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 Year 2, Long-Term, Open-Label, Safety Extension Study of the Combination of ABT-335 and Statin Therapy for Subjects with Mixed Dyslipidemia		
Coordinating Investigator: Mark Kipnes, MD, [redacted]		
Study Sites: Multicenter; 50 sites in the United States (US) enrolled subjects		
Publications: None redacted information - 03Jul2014		
Studied Period (Years): First Subject First Dose: 28 June 2007 Last Subject Last Dose: 02 November 2008	**Phase of Development:** 3	
Objective: The objective of the study was to assess the continued safety of the daily (QD) coadministration of oral 135 mg ABT-335 in combination with either oral 20 mg rosuvastatin calcium QD, 40 mg simvastatin QD, or 40 mg atorvastatin calcium QD in subjects who completed participation in Study M05-758.		
Methodology: This was a phase 3, multicenter, long-term, open-label, second year, safety study in subjects with mixed dyslipidemia (Fredrickson Type IIb) who had completed one of three ABT-335/statin double-blind, controlled studies (Study M05-748, Study M05-749, or Study M05-750) and the year 1 open-label study (Study M05-758). The current safety study was designed to further assess the continued safety of QD 135 mg ABT-335 in combination with either 20 mg rosuvastatin QD, 40 mg simvastatin QD, or 40 mg atorvastatin QD. A subset of sites from Study M05-758 was selected to participate in Study M06-884, based on enrollment and performance in Study M05-748, Study M05-749, Study M05-750, and Study M05-758. Approximately 300 subjects who completed Study M05-758 were to be enrolled in Study M06-884. All subjects enrolled in Study M06-884 received the same treatment they received in Study M05-758, i.e., once daily open-label ABT-335 (equivalent to 135 mg fenofibric acid) in combination with either 20 mg rosuvastatin (~150 subjects), or 40 mg simvastatin (~75 subjects), or 40 mg atorvastatin (~75 subjects). The number of enrolled subjects was to reflect the 2:1:1 ratio of subjects randomized in Study M05-748, Study M05-749, and Study M05-750. The planned duration of Study M06-884 was 52 weeks (12 months) of therapy, followed by a safety follow-up phase for 30 days after the last dose of study drug. There was no screening phase for Study M06-884. The Baseline Visit of this open-label extension study corresponded to the Final Visit of M05-758. If a subject chose not to enroll into Study M06-884 at the last visit of Study M05-758, the subject was allowed to enroll into the Study M06-884 study up to 7 days after the Final Visit of Study M05-758.		

Methodology (Continued):

During the Treatment Phase of Study M06-884, subjects took study drug once daily, recording missed doses as well as adverse events and use of concomitant medications in a subject diary, and returned to the study site for four Interim Visits and one Final/Discontinuation Visit. The first Interim Visit took place approximately eight weeks (± 2 weeks) after the Baseline Visit; no laboratory assessments were performed at this visit. The Final Visit laboratory assessments from Study M05-758 were used as the baseline laboratory assessments in Study M06-884. Based on subject or site availability, subsequent Interim Visits occurred at Week 16 (± 6 days), Week 28 (± 6 days), and Week 40 (± 6 days). During the Interim Visits, a symptom-directed physical examination was performed if indicated; vital signs and weight were measured; routine hematology, serum chemistry, and urinalysis were performed in all subjects (except at Visit 2), with serum pregnancy tests in females of childbearing potential; creatinine clearance was calculated (except at Visit 2) using the Cockcroft-Gault formula; samples were collected for measurements of high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, very-low-density lipoprotein cholesterol (VLDL-C), and total cholesterol (total-C) (except Visit 2); subject diaries were reviewed and new diaries were dispensed; diet compliance, adverse events, and use of concomitant medications were assessed; pregnancy status of the subject or the subject's partner was assessed; study drug was accounted for and additional study drug was dispensed.

At the Final/Discontinuation Visit (Visit 6, Week 52), procedures that had been performed at the Interim Visits were repeated (except study drug and subject diaries were not dispensed), an electrocardiogram (ECG) was performed, and blood samples were drawn for NMR LipoProfile® testing at a subset of sites. During the Safety Follow-up Phase (the 30 days following the last dose of study drug), subjects were responsible for notifying the site of any adverse events, positive pregnancy test results, or confirmation of a pregnancy in the subject or partner.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 300 subjects from Study M05-758

Enrolled in Treatment Phase: 310 subjects were enrolled and 310 subjects were treated.

ABT-335 in combination with 20 mg rosuvastatin (N = 174)

ABT-335 in combination with 40 mg simvastatin (N = 50)

ABT-335 in combination with 40 mg atorvastatin (N = 86)

Diagnosis and Main Criteria for Inclusion:

Subjects who completed the Treatment Phase of Study M05-758, met the enrollment criteria for Study M06-884 (all of the inclusion criteria and none of the exclusion criteria), and elected to enter the second year, open-label extension study were enrolled.

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

ABT-335 (equivalent to 135 mg fenofibric acid) capsule and rosuvastatin calcium (equivalent to 20 mg rosuvastatin) tablet, once daily, orally

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

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

For the respective lot numbers, please refer to the table that follows.

Study Drug	Dosage Form	Bulk Lot Number	Finishing Lot Number
135 mg ABT-335 in combination with 20 mg rosuvastatin calcium kits:			
ABT-335	135 mg capsule	06-007702 07-012900	07-011634, 07-011646 07-013011
Rosuvastatin calcium	20 mg tablet	07-011318 07-011833 07-013245	07-011634 07-011646 07-013011
135 mg ABT-335 in combination with 40 mg simvastatin kits:			
ABT-335	135 mg capsule	06-007702 07-012900	07-011638, 07-011650, 07-011855 07-013012
Simvastatin	40 mg tablet	07-011319 07-011844 07-011842 07-013314	07-011638 07-011650 07-011855 07-013012
135 mg ABT-335 in combination with 40 mg atorvastatin calcium kits:			
ABT-335	135 mg capsule	06-007702 07-012900	07-011965, 07-011969 07-013013
Atorvastatin calcium	40 mg tablet	07-011320 07-011839 07-013246	07-011965 07-011969 07-013013

Duration of Treatment: 52 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None

Criteria for Evaluation

Efficacy: The efficacy analysis included evaluation of LDL-C (direct methodology), HDL-C, TG, non-HDL-C, VLDL-C, and total-C at Visits 1, 3, 4, 5, and 6. At a subset of sites, the following parameters were derived by the NMR LipoProfile test at the Final/Discontinuation Visit: 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-C.

Safety: Safety evaluations included physical exams, ECGs, vital signs, adverse event monitoring, and clinical laboratory testing (hematology, clinical chemistry, and urinalysis).

Statistical Methods

The Full Analysis Set was the dataset used for analyses of efficacy and safety data. The Full Analysis Set included all subjects who enrolled in Study M06-884 and received at least one dose of study drug (i.e., ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin) in Study M06-884. All data collected during exposure to ABT-335 in combination with either 10 or 20 mg rosuvastatin, 20 or 40 mg simvastatin, or 20 or 40 mg atorvastatin across the double-blind studies (Study M05-748, Study M05-749, and Study M05-750) and the open-label safety studies (Study M05-758 and Study M06-884) were summarized for this analysis set.

Efficacy: Summary tables of all efficacy variables were provided including all data as observed. For each efficacy variable, the within-group percent changes from baseline were summarized at each visit for each treatment group and overall with the mean, standard deviation, median, and range. The baseline and visit means were also calculated for subjects who had both the baseline and visit values.

Statistical Methods (Continued):

The NMR parameters were analyzed as percent change from the baseline value to the final value measured in Study M06-884. In addition, a cross tabulation of baseline and Final Visit values for LDL size was provided.

Safety: Safety data were summarized with descriptive statistics. In addition, listings were provided of laboratory parameters and vital signs (diastolic and systolic blood pressure and pulse) determinations meeting criteria for potentially clinically significant values.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events, defined as adverse events with a start date on or after the first dose of combination therapy through 30 days following the last dose of combination therapy, were summarized for each treatment group. Frequencies and percentages of subjects with adverse events were calculated for each treatment group.

For laboratory and vital sign parameters, the within-group changes were summarized for each treatment group and overall, with the mean, standard deviation, median. The Baseline and Visit means were also calculated for each visit for subjects who had both the Baseline and Visit values. In addition, laboratory parameters, as well as certain vital sign parameters, were evaluated using criteria for potentially clinically significant values.

Summary/Conclusions

A total of 310 subjects were enrolled and received at least one dose of combination therapy in Study M06-884; 174 received ABT-335 in combination with 20 mg rosuvastatin, 50 received ABT-335 in combination with simvastatin, and 86 received ABT-335 in combination with atorvastatin. Of the 310 treated subjects, 287 (92.6%) completed the study and 23 (7.4%) prematurely discontinued.

Median duration of treatment with combination therapy across the double-blind and open-label studies was 729 days, with a total of 293 (94.5%) subjects treated with combination therapy for ≥ 88 weeks, 287 subjects (92.6%) treated with combination therapy for ≥ 100 weeks, and 104 (33.5%) subjects treated with combination therapy for ≥ 112 weeks.

Efficacy Results:

Efficacy variables were changes in lipid parameters, including HDL-C, TG, LDL-C, non HDL-C, VLDL-C, and total-C. In addition, NMR LipoProfile measurements were obtained in a subset of subjects. In all combination therapy groups, the treatment effect of combination therapy was observed early, typically within four weeks, and was sustained over the duration of treatment.

In the Full Analysis Set, baseline represented the last value prior to the first dose of combination therapy, whether in the double-blind, controlled studies or in the open-label study (Study M05-758) that preceded Study M06-884. Mean values (mean percent change from baseline) after 104 weeks of combination therapy were 45.1 mg/dL (+11.0%) for HDL-C, 133.9 mg/dL (–29.7%) for TG, 89.9 mg/dL (–19.7%) for LDL-C, 115.1 mg/dL (–25.9%) for non-HDL C, 25.3 mg/dL (–29.5%) for VLDL-C, and 160.2 mg/dL (–19.9%) for total-C.

In the Initial Combination Therapy subgroup, subjects had an additional 12 weeks of combination therapy and efficacy data were available for a total of 116 weeks of combination therapy. Baseline for these subjects was after a washout of lipid-modifying drugs and prior to initiation of combination therapy.

Efficacy Results (Continued):

Mean values (mean percent change from baseline) in the Initial Combination Therapy subgroup after 116 weeks of combination therapy were 44.0 mg/dL (+16.8%) for HDL-C, 139.6 mg/dL (–45.1%) for TG, 87.5 mg/dL (–40.5%) for LDL-C, 114.8 mg/dL (–46.7%) for non-HDL C, 27.3 mg/dL (–49.0%) for VLDL-C, and 158.7 mg/dL (–37.5%) for total C.

In the Initial ABT-335 Monotherapy and Initial Statin Monotherapy subgroups, baseline was after 12 weeks of monotherapy with ABT-335 or a low-, moderate-, or high-dose statin. Although mean percent changes were not as marked as those in the Initial Combination Therapy subgroup, mean final visit values for all lipid parameters at Week 104 were consistent and similar to overall values in the Full Analysis Set at Week 104.

Regardless of the statin used in combination therapy, mean values for all lipid parameters were generally similar, and were within the therapeutic targets recommended for the population. In the Full Analysis Set, following coadministration of ABT-335 with rosuvastatin, simvastatin, or atorvastatin, mean values at Week 104 for HDL-C ranged from 43 to 46 mg/dL, for TG ranged from 130 to 136 mg/dL, for LDL-C ranged from 88 to 99 mg/dL, for non HDL-C ranged from 113 to 125 mg/dL, for VLDL-C ranged from 24 to 27 mg/dL, and for total-C ranged from 156 to 172 mg/dL.

Safety Results:

ABT-335 administered in combination with rosuvastatin, simvastatin, or atorvastatin for up to 116 weeks was generally well tolerated. Adverse events tended to occur early in treatment with combination therapy, without the emergence of new adverse events or cumulative toxicity over time. No clinically meaningful evidence of increased incidence of first occurrence or increased prevalence of any specific adverse event over time was observed in any treatment group. No new safety signals were identified with long-term combination therapy in Study M06-884.

The overall incidence of treatment-emergent adverse events was 94.8%, and was generally similar across treatment groups (90.0% to 97.7%). Overall, the most frequently reported (≥ 10.0%) adverse events were upper respiratory tract infection, headache, back pain, bronchitis, nasopharyngitis, arthralgia, sinusitis, pain in extremity, and nausea.

The incidence of the majority of specific treatment-emergent events was generally similar across treatment groups. Most adverse events were mild or moderate in intensity.

The overall incidence of treatment-related adverse events was 30.3% and was generally similar across treatment groups. Overall, the most frequently reported (≥ 2.0%) treatment-related adverse events were muscle spasms, blood CK increased, headache, myalgia, dyspepsia, and nausea. The incidence of the majority of specific treatment-related events was generally similar across treatment groups.

A total of 35 (11.3%) subjects had treatment-emergent serious adverse events. Overall, the most common serious adverse events were non-cardiac chest pain, intervertebral disc degeneration, and osteoarthritis (three subjects each) and diverticulitis (two subjects). All other serious adverse events were reported by one subject.

Only nine (2.9%) subjects had adverse events that led to discontinuation from the study. Myalgia leading to discontinuation was reported by two subjects; all other adverse events leading to discontinuation were reported by one subject.

Safety Results (Continued):

Adverse events and laboratory evaluations of special interest included those related to muscle events, renal events, and hepatic events. No unexpected muscle, renal, or hepatic safety signals were identified. The discontinuation rate due to these events was low and generally similar across treatment groups.

Myalgia was the only adverse event that led to discontinuation in more than one subject (two subjects in the ABT-335 in combination with rosuvastatin treatment group).

Overall, the incidence of muscle adverse events was 15.5% and ranged from 9.3% to 22.0% across treatment groups. No cases of rhabdomyolysis were reported. The two most common treatment emergent muscle-related adverse events overall were myalgia, occurring in 6.8% of subjects, and musculoskeletal pain, occurring in 6.1% of subjects. There was no clinically meaningful evidence of increased incidence of first occurrence or increased prevalence of either myalgia or musculoskeletal pain over time. The only muscle-related adverse event leading to discontinuation was myalgia (two subjects in the ABT-335 in combination with rosuvastatin). Of the 15 subjects with reported muscle events of blood CK abnormal, blood CK increased, muscle enzyme increased, or blood CK MM increased, three had post-baseline CK values > 5 × ULN. Overall, a total of four subjects (three subjects in the ABT-335 in combination with rosuvastatin treatment group and one subject in the ABT-335 in combination with atorvastatin treatment group) had a post-baseline CK value > 10 × ULN.

The incidence of reported renal adverse events, including changes in the laboratory parameters of creatinine, BUN, and calculated creatinine clearance, was low. The overall percentage of subjects with renal adverse events was 4.5%. Greater percentages of subjects in the ABT-335 in combination with rosuvastatin (6.3%) and ABT-335 in combination with atorvastatin (3.5%) treatment groups had renal adverse events compared with subjects in the ABT-335 in combination with simvastatin treatment group (0.0%). The most common renal-related adverse events were creatinine renal clearance decreased (1.9% overall) and blood creatinine increased (1.6% overall). Only one subject (ABT-335 in combination with rosuvastatin) discontinued due to a renal-related adverse event (creatinine renal clearance decreased). No clinically meaningful evidence of increased incidence of first occurrence or increased prevalence of any specific adverse event over time was observed in any treatment group. Of the ten subjects with reported renal adverse events associated with changes in renal laboratory parameters, one prematurely discontinued and two had post-baseline creatinine values > 2 mg/dL or that increased ≥ 100% from baseline. While a total of ten subjects had a creatinine value > 2 mg/dL or that increased ≥ 100% from baseline, only three subjects had a reported adverse event associated with the laboratory elevation; at the final evaluation, creatinine values were ≤ 1.7 g/dL in all ten of these subjects.

The overall percentage of subjects with hepatic adverse events was 4.8%. The percentage of subjects experiencing hepatic adverse events was greatest in the ABT-335 in combination with simvastatin treatment group (8.0%) compared with the ABT-335 in combination with atorvastatin (5.8%) and ABT-335 in combination with rosuvastatin (3.4%) treatment groups. The percentage of subjects that discontinued due to hepatic events was low. One subject (ABT-335 in combination with rosuvastatin) discontinued due to hepatic adverse events (ALT increased and AST increased). Hepatic adverse events were most commonly associated with modest elevations in ALT or AST that in most cases did not reach potentially clinically significant values. Of the 13 subjects with reported hepatic adverse events associated with changes in laboratory parameters, one subject prematurely discontinued and four had post-baseline ALT or AST values > 3 × ULN on two consecutive visits or > 5 × ULN on any occasion. The overall percentage of subjects with at least one post-baseline ALT value > 5 × ULN was 1.3%.

Safety Results (Continued):

Two subjects (1.1%) in the ABT-335 in combination with rosuvastatin group had post-baseline ALT > 3 × ULN on two consecutive occasions. The overall percentage of subjects with at least one post-baseline AST value > 5 × ULN was 0.6%. One subject (0.6%) in the ABT-335 in combination with rosuvastatin group had post-baseline AST > 3 × ULN on two consecutive occasions. Elevations in ALT and AST generally showed improvement or resolution upon repeat testing, even with ongoing therapy, or were reversible upon study drug discontinuation. Elevations in ALT and AST were not accompanied by a concomitant increase in bilirubin above the upper limit of normal or alkaline phosphatase to PCS levels.

Minor mean changes 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.

Analysis of long-term safety data found no evidence of hepatotoxicity, worsening renal function, or adverse muscle effects with combination therapy.

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

Conclusions:

Administration of ABT-335 in combination with a moderate-dose statin resulted in clinically meaningful improvements in key lipid parameters (LDL-C, TG, HDL-C, and non-HDL-C) that are independently associated with CHD risk; abnormalities in these parameters occur simultaneously in patients with mixed dyslipidemia. In addition, combination therapy with moderate-dose statins resulted in comprehensive improvement in multiple lipid parameters, including non-HDL-C, VLDL-C, and total-C, demonstrating a positive impact on overall atherogenicity. Efficacy of combination therapy persisted throughout the treatment period of the open-label extension study.

Long-term combination therapy with ABT-335 and a statin was generally safe and well tolerated in adults with mixed dyslipidemia. The long-term safety profiles of ABT-335 in combination with rosuvastatin, simvastatin, or atorvastatin were consistent with the known safety profiles of the individual drugs. ABT-335 administered in combination with a statin for up to 116 weeks did not result in cumulative toxicity or the emergence of late-onset adverse events. No additional safety signals were observed with continued, long-term therapy, including no new or unexpected muscle, renal, or hepatic safety signals.