2.0   Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Trilipix® (ABT-335)	**Volume:** **Page:**	
Name of Active Ingredient: choline salt of fenofibric acid		

Title of Study: Evaluation of Choline Fenofibrate (ABT-335) on Carotid Intima-Media Thickness (cIMT) in Subjects with Type IIb Dyslipidemia with Residual Risk in Addition to Atorvastatin Therapy (FIRST) Trial

Coordinating Investigator: Christie M. Ballantyne, MD redacted information 03Jul2014

Study Site: 94 sites in the United States of America (USA)

Publications: 1 manuscript, 1 abstract

Studied Period (Years):
    First Subject First Visit: 10 February 2008
    Last Subject Last Visit: 13 September 2012
	Phase of Development: 3

Objective: The objective of this study was to evaluate the effect on cIMT progression of once daily ABT-335 135 mg or placebo in addition to atorvastatin therapy in a population of subjects with mixed dyslipidemia who had achieved low-density lipoprotein cholesterol (LDL-C) target goals while receiving atorvastatin.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled comparative study in subjects with mixed dyslipidemia who had achieved National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) LDL-C target goals (≤ 100 mg/dL) for high-risk subjects on atorvastatin therapy. This study included: • A 10-week maximum to 2-week minimum diet and atorvastatin run-in phase, • A 104-week (24-month) treatment phase, and • A 30-day safety follow-up contact.

Methodology (Continued):
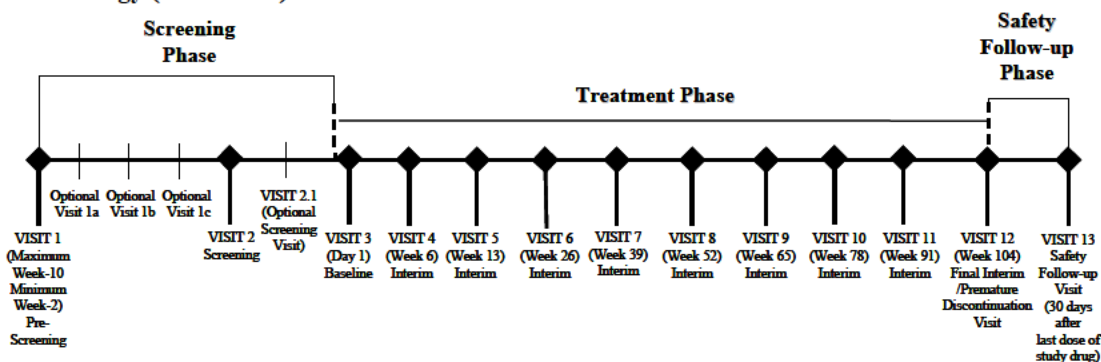
A subject's participation in the study was anticipated to be up to approximately 118 weeks.

Subjects followed 1 of 3 screening procedures based on their statin use and LDL-C level. At the Pre-screening Visit, subjects were instructed to continue their standard-of-care atorvastatin therapy to maintain target LDL-C goal of ≤ 100 mg/dL, or to discontinue any statin other than atorvastatin. For subjects already receiving atorvastatin, the dose was maintained if already at LDL-C goal of ≤ 100 mg/dL or titrated to achieve the target LDL-C level. For subjects who were receiving a different statin or were not receiving statin therapy, atorvastatin was initiated and the dose was titrated to achieve the target LDL-C level over ≥ 4 weeks. The LDL-C goal was to be maintained for ≥ 2 weeks prior to the baseline, with an average of 2 consecutive values ≤ 105 mg/dL. All subjects were to take atorvastatin for ≥ 4 weeks prior to baseline (Visit 3).

At the Baseline Visit, eligible subjects (i.e., met the enrollment criteria) were randomized to either once daily ABT-335 135 mg or placebo. Subjects were instructed to continue their previous atorvastatin therapy to maintain target LDL-C levels and follow the American Heart Association (AHA)-recommended healthy choices diet. The central laboratory reviewed unblinded lipid parameters and informed the investigator, who remained blinded to study drug, when any subject's LDL-C therapy required modification. The investigator followed an algorithm to maintain LDL-C within the target range, by incrementally adjusting the atorvastatin dose to a maximum of 40 mg daily or adding ezetimibe 10 mg to the treatment regimen if the subject was already receiving atorvastatin 40 mg daily.

During the Treatment Phase, subjects returned to the study site for 8 interim visits (refer to figure above) and 1 Final Interim/Premature Discontinuation Visit (Week 104). A non-invasive ultrasound measuring the intima-media thickness (IMT) of the carotid artery was performed at a central facility within 17 days prior to Day 1 (baseline) and at Weeks 26, 52, 78, and 104 (the latter only for subjects who completed ≥ 6 months (26 weeks) of study drug treatment. Safety and efficacy data were obtained throughout the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 670 subjects

Actual: 682 subjects: ABT-335 + atorvastatin, 340 subjects; placebo + atorvastatin, 342 subjects

Diagnosis and Main Criteria for Inclusion:

Male and female subjects at least 45 years of age who had posterior wall IMT of the common carotid ≥ 0.7 mm on 1 side at baseline were eligible for the study if they had: a triglyceride (TG) level ≥ 150 mg/dL, and low value for high-density lipoprotein cholesterol (HDL-C) (male, ≤ 45 mg/dL; female, ≤ 55 mg/dL) after a 12-hour fasting period at Screening Visit(s); and, 1 LDL-C value ≤ 100 mg/dL and an average of 2 consecutive LDL-C values ≤ 105 mg/dL for ≥ 2 weeks prior to randomization, while receiving atorvastatin therapy at a daily dose ≤ 40 mg. They must also have had known coronary heart disease (CHD) or ≥ 1 prespecified CHD risk equivalents (e.g., previous myocardial infarction [MI] or stroke; type 2 diabetes mellitus). In addition, subjects must have had, in the opinion of the investigator, life expectancy longer than 30 months at the Pre-screening Visit.

Eligible subjects could not have had:

- evidence of unstable cardiovascular (CV) disease – MI, coronary artery bypass graft (CABG) surgery, or percutaneous coronary intervention (PCI) within 6 months of the Pre-screening Visit; unstable angina pectoris or uncontrolled cardiac arrhythmias within 3 months prior to the Pre-screening Visit; peripheral artery surgery (e.g., femoral-popliteal revascularization, abdominal aortic aneurysm repair, etc.) within 3 months of the Pre-screening Visit; or, $\geq 70\%$ stenosis of the carotid artery; OR

- any of the following diabetic conditions – type 1 diabetes mellitus, history of diabetic ketoacidosis, or uncontrolled type 2 diabetes mellitus (defined as hemoglobin A1c [HbA_{1c}] $> 10.5\%$); OR

- symptomatic heart failure (dyspnea at rest or with exertion); OR

- any of the following laboratory analyses at the Screening Visit(s): alanine transaminase (ALT), aspartate transaminase (AST), or bilirubin concentration $> 1.5 \times$ Upper Limit of Normal (ULN); creatine phosphokinase level $> 3.0 \times$ ULN; or estimated Glomerular Filtration Rate (eGFR) < 50 mL/min/1.73 m^2; OR

- history of prior surgical intervention to the carotid artery (including carotid endarterectomy).

Subjects could not have used any of the following excluded medications within the specified time frame relative to the Baseline Visit:

- bile acid binding resins, fish oil, or other agents, supplements, or nutritionals that alter lipid levels within 2 weeks,

- coumarin anticoagulants or systemic cyclosporine within 2 weeks,

- fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, pitavastatin, ezetimibe, or combination products containing any of these statins within 4 weeks,

- any investigational drug within 30 days,

- sibutramine or orlistat within 6 weeks,

- fibrate, niacin products (therapeutic dosages of niacin containing product for ≥ 1 month in the prior year or in the context of a clinical trial), and ABT-335 as part of a clinical study within 12 months.

Furthermore, eligible subjects could not have met the other criteria for exclusion.

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

ABT-335 (135 mg capsules): oral administration; bulk lot numbers 07-010421, 08-017869, 10-002303

Duration of Treatment:

Subjects self-administered study drug for up to 104 weeks during the Treatment Phase of the study.

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

ABT-335 matching placebo: capsule; oral administration; bulk lot numbers 07-010779, 08-019289

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the rate of change from baseline through Month 24 (Week 104) in mean posterior-wall IMT of the left and right common carotid arteries (CCA).

Safety:

Safety assessments included the monitoring and recording of adverse events throughout the study. In addition, physical examination was performed at baseline and at all study visits to evaluate symptoms or adverse events and clinical laboratory measurement and vital signs were evaluated at Screening, baseline, and routinely throughout the study. Electrocardiograms (ECGs) were evaluated at baseline and Week 104.

Statistical Methods

Efficacy:

Analysis Data Sets: For each cIMT parameter, the primary efficacy analysis set is the set of all randomized subjects who had both a baseline value and at least 1 postbaseline value for that parameter. For purposes of subject accountability, the Full Analysis Set is defined as the primary efficacy analysis set with mean posterior-wall IMT of the left and right CCA as the efficacy parameter.

For analyses of the laboratory efficacy parameters, the analysis set includes all randomized subjects who had both a baseline value and at least 1 postbaseline value for the parameter that was analyzed. Last observation carried forward (LOCF) was used to impute values for subjects missing a postbaseline value. Only postbaseline values were carried forward.

For analyses of CV outcome variables, the analysis set includes all randomized subjects. Subjects who were lost to follow-up or completed the study without having an event were censored at the date of last contact.

Primary Endpoint: The rate of change from baseline through Month 24 (Week 104) in mean posterior-wall IMT of the left and right CCAs was analyzed using a repeated measures linear mixed effects model with fixed effects for baseline mean cIMT value, central imaging site, baseline atorvastatin dose (10 mg, 20 mg, 40 mg), treatment group, time, and the interaction between treatment group and time. All analyses of the cIMT variables used an unstructured covariance matrix.

Statistical Methods (Continued)

Efficacy (Continued):

Primary Endpoint (Continued): Three sensitivity analyses were performed on the primary efficacy variable to assess the impact of missing data: 1) analysis of covariance (ANCOVA) with baseline mean cIMT value as the covariate, effects for central imaging site, baseline atorvastatin dose (10 mg, 20 mg, 40 mg), and treatment group and LOCF imputation, 2) repeated measures analysis using the multiple imputation approach to impute missing cIMT values, and 3) repeated measures analysis excluding all subjects enrolled and treated at 2 investigative sites ███████████ that had significant issues related to study non-compliance with Good Clinical Practice (GCP) and protocol requirements. This analysis was conducted to assess any potential impact of these investigative sites on the primary endpoint.

Subgroup analyses were specified for the following subgroups (based on baseline characteristics or values): age, gender, tobacco use, medical history of diabetes, metabolic syndrome status, medical history of hypertension, medical history of coronary artery disease, medical history of myocardial infarction, LDL-C levels, HDL-C levels, TG levels, non-HDL-C levels, high sensitivity C-reactive protein (hsCRP) levels, HDL-C and TG categories, apolipoprotein (apo) C3 levels, cIMT levels, statin usage, central imaging site, and anti-hypertensive medication usage.

Secondary Endpoints: `redacted information 03Jul2014`

If a statistically significant difference between treatment groups was observed for the primary analysis of the primary endpoint, the following 4 secondary endpoints were to be tested at the alpha = 0.05 level in the following fixed sequence:

1. Rate of change from baseline through Month 24 (Week 104) in mean of the maximal posterior-wall IMT of the left and right CCA.

2. Rate of change from baseline through Month 24 (Week 104) in the composite of the mean of the mean posterior-wall IMT of the left and right CCA, ICA, and carotid bifurcation.

3. Rate of change from baseline through Month 24 (Week 104) in the composite of the mean of the maximal posterior-wall IMT of the left and right CCA, ICA and carotid bifurcation.

4. Rate of change from baseline through Month 24 (Week 104) in the composite of the mean of the maximal posterior-wall and anterior-wall IMT of the left and right CCA, ICA and carotid bifurcation.

The rate of change in each secondary cIMT endpoint was to be analyzed in the same manner as the primary endpoint using a repeated measures linear mixed effects model.

Additional Efficacy Variables:

cIMT Variables

Additional cIMT endpoints included:

-   Rate of change from baseline through Month 24 (Week 104) in mean of the median, 10th percentile, and 90th percentile posterior-wall IMT of the left and right CCA, and

-   Rate of changes from baseline through Month 24 (Week 104) in mean posterior-wall IMT of the right and left carotid bifurcation and ICA.

The rate of change in each cIMT endpoint was analyzed in the same manner as the primary endpoint using a repeated measures linear mixed effects model.

Statistical Methods (Continued)

Additional Efficacy Variables:

Cardiovascular Events

Two composite clinical endpoints were analyzed: 1) the composite of CV mortality, non-fatal MI, and non-fatal stroke, and 2) the composite of CV mortality, non-fatal MI, non-fatal stroke, coronary revascularization, carotid endarterectomy/stenting, hospitalization for unstable angina, and hospitalization for congestive heart failure. The time to first event was compared between treatment groups using the Log-Rank test stratified by baseline atorvastatin dose (10 mg, 20 mg, 40 mg). A Cox proportional hazards model with baseline atorvastatin dose (10 mg, 20 mg, 40 mg) as a covariate was used to obtain the hazard ratio and the 95% CI for the hazard ratio. The analysis was based on adjudicated events.

Laboratory Parameters

For all efficacy laboratory parameters (including advanced lipid parameters by nuclear magnetic resonance [NMR] methodology) other than TG and hsCRP, the percent changes from baseline to each visit were compared between treatment groups using contrast statements within an ANCOVA with baseline value (lab parameter corresponding to the outcome variable modeled) as the covariate and with effects for baseline atorvastatin dose (10 mg, 20 mg, 40 mg), and treatment group.

A non-parametric analysis of the percent changes from baseline to each visit in TG and hsCRP was performed. That is, a Cochran-Mantel-Haenszel (CMH) mean score test using baseline atorvastatin dose (10 mg, 20 mg, 40 mg) as the stratification factor and modified ridit scores (i.e., van Elteren test) was performed to compare treatment groups.

Safety:

All randomized subjects who receive at least one dose of study drug were assessed for safety.

Analyses of adverse events included only treatment-emergent adverse events, defined as any adverse event that began on or after the first dose of study drug and no more than 30 days after the last dose of study drug. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percentage of subjects who reported treatment-emergent adverse events were tabulated by primary MedDRA system organ class and preferred term for each treatment group. Percentages for "any event" and for each preferred term were compared between treatment groups using Fisher's exact test.

Adverse events of special interest (renal, hepatic, and muscle events) were identified utilizing the most updated version of the appropriate MedDRA Standardized Medical Query (SMQ). The appropriate SMQs of MedDRA version 15.0 were "Rhabdomyolysis/myopathy (narrow search)," "Acute Renal Failure (narrow search)," and "Drug related hepatic disorder – comprehensive search."

Treatment group differences for mean changes from baseline to each visit were analyzed using one-way ANOVA for laboratory measurements (hematology, chemistry, and urinalysis) and vital sign measurements. An additional analysis was performed using the final value defined as the last nonmissing, postbaseline value collected within 30 days following the last dose of study drug. An analysis of changes in creatinine and eGFR from baseline to the Safety Follow-up Visit was also performed using a 1-way ANOVA.

The number and percentage of subjects in each treatment group who had at least 1 postbaseline value meeting criteria for potentially clinically significant values were provided for each laboratory parameter. Percentages were compared between the treatment groups using Fisher's exact test.

Summary/Conclusions

Efficacy Results:

In the primary analysis of the primary endpoint, ABT-335 therapy resulted in a decrease in mean posterior-wall IMT of the left and right CCA from baseline through Week 104 at a rate of –0.006 mm/yr, as compared to no change (0.000 mm/yr) with placebo, each added to background atorvastatin; the difference in the rate of change of posterior-wall cIMT between the 2 treatment groups was not statistically significant ($P = 0.220$). When analyzed for the absolute changes in mean posterior-wall cIMT using LOCF imputation, both treatment groups showed a decrease in posterior-wall cIMT at Week 104 compared to baseline, with results favoring the ABT-335 group but showing no statistically significant between-group differences.

There were 24 prespecified subgroup analyses based on demographics, lipids, medical history, or cIMT levels at baseline. In subgroup analyses of the primary efficacy endpoint (rate of change in posterior-wall IMT of CCA), the treatment-by-time-by-subgroup interaction test was statistically significant ($P \leq 0.05$) for subgroups based on: age, medical history of CAD, baseline TG by tertile, baseline cIMT by tertile, and baseline statin use. Treatment effect was larger (i.e., favored the ABT-335 group to a greater degree) among subjects ≥ 60 years old at baseline, those with a history of CAD (compared to no history of CAD), those with prior statin use (defined as any statin use in the 30-day period prior to the Pre-screening Visit), those in the highest tertile of baseline cIMT, and those in the middle tertile of baseline TG. The treatment effect favored the placebo group only for subjects categorized as statin naïve.

Since the primary endpoint did not demonstrate statistically significant between-group differences, the ranked order of the 4 secondary endpoints could not be tested as planned. Regardless, none of the secondary endpoints, or additional cIMT analyses, showed difference between two treatment groups that were statistically significant.

The event rate for the first occurrence of CV mortality, nonfatal MI, or nonfatal stroke was low in both treatment groups (1.8%), with no significant differences between the treatment groups (hazard ratio = 1.013; 95% CI 0.327, 3.141). The event rate for the first occurrence of CV mortality, non-fatal MI, non-fatal stroke, coronary revascularization, carotid endarterectomy/stenting, hospitalization for unstable angina, and hospitalization for congestive heart failure was also similar, with no significant differences between the two treatment groups (ABT-335: 4.1%, placebo: 4.7%).

ABT-335 therapy resulted in statistically significant decreases in TG (median change ranging from –27.6% to –31.3%) and increases in HDL-C (mean change ranging from 8.2% to 10.3%) throughout the treatment period, as compared to placebo. Changes in non-HDL-C (ranging from –0.1% to –3.7%) and VLDL-C (ranging from –5.0% to 2.9%) were also in favor of ABT-335 versus the placebo group. For LDL-C, both treatment groups increased LDL-C levels, with a greater increase in the ABT-335 group from baseline through Week 52, but the final visit values (Week 104) of LDL-C were similar in both treatment groups (ABT-335: 89.2 mg/dL, placebo: 90.6 mg/dL). However, the increase in apo B at the Week 104 visit was significantly greater in the placebo group compared to ABT-335 group (5.0% versus 0.7%, respectively; $P = 0.011$). Of note, the mean dose of atorvastatin background therapy at baseline was similar (21.2 mg) for both treatments. Atorvastatin dose or compliance to background therapy was not captured during the treatment period; however the atorvastatin dose was based on a prespecified algorithm to maintain LDL-C within the target range. For the analyses of other lipoproteins, there was a greater improvement in apo C3, apo B/apo A1, and apo B/(apo A1 + apo A2) at the Week 104 visit with ABT-335 treatment versus placebo.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Analyses of advanced lipid parameters by NMR were performed to assess changes in lipid particle size and concentration. ABT-335 therapy resulted in statistically significantly greater mean percent increases in LDL particle size. The change in total LDL particle concentration was also significantly greater with ABT-335 therapy, however the change in the concentration of small LDL particle was similar in the two treatment groups. For HDL, ABT-335 therapy resulted in statistically significantly greater mean percent increases in small, medium, and total particle concentrations and a greater mean decrease in particle size. For VLDL, ABT-335 therapy resulted in statistically significantly greater mean percent decreases in VLDL total concentration and particle size.

Exposure and Safety Results:

Approximately 87% of treated subjects completed at least 6 months of therapy and 69% of subjects completed the full 2 years of study.

Overall, the safety profile of adding ABT-335 to atorvastatin therapy over 2 years demonstrated that the combination therapy was safe and well tolerated. No new safety signals were identified.

A significantly greater percentage of subjects in the ABT-335 group discontinued from the study due to an adverse event (13.9% versus 6.5% in the placebo group, $P = 0.001$). Five subjects (1 in the ABT-335 group and 4 in the placebo group) died during the study. A similar proportion of subjects in the ABT-335 group and the placebo group experienced treatment-emergent adverse events (87.2% versus 90.9%, respectively). There were no statistically significant differences between treatment groups in the incidences of subjects experiencing possibly or probably drug-related adverse events, severe adverse events, or serious adverse events.

Overall, the adverse events associated with ABT-335 treatment were consistent with the known safety profile of ABT-335, except for diabetes mellitus or diabetes mellitus inadequate control. In this regard, the mean change in fasting glucose from Baseline to every visit was similar between the treatment groups, as was the mean change in HbA_{1c} at Week 104. There was a statistically significant between-group difference in HbA_{1c} at Week 52, most likely due to a reduction in HbA_{1c} in the placebo group. Of note, the change in HbA_{1c} from Baseline to final value was similar between the two treatment groups. A greater percentage of subjects in this study experienced adverse events of preferred terms of increased blood creatinine (6.5% versus 2.1%, $P = 0.004$), GFR decreased (4.2% versus 0.9%, $P = 0.007$), and renal failure (2.7% versus 0.3%, $P = 0.011$) with ABT-335 treatment than with placebo. However, most of these subjects with events of renal failure in the ABT-335 group were due to worsening of pre-existing renal impairment or due to increases in serum creatinine levels. In addition, most of these subjects had other comorbidities: 8 out of 9 subjects had hypertension and 5 out of 9 subjects had diabetes at baseline. Of note, there were no reported events of renal failure that required dialysis or renal transplant.

There was a statistically significantly higher incidence of reported adverse events of diabetes mellitus (8.0% versus 3.2%, $P = 0.007$) and diabetes mellitus inadequate control (1.5% versus 0%, $P = 0.030$) in the ABT-335 group than the placebo group. However, the majority of these events were due to worsening or exacerbation of pre-existing diabetes; 29 out of 32 subjects had prior medical history of diabetes mellitus, diabetes mellitus inadequate control, or glucose intolerance in the ABT-335 treatment group versus 11 of 11 subjects in the placebo group. Other reported adverse events with a statistically significantly higher incidence in the ABT-335 group than in the placebo group were the preferred terms of muscular weakness (2.1% versus 0.3%, $P = 0.038$) and pain in extremity (13.1% versus 7.7%, $P = 0.023$).

Summary/Conclusions (Continued)

Exposure and Safety Results (Continued):

Adverse events reported with a statistically significantly lower incidence in the ABT-335 group versus the placebo group were preferred terms of tooth infection (0.6% versus 3.5%, $P = 0.012$), laceration (0.6% versus 2.9%, $P = 0.037$), and hypertension (5.0% versus 10.6%, $P = 0.009$).

Safety Results:

The collective incidences of adverse events of special interest, based on Standard MedDRA Queries for "Rhabdomyolysis/myopathy (narrow search)," "Acute Renal Failure (narrow search)," and "Drug related Hepatic Disorder (comprehensive search)," were reported in a greater percentage of subjects in the ABT-335 group (8.9% versus 2.7% in the placebo group, $P < 0.001$). The majority of these cases were based on renal adverse events of special interest that occurred in 6.5% of subjects in the ABT-335 group and 0.9% of subjects in the placebo group. No subject experienced a muscle adverse event of special interest, and 2.7% and 1.8% of subjects experienced a hepatic adverse event of special interest in ABT-335 group versus placebo group, respectively.

In laboratory analyses, there were no clinically meaningful changes in hematology and in most chemistry variables over time. Consistent with expectations, the ABT-335 group showed mean increases in creatinine and BUN and mean decreases in eGFR at every visit from Week 6 to Week 104 (each $P < 0.001$ versus placebo at all visits).

Few subjects had potentially clinically significant hematology values, vital signs measurements, or ECGs, and subjects with potentially clinically significant observations either did not have associated adverse events or the events were considered not related or probably not related to study drug. More subjects in the ABT-335 group than in the placebo group had potentially clinically significant values for BUN (≥ 40 mg/dL) (5.4% versus 2.1%, $P = 0.039$) and eGFR (< 45 mL/min/BSA) (18.6% versus 5.1%, $P < 0.001$).

Conclusions:

In the study population of subjects with mixed dyslipidemia who had achieved LDL-C target goals while receiving atorvastatin, the addition of ABT-335 did not significantly produce an additional benefit in cIMT improvement above and beyond statin monotherapy. When LDL-C is optimally controlled by statin therapy, subjects in higher risk categories such as older age, prior history of CAD, or having thicker cIMT at baseline may achieve benefit from adding ABT-335 to statin therapy.