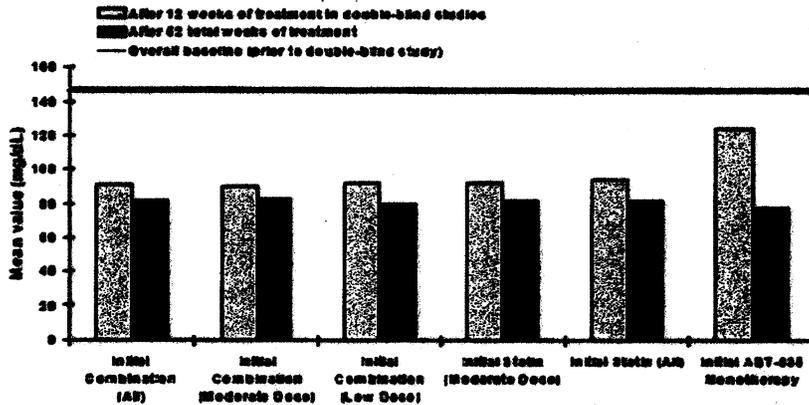


Figure 6.1.9.E. Mean Values for ApoB after 12 Weeks of Double-blind Treatment and after 52 Total Weeks of Treatment



### 6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses that were not already addressed in the subsections above.

## 7. INTEGRATED REVIEW OF SAFETY

### Summary of Safety Results and Conclusions

The safety of ABT-335 alone or in combination was primarily established from the three 12-week controlled trials, and the safety of the combination from the 1-year extension study of the moderate-dose statin + ABT-335 combinations.

There were eight deaths in the program; none appeared to be directly related to ABT-335 or combination therapy. The most common serious adverse events in the controlled studies were coronary artery disease and myocardial infarction. The most common serious adverse events in the All Combination Therapy analysis set were osteoarthritis, coronary artery disease, DVT, MI, chest pain, diverticulitis, and intervertebral disc protrusion.

The most common ( $\geq 1.0\%$  in any treatment group) adverse events that led to discontinuation from the controlled studies were myalgia, nausea, ALT increased, AST increased, and headache. The most common adverse events that led to discontinuation from the All Combination Therapy analysis set were ALT increased, AST increased, blood CPK increased, and myalgia.

The most frequently reported ( $\geq 5.0\%$  in any treatment group) adverse events in the controlled studies were headache, back pain, nasopharyngitis, nausea, myalgia, diarrhea, and upper respiratory tract infection. The most frequently reported adverse events in the All Combination Therapy analysis set were nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, arthralgia, back pain, and headache.

The sponsor appropriately focused the safety presentation on issues that are well-known to occur with fenofibrate and statins, and are likely to be enhanced with combination therapy: hepatic, muscle, and renal events. Although the focus was on the safety of the combination, the safety of ABT-335 as monotherapy was considered by this reviewer as well. The following table summarizes the incidence of adverse events of special interest in the controlled studies:

Table 7.A. Adverse Events of Special Interest, Controlled Studies

	ABT-335 N=490	Low-dose statin N=493	ABT-335 + low statin N=490	Moderate- dose statin N=491	ABT-335 + moderate statin N=489	High-dose statin N=245
Any AE of special interest	54 (11.0)	37 (7.5)	71 (14.5)	45 (9.2)	50 (10.2)	33 (13.5)
Hepatic events	19 (3.9)	3 (0.6)	31 (6.3)	4 (0.8)	22 (4.5)	6 (2.4)
Muscle events	27 (5.5)	32 (6.5)	38 (7.8)	41 (8.4)	26 (5.3)	25 (10.2)
Renal events	9 (1.8)	2 (0.4)	10 (2.0)	0	8 (1.6)	3 (1.2)

Findings are summarized as follows:

- **Hepatobiliary** (this reviewer includes biliary events given the described association of cholelithiasis with fenofibrate therapy): Overall, subjects treated with ABT-335, either alone or in combination with statins demonstrated more frequent increases in transaminases than subjects treated with statins alone (incidence: 3.9-6.3% vs. low- and moderate-dose statin incidence: 0.6-0.8%). An increase in risk of liver enzyme elevations in the combination of statin + ABT-335 as compared to the ABT-335 monotherapy, if any, was small. The risk of the combination appears to be somewhat higher with the addition of atorvastatin at the studied doses, in contrast to simvastatin or rosuvastatin. It is reassuring that no subject treated with ABT-335 met criteria for Hy's law and no subject experienced hepatic failure. Most of the findings were seen early on, in the first 3-6 months. Biliary events, such as cholelithiasis and cholecystitis were infrequent (< 1%).
- **Muscle**: In the clinical studies, increases in CK and adverse events of myalgia appear to be associated with statin use. Given that the combination therapy did not have consistently higher incidences of muscle events than statin therapy alone, and the greatest proportions of events appear to be in the high dose statin monotherapy groups, co-administration within this clinical program did not highlight any particular muscle safety concerns. This reviewer agrees that ABT-335 should not be administered with the highest dose of statin until this combination is specifically studied and safety is demonstrated. It appears that the incidence of CK elevations (but not adverse events of muscle events) were highest in the groups that included rosuvastatin, which is consistent with mean changes in CK laboratory values. It is reassuring that there were no cases of 'rhabdomyolysis' or 'myopathy' in any of the submitted AE datasets, although one case of rhabdomyolysis was described in a narrative of a patient hospitalized with gastroenteritis and dehydration, who ultimately remained on the drug, and one case of rhabdomyolysis was reported in a still-blinded study (described in the 4-month safety update). The majority of subjects who had reported muscle-related adverse events did not prematurely discontinue due to the event. For the most part, CK elevations

that occurred on drug decreased or were decreasing after study drug was discontinued, and in some cases decreased while the treatment was continued.

- **Renal:** In general, the renal events associated with ABT-335 treatment were comprised primarily of increases in BUN and serum creatinine (reflected by decreases in calculated creatinine clearance), a described effect of fenofibrate treatment.<sup>10</sup> The combination of ABT-335 and a statin did not appear to increase the risk of renal events beyond that of ABT-335 alone. Modest renal laboratory changes (increases in BUN and creatinine > ULN) were relatively common in the ABT-335 groups, but laboratory changes considered to be clinically important and events of renal failure or insufficiency occurred infrequently. Subjects with renal impairment (calculated creatinine clearance < 60 mL/min) appeared to be more susceptible to the serum creatinine increasing effects of ABT-335, but there were few subjects in this subgroup. Subjects with diabetes had slightly higher incidences of renal events overall (primarily due to elevations in creatinine) in the ABT-335 groups, which may be a reflection of an increased incidence of renal dysfunction. The numbers of events, however, were small and the patients with diabetes in these studies were relatively well-controlled, so safety in this group may not be generalizable to the overall diabetes population. Older subjects also appear to be more susceptible to increased creatinine with the combination of ABT-335 + statin as compared to younger subjects; again, this may reflect decreased renal function in this population. Serum creatinine should be monitored in those with renal insufficiency, and at-risk groups such as diabetics and the elderly. A lower dose of ABT-335 is indicated based on PK data in subjects with mild to moderate renal insufficiency. ABT-335 is contraindicated in patients with severe renal insufficiency.

## 7.1 Methods

### 7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

This reviewer primarily focused on the phase 3 clinical studies for assessment of safety: the controlled studies M05-748, -749, and -750, and the open-label extension study M05-758. The phase 1 studies were reviewed for deaths, SAEs, and AEs of particular importance or interest.

In study M05-758, each subject received once daily ABT-335 135 mg in combination with the statin used in the controlled study that the subject completed. The statin used in combination with ABT-335 was rosuvastatin 20 mg in 1029 subjects from M05-748, simvastatin 40 mg in 432 subjects from M05-749, and atorvastatin 40 mg in 434 subjects from M05-750. The duration of M05-758 was 52 weeks of therapy, followed by a safety follow-up period for 30 days after the last dose of study drug.

### 7.1.2 Adequacy of Data

This reviewer audited the datasets by looking at verbatim terms of subjects prematurely discontinued from study M05-758, and focusing on adverse events of interest (hepatobiliary, muscle, and renal). For the most part, the mapped MedDRA Preferred Terms were a reasonable match to the verbatim terms, with the exception of one subject treated with ABT-335 + rosuvastatin who had a verbatim term of 'abnormal serum c.k. 888 (nl 18-198)', which mapped to the PT 'laboratory test abnormal'. This would underestimate the number of muscle events in that group. However, this reviewer did not detect a systemic problem with the data overall.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

#### *Phase 1 Studies*

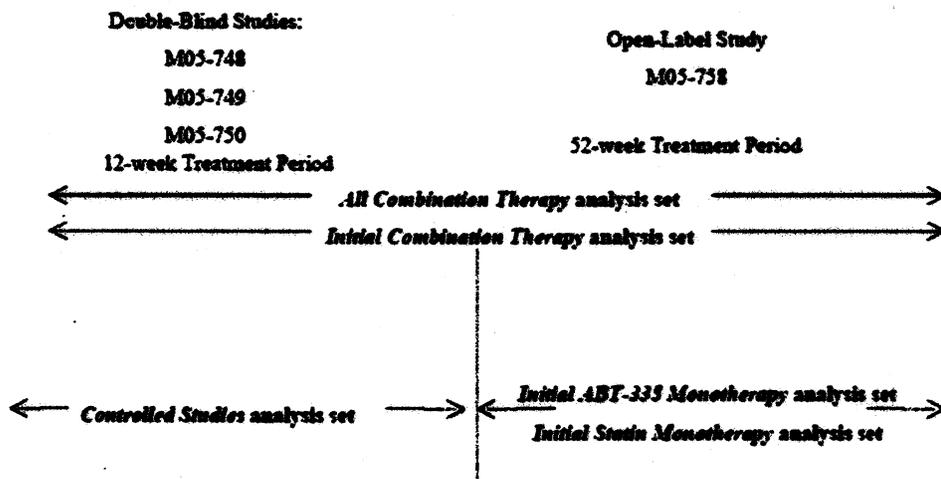
Safety data from the Phase 1 studies were based on one analysis set that combined all subjects receiving ABT-335.

#### *Phase 3 Studies*

The figure below describes the various analysis sets the sponsor used to evaluate the safety in the Phase 3 trials. This reviewer focused most of the review on the safety findings from the three controlled studies individually and combined (Controlled Studies analysis set) and those of the open-label study, for the most part combined with its corresponding double-blind studies (All Combination Therapy and Initial Combination Therapy analysis sets). Other analyses are presented when relevant. The descriptions of these analyses provided by the sponsor are included below for completeness.

**Comment:** The sponsor's pooling strategy (analysis sets described below) was an acceptable approach to the safety analysis.

Figure 7.1.3.A. Phase 3 Controlled Studies and Integrated Long-Term Analysis Sets



#### Controlled Studies Analysis Set

The Controlled Studies analysis set included all subjects who were randomized in one of the double-blind, controlled studies (M05-748, M05-749, and M05-750) and received at least one dose of study drug. Data were integrated by combining the following treatment groups to form six treatment groups:

- ABT-335 monotherapy

- Low-dose statin monotherapy (10 mg rosuvastatin, 20 mg simvastatin, 20 mg atorvastatin)
- ABT-335 in combination with low-dose statin therapy (ABT-335 + 10 mg rosuvastatin, ABT-335 + 20 mg simvastatin, ABT-335 + 20 mg atorvastatin)
- Moderate-dose statin monotherapy (20 mg rosuvastatin, 40 mg simvastatin, 40 mg atorvastatin)
- ABT-335 in combination with moderate-dose statin therapy (ABT-335 + 20 mg rosuvastatin, ABT-335 + 40 mg simvastatin, ABT-335 + 40 mg atorvastatin)
- High-dose statin monotherapy (40 mg rosuvastatin, 80 mg simvastatin, 80 mg atorvastatin)

### Phase 3 Integrated Long-Term Analysis Sets

In the open-label safety study (M05-758), all subjects received combination therapy with ABT-335 and a statin at the moderate dose. The statin used by each subject in Study M05-758 was the same statin used in the double-blind, controlled study in which that subject was enrolled.

Analyses of data collected across both the double-blind, controlled and open-label studies (Studies M05-748, M05-749, M05-750 and M05-758) were performed for the following four analysis sets:

- **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 the open-label study. All data collected across the double-blind, controlled studies as well as the open-label study during exposure to ABT-335 in combination with the low or moderate statin dose were summarized by type of statin as well for all subjects in this analysis set combined.
- **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 the open-label study. Subjects who received combination therapy with the low statin dose in the double-blind, controlled studies and did not enroll in the open-label study were excluded from this analysis set. All data collected across the double-blind, controlled studies as well as the open-label study during exposure to ABT-335 in combination with the moderate statin dose were summarized by type of statin as well for all subjects in this analysis set combined.
- **Initial Combination Therapy:** Included all subjects who were randomized to and 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. Subjects who received ABT-335 monotherapy or statin monotherapy in the double-blind, controlled studies were excluded from this analysis set. All data collected across the double-blind, controlled studies as well as the open-label study during exposure to ABT-335 in combination with the low or moderate statin dose were summarized by type of statin as well for all subjects in this analysis set combined.
- **Initial Combination Therapy at the Moderate Statin Dose:** Included all subjects who were randomized to and 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. Subjects who received ABT-335 monotherapy, statin monotherapy, or ABT-335 in combination with either 10 mg rosuvastatin, 20 mg simvastatin, or 20 mg atorvastatin in the double-blind, controlled studies were excluded from this analysis set. All data collected across the double-blind, controlled studies as well as the open-label study during exposure to

ABT-335 in combination with the moderate statin dose were summarized by type of statin as well for all subjects in this analysis set combined.

### Open-Label Study Analysis Sets

Analyses for the following two analysis sets were limited to data of ABT-335 in combination with moderate-dose statin from the open-label study (M05-758):

- **Initial Statin Monotherapy:** Included all subjects who were randomized to and received at least one dose of statin 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 ABT-335 in combination with moderate-dose statin in the open-label study. Data collected in the open-label study during exposure to ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin were summarized by type of statin as well for all subjects in this analysis set combined.
- **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 ABT-335 in combination with moderate-dose statin in the open-label study. Data collected in the open-label study during exposure to ABT-335 in combination with either 20 mg rosuvastatin, 40 mg simvastatin, or 40 mg atorvastatin were summarized by type of statin as well for all subjects in this analysis set combined.

## **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

#### *Phase 1 trials*

A total of 500 subjects received study drug in the 13 Phase 1 studies. Of these, 495 received at least one dose of ABT-335 (477 single dose, 18 multiple dose) and five subjects received a single dose of placebo.

#### *Phase 3 trials*

### Duration of exposure to study drug for the Controlled Studies Analysis Set

Study drug interruption data were not used in calculating duration of treatment and, therefore, some subjects had a calculated treatment duration > 12 weeks. A total of 1230 subjects were exposed for > 75 days (10+ weeks) to ABT-335, either as monotherapy or in combination with a statin. A total of 828 subjects were randomized to combination therapy for this duration in the controlled studies.

**Table 7.2.1.A. Duration of Exposure, Controlled Studies Analysis Set**

Duration Interval (days)	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + low statin (N=490)	Moderate-dose statin (N=491)	ABT-335 + moderate statin (N=489)	High-dose statin (N=245)
1 to 15	26 (5.3)	11 (2.2)	14 (2.9)	16 (3.3)	17 (3.5)	10 (4.1)
16 to 30	15 (3.1)	7 (1.4)	12 (2.4)	10 (2.0)	18 (3.7)	9 (3.7)
31 to 45	18 (3.7)	11 (2.2)	26 (5.3)	11 (2.2)	13 (2.7)	4 (1.6)
46 to 60	16 (3.3)	4 (0.8)	12 (2.4)	7 (1.4)	10 (2.0)	5 (2.0)
61 to 75	13 (2.7)	12 (2.4)	12 (2.4)	5 (1.0)	17 (3.5)	5 (2.0)
> 75	402 (82.0)	448 (90.9)	414 (84.5)	442 (90.0)	414 (84.7)	212 (86.5)
<b>Summary Statistics (days)</b>						
Mean (SD)	76.4 (22.86)	81.4 (15.90)	78.6 (20.19)	80.5 (18.40)	78.3 (20.61)	78.6 (20.58)
Median	85	85	85	85	85	85
Min, max	1, 113	1, 107	1, 127	1, 119	1, 110	1, 142

**Duration of exposure to study drug for the All Combination Therapy Analysis Set**

A total of 1661 subjects have been exposed to the ABT-335 + statin combination for  $\geq 24$  weeks and 568 subjects have been exposed to this combination for at least one year.

**Table 7.2.1.B. Duration of Exposure, All Combination Therapy Analysis Set**

Duration Category (weeks)	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	Total (N = 2201)
< 4	31 (2.6)	20 (3.9)	17 (3.4)	68 (3.1)
$\geq 4$	1155 (97.4)	494 (96.1)	484 (96.6)	2133 (96.9)
$\geq 8$	1093 (92.2)	480 (93.4)	457 (91.2)	2030 (92.2)
$\geq 12$	1038 (87.5)	456 (88.7)	439 (87.6)	1933 (87.8)
$\geq 24$	911 (76.8)	366 (71.2)	384 (76.6)	1661 (75.5)
$\geq 36$	808 (68.1)	247 (48.1)	297 (59.3)	1352 (61.4)
$\geq 48$	484 (40.8)	108 (21.0)	164 (32.7)	756 (34.3)
$\geq 52$	365 (30.8)	81 (15.8)	122 (24.4)	568 (25.8)
$\geq 64$	93 (7.8)	16 (3.1)	30 (6.0)	139 (6.3)
<b>Summary Statistics (days)</b>				
Mean (SD)	267.9 (127.32)	223.2 (114.62)	252.3 (124.15)	254.4 (124.89)
Median	281	216	279	279
Min, max	1, 482	1, 460	1, 476	1, 482

**Duration of exposure to study drug for the All Combination Therapy at the Moderate Statin Dose Set**

A total of 1636 subjects have been exposed to the ABT-335 + moderate-dose statin combination for  $\geq 24$  weeks and 425 subjects have been exposed to this combination for at least 1 year.

Table 7.2.1.C. Duration of Exposure, All Combination Therapy at the Moderate Statin Dose Analysis Set

Duration Category (weeks)	ABT-335 + rosuva (N = 1112)	ABT-335 + simva (N = 473)	ABT-335 + atorva (N = 469)	Total (N = 2054)
< 4	31 (2.8)	15 (3.2)	15 (3.2)	61 (3.0)
≥ 4	1081 (97.2)	458 (96.8)	454 (96.8)	1993 (97.0)
≥ 8	1037 (93.3)	446 (94.3)	435 (92.8)	1918 (93.4)
≥ 12	996 (89.6)	429 (90.7)	423 (90.2)	1848 (90.0)
≥ 24	899 (80.8)	356 (75.3)	381 (81.2)	1636 (79.6)
≥ 36	782 (70.3)	217 (45.9)	275 (58.6)	1274 (62.0)
≥ 48	408 (36.7)	84 (17.8)	140 (29.9)	632 (30.8)
≥ 52	276 (24.8)	59 (12.5)	90 (19.2)	425 (20.7)
≥ 64	47 (4.2)	7 (1.5)	12 (2.6)	66 (3.2)
<b>Summary Statistics (days)</b>				
Mean (SD)	267.2 (114.52)	224.6 (103.74)	251.2 (110.65)	253.7 (112.51)
Median	280	203	279	279
Min, max	1, 482	1, 460	1, 460	1, 482

**Comment:** The exposure to the investigational drug ABT-335 is adequate to assess its safety. The exposure of the combination of ABT-335 with the HMG-CoA reductase inhibitors rosuvastatin, simvastatin, and atorvastatin is adequate to rule out a significant safety concern for combination therapy at statin low- and moderate-doses, although rare events, such as rhabdomyolysis, cannot be excluded. The combination was not studied with statins at high doses, and therefore safety of this combination cannot be determined.

#### *Demographics*

##### Phase 1 trials

Of the 495 subjects who received at least one dose of ABT-335 in the Phase 1 studies, the majority were male (62.6%), White (73.3%), and non-Hispanic (91.1%). Per protocol, all subjects were required to be < 65 years of age; mean age was 35.8 years. Most subjects had a body weight ≥ 70 kg.

##### Phase 3 trials

The demographics for the controlled studies were presented in Section 6.1.3 in the Efficacy section. The following table summarizes the demographic and other baseline characteristics for those subjects who continued on into the open-label study.

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Table 7.2.1.D. Demographic and Baseline Characteristics for Study M05-758

Demographic Characteristic	Treatment Group n (%)			Total (N = 1809)
	ABT-335 + 20 mg rosuv (N = 1029)	ABT-335 + 40 mg simva (N = 432)	ABT-335 + 40 mg atorva (N = 434)	
<b>Sex</b>				
Female	521 (50.6)	216 (50.0)	213 (49.1)	950 (50.1)
Male	508 (49.4)	216 (50.0)	221 (50.9)	945 (49.9)
<b>Race</b>				
White	959 (93.2)	413 (95.0)	407 (93.8)	1779 (98.9)
Black	53 (5.2)	9 (2.1)	12 (2.8)	74 (3.9)
Other	17 (1.7)	10 (2.3)	15 (3.5)	42 (2.2)
<b>Ethnicity</b>				
Hispanic	91 (8.8)	43 (10.0)	30 (6.9)	164 (8.7)
No ethnicity	938 (91.2)	389 (90.0)	404 (93.1)	1731 (95.3)
<b>Nicotine Use</b>				
User	239 (23.2)	95 (22.0)	79 (18.2)	413 (21.8)
Ex-User	296 (28.8)	130 (30.1)	132 (30.4)	558 (29.4)
Non-User	494 (48.0)	207 (47.9)	223 (51.4)	924 (48.8)
<b>Alcohol Use</b>				
Drinker	518 (50.3)	236 (54.6)	238 (54.8)	992 (52.3)
Ex-Drinker	77 (7.5)	33 (7.6)	26 (6.0)	136 (7.2)
Non-Drinker	434 (42.2)	163 (37.7)	170 (39.2)	767 (40.5)
<b>Age Group (years)</b>				
< 65	847 (82.3)	374 (86.6)	348 (79.2)	1569 (82.8)
≥ 65	182 (17.7)	58 (13.4)	86 (19.8)	326 (17.2)
<b>Body Weight (kg)</b>				
< 70	128 (12.4)	56 (13.0)	45 (10.4)	229 (12.1)
≥ 70	901 (87.6)	376 (87.0)	389 (89.6)	1666 (87.9)

Note: Includes data collected in Studies M05-748, M05-749, and M05-750 for subjects who enrolled in Study M05-758.

## 7.2.2 Explorations for Dose Response

Only one dose of ABT-335 was studied in the Phase 3 studies: the higher 135 mg dose. A biowaiver has been requested for the 45 mg dose to be used in patients with decreased renal function and for certain patients with hypertriglyceridemia. ABT-335 was studied in combination with statins at a low-dose and moderate-dose, which in practice would allow for some statin titration if necessary prior to adding ABT-335.

**Comment:** The study of a single dose adequately represents how fibrates are administered in clinical practice for most patients with mixed dyslipidemia.

It should be recognized that the potency of the statins differ, and therefore this difference should be taken into consideration when comparing the safety profile across the combinations. In the CURVES study, which compared efficacy of atorvastatin versus other statins, simvastatin was approximately 75% as potent as atorvastatin (evaluating TC).<sup>25</sup> In the STELLAR trial, atorvastatin was 80-87% and simvastatin was 60-70% as

25 Jones P, et al. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and

potent as rosuvastatin (evaluating LDL-C).<sup>26</sup> Nevertheless, in these studies, low-dose for both atorvastatin and simvastatin was considered to be 20 mg and moderate-dose 40 mg. The low- and moderate-dose for rosuvastatin was considered to be 20 mg and 40 mg, respectively in the STELLAR trial, despite the fact that 40 mg is the highest approved dose for rosuvastatin.

### 7.2.3 Special Animal and/or In Vitro Testing

Animal and *in vitro* studies were conducted under NDA 19-304, the original NDA for fenofibrate, and reports of the pharmacological activity, metabolism, pharmacokinetics, and toxicology refer to the fenofibrate NDA. FDA agreed with the conduct of 13-week bridging studies in rat and dog with fenofibric acid and fenofibrate during a pre-IND meeting on May 25, 2004, assuming exposure to fenofibric acid in humans was no greater than 200 mg of micronized fenofibrate.

### 7.2.4 Routine Clinical Testing

In the three randomized, controlled trials, the following safety assessments were done at baseline and each study visit:

- Vital signs: blood pressure, pulse rate, body temperature, and weight
- Laboratory: chemistry (sodium, potassium, BUN, creatinine, calculated creatinine clearance, glucose, total protein, albumin, total bilirubin, calcium, inorganic phosphorus, uric acid, AST, ALT, CPK, alkaline phosphatase, TSH, and hemoglobin A<sub>1c</sub>), hematology (WBC, basophils, eosinophils, neutrophils, lymphocytes, monocytes, RBC, hemoglobin, hematocrit, and platelet count), urinalysis (specific gravity, ketones, pH, protein, blood, glucose and microscopic analysis as needed), and pregnancy tests in females of childbearing potential

In the randomized, controlled trials, ECG was performed at baseline and at the Final/Discontinuation visit.

This schedule of routine clinical testing was continued into the open-label study, M05-758.

**Comment:** It is noted that homocysteine was not measured as a safety variable.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 (Clinical Pharmacology).

**Comment:** Evaluation of interactions between the studied statins and ABT-335 (or fenofibrate) appears reasonable.

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fluvastatin in patients with hypercholesterolemia (The CURVES Study). *Amer J Cardiol* 1998. 81(5):582-7.  
26 Jones PH, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003. 92(2):152-60.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Because the safety profile of gemfibrozil, the other fibrate approved in the U.S., has a somewhat different safety profile than fenofibrate<sup>27</sup> (the pro-drug of fenofibric acid, ABT-335) this review will focus on fenofibrate-related issues specifically. Fenofibrate is associated with elevations in transaminases, and rarely, liver toxicity; myalgias and increases in CKs, and rarely, rhabdomyolysis; increases in creatinine of undetermined significance, and gallbladder events, including cholelithiasis. Furthermore, in a large outcomes study in patients with type 2 diabetes (FIELD study<sup>6</sup>), increased numbers of deep vein thrombosis, pulmonary embolus, and pancreatitis were noted as compared to placebo.

**Comment:** The sponsor analyzed the following adverse events of special interest separately: muscle events, renal events, and hepatic events, and these analyses are reviewed under Section 7.3.5. Laboratory abnormalities associated with these events were evaluated by the sponsor, and in general, cutoffs and analyses were appropriate. MedDRA Preferred Terms searched by the sponsor in the NDA database for these events are listed below. In terms of assessing the adequacy of these pre-specified lists, this reviewer noted that the Preferred Term *hepatitis* was omitted from the hepatic events list. One case of treatment-emergent hepatitis as a lower level term identified by this reviewer was not captured in the sponsor's liver analysis. In addition, in the Preferred Terms for renal events list, *renal disorder* and *blood urea increased* were omitted, with 1 and 4 subjects in the controlled trials, and 0 and 15 additional subjects in the open-label trial reporting these events, respectively.

This reviewer conducted several additional analyses, which are presented in section 7.3.5. Other events deemed important with use of fenofibrate are also evaluated in section 7.3.5.

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<sup>27</sup> Holoshitz N, et al. Relative Safety of Gemfibrozil and Fenofibrate in the Absence of Concomitant Cerivastatin Use. *Amer J Cardiol* (2008). 101(1):95-7.

Table 7.2.6.A. Preferred Terms – Muscle and Renal Events

Preferred Terms for Muscle Events	Preferred Terms for Renal Events
Muscle enzymes increased	Creatinine renal clearance decreased
Myositis	Blood creatinine increased
Muscle necrosis	Blood creatinine abnormal
Rhabdomyolysis	Renal failure
Blood creatine phosphokinase MM increased	Renal failure acute
Blood creatine phosphokinase increased	Renal failure chronic
Blood creatine phosphokinase abnormal	Renal impairment
Myalgia	Acute prerenal failure
Musculoskeletal discomfort	Anuria
Musculoskeletal pain	Azotaemia
Myoglobin blood increased	Dialysis
Myoglobin urine present	Haemodialysis
Mitochondrial myopathy	Hepatorenal failure
Myoglobinuria	Hepatorenal syndrome
Myoglobinuriaemia	Nephropathy toxic
Myopathy	Oliguria
Myopathy toxic	Postrenal failure
	Renal tubular necrosis
	Nephritis interstitial
	Glomerulonephritis

Table 7.2.6.B. Preferred Terms – Hepatic Events

Hepatic enzyme abnormal	Cytolytic hepatitis
Hepatic enzyme increased	Hepatic calcification
Liver function test abnormal	Hepatic fibrosis
Hepatic cirrhosis	Hepatic infiltration eosinophilic
Hepatocellular damage	Hepatic steatosis
Hepatic necrosis	Hepatitis acute
Liver disorder	Hepatitis cholestatic
Hepatic encephalopathy	Hepatitis fulminant
Hepatic failure	Hepatitis toxic
Coma hepatic	Hepatobiliary disease
Hepatic function abnormal	Hepatorenal failure
Alanine aminotransferase increased	Hepatorenal syndrome
Aspartate aminotransferase increased	Hepatotoxicity
Alanine aminotransferase abnormal	Hyperammonaemia
Aspartate aminotransferase abnormal	Jaundice cholestatic
Gamma-glutamyltransferase increased	Jaundice hepatocellular
Gamma-glutamyltransferase abnormal	Liver transplant
Jaundice	Ocular icterus
Ascites	Yellow skin
Asterixis	Blood bilirubin increased
Biliary cirrhosis	Blood bilirubin abnormal
Biliary cirrhosis primary	Bilirubin conjugated increased
Biliary fibrosis	Blood bilirubin unconjugated increased
Cryptogenic cirrhosis	

## 7.3 Major Safety Results and Discussion

### 7.3.1 Deaths

There were no deaths in the Phase 1 studies.

There were eight deaths in the Phase 3 studies: one in study M05-748, one in study M05-749, none in study M05-750, and six in study M05-758. Deaths are tabulated for the *Controlled Studies* and *Combination Therapy* analysis sets, respectively. Because only two subjects' adverse events were actually reported in the study M05-758 dataset as leading to death – the other subjects either died after the AE follow period (> 30 days after discontinuation of the study) or were presumably discontinued from the study prior to death – MedDRA SOCs and Preferred Terms were not assigned the deaths for Combination Therapy table (Table 7.3.1.B); rather, they are listed and grouped as deemed appropriate by this reviewer.

Table 7.3.1.A. Deaths, Controlled Studies

System Organ Class Preferred Term	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + low statin (N=490)	Moderate-dose statin (N=491)	ABT-335 + moderate statin (N=489)	High-dose statin (N=245)
Any Death	1 (0.20)	0	0	0	0	1 (0.41)
Infections and Infestations	1 (0.20)	0	0	0	0	0
Sepsis	1 (0.20)	0	0	0	0	0
Injury, Poisoning and Procedural Complications	0	0	0	0	0	1 (0.41)
Gun shot wound	0	0	0	0	0	1 (0.41)

Table 7.3.1.B. Deaths, Combination Therapy

	Treatment Group a (%)			Total (N=2201)
	ABT-335 + rosuva (N=1186)	ABT-335 + simva (N=514)	ABT-335 + atorva (N=501)	
Any Death	3 (0.25)	2 (0.39)	1 (0.20)	6 (0.27)
Cardiac Disorders	3 (0.25)	1 (0.19)	1 (0.20)	5 (0.23)
Congestive heart failure and myocardial infarction	1 (0.08)	0	0	1 (0.04)
Unresponsive cardiac arrest	1 (0.08)	0	0	1 (0.04)
Coronary artery disease, post-CABG complications	1 (0.08)	0	0	1 (0.04)
Sudden death	0	1 (0.19)	0	1 (0.04)
Found dead	0	0	1 (0.20)	1 (0.04)
Respiratory, Thoracic And Mediastinal Disorders	0	1 (0.19)	0	1 (0.04)
Post-syncopal respiratory arrest	0	1 (0.19)	0	1 (0.04)

Narratives and CRFs for all the deaths were reviewed. Narratives are summarized below under study by subject number and treatment group in parentheses. The reviewer's impression of the case is presented at the end of each narrative.

#### Study M05-748

Subject 13315 (ABT-335 135 mg) was a 76-year-old white female with a history of peripheral vascular disease, hypertension, chronic normochromic normocytic anemia, obesity, and mixed hyperlipidemia. Concomitant medications included indomethacin, furosemide, potassium,

levothyroxine, moexipril, cilostazol, telmisartan, and loperamide. She was a non-smoker and non-drinker.

The subject was treated with study drug for five days after a diet run-in and hypolipidemic washout, at which time she was discontinued due to an adverse event of diarrhea. Of note, the subject had taken cefdinir and cetirizine from Day -7 and Day -1 for "sinusitis". Five days after the study drug was discontinued, the subject presented to the emergency room with complaints of severe coughing and wheezing, which had reportedly worsened over the last 3 days, although she reported being "sick" for 3 weeks. The subject was found to have a temperature of 99.3 degrees F, scattered rhonchi and wheezing, with a non-productive cough. Blood urea nitrogen was 57 mg/dL and creatinine 2.2 mg/dL (creatinine on the first day of drug administration was 1.0 mg/dL). A chest x-ray showed no pulmonary disease. She was hospitalized for further evaluation and was treated with IV corticosteroids and vancomycin.

On Day 11, a physical assessment revealed the subject's left leg pulse was undetectable. Following a surgical consultation, the subject was apparently going to be taken to the operating room with a diagnosis of deep vein thrombosis. En route to surgery, the subject had a cardiac arrest with successful cardiopulmonary resuscitation. She was transferred to the intensive care unit, placed on a ventilator, and subsequently developed a tachyarrhythmia and was started on amiodarone. She was also treated with moxifloxacin. At that time, her husband reported the subject's request for refusal of resuscitative measures. The subject experienced a subsequent cardiac arrest and was not resuscitated. According to the investigator, the probable cause of death was septic shock, although pulmonary embolus was also mentioned on the CRF, but changed as it contradicted a diagnosis written elsewhere. Next of kin declined an autopsy and further information regarding the subject's condition prior to her death was not provided.

**Comment:** This case is somewhat confusing, in that the subject had several symptoms consistent with infection (diarrhea, cough, history of sinusitis) and treatment with multiple antibiotics, she presented to the emergency room with respiratory symptoms and renal failure, and the event that appeared to immediately precede the arrest was an arterial compromise (lack of leg pulse) in this patient with a history of peripheral vascular disease. However, she apparently was going to surgery for treatment of deep vein thrombosis. The cause of death by the investigator was initially reported as pulmonary embolus, which was subsequently changed to septic shock. The cause of her renal failure was not explained. Unfortunately, an autopsy was not done. It seems unlikely that ABT-335 directly contributed to death as she was only exposed for five days, although given the uncertainty of the diagnosis and the rapidity of decline, it is conceivable that an adverse drug reaction could have contributed to some portion of the presentation and/or outcome. The renal failure upon presentation is concerning, but there is not enough information in the setting of other findings to determine its etiology.

#### Study M05-749

Subject 21045 (simvastatin 80 mg) was a 50-year-old white female with a history of depression/bipolar disorder, angina, transient ischemic attack, hypertension, gastroesophageal reflux disease, diabetes mellitus, obesity, hyperlipidemia, and urinary tract infection, who was

taking the following medications: aripiprazole, valproic acid, hyoscyamine, benazepril, fluvoxamine, nitrofurantoin, rosiglitazone, insulin glargine, and triamterene/hydrochlorothiazide. The subject had a 27-pack-year history of cigarette smoking and was a light drinker. On Day 41, the subject died from a gunshot wound to the head. On Day 45, the investigator learned of the subject's death from local media coverage. No further information was provided.

**Comment:** It is difficult to attribute this event to the study drug (simvastatin) as few details were provided. This reviewer is assuming that the incident was a suicide without evidence suggesting otherwise. Large trials of simvastatin and other statins have not demonstrated an increased risk of suicide mortality,<sup>28</sup> although psychiatric adverse events, including depression, have been reported with the statins (simvastatin in particular).<sup>29,30,31</sup> The subject's history of mental illness is the most likely contributing factor, however.

#### Study M05-758

Subject 11007 (ABT-335 135 mg and rosuvastatin 20 mg) was a 52-year-old white Hispanic female with a history of diabetes mellitus, hypertension, chronic anemia, angina, left ventricular hypertrophy, left axis deviation and flattened T-waves on ECG, peripheral vascular disease, hyperlipidemia, and decreased creatinine clearance who was taking metformin, glibenclamide, acetylsalicylic acid, isosorbide, nifedipine, pioglitazone, metoprolol, telmisartan, hydrochlorothiazide, and ferrous sulfate. The subject was a non-smoker and non-drinker. She was originally treated with ABT-335 + rosuvastatin 10 mg in the M05-748 study. On Day 330, the subject was reported to have pedal edema and was taken to \_\_\_\_\_ ER where she received unknown treatment, and was released the same day. On Day 333, the subject was hospitalized with shortness of breath and edema. Study drug was discontinued on Day 333. On Day 334 (Post Treatment Day 1), the subject was reported to have suffered two heart attacks prior to her death. The death certificate reports the cause of death as acute myocardial infarction, ischemic cardiopathy, and diabetes mellitus. No further information was available. The investigator reported AEs of congestive heart failure and myocardial infarction, with MI as the cause of death.

b(6)

**Comment:** The subject's medical history, including diabetes, left ventricular hypertrophy, and vascular disease were the likely contributors to CHF and MI leading to death.

Subject 12121 (ABT-335 135 mg and rosuvastatin 20 mg) was a 66-year-old white female with a history of hypertension, diabetes mellitus, chronic mild kidney disorder, emphysema/chronic obstructive pulmonary disorder, schizoaffective disorder, insomnia, anxiety disorder, osteoarthritis, and hyperlipidemia. Concomitant medications at the time of the event included lorazepam, zopiclone, benzatropine, olanzapine, metformin, ipratropium, bisoprolol, pregabalin,

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28 Brunner J, et al. Cholesterol, essential fatty acids, and suicide. *Pharmacopsychiatry* 2002. 35(1):1-5.

29 Boumendil E and Tubert-Bitter P. Depression-induced absenteeism in relation to antihyperlipidemic treatment: A study using GAZEL cohort data. *Epidemiology* 1995;6: 322-325.

30 Young-Xu Y, et al. Long-term statin use and psychological well-being. *J Am Coll Cardiol* 2003;42: 690-697.

31 Morales K, et al. Simvastatin Causes Changes in Affective Processes in Elderly Volunteers. *J Am Geriatr Soc.* 2006;54(1):70-76.

repaglinide, pioglitazone, and clarithromycin. The subject is an ex-smoker of cigarettes and a non-drinker of alcohol.

The subject was originally treated with ABT-335 + rosuvastatin 20 mg in study M05-748. On Day 285, she was reported to have flu-like symptoms and was treated with clarithromycin. On Day 290, the subject's husband found her unresponsive and called Emergency Medical Services. The subject was asystolic, intubated and administered epinephrine and atropine. She was admitted to the intensive care unit. Upon admission the subject's WBC was  $21.8 \times 10^9/L$  (reference range:  $3.0-11.0 \times 10^9/L$ ), hemoglobin 93 g/dL (reference range: 12-150 g/dL), platelet count  $177 \times 10^9/L$  (reference range:  $150-450 \times 10^9/L$ ), hematocrit 0.27% (reference range: 0.33%-0.42%), total protein 5.2 mmol/L (reference range: 3.5-5.0 mmol/L), and creatinine 243 mmol/L (reference range: 50-130 mmol/L). A computed tomography of the head showed diffuse cerebral edema. A chest x-ray showed infiltration in the right lung. The subject remained unresponsive. Study drug was discontinued on Day 290. On Day 291 (Post Treatment Day 1), chest x-ray was negative and ECG showed sinus bradycardia (59 beats per minute). The subject's troponin was 1.0 ug/L (reference range: < 0.1 ug/L). On Day 292 (Post Treatment Day 2), AST was 275 U/L (reference range: < 50 U/L) and ALT was 174 U/L (reference range: < 50 U/L). On Day 293 (Post Treatment Day 3), an echocardiogram showed mild concentric left ventricular hypertrophy, an aneurysm in the left ventricular apex with a 2 cm thrombus, ejection fraction of approximately 50%, mildly dilated right ventricle, mild to moderate tricuspid regurgitation, and evidence of mild pulmonary hypertension (estimated pulmonary artery pressure of 45 mmHg). The consulting physician's impression of the subject's condition was that she had anoxic encephalopathy and cardiopulmonary arrest of undetermined etiology. On Day 294 (Post Treatment Day 4), the patient expired. The investigator reported an autopsy was not performed and the death certificate was not available. No further information was provided.

**Comment:** The investigator reported AEs of 'unresponsive to stimuli' and 'brain edema', but it is likely that the initial insult was cardiac given the troponin elevation and echo findings. Whether there was an additional contributing event that preceded the cardiac event is unclear. Brain edema was likely a result of anoxia. It is unclear how her "flu-like" symptoms five days before the event may have played a role in her death, but her medical history of cardiovascular risk factors including diabetes, hypertension, and hyperlipidemia were the most likely contributors.

Subject 14145 (ABT-335 135 mg and rosuvastatin 20 mg) was a 65-year-old white male with a history of hypertension, coronary artery disease, peripheral vascular disease, renal artery stenosis, obesity, and hyperlipidemia. Concomitant medications at the time of the event included metoprolol, nifedipine, and ticlopidine. The subject was a non-smoker and a light drinker.

The subject was originally treated with ABT-335 monotherapy in the M05-748 study. On Day 148, he had a routine stress test, which was positive for ischemia with high probability for coronary artery disease progression. On Day 188, study drug was interrupted (and never restarted) for admission to the hospital the following day for a cardiac catheterization. Catheterization showed 80% occlusion of the left main artery, 80% stenosis of the left anterior descending artery, 50% stenosis of the posterolateral artery, and an abdominal aortic aneurysm. Emergent coronary bypass graft (three vessels) was performed. The subject was treated with

heparin, acetylsalicylic acid, clopidogrel, and warfarin. On Day 191 (Post Treatment Day 3), the subject was extubated. The subject was started on vancomycin prophylactically on Day 192 (Post Treatment Day 4). On Day 193 (Post Treatment Day 5), the subject was started on amiodarone. On Day 195 (Post Treatment Day 7), the subject had shortness of breath and a computed tomography scan of the chest revealed pulmonary emboli at the left lung base, and bilateral pleural effusions with compressive atelectasis in both lung bases. On Day 202 (Post Treatment Day 14), the subject experienced shortness of breath after a blood transfusion and was started on furosemide. The subject was reintubated on Day 206 (Post Treatment Day 18). On Day 208 (Post Treatment Day 20), the subject was started on total parenteral nutrition. The subject developed a fever, an elevated white count, and had blood cultures positive for coagulase negative staphylococcus and pseudomonas aeruginosa on Day 209 (Post Treatment Day 21). He was treated with ciprofloxacin and linezolid. On Day 210 (Post Treatment Day 22), the subject was transferred to a different medical facility. Vancomycin was re-started for bacteremia on Day 211 (Post Treatment Day 23). On Day 221 (Post Treatment Day 33), a tracheostomy was placed. The subject then experienced a drop in blood pressure and was started on dopamine. On Day 222 (Post Treatment Day 34), he had decreased urinary output and was placed on continuous venous hemodialysis. The subject's condition continued to deteriorate despite the use of vasopressors to maintain both the blood pressure and renal perfusion. On Day 223 (Post Treatment Day 35), the subject experienced respiratory failure after the family decided to remove the subject from ventilatory support, and died.

**Comment: Drug treatment was stopped for a cardiac catheterization after findings on a routine stress test in this patient with known CAD. Subsequent events leading to death are most likely post-operative complications.**

Subject 23021 (ABT-335 and simvastatin 40 mg) was a 57-year-old white male with a history of depression, hypertension, hypertensive heart disease, atherosclerosis, hyperlipidemia, anteriolateral ischemia, and sexual dysfunction. Concomitant medications at the time of the event included acetylsalicylic acid, trazodone, sildenafil, and losartan potassium-hydrochlorothiazide. The subject had a 30-pack-year history of cigarette smoking and was a light drinker. The subject was originally treated with ABT-335 monotherapy in the M05-749 study. On Day 257, he was reported to have suffered sudden cardiac arrest at home with unsuccessful cardiopulmonary resuscitation by the paramedics. The death certificate reports the cause of death as sudden death unattended by a physician, ischemic heart disease, and cardiopulmonary arrest. The subject's last dose of study medication was on Day 256. No further information was provided.

**Comment: Sudden death in a subject with known atherosclerosis is most likely due to a myocardial infarction.**

Subject 24102 (ABT-335 135 mg and simvastatin 40 mg) was a 69-year-old white female with a medical history of hypertension, hyperlipidemia, trigeminal neuralgia, chronic lower extremity edema, osteoarthritis, and degenerative joint disease. Concomitant medications at the time of the event included extended release metoprolol, baclofen, carbamazepine, gabapentin, etodolac, acetylsalicylic acid, and acetaminophen. The subject was a non-smoker and non-drinker.

The subject was originally treated with ABT-335 monotherapy in the M05-749 study. On Day 132, she developed a persistent upper respiratory tract infection. Treatment with trimethoprim/sulfamethoxazole and hydrocodone/guaifenesin was initiated on Day 147. During the evening or early morning of Day 149-150, the subject experienced apparent syncope and fell in the bathtub face down, with the chin wedged in a flexed position that resulted in airway restriction, asphyxiation, and respiratory arrest. On Day 150, the subject was found dead in the bathroom from a presumed post-syncopal respiratory arrest. Per the death certificate, the cause of death was respiratory arrest due to asphyxiation with loss of airway due to fall with syncope. The manner of death was noted as an accident. No further information was provided.

**Comment:** Although the investigator considered the syncope and fall due to a vasovagal event, the cause is unclear in the absence of further information: syncope has a broad differential diagnosis. It is also unclear whether the persistent upper respiratory infection or its treatment could have played a role. Without further information, it is difficult to make a determination about the role of the study drugs.

Subject 32071 (ABT-335 135 mg and atorvastatin 40 mg) was a 67-year-old white female with a medical history of hypertension, hyperlipidemia, diabetes mellitus, diabetic neuropathy, ear pain, and hypothyroidism. She had a recent total hip arthroplasty surgery complicated by peptic ulcer disease and renal insufficiency. Concomitant medications at the time of the event included amlodipine, verapamil/trandolapril, glibenclamide/metformin, carbamazepine, hydrocodone/acetaminophen, pregabalin, alendronic acid, calcium/cholecalciferol, pantoprazole, and multivitamin supplements. The subject was an ex-smoker with a 2 pack-year history and a current light drinker.

The subject was treated with ABT-335 + atorvastatin 40 mg in the M05-750 study, during which she had a serious adverse event of accidental overdose of carbamazepine with vomiting, slurred speech, and delirium. She was hospitalized for right hip replacement surgery due to a right hip fracture from an accidental fall. This event was considered resolved on Day 196.

On Day 228, the subject was last seen alive. On Day 231, she was found dead at home by family members. There was no information regarding the circumstances surrounding her death and no autopsy. The death certificate noted the cause of death as cardiopulmonary arrest due to diabetes, renal insufficiency, and gastric bleed.

**Comment:** Given that the circumstances surrounding the death are unknown, it is difficult to determine what role the drugs might have played in this patient with multiple comorbidities.

### 7.3.2 Serious Adverse Events

#### *Phase 1 Studies*

In the Phase 1 studies, two subjects had serious adverse events (SAEs): one with hemorrhoids and one with injury due to a road traffic accident.

### *Phase 3 Studies*

In the Phase 3 controlled studies (M05-748, -749, and -750), the highest percentage of any SAE was in the ABT-335-only group, with 3.9% of subjects. Table 7.3.2.A. is a summary of treatment-emergent SAEs reported by system organ class (SOC), SAEs reported for at least two subjects in a particular preferred term (PT), and several other PTs of interest, such as those in the cardiac, renal, and hepatobiliary SOCs. The table shows the pooled data, due to a small number of individual events per group in any one study. The SAE of 'deep vein thrombosis' (ABT-335-treated subject) reported in the controlled trial M05-750 is described with other AEs of DVT in Section 7.3.5, Submission Specific Primary Safety Concerns.

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Table 7.3.2.A. Serious Adverse Events: Controlled Phase 3 Studies

System Organ Class Preferred Term	Treatment Group n (%)					
	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + low statin (N=490)	Moderate-dose statin (N=491)	ABT-335 + moderate statin (N=489)	High-dose statin (N=245)
<b>Any Serious Adverse Event</b>	19 (3.9)	6 (1.2)	12 (2.4)	10 (2.0)	8 (1.6)	6 (2.4)
<b>Cardiac disorders</b>	5 (1.0)	1 (0.2)	5 (1.0)	1 (0.2)	3 (0.6)	0
Angina pectoris	0	0	1 (0.2)	0	0	0
Angina unstable	1 (0.2)	0	0	0	0	0
Coronary artery disease	2 (0.4)	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Mitral valve incompetence	0	0	0	0	1 (0.2)	0
Myocardial infarction	2 (0.4)	0	2 (0.4)	0	0	0
Myocardia ischemia	0	0	0	0	1 (0.2)	0
Pericarditis	0	0	1 (0.2)	0	0	0
Wolff-Parkinson-White Syndrome	0	1 (0.2)	0	0	0	0
<b>Gastrointestinal Disorders</b>	0	2 (0.4)	1 (0.2)	2 (0.4)	0	1 (0.4)
<b>General disorders and Administration Site Conditions</b>	1 (0.2)	0	1 (0.2)	0	0	1 (0.4)
Chest pain	0	0	1 (0.2)	0	0	1 (0.4)
<b>Hepatobiliary Disorders</b>	0	0	0	0	1 (0.2)	0
Cholecystitis	0	0	0	0	1 (0.2)	0
Cholelithiasis	0	0	0	0	1 (0.2)	0
<b>Infections and Infestations</b>	5 (1.0)	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)	0
Diverticulitis	1 (0.2)	0	0	0	1 (0.2)	0
Gastroenteritis	1 (0.2)	0	1 (0.2)	0	0	0
<b>Injury, Poisoning and Procedural Complications</b>	1 (0.2)	0	0	0	1 (0.2)	1 (0.4)
<b>Musculoskeletal and Connective Tissue Disorders</b>	1 (0.2)	0	1 (0.2)	1 (0.2)	0	1 (0.4)
<b>Neoplasms Benign, Malignant and Unspecified</b>	3 (0.4)	0	0	1 (0.2)	0	0
Breast cancer	2 (0.4)	0	0	0	0	0
Prostate cancer	1 (0.2)	0	0	1 (0.2)	0	0
<b>Nervous System Disorders</b>	0	1 (0.2)	2 (0.4)	2 (0.4)	1 (0.2)	0
Syncope	0	0	2 (0.4)	0	0	0
<b>Psychiatric Disorders</b>	0	0	0	0	1 (0.2)	0
<b>Renal and Urinary Disorders</b>	2 (0.4)	0	0	2 (0.4)	0	0
Renal failure	1 (0.2)	0	0	0	0	0
<b>Reproductive System and Breast Disorders</b>	1 (0.2)	0	0	1 (0.2)	0	1 (0.4)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	1 (0.2)	1 (0.2)	2 (0.4)	0	0	0
<b>Vascular Disorders</b>	3 (0.6)	0	0	0	0	1 (0.4)
Deep vein thrombosis	1 (0.2)	0	0	0	0	0
Peripheral vascular disease	1 (0.2)	0	0	0	0	1 (0.4)

**Comment:** It is noted that cardiac SAEs occurring in the 12-week controlled studies are numerically higher in the ABT-335-only and combined groups as compared to the statin-only groups. Numbers are small, so it is hard to know what to make of this. Overall and coronary heart disease (CHD) mortality findings from fibrate outcome trials are discussed in Section 2.4.

In the open-label continuation study, M05-758, a total of 132 (6.0%) subjects had treatment-emergent serious adverse events: 6.8% of subjects treated with ABT-335 in combination with rosuvastatin, 6.0% of subjects treated with ABT-335 in combination with simvastatin, and 4.0%

of subjects treated with ABT-335 in combination with atorvastatin. Overall, the most common serious adverse events were osteoarthritis (nine subjects), coronary artery disease and deep vein thrombosis (five subjects each), myocardial infarction, chest pain, diverticulitis, and intervertebral disc protrusion (four subjects each). DVT and PE adverse events are discussed further in Section 7.3.5. There were no SAEs of myalgia or other Preferred Terms that would indicate severe myopathy. Hepatobiliary and renal SAEs were uncommon.

Table 7.3.2.B. Serious Adverse Events Reported for at Least Two Subjects Overall and Selected Preferred Terms of Interest: All Combination Therapy Analysis Set

System Organ Class Preferred Term	Treatment Group n (%)			Total (N=2201)
	ABT-335 + rosuva (N=1186)	ABT-335 + simva (N=514)	ABT-335 + atorva (N=501)	
<b>Any serious adverse event</b>	<b>81 (6.8)</b>	<b>31 (6.0)</b>	<b>20 (4.0)</b>	<b>132 (6.0)</b>
<b>Cardiac Disorders</b>	<b>13 (1.1)</b>	<b>8 (1.6)</b>	<b>0</b>	<b>21 (1.0)</b>
Acute myocardial infarction	1 (<0.1)	1 (0.2)	0	2 (<0.1)
Angina pectoris	1 (<0.1)	1 (0.2)	0	2 (<0.1)
Atrial flutter	1 (<0.1)	1 (0.2)	0	2 (<0.1)
Coronary artery disease	5 (0.4)	0	0	5 (0.2)
Myocardial infarction	3 (0.3)	1 (0.2)	0	4 (0.2)
<b>Gastrointestinal Disorders</b>	<b>8 (0.7)</b>	<b>0</b>	<b>2 (0.4)</b>	<b>10 (0.5)</b>
Pancreatitis	1 (<0.1)	0	1 (0.2)	2 (<0.1)
<b>General Disorders and Administration Site Conditions</b>	<b>4 (0.3)</b>	<b>2 (0.4)</b>	<b>2 (0.4)</b>	<b>8 (0.4)</b>
Chest discomfort	1 (<0.1)	0	1 (0.2)	2 (<0.1)
Chest pain	2 (0.2)	1 (0.2)	1 (0.2)	4 (0.2)
Non-cardiac chest pain	1 (<0.1)	1 (0.2)	0	2 (<0.1)
<b>Hepatobiliary Disorders</b>	<b>4 (0.3)</b>	<b>3 (0.6)</b>	<b>1 (0.2)</b>	<b>8 (0.4)</b>
Cholecystitis	2 (0.2)	0	1 (0.2)	3 (0.1)
Cholecystitis acute	2 (0.2)	0	0	2 (<0.1)
Cholelithiasis	0	1 (0.2)	1 (0.2)	2 (<0.1)
Cholecystitis chronic	0	1 (0.2)	0	1 (<0.1)
Bile duct obstruction	0	1 (0.2)	0	1 (<0.1)
<b>Infections and Infestations</b>	<b>14 (1.2)</b>	<b>3 (0.6)</b>	<b>1 (0.2)</b>	<b>18 (0.8)</b>
Diverticulitis	4 (0.3)	0	0	4 (0.2)
Pneumonia	1 (<0.1)	1 (0.2)	0	2 (<0.1)
<b>Injury, Poisoning and Procedural Complications</b>	<b>5 (0.4)</b>	<b>2 (0.4)</b>	<b>2 (0.4)</b>	<b>9 (0.4)</b>
Accidental overdose	1 (<0.1)	0	1 (0.2)	2 (<0.1)
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>14 (1.2)</b>	<b>5 (1.0)</b>	<b>0</b>	<b>19 (0.9)</b>
Intervertebral Disc Protrusion	3 (0.3)	1 (0.2)	0	4 (0.2)
Osteoarthritis	6 (0.5)	3 (0.6)	0	9 (0.4)
<b>Neoplasms Benign, Malignant and Unspecified</b>	<b>7 (0.6)</b>	<b>1 (0.2)</b>	<b>0</b>	<b>8 (0.4)</b>
Colon cancer	1 (<0.1)	1 (0.2)	0	2 (<0.1)
<b>Nervous System Disorders</b>	<b>7 (0.6)</b>	<b>2 (0.4)</b>	<b>7 (1.4)</b>	<b>16 (0.7)</b>
Syncope	2 (0.2)	0	1 (0.2)	3 (0.1)
<b>Pregnancy, Perinatal and Fetal Conditions</b>	<b>1 (&lt;0.1)</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>3 (0.1)</b>
Abortion spontaneous	1 (<0.1)	1 (0.2)	1 (0.2)	3 (0.1)
<b>Psychiatric Disorders</b>	<b>2 (0.2)</b>	<b>2 (0.4)</b>	<b>0</b>	<b>4 (0.2)</b>
Anxiety disorder	1 (<0.1)	0	1 (0.2)	2 (<0.1)
<b>Renal and Urinary Disorder</b>	<b>4 (0.3)</b>	<b>3 (0.6)</b>	<b>1 (0.2)</b>	<b>8 (0.4)</b>
Renal colic	1 (<0.1)	1 (0.2)	0	2 (<0.1)
Renal failure acute	0	1 (0.2)	0	1 (<0.1)
Renal impairment	0	1 (0.2)	0	1 (<0.1)
<b>Reproductive System and Breast Disorders</b>	<b>4 (0.3)</b>	<b>0</b>	<b>1 (0.2)</b>	<b>5 (0.2)</b>
Uterine prolapse	2 (0.2)	0	1 (0.2)	3 (0.1)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>5 (0.4)</b>	<b>0</b>	<b>1 (0.2)</b>	<b>6 (0.3)</b>

System Organ Class Preferred Term	Treatment Group n (%)			Total (N=2201)
	ABT-335 + rosuva (N=1186)	ABT-335 + simva (N=514)	ABT-335 + atorva (N=501)	
Any serious adverse event	81 (6.8)	31 (6.0)	20 (4.0)	132 (6.0)
Dyspnoea	2 (0.2)	0	0	2 (<0.1)
Pulmonary embolism	2 (0.2)	0	1 (0.2)	3 (0.1)
Vascular disorders	7 (0.6)	1 (0.2)	4 (0.8)	12 (0.5)
Deep vein thrombosis	4 (0.3)	0	1 (0.2)	5 (0.2)
Hypotension	1 (<0.1)	0	1 (0.2)	2 (<0.1)

### 7.3.3 Dropouts and/or Discontinuations

#### Phase 1

Six subjects treated with ABT-335 discontinued a Phase 1 study due to an adverse event: increased ALT (1), hemorrhoid (1), urinary tract infection (2), motor vehicle accident (1), and increased AST (1).

The narrative of the subjects with AEs of increased ALT and AST, respectively, are as follows:

Subject 107, a 43 year old white male, with a history of heavy previous alcohol use was discontinued from study M06-804 due to an adverse event of elevated ALT prior to dosing on Study Day 1 in Period 3. In Period 1, the subject received Regimen C, omeprazole 40 mg once daily on Study Days 1-5 and ABT-335 135 mg on Study Day 5. In Period 2, the subject received Regimen B, omeprazole 40 mg once daily on Study Days 1-5 and ABT-335 135 mg on Study Day 5. The subject did not receive study drug in Period 3. The ALT was 77 IU/L (reference range 0-35). There was no elevation of AST or total bilirubin. A physical examination revealed minimal liver enlargement and a presumptive diagnosis of a viral infection with potential mild hepatitis was made. The subject enrolled into the study with a baseline ALT value at the upper limit of normal, 47 IU/L. Approximately 5 days after the discontinuation from the study, the ALT decreased to 39 IU/L.

Subject 134 was a 30-year-old black male who was prematurely discontinued the study following Period 1 [Regimen A, ABT-335 135 mg (Fournier manufactured) on Study Day 1], on Study Day 14, due to an elevated AST. There was no significant reported medical history. The subject was not taking any concomitant medications at the time of the event. The subject is an ex-smoker of cigarettes (less than one pack year) and a current light drinker. Relevant laboratory values leading to the AE and discontinuation are provided in the table below. The event was considered resolved on Study Day 21.

Table 7.3.3.A.

**Subject 134 Laboratory Data**

Study Day	AST (SGOT) Reference Range (9-38 IU/L)	ALT (SGPT) Reference Range (0-38 IU/L)	Total Bilirubin Reference Range (0.2-1.3 mg/dL)
Study Day -1	18	12	0.6
Study Day 14	121	48	0.4
Study Day 15	88	44	0.4
Study Day 21	24	22	Not performed

*Phase 3*

**Study M05-748**

In study M05-748, 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) and similar to the ABT-335 monotherapy group (10.8%). A total of 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. Similar proportions of subjects across groups discontinued due to nausea.

Hepatic and muscle events are events of special interest in this NDA and are discussed further in Section 7.3.5.

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**Table 7.3.3.B. Adverse Events Leading to Premature Discontinuation in at Least Two Subjects in Any Treatment Group (Safety Analysis Set), Study M05-748**

<b>MedDRA Preferred Term</b>	<b>ABT-335 (N=259)</b>	<b>10 mg rosuva (N=261)</b>	<b>ABT-335 + 10 mg rosuva (N=261)</b>	<b>20 mg rosuva (N=266)</b>	<b>ABT-335 + 20 mg rosuva (N=261)</b>	<b>40 mg rosuva (N=131)</b>
Any adverse event leading to discontinuation	28 (10.8)	10 (3.8)	25 (9.6)	13 (4.9)	25 (9.6)	10 (7.6)
Myalgia	2 (0.8)	1 (0.4)	2 (0.8)	2 (0.8)	2 (0.8)	4 (3.1)
Headache	4 (1.5)	1 (0.4)	3 (1.1)	0	1 (0.4)	3 (2.3)
ALT increased	4 (1.5)	1 (0.4)	3 (1.1)	0	5 (1.9)	0
AST increased	3 (1.2)	1 (0.4)	3 (1.1)	0	4 (1.5)	0
Nausea	2 (0.8)	2 (0.8)	0	3 (1.1)	1 (0.4)	1 (0.8)
Dizziness	1 (0.4)	0	2 (0.8)	1 (0.4)	1 (0.4)	0
Muscle spasms	1 (0.4)	1 (0.4)	0	2 (0.8)	0	1 (0.8)
Blood CPK increased	0	1 (0.4)	1 (0.4)	0	2 (0.8)	0
Arthralgia	1 (0.4)	0	0	0	1 (0.4)	2 (1.5)
Constipation	0	0	3 (1.1)	0	0	0
Dyspepsia	0	0	1 (0.4)	0	2 (0.8)	0
Fatigue	0	0	1 (0.4)	2 (0.8)	0	0
Abdominal distension	0	0	0	2 (0.8)	1 (0.4)	0
Back pain	3 (1.2)	0	0	0	0	0
Pain	2 (0.8)	1 (0.4)	0	0	0	0
Abdominal pain upper	0	0	2 (0.8)	0	0	0
Rheumatoid arthritis	0	0	2 (0.8)	0	0	0
Breast cancer	2 (0.8)	0	0	0	0	0

**Study M05-749**

The groups with the highest proportion of adverse events leading to discontinuation were the ABT-335 group (10.9%) and the simvastatin 40 mg group (9.5%). Adverse events leading to discontinuation were most commonly associated with Gastrointestinal Disorders, Investigations, and Musculoskeletal and Connective Tissue Disorders. Overall, the most common adverse events that led to discontinuation were nausea (six subjects), myalgia (four subjects), and blood CPK increased (four subjects).

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Table 7.3.3.C. Adverse Events Leading to Premature Discontinuation in at Least Two Subjects in Any Treatment Group (Safety Analysis Set), Study M05-749

MedDRA Preferred Term	ABT-335 (N=119)	20 mg simva (N=119)	ABT- 335 + 20 mg simva (N=119)	40 mg simva (N=116)	ABT- 335 + 40 mg simva (N=118)	80 mg simva (N=59)
Any adverse event leading to discontinuation	13 (10.9)	8 (6.7)	8 (6.7)	11 (9.5)	7 (5.9)	4 (6.8)
Nausea	2 (1.7)	1 (0.8)	1 (0.8)	0	2 (1.7)	0
Blood CPK increased	0	0	2 (1.7)	2 (1.7)	0	0
Myalgia	2 (1.7)	1 (0.8)	0	1 (0.9)	0	0
Liver function test abnormal	2 (1.7)	1 (0.8)	0	0	0	0

**Comment:** The three cases of 'liver function test abnormal' were cases of elevated transaminases (+ increased alkaline phosphatase in the two subjects treated with ABT-335). None of these subjects had elevations in total bilirubin.

Study M05-750

The difference between the ABT-335 in combination with 20 mg atorvastatin and the 20 mg atorvastatin monotherapy groups in the incidence of adverse events leading to discontinuation was statistically significant (10.9% vs. 2.7%,  $p = 0.016$ ); however, the incidence was similar between the ABT-335 in combination with 40 mg atorvastatin and 40 mg atorvastatin monotherapy groups. Adverse events leading to discontinuation were most commonly associated with the Investigations, Gastrointestinal Disorders, and Musculoskeletal and Connective Tissue Disorders SOCs. Overall, the most common adverse events that led to discontinuation were myalgia (nine subjects), nausea (eight subjects), ALT and/or AST increased (seven subjects), and hepatic enzyme increased (six subjects, one of whom also discontinued due to adverse events of ALT and AST increased).

Table 7.3.3.D. Adverse Events Leading to Premature Discontinuation in at Least Two Subjects in Any Treatment Group (Safety Analysis Set), Study M05-750

MedDRA Preferred Term	ABT-335 (N=112)	20 mg atorva (N=113)	ABT-335 + 20 mg atorva (N=110)	40 mg atorva (N=109)	ABT-335 + 40 mg atorva (N=110)	80 mg atorva (N=55)
Any adverse event leading to discontinuation	8 (7.1)	3 (2.7)	12 (10.9)	12 (11.0)	14 (12.7)	6 (10.9)
Myalgia	2 (1.8)	0	1 (0.9)	3 (2.8)	2 (1.8)	1 (1.8)
Nausea	3 (2.7)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	1 (1.8)
ALT increased	1 (0.9)	0	4 (3.6)	0	1 (0.9)	1 (1.8)
AST increased	1 (0.9)	0	3 (2.7)	0	1 (0.9)	1 (1.8)
Hepatic enzyme increased	0	0	2 (1.8)	1 (0.9)	3 (2.7)	0
Asthenia	0	0	2 (1.8)	1 (0.9)	0	0
Liver function test abnormal	0	0	1 (0.9)	0	2 (1.8)	0
Vomiting	0	0	0	0	0	2 (3.6)