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 Long-Term, Open-Label, Safety Extension Study of the Combination of Fenofibric Acid and Statin Therapy for Subjects with Mixed Dyslipidemia

Coordinating Investigator: Harold Bays, MD, [redacted] redacted information - 01Jul2014

Study Sites: Multicenter; 360 sites in the United States, Puerto Rico, and Canada enrolled subjects

Publications: None

Studied Period (Years): Date First Subject Dosed: 13 June 2006 Date Last Subject Completed Dosing: 10 March 2008	**Phase of Development:** 3

Objective: The objective of this study was to assess the long-term safety and efficacy of (open-label) 135 mg ABT-335 in combination with (open-label) 20 mg rosuvastatin calcium (rosuvastatin), 40 mg simvastatin or 40 mg atorvastatin calcium (atorvastatin) in subjects with mixed dyslipidemia (Fredrickson Type IIb).

Methodology: This was a Phase 3, multicenter, long-term, open-label extension study in subjects with mixed dyslipidemia (Fredrickson Type IIb) who had completed one of three double-blind, controlled studies (M05-748, M05-749, or M05-750). The study was designed to assess the safety and efficacy of once daily 135 mg ABT-335 in combination with either once daily 20 mg rosuvastatin, once daily 40 mg simvastatin, or once daily 40 mg atorvastatin. In addition to evaluating the efficacy and safety respective to this open-label extension study, included in this analysis of long-term exposure of ABT-335 are also prespecified efficacy and safety data sets that included data from the double-blind, controlled studies (see Statistical Methods section below).

The planned duration of this extension study was 52 weeks (12 months) of therapy with a 1-month Safety Follow-up Period. The Baseline Visit of this study corresponded to the last visit of the preceding double-blind, controlled study. During the Treatment Period, subjects took study drug once daily, recording missed doses, adverse events and use of concomitant medications in a subject diary, and returned to the study site for six Interim Visits and one Final/Discontinuation Visit. Interim Visits occurred every four weeks for the first 16 weeks and then every 12 weeks for the remainder of the Treatment Period. During the Interim Visits, symptom-directed physical examination was performed if indicated; vital signs were measured; routine hematology, serum chemistry, and urinalysis were performed in all subjects, with serum pregnancy tests in females of childbearing potential; creatinine clearance was calculated, 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); subject diaries were reviewed and new

Methodology (Continued):

diaries were dispensed; diet compliance, adverse events, and use of concomitant medications were assessed; study drug was accounted for and a new study drug kit was dispensed. In addition, blood samples were obtained for measurement of apolipoprotein B (ApoB) and high sensitivity C-reactive protein (hsCRP) at each visit except Visit 5 (Week 16) and for measurement of apolipoprotein AI (ApoAI), apolipoprotein CIII (ApoCIII), adiponectin, and lipoprotein-associated phospholipase A2 (LpPLA2) at Visits 4, 6, 7, and 8 (Weeks 12, 28, 40, and 52).

At the Final/Discontinuation Visit (Visit 8, Week 52), procedures that had been performed at the Interim Visits were repeated (except study drug and subject diaries were not dispensed) and electrocardiogram (ECG) was performed. During the 30 days following the last dose of study drug (Safety Follow-up Period), subjects were responsible for notifying the site of any adverse events and any positive pregnancy test results or pregnancy confirmation in the subject or partner.

Number of Subjects (Planned and Analyzed):

Planned: A maximum of 2370 subjects

Enrolled in Treatment Period: 1911 subjects were enrolled and 1895 subjects were treated.

ABT-335 in combination with 20 mg rosuvastatin (N = 1029)

ABT-335 in combination with 40 mg simvastatin (N = 432)

ABT-335 in combination with 40 mg atorvastatin (N = 434)

Diagnosis and Main Criteria for Inclusion:

Subjects who completed the Treatment Period of one of the three double-blind, controlled studies comparing the safety and efficacy of ABT-335 and statin combination therapy to ABT-335 and statin monotherapy (M05-748, M05-749, or M05-750), met the enrollment criteria for M05-758 (all of the inclusion criteria and none of the exclusion criteria), and elected to enter the open-label extension study were enrolled.

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

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 number, please refer to the table that follows.

Study Drug	Dosage Form	Bulk Lot Number	Finishing Lot Number
135 mg ABT-335/20 mg rosuvastatin calcium kits:			
ABT-335	135 mg capsule	05-003336 06-004932 06-005437 06-008198 06-008199 06-008200	06-006206 06-006898 06-006902 06-009607 06-009608 06-009609
Rosuvastatin calcium	20 mg tablet	05-003673 06-006920 06-006921 06-009788	06-006206 06-006898 06-006902 06-009607, 06-009608, 06-009609
135 mg ABT-335/40 mg simvastatin kits:			
ABT-335	135 mg capsule	05-003336 06-005437 06-005591 06-008201 06-008200	06-006210 06-006907 06-006911 06-009734 06-009735
Simvastatin	40 mg tablet	05-003672 06-006922 06-009949	06-006210 06-006907, 06-006911 06-009734, 06-009735
135 mg ABT-335/40 mg atorvastatin calcium kits:			
ABT-335	135 mg capsule	05-003336 06-005591 06-008202 06-008200	06-006214 06-006915 06-009736 06-009737
Atorvastatin calcium	40 mg tablet	05-003676 06-006923 06-009951	06-006214 06-006915 06-009736, 06-009737

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 evaluations of total-C, LDL-C, HDL-C, non-HDL-C, VLDL-C, and TG at each visit; hsCRP and ApoB at each visit except Visit 5 (Week 16); and ApoAI, ApoCIII, adiponectin, and LpPLA2 at Visits 4, 6, 7, and 8 (Weeks 12, 28, 40, and 52).

Safety: Safety assessments included physical examinations, vital signs, clinical laboratory testing (hematology, chemistry, and urinalysis), ECG, and the assessment of adverse events.

Statistical Methods

All data collected across both the double-blind, controlled studies and the open-label study during exposure to ABT-335 in combination with a statin were analyzed. There were eight analysis sets.

Four analysis sets were analyzed for both efficacy and safety, including:

1. *Initial Combination Therapy* included all subjects who received at least one dose of combination therapy with ABT-335 and a statin at either the low or moderate dose in one of the double-blind, controlled studies. Data collected across the double-blind and open-label studies 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 were summarized for this analysis set; subjects who did not enroll in M05-758 were included.
2. *Initial Combination Therapy at the Moderate Statin Dose* included all subjects who received at least one dose of combination therapy with ABT-335 and the moderate-dose statin in one of the double-blind, controlled studies. Data collected across the double-blind and open-label studies during exposure to ABT-335 in combination with 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin were summarized for this analysis set; subjects who did not enroll in M05-758 were included.
3. *Initial Statin Monotherapy* included all subjects who were randomized to monotherapy with either 10, 20, or 40 mg rosuvastatin; 20, 40, or 80 mg simvastatin; or 20, 40, or 80 mg atorvastatin in one of the double-blind, controlled studies and received at least one dose of study drug in M05-758. Data collected during exposure to ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin in Study M05-758 were summarized for this analysis set. Subjects must have received at least one dose of study drug in M05-758 in order to be included in the analysis set.
4. *Initial ABT-335 Monotherapy* included all subjects who were randomized to ABT-335 monotherapy in one of the double-blind, controlled studies and received at least one dose of study drug in M05-758. Data collected during exposure to ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin in M05-758 were summarized for this analysis set. Subjects must have received at least one dose of study drug in M05-758 in order to be included in the analysis set.

Two analysis sets were analyzed for efficacy only, including:

5. *Initial Combination Therapy at the Low Statin Dose* included all subjects who were randomized to combination therapy with ABT-335 and the low-dose statin in one of the double-blind, controlled studies and received at least one dose of study drug in M05-758. Data collected during exposure to ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin in Study M05-758 were summarized for this analysis set. Subjects must have received at least one dose of study drug in M05-758 in order to be included in the analysis set.
6. *Initial Stain Monotherapy at the Moderate Statin Dose* included all subjects who were randomized to monotherapy with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin in one of the double-blind, controlled studies and received at least one dose of study drug in M05-758. Data collected during exposure to ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin in Study M05-758 were summarized for this analysis set. Subjects must have received at least one dose of study drug in M05-758 in order to be included in the analysis set.

Statistical Methods (Continued):

Two analysis sets were analyzed for safety only, including:

7. *All Combination Therapy* included all subjects who received at least one dose of ABT-335 in combination with either 10 or 20 mg rosuvastatin, 20 or 40 mg simvastatin, or 20 or 40 mg atorvastatin in one of the double-blind, controlled studies or in M05-758. Data collected across the double-blind and open-label studies during exposure to ABT-335 in combination with low or moderate-dose statins were summarized for this analysis set. Subjects who did not enroll in M05-758 were included.
8. *All Combination Therapy at the Moderate Statin Dose* included all subjects who received at least one dose of ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin in one of the double-blind, controlled studies or in M05-758. Data collected across the double-blind and open-label studies during exposure to ABT-335 in combination with moderate-dose statins were summarized for this analysis set. Subjects who did not enroll in M05-758 were included.

Efficacy: Efficacy analyses were performed for all analysis sets except *All Combination Therapy* and *All Combination Therapy at the Moderate Statin Dose*. Summary tables of all efficacy variables were provided including all data as observed. The within-group percent changes from baseline in the efficacy parameters were summarized at each visit for each treatment group with the mean, median, standard deviation, and range. The baseline and visit means were also calculated for subjects who had both the baseline and visit values.

Safety: Safety data were summarized with descriptive statistics for all safety analysis sets. However, for the *Initial Statin Monotherapy* and *Initial ABT-335 Monotherapy* analysis sets, adverse event data included only summaries of the prevalence and incidence of adverse events. In addition, listings were provided of laboratory parameters and vital signs (diastolic and systolic blood pressure and heart rate) determinations meeting criteria for potentially clinically significant values.

Summary/Conclusions:

A total of 1911 subjects were enrolled into M05-758 and 1895 of these subjects received at least one dose of combination therapy; 1029 received ABT-335 in combination with 20 mg rosuvastatin, 432 received ABT-335 in combination with 40 mg simvastatin, and 434 received ABT-335 in combination with 40 mg atorvastatin. Of the 1895 treated subjects,1514 (79.9%) completed treatment and 381 (20.1%) prematurely discontinued. Median duration of treatment with combination therapy in the *All Combination Therapy* analysis set was 364 days, with a total of 1682 subjects (76.4%) treated with combination therapy for ≥ 24 weeks and 1139 (51.7%) of these subjects treated with combination therapy for ≥ 52 weeks; 441 (20.0%) subjects were treated with combination therapy for ≥ 64 weeks.

Efficacy Results:

Long-term efficacy was assessed in six analysis sets that were designed to take into consideration the treatment subjects received in the double-blind, controlled studies: *Initial Combination Therapy* (N = 979), *Initial Combination Therapy at Moderate Statin Dose* (N = 489), *Initial Combination Therapy at Low Statin Dose* (N = 343), *Initial Statin Monotherapy* (N = 893), *Initial Statin Monotherapy at Moderate Statin Dose* (N = 364), and *Initial ABT-335 Monotherapy* (N = 329). Efficacy variables were changes in lipid parameters, including HDL-C, TG, LDL-C, non-HDL-C, VLDL-C, total-C, and ApoB, as well as changes in hsCRP. Whether combination therapy was initiated during the double-blind, controlled studies or introduced during M05-758, the treatment effect of combination therapy was observed early, typically within four weeks, and was sustained over the duration of treatment.

Efficacy Results (Continued):

For subjects who were initially treated with ABT-335 in combination with a moderate-dose statin, efficacy persisted throughout long-term therapy in Study M05 758. After 12 weeks of double-blind treatment, mean values (mean percent change) were 45.0 mg/dL (+17.9%) for HDL-C, 141.0 mg/dL (–45.5%) for TG, 99.8 mg/dL (–33.2%) for LDL-C, 126.3 mg/dL (–41.9%) for non-HDL-C, 26.3 mg/dL (–51.5%) for VLDL-C, 171.2 mg/dL (–33.1%) for total-C, and 90.2 mg/dL (–37.4%) for ApoB. After an additional 52 weeks of open-label combination therapy, mean values (mean percent change) were 47.7 mg/dL (+25.9%) for HDL-C, 138.0 mg/dL (–47.3%) for TG, 94.2 mg/dL (–36.3%) for LDL-C, 121.0 mg/dL (–44.1%) for non-HDL-C, 27.0 mg/dL (–51.3%) for VLDL-C, 168.5 mg/dL (–33.8%) for total-C, and 84.7 mg/dL (–41.2%) for ApoB. Median percent decreases in hsCRP were observed throughout treatment; after 64 total weeks of combination therapy, the median percent changes in hsCRP was –38.7%.

For subjects who were initially treated with ABT-335 in combination with a low-dose statin, changing to ABT-335 in combination with a moderate-dose statin resulted, after 52 weeks of combination therapy at the moderate statin dose, in an incremental mean percent increase in HDL-C (4.8%, from a mean of 45 mg/dL to 47 mg/dL); incremental mean percent decreases in LDL-C (–9.7%, from 102 mg/dL to 91 mg/dL), non-HDL-C (–7.5%, from 130 mg/dL to 118 mg/dL), total-C (–4.7%, from 174 mg/dL to 164 mg/dL), and ApoB (–9.4%, from 91 mg/dL to 82 mg/dL); and a marginal mean percent increase (+4.9%) but median percent decrease (–4.2%) in TG (from 140 mg/dL to 139 mg/dL). The incremental mean percent decreases in LDL-C, non HDL-C, and ApoB are consistent with what would be expected with a doubling of statin dose.20 In addition, median percent decreases from baseline in VLDL C were generally observed after four weeks of open-label treatment, ranging from –5.6% to –8.6% between eight weeks and 40 weeks. Median percent decreases in hsCRP were also observed throughout treatment; after 52 weeks of open-label combination therapy, the median percent change in hsCRP was –12.7%.

For subjects who were initially treated with statin or ABT-335 monotherapy during the double-blind, controlled studies, additional incremental improvements in multiple parameters occurred during long-term treatment with ABT-335 in combination with a moderate-dose statin. In subjects initially treated with moderate-dose statin monotherapy, adding ABT-335 to the moderate-dose statin resulted in an incremental mean percent increase in HDL-C (13.1%, from 41 mg/dL to 46 mg/dL); incremental mean percent decreases in TG (–21.0%, from 188 mg/dL to 134 mg/dL), non-HDL-C (–4.6%, from 127 mg/dL to 119 mg/dL), VLDL-C (–11.2%, from 35 mg/dL to 26 mg/dL), total-C (–0.7%, from 168 mg/dL to 165 mg/dL), and ApoB (–7.0%, from 91 mg/dL to 83 mg/dL), and a minimal mean percent increase (3.1%) in LDL-C (from 92.3 mg/dL to 92.5 mg/dL) after 52 weeks of combination therapy. However, mean final LDL-C was almost identical to the mean baseline value of 92.3 mg/dL following 12 weeks of treatment with moderate-dose statin monotherapy, and was below recommended targeted goals for this subject population.

In subjects initially treated with ABT-335 monotherapy, the change to combination therapy with ABT-335 and the moderate-dose statin resulted in an incremental mean percent increase in HDL-C (6.2%, from a mean of 45 mg/dL to 47 mg/dL) and mean percent decreases in TG (–15.7%, from 170 mg/dL to 134 mg/dL), LDL-C (–38.1%, from 149 mg/dL to 92 mg/dL), non-HDL-C (–35.2%, from 184 mg/dL to 118 mg/dL), VLDL-C (–3.7%, from 35 mg/dL to 26 mg/dL), total-C (–27.2%, from 229 mg/dL to 165 mg/dL), and ApoB (–32.3%, from 123 mg/dL to 82 mg/dL) after 52 weeks of combination therapy. In addition, in both groups of subjects who changed from monotherapy to combination therapy, median percent decreases in hsCRP were observed throughout treatment. After 52 weeks of open-label combination therapy, the incremental median percent changes in hsCRP were –21.1% in subjects initially

Efficacy Results (Continued):

treated with statin monotherapy and –27.1% in the subjects initially treated with ABT-335 monotherapy.

Mean values for all lipid parameters were similar in all the long-term efficacy analysis sets after 52 weeks of open-label combination treatment or 64 weeks of double-blind and open label combination treatment, and were within the therapeutic targets recommended for the subject population. After 64 weeks of treatment, mean values (mean percent change from baseline) in the *Initial Combination Therapy* analysis set were 47 mg/dL (+23.8%) for HDL-C, 93 mg/dL (–38.2%) for LDL-C, 138 mg/dL (–47.2%) for TG, 119 mg/dL (–45.0%) for non-HDL-C, 27.0 mg/dL (–51.4%) for VLDL-C, 166 mg/dL (–34.8%) for total-C, and 83 mg/dL (–42.3%) for ApoB. In addition, median percent decreases in hsCRP were observed throughout treatment, with a median percent change in hsCRP of –37.0% after 64 weeks of combination therapy.

Safety Results:

A total of 2201 subjects received ABT-335 in combination with a statin in the double blind, controlled studies and/or Study M05-758 for up to 64 weeks of total treatment; these subjects are included in the *All Combination Therapy* analysis set, and represent the total number of subjects who received at least one dose of ABT-335 in combination with a statin in the Phase 3 program. Median duration of treatment with combination therapy across the double-blind and open-label studies was 364 days, with a total of 1682 subjects (76.4%) treated with combination therapy for ≥ 24 weeks and 1139 (51.7%) of these subjects treated with combination therapy for ≥ 52 weeks; 441 (20.0%) subjects were treated with combination therapy for ≥ 64 weeks.

ABT-335 administered in combination with a statin for up to 64 weeks was generally well tolerated. Adverse events tended to occur early in treatment with combination therapy, with no evidence of increasing prevalence of adverse events or cumulative toxicity over time. No new safety signals were identified with long-term combination therapy in Study M05-758. Safety of long-term combination therapy was demonstrated regardless of the statin used (rosuvastatin, simvastatin, or atorvastatin).

Among the 2201 subjects in the *All Combination Therapy* analysis set, the overall incidence of treatment emergent adverse events was 84.3%, and was generally similar across the three combination therapy groups (83.1% to 86.2%). Overall, the most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, back pain, arthralgia, sinusitis, muscle spasms, pain in extremity, nausea, and cough. The incidence of the majority of specific events was generally similar across treatment groups and most adverse events were mild or moderate in intensity. In the *All Combination Therapy* analysis set, treatment-emergent adverse events occurring in ≥ 2.0% of subjects in any treatment group and with at least a two-fold greater incidence between a single treatment group and both of the other treatment groups were herpes simplex (highest incidence in the ABT-335 in combination with simvastatin treatment group), tooth abscess (highest incidence in the ABT-335 in combination with atorvastatin treatment group), hepatic enzyme increased (highest incidence in the ABT-335 in combination with atorvastatin treatment group), and anxiety (highest incidence in the ABT-335 in combination with rosuvastatin treatment group).

Safety Results (Continued):

The percentage of subjects with at least one possibly or probably treatment-related adverse event, as assessed by the investigator, was 27.4%, and was generally similar across the three combination therapy groups (27.1% to 27.7%). Overall, the most frequently reported treatment-related adverse events were blood CPK increased, headache, myalgia, ALT increased, AST increased, muscle spasms, dyspepsia, nausea, and hepatic enzyme increased. The incidence of the majority of specific events was generally similar across treatment groups. Possibly or probably treatment-related adverse events occurring in ≥ 1.0% of subjects in any treatment group and with at least a two-fold greater incidence between a single treatment group and both of the other treatment groups were fatigue (highest incidence in the ABT-335 in combination with rosuvastatin treatment group) and hepatic enzyme increased (highest incidence in the ABT-335 in combination with atorvastatin treatment group).

Six subjects who participated in Study M05-758 died; five subjects died during the study (myocardial infarction, cerebral edema, cardiac arrest, respiratory arrest and syncope, cardio-respiratory arrest) and one subject died from an event (respiratory failure) that began more than 30 days after the last dose of study drug (non-treatment-emergent). The adverse events that led to death in all six subjects were not considered by the investigator to be possibly or probably related to study drug. A total of 148 (6.7%) subjects in the *All Combination Therapy* analysis set had treatment-emergent serious adverse events. Overall, the most common serious adverse events were osteoarthritis (ten subjects), deep vein thrombosis (six subjects), coronary artery disease, myocardial infarction, and chest pain (five subjects each), and diverticulitis, syncope, and intervertebral disc protrusion (four subjects each). In each of the six reports of DVT, there were risk factors for the reported event of DVT.

A total of 263 (11.9%) subjects had adverse events leading to discontinuation from combination therapy; across the three treatment groups, 10.1% to 13.8% of subjects discontinued due to adverse events. Overall, the most common adverse events that led to discontinuation were ALT increased (1.0%), blood CPK increased (1.0%), AST increased (0.9%), myalgia (0.9%), and hepatic enzyme increased (0.6%).

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 in subjects receiving ABT-335 in combination with statins for up to 64 weeks in the *All Combination Therapy* analysis set. The overall incidence of adverse events of special interest (muscle, renal, and hepatic) was 18.6% and was similar across treatment groups. The discontinuation rate due to adverse events of special interest was low and generally similar across treatment groups. Discontinuation due to an adverse event was at the discretion of the investigator. Overall, the reported adverse events of ALT increased (1.0%) and blood CPK increased (1.0%) were the only adverse events of special interest leading to discontinuation in ≥ 1.0% of subjects.

Overall, the incidence of muscle events in the *All Combination Therapy* analysis set was 11.2% and ranged from 10.5% to 12.6% across treatment groups. No cases of rhabdomyolysis were reported. The most common treatment emergent muscle-related adverse events overall were myalgia (5.1%) and blood CPK increased (3.8%), which led to discontinuation in 0.9% and 1.0% of subjects, respectively. The only specific muscle adverse events of special interest that led to discontinuation in > 1.0% of subjects in any treatment group were blood CPK increased (ABT-335 in combination with simvastatin [1.4%]) and myalgia (ABT-335 in combination with atorvastatin [1.4%]). The incidence of the first occurrence of the reported adverse events of blood CPK increased and myalgia was highest during the first 12 weeks of combination therapy; the prevalence of these two adverse events remained relatively constant over time.

Safety Results (Continued):

Of the 84 subjects with reported muscle events of blood CPK abnormal, blood CPK increased, muscle enzyme increased, or blood CPK MM increased, 22 subjects prematurely discontinued and 18 had post-baseline CPK values > 5 × ULN. Of all subjects in the *All Combination Therapy* analysis set, only 0.4% of subjects had a post-baseline CPK value > 10 × ULN and 1.3% of subjects had a post-baseline CPK > 5 × ULN.

The incidence of reported renal adverse events, including changes in the laboratory parameters of creatinine, BUN, and calculated creatinine clearance, was low. Renal adverse events were reported for 3.8% of subjects and ranged from 2.5% to 4.2% across treatment groups. The most common renal-related adverse events were blood creatinine increased (1.5%) and creatinine renal clearance decreased (1.7%); these events led to discontinuation in 0.4% and 0.3% of subjects, respectively. Mean creatinine values increased during the first four weeks of combination therapy, then stabilized thereafter. The incidence of the first occurrence of the reported adverse events of creatinine renal clearance decreased and blood creatinine increased was highest during the first 12 weeks of combination therapy and decreased thereafter; in general, the prevalence of these two adverse events remained relatively constant over time. Of the 62 subjects with reported renal adverse events associated with changes in renal laboratory parameters, 14 prematurely discontinued and eight had post-baseline creatinine values > 2 mg/dL or that increased ≥ 100% from baseline. While a total of 19 (0.9%) subjects in the *All Combination Therapy* analysis set had a creatinine value that increased ≥ 100% from baseline, most did not have reported adverse events associated with the laboratory elevation. In those subjects with elevations in creatinine in whom study drug was discontinued and follow-up values were available, the increases in creatinine were generally reversible.

Hepatic adverse events were reported for 5.3% of subjects in the *All Combination Therapy* analysis set and ranged from 4.5% to 7.4% across treatment groups. The vast majority of hepatic adverse events were reported adverse events of changes in hepatic laboratory test values. The most common hepatic adverse events were reported adverse events of ALT increased (2.5%), AST increased (2.4%), hepatic enzyme increased (1.3%), and liver function test abnormal (1.1%); these events led to discontinuation in 1.0%, 0.9%, 0.6%, and 0.4% of subjects, respectively. Specific hepatic adverse events leading to discontinuation in > 1.0% of subjects in any treatment group were ALT increased (ABT-335 in combination with rosuvastatin [1.3%]), AST increased (ABT-335 in combination with rosuvastatin [1.2%]) and hepatic enzyme increased (ABT-335 in combination with atorvastatin [1.8%]). 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 112 subjects with reported hepatic adverse events associated with changes in laboratory parameters, 45 subjects prematurely discontinued and 32 had post-baseline ALT or AST values > 3 × ULN on two consecutive visits or > 5 × ULN on any occasion. Among subjects in the *All Combination Therapy* analysis set, 1.1% of subjects receiving ABT 335 in combination with a statin had at least one post-baseline ALT value > 5 × ULN on any occasion and 1.2% had an ALT > 3 × ULN on two consecutive visits. The overall percentage of subjects with at least one post-baseline AST value > 5 × ULN on any occasion was 0.6%, with 0.5% having an AST > 3 × ULN on two consecutive visits. 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 or alkaline phosphatase to PCS levels.

Safety Results (Continued):

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. Chemistry laboratory results from the *Initial Statin Monotherapy* and *Initial ABT-335 Monotherapy* analysis sets demonstrated that addition of ABT-335 to statin monotherapy or addition of a statin to ABT-335 monotherapy did not result in adverse effects on muscle or hepatic laboratory parameters. Specifically, the addition of ABT-335 to statin monotherapy did not have a clinically meaningful effect on ALT, AST, alkaline phosphatase, or CPK. However, there was an initial modest mean increase in creatinine and BUN, which then stabilized without evidence of progressive increase in creatinine with continued exposure. Addition of a statin (20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin) to ABT-335 monotherapy resulted in mean decreases from baseline in ALT and AST and did not result in clinically meaningful effects on any other chemistry laboratory parameter.

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

Minor mean increases and decreases 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 moderate-dose statins resulted in clinically meaningful improvements in three lipid parameters that are independently associated with CHD risk (LDL-C, TG, and HDL-C); abnormalities in these parameters occur simultaneously in patients with mixed dyslipidemia. In addition, combination therapy resulted in comprehensive improvement in multiple lipid parameters, including non-HDL-C, ApoB, total-C, and VLDL-C, as well as in hsCRP, demonstrating a positive impact on multiple lipid parameters. Subjects treated with ABT-335 in combination with a low-dose statin in the double-blind, controlled studies achieved incremental clinically meaningful improvements in lipid parameters when switched to therapy with ABT-335 in combination with a moderate-dose statin in the open-label extension study. Subjects initially treated with moderate-dose statin monotherapy had an incremental mean percent increase in HDL-C; incremental mean percent decreases in TG, non HDL-C, VLDL-C, total-C, and ApoB; a median percent decrease in hsCRP; and a modest, clinically insignificant mean percent increase in LDL-C when ABT-335 was added. Subjects initially treated with ABT-335 monotherapy had an incremental modest mean percent increase in HDL-C; mean percent decreases in LDL-C, TG, non HDL-C, VLDL-C, total-C, and ApoB; and an incremental median percent decrease in hsCRP when a moderate-dose statin was added. 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 overall adverse event profile of combination therapy in the long-term study was consistent with that observed with combination therapy during the double-blind, controlled studies.

The long-term safety of combination therapy was demonstrated in the open-label extension study, regardless of initial therapy (ABT-335 monotherapy, statin monotherapy, or combination therapy) received in the double-blind, controlled study. ABT-335 administered in combination with a moderate-dose statin for up to 64 weeks did not demonstrate evidence of 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 hepatic, renal, or muscle safety signals.