2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Choline Fenofibrate (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 Fenofibric Acid and Rosuvastatin Calcium Combination Therapy to Fenofibric Acid and Rosuvastatin Calcium Monotherapy in Subjects with Mixed Dyslipidemia

Coordinating Investigator: Peter H. Jones, MD [redacted]

Study Sites: Multicenter; 224 study sites in the United States, Canada and Puerto Rico screened subject, with 205 of these sites randomizing subjects. redacted information 10Jun2014

Publications: None

Studied Period (Years): Date First Subject Dosed: 21 March 2006 Date Last Subject Completed Dosing: 14 December 2006	**Phase of Development:** 3

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

Methodology:

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 rosuvastatin to ABT-335 monotherapy and rosuvastatin monotherapy on the primary lipid parameters associated with increased risk of CHD in a population of subjects with mixed dyslipidemia (Fredrickson Type IIb). Subjects were randomized in a double-blind 2:2:2:2:2:1 ratio to one of six treatment groups as follows: 135 mg ABT-335 monotherapy, 10 mg rosuvastatin monotherapy, ABT-335 in combination with 10 mg rosuvastatin, 20 mg rosuvastatin monotherapy, ABT-335 in combination with 20 mg rosuvastatin, and 40 mg rosuvastatin monotherapy.

Methodology (Continued):

The planned duration of the study was approximately 22 weeks, consisting of a 42-day diet run-in/hypolipidemic washout period (Screening Period), a 12-week Treatment Period, and a 30-day Safety Follow-up Period. During the Treatment Period, subjects took study drug orally once daily, recorded missed doses as well as adverse events and use of concomitant medications in a subject diary, and returned to the study site for two Interim Visits at approximately Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 3 days) and a Week 12 Final/Discontinuation Visit (Day 85 or earlier for premature discontinuation ± 3 days). After one or two Screening Visits, subjects were randomized at the Baseline Visit and dispensed study drug. At the Baseline and Interim Visits, physical examination was performed (full physical at baseline with symptom-directed exam if indicated at the Interim Visits); electrocardiogram (ECG, at Baseline and Final Visits); vital signs were measured; routine hematology, serum chemistry and urinalysis were performed in all subjects, with serum pregnancy tests in females of childbearing potential; samples were collected for measurements of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides (TG), very-low-density lipoprotein cholesterol (VLDL-C), high sensitivity C-reactive protein (hsCRP), and apolipoprotein B (ApoB); study drug and subject diaries were dispensed; subject diaries were reviewed (at Interim Visits); diet compliance, adverse events and use of concomitant medications were assessed; study drug was accounted for and a new study drug kit was dispensed. Nuclear Magnetic Resonance (NMR) samples (Baseline and Final Visits) were obtained at a subset of sites.

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

Number of Subjects (Planned and Analyzed):

Planned: Approximately 1250 subjects (228 subjects in each of the following treatment groups: ABT-335 monotherapy, 10 mg rosuvastatin monotherapy, ABT-335 in combination with 10 mg rosuvastatin, 20 mg rosuvastatin monotherapy, and ABT-335 in combination with 20 mg rosuvastatin, and 114 subjects in 40 mg rosuvastatin monotherapy).

Enrolled in Treatment Period: 1445 subjects were randomized, with 1439 subjects treated:

ABT-335 monotherapy (N=259)
10 mg rosuvastatin monotherapy (N=261)
ABT-335 in combination with 10 mg rosuvastatin (N=261)
20 mg rosuvastatin monotherapy (N=266)
ABT-335 in combination with 20 mg rosuvastatin (N=261)
40 mg rosuvastatin monotherapy (N=131)

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 recommended 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 rosuvastatin calcium (equivalent to 10 mg rosuvastatin) capsule, once daily, orally

ABT-335 (135 mg) capsule and rosuvastatin calcium (equivalent to 20 mg rosuvastatin) 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 05-002450	06-004740 06-005537 06-005881 06-006681 06-006029
ABT-335 placebo	Matching 135 mg placebo capsule (blinded)	05-003032	06-004740 06-005537 06-005881 06-006681 06-006029
Rosuvastatin calcium	10 mg capsule (blinded)	05-003745 06-006963	06-004740 06-005537 06-005881 06-006681 06-006029
Rosuvastatin calcium	20 mg capsule (blinded)	05-003744 06-006979	06-004740 06-005537 06-005881 06-006681 06-006029
Rosuvastatin calcium placebo	Matching 10 mg or 20 mg placebo capsule (blinded)	05-003750 06-006961	06-004740 06-005537 06-005881 06-006681 06-006029

Duration of Treatment: 12 weeks.

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

Rosuvastatin (10 mg), once daily, orally

Rosuvastatin (20 mg), once daily, orally

Rosuvastatin (40 mg), once daily, orally, given as two rosuvastatin 20 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 rosuvastatin vs. the corresponding rosuvastatin monotherapy).
2. Triglycerides (Combination therapy with each dose of rosuvastatin vs. the corresponding rosuvastatin monotherapy).
3. LDL C (Combination therapy with each dose of rosuvastatin 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 rosuvastatin combination dose. The study was declared successful when the superiority of the combination was demonstrated for all three primary comparisons for at least one rosuvastatin dose.

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

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

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 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.

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 rosuvastatin 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 rosuvastatin dose. Hence, adjustments for multiple comparisons were performed using the Hochberg method in order to adjust for treatment group comparisons being performed for two rosuvastatin 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 40 mg rosuvastatin 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 40 mg rosuvastatin 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 1439 treated subjects, 750 (52.1%) were female and 689 (47.9%) were male; 92.3% of subjects were White. Mean age was 55 years. The majority (61.5%) of subjects were between 40 and 60 years of age; 8.1% were younger than 40 years and 30.4% were older than 60 years. In addition to hyperlipidemia, common medical history conditions included hypertension (54.0%), gastroesophageal reflux disease (30.9%), obesity (22.0%), and diabetes mellitus (19.8%).

Of 1439 treated subjects, 1243 (86.4%) completed the study and 196 (13.6%) prematurely discontinued study drug. Overall, the most common reasons for prematurely discontinuing study drug were adverse event (7.7%) and withdrawal of consent (4.7%).

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 10 mg and 20 mg rosuvastatin, compared to 10 mg and 20 mg rosuvastatin monotherapy, respectively, resulted in significantly greater mean percent increase in HDL-C and significantly greater mean percent decrease in TG. ABT-335 in combination with 10 mg and 20 mg rosuvastatin, 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	10 mg rosuva	ABT-335 + 10 mg rosuva	p-value	20 mg rosuva	ABT-335 + 20 mg rosuva	p-value	40 mg rosuva
HDL-C								
BL mean	38.5	38.2	38.5		38.5	38.0		37.4
Mean % Δ	15.0%	8.5%	20.3%	< 0.001[a]	10.3%	19.0%	< 0.001[a]	9.3%
TG								
BL mean	267.4	295.9	282.8		292.8	292.9		284.5
Mean % Δ	-32.6%	-24.4%	-47.1%	< 0.001[a]	-25.6%	-42.9%	< 0.001[a]	-32.1%
LDL-C								
BL mean	155.8	152.2	152.7		154.4	155.5		153.5
Mean % Δ	-6.5%	-38.0%	-37.2%	< 0.001[b]	-45.0%	-38.8%	< 0.001[b]	-50.6%

a. Combination therapy vs. rosuvastatin monotherapy.

b. Combination therapy vs. ABT-335 monotherapy.

Efficacy Results (Continued):

Results of the analysis of secondary endpoints are shown below. ABT-335 in combination with both 10 mg and 20 mg rosuvastatin resulted in significantly greater mean percent decreases in non-HDL-C compared to ABT-335 monotherapy. ABT-335 in combination with 10 mg rosuvastatin demonstrated a significantly greater mean percent decrease in non-HDL-C compared to 10 mg rosuvastatin monotherapy, while results were similar between ABT-335 in combination with 20 mg rosuvastatin and 20 mg rosuvastatin monotherapy. Compared to the corresponding rosuvastatin monotherapy, greater mean percent decreases in VLDL-C were observed with ABT-335 in combination with 10 mg rosuvastatin and ABT-335 in combination with 20 mg rosuvastatin. No differences were observed between combination therapy and rosuvastatin monotherapy in total-C. ABT-335 in combination with 10 mg rosuvastatin resulted in greater mean percent decreases in ApoB compared to 10 mg rosuvastatin monotherapy; the mean percent decrease in ApoB with ABT-335 in combination with 20 mg rosuvastatin was similar to that of 20 mg rosuvastatin monotherapy. Nonparametric analysis of hsCRP demonstrated that, compared to rosuvastatin monotherapy, greater median percent decreases in hsCRP were observed with both doses of combination therapy. 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 20 mg rosuvastatin, on ApoB with ABT-335 in combination with 10 mg rosuvastatin, or on comparisons of hsCRP.

Secondary Endpoints	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	< 0.001[a]	220.9	220.8	< 0.001[a]	219.0
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
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
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
Mean % Δ	-16.2%	-34.1%	-39.2%	< 0.001[b]	-39.6%	-39.2%	0.729[b]	-45.0%
hsCRP[c]								
BL median	0.28	0.27	0.35		0.29	0.31		0.29
Median % Δ	-12.1%	-22.9%	-33.8%	0.013[bc]	-29.9%	-40.8%	0.010[bc]	-33.1%

a. Combination therapy vs. ABT-335 monotherapy.

b. Combination therapy vs. rosuvastatin 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 rosuvastatin monotherapy. No consistent pattern was seen for adiponectin. For LpPLA2, a mean percent increase was observed in the ABT-335 monotherapy group with mean percent decreases in the rosuvastatin monotherapy and combination therapy groups; greater mean decreases in LpPLA2 were observed with rosuvastatin monotherapy compared to the corresponding combination therapy.

Exploratory Endpoints	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	0.249[a]	141.4	141.6	0.428[a]	142.7
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	0.014[a]	19.0	18.6	0.362[a]	17.8
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	0.925[a]	5950.6	6158.7	0.165[a]	5886.5
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	< 0.001[a]	277.6	273.3	< 0.001[a]	279.9
Mean % Δ	4.2%	-13.6%	-7.4%	0.007[b]	-13.7%	-9.9%	0.095[b]	-22.1%

a. Combination therapy vs. ABT-335 monotherapy

b Combination therapy vs. rosuvastatin monotherapy

Both doses of combination therapy had positive effects on additional measures of atherogenicity. In general, combination therapy resulted in favorable effects on all lipid ratios reflecting atherogenic vs. non-atherogenic lipid particles, including the ratios of 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 10 mg rosuvastatin, the results were superior to both ABT-335 monotherapy and rosuvastatin monotherapy; for ABT-335 in combination with 20 mg rosuvastatin, results were superior to ABT-335 monotherapy and were similar to or more favorable than those for 20 mg rosuvastatin monotherapy.

Efficacy Results (Continued):

These observations were reinforced by favorable effects of ABT-335 in combination with 10 mg and 20 mg rosuvastatin on LDL-P, VLDL-P and VLDL-TG, additional emerging measures of atherogenicity. Mean percent decreases in LDL-P were similar between ABT-335 in combination with 10 mg and 10 mg rosuvastatin monotherapy (-38.4% vs. -40.3%) and were lower with ABT-335 in combination with 20 mg rosuvastatin than with 20 mg rosuvastatin monotherapy (-38.3% vs. -44.4%). Compared to the corresponding rosuvastatin monotherapy, greater mean percent decreases were observed with ABT-335 in combination with both 10 mg and 20 mg rosuvastatin on VLDL-P (-51.4% vs. -32.3% and -50.1% vs. -36.0%, respectively) and VLDL-TG (-56.0% vs. -31.3% and -51.0% vs. -33.9%, respectively). In addition, greater mean percent increases in LDL particle size were observed with combination therapy than with rosuvastatin 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 rosuvastatin monotherapy group.

For high risk subjects, higher proportions of subjects in the 10 mg and 20 mg rosuvastatin monotherapy groups (76% and 82%, respectively) than in the corresponding combination therapy groups (69% and 64%, respectively) achieved NCEP ATP III goals for LDL-C; higher proportions of subjects in the ABT-335 in combination with 10 mg and 20 mg rosuvastatin groups (71% and 70%, respectively) achieved NCEP ATP III goals for non-HDL-C than in the corresponding rosuvastatin monotherapy groups (55% and 64%, respectively). A higher proportion of high risk subjects treated with ABT-335 in combination with 10 mg rosuvastatin achieved both LDL and non-HDL-C goals than high risk subjects treated with 10 mg rosuvastatin monotherapy (64% vs. 55%), with similar proportions in the ABT-335 in combination with 20 mg rosuvastatin and 20 mg rosuvastatin monotherapy groups (59% vs. 60%) achieving both LDL and non-HDL-C goals.

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 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 ABT-335 combination with 20 mg rosuvastatin relative to the ABT-335 combination with 10 mg rosuvastatin.

The overall incidence of treatment-emergent adverse events was generally similar across treatment groups (60.2 to 68.6%). One or more adverse events were reported by 66.4% of ABT-335 monotherapy, 60.2% of 10 mg rosuvastatin monotherapy, 68.6% of ABT-335 in combination with 10 mg rosuvastatin, 63.5% of 20 mg rosuvastatin monotherapy, 62.8% of ABT-335 in combination with 20 mg rosuvastatin, and 67.9% of 40 mg rosuvastatin monotherapy. Overall, the most frequently reported treatment-emergent adverse events were headache, back pain, nausea, arthralgia, myalgia, pain in extremity, and nasopharyngitis.

Safety Results (Continued):

The incidence of specific events was generally similar across treatment groups. Statistically significant differences were observed between ABT-335 in combination with 10 mg rosuvastatin and ABT-335 monotherapy in the event, pain in extremity (1.9% and 5.4%, respectively), and between ABT-335 in combination with 20 mg rosuvastatin and 20 mg rosuvastatin monotherapy in the events, AST increased (3.1% and 0.4%, respectively), ALT increased (3.4% and 0.8%, respectively), and headache (8.8% and 16.5%, respectively). Most adverse events were mild or moderate in intensity.

One or more possibly or probably treatment-related adverse events were reported by 24.3% of the ABT-335 monotherapy group; 27.2% and 23.8% of the ABT-335 in combination with 10 mg and 20 mg rosuvastatin groups, respectively; and 16.9%, 19.5%, and 22.9% of the 10 mg, 20 mg, and 40 mg rosuvastatin monotherapy groups, respectively. Statistically significant differences were observed between ABT-335 in combination with 10 mg rosuvastatin and 10 mg rosuvastatin monotherapy in the overall incidence of treatment-related adverse events (27.2% and 16.9%, respectively) and between ABT-335 in combination with 20 mg rosuvastatin and 20 mg rosuvastatin monotherapy in the incidence of treatment-related AST increased (3.1% and 0.4%, respectively) and ALT increased (3.4% and 0.8%, respectively). Across treatment groups, the most frequently reported possibly or probably treatment-related adverse events were headache, myalgia, and nausea.

One subject in the ABT-335 monotherapy group died during the conduct of the study due to septic shock that was considered not related to study drug. A total of 35 subjects had treatment-emergent serious adverse events: ten subjects each on ABT-335 monotherapy and ABT-335 in combination with 10 mg rosuvastatin, three subjects each on ABT-335 in combination with 20 mg rosuvastatin and 10 mg rosuvastatin monotherapy, seven subjects on 20 mg rosuvastatin monotherapy, and two subjects on 40 mg rosuvastatin monotherapy. Overall, the most common serious adverse events were coronary artery disease, reported by four subjects (one subject each on ABT-335 monotherapy, ABT-335 in combination with 10 mg rosuvastatin, 20 mg rosuvastatin monotherapy, and ABT-335 in combination with 20 mg rosuvastatin), and myocardial infarction, reported by three subjects (one on ABT-335 monotherapy and two on ABT-335 in combination with 10 mg rosuvastatin). An additional four subjects had serious adverse events (ischemia and coronary artery disease; retinal detachment; breast cancer; cholelithiasis) during the hypolipidemic washout period prior to receiving study drug.

The overall incidence of adverse events that led to discontinuation from the study was higher in each combination therapy group (9.6%) than in the corresponding 10 mg and 20 mg rosuvastatin monotherapy groups (3.8% and 4.9%, respectively), but similar to the ABT-335 monotherapy group (10.8%); 7.6% of subjects in the 40 mg rosuvastatin monotherapy group had adverse events that led to discontinuation. Overall, the most common adverse events that led to discontinuation were myalgia (13 subjects), headache (12 subjects), ALT and/or AST increased (13 subjects), and nausea (nine subjects). Myalgia and headache were reasons for discontinuation by higher proportions of subjects in the 40 mg rosuvastatin monotherapy group. ALT and AST increased were reasons for discontinuation by higher proportions of subjects in the ABT-335 monotherapy and combination therapy groups but, in the majority of subjects, the magnitude of the increase did not meet the criterion for a potentially clinically significant elevation. Similar proportions of subjects across groups discontinued due to nausea.

Safety Results (Continued):

Adverse events and laboratory evaluations of special interest included those related to muscle events, renal events, and hepatic events. No cases of rhabdomyolysis were reported. Myalgia was reported in lower proportions of subjects in the ABT-335 monotherapy (2.7%) and ABT-335 in combination with 20 mg rosuvastatin (2.7%) groups than in the 10 mg and 40 mg rosuvastatin monotherapy groups (5.7% and 6.9%, respectively). A total of 13 subjects (two subjects [0.8%] each on ABT-335 monotherapy, each combination therapy, and 20 mg rosuvastatin monotherapy; one subject [0.4%] on 10 mg rosuvastatin monotherapy; four subjects [3.1%] on 40 mg rosuvastatin monotherapy) discontinued study drug due to myalgia, with a higher proportion of discontinuations due to myalgia in the 40 mg rosuvastatin monotherapy than in the other groups. An adverse event of blood CPK increased was reported by 1.5% of the ABT-335 monotherapy group, 1.9% of the ABT-335 in combination with 20 mg rosuvastatin, 1.1% of the 10 mg rosuvastatin monotherapy group, 1.9% of the ABT-335 in combination with 10 mg rosuvastatin, 2.6% of the 20 mg rosuvastatin monotherapy group; and 3.1% of the 40 mg rosuvastatin monotherapy group.

No subject on ABT-335 monotherapy had any CPK value > 5 × ULN. Six subjects on combination therapy (four on ABT-335 in combination with 10 mg rosuvastatin and two on ABT-335 in combination with 20 mg rosuvastatin) and five subjects on rosuvastatin monotherapy (one each on 10 mg and 20 mg rosuvastatin, and three on 40 mg rosuvastatin) had elevations in CPK > 5 × ULN. One subject receiving ABT-335 in combination with 10 mg rosuvastatin had an elevation in CPK > 10 × ULN in the setting of an acute myocardial infarction. No subject receiving ABT-335 in combination with 20 mg rosuvastatin had an elevation in CPK > 10 × ULN. One subject on 20 mg rosuvastatin monotherapy and two subjects on 40 mg rosuvastatin monotherapy had elevations in CPK > 10 × ULN.

Renal events were infrequently reported in all treatment groups and no new safety signals were identified. The incidence of renal events was higher with ABT-335 in combination with 20 mg rosuvastatin (1.9%) than with 20 mg rosuvastatin (0%). Events of blood creatinine increased were reported only in the ABT-335 monotherapy and both combination therapy groups; however, the incidence of this event was ≤ 1.1% across groups. Two subjects discontinued study drug due to renal adverse events. Subject [redacted] (ABT-335 in combination with 10 mg rosuvastatin) discontinued study drug due to renal failure acute, with elevations in BUN and creatinine. Subject [redacted] (ABT-335 in combination with 20 mg rosuvastatin) discontinued study drug due to events of blood creatinine increased, blood uric acid increased, and blood urea 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 rosuvastatin monotherapy. For creatinine, the mean increases from baseline to final value with ABT-335 monotherapy, ABT-335 in combination with 10 mg rosuvastatin, and ABT-335 in combination with 20 mg rosuvastatin were 0.13, 0.15, and 0.13 mg/dL, respectively. In comparison, the mean increase from baseline in the 10 mg, 20 mg, and 40 mg rosuvastatin monotherapy groups were 0.02, 0.00, and 0.01 mg/dL, respectively. Twelve subjects had creatinine values > 2.0 mg/dL at any visit (three on ABT-335 monotherapy, two each on 10 mg rosuvastatin monotherapy and ABT-335 in combination with 20 mg rosuvastatin, and five on ABT-335 in combination with 10 mg rosuvastatin), eight of whom had baseline values above the ULN.

redacted information 10Jun2014

Safety Results (Continued):

For calculated creatinine clearance, the mean decreases from baseline to final value with ABT-335 monotherapy, ABT-335 in combination with 10 mg rosuvastatin, and ABT-335 in combination with 20 mg rosuvastatin were -15.881, -15.221, and -13.183 mL/min, respectively. In comparison, the mean decreases from baseline in the 10 mg, 20 mg, and 40 mg rosuvastatin monotherapy groups were -0.928, -1.093, and -2.109 mL/min, respectively. Only two subjects (one each one ABT-335 monotherapy and ABT-335 in combination with 20 mg rosuvastatin) had calculated creatinine clearance values of < 30 mL/min reported during the study. Of note, both of these subjects had abnormal baseline values for creatinine clearance (31.8 and 47.0 mL/min).

The incidence of hepatic events was generally similar across treatment groups. A statistically significant difference was observed between the ABT-335 in combination with 20 mg rosuvastatin and 20 mg rosuvastatin monotherapy groups in the event, AST increased (3.1% and 0.4%, respectively). Thirteen subjects discontinued study drug due to AST increased and/or ALT increased (four subjects on ABT-335 monotherapy, one subject on 10 mg rosuvastatin monotherapy, three subjects on ABT-335 in combination with 10 mg rosuvastatin, and five subjects on ABT-335 in combination with 20 mg rosuvastatin). One subject (ABT-335 in combination with 10 mg rosuvastatin) discontinued due to the event, hepatic enzyme increased. One subject (ABT-335 in combination with 20 mg rosuvastatin) discontinued due to jaundice, although available laboratory data revealed normal total bilirubin and AST throughout the study, with a maximal elevation in ALT to 90 U/L; this subject was subsequently diagnosed with cholelithiasis.

No subject had an increase in ALT or AST to > 10 × ULN. Ten subjects (four on ABT-335 monotherapy, three on ABT-335 in combination with 10 mg rosuvastatin, two on ABT-335 in combination with 20 mg rosuvastatin and one on 10 mg rosuvastatin monotherapy) had post-baseline increases in ALT and/or AST to > 5 × ULN on any single occasion; five of these subjects prematurely discontinued due to adverse events of ALT increased and/or AST increased. Twelve subjects (five on ABT-335 monotherapy, three on ABT-335 in combination with 10 mg rosuvastatin, and four on ABT-335 in combination with 20 mg rosuvastatin) had post-baseline increases in ALT and/or AST to > 3 × ULN on two consecutive visits; six of these subjects prematurely discontinued due to adverse events of ALT increased and/or AST increased.

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. Most subjects had ECG results that were either normal or abnormal but not clinically significant. One subject with normal baseline ECG results (ABT-335 monotherapy) and four subjects with abnormal but not clinically significant baseline ECG results (one subject each on ABT-335 monotherapy and ABT-335 in combination with 20 mg rosuvastatin; two subjects on 20 mg rosuvastatin monotherapy) shifted to clinically significant abnormal findings.

Conclusions:

Both doses of combination therapy were demonstrated to be superior to corresponding monotherapy. For the primary endpoints, ABT-335 in combination with both rosuvastatin doses resulted in significantly greater mean percent increases in HDL-C and mean percent decreases in TG compared to statin 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 many secondary and exploratory efficacy analyses, demonstrated the efficacy of combination therapy with ABT-335 and 10 mg or 20 mg rosuvastatin in reducing CHD lipid and non-lipid risk factors in subjects with mixed dyslipidemia.

ABT-335, administered as monotherapy or as part of combination therapy with rosuvastatin, was generally safe and well tolerated in this population of adults with mixed dyslipidemia. The safety profiles in this study were consistent with known safety profiles of each monotherapy. No unexpected hepatic, renal, or muscular safety signals were observed.

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