

Table 7.3.5.GG.

**Subject 024017 Fasting Laboratory Data**

Treatment Day	CPK Reference Range 10-200 U/L	AST Reference Range 11-30 U/L	ALT Reference Range 6-40 U/L	Total Bilirubin Reference Range 0.2-1.2 mg/dL
Screening Visit (A01-740)	212	38	37	0.9
Baseline Visit (A01-740)	289	38	31	0.8
Day 28 (A01-740)	357	34	30	0.6
Day 37 (A01-740)	390	38	27	0.8
Day 87 Final Visit (A01-740)	31	19	16	0.4
Day 26 (A01-738)	64	19	12	0.3
Day 41 (A01-738)	123	21	16	0.4
Day 83 (A01-738)	2493	540	178	0.3
Day 84 (1 day post study drug) (A01-738)	7314	236	170	0.4
Day 97 (14 days post study drug) (A01-738)	171	19	34	Not performed
Day 113 (30 days post study drug; Final Visit (A01-738)	115	22	19	0.1

**Comment:** It is unclear how the fall, fractures, surgery, and infection may have played a role in the CK and transaminase elevations. Fortunately, CK, ALT, and AST decreased to normal after therapy was stopped.

**Overall**

No cases of rhabdomyolysis were reported. Overall, the incidence of muscle events was highest in the high-dose statin monotherapy group and lowest in the ABT-335 monotherapy group and the ABT-335 in combination with moderate-dose statin group (See Table 7.3.5.HH, below). No statistically significant differences between treatment groups were observed for the overall incidence of muscle-related adverse events. The most common treatment-emergent muscle-related adverse event was myalgia, with lower incidences in each combination therapy treatment group compared with the corresponding statin monotherapy groups; however, no statistically significant differences were observed. A statistically significantly higher percentage of subjects in the ABT-335 in combination with low-dose statin group had an adverse event of blood CPK increased (2.7%) compared with the low-dose statin monotherapy (0.8%) and ABT-335 monotherapy (0.8%) groups; however, the incidence of blood CPK increased was 1.2% in the ABT-335 in combination with moderate-dose statin group.

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Table 7.3.5.HH. Treatment Emergent Adverse Events of Special Interest (Muscle Events) for the Controlled Studies Analysis Set

	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>Muscle Events</b>	27 (5.5)	32 (6.5)	38 (7.8)	41 (8.4)	26 (5.3)	25 (10.2)
Blood CPK abnormal	0	0	0	0	0	1 (0.4)
Discontinuations	0	0	0	0	0	0
Blood CPK increased	4 (0.8)	4 (0.8)	13 (2.7) <sup>ab</sup>	11 (2.2)	6 (1.2)	8 (3.3)
Discontinuations	0	1 (0.2)	4 (0.8)	2 (0.4)	2 (0.4)	0
Musculoskeletal discomfort	1 (0.2)	1 (0.2)	0	0	1 (0.2)	0
Discontinuations	0	0	0	0	0	0
Musculoskeletal pain	6 (1.2)	5 (1.0)	7 (1.4)	10 (2.0)	7 (1.4)	2 (0.8)
Discontinuations	0	0	0	0	0	0
Myalgia	16 (3.3)	24 (4.9)	17 (3.5)	23 (4.7)	15 (3.1)	15 (6.1)
Discontinuations	6 (1.2)	2 (0.4)	3 (0.6)	6 (1.2)	4 (0.8)	5 (2.0)
Myositis	0	0	1 (0.2)	0	0	0
Discontinuations	0	0	0	0	0	0
<b>Muscle Events – Changes in Laboratory Tests<sup>c</sup></b>	4 (0.8)	4 (0.8)	13 (2.7)	11 (2.2)	6 (1.2)	9 (3.7)
Discontinuations	0	1	4	2	2	0
CK > 5x ULN	0/472	2/484 (0.4)	6/481 (1.2)	3/480 (0.6)	1/472 (0.2)	3/238 (1.3)
CK > 10x ULN	0/472	0/484	1/481 (0.2)	3/480 (0.6)	0/472	1/238 (0.4)

Note: Includes data from Studies M05-748, M05-749, and M05-750.  
a. Statistically significant difference between ABT-335 + low statin and low-dose statin,  $p \leq 0.05$   
b. Statistically significant difference vs. ABT-335,  $p \leq 0.05$   
c. Includes adverse events of blood CPK abnormal and blood CPK increased.

A total of five subjects in the controlled studies overall had CK values > 10x ULN; however, no subject had a CK > 5000 U/L. The following table enumerates the subjects meeting CK PCS criteria in the controlled studies:

Table 7.3.5.II. Controlled Studies Analysis Set: Subjects meeting Post-Baseline CK PCS Criteria

	ABT-335 (N=472)	Low-dose statin (N=484)	ABT-335 + low statin (N=481)	Moderate-dose statin (N=480)	ABT-335 + moderate statin (N=472)	High-dose statin (N=238)
CK $\geq$ 850 (F); $\geq$ 1000 (M) U/L	0	2 (0.4)	6 (1.2) <sup>a</sup>	3 (0.6)	1 (0.2)	3 (1.3)

Note: Includes data from Studies M05-748, M05-749, and M05-750.  
Note: Baseline was defined as the last value before the first dose of study drug.  
a. Statistically significant difference vs. ABT-335,  $p \leq 0.05$

In the All Combination Therapy Analysis Set, which included any subject who was exposed to combination therapy in the controlled or open-label studies, the incidence of muscle events was similar between the ABT-335 + rosuvastatin (10.0%), ABT + simvastatin (10.7%), and ABT + atorvastatin (10.8%) groups. The individual Preferred Terms that were the highest in these groups (and similar between groups) was 'blood CPK increased' (3.4-3.9%) and 'myalgia' (4.1-4.8%). Similar findings were seen in the muscle events assessed for the Initial Combination Therapy Analysis Set.

The incidence of CK meeting potentially significant criteria [ $\geq 850$  (F);  $\geq 1000$  (M) U/L] was highest in the ABT-335 + rosuvastatin group (1.5%), moderate in the ABT-335 + simvastatin group (1.2%), and lowest in the ABT-335 + atorvastatin group (0.6%). Similarly, although the numbers were small, the proportion of subjects meeting the criteria of CK > 10x ULN on any occasion was highest in the ABT-335 + rosuvastatin group (0.5%), moderate in the ABT-335 + simvastatin group (0.4%), and lowest in the ABT-335 + atorvastatin group (0.2%). Subjects who met these criteria are described in the reviews of muscle events from the individual studies, above. These findings are consistent with those seen in the Initial Combination Therapy Analysis Set.

**Comment:** Just as increased liver enzymes are associated with ABT-335 administration, 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, the combination appears relatively safe from a muscle point of view, at least from the data gathered in this NDA. However, ABT-335 should not be administered with the highest dose of statin until this combination is specifically studied and safety is demonstrated. From the modest differences between groups in the All Combination Therapy Analysis Set, it appears that the incidence of CK elevations (but not adverse events of muscle events) were highest in the groups that included rosuvastatin. This is consistent with the fact that a greater mean increase in CK was seen in the ABT-335 + rosuvastatin group (17.6 U/L) than the ABT-335 + simvastatin group (13.6 U/L) or the ABT-335 + atorvastatin group (9.0 U/L) in the Initial Combination Therapy Analysis Set. It is reassuring that there were no cases of 'rhabdomyolysis' or 'myopathy' in any of the submitted AE datasets. 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 drug was continued.

#### *Renal Findings*

Fenofibrate is associated with increases in serum creatinine<sup>10</sup>; whether this is reflective of renal pathology (decrease in creatinine clearance/glomerular filtration rate) versus a less concerning increase in creatinine production is somewhat unclear.<sup>32,33</sup> In Davidson's review of the topic,<sup>34</sup>

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32 Hottelart C, et al. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. *Nephron*. 2002; 92(3): 536-41.

33 Angeles C, et al. Fenofibrate-associated reversible acute allograft dysfunction in 3 renal transplant recipients: biopsy evidence of tubular toxicity. *Am J Kidney Dis*. 2004 Sep; 44(3): 543-50.

he notes that although urea, cystatin C, and homocysteine increase with creatinine after fenofibrate therapy indicative of an expected reduction in the glomerular filtration rate (GFR), studies that have measured GFR directly have failed to show any such change. Large clinical trials with fenofibrate have suggested that the drug is safe from a renal standpoint in patients with diabetes<sup>6,35</sup>, a population who may be more susceptible to renal injury. Therefore, more of concern for this reviewer than AEs of or laboratory data demonstrating serum increases in creatinine was reports of diagnosed renal insufficiency or failure.

In addition, as noted in Section 7.2.6, adverse events of *blood urea increased* and *renal disorder* were not included in the prespecified list of renal terms, and therefore, clinically important adverse renal events may have been missed. This reviewer has included these adverse events in the summary tables.

#### Study M05-748

Renal events were more frequent in the arms with ABT-335 than in the rosuvastatin monotherapy groups, primarily due to adverse events of increased serum creatinine, as discussed above.

Table 7.3.5.JJ. Renal Events, Study M05-748

	ABT-335 (N=259)	10 mg rosuva (N=261)	ABT-335 + 10 mg rosuva (N=261)	20 mg rosuva (N=266)	ABT-335 + 20 mg rosuva (N=261)	40 mg rosuva (N=131)
<b>Renal Events</b>	<b>6 (2.3)</b>	<b>2 (0.8)</b>	<b>7 (2.7)</b>	<b>0†</b>	<b>5 (1.9)†</b>	<b>2 (1.5)</b>
Blood creatinine increased	1 (0.4)	0	2 (0.8)	0	3 (1.1)	0
Creatinine renal clearance decreased	3 (1.2)	0	3 (1.1)	0	2 (0.8)	2 (1.5)
Renal failure acute	0	1 (0.4)	1 (0.4)	0	1 (0.4)	0
Renal failure	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0
Renal impairment	2 (0.8)	0	0	0	0	0
Blood urea increased <sup>a</sup>	1 (0.4)	0	0	0	2 (0.8)	0

† Statistically significant difference ABT-335 + 20 mg rosuvastatin vs. 20 mg rosuvastatin, p ≤ 0.05.  
<sup>a</sup> Not included in the sponsor's analysis of renal events.

Adverse events of renal failure were reported for three subjects, one each in the ABT-335 monotherapy, 10 mg rosuvastatin monotherapy, and ABT-335 in combination with 10 mg rosuvastatin groups. Renal failure acute was reported for three subjects, one each in the 10 mg rosuvastatin monotherapy, ABT-335 in combination with 10 mg rosuvastatin, and ABT-335 in combination with 20 mg rosuvastatin groups. Renal impairment was reported for one subject in the ABT-335 monotherapy group. All of these events were mild or moderate in intensity and only one of these subjects (PT 'renal failure acute') discontinued study drug, as discussed in the following narrative:

34 Davidson MH, et al. Safety considerations with fibrate therapy. *Am J Cardiol.* 2007 Mar 19;99(6A):3C-18C.

35 No authors listed. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet.* 2001 Mar 24; 357(9260): 905-10.

Subject 14431 (ABT-335 and rosuvastatin 10 mg) is a 53-year-old white female with a history of post-nasal drip, restless leg syndrome, asthma, hypertension, gastroesophageal reflux disease, hyperlipidemia, menopause, sleeplessness, and environmental allergies, who prematurely discontinued study drug on Day 70 due to nausea, elevated creatinine, and BUN. She was on the following concomitant medications at the time of the event: fexofenadine hydrochloride, fluticasone, omeprazole, alprazolam, provella-14 (conjugated estrogens/medroxyprogesterone acetate), omalizumab, salbutamol, salmeterol xinafoate/fluticasone propionate, zafirlukast, felodipine, lisinopril, and ropinirole. The subject is a non-smoker and non-drinker.

On Day 60, the subject reported nausea and had an elevated creatinine and BUN. Laboratory values are provided in Table 7.3.5.KK, below. Study drug was discontinued on Day 70. The clinician did not feel follow-up was necessary. No further information was provided.

**Comment:** This was a clear deterioration of renal function in a subject with normal BUN and creatinine at baseline. It is unfortunate that follow-up of this subject was not available to determine if there was resolution of the elevated BUN (52 mg/dL) and creatinine (2.3 mg/dL) upon study drug discontinuation.

Table 7.3.5.KK. Subjects Who Prematurely Discontinued Study Drug Due to Renal Adverse Events, Study M05-748

(Site No./ Subject No. Renal AE	Age/Gender	Treatment Group	Study Day <sup>a</sup>	BUN mg/dL	Creatinine (mg/dL)	PCS Criteria (BUN only) ≥ 40 mg/dL
(33246)/14431 Renal Failure Acute	53/F	ABT-335 in combination with 10 mg rosuvastatin	-4	14.0	0.7	
			1	18.0	0.7	
			30	22.0	0.8	
			60	52.0	2.3	X
			70	45.0	2.2	X
(4662)/11065 Blood Creatinine Increased	67/M	ABT-335 in combination with 20 mg rosuvastatin	-9	18.0	0.8	
			1	14.0	0.9	
			29	44.0	1.6	X
			35 (2)	30.0	1.3	
			42 (9)	20.0	1.0	

AE = adverse event; PCS = potentially clinically significant; BUN ULN = 24.0 mg/dL; creatinine ULN = 1.2 mg/dL

a. Study days in parentheses indicate the number of days after the final dose of study drug.

A total of six subjects had a reported adverse event of blood creatinine increased: one subject receiving ABT-335 monotherapy, two subjects receiving ABT-335 in combination with 10 mg rosuvastatin, and three subjects receiving ABT-335 in combination with 20 mg rosuvastatin. All of these events were mild or moderate in intensity, none of the creatinine values were > 2 mg/dL, and only one of these subjects (11065) discontinued study drug, as discussed in the following narrative:

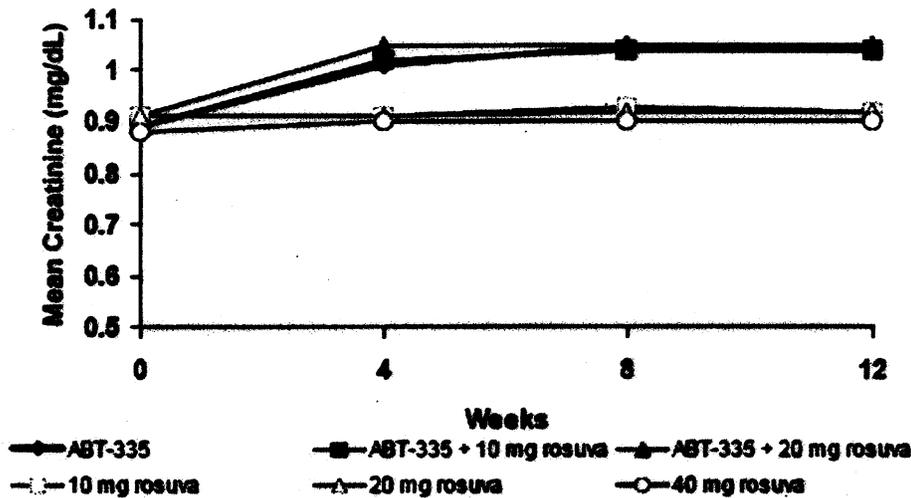
Subject 11065 (ABT-335 + rosuvastatin 20 mg) is a 67-year-old white male who prematurely discontinued study drug on Day 33 due to elevated creatinine, uric acid, and urea nitrogen (discovered on Day 29). He had a medical history of hypertension, bilateral lower extremity

edema, diabetes mellitus, congestive heart failure, and hyperlipidemia and concomitant medications at the time of event included furosemide, moexipril, acetylsalicylic acid, pioglitazone hydrochloride, and rosiglitazone maelate. He is a non-smoker and non-drinker. His BUN and creatinine values are presented in Table 7.3.5.KK, above. Uric acid was elevated at 9.3 mg/dL, but was essentially unchanged from baseline.

**Comment: Renal function was improving nine days after discontinuation.**

The following figure is consistent with adverse events of increased creatinine with ABT-335, as well as the known increases seen with fenofibrate, in that mean creatinine increased in all of the ABT-335 groups. The addition of rosuvastatin does not appear to have affected this mean increase.

Figure 7.3.5.G. Mean Change in Creatinine Values over Time by Treatment Group, Study M05-748



**Study M05-749**

Three subjects had renal adverse events of interest: two subjects had AEs of blood creatinine increased (1 ABT-335 and 1 ABT-335 + simvastatin 20 mg) and one had an AE of renal failure acute (ABT-335). Two of these subjects prematurely discontinued; BUN and creatinine values are presented below. In addition, there was one AE of 'renal disorder' in the ABT-335 + simvastatin 20 mg group and one AE of 'blood urea increased' in the ABT-335 monotherapy group, which were not captured in the sponsor's analysis.

Table 7.3.5.LL. Subjects Who Prematurely Discontinued Study Drug Due to Renal Adverse Events, Study M05-749

(Site No./ Subject No.)	Age/ Gender	Treatment Assignment	Study Day	BUN mg/dL	Creatinine mg/dL	PCS Criteria
						(for BUN only) ≥40 mg/dL
(12820)/22030 Renal Failure Acute	59/M	ABT-335 monotherapy	-8	25.0	1.0	-
			-1	23.0	1.3	-
			29	28.0	1.3	-
			57	34.0	1.5	-
(16924)/23108 Blood Creatinine Increased	57/M	ABT-335 in combination with 20 mg simvastatin	-6	18.0	1.3	-
			1	19.0	1.4	-
			35	21.0	1.5	-
			38	23.0	1.7	-
			51	20.0	1.5	-
			62 (1)	20.0	1.5	-

BUN ULN = 24.0 mg/dL; Creatinine ULN = 1.3 mg/dL

a. Number in parentheses indicates the number of days after treatment.

BUN = blood urea nitrogen; PCS = potentially clinically significant.

Narratives for these cases are as follows:

Subject 22030 (ABT-335) is a 59-year-old white male who was hospitalized on Day 81 for dyspnea, fever, chills, and headache. Relevant medical history includes emphysema/chronic obstructive pulmonary disease, pneumonia, asthma, coronary artery disease, myocardial infarction, coronary artery bypass graft, hypertension, edema, diabetes mellitus, obesity, and hyperlipidemia/increased triglyceride. Concomitant medications at the time of the event included acetylsalicylic acid, potassium, lisinopril, zafirlukast, fluticasone/salmeterol, salbutamol, formoterol, furosemide, metformin, theophylline, rosiglitazone, nicotine, tiotropium, and prednisone. The subject is a current cigarette smoker for 41 years (1 to 2 packs per day) and a non-drinker.

On Day 77, the subject reported dyspnea, fever, chills, and headaches. On Day 81 he was hospitalized with chronic obstructive pulmonary disease exacerbation. A chest x-ray suggested an infiltrate with air entrapment. An electrocardiogram revealed no acute ST elevations. Troponin level was < 0.04 ng/mL and CK was 775 U/L. He was treated with levothyroxine, oxygen, methylprednisolone, prednisone, levosalbutamol, paracetamol, and ibuprofen. Study drug was discontinued on Day 81. On Day 82, the subject was diagnosed with acute renal failure and uncontrolled blood sugars. Relevant labs included BUN 30 mg/dL, CK 697 U/L, creatinine 1.7 mg/dL, glucose of 238 mg/dL, and HbA<sub>1c</sub> of 7.5%. The subject was treated with IV fluids and insulin and the subject's furosemide, lisinopril, potassium, and metformin were discontinued due to the acute renal failure. The subject was treated with amlodipine for hypertension and rabeprazole for GERD. On Day 86, the event of acute renal failure was considered resolved associated with other clinical improvements; the subject was discharged home with oxygen.

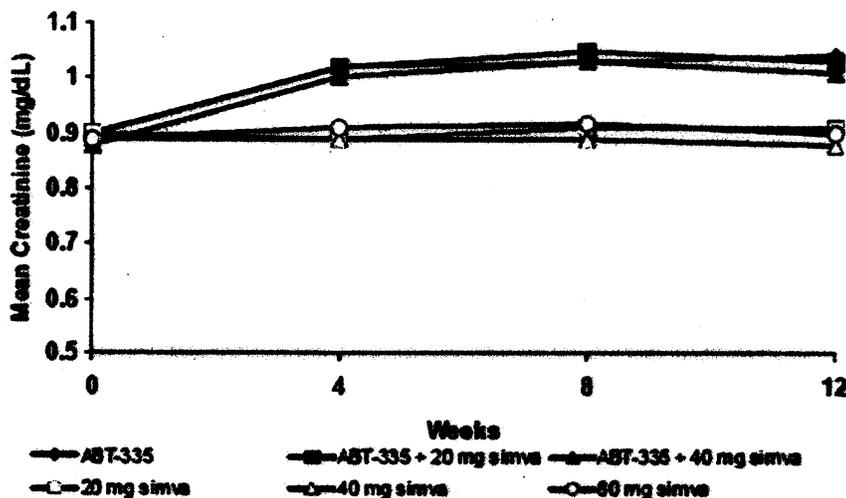
**Comment:** According to the narrative, the acute renal failure appears consistent with prerenal azotemia related to the acute respiratory infection +/- hyperglycemia; however, the laboratory data suggest that the creatinine was gradually increasing during the course

of the study. Therefore the renal failure/creatinine increase appears to be subacute (and therefore possibly drug-related), rather than a direct result of the acute illness.

Subject 23108 (ABT-335 + simvastatin 20 mg) is a 57-year-old black male who prematurely discontinued study drug on Day 61 due to an elevated creatinine concentration. Relevant medical history included hypertension, mixed hyperlipidemia, and elevated creatinine. Concomitant medication at the time of the event included valsartan. The subject is a non-smoker and a non-drinker. On Day 1, the subject was reported to have an elevated creatinine concentration (Table 7.3.5.LL). Study drug was discontinued on Day 61. On Day 62, the event was considered ongoing. No further information was provided.

The following figure, demonstrating mean changes in serum creatinine over time in each of the treatment groups is similar to that seen in study M05-748:

Figure 7.3.5.H. Mean Change in Creatinine Values over Time by Treatment Group, Study M05-749



#### Study M05-750

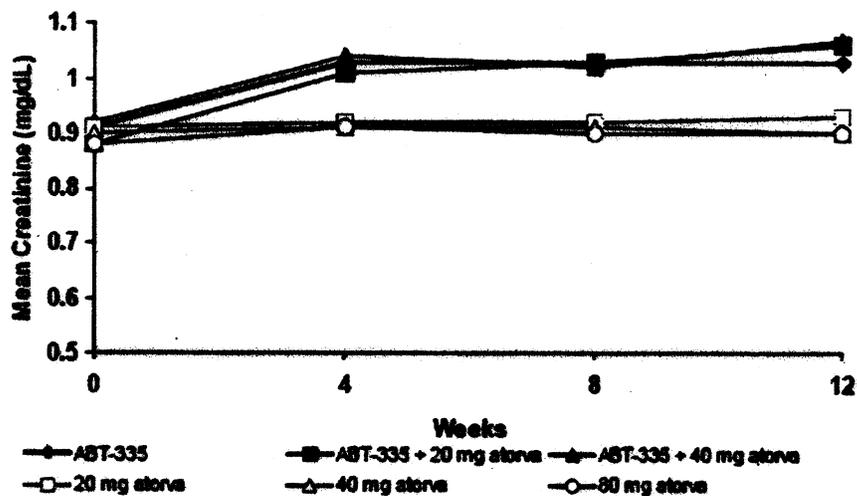
The adverse event of 'creatinine clearance decreased' was reported for seven subjects (three on ABT-335 in combination with 40 mg atorvastatin, two on ABT-335 in combination with 20 mg atorvastatin, and one each on ABT-335 and 80 mg atorvastatin monotherapy), as seen in Table 7.3.5.MM. 'Blood creatinine increased' was reported for three subjects (two on ABT-335 in combination with 40 mg atorvastatin and one on ABT-335 in combination with 20 mg atorvastatin). No subjects discontinued due to increases in serum creatinine or decreases in calculated creatinine clearance.

Table 7.3.5.MM. Renal Events, Study M05-750

	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 Renal Event	1 (0.9)	0	2 (1.8)	0	3 (2.7)	1 (1.8)
Blood creatinine increased	0	0	1 (0.9)	0	2 (1.8)	0
Creatinine renal clearance decreased	1 (0.9)	0	2 (1.8)	0	3 (2.7)	1 (1.8)

Again, as with the other two controlled trials, ABT-335 increased mean serum creatinine:

Figure 7.3.5.I. Mean Creatinine Values over Time by Treatment Group, Study M05-750



### Study M05-758

The renal events from this open-label study are discussed in the overall integrated long-term analysis, below.

### Overall

As with the individual controlled studies, the controlled studies pooled demonstrated increased incidence of renal events in the ABT-335 groups as compared to the statin monotherapy groups. This was primarily due to events of increased blood creatinine and creatinine clearance decreased.

**Comment:** Reassuringly, the number of events in total, and in particular, the more concerning incidence of renal failure was low.

**Table 7.3.5.NN. Renal Events, Controlled Studies Analysis Set**

	<b>ABT-335 (N=490)</b>	<b>Low-dose statin (N=493)</b>	<b>ABT-335 + low statin (N=490)</b>	<b>Moderate- dose statin (N=491)</b>	<b>ABT-335 + moderate statin (N=489)</b>	<b>High- dose statin (N=245)</b>
<b>Renal Events</b>	9 (1.8)	2 (0.4)	10 (2.0) <sup>a</sup>	0	8 (1.6) <sup>b</sup>	3 (1.2)
Blood creatinine increased	2 (0.4)	0	4 (0.8)	0	5 (1.0) <sup>b</sup>	0
Discontinuations	0	0	1 (0.2)	0	1 (0.2)	0
Creatinine renal clearance decreased	4 (0.8)	0	5 (1.0) <sup>a</sup>	0	5 (1.0) <sup>b</sup>	3 (1.2)
Discontinuations	0	0	0	0	0	0
Renal failure	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Discontinuations	0	0	0	0	0	0
Renal failure acute	1 (0.2)	1 (0.2)	1 (0.2)	0	1 (0.2)	0
Discontinuations	1 (0.2)	0	1 (0.2)	0	0	0
Renal impairment	2 (0.4)	0	0	0	0	0
Discontinuations	0	0	0	0	0	0
Blood urea increased *	2 (0.4)	0	0	0	2 (0.4)	0
Renal disorder*	0	0	1 (0.2)	0	0	0

\* Not included in the sponsor's analysis of renal events

In the long-term all combination therapy analysis set, greater percentages of subjects in the ABT-335 in combination with rosuvastatin (3.7%) and ABT-335 in combination with atorvastatin (3.8%) treatment groups had renal adverse events compared with subjects in the ABT-335 in combination with simvastatin treatment group (2.1%). The most common renal-related adverse events were blood creatinine increased (1.4% overall) and creatinine renal clearance decreased (1.6% overall).

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Table 7.3.5.OO. Renal Events, All Combination Therapy Analysis Set

	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	Total (N = 2201)
<b>Renal Events</b>	44 (3.7)	11 (2.1)	19 (3.8)	74 (3.4)
Blood creatinine increased	20 (1.7)	4 (0.8)	6 (1.2)	30 (1.4)
Discontinuations	5 (0.4)	1 (0.2)	1 (0.2)	7 (0.3)
Creatinine renal clearance decreased	21 (1.8)	3 (0.6)	12 (2.4)	36 (1.6)
Discontinuations	5 (0.4)	1 (0.2)	0	6 (0.3)
Renal failure	2 (0.2)	2 (0.4)	2 (0.4)	6 (0.3)
Discontinuations	0	1 (0.2)	1 (0.2)	2 (<0.1)
Renal failure acute	2 (0.2)	1 (0.2)	0	3 (0.1)
Discontinuations	1 (<0.1)	0	0	1 (<0.1)
Renal impairment	1 (<0.1)	2 (0.4)	2 (0.4)	5 (0.2)
Discontinuations	0	0	2 (0.4)	2 (<0.1)
Blood urea increased*	13 (1.1)	2 (0.4)	2 (0.4)	17 (0.8)
Renal disorder*	0	1 (0.2)	0	1 (<0.1)

\* Not included in the sponsor's analysis of renal events

Because adverse events of 'elevated BUN' were not captured in renal Preferred Terms, these events were not included as part of the renal analysis. The following narrative describes a case in which creatinine increased and creatinine clearance decreased in addition to the BUN increase:

Subject 14231 was a 74-year-old white female who was prematurely discontinued study drug on Day 63 due to elevated urea nitrogen. She was originally randomized to ABT-335 135 mg and rosuvastatin 20 mg in the M05-748 study. Medical history included chronic kidney disease, left kidney cyst, mixed dyslipidemia, hypertension, right carotid artery stenosis, and metabolic syndrome. Concomitant medications at the time of the event included acetylsalicylic acid, calcium, lisinopril/hydrochlorothiazide, and pioglitazone. She is an ex-smoker and a non-drinker. On Day 60, the subject was reported to have elevated urea nitrogen. Laboratory values are provided in the table below. The study drug was discontinued on Day 63. The event was considered resolved on Day 107 (Post Treatment Day 44) and the subject started rosuvastatin and fenofibrate therapy.

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Table 7.3.5.PP.

**Subject #14231 Fasting Laboratory Data**

Treatment Day	Urea Nitrogen Reference Range 4-29 mg/dL	Creatinine Reference Range 0.4-1.2 mg/dL	Creatinine Clearance Reference Range 78-118 mL/min
Screening (A05-748)	30	1.0	51
Baseline (A05-748)	34	1.0	47
Day 29 (A05-748)	39	1.6	29
Day 57 (A05-748)	33	1.4	35
Day 85 (A05-748)	41	1.5	32
Day 29 (A05-758)	37	1.4	34
Day 60 (A05-758)	54	1.9	26
Day 63 (A05-758)	41	1.3	37
Day 65 (2 days post study drug) (A05-758)	35	1.2	40

**Comment:** It would have been useful to have follow-up to see how her renal laboratory data were affected on the combination of fenofibrate and rosuvastatin.

The following laboratory data were compiled in order to describe the shifts in calculated creatinine clearance, BUN, and creatinine changes that occur with ABT-335 therapy in the controlled studies, and the proportion of subjects who experienced increases in creatinine and BUN and decreases in calculated creatinine clearance to  $\leq 30$  mL/min.

Table 7.3.5.QQ. Shifts in Creatinine, BUN, and Calculated Creatinine Clearance and Number of Subjects Meeting Criteria after Baseline for Potentially Clinically Significant Laboratory Values, Controlled Studies

	ABT-335 (N = 490)	Low-dose statin (N = 493)	ABT-335 + low statin (N = 499)	Moderate- dose statin (N = 491)	ABT-335 + moderate statin (N = 489)	High-dose statin (N = 245)
Calculated creatinine clearance: normal/high (baseline) shift to < LLN (minimum anytime during study)	81 (20.3)	32 (7.7)	104 (25.2)	37 (8.8)	87 (21.5)	11 (5.6)
Creatinine: low/normal (baseline) shift to > ULN (maximum anytime during the study)	67 (14.9)	13 (2.8)	79 (17.1)	15 (3.2)	69 (15.2)	6 (2.6)
BUN: low/normal (baseline) shift to > ULN (maximum anytime during the study)	64 (14.3)	28 (6.0)	66 (12.9)	21 (4.5)	56 (12.5)	12 (5.2)
Creatinine > 2 mg/dL	4/473 (0.8)	2/494 (0.4)	6/479 (1.3)	0/480	5/472 (1.1)	1/238 (0.4)
Creatinine $\geq 100\%$ increase from baseline	0/473	0/494	4/479 (0.8)	0/480	1/472 (0.2)	1/238 (0.4)
Creatinine $\geq 3$ (F); $\geq 3.5$ (M) mg/dL	0/473	0/474	0/479	0/480	1/472 (0.2)	0/238
BUN $\geq 40$ mg/dL	4/473 (0.8)	3/494 (0.6)	3/479 (0.6)	0/480	7/472 (1.5)	2/238 (0.4)
Creatinine clearance $\leq 30$ mL/min	1/473 (0.2)	0/494	0/479	0/480	2/472 (0.4)	0/238

**Comment:** Elevations in BUN and creatinine > ULN (and therefore decreases in calculated creatinine clearance) are common with ABT-335 as monotherapy or in combination with a statin. By contrast, the incidence of clinically significant changes in renal parameters is

infrequent, but these changes still occur at a greater rate than subjects treated with statins. There are too few events to determine if combination therapy leads to a greater incidence of clinically significant changes. Two of the subjects with creatinine clearance  $\leq 30$  mL/min during the study had calculated creatinine clearance  $< 50$  mL/min at baseline. The listing of these subjects is in the following table, and the one subject with creatinine  $\geq 3$  mg/dL is further described:

Table 7.3.5.RR.

LISTING OF SUBJECTS MEETING CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT CHEMISTRY VALUES IN PHASE 3 STUDIES  
(CONTROLLED STUDIES KINDELIS 007)

VARIABLE (UNIT) INVESTIGATION	TREATMENT	SUBJECT	AGE/ SEX	EVENTS	VALUES	CRITERIA
<b>CALCULATED CREATININE CLEARANCE (ML/MIN)</b>						
METHASA (13263)	ABT-338+STATIN MOD	32331	74F	-3	51.0	
				1 BL	47.0	
				23	29.0	$\leq 30$ ML/MIN
				27	35.0	
				28	31.0	
MIDOLETUM (31013)	ABT-338+STATIN MOD	33017	64F	-7	47.0	
				1 BL	49.0	
				24	42.0	
				27	25.0	
				28 (1)	18.0	$\leq 30$ ML/MIN
O'MANORF (33376)	ABT-338	31004	82F	-10	33.2	
				1 BL	31.2	
				23	25.2	$\leq 30$ ML/MIN
				28	33.2	
				27 (8)	29.8	$\leq 30$ ML/MIN

The datasets provided follow-up of the creatinine in subject 33017, the subject with the largest decrease in calculated creatinine clearance from baseline, and the one subject with serum creatinine  $\geq 3$  mg/dL in the controlled studies. This subject had a creatinine value of 3.4 mg/dL one day after study completion, but 23 days later the value had returned to 0.7 mg/dL. The datasets revealed the subject had AEs of abdominal distention, nasal congestion, and nausea six days before study completion.

**Comment:** Without a narrative or CRF, it is hard to know if this value was spurious, if there was a coincident event, or if this is a true drug-related event.

The following table presenting creatinine, BUN, and calculated creatinine clearance from study M05-758 demonstrate the long-term mean changes in these values.

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**Table 7.3.5.SS. Mean Change from Baseline to Final Value for Creatinine, BUN, and Calculated Creatinine Clearance**

	<b>ABT-335 + 20 mg rosuva</b>	<b>ABT-335 + 40 mg simva</b>	<b>ABT-335 + 40 mg atorva</b>	<b>Total</b>
<b>Initial ABT-335 Monotherapy<sup>a</sup></b>	<b>N=171</b>	<b>N=62</b>	<b>N=76</b>	<b>N=329</b>
Creatinine (mg/dL)	-0.00 (0.133)	0.01 (0.157)	-0.0 (0.154)	-0.00 (0.144)
BUN (mg/dL)	-0.80 (4.570)	-0.13 (4.054)	-0.48 (4.548)	-0.56 (4.437)
Calculated CrCl (mL/min)	-0.442 (13.4921)	-0.702 (16.4491)	-0.147 (15.0761)	-0.440 (14.6023)
<b>Initial Statin Monotherapy<sup>a</sup></b>	<b>N=493</b>	<b>N=195</b>	<b>N=205</b>	<b>N=893</b>
Creatinine (mg/dL)	0.13 (0.138)	0.14 (0.129)	0.14 (0.158)	0.14 (0.141)
BUN (mg/dL)	2.25 (3.957)	2.52 (3.847)	2.55 (4.149)	2.38 (3.977)
Calculated CrCl (mL/min)	-14.895 (15.6271)	-14.785 (15.0871)	-14.241 (15.3678)	-14.720 (15.4372)
<b>Initial Combination Therapy<sup>b</sup></b>	<b>N=522</b>	<b>N=237</b>	<b>N=220</b>	<b>N=979</b>
Creatinine (mg/dL)	0.13 (0.149)	0.13 (0.138)	0.12 (0.158)	0.13 (0.148)
BUN (mg/dL)	1.55 (4.415)	1.86 (4.395)	2.26 (4.591)	1.78 (4.454)
Calculated CrCl (mL/min)	-12.745 (16.9550)	-14.147 (15.8394)	-14.953 (19.2393)	-13.582 (17.2374)
<sup>a</sup> Baseline was defined as the last value before the first dose of combination therapy in M05-758. <sup>b</sup> Baseline was defined as the last value before the first dose of combination therapy in the double-blind study.				

**Comment:** The results in this table suggest that the incidence of adverse renal laboratory changes (with the possible exception of a slight increase in BUN) with ABT-335 therapy do not increase with the addition of statins. Because the mean changes are similar to what was seen in the controlled studies (see Table 7.4.2.H), this suggests that the risk of adverse renal laboratory changes does not significantly increase over time. The time course of laboratory renal findings is further discussed under Section 7.5.4, Drug-Disease Interactions.

In the open-label extension study, the incidence of subjects meeting criteria for potentially clinically significant renal laboratory values (see Table 7.3.5.TT) reflects the percentage of subjects who developed AEs of renal failure or insufficiency; that is, creatinine  $\geq 3$  (F) and  $\geq 3.5$  (M) mg/dL or calculated creatinine clearance  $\leq 30$  mL/min was 0.2% and 0.3%, respectively. The incidence of BUN  $\geq 40$  mg/dL was somewhat higher at 1.7%.

**Table 7.3.5.TT. Number of Subjects Meeting Criteria after Baseline for Chemistry Values of Special Interest for the All Combination Therapy Analysis Set**

<b>Laboratory Parameter Criteria</b>	<b>ABT-335 + rosuva (N=1186)</b>	<b>ABT-335 + simva (N=514)</b>	<b>ABT-335 + atorva (N=501)</b>	<b>Total (N=2201)</b>
<b>Creatinine &gt; 2 mg/dL</b>	15/1166 (1.3)	7/58 (1.4)	7/492 (1.4)	29/2166 (1.3)
<b>Creatinine ≥ 100% increase from baseline</b>	8/1166 (0.7)	6/508 (1.2)	5/492 (1.0)	19/2166 (0.9)

***Thrombosis Events***

This reviewer wanted to get a better understanding of the nature of deep vein thrombosis (DVT) and pulmonary embolus (PE) in the clinical trials and the potential risk of these conditions, including identified risk factors. The numbers of DVT and PE events were numerically higher in subjects treated with ABT-335 in the current NDA, and were found in excess in the fenofibrate group in the FIELD study<sup>6</sup> prompting labeling changes in the postmarketing section. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,875 in the fenofibrate group. For DVT, there were 48 events (0.98%) in the placebo group and 67 (1.37%) in the fenofibrate group ( $p = 0.074$ ); and for PE, there were 32 (0.65%) events in the placebo group and 53 (1.09%) in the fenofibrate group ( $p = 0.022$ ). A postmarketing review by the sponsor for Tricor (Abbott Laboratories, the sponsor of this NDA) was inconclusive with regards to DVT and PE adverse events.

The sponsor reviewed the serious adverse events of DVT in Study M05-758, and alternative risk factors were reported by the investigator in each case, although one of these cases (subject 32073) did not have recent surgery, prolonged immobility, or a hypercoagulable disorder. These cases are listed here, including one report from the safety update:

- Subject 14318 (ABT-335 + rosuvastatin) had the reported adverse event attributed by the investigator to a long car ride.
- Subject 14165 (ABT-335 + rosuvastatin) had the reported adverse event attributed by the investigator to the wearing of an orthopedic brace following a knee injury.
- Subject 14527 (ABT-335 + rosuvastatin) had the reported adverse event occur 23 days postoperatively following a protracted and complicated hospital course. The investigator attributed the event to a peripheral intravenous catheter used during the subject's hospitalization.
- Subject 12043 (ABT-335 + rosuvastatin) had the reported adverse event attributed by the investigator to prolonged sitting (> 5 hours) the day prior to the event, diabetes, dyslipidemia, hypertension, and smoking.
- Subject 32073 (ABT-335 + atorvastatin) had the reported adverse event attributed by the investigator to history of diabetes, sedentary lifestyle, obesity, and hyperlipidemia.

- **Subject 23132 (ABT-335 + simvastatin) had the reported adverse event attributed by the investigator to inactivity during a one-week boat trip.**

**In previous reviews of this topic, homocysteine has been invoked as a possible contributor<sup>34</sup> (fenofibrate is associated with homocysteine increases), but homocysteine was not available from these trials for review.**

**The following tables enumerate the subjects who experienced events of DVT and PE in the clinical trials. No subjects from studies M05-748 (+ rosuvastatin) or M05-749 (+ simvastatin) experienced these events. The only two subjects from M05-750 (+ atorvastatin) who had DVT or thrombophlebitis were randomized to ABT-335 (Table 7.3.5.UU). The majority of events were seen in Study M05-758 (Table 7.3.5.VV).**

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Table 7.3.5.UU. Venous thrombosis events, Study M05-750

Investigator/subject	Group	Age	Race	Sex	DM status	BL GFR	Exposure	Status	AE study day	FT	Discontinuation	Severity	SAE	Death
30962/1030	ABT-335 + raltegravir 20 mg	≥ 65 years	White	M	DM	≥ 60 ml/min/1.73m <sup>2</sup>	83	Completed	78	Deep vein thrombosis	No	Severe	Yes	No
33221/24130	ABT-335 + raltegravir 20 mg	< 65 years	White	F	Non-DM	≥ 60 ml/min/1.73m <sup>2</sup>	84	Completed	75	Thrombocytopenia	No	Moderate	No	No

Table 7.3.5.VV. Venous thrombosis events, Study M05-758

Investigator/subject	Controlled study group	OL study group	Age	Race	Sex	DM status	BL GFR	FT	Days in OL study	Days in prior to end of study	Discontinuation	Severity	SAE	Death
33509/12043	ABT-335 + raltegravir 20 mg	ABT-335 + raltegravir 20 mg	≥ 65 years	White	M	DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Deep vein thrombosis	15	-3	Yes	Severe	Yes	No
33501/12219	ABT-335	ABT-335 + raltegravir 20 mg	< 65 years	White	M	Non-DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Deep vein thrombosis	101	-1	Yes	Moderate	No	No
33363/14145	ABT-335	ABT-335 + raltegravir 20 mg	≥ 65 years	White	M	Non-DM	< 60 ml/min/1.73 m <sup>2</sup>	Pulmonary embolism	195	7	No	Severe	Yes	Yes
33368/14165	ABT-335 + raltegravir 10 mg	ABT-335 + raltegravir 20 mg	< 65 years	White	M	Non-DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Deep vein thrombosis	195	-3	Yes	Mild	Yes	No
33353/14318	Raltegravir 20 mg	ABT-335 + raltegravir 20 mg	< 65 years	White	F	Non-DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Pulmonary embolism	107	-3	Yes	Severe	Yes	No
33366/14903	Raltegravir 10 mg	ABT-335 + raltegravir 20 mg	< 65 years	White	M	Non-DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Deep vein thrombosis	110	1	No	Severe	Yes	No
12538/14527	ABT-335 + raltegravir 20 mg	ABT-335 + raltegravir 20 mg	< 65 years	White	M	Non-DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Thrombosis	101	-173	No	Moderate	No	No
31203/22057	ABT-335	ABT-335 + raltegravir 40 mg	< 65 years	White	M	Non-DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Deep vein thrombosis	151	-28	Yes	Severe	Yes	No
33473/22051	ABT-335	ABT-335 + raltegravir 40 mg	< 65 years	Black	M	DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Deep vein thrombosis	18	-30	No	Moderate	No	No
33285/22073	ABT-335	ABT-335 + raltegravir 40 mg	< 65 years	White	M	DM	≥ 60 ml/min/1.73 m <sup>2</sup>	Thrombosis	59	-12	Yes	Severe	Yes	No
								Deep vein thrombosis	76	-10	Yes	Mild	Yes	No
								Pulmonary embolism	76	-10	Yes	Moderate	Yes	No

The incidence of venous thrombosis from the Controlled Studies Analysis Set is 2/490 (0.41%) for the ABT-335 treatment group, and none in the other groups (N=489-493 for the low- and moderate-doses monotherapy and combination groups, and N=245 for the high-dose statin group). In the All Combination Therapy Analysis Set there were 2201 patients exposed, with 1534.1 patient-years of exposure. Therefore, the incidence of venous thrombosis was calculated by this reviewer as 10/2201 (0.45%), or 8 events/1000 PY in subjects treated with combined therapy.

**Comment:** A Norwegian population-based study<sup>36</sup> estimated the incidence of venous thrombosis events in a population of all residents in the Nord-Trøndelag county in central Norway, aged 20 years or more (n=94,194). In this study, the first event of DVT was estimated to be 0.93 per 1000 person-years (95% CI: 0.85-1.02) and that of PE 0.50 per 1000 PY (95% CI: 0.44-0.56). The incidence of all first venous thrombosis (VT) events was 1.43 per 1000 PY (95% CI: 1.33-1.54). Although dyslipidemia was not an identified risk factor in this publication, this reviewer located a case control study that did suggest an association, with an odds ratio of 5.1 (95% CI 2.0-13.0) of DVT for dyslipidemia (hypercholesterolemia + hypertriglyceridemia).<sup>37</sup> To the knowledge of this reviewer, there is no estimate of the incidence of DVT in the dyslipidemia population. The incidence of 8 events /1000 PY is more than five times the upper limit of the 95% CI for total first VTEs based on the Norwegian study; nevertheless, without knowing the incidence in the dyslipidemia population and without clear corroborating postmarketing data, it is hard to know how strong this signal is. It appears that the data from the NDA may be consistent with the fenofibrate and DVT/PE finding from the FIELD study.

#### *Pancreatitis*

There were three cases of pancreatitis in the Phase 3 trials (1 ABT-335 + rosuvastatin 10 mg, study M05-748; 1 ABT-335 + rosuvastatin 20 mg, study M05-758; 1 ABT-335 + atorvastatin 40 mg, study M05-758); all were SAEs, and the narratives are presented below.

Subject 14116 (ABT-335 and rosuvastatin 10 mg) is a 66-year-old white female who was hospitalized on \_\_\_\_\_ (Day 29) for nausea, diaphoresis, dizziness, and shortness of breath and hospitalized on \_\_\_\_\_ (Day 44) for sharp, shooting pain in the epigastric region, with nausea and bilious vomiting. Relevant medical history included hypertension, mixed hyperlipidemia, gastroesophageal reflux disease, diverticulosis, palpitations, lumbar back pain, first-degree atrio-ventricular block, leg cramps, restless leg, cold sores, and allergic rhinitis. Concomitant medications at the time of the event included paracetamol/codeine phosphate, ibuprofen, losartan potassium/hydrochlorothiazide, acyclovir, quinine, paracetamol, dextropropoxyphene napsylate/paracetamol hydrochlorothiazide, and pregabalin. The subject is a current smoker of cigarettes (37.5 pack-years) and a current light drinker.

b(6)

36 Naess IA, et al. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost.* 2007 5(4):692-9.

37 Kawasaki T, et al. Hypercholesterolemia as a risk factor for deep-vein thrombosis. *Thromb Res.* 1997 88(1):67-73.

The first event occurred on Day 29 when the subject reported nausea, diaphoresis, dizziness, and shortness of breath and was hospitalized for unspecified chest pain. Peak CPK-MB was 5.2 mg/mL (reference range  $\leq 5.0$  mg/mL) and troponin level was  $< 0.1$  ng/mL (reference range  $\leq 0.3$  ng/mL). On Day 29, the study drug was discontinued and acetylsalicylic acid was started. On Day 30, the subject began treatment with simvastatin. On Day 31, the subject underwent a cardiac catheterization, which showed insignificant coronary artery disease, normal left ventricular systolic function and mild dilatation of the aorta without dissection. On Day 31, the subject recovered from the unspecified chest pain and was discharged in stable condition.

The second event occurred on Day 44, when the subject reported sharp, shooting pain, which started in the epigastric region and was associated with nausea and vomiting after eating. The subject had an acute elevation in amylase of 1261 U/L (reference range 25-125 U/L) and lipase 3371 U/L (reference range 7-58 U/L), which decreased over the course of approximately three days and improved with intravenous fluids. A computed tomography scan was consistent with pancreatitis. An abdominal ultrasound revealed a normal gallbladder without indication of biliary dilatation and a tiny  $17 \times 10$  mm cyst in the head of the pancreas. The subject reported taking 2400 mg per day of ibuprofen for the past 10 months. During the hospitalization the subject developed a decrease in bowel movements and an acute abdominal series performed revealed retained contrast (from computed tomography scan performed on admission) in prominent small bowel loops. A surgical consult diagnosed ileus. The subject was given bowel protocols improving the condition. An upper gastrointestinal endoscopy performed revealed reflux esophagitis, hiatal hernia, non-bleeding erythematous gastropathy and normal duodenum. Treatment medications included hydromorphone hydrochloride, promethazine, losartan, heparin, famotidine, pantoprazole, vancomycin, salbutamol, ipratropium bromide/albuterol sulfate, furosemide, bisacodyl, potassium, sucralfate, and docusate. On Day 54, the subject recovered from the acute pancreatitis and was discharged in stable condition. The investigator considered the event of chest pain to be probably not related to study drug, but rather to heart disease. The investigator considered the event of acute pancreatitis to be not related to study drug, but rather to simvastatin.

**Comment: The event might have been related to the initial presentation of chest pain and nausea two weeks earlier. The patient's triglyceride concentrations were not presented in the case, although the datasets report a final TG of 143 mg/dL.**

Subject 11083 (ABT-335 135 mg and rosuvastatin 20 mg) is a 59-year-old white male who was hospitalized on Day 111 with epigastric abdominal pain with a final diagnosis of pancreatitis and gallstones. Relevant medical history included coronary artery disease with prior stent placement, hypertension, diabetes mellitus, hypercholesterolemia, and right upper extremity pain. Concomitant medications at the time of the event included lisinopril, glimepiride, clopidogrel, metoprolol, hydrocodone/acetaminophen, and oxycodone. The subject is an ex-smoker (40 pack-years) and a current light drinker.

On Day 110, the subject reported severe epigastric abdominal pain and presented to the emergency department and was admitted on Day 111 for pancreatitis and gallstones. Relevant labs included amylase 1829 (reference range: 36-128 IU/L) and lipase 1656 (reference range: 22-51 IU/L). On Day 111, an ultrasound confirmed the final diagnosis of gallstones. On Day 115, a

laparoscopic cholecystectomy with intraoperative cholangiogram was performed. A possible intraoperative filling defect was noted on the cholangiogram. The subject was treated with hyoscyamine, morphine, ondansetron, hydrocodone/acetaminophen, and gentamicin. Study drug was interrupted on Day 112 and re-introduced on Day 116. The events of pancreatitis and gallstones were considered resolved on Day 116 and the subject was discharged from the hospital in stable condition.

On Day 149, study drug was discontinued and the subject returned for an early termination visit due to these events. No further information was provided. The investigator considered the event of pancreatitis to be probably not related to study drug but rather to hyperlipidemia and the non-serious adverse event of cholelithiasis to be probably not related to study drug.

**Comment: It is not clear why the study drug was discontinued 33 days after it was reintroduced and the event (gallstone pancreatitis) was considered resolved.**

Subject 34047 (ABT-335 135 mg and atorvastatin 40 mg) is a 63-year-old white male who was hospitalized on Day 136 for abdominal pain that was diagnosed as pancreatitis. Relevant medical history included abdominal pain, gastroesophageal reflux disease, hyperlipidemia with elevated triglycerides, hypertension, obesity, osteoarthritis, deep venous thrombosis, headache, and benign prostatic hyperplasia. Concomitant medications at the time of the event included metoprolol, quinapril, triamterene/hydrochlorothiazide, and acetaminophen. The subject is a non-smoker and a non-drinker.

On Day 136, the subject awoke five hours after eating dinner with severe periumbilical abdominal pain and nausea, followed by emesis, melanic stool and diarrhea that prompted hospital admission. The subject reported a similar postprandial episode 2 years previously that resolved spontaneously. Per the admission summary, there was minimal periumbilical tenderness with normal bowel sounds and no guarding on abdominal exam.

Admission labs showed a glucose of 172 mg/dL (reference range: 70-99 mg/dL), hemoglobin of 14.9 g/dL (reference range: 13-16.5 g/dL), platelets of 312,000/uL (reference range: 140,000-440,000/uL), lipase of 405, lactate of 3.7 (laboratory normal ranges and units not provided), and leukocytosis of 15,100 (reference range: 4,000-12,000/uL) with 83% neutrophils. Liver function tests (including transaminases, bilirubin, and alkaline phosphatase) were reported as normal.

Acute abdominal x-ray series suggested an early or incomplete small bowel obstruction, as did computed tomography scan of the abdomen. There was no evidence of pancreatic or gallbladder disease on CT. Subsequent small bowel follow-through study was noted as unremarkable. Esophagogastroduodenoscopy revealed esophagitis and hiatal hernia (as well as a possible small finger of Barrett's esophagus) that prompted initiation of esomeprazole therapy. Hepatobiliary scan showed normal gallbladder function with an ejection fraction of 56%. There was some reproducibility of pain with cholecystikinin administration, which was thought to suggest irritable bowel syndrome in the setting of normal gallbladder function. The subject received intravenous fluids, morphine, hydrocodone/acetaminophen, fentanyl, acetaminophen, midazolam, ondansetron, promethazine, levofloxacin, and tamsulosin. The subject had pain resolution and diet tolerance and was felt to be stable for discharge. Study drug was interrupted

from Day 136 to Day 141. The event was considered resolved on Day 140. The subject completed M05-758 study drug therapy on Day 363.

**Comment:** Although the lipase was modestly elevated, the CT evaluation of the pancreas was negative. Triglyceride concentrations for this subject are not provided, although the datasets report TGs in the range of 163-297 mg/dL. It is notable that the subject was rechallenged with the drug without obvious adverse sequelae.

**Overall comment:** In summary, an association between ABT-335 as monotherapy or in combination and pancreatitis is difficult to establish from these three cases. At least one of the cases appears to be due to gallstones rather than the drug, *per se*, although the drug may have played a role indirectly if in fact there is an increase in the risk of gallstone formation with ABT-335 (an infrequent adverse event in these trials). None of these cases exhibited evidence of necrotizing or hemorrhagic pancreatitis.

## 7.4 Supportive Safety Results and Discussion

### 7.4.1 Common Adverse Events

#### *Phase 1 Studies*

A total of 181 (36.6%) of subjects who received at least one dose of ABT-335 in the Phase 1 studies had at least one treatment-emergent adverse event. The most frequently reported treatment-emergent adverse event was headache (11.5%). The next most frequent were: nausea (3.4%), diarrhea (3.0%), viral upper respiratory infection (2.8%), and pharyngolaryngeal pain (2.2%).

#### Phase 3 Studies

#### Controlled Studies

A statistically significantly greater percentage of subjects had treatment-emergent adverse events in the ABT-335 in combination with low-dose statin group compared to the low-dose statin group (68.4% vs. 60.4%). Across all other treatment groups, one or more treatment-emergent adverse events were reported for similar proportions of subjects (64.1 to 66.7%).

Overall, the most frequently reported ( $\geq 5.0\%$  in any treatment group) adverse events were headache, back pain, nasopharyngitis, nausea, myalgia, diarrhea, and upper respiratory tract infection (Table 7.4.1.A). Of these events, myalgia and diarrhea were reported as adverse events for 6.1% and 6.9% of subjects, respectively, in the high-dose statin monotherapy group and  $\leq 5.0\%$  of subjects in each of the other treatment groups.

As discussed in Section 7.3.5, adverse events of ALT and AST increased were greater in the ABT-335 groups than in the statin monotherapy groups. The incidence of PT 'blood CPK increased' was statistically significantly greater in the ABT-335 + low-dose statin group as compared to the low-dose statin monotherapy group.

Table 7.4.1.A. Summary of Treatment-Emergent Adverse Events Reported for at Least 2.0% of Subjects in Any Treatment Group for the Controlled Studies Analysis Set

System Organ Class MedDRA Preferred Term	Treatment Group n (%)					
	ABT-336 (N = 490)	Low-dose statin (N = 493)	ABT-336 + low statin (N = 490) <sup>a</sup>	Moderate- dose statin (N = 491)	ABT-336 + moderate statin (N = 489)	High-dose statin (N = 246)
Any Adverse Event	327 (66.7)	296 (60.4)	335 (68.4) <sup>a</sup>	327 (66.6)	323 (66.1)	157 (64.1)
<b>Gastrointestinal Disorders</b>						
Abdominal pain	10 (2.0)	5 (1.0)	7 (1.4)	5 (1.0)	9 (1.8)	4 (1.6)
Abdominal pain upper	11 (2.2)	8 (1.6)	13 (2.7)	8 (1.6)	8 (1.6)	4 (1.6)
Constipation	16 (3.3)	11 (2.2)	16 (3.3)	13 (2.6)	15 (3.1)	6 (2.4)
Diarrhea	19 (3.9)	16 (3.2)	15 (3.1)	24 (4.9)	18 (3.7)	17 (6.9)
Dyspepsia	18 (3.7)	13 (2.6)	13 (2.7)	17 (3.5)	23 (4.7)	6 (2.4)
Flattulence	5 (1.0)	4 (0.8)	8 (1.6)	6 (1.2)	7 (1.4)	5 (2.0)
Nausea	21 (4.3)	18 (3.7)	17 (3.5)	22 (4.5)	27 (5.5)	10 (4.1)
Stomach discomfort	8 (1.6)	6 (1.2)	7 (1.4)	7 (1.4)	6 (1.2)	7 (2.9)
Vomiting	8 (1.6)	7 (1.4)	5 (1.0)	4 (0.8)	7 (1.4)	7 (2.9)
<b>General Disorders and Administration Site Conditions</b>						
Fatigue	10 (2.0)	13 (2.6)	13 (2.7)	13 (2.6)	16 (3.3)	5 (2.0)
Oedema peripheral	4 (0.8)	9 (1.8)	8 (1.6)	10 (2.0) <sup>b</sup>	2 (0.4)	4 (1.6)
Pain	17 (3.5)	9 (1.8)	16 (3.3)	8 (1.6)	7 (1.4)	8 (3.3)
<b>Infections and Infestations</b>						
Influenza	1 (0.2)	6 (1.2)	7 (1.4)	6 (1.2)	6 (1.2)	5 (2.0)
Nasopharyngitis	17 (3.5)	29 (5.9)	23 (4.7)	16 (3.3)	21 (4.3)	9 (3.7)
Sinusitis	16 (3.3)	4 (0.8)	14 (2.9) <sup>a</sup>	8 (1.6)	17 (3.5)	4 (1.6)
Upper respiratory tract infection	26 (5.3)	13 (2.6)	18 (3.7)	23 (4.7)	23 (4.7)	7 (2.9)

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System Organ Class MedDRA 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 = 248)
<b>Injury, Poisoning and Procedural Complications</b>						
Procedural pain	2 (0.4)	1 (0.2)	0	2 (0.4)	2 (0.4)	5 (2.0)
<b>Investigations</b>						
ALT increased	6 (1.2)	2 (0.4)	15 (3.1) <sup>a</sup>	2 (0.4)	12 (2.5) <sup>b</sup>	4 (1.6)
AST increased	4 (0.8)	2 (0.4)	14 (2.9) <sup>a,c</sup>	1 (0.2)	11 (2.2) <sup>b</sup>	4 (1.6)
Blood CPK increased	4 (0.8)	4 (0.8)	13 (2.7) <sup>a,c</sup>	11 (2.2)	6 (1.2)	8 (3.3)
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Arthralgia	19 (3.9)	22 (4.5)	21 (4.3)	21 (4.3)	17 (3.5)	12 (4.9)
Back pain	31 (6.3)	31 (6.3)	30 (6.1)	32 (6.5)	20 (4.1)	8 (3.3)
Muscle spasms	8 (1.6)	18 (3.7)	12 (2.4)	24 (4.9)	15 (3.1)	6 (2.4)
Musculoskeletal pain	6 (1.2)	5 (1.0)	7 (1.4)	10 (2.0)	7 (1.4)	2 (0.8)
Myalgia	16 (3.3)	24 (4.9)	17 (3.5)	23 (4.7)	15 (3.1)	15 (6.1)
Osteoarthritis	3 (0.6)	1 (0.2)	3 (0.6)	2 (0.4)	4 (0.8)	5 (2.0)
Pain in extremity	22 (4.5)	24 (4.9)	14 (2.9)	21 (4.3)	13 (2.7)	9 (3.7)
<b>Nervous System Disorders</b>						
Dizziness	20 (4.1)	8 (1.6)	19 (3.9) <sup>a</sup>	11 (2.2)	16 (3.3)	2 (0.8)
Headache	62 (12.7)	64 (13.0)	64 (13.1)	82 (16.7) <sup>b</sup>	58 (11.9)	32 (13.1)
<b>Psychiatric Disorders</b>						
Insomnia	10 (2.0)	7 (1.4)	8 (1.6)	8 (1.6)	13 (2.7)	6 (2.4)
<b>Vascular Disorders</b>						
Hypertension	2 (0.4)	1 (0.2)	10 (2.0) <sup>a,c</sup>	4 (0.8)	6 (1.2)	3 (1.2)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Cough	11 (2.2)	10 (2.0)	11 (2.2)	7 (1.4)	12 (2.5)	10 (4.1)
Pharyngolaryngeal pain	9 (1.8)	12 (2.4)	9 (1.8)	9 (1.8)	10 (2.0)	4 (1.6)
Rhinorrhoea	7 (1.4)	1 (0.2)	4 (0.8)	2 (0.4)	1 (0.2)	5 (2.0)

Note: Includes data from Studies M05-748, M05-749, and M05-750.

a. Statistically significant difference between ABT-335 in combination with low statin and low-dose statin,  $p \leq 0.05$

b. Statistically significant difference between ABT-335 in combination with moderate statin and moderate-dose statin,  $p \leq 0.05$

c. Statistically significant difference vs. ABT-335,  $p \leq 0.05$

### All Combination Therapy

Across the three treatment groups in the All Combination Therapy analysis set, one or more treatment-emergent adverse events were reported for 81.6% of subjects (ABT-335 + rosuvastatin: 81.8%, ABT-335 + simvastatin: 82.3%, and ABT-335 + atorvastatin: 80.6%) across the double-blind and open-label studies.

Overall, the most frequently reported ( $\geq 5.0\%$  in any treatment group) adverse events were headache, upper respiratory tract infection, nasopharyngitis, back pain, diarrhea, dyspepsia, nausea, sinusitis, muscle spasms, pain in extremity, cough and arthralgia (Table 7.4.1.B).

Treatment-emergent adverse events occurring in  $\geq 2.0\%$  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 hepatic enzyme increased (highest incidence in the ABT-335 +

atorvastatin group), tooth abscess (highest incidence in the ABT-335 + atorvastatin group), and anxiety (highest incidence in the ABT-335 + rosuvastatin group). Hepatic enzyme elevations were discussed with other hepatic adverse events of interest in Section 7.3.5.

Table 7.4.1.B. Summary of Treatment-Emergent Adverse Events Reported for at Least 2.0% of Subjects in Any Treatment Group for the All Combination Therapy Analysis Set

System Organ Class MedDRA Preferred Term	Treatment Group n (%)			Total (N = 2201)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	
Any Adverse Event	970 (81.8)	423 (82.3)	404 (80.6)	1797 (81.6)
<b>Gastrointestinal Disorders</b>				
Abdominal pain	18 (1.5)	10 (1.9)	11 (2.2)	39 (1.8)
Abdominal pain upper	27 (2.3)	15 (2.9)	9 (1.8)	51 (2.3)
Constipation	54 (4.6)	16 (3.1)	14 (2.8)	84 (3.8)
Diarrhoea	48 (4.0)	25 (4.9)	30 (6.0)	103 (4.7)
Dyspepsia	41 (3.5)	24 (4.7)	26 (5.2)	91 (4.1)
Gastroesophageal reflux disease	25 (2.1)	14 (2.7)	12 (2.4)	51 (2.3)
Nausea	61 (5.1)	22 (4.3)	34 (6.8)	117 (5.3)
Toothache	21 (1.8)	14 (2.7)	10 (2.0)	45 (2.0)
Vomiting	25 (2.1)	7 (1.4)	12 (2.4)	44 (2.0)
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	42 (3.5)	17 (3.3)	15 (3.0)	74 (3.4)
Oedema peripheral	28 (2.4)	8 (1.6)	12 (2.4)	48 (2.2)
Pain	28 (2.4)	17 (3.3)	13 (2.6)	58 (2.6)
Pyrexia	15 (1.3)	7 (1.4)	10 (2.0)	32 (1.5)
<b>Infections and Infestations</b>				
Bronchitis	57 (4.8)	23 (4.5)	18 (3.6)	98 (4.5)
Gastroenteritis	20 (1.7)	6 (1.2)	10 (2.0)	36 (1.6)
Gastroenteritis viral	22 (1.9)	11 (2.1)	8 (1.6)	41 (1.9)
Influenza	28 (2.4)	17 (3.3)	23 (4.6)	68 (3.1)
Nasopharyngitis	107 (9.0)	59 (11.5)	52 (10.4)	218 (9.9)
Sinuzitis	82 (6.9)	31 (6.0)	33 (6.6)	146 (6.6)
Tooth abscess	12 (1.0)	4 (0.8)	10 (2.0)	26 (1.2)
Upper respiratory tract infection	139 (11.7)	52 (10.1)	50 (10.0)	241 (10.9)
Urinary tract infection	47 (4.0)	8 (1.6)	19 (3.8)	74 (3.4)
<b>Investigations</b>				
ALT increased	27 (2.3)	10 (1.9)	14 (2.8)	51 (2.3)
AST increased	26 (2.2)	9 (1.8)	15 (3.0)	50 (2.3)
Blood CPK increased	42 (3.5)	20 (3.9)	17 (3.4)	79 (3.6)
Creatinine renal clearance decreased	21 (1.8)	3 (0.6)	12 (2.4)	36 (1.6)
Hepatic enzyme increased	8 (0.7)	3 (0.6)	16 (3.2)	27 (1.2)

System Organ Class MedDRA Preferred Term	Treatment Group n (%)			Total (N = 2201)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Arthralgia	84 (7.1)	48 (9.3)	31 (6.2)	163 (7.4)
Back pain	111 (9.4)	47 (9.1)	36 (7.2)	194 (8.8)
Muscle spasms	51 (4.3)	26 (5.1)	28 (5.6)	105 (4.8)
Musculoskeletal pain	31 (2.6)	18 (3.5)	12 (2.4)	61 (2.8)
Myalgia	54 (4.6)	21 (4.1)	24 (4.8)	99 (4.5)
Neck pain	19 (1.6)	11 (2.1)	6 (1.2)	36 (1.6)
Pain in extremity	48 (4.0)	27 (5.3)	30 (6.0)	105 (4.8)
<b>Nervous System Disorders</b>				
Dizziness	48 (4.0)	15 (2.9)	21 (4.2)	84 (3.8)
Headache	151 (12.7)	67 (13.0)	71 (14.2)	289 (13.1)
Sinus headache	24 (2.0)	10 (1.9)	7 (1.4)	41 (1.9)
<b>Psychiatric Disorders</b>				
Anxiety	28 (2.4)	5 (1.0)	3 (0.6)	36 (1.6)
Depression	20 (1.7)	14 (2.7)	6 (1.2)	40 (1.8)
Insomnia	39 (3.3)	16 (3.1)	15 (3.0)	70 (3.2)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>				
Cough	43 (3.6)	30 (5.8)	26 (5.2)	99 (4.5)
Nasal congestion	13 (1.1)	15 (2.9)	12 (2.4)	40 (1.8)
Pharyngolaryngeal pain	22 (1.9)	19 (3.7)	21 (4.2)	62 (2.8)
Sinus congestion	28 (2.4)	8 (1.6)	13 (2.6)	49 (2.2)
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash	21 (1.8)	8 (1.6)	14 (2.8)	43 (2.0)
<b>Vascular Disorders</b>				
Hypertension	41 (3.5)	12 (2.3)	7 (1.4)	60 (2.7)

Note: Includes data from Studies M05-748, M05-749, M05-750, and M05-758.

rosuva = 10 or 20 mg rosuvastatin; simva = 20 or 40 mg simvastatin; atorva = 20 or 40 mg atorvastatin

### *Less Common Adverse Events*

Less common adverse events of interest are discussed in Section 7.3.5.

### 7.4.2 Laboratory Findings

#### *Hematology*

The following table presents mean hematological changes in the Controlled Studies Analysis Set:

**Table 7.4.2.A. Statistically Significant Differences between Combination Therapy and Monotherapy in Mean Change from Baseline to Final Hematology Value for the Controlled Studies Analysis Set, Red Cells and Platelets**

Hematology Parameter	Treatment Group n (%)					
	ABT-335	Low-dose statin	ABT-335 + low statin	Moderate-dose statin	ABT-335 + moderate statin	High-dose statin
	(N = 469)	(N = 483)	(N = 469)	(N = 491)	(N = 489)	(N = 246)
<b>Hemoglobin (g/dL)</b>	(N=471)	(N=483)	(N=477)	(N=488)	(N=471)	(N=238)
Baseline mean	14.0	14.1	14.0	14.1	14.1	14.3
Mean $\Delta$ to Final Value	-0.3 (0.73)	-0.1 (0.71)	-0.4 (0.70) <sup>a</sup>	-0.1 (0.70)	-0.4 (0.70) <sup>b</sup>	-0.2 (0.70)
<b>Hematocrit</b>	(N=471)	(N=483)	(N=477)	(N=479)	(N=471)	(N=238)
Baseline mean	0.429	0.432	0.428	0.433	0.431	0.435
Mean $\Delta$ to Final Value	-0.010 (0.0242)	-0.005 (0.0240)	-0.012 (0.0248) <sup>a</sup>	-0.005 (0.0233)	-0.012 (0.0232) <sup>b</sup>	-0.008 (0.0247)
<b>RBC (<math>\times 10^{12}/L</math>)</b>	(N=471)	(N=483)	(N=477)	(N=488)	(N=471)	(N=238)
Baseline mean	4.92	4.96	4.95	5.01	4.97	4.96
Mean $\Delta$ to Final Value	-0.12 (0.270)	-0.06 (0.264)	-0.15 (0.266) <sup>a</sup>	-0.07 (0.270)	-0.15 (0.259) <sup>b</sup>	-0.09 (0.264)
<b>Platelet Count (<math>\times 10^9/L</math>)</b>	(N=469)	(N=483)	(N=474)	(N=473)	(N=470)	(N=238)
Baseline mean	268.3	264.8	262.7	264.5	268.3	258.0
Mean $\Delta$ to Final Value	33.3 (45.65)	-1.0 (36.41)	24.0 (38.45) <sup>a,c</sup>	-4.2 (37.14)	20.3 (43.31) <sup>b,c</sup>	-0.8 (33.18)

Note: Includes data from Studies 3005-748, 3005-749, and 3005-750.

Note: Baseline was defined as the last value before the first dose of study drug.

$\Delta$  = change; SD = standard deviation

- Statistically significant difference between ABT-335 in combination with low statin and low-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference between ABT-335 in combination with moderate statin and moderate-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference vs. ABT-335 ( $p \leq 0.05$ ) based on a one-way ANOVA

Mean changes in hematocrit or hemoglobin were small, but statistically significant between the ABT-335 in combination with statin groups as compared to their respective monotherapy statin groups. Hematological changes are a known risk of fenofibrate and are described in the Tricor label as follows (under Precautions):

*Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.*

Reassuringly, the incidence of adverse events of anemia was low and no consistent pattern was evident for the ABT-335-treated groups as compared to statin monotherapy in the controlled studies, as seen in Table 7.4.2.B (this reviewer did not include cases of anemia due to other causes, such as B12 deficiency anemia). In addition, no subject in any group in the controlled studies dataset (first 12 weeks) experienced  $Hb \leq 8$  g/dL; see Table 7.4.2.G below for the findings from the All Combination Therapy Analysis Set. There were no events of

agranulocytosis, red cell aplasia, or bone marrow failure in any of the provided datasets. One event of neutropenia was seen in a subject randomized to rosuvastatin 10 mg in the M05-748 study.

Table 7.4.2.B. Anemia adverse events, All 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)
PT: Anemia	0 (0%)	1 (0.2%)	2 (0.4%)	4 (0.8%)	3 (0.6%)	0 (0%)
Note: Includes data from Studies M05-748, M05-749, and M05-750.						

Somewhat contrary to what has been seen with platelet count with fenofibrate (lowered) as well as with the other hematological parameters with ABT-335 treatment (hematocrit and hemoglobin lowered), the platelet count appears to increase with ABT-335 treatment. As seen in Table 7.4.2.A., the mean increase in platelet count in the ABT-335 group from the controlled studies was  $33.3 \times 10^9/L$ . This increase appears to be attenuated with the addition of a statin, in a dose-related fashion. The following tables enumerate the adverse events associated with increased platelet counts or thrombocytosis ('thrombocytæmia').

Table 7.4.2.C. Adverse Events of Increased Platelet Count, Randomized Studies

Randomized Study	Investigator	Subject	Treatment Group	Days of Exposure to Study Drug	SOC	PT	Discontinuation	Severity	AE	Death
M05-748	33189	14526	ABT-335	57	Blood and Lymphatic System Disorders	Thrombocytæmia	No	Mild	No	No
M05-749	33227	23088	ABT-335 + simvastatin 20 mg	28	Investigations	Platelet Count Increased	Yes	Severe	No	No

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Table 7.4.2.D. Adverse Events of Increased Platelet Count, Study M05-758

Investigator	Subject	Treatment In The Randomized Trial	Treatment Group In Study M05-758	Days Of Exposure To Combination Therapy	SOC	PT	Discontinuation	Severity	SAE	Death
17166	13265	ABT-335 + rosuvastatin 20 mg	ABT-335 + rosuvastatin 20 mg	287	Blood and Lymphatic System Disorders	Thrombocythaemia	No	Mild	No	No
17166	13443	ABT-335 + rosuvastatin 10 mg	ABT-335 + rosuvastatin 20 mg	197	Blood and Lymphatic System Disorders	Thrombocythaemia	No	Mild	No	No
33370	12114	Rosuvastatin 20 mg	ABT-335 + rosuvastatin 20 mg	28	Investigations	Platelet Count Increased	No	Mild	No	No
				85	Investigations	Platelet Count Increased	Yes	Moderate	No	No
33498	13331	Rosuvastatin 20 mg	ABT-335 + rosuvastatin 20 mg	58	Investigations	Platelet Count Increased	Yes	Moderate	No	No
12314	24058	ABT-335 + simvastatin 40 mg	ABT-335 + simvastatin 40 mg	173	Investigations	Platelet Count Increased	No	Moderate	No	No
15205	23270	Simvastatin 40 mg	ABT-335 + simvastatin 40 mg	72	Blood and Lymphatic System Disorders	Thrombocythaemia	No	Mild	No	No

One subject had a platelet count  $\geq 1,000 \times 10^9/L$  in any of the trials and was subsequently discontinued: this was an 81-year-old female who had a baseline platelet count of  $893 \times 10^9/L$  and was treated with rosuvastatin 20 mg during study M05-748. During that time, her platelet count was essentially unchanged. During the M05-758, when she was treated with ABT-335 + rosuvastatin 20 mg, her platelet count increased as follows, and she was discontinued and treated with aspirin for stroke prevention.

Table 7.4.2.E.

**Subject #13331 Fasting Laboratory Data**

Treatment Day	Platelets ( $\times 10^3 / \mu L$ ) Reference Range $130-394 \times 10^3 / \mu L$
Screening (M05-748)	771
Baseline (M05-748)	893
Day 30 (M05-748)	777
Day 59 (M05-748)	885
Day 92/Final Visit (M05-748)	883
Day 29 (M05-758)	967
Day 56 (M05-758)	1037
Day 61 (3 days post study drug) (M05-758)	1040
Day 98 (40 days post study drug)/Final Visit (M05-758)	1045

In the controlled trials, there is some suggestion that ABT-335 lowers WBC and neutrophils, and perhaps that statins may attenuate this decrease (Table 7.4.2.F). Two subjects in the controlled studies had a WBC  $\leq 2.5 \times 10^9/L$ ; both were randomized to ABT-335 monotherapy.

**Table 7.4.2.F. Statistically Significant Differences between Combination Therapy and Monotherapy in Mean Change from Baseline to Final Hematology Value for the Controlled Studies Analysis Set, White Cells**

Hematology Parameter	Treatment Group n (%)					
	ABT-335 (N = 490)	Low-dose statin (N = 493)	ABT-335 + low statin (N = 490)	Moderate- dose statin (N = 493)	ABT-335 + moderate statin (N = 489)	High-dose statin (N = 248)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<b>WBC (<math>\times 10^9/L</math>)</b>						
Baseline mean	(N=471) 6.61	(N=483) 6.57	(N=477) 6.38	(N=480) 6.56	(N=471) 6.54	(N=238) 6.55
Mean $\Delta$ to Final Value	-0.10 (1.346)	0.27 (1.193)	0.05 (1.271) <sup>a</sup>	0.30 (1.423)	-0.02 (1.276) <sup>b</sup>	0.28 (1.273)
<b>Neutrophils (<math>\times 10^9/L</math>)</b>						
Baseline mean	(N=471) 3.990	(N=483) 3.983	(N=477) 3.792	(N=480) 3.941	(N=471) 3.933	(N=238) 3.928
Mean $\Delta$ to Final Value	-0.110 (1.1828)	0.211 (1.0242)	0.029 (1.0438) <sup>a</sup>	0.259 (1.2460)	-0.045 (1.0783) <sup>b</sup>	0.233 (1.0329)
<b>Eosinophils (<math>\times 10^9/L</math>)</b>						
Baseline mean	(N=471) 0.154	(N=483) 0.148	(N=477) 0.148	(N=480) 0.150	(N=471) 0.144	(N=238) 0.138
Mean $\Delta$ to Final Value	0.022 (0.1031)	0.015 (0.0981)	0.019 (0.0913)	0.007 (0.0919)	0.021 (0.1011) <sup>b</sup>	0.006 (0.0781)

Note: Includes data from Studies M05-748, M05-749, and M05-750.

Note: Baseline was defined as the last value before the first dose of study drug.

$\Delta$  = change; SD = standard deviation

- Statistically significant difference between ABT-335 in combination with low statin and low-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference between ABT-335 in combination with moderate statin and moderate-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference vs. ABT-335 ( $p \leq 0.05$ ) based on a one-way ANOVA

There was only one adverse event of 'neutropenia' in the clinical trials, in a subject randomized to rosuvastatin 10 mg in study M05-748.

The following table described the number of subjects from the All Combination Therapy Analysis Set (including open-label study M05-758), who met potentially clinically significant values for the following hematology parameters:

**Table 7.4.2.G. Number of Subjects Meeting Criteria after Baseline for Potentially Clinically Significant Laboratory Values for the All Combination Therapy Analysis Set**

Laboratory Parameter Criteria <sup>a</sup>	Treatment Group n/N (%)			Total (N = 2201)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	
<b>Hemoglobin:</b>				
≤ 8 g/dL	2/1166 (0.2)	2/506 (0.4)	0/492	4/2164 (0.2)
≥ 18 g/dL	7/1166 (0.6)	1/506 (0.2)	2/492 (0.4)	10/2164 (0.5)
<b>Hematocrit:</b>				
≤ 0.28 (F); ≤ 0.3 (M)	2/1166 (0.2)	2/506 (0.4)	0/492	4/2164 (0.2)
≥ 0.52 (F); ≥ 0.6 (M)	5/1166(0.4)	0/506	1/492 (0.2)	6/2164 (0.3)
<b>Platelet count:</b>				
≤ 50 × 10 <sup>9</sup> /L	3/1165 (0.3)	0/506	0/491	3/2162 (0.1)
≥ 1000 × 10 <sup>9</sup> /L	1/1165 (< 0.1)	0/506	0/491	1/2162 (< 0.1)
<b>WBC count:</b>				
≤ 2.5 × 10 <sup>9</sup> /L	1/1166 (< 0.1)	2/506 (0.4)	0/492	3/2162 (0.1)
≥ 30 × 10 <sup>9</sup> /L	0/1166	0/506	1/492 (0.2)	1/2162 (< 0.1)
aPTT: ≥ 60 sec	1/6 (16.7)	0/5	0/2	1/13 (7.7)

### *Chemistry*

The sponsor conducted several analyses of laboratory data, with particular emphasis on the following:

- Creatinine: a post-baseline value increased ≥ 100% from baseline
- Creatinine: a post-baseline value > 2.0 mg/dL at any visit
- CPK: a post-baseline value > 5 × ULN at any visit
- CPK: a post-baseline value > 10 × ULN at any visit
- ALT and AST: a post-baseline value > 3 × ULN on two consecutive occasions
- ALT and AST: a post-baseline value > 5 × ULN at any visit

These analyses are presented in Section 7.3.5., under discussion of events of special interest (hepatobiliary, muscle, and renal).

Mean changes from baseline in chemistry laboratory values are presented in the following tables; however, because changes in CPK were not statistically significantly different between the combination and monotherapies, the results are not included in the sponsor's Controlled Studies Analysis Set Table 7.4.2.H. Mean increases to final visit in CPK were similar in the ABT-335 in combination with low-dose statin (11.1 U/L), ABT-335 in combination with moderate-dose statin (9.1 U/L), and low-dose statin monotherapy (9.4 U/L) groups, and were 4.5, 5.5, and 16.7 U/L in the ABT-335 monotherapy, moderate-dose statin monotherapy, and high-dose statin monotherapy groups, respectively.

**Table 7.4.2.H. Statistically Significant Differences between ABT-335 + Statin Combination Therapy and Monotherapy in Mean Change from Baseline to Final Chemistry Value for the Controlled Studies Analysis Set**

Chemistry Parameter	Treatment Group n (%)					
	ABT-335 (N = 499)	Low-dose statin (N = 484)	ABT-335 + low dose statin (N = 479)	Moderate-dose statin (N = 480)	ABT-335 + moderate dose statin (N = 472)	High-dose statin (N = 480)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<b>SGPT/ALT (U/L)</b>	(N=472)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	24.1	23.8	24.7	26.1	23.4	23.1
Mean Δ to Final Value	4.8 (13.83)	2.6 (10.85)	5.7 (16.27) <sup>a</sup>	1.8 (13.17)	5.1 (18.77) <sup>b</sup>	4.6 (13.61)
<b>SGOT/AST (U/L)</b>	(N=472)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	22.3	22.9	22.6	23.3	23.0	22.8
Mean Δ to Final Value	3.5 (8.84)	1.5 (7.04)	4.4 (11.02) <sup>a</sup>	0.3 (8.92)	3.8 (11.84) <sup>b</sup>	2.3 (7.58)
<b>Alkaline Phosphatase (U/L)</b>	(N=473)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	82.1	81.7	82.8	83.6	83.5	82.3
Mean Δ to Final Value	-19.4 (14.41)	1.1 (10.25)	-17.4 (17.90) <sup>a</sup>	1.1 (12.94)	-18.1 (18.47) <sup>b</sup>	3.5 (21.79)
<b>Total Bilirubin (mg/dL)</b>	(N=472)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	0.5	0.5	0.5	0.5	0.5	0.5
Mean Δ to Final Value	-0.1 (0.17)	0.0 (0.17)	-0.0 (0.16) <sup>a</sup>	0.0 (0.16)	-0.0 (0.19) <sup>b</sup>	0.1 (0.20)
<b>Creatinine (mg/dL)</b>	(N=473)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	0.90	0.91	0.89	0.90	0.91	0.89
Mean Δ to Final Value	0.13 (0.132)	0.01 (0.118)	0.14 (0.148) <sup>a</sup>	-0.00 (0.097)	0.12 (0.136) <sup>b</sup>	0.01 (0.118)

Note: Includes data from Studies 3025-748, 3025-749, and 3025-750.

Note: Baseline was defined as the last value before the first dose of study drug.

Δ = change; CrCl = creatinine clearance

- Statistically significant difference between ABT-335 in combination with low statin and low-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference between ABT-335 in combination with moderate statin and moderate-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference vs. ABT-335 ( $p \leq 0.05$ ) based on a one-way ANOVA

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Chemistry Parameter	Treatment Group n (%)					
	ABT-335 (N=499)	Low-dose statin (N=488)	ABT-335 + low statin (N=499)	Moderate-dose statin (N=493)	ABT-335 + moderate statin (N=489)	High-dose statin (N=249)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<b>BUN (mg/dL)</b>	(N=473)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	14.41	16.00	14.18	14.11	14.32	14.20
Mean Δ to Final Value	2.09 (4.053)	-0.31 (4.125)	1.77 (4.239) <sup>a</sup>	-0.59 (3.454)	1.89 (4.184) <sup>b</sup>	-0.44 (3.692)
<b>Uric Acid (mg/dL)</b>	(N=473)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	6.3	6.4	6.4	6.5	6.5	6.4
Mean Δ to Final Value	-1.3 (1.06)	-0.5 (0.90)	-1.6 (1.15) <sup>a,c</sup>	-0.6 (0.94)	-1.7 (1.18) <sup>b,c</sup>	-0.3 (0.96)
<b>Inorganic Phosphate (mg/dL)</b>	(N=472)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	3.586	3.523	3.549	3.579	3.550	3.526
Mean Δ to Final Value	-0.129 (0.4914)	0.114 (0.4545)	-0.091 (0.4491) <sup>a</sup>	0.043 (0.4813)	-0.036 (0.4874) <sup>b</sup>	0.084 (0.4315)
<b>Calcium (mg/dL)</b>	(N=473)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	9.811	9.777	9.783	9.783	9.766	9.807
Mean Δ to Final Value	0.039 (0.4123)	-0.007 (0.3439)	0.091 (0.3720) <sup>a</sup>	-0.016 (0.3765)	0.110 (0.3524) <sup>b</sup>	-0.012 (0.3767)

Note: Includes data from Studies M05-748, M05-749, and M05-750.

Note: Baseline was defined as the last value before the first dose of study drug.

Δ = change; CrCl = creatinine clearance

- Statistically significant difference between ABT-335 in combination with low statin and low-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference between ABT-335 in combination with moderate statin and moderate-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference vs. ABT-335 ( $p \leq 0.05$ ) based on a one-way ANOVA

Chemistry Parameter	Treatment Group n (%)					
	ABT-335 (N=499)	Low-dose statin (N=498)	ABT-335 + low statin (N=499)	Moderate-dose statin (N=493)	ABT-335 + moderate statin (N=489)	High-dose statin (N=249)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<b>Total Protein (g/dL)</b>	(N=473)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	7.2	7.2	7.2	7.2	7.2	7.2
Mean Δ to Final Value	0.1 (0.33)	0.0 (0.30)	0.0 (0.36) <sup>c</sup>	0.0 (0.30)	0.0 (0.35) <sup>c</sup>	-0.0 (0.34)
<b>Calculated CrCl (mL/min)</b>	(N=473)	(N=484)	(N=479)	(N=480)	(N=472)	(N=238)
Baseline mean	115.342	117.104	113.067	115.084	115.684	117.226
Mean Δ to Final Value	-14.439 (14.899)	-1.131 (13.6957)	-15.062 (15.3999) <sup>a</sup>	-0.574 (13.5056)	-12.949 (17.4317) <sup>b</sup>	-2.092 (14.3473)

Note: Includes data from Studies M05-748, M05-749, and M05-750.

Note: Baseline was defined as the last value before the first dose of study drug.

Δ = change; CrCl = creatinine clearance

- Statistically significant difference between ABT-335 in combination with low statin and low-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference between ABT-335 in combination with moderate statin and moderate-dose statin ( $p \leq 0.05$ ) based on a one-way ANOVA
- Statistically significant difference vs. ABT-335 ( $p \leq 0.05$ ) based on a one-way ANOVA