy, and combination therapy resulted in a shift from a more atherogenic, small LDL (pattern B) to a less atherogenic, large LDL (pattern A) that was not observed in either simvastatin monotherapy group.

Across all risk categories, higher proportions of subjects in the 20 mg and 40 mg simvastatin monotherapy groups than in the corresponding combination therapy groups achieved NCEP ATP III goals for LDL-C (60.3% vs. 56.9% and 71.7% vs. 64.2%, respectively). Conversely, higher proportions of subjects in the ABT-335 in combination with 20 mg and 40 mg simvastatin groups than in the corresponding simvastatin monotherapy groups achieved NCEP ATP III goals for non-HDL-C (54.1% vs. 43.1% and 66.1% vs. 60.4%, respectively). For achievement of NCEP ATP III goals for both LDL-C and non-HDL-C, there were higher proportions of subjects in the ABT-335 in combination with 20 mg and 40 mg simvastatin groups than in the corresponding simvastatin monotherapy groups (47.4% vs. 41.4% and 60.6% vs. 57.5%, respectively. The moderate dose combination had a more favorable effect on achievement of NCEP ATP III goals than the low dose combination, with higher proportions of subjects treated with the moderate dose combination achieving goals for non-HDL-C and for both LDL-C and non-HDL-C.

Across subgroups stratified by diabetic status, gender, baseline HDL-C level, baseline TG level, and baseline LDL-C level, greater mean percent changes in HDL-C, TG, and LDL-C were generally observed in the combination therapy groups than in the corresponding monotherapy groups. The treatment effect of both doses of combination therapy was similar in diabetic and non-diabetic subjects. In general, greater mean percent changes were observed in the primary efficacy variables among females than among males. Among subgroups with lower baseline HDL-C, higher baseline TG, and higher baseline LDL-C, greater mean percent changes in HDL-C, TG, and LDL-C, respectively, were observed with combination therapy.

Safety Results:

All treatments were generally well tolerated. The adverse event profiles of the monotherapy comparators were consistent with the known or expected safety profiles. In addition, the safety profiles were similar between the two doses of combination therapy, with no indication of additional adverse effects of the combination of ABT-335 with 40 mg simvastatin relative to the combination with 20 mg simvastatin.

The lowest incidence of treatment-emergent adverse events occurred in the 80 mg simvastatin monotherapy group (52.5%); the overall incidence of adverse events was generally similar across the other treatment groups (67.2% to 74.6%). Overall, the most frequently reported adverse events were headache, back pain, nasopharyngitis, upper respiratory tract infection, arthralgia, diarrhea, and dyspepsia.

A statistically significant difference was observed between the ABT-335 in combination with 20 mg simvastatin and 20 mg simvastatin monotherapy groups in the overall incidence of adverse events associated with Investigations (10.1% and 2.5%, respectively, $p = 0.030$). The incidence of specific events was generally similar across treatment groups, with no statistically significant pairwise differences. Most adverse events were mild or moderate in intensity.

One or more possibly or probably treatment-related adverse events were reported by 32.8% of the ABT-335 monotherapy group; 22.7% and 23.7% of the ABT-335 in combination with 20 mg and 40 mg

Safety Results (Continued):

simvastatin groups, respectively; and 16.0%, 24.1%, and 20.3% of the 20 mg, 40 mg, and 80 mg simvastatin monotherapy groups, respectively. Statistically significant differences were observed between the ABT-335 in combination with 40 mg simvastatin and the 40 mg simvastatin monotherapy groups in the overall incidence of treatment-related adverse events associated with Nervous System Disorders (1.7% and 8.6%, respectively). No statistically significant pairwise differences were observed for any specific treatment-related adverse event. Across treatment groups, the most frequently reported possibly or probably treatment-related adverse events were headache, myalgia, and nausea.

One subject died during the study due to an event considered not related to study drug (gun shot wound). A total of 14 subjects had serious adverse events: six subjects in the ABT-335 monotherapy group (5.0%), three subjects in the ABT-335 in combination with 40 mg simvastatin group (2.5%), two subjects in the 80 mg simvastatin monotherapy group (3.4%), and one subject each in the 20 mg simvastatin monotherapy (0.8%), ABT-335 in combination with 20 mg simvastatin (0.8%), and 40 mg simvastatin monotherapy (0.9%) groups. No serious adverse event was reported by more than one subject.

A total of 51 subjects had adverse events that led to discontinuation from the study. Adverse events that led to discontinuation were reported by 10.9% of in the ABT-335 monotherapy group; 6.7% and 5.9% of the ABT-335 in combination with 20 mg and 40 mg simvastatin groups, respectively; and 6.7% of the 20 mg simvastatin monotherapy, 9.5% of the 40 mg simvastatin monotherapy, and 6.8% of the 80 mg simvastatin monotherapy groups. No statistically significant differences were observed between groups in the overall incidence of adverse events that led to discontinuation. Overall, the most common adverse events that led to discontinuation were nausea (six subjects), myalgia (four subjects), blood CPK increased (four subjects), and liver function test abnormal (three subjects).

Adverse events and laboratory evaluations of special interest included those related to muscle events, renal events, and hepatic events. ABT-335 in combination with 20 mg simvastatin, compared with 20 mg simvastatin monotherapy, had a higher overall incidence of adverse events of special interest (16.0% vs. 5.9%), including a higher incidence of hepatic adverse events (6.7% vs. 0.8%). However, the overall incidence adverse events of special interest was lower in the ABT-335 in combination with 40 mg simvastatin group than in the 40 mg simvastatin monotherapy group (6.8% vs. 10.3%), and the incidence of hepatic events was 2.5% and 0%, respectively.

No cases of rhabdomyolysis were reported. Myalgia was reported in lower proportion of subjects in the ABT-335 in the combination with 40 mg simvastatin group (2.5%) than in the ABT-335 monotherapy (5.0%), 40 mg simvastatin monotherapy (5.2%), or 80 mg simvastatin monotherapy (5.1%) groups; 3.4% of the 20 mg simvastatin monotherapy group and 4.2% of the ABT-335 in combination with 20 mg simvastatin group reported myalgia. Four subjects discontinued study drug due to myalgia, two each on ABT-335 monotherapy and simvastatin monotherapy. Eleven subjects (four on ABT-335 in combination with 20 mg simvastatin, three on 40 mg simvastatin monotherapy, two on 80 mg simvastatin monotherapy, and one each on 20 mg simvastatin monotherapy and ABT-335 in combination with 40 mg simvastatin) experienced an event of blood CPK increased, with the highest incidence (3.4%) in the ABT-335 in combination with 20 mg simvastatin and 80 mg simvastatin monotherapy groups.

Four subjects, one on combination therapy and three on simvastatin monotherapy, had post-baseline elevations in CPK > 5 × ULN, which also met the potentially clinically significant criteria. In one of these four subjects, the CPK increase occurred 169 days after study drug discontinuation. Two of these subjects (simvastatin monotherapy) had post-baseline elevations in CPK > 10 × ULN, one of whom prematurely discontinued due to the adverse event, blood CPK increased.

Safety Results (Continued):

Renal events were infrequently reported in all treatment groups and no new safety signals were identified with combination therapy. Events of blood creatinine increased were reported by one subject each on ABT-335 monotherapy and ABT-335 in combination with 20 mg simvastatin; the subject on combination therapy discontinued study drug due to blood creatinine increased. ABT-335 monotherapy and combination therapy resulted in greater mean increases from baseline in creatinine and greater mean decreases from baseline in calculated creatinine clearance compared to simvastatin monotherapy.

The incidence of hepatic events was statistically significantly higher in the ABT-335 in combination with 20 mg simvastatin group than in the 20 mg simvastatin monotherapy group (6.7% vs. 0.8%); however, the incidence of hepatic events was low in the ABT-335 in combination with 40 mg simvastatin group (2.5%). No statistically significant differences were observed between treatment groups in the incidence of specific hepatic events.

Six subjects on combination therapy had events of aspartate aminotransferase (AST) increased; however, only one subject on combination therapy discontinued study drug due to the events of AST increased and alanine aminotransferase (ALT) increased and no subject on combination therapy had a potentially clinically significant value for AST or ALT. Four subjects on ABT-335 monotherapy and one subject on 80 mg simvastatin monotherapy had potentially clinically significant values for ALT; four of these subjects discontinued study drug due to hepatic adverse events (liver function test abnormal, hepatic enzyme increased, hepatitis). Most elevations in ALT and/or AST were modest. One subject had an increase in ALT or AST to > 10 × ULN. A total of seven subjects, five on ABT-335 monotherapy, one on combination therapy, and one on simvastatin monotherapy, had post-baseline increases in ALT and/or AST to > 5 × ULN on any single occasion. Five subjects on ABT-335 monotherapy, no subject on combination therapy, and one subject on 80 mg simvastatin monotherapy had an increase in ALT and/or AST to > 3 × ULN on two consecutive visits.

Minor mean increases and decreases from baseline in hematology and chemistry parameters were observed in all treatment groups, none of which were clinically meaningful. The majority of subjects had hematology and chemistry values that were within normal range both at baseline and following study drug administration.

Minor mean increases and decreases from baseline in vital sign parameters were observed in all treatment groups, none of which were clinically meaningful.

Conclusions:

Both doses of combination therapy were demonstrated to be superior to corresponding monotherapy. For the primary endpoints, ABT-335 in combination with both simvastatin doses resulted in significantly greater mean percent increases in HDL-C and decreases in TG compared to simvastatin monotherapy and significantly greater mean percent decreases in LDL-C compared to ABT-335 monotherapy. Results of all sensitivity analyses, including a worst-case analysis, were consistent with the primary analysis. All primary efficacy analyses, as well as most secondary and exploratory efficacy analyses demonstrated the efficacy of combination therapy with ABT-335 and 20 mg or 40 mg simvastatin in reducing CHD lipid risk factors in subjects with mixed dyslipidemia.

Conclusions (Continued):

ABT-335, administered as monotherapy or as part of combination therapy with simvastatin, was generally safe and well tolerated in this population of adults with mixed dyslipidemia. The safety profiles in this study were consistent with known or expected safety profiles of each monotherapy. Adverse events and laboratory abnormalities were similar between the two doses of combination therapy, with no indication of additional adverse effects with the moderate dose combination relative to the low dose combination. No unexpected hepatic, renal, or muscular safety signals were observed.

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