Comment: Events of 'liver function test abnormal' again referred to transaminase elevation and did not include any instances of hyperbilirubinemia.

Study M05-758

A total of 246 (11.2%) subjects had adverse events leading to discontinuation. These events are presented below with the All Combination Therapy Analysis Set in Table 7.3.3.F.

Overall

In the controlled studies, overall, discontinuations were somewhat higher in the treatment arms that included ABT-335 than in the statin groups, particularly the low-dose statin group. This difference is particularly seen in the 'Investigations' SOC, in which more subjects randomized to ABT-335 were discontinued for increased ALT and AST events than in the statin groups. Otherwise, there is no clear pattern of discontinuations in the 12 weeks of randomized controlled testing.

Table 7.3.3.E. Adverse Events Leading to Discontinuation Reported for at Least Two Subjects Overall and Selected Adverse Events of Interest: Controlled Phase 3 Studies

	Treatment Group n (%)					
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 adverse event leading to discontinuation	49 (10.0)	21 (4.3)	45 (9.2)	36 (7.3)	46 (9.4)	20 (8.2)
Blood and Lymphatic System Disorders	0	0	0	1 (0.2)	0	0
Cardiac Disorders	3 (0.6)	1 (0.2)	1 (0.2)	2 (0.4)	3 (0.6)	0
Myocardial infarction	2 (0.4)	0	1 (0.2)	0	0	0
Gastrointestinal Disorders	13 (2.7)	6 (1.2)	10 (2.0)	9 (1.8)	12 (2.5)	7 (2.9)
Abdominal distention	0	0	0	2 (0.4)	1 (0.2)	0
Abdominal pain upper	0	0	3 (0.6)	0	1 (0.2)	2 (0.8)
Constipation	0	0	3 (0.6)	0	0	0
Diarrhoea	2 (0.4)	1 (0.2)	1 (0.2)	2 (0.4)	3 (0.6)	1 (0.4)
Dyspepsia	0	0	1 (0.2)	0	3 (0.6)	0
Nausea	7 (1.4)	4 (0.8)	2 (0.4)	4 (0.8)	4 (0.8)	2 (0.8)
Stomach discomfort	0	0	1 (0.2)	0	1 (0.2)	0
Vomiting	1 (0.2)	0	0	0	1 (0.2)	2 (0.8)
General Disorders and Administration Site Conditions	4 (0.8)	2 (0.4)	7 (1.4)	7 (1.4)	2 (0.4)	1 (0.4)
Asthenia	0	0	3 (0.6)	3 (0.6)	0	1 (0.4)
Fatigue	0	0	1 (0.2)	2 (0.4)	1 (0.2)	0
Pain	2 (0.4)	1 (0.2)	1 (0.2)	0	0	0
Hepatobiliary Disorders	1 (0.2)	0	0	0	2 (0.4)	0
Jaundice	1 (0.2)	0	0	0	0	0
Hepatitis	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
Infections and Infestations	1 (0.2)	2 (0.4)	1 (0.2)	5 (1.0)	1 (0.2)	1 (0.4)
Gastroenteritis viral	0	0	0	2 (0.4)	0	0
Injury, Poisoning and Procedural Complications	0	0	0	0	0	1 (0.4)

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)
Investigations	9 (1.8)	3 (0.6)	16 (3.3)	5 (1.0)	13 (2.7)	3 (1.2)
ALT increased	5 (1.0)	1 (0.2)	8 (1.6)	0	6 (1.2)	1 (0.4)
AST increased	4 (0.8)	1 (0.2)	7 (1.4)	0	5 (1.0)	1 (0.4)
Blood alkaline phosphatase increased	0	0	2 (0.4)	0	1 (0.2)	1 (0.4)
Blood CPK increased	0	1 (0.2)	4 (0.8)	2 (0.4)	2 (0.4)	0
Hepatic enzyme increased	1 (0.2)	0	3 (0.6)	1 (0.2)	3 (0.6)	1 (0.4)
Liver function test abnormal	2 (0.4)	1 (0.2)	1 (0.2)	0	2 (0.4)	0
Metabolism and Nutrition Disorders	2 (0.4)	0	1 (0.2)	0	1 (0.2)	0
Musculoskeletal and Connective Tissue Disorders	11 (2.2)	6 (1.2)	6 (1.2)	9 (1.8)	8 (1.6)	10 (4.1)
Arthralgia	2 (0.4)	0	0	0	1 (0.2)	2 (0.8)
Back pain	3 (0.6)	0	0	0	0	0
Muscle spasms	1 (0.2)	2 (0.4)	0	2 (0.4)	0	1 (0.4)
Myalgia	6 (1.2)	2 (0.4)	3 (0.6)	6 (1.2)	4 (0.8)	5 (2.0)
Pain in extremity	2 (0.4)	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Rheumatoid arthritis	0	0	2 (0.4)	0	0	0
Neoplasms Benign, Malignant and Unspecified	2 (0.4)	0	1 (0.2)	0	0	0
Breast cancer	2 (0.4)	0	0	0	0	0
Nervous System Disorders	7 (1.4)	4 (0.8)	7 (1.4)	6 (1.2)	2 (0.4)	3 (1.2)
Dizziness	2 (0.4)	1 (0.2)	3 (0.6)	2 (0.4)	1 (0.2)	0
Headache	4 (0.8)	2 (0.4)	3 (0.6)	1 (0.2)	1 (0.2)	3 (1.2)
Somnolence	1 (0.2)	0	2 (0.4)	0	0	0
Psychiatric Disorders	0	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.4)	1 (0.4)
Anxiety	0	2 (0.4)	0	1 (0.2)	0	0
Renal and Urinary Disorders	2 (0.4)	0	2 (0.4)	0	0	0
Renal failure acute	1 (0.2)	0	1 (0.2)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.2)	1 (0.2)	1 (0.2)	0	1 (0.2)	0
Skin and Subcutaneous Tissue Disorders	6 (1.2)	1 (0.2)	1 (0.2)	3 (0.6)	3 (0.6)	1 (0.4)
Rash	2 (0.4)	0	0	0	0	0
Vascular Disorders	1 (0.2)	0	0	1 (0.2)	2 (0.4)	0

In the All Combination Therapy Analysis Set, a total of 246 (11.2%) subjects had adverse events leading to discontinuation: 11.6% of subjects treated with ABT-335 in combination with rosuvastatin, 8.8% of subjects treated with ABT-335 in combination with simvastatin, and 12.6% of subjects treated with ABT-335 in combination with atorvastatin. There is a suggestion that fewer subjects in the ABT-335 + simvastatin group discontinued due to Preferred Terms related to liver function test abnormalities and myalgia, and the atorvastatin group had slightly higher discontinuations due to hepatobiliary and related investigations AEs. Hepatobiliary findings are discussed further in Section 7.3.5.

Table 7.3.3.F. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation in at Least Two Subjects in Any Treatment Group and All Hepatobiliary Events for the All Combination Therapy Analysis Set

	ABT-335 + rosuva (N=1186)	ABT-335 + simva (N=514)	ABT-335 + atorva (N=501)	Total (N=2201)
Any adverse event leading to discontinuation	138 (11.6)	45 (8.8)	63 (12.6)	246 (11.2)
Cardiac Disorders	7 (0.6)	3 (0.6)	1 (0.2)	11 (0.5)
Myocardial infarction	2 (0.2)	0	0	2 (< 0.1)
Gastrointestinal Disorders	21 (1.8)	9 (1.8)	10 (2.0)	40 (1.8)
Abdominal distension	2 (0.2)	0	2 (0.4)	4 (0.2)
Abdominal pain	4 (0.3)	2 (0.4)	2 (0.4)	8 (0.4)
Abdominal pain upper	2 (0.2)	1 (0.2)	2 (0.4)	5 (0.2)
Constipation	5 (0.4)	0	0	5 (0.2)
Diarrhoea	1 (< 0.1)	2 (0.4)	2 (0.4)	5 (0.2)
Dyspepsia	5 (0.4)	1 (0.2)	1 (0.2)	7 (0.3)
Nausea	2 (0.2)	3 (0.6)	2 (0.4)	7 (0.3)
General Disorders and Administration Site Conditions	10 (0.8)	3 (0.6)	4 (0.8)	17 (0.8)
Asthenia	1 (< 0.1)	1 (0.2)	2 (0.4)	4 (0.2)
Oedema peripheral	4 (0.3)	0	0	4 (0.2)
Hepatobiliary Disorders	2 (0.2)	2 (0.4)	3 (0.6)	7 (0.3)
Cholelithiasis	1 (< 0.1)	1 (0.2)	2 (0.4)	4 (0.2)
Jaundice	1 (< 0.1)	0	0	1 (< 0.1)
Bile duct obstruction	0	1 (0.2)	0	1 (< 0.1)
Cholecystitis	0	0	1 (0.2)	1 (< 0.1)
Hepatic function abnormal	0	0	1 (0.2)	1 (< 0.1)
Investigations	45 (3.8)	13 (2.5)	25 (5.0)	83 (3.8)
ALT increased	15 (1.3)	2 (0.4)	5 (1.0)	22 (1.0)
AST increased	14 (1.2)	2 (0.4)	4 (0.8)	20 (0.9)
Blood alkaline phosphatase increased	2 (0.2)	1 (0.2)	1 (0.2)	4 (0.2)
Blood CPK increased	9 (0.8)	7 (1.4)	5 (1.0)	21 (1.0)
Blood creatinine increased	5 (0.4)	1 (0.2)	1 (0.2)	7 (0.3)
Blood glucose increased	1 (< 0.1)	2 (0.4)	0	3 (0.1)
Blood urea increased	4 (0.3)	0	0	4 (0.2)
Creatinine renal clearance decreased	5 (0.4)	1 (0.2)	0	6 (0.3)
Hepatic enzyme increased	4 (0.3)	0	9 (1.8)	13 (0.6)
Liver function test abnormal	2 (0.2)	2 (0.4)	4 (0.8)	8 (0.4)
Platelet count increased	2 (0.2)	1 (0.2)	0	3 (0.1)
Musculoskeletal and Connective Tissue Disorders	33 (2.8)	6 (1.2)	12 (2.4)	51 (2.3)
Arthralgia	5 (0.4)	0	0	5 (0.2)
Muscle spasms	5 (0.4)	1 (0.2)	3 (0.6)	9 (0.4)
Myalgia	12 (1.0)	1 (0.2)	7 (1.4)	20 (0.9)
Pain in extremity	5 (0.4)	1 (0.2)	0	6 (0.3)
Rheumatoid arthritis	2 (0.2)	0	0	2 (< 0.1)
Nervous System Disorders	13 (1.1)	1 (0.2)	3 (0.6)	17 (0.8)
Dizziness	3 (0.3)	1 (0.2)	1 (0.2)	5 (0.2)
Headache	8 (0.7)	0	1 (0.2)	9 (0.4)
Renal and Urinary Disorders	2 (0.2)	2 (0.4)	3 (0.6)	7 (0.3)
Renal Impairment	0	0	2 (0.4)	2 (<0.1)

	ABT-335 + rosuva (N=1186)	ABT-335 + simva (N=514)	ABT-335 + atorva (N=501)	Total (N=2201)
Skin and Subcutaneous Tissue Disorders	6 (0.5)	2 (0.4)	4 (0.8)	12 (0.5
Urticaria	2 (0.2)	0	1 (0.2)	3 (0.1)
Vascular Disorders	5 (0.4)	1 (0.2)	3 (0.6)	9 (0.4)
Deep vein thrombosis	4 (0.3)	0	1 (0.2)	5 (0.2)

No events of 'liver function test abnormal' were associated with hyperbilirubinemia.

One subject with a discontinuation due to 'liver function test abnormal' had concurrent elevations of CK of 5026 U/L and thigh cramping. The investigator reported the subject had increased activity during the event.

Table 7.3.3.G. Subject #24104 Fasting Laboratory Data

Treatment Day	AST Reference Range 11-36 U/L	ALT Reference Range 6-43 U/L	Total Bilirubin Reference Range 0.2-1.2 mg/dL	Creatine Phosphokinase Reference Range < 18-198 U/L
Screening (M05-749)	26	31	0.3	98
Baseline (M05-749)	28	34	0.5	127
Day 28 (M05-749)	24	30	0.4	134
Day 55 (M05-749)	35	44	0.5	149
Day 1 (M05-758)	23	33	0.3	140
Day 29 (M05-758)	28	35	0.3	169
Day 59 (M05-758)	29	39	0.4	150
Day 84 (M05-758)	36	49	0.3	92
Day 113 (M05-758)	28	39	0.3	104
Day 196 (M05-758)	202	139	0.7	5026
Day 210/Final Visit (M05-758)	53	71	0.6	736

7.3.4 Significant Adverse Events

No significant adverse events beyond deaths, discontinuations, adverse events of special interest (Section 7.3.5), and those observed based on laboratory evaluations (Section 7.4.2) have been identified.

7.3.5 Submission Specific Primary Safety Concerns

The sponsor identified three issues on which to conduct separate safety analyses: liver, muscle, and renal findings, based on the known safety profiles of fenofibrate and statins. In order to ensure that all cases were captured and that individual outliers were addressed, this reviewer supplemented the sponsor's analyses with evaluations of adverse event and laboratory datasets, as well as review of case report forms and narratives. Studies were evaluated individually, as well as combined as part of the ISS to assess whether there were any statin-specific interactions. Liver events were expanded to include biliary events as well, since there was some overlap with hepatic events and effects on the gallbladder (cholelithiasis and cholecystitis) are also labeled risks of fenofibrate therapy. Furthermore, this reviewer evaluated safety concerns that have

arisen with reviews of fenofibrate studies: deep venous thrombosis and pulmonary embolus, and pancreatitis.

Hepatobiliary Findings

Study M05-748

As discussed in Section 7.2.6, the sponsor searched the data for hepatic events by conducting a query using pre-specified MedDRA Preferred Terms associated with the liver (jaundice, hepatic failure, liver function test abnormal, etc.), and combined those terms into one analysis, as illustrated in Table 7.3.5.A:

Table 7.3.5.A. Hepatic Events, Study M05-748

	Treatment Group n (%)					
	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)
Hepatic Events	9 (3.5)	2 (0.8)$	12 (4.6)$	3 (1.1)†	11 (4.2)†	2 (1.5)
ALT increased	4 (1.5)	2 (0.8)	4 (1.5)	2 (0.8)†	9 (3.4)†	2 (1.5)
AST increased	3 (1.2)	2 (0.8)	4 (1.5)	1 (0.4)†	8 (3.1)†	2 (1.5)
Hepatic enzyme increased	3 (1.2)	0	2 (0.8)	1 (0.4)	0	0
Jaundice	0	0	0	0	1 (0.4)	0
Liver function test abnormal	2 (0.8)	0	5 (1.9)	1 (0.4)	1 (0.4)	1 (0.8)

$ Statistically significant difference ABT-335 + 10 mg rosuvastatin vs. 10 mg rosuvastatin, $p \leq 0.05$.

† Statistically significant difference ABT-335 + 20 mg rosuvastatin vs. 20 mg rosuvastatin, $p \leq 0.05$.

As mentioned in Section 7.2.6, there was a possibility that such a query could miss some AEs; for example, biliary events were not included in the list of hepatic events. Additionally, the sponsor's analysis does not discuss individual cases of interest. Therefore, this reviewer searched for events in the 'hepatobiliary' SOC to gain more information about individual cases. Two events from this study were listed in the 'hepatobiliary' SOC (the reminder of Hepatic Events were from the 'investigations' SOC): these hepatobiliary PTs – jaundice and cholelithiasis – were from the same subject (12142, ABT-335 + rosuvastatin 20 mg), and neither was classified as an SAE. The event of jaundice was captured in the sponsor's table above, as well. This patient was discontinued from the study for this adverse event:

Subject 12142 (ABT-335 and rosuvastatin 20 mg) was a 44-year-old white male who prematurely discontinued study drug on Day 78 due to jaundice. Relevant medical history included elevated liver function, fatty infiltration of liver, anxiety, hypertension, gout, degenerative disc disease, diabetes mellitus, hypercholesterolemia, and herpes simplex. Concomitant medications at the time of the event included paracetamol/codeine phosphate. The subject had a 23 pack-year history of smoking (current) and drank a light amount of alcohol.

On Day 43, the subject reported being jaundiced. Laboratory values are provided in Table 7.3.5.B. The investigator considered the event resolved as of Day 53. Study drug was

discontinued on Day 78. No further information regarding diagnostic evaluation was provided although the dataset lists cholelithiasis occurring 12 days after the study drug was discontinued. The investigator considered the event of jaundice to be possibly related to study drug and cholelithiasis as not related.

Comment: These investigator attributions make little sense, as the CRF lists cholelithiasis as the cause of the jaundice, according to the investigator. The CRF states that the diagnosis of cholelithiasis was made by ultrasound. The bilirubin results do not reflect the AE of jaundice.

Table 7.3.5.B. Laboratory Data, Subject 12142

Treatment Day	Bilirubin Reference Range 0.2-1.2 mg/dL	AST Reference Range 11-36 U/L	ALT Reference Range 6-43 U/L
Screening	0.6	26	64
Baseline	0.5	27	51
Day 23	0.4	36	90
Day 78	0.5	23	46

There were no adverse events of increased total bilirubin reported in this study.

To further quantify the ALT and total bilirubin elevations (i.e., rule out Hy's law cases) this reviewer evaluated the safety laboratory dataset. Table 7.3.5.C, below, describes the increases in ALT by treatment group. One subject (14522, rosuvastatin 40 mg) had a total bilirubin $\geq$ 2x ULN on study day 57 (value: 2.3 mg/dL), which was not associated with increased transaminases.

Table 7.3.5.C. Alanine transaminase elevations, n (%)

Randomization Group	$\geq$3x ULN	$\geq$5x ULN	$\geq$10x ULN
ABT-335 (N=259)	7 (2.7)	3 (1.6)	0
Rosuvastatin 10 mg (N=261)	0	0	0
ABT-335 and rosuvastatin 10 mg (N=261)	10 (3.8)	3 (1.1)	0
Rosuvastatin 20 mg (N=266)	1 (0.4)	0	0
ABT-335 and rosuvastatin 20 mg (N=261)	5 (1.9)	1 (0.4)	0
Rosuvastatin 40 mg (N=131)	1 (0.8)	0	0

One subject's elevation of transaminases illustrates a positive rechallenge with ABT-335:

Subject 13301 was treated with ABT-335 monotherapy. She was a 55-year-old white female who was prematurely discontinued study drug on Day 61 due to an elevated AST and ALT. Medical history included sarcoidosis, mixed dyslipidemia, and hayfever. Concomitant medications at the time of the event included acetylsalicylic acid and acetaminophen/aspirin/caffeine. The subject is a non-smoker and non-drinker.

On Day 30, the subject was reported to have an elevated AST and ALT. Laboratory values are provided in the table below. Study drug was interrupted from Day 32 to Day 49. On Day 36, the investigator considered the event of elevated AST resolved. Study drug was resumed on Day 50

and again discontinued on Day 61. On Day 64, the investigator considered the event of elevated ALT resolved.

Table 7.3.5.D.

Subject #13301 Fasting Laboratory Data

Treatment Day	ALT Reference Range 6-34 U/L	AST Reference Range 9-34 U/L
Screening	13	18
Baseline	13	19
Day 30	196	249
Day 36	55	30
Day 57	132	81
Day 64	31	22

Comment: Although this was a positive rechallenge, it also demonstrates resolution (or at least improvement) upon study drug withdrawal.

Study M05-749

The following are the sponsor's assessment of hepatic events:

Table 7.3.5.E. Hepatic Events, Study M05-749

	Treatment Group n (%)					
	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)
Hepatic	7 (5.9)	1 (0.8)	8 (6.7)†	0	3 (2.5)	1 (1.7)
ALT increased	1 (0.8)	0	5 (4.2)	0	2 (1.7)	0
AST increased	0	0	4 (3.4)	0	2 (1.7)	0
Hepatic enzyme increased	3 (2.5)	0	1 (0.8)	0	0	1 (1.7)
Liver function test abnormal	3 (2.5)	1 (0.8)	2 (1.7)	0	1 (0.8)	0

† Statistically significant difference ABT-335 + 20 mg simvastatin vs. 20 mg simvastatin, $p \leq 0.05$.

In the sponsor's analysis, there were four subjects who prematurely discontinued due to these hepatic adverse events, all in the ABT-335 group (hepatic enzyme increased, hepatitis, and two reports of liver function test abnormal).

One additional event was found by this reviewer from the 'hepatobiliary' SOC: Preferred Term 'hepatitis' in subject 23218, who was prematurely discontinued as described below.

Subject 23218 (ABT-335) was a 35-year-old white male who was prematurely discontinued from study drug on Day 63 due to elevated AST and ALT enzymes. Relevant medical history included intermittent headache, gastroenteritis, right lumbar pain, diarrhea, and mixed

dyslipidemia. Concomitant medications at the time of the event included paracetamol. The subject is an ex-smoker (5 pack-years) and a current light drinker.

On Day 63, the subject was reported to have elevated AST and ALT enzymes and diagnosed with hepatitis related to medication (probably related to study drug, according to the investigator). Laboratory values are reported in Table 7.3.5.F, below. Study drug was discontinued on Day 63. The event was considered resolved on Day 76.

Table 7.3.5.F. Laboratory Data, Subject 23218

Treatment Day	ALT Reference Range 6-43 U/L	AST Reference Range 11-36 U/L
Screening	103	55
Retest	42	21
Baseline	28	21
Day 27	87	36
Day 57	115	59
Day 63	253	147
Day 65	365	164
Day 76	120	30
Day 78	107	40

With respect to this reviewer's analysis of ALT and total bilirubin elevations, the following table represents ALT elevations. No subject had a total bilirubin value ≥ 2x ULN.

Table 7.3.5.G. Alanine transaminase elevations, n (%)

Randomization Group	≥ 3x ULN	≥ 5x ULN	≥ 10x ULN
ABT-335 (N=119)	6 (5.0)	5 (4.2)	0
Simvastatin 20 mg (N=119)	0	0	0
ABT-335 and simvastatin 20 mg (N=119)	2 (1.7)	0	0
Simvastatin 40 mg (N=116)	0	0	0
ABT-335 and simvastatin 40 mg (N=118)	3 (2.5)	1 (0.8)	0
Simvastatin 80 mg (N=59)	1 (1.7)	1 (1.7)	1 (1.7)

The one subject with ALT ≥ 10x ULN occurred in a subject treated with simvastatin 80 mg monotherapy.

Study M05-750

The following are the sponsor's assessment of hepatic events:

Table 7.3.5.H. Hepatic Events, Study M05-750

	Treatment Group n (%)					
	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 Hepatic Event	3 (2.7)	0	11 (10.0)#$	1 (0.9)	8 (7.3)$	3 (5.5)
ALT increased	1 (0.9)	0	6 (5.5)$	0	1 (0.9)	2 (3.6)
AST increased	1 (0.9)	0	6 (5.5)$	0	1 (0.9)	2 (3.6)
Hepatic enzyme increased	1 (0.9)	0	4 (3.6)	1 (0.9)	5 (4.5)	1 (1.8)
Hepatic steatosis	1 (0.9)	0	0	0	0	0
Liver function test abnormal	0	0	2 (1.8)	0	2 (1.8)	0

Statistically significant difference ABT-335 + 20 mg atorvastatin vs. ABT-335 monotherapy, $p \leq 0.05$.

$ Statistically significant difference ABT-335 + 20 mg or 40 mg atorvastatin vs. 20 mg or 40 mg atorvastatin monotherapy, $p \leq 0.05$.

In this reviewer's assessment of the 'hepatobiliary' SOC, three subjects had five events; four events were biliary AEs and therefore were not captured in the table above:

- Subject 31053 (atorvastatin 40 mg) – biliary colic, which was neither an SAE nor was the subject discontinued;
- Subject 34102 (ABT-335 + atorvastatin 40 mg) – cholecystitis and cholelithiasis, both were SAEs and both led to discontinuation;
- Subject 34136 (ABT-335) – cholecystitis and hepatic steatosis (hepatic steatosis was captured in the sponsor's table of hepatic events, above); neither events were SAEs nor was the subject discontinued.

Subject 33086 (ABT-335 + atorvastatin 20 mg) was prematurely discontinued for elevated liver enzymes and demonstrated a positive rechallenge. This 60-year-old white female prematurely discontinued study drug on Day 57 due to elevated liver enzymes. Medical history included hypertension, sterno-clavicular joint prominence, median nail dystrophy, osteoarthritis, mixed dyslipidemia, Chlamydia, genital herpes, degenerative disc disease of the lower back, seborrhea of the scalp, canker sore, and obesity. Concomitant medications at the time of the event included valacyclovir, fluocinonide, paracetamol, acetylsalicylic acid, ibuprofen, atenolol, lysine, ketoconazole, and furosemide. The subject is an ex-smoker and a non-drinker. On Day 30, the subject was reported to have elevated liver enzymes. On Day 32, the study drug was interrupted. ALT, AST and alkaline phosphatase laboratory values are provided in the table below. On Day 46, the event was considered resolved. On Day 49, the study drug was restarted. On Day 57, the subject was again reported to have elevated liver enzymes. Study drug was discontinued on Day 57. The event of elevated liver enzymes was considered resolved on Day 78.

Table 7.3.5.I.

Subject #33086 Fasting Laboratory Data

Treatment Day	ALT Reference Range 6-34 U/L	AST Reference Range 9-34 U/L	Alkaline Phosphatase Reference Range 38-123 U/L
Screening	31	26	84
Baseline	22	19	79
Day 30	178	76	172
Day 39	64	30	Not performed
Day 46	37	24	Not performed
Day 57	170	54	157
Day 60	93	37	124
Day 78	29	20	Not performed

With respect to this reviewer's analysis of ALT and total bilirubin elevations, the following table represents ALT elevations. One subject treated with atorvastatin 80 mg had a total bilirubin value ≥ 2x ULN (2.4 mg/dL) on day 57.

Table 7.3.5.J. Alanine transaminase elevations, n (%)

Randomization Group	≥ 3x ULN	≥ 5x ULN	≥ 10x ULN
ABT-335 (N=112)	1 (0.9)	0	0
Atorvastatin 20 mg (N=113)	1 (0.9)	0	0
ABT-335 and atorvastatin 20 mg (N=110)	6 (5.5)	4 (3.6)	0
Atorvastatin 40 mg (N=109)	0	0	0
ABT-335 and atorvastatin 40 mg (N=110)	6 (5.5)	1 (0.9)	0
Atorvastatin 80 mg (N=55)	1 (1.8)	0	0

Comment: In contrast to the other statin + ABT-335 combinations, it appears that the combination of atorvastatin and ABT-335 leads to increases in ALT at a greater incidence than either drug alone. However, it is also noted that the incidence of ALT elevations in the ABT-335-only group was lower in this study (0.9%) than the others (2.7-5.0%).

Study M05-758

In the sponsor's analysis, the percentage of subjects with hepatic adverse events in the ABT-335 + rosuvastatin, + simvastatin, and + atorvastatin was 4.9%, combined. The percentage of subjects experiencing hepatic adverse events was greatest in the ABT-335 + atorvastatin treatment group (7.2%) compared with the ABT-335 + rosuvastatin (4.4%) and ABT-335 + simvastatin (3.9%) treatment groups. The larger incidence seen in the ABT-335 + atorvastatin group was driven by the relatively higher percentage of subjects with the PT 'hepatic enzyme increased' in this group.

The incidence of discontinuations due to the adverse event of ALT increased was 1.0% overall (ABT-335 + rosuvastatin, 1.3%; ABT-335 + simvastatin, 0.4%; and ABT-335 + atorvastatin, 1.0%). The incidence of discontinuations due to the adverse event of AST increased was 0.9%

overall (ABT-335 + rosuvastatin, 1.2%; ABT-335 + simvastatin, 0.4%; and ABT-335 + atorvastatin, 0.8%).

The one subject each with 'hepatic function abnormal' and 'jaundice' discontinued due to these adverse events. Adverse events of 'hepatic enzyme increased' and 'liver function test abnormal' led to discontinuation in 0.6% and 0.4% of subjects, respectively, overall. No subject discontinued prematurely due to 'blood bilirubin increased' or 'hepatic steatosis'.

Table 7.3.5.K. Hepatic Events, All Combination Therapy Analysis Set

	Treatment Group a (%)			
Subjects with:	ABT-335 + rosuva (N=1186)	ABT-335 + simva (N=514)	ABT-335 + atorva (N=501)	Total (N=2201)
Hepatic Events	52 (4.4)	20 (3.9)	36 (7.2)	108 (4.9)
ALT increased	27 (2.3)	10 (1.9)	14 (2.8)	51 (2.3)
Discontinuations	15 (1.3)	2 (0.4)	5 (1.0)	22 (1.0)
AST increased	26 (2.2)	9 (1.8)	15 (3.0)	50 (2.3)
Discontinuations	14 (1.2)	2 (0.4)	4 (0.8)	20 (0.9)
Blood bilirubin increased	0	1 (0.2)	2 (0.4)	3 (0.1)
Discontinuations	0	0	0	0
Hepatic enzyme increased	8 (0.7)	3 (0.6)	16 (3.2)	27 (1.2)
Discontinuations	4 (0.3)	0	9 (1.8)	13 (0.6)
Hepatic function abnormal	0	0	1 (0.2)	1 (< 0.1)
Discontinuations	0	0	1 (0.2)	1 (< 0.1)
Hepatic Steatosis	1 (< 0.1)	1 (0.2)	0	2 (< 0.1)
Discontinuations	0	0	0	0
Jaundice	1 (< 0.1)	0	0	1 (< 0.1)
Discontinuations	1 (< 0.1)	0	0	1 (< 0.1)
Liver function test abnormal	14 (1.2)	5 (1.0)	5 (1.0)	24 (1.1)
Discontinuations	2 (0.2)	2 (0.4)	4 (0.8)	8 (0.4)

Note: Includes data from Studies M05-748, M05-749, M05-750, and M05-758.
AE = adverse event; rosuva = 10 or 20 mg rosuvastatin; simva = 20 or 40 mg simvastatin; atorva = 20 or 40 mg atorvastatin

Events from the 'hepatobiliary' SOC not presented in the sponsor's table are below, in order to capture the incidence of biliary events:

Table 7.3.5.L. Biliary Adverse Events, Study M05-758

Preferred Term	ABT-335 and rosuvastatin 20 mg N=1186	ABT-335 and simvastatin 40 mg N=514	ABT-335 and atorvastatin 40 mg N=501
Bile Duct Obstruction	0	1 (0.2)	0
Bile Duct Stone	0	1 (0.2)	0
Biliary Colic	0	0	1 (0.2)
Cholecystitis	2 (0.2)	0	1 (0.2)
Cholecystitis Acute	2 (0.2)	0	0
Cholecystitis Chronic	0	1 (0.2)	0
Cholelithiasis	5 (0.4)	3 (0.6)	3 (0.6)
Gallbladder Polyp	1 (0.1)	0	0

Overall, the incidence of biliary events was low: ABT-335 + rosuvastatin [10 (0.8%)], ABT-335 + simvastatin [5 (1.0%)], and ABT-335 + atorvastatin [4 (0.8%)].

The following table represents ALT elevations found in the datasets. A similar proportion of subjects in each group had ALT increases ≥ 3x ULN and ≥ 5x ULN.

Table 7.3.5.M. Alanine transaminase elevations

Treatment Group	≥ 3x ULN	≥ 5x ULN	≥ 10x ULN
ABT-335 and rosuvastatin 20 mg (N=1186)	22 (1.9)	6 (0.5)	0
ABT-335 and simvastatin 40 mg (N=514)	11 (2.1)	3 (0.6)	0
ABT-335 and atorvastatin 40 mg (N=501)	11 (2.2)	3 (0.6)	1 (0.2)

The case of the one subject with the ALT ≥ 10x ULN is presented here:

Subject 34165 (ABT-335 135 mg and atorvastatin 40 mg) was a 49-year-old white male who had been treated with 12 weeks of ABT-335 135 mg in the M05-750 study. Relevant medical history included mixed dyslipidemia, sleep apnea, and impingement syndrome left shoulder. Concomitant medications at the time of the event included meloxicam. He was a non-smoker and non-drinker. On Day 48, the subject was hospitalized for right upper quadrant pain accompanied with nausea and vomiting. Computed tomography of the abdomen showed gallbladder sludge and a questionable dilated common hepatic duct. Magnetic resonance cholangiopancreatography showed no definite gallstones within the gallbladder, visualized portions of the common hepatic duct were within normal limits, and partially visualized portions of the liver demonstrated no significant abnormality. An acute abdominal x-ray series showed non-specific bowel gas without evidence of any dilation to suggest obstruction.

Electrocardiogram and chest x-ray were considered to be normal. Relevant laboratory data are provided in the table below. The subject was diagnosed with acute viral hepatitis and gallbladder sludge. On Day 52, the subject was discharged from the hospital and the event was considered resolved. Study drug was continued without interruption.

Table 7.3.5.N. Subject 34165 Laboratory Data – M05-758 Study Report

Subject #34165 Fasting Laboratory Data

Local Labs

Treatment Day	AST Reference Range 10-42 U/L	ALT Reference Range 10-60 U/L	Total Bilirubin Reference Range 0.2-1.0 mg/dL	Amylase Reference Range 43-75%
Initial Labs (Day 48)	233	130	1.4	65
Admission (Day 48)	239	128	1.1	Not provided
Follow up (Date not provided)	325	490	3.0	Not provided
Follow up (Date not provided)	187	381	3.7	Not provided
Final (Day 52)	233	130	1.4, 1.1	Not provided

Local Labs

Treatment Day	WBC Reference Range $4.8\text{-}11.8 \times 10^3$/UL	Hepatitis C Antibody Reference Range Non-reactive	Hepatitis B Surface Antigen Reference Range Non-reactive
Initial Labs (Day 48)	14.9	Non-reactive	Non-reactive
Final (Day 52)	5.8	Not provided	Not provided

The investigator considered the event of hepatitis viral to be probably not related to study drug but rather to a history of hyperlipidemia.

Table 7.3.5.O. Subject 34165 Laboratory Data – Datasets

Lab Test	Day 1	Day 31	Day 52	Day 55	Day 63	Day 70	Day 108	Day 142	Day 196
ALT	25	29	130	561	108	39	27	28	19
Albumin	4.4	4.3	41	4.4	3.8	4	4.3	4.4	4.3
Alkaline Phosphatase	56	58	66	113	80	71	59	59	54
AST	20	27	233	290	32	25	19	19	17
Total Bilirubin	0.6	0.5	.	1.5	0.9	0.8	0.6	0.7	1

Comment: It is unclear why this subject was given a diagnosis of viral hepatitis with negative hepatitis B and C serologies – it is assumed that the subject was diagnosed with hepatitis A, but the results of Hep A testing were not provided. It is also unclear why the investigator considered the event related to a history of hyperlipidemia, since to the knowledge of this reviewer, hyperlipidemia does not predispose to viral hepatitis. The hyperbilirubinemia noted from blood work done at an off-site laboratory is noted (Table 7.3.5.N). This case did not register as a case of Hy's law because these bilirubin values were not in the NDA datasets. Nevertheless, it is reassuring that the study drug was continued with resolution of the transaminitis and hyperbilirubinemia while on therapy.

With the exception of the subject discussed above, no subject in study M05-758 had a total bilirubin $\geq$ 2x ULN.

A discontinuation of a subject treated with ABT-335 and simvastatin 40 mg (#23143) due to elevated liver funtion tests (originally treated with simvastatin 40 mg monotherapy in Study M05-749) is presented here to describe a positive rechallenge.

This 47-year-old white female prematurely discontinued study drug on Day 97 due to elevated liver function tests. Medical history included migraine headaches, osteoarthritis, history of multiple fractures secondary to a motor vehicle accident, muscle spasms, partial hepatectomy and splenectomy secondary to trauma (1979), and hyperlipidemia. Concomitant medications at the time of the event included pentazocine, butalbital/acetylsalicylic acid, amitriptyline, tramadol, and tizanidine. The subject is a current cigarette smoker for 30 years (3/4 pack per day) and a non-drinker of alcohol.

On Day 37, the subject was reported to have elevated liver function tests. Laboratory values are provided in the table below. The study drug was interrupted for three weeks due to the elevated liver function tests. The investigator reported that the ALT and AST had returned to normal and the study drug was re-introduced.

On Day 97, the study drug was discontinued due to another elevation of liver function tests. On Day 110 (Post Treatment Day 13), the event was considered resolved.

Table 7.3.5.P.

Subject #23143 Fasting Laboratory Data

Treatment Day	AST Reference Range 9-34 U/L	ALT Reference Range 6-34 U/L	Total Bilirubin Reference Range 0.2-1.2 mg/dL
Baseline Visit (M05-749)	19	18	0.3
Day 83/Final Visit (M05-749)	22	24	0.3
Day 37 (M05-758)	87	105	0.3
Day 44 (M05-758)	106	133	Not performed
Day 71 (M05-758)	28	38	Not performed
Day 82 (M05-758)	31	35	0.2
Day 97 (M05-758)	122	139	Not performed
Day 110 (13 days post study drug)/Final Visit (M05-758)	31	46	0.2

Overall

The sponsor prepared a table looking at hepatic events in the three randomized trials and found a statistically significantly greater percentage of subjects in the combination therapy groups had hepatic adverse events compared with the corresponding statin monotherapy groups (6.3% vs. 0.6% for low-dose statin and 4.5% vs. 0.8% for moderate-dose statin). The percentage of subjects in the ABT-335 in combination with moderate-dose statin group with hepatic events was slightly lower than that in the ABT-335 in combination with low-dose statin group (4.5% vs.

6.3%). The ABT-335 monotherapy group had a similar percentage of events to the ABT-335 + moderate-dose statin group (3.9% vs. 4.5%, respectively).

Comment: With the possible exception of atorvastatin (see further discussion below), the 12-week data suggest that the combination of ABT-335 + statin administered at the low or moderate dose level does not appear to increase the risk of hepatotoxicity.

Table 7.3.5.Q. Sponsor's Treatment Emergent Adverse Events of Special Interest (Hepatic 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)
Hepatic Events	19 (3.9)	3 (0.6)	31 (6.3)[a]	4 (0.8)	22 (4.5)[b]	6 (2.4)
ALT increased	6 (1.2)	2 (0.4)	15 (3.1)[a]	2 (0.4)	12 (2.5)[b]	4 (1.6)
Discontinuations	5 (1.0)	1 (0.2)	8 (1.6)	0	6 (1.2)	1 (0.4)
AST increased	4 (0.8)	2 (0.4)	14 (2.9)[a,c]	1 (0.2)	11 (2.2)[b]	4 (1.6)
Discontinuations	4 (0.8)	1 (0.2)	7 (1.4)	0	5 (1.0)	1 (0.4)
Hepatic enzyme increased	7 (1.4)	0	7 (1.4)[a]	2 (0.4)	5 (1.0)	2 (0.8)
Discontinuations	1 (0.2)	0	3 (0.6)	1 (0.2)	3 (0.6)	1 (0.4)
Hepatic steatosis	1 (0.2)	0	0	0	0	0
Discontinuations	0	0	0	0	0	0
Jaundice	0	0	0	0	1 (0.2)	0
Discontinuations	0	0	0	0	1 (0.2)	0
Liver function test abnormal	5 (1.0)	1 (0.2)	9 (1.8)[a]	1 (0.2)	4 (0.8)	1 (0.4)
Discontinuations	2 (0.4)	1 (0.2)	1 (0.2)	0	2 (0.4)	0

Note: Includes data from Studies M05-748, M05-749, and M05-750.
AE = adverse event
a Statistically significant difference between ABT-335 + low statin and low-dose statin, $p \leq 0.05$
b. Statistically significant difference between ABT-335 + moderate statin and moderate-dose statin, $p \leq 0.05$
c. Statistically significant difference vs. ABT-335, $p \leq 0.05$

Table 7.3.5.R. Sponsor's Treatment Emergent Adverse Events of Special Interest (Hepatic Events – Changes in Laboratory Tests) 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)
Hepatic Events – Changes in Laboratory Tests[a]	18 (3.7)	3 (0.6)	31 (6.3)	4 (0.8)	21 (4.3)	6 (2.4)
Led to discontinuation	8	2	11	1	11	2
Met ALT or AST criterion[b]	9	0	8	0	8	2

Note: Includes data from Studies M05-748, M05-749, and M05-750.
AE = adverse event
a Includes adverse events of ALT increased, AST increased, hepatic enzyme increased, and liver function test abnormal.
b ALT or AST post-baseline > 3x ULN on two consecutive visits or > 5x ULN on any occasion.

Table 7.3.5.S. Number of Subjects Meeting Criteria After Baseline for Chemistry Values of Special Interest for the Controlled Studies Analysis Set: ALT and AST

	Treatment Group n/N (%)					
Laboratory Parameter Criteria[a]	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)
ALT > 5 × ULN on any occasion	9/472 (1.9)	0/484	7/479 (1.5)	0/480	5/472 (1.1)	2/238 (0.8)
ALT > 3 × ULN on 2 consecutive occasions	9/472 (1.9)	0/484	6/479 (1.3)	0/480	6/472 (1.3)	2/238 (0.8)
AST > 5 × ULN on any occasion	1/472 (0.2)	0/484	1/479 (0.2)	0/480	1/472 (0.2)	1/238 (0.4)
AST > 3 × ULN on 2 consecutive occasions	1/472 (0.2)	0/484	2/479 (0.4)	0/480	2/472 (0.4)	1/238 (0.4)

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. To meet PCS criteria, value had to be more extreme than the baseline value.

Comment: The highest ALT values (U/L) from any individual patient with ALT values > 5x ULN, are as follows:
ABT-335 monotherapy (9 subjects): 184, 340, 249, 322, 365, 295, 231, 197, 201
ABT-335 + low-dose statin (7 subjects): 251, 175, 178, 189, 189, 235, 176
ABT-335 + moderate-dose statin (5 subjects): 188, 244, 204, 213, 205
High-dose statin (2 subjects): 1132, 187

Table 7.3.5.K, above, described the sponsor's analysis of hepatic events that occurred in the All Combination Analysis set, that is, subjects who were assigned to combination therapy in any of the three controlled studies or in the open-label study. By contrast, the following table describes the incidence of hepatic events in only those patients that were assigned to combination therapy

from the randomized controlled study ('Initial Combination Therapy Analysis Set'). The incidence of hepatic events was overall modestly higher (lower overall, but higher percentage due to smaller denominator) in the Initial Combination Therapy Analysis Set. The proportional increase of events seen in the atorvastatin group is similar (approximately twice as high) in this analysis set as in the All Combination Therapy Analysis Set.

Comment: The difference in incidence in hepatic events between this analysis set and the All Combination Therapy Analysis Set (Table 7.3.5.K) might be due to the higher risk of hepatic events in the ABT-335-only group, which was diluted in All Combination with the inclusion of some initial statin monotherapy arms. Alternatively, there might be a modest increase in risk for the combination as opposed to the monotherapy.

Table 7.3.5.T. Sponsor's Treatment Emergent Adverse Events of Special Interest (Hepatic Events) for the Initial Combination Therapy Analysis Set

	ABT-335 + rosuva (N = 522)	ABT-335 + simva (N = 237)	ABT-335 + atorva (N = 220)	Total (N=979)
Hepatic Events	28 (5.4)	12 (5.1)	23 (10.5)	63 (6.4)
ALT increased	15 (2.9)	7 (3.0)	8 (3.6)	30 (3.1)
Discontinuations	10 (1.9)	1 (0.4)	5 (2.3)	16 (1.6)
AST increased	14 (2.7)	6 (2.5)	8 (3.6)	28 (2.9)
Discontinuations	8 (1.5)	1 (0.4)	4 (1.8)	13 (1.3)
Blood bilirubin increased	0	0	1 (0.5)	1 (0.1)
Discontinuations	0	0	0	0
Hepatic enzyme increased	3 (0.6)	1 (0.4)	12 (5.5)	16 (1.6)
Discontinuations	2 (0.4)	0	8 (3.6)	10 (1.0)
Hepatic steatosis	1 (0.2)	0	0	1 (0.1)
Discontinuations	0	0	0	0
Jaundice	1 (0.2)	0	0	1 (0.1)
Discontinuations	1 (0.2)	0	0	1 (0.1)
Liver function test abnormal	8 (1.5)	4 (1.7)	4 (1.8)	16 (1.6)
Discontinuations	2 (0.4)	1 (0.4)	3 (1.4)	6 (0.6)
Hepatic Events – Changes in Laboratory Tests[a]	26 (5.0)	12 (5.1)	22 (10.0)	60 (6.1)
Led to discontinuation	14	2	15	31
Met ALT or AST criterion[b]	10	2	7	19

Note: Includes data from Studies M05-748, M05-749, M05-750, and M05-758.
a. Includes adverse events of ALT increased, AST increased, hepatic enzyme increased, and liver function test abnormal.
b. ALT or AST post-baseline value > 3 × ULN on two consecutive visits or > 5 × ULN on any occasion.

The incidence of the first occurrence of the reported adverse events of 'ALT increased', 'AST increased', 'hepatic enzyme increased', and 'liver function test abnormal' was highest during the first 12 weeks of combination therapy and decreased thereafter in each of the three treatment groups. The prevalence of these adverse events was highest during the first 12 or 26 weeks and generally decreased over time.

The sponsor also evaluated the All Combination Therapy Set for subjects who met certain ALT and AST criteria, as seen in the following table:

Table 7.3.5.U. Subjects Who Met ALT and AST Criteria, All Combination Therapy Set

Laboratory Parameter Criteria[a]	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	Total (N = 2201)
ALT: ≥ 200 U/L	9/1166 (0.8)	3/508 (0.6)	6/492 (1.2)	18/2166 (0.8)
AST: ≥ 175 U/L	3/1166 (0.3)	3/508 (0.6)	3/492 (0.6)	9/2166 (0.4)
ALT > 5 × ULN on any occasion	10/1166 (0.9)	4/508 (0.8)	9/492 (1.8)	23/2166 (1.1)
ALT > 3 × ULN on 2 consecutive occasions	14/1166 (1.2)	4/508 (0.8)	8/492 (1.6)	26/2166 (1.2)
AST > 5 × ULN on any occasion	5/1166 (0.4)	3/508 (0.6)	3/492 (0.6)	11/2166 (0.5)
AST > 3 × ULN on 2 consecutive occasions	5/1166 (0.4)	1/508 (0.2)	4/492 (0.8)	10/2166 (0.5)

Comments:

It is not clear why the incidence of hepatic events and hepatic laboratory abnormalities is higher in the atorvastatin combination group as compared to the rosuvastatin and simvastatin combination groups. In a summary of Treatment-Emergent Adverse Events (Preferred Terms with at least 5 events per 100 Patient-Years in any treatment group) for the All Combination Therapy Analysis Set conducted by the sponsor, the PT of 'hepatic enzyme increased' was 0.9/100 PY in the ABT-335 + rosuvastatin and ABT-335 + simvastatin groups and 5.2/100 PY in the ABT-335 + atorvastatin group.

In Study M05-750 (ABT-335 + atorvastatin), the hepatic events were seen more frequently in the combination therapy as compared to the ABT-335 monotherapy group. However, because the ABT-335-only group in that study had a lower incidence of AEs of increases in hepatic enzymes than in the other studies it is unclear if this reflects a true adverse effect of the combination. It is furthermore noted that whereas the atorvastatin monotherapy doses were similar in hepatic events to simvastatin and rosuvastatin as the low and moderate doses in their respective controlled trials, 5.5% of subjects treated with atorvastatin 80 mg had a hepatic event, as compared with 1.7% of subjects treated with simvastatin 80 mg and 1.5% of subjects treated with rosuvastatin 40 mg. It may be that atorvastatin is more hepatotoxic than other statins, particularly in combination with a fibrate (ABT-335). Alternatively, it may be a reflection of atorvastatin's relatively higher potency as the doses are defined in this trial, as discussed in Section 7.2.2. This explanation, however, is difficult to reconcile with the fact that rosuvastatin at the moderate dose appears more potent than atorvastatin in terms of lipid-altering efficacy (Section 6).

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. The differences in incidence seen between the All Combination Therapy Analysis Set and the Initial Combination Therapy Analysis Set – which was slightly higher – highlight the fact that there may be a slightly higher risk of liver enzyme elevations in the combination of statin + ABT-335 as compared to the monotherapy. However, it may also be that because there were proportionally more subjects exposed to statin monotherapy as compared to ABT-335 in the randomized trials, the Initial Combination Analysis Set might simply be reflecting a higher proportion of subjects exposed to ABT-335 from the outset. This is supported by the controlled data, which for the most part, did not demonstrate an additive effect on hepatic events in the combination groups. In any event, it is clear that

ABT-335 increases the risk of hepatic events, primarily elevations in hepatic enzymes, and the contribution of rosuvastatin and simvastatin to this risk, if any, is small. The risk appears to be somewhat higher with the addition of atorvastatin at the studied doses. However, 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 (first 3-6 months).

Biliary events, such as cholelithiasis and cholecystitis were infrequent (< 1%).

Muscle Findings

The review strategy for muscle findings is as follows: because review of the datasets for muscle events was not as straightforward as with hepatobiliary events, given the large number of unrelated Preferred Terms under the musculoskeletal SOC, this reviewer evaluated the sponsor's data presentation of these events, with further review of cases of interest. The sponsor's pre-selected Preferred Terms were adequate for this assessment (see Section 7.2.6). Further evaluation included tracking high CK values for individual subjects to follow their natural course. CK (creatine kinase) and CPK (creatine phosphokinase) will be used interchangeably throughout the review.

Study M05-748

No cases of rhabdomyolysis were reported.

There does not appear to be a dose-related or combination-related trend in muscle events for ABT-335 or the moderate doses of rosuvastatin. The incidence increased somewhat in the rosuvastatin 40 mg group, driven by the **Preferred Terms 'myalgia' and 'blood CPK increased/abnormal'**.

Table 7.3.5.V. Muscle 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)
Muscle Events	15 (5.8)	20 (7.7)	20 (7.7)	19 (7.1)	14 (5.4)	15 (11.5)
Musculoskeletal discomfort	0	0	0	0	1 (0.4)	0
Musculoskeletal pain	4 (1.5)	3 (1.1)	4 (1.5)	4 (1.5)	3 (1.1)	2 (1.5)
Myalgia	7 (2.7)	15 (5.7)	10 (3.8)	9 (3.4)	7 (2.7)	9 (6.9)
Myositis	0	0	1 (0.4)	0	0	0
Blood CPK increased	4 (1.5)	3 (1.1)	5 (1.9)	7 (2.6)	5 (1.9)	4 (3.1)
Blood CPK abnormal	0	0	0	0	0	1 (0.8)

None of these events was considered serious, although several subjects discontinued study drug due to muscle events; in fact, myalgia was one of the most common adverse events that led to discontinuation – and this was proportionally higher in the rosuvastatin 40 mg group than in the other groups.

Table 7.3.5.W. Muscle events leading to discontinuation, 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)
Muscle Events	2 (0.8)	2 (0.8)	3 (1.1)	2 (0.8)	4 (1.5)	4 (3.1)
Myalgia	2 (0.8)	1 (0.4)	2 (0.8)	2 (0.8)	2 (0.8)	4 (3.1)
Blood CPK increased	0	1 (0.4)	1 (0.4)	0	2 (0.8)	0

One subject who discontinued met the potentially significant criterion for elevated CK [≥ 850 U/L (F)]. Subject 13538 (ABT-335 in combination with 10 mg rosuvastatin) was a 44-year-old female who had CK levels of 202 U/L on Day -7 and 175 U/L on Day 1 that increased to 978 U/L on Day 28 (6x ULN). This was reported as an adverse event of blood CK increased and was considered severe. Study drug was discontinued and CK returned to baseline levels (179 U/L) on Day 40.

None of the other subjects with either adverse events of myalgia or elevated CK that led to discontinuation had CK ≥ 5x ULN. One subject receiving ABT-335 in combination with 10 mg rosuvastatin had an elevation in CPK > 10 x ULN in the setting of an acute myocardial infarction. The following table describes subjects with post-baseline elevations in CK:

Table 7.3.5.X. Subjects with Post-Baseline Elevations in Creatine Phosphokinase, Study M05-748

(Site Number)/ Subject Number	Age/ Gender	ULN (U/L)	Elevated Value (U/L)/ Study Day	Final Value (U/L)/ Final Day[a]	Relevant Clinical Information
Creatine Phosphokinase > 10 × ULN					
ABT-335 in Combination with Rosuvastatin 10 mg					
(33362)/13566	63/M	198	4709 / 33	2467 / 34	Subject with known 3-vessel coronary artery disease (prior myocardial infarction and coronary artery bypass grafting) had elevated CPK in the context of an acute myocardial infarction. Peak CPK of 4709 was accompanied by MB fraction of 469.2 (normal range 0.1–4.0). The patient underwent percutaneous transluminal coronary angioplasty (PTCA) × 2 and was discharged home three days after hospital admission. He permanently discontinued from the study due to this event.
20 mg Rosuvastatin Monotherapy					
(33156)/14222	56/M	198	4154 / 29	369 / 86	Subject had an elevated CPK of 261 U/L at the screening visit (D –7) and 253 U/L on Day 1. An adverse event of elevated CPK was reported by the investigator with no action taken. Elevated CPK did not resolve during the study; however, the subject continued into the M05-758 Safety Study with the CPK remaining stable at 259 to 311 U/L.
40 mg Rosuvastatin Monotherapy					
(33309)/13381-4	69/M	198	3722 / 133 (104)	454 / 137 (108)	Subject had elevated CPK reported 104 days after study drug was discontinued. An adverse event of elevated CPK was reported by the investigator. Elevated CPK did not resolve during study and the subject did not continue into the M05-758 Safety Study. (This subject also had elevation > 5 × ULN, described below.)
(32403)/14529	50/M	198	2517 / 57	104 / 87	Subject had normal CPK at baseline. An adverse event of elevated CPK was reported by the investigator; however, it was noted that the subject had done 1.5 hours of vigorous weight training 1 day prior to the elevated CPK value. Study drug was interrupted and then resumed with the CPK values returning to normal range. Subject completed the study but did not continue into the M05-758 Safety Study. (This subject also had elevation > 5 × ULN, described below.)
(Site Number)/ Subject Number	Age/ Gender	ULN (U/L)	Elevated Value (U/L)/ Study Day	Final Value (U/L)/ Final Day[a]	Relevant Clinical Information
Creatine Phosphokinase > 5 × ULN					
Rosuvastatin 10 mg Monotherapy					
(31372)/13141	20/M	198	1611/29	119 / 85	Subject's CPK was elevated at the Screening Visit (Day –7, 266 U/L) and rose more on Day 29 (1611 U/L). The subject's CPK returned to normal on Day 40, prior to rolling over into M05-758. During M05-758, the CPK was sporadically elevated (with values from 168 to 283 U/L).
ABT-335 in combination with Rosuvastatin 10 mg					
(33089)/13086	45/M	198	1015 / 53	214 / 80 (1)	Subject's CPK was elevated at the Screening Visit (Day –14, 235 U/L) and on Day 29 (334 U/L). Subject sporadically took ibuprofen and naproxen for headaches during participation in the study. Subject enrolled into the M05-758 study where the CPK was sporadically elevated (values were from 131 to 917).
(33510)/13538	44/F	169	978 / 28	179 / 46 (9)	Subject's CPK was elevated at the Screening Visit (Day –7, 202 U/L), on Day 1 (175 U/L) and remained elevated during study participation. Subject permanently discontinued the study on Day 28 due to elevation in CPK.
(33136)/14142	40/M	198	1328 / 58	125 / 86	On Day 58, the subject had an elevated CPK. Study drug was interrupted for less than three days and upon returning (Day 65), the CPK had returned to normal. The subject enrolled into M05-758 study, where the CPK remains within normal limits.
(33135)/14539	60/M	198	1076 / 57	121 / 87	On Day 57, the subject's CPK was elevated. According to the investigator, the subject had a "heavy workout" the day prior to the lab draw. CPK returned to normal at the next visit (Day 87). Subject enrolled into M05-758 study, where the CPK remains within normal limits.
Rosuvastatin 20 mg Monotherapy					
(33156)/14222	56/M	198	4154 / 29	369 / 86	Subject's CPK was elevated at the Screening Visit (Day –7, 261 U/L) and on Days 1, 31, and 57 (253, 273, and 218, respectively). Elevated CPK did not resolve during the study; however, the subject continued into the M05-758 Safety Study with the CPK remaining stable at 259 to 311 U/L.

(Site Number)/ Subject Number	Age/ Gender	ULN (U/L)	Elevated Value (U/L)/ Study Day	Final Value (U/L)/ Final Day[a]	Relevant Clinical Information
Creatine Phosphokinase > 5 x ULN (continued)					
ABT-335 in Combination with Rosuvastatin 20 mg					
(33283)/13407	59/F	169	1134 / 88 (4)	1134 / 88 (4)	Subject's CPK was not elevated until Final Discontinuation visit (Day 85, 226 U/L). The subject continued into the M05-758 Safety Study where the elevated CPK did not resolve and the subject was discontinued from the study on Day 4.
(2446)/14468	64/F	169	1394 / 81	389 / 99 (18)	Subject's CPK was not elevated until Final Discontinuation visit (Day 81). The subject continued into the M05-758 Safety Study. Study drug was temporarily interrupted. No diagnostic tests were performed and subject had not recently experienced any trauma/illness. CPK in M05-758 study was between 108-204 U/L.
Rosuvastatin 40 mg Monotherapy					
(33369)/13381*	69/M	198	3722 / 133 (104)	454 / 137 (106)	Subject's CPK was not elevated until Final/Discontinuation visit (Day 104). The subject lost the study drug and the study drug end date is unknown. No diagnostic tests were performed and the subject had not recently experienced any trauma/illness. Per the investigator, "Pt. Saw PCP, not concerned per pt." Subject completed the study with elevated CPK noted on Day 106. Subject did not roll over to M05-758 study.
(33369)/14027	48/M	198	904 / 29 1628 / 32	82 / 88	Subject's CPK was elevated on Day 29 and with the retest on Day 32. The subject had started ibuprofen on Day 26 for the adverse event of cold (started on Day 4) and headache (started on Day 26). The CPK returned to normal on Day 37. The subject enrolled into M05-758 (CPKs continued to be WNL).
(33403)/14529	50/M	198	2517 / 57	104 / 87	Subject had normal CPK at baseline. The investigator reported an adverse event of elevated CPK on Day 57; however, it was noted that the subject had done 1.5 hours of vigorous weight training 1 day prior to the elevated CPK value. Study drug was interrupted and then resumed with the CPK values returning to normal at the retest on Day 62. Subject completed the M05-748 study but chose not to continue into the M05-758 Safety Study.

F = female; M = male; ULN = upper limit of the normal range; WNL = within normal limits

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

* Subject prematurely discontinued.

Study M05-749

No cases of rhabdomyolysis were reported.

Table 7.3.5.Y. Muscle events, Study M05-749

	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)
Muscle events	7 (5.9)	6 (5.0)	12 (10.1)	12 (10.3)	5 (4.2)	5 (8.5)
Blood CPK increased	0	1 (0.8)	4 (3.4)	3 (2.6)	1 (0.8)	2 (3.4)
Musculoskeletal discomfort	1 (0.8)	0	0	0	0	0
Musculoskeletal pain	0	2 (1.7)	3 (2.5)	4 (3.4)	2 (1.7)	0
Myalgia	6 (5.0)	4 (3.4)	5 (4.2)	6 (5.2)	3 (2.5)	3 (5.1)

None of these events was considered serious. Individually and combined, muscle events were not clearly dose- or combination-related. Table 7.3.5.AA describes the muscle events that led to subject discontinuation.

Table 7.3.5.Z. Muscle events leading to discontinuation, Study M05-749

	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)
Muscle Events	2 (1.7)	1 (0.8)	2 (1.7)	3 (2.6)	0	0
Myalgia	2 (1.7)	1 (0.8)	0	1 (0.9)	0	0
Blood CPK increased	0	0	2 (1.7)	2 (1.7)	0	0

Four subjects (two on ABT-335 monotherapy and one each on 20 mg and 40 mg simvastatin monotherapy) prematurely discontinued study drug due to 'myalgia', out of 27 with a 'myalgia' AE. None of these subjects had CK values > 5x ULN. Four additional subjects discontinued drug due to an AE of 'blood CPK increased'. Only one of these subjects had a CK > 10x ULN (subject 24210 on simvastatin 40 mg monotherapy).

The following table describes subjects with post-baseline elevations in CK:

Table 7.3.5.AA. Subjects with Post-Baseline Elevations in Creatine Phosphokinase, Study M05-749

(Site Number)/ Subject Number	Age/ Gender	ULN (U/L)	Elevated Value (U/L)/ Study Day	Final Value (U/L)/ Final Day[a]	Relevant Clinical Information
Creatine Phosphokinase > 10 × ULN					
40 mg Simvastatin Monotherapy					
(33275)/24210[#]	55/M	198	4558 / 57	435 / 84 (27)	Subject's screening and baseline CPK values were elevated (409 U/L and 588 U/L). On Day 57, the subject's CPK was > 10 × ULN which resulted in study drug discontinuation on Day 57. On Day 61, the CPK had decreased but remained elevated. On Day 84, the investigator considered the event resolved. The subject did not enroll in the M05-758 Safety Study.
(11288)/24076	43/M	198	4654 / 29	218 / 88 (1)	Subject's CPK was > 10 × ULN on Day 29. Subject had been in a motor vehicle accident, several days prior to Day 29, which resulted in residual back and neck pain for which the subject was taking acetaminophen. On Day 60, the CPK returned to within normal limits. Subject completed the study but did not enroll in the M05-758 Safety Study.
Creatine Phosphokinase > 5 × ULN					
ABT-335 in Combination with 20 mg Simvastatin					
(33215)/23222	54/F	169	887 / 57	86 / 88 (1)	Subject had a prior history of multiple musculoskeletal complaints (shoulder pain, lumbar muscle strain, bilateral plantar fasciitis, diffuse joint pain and ankle pain). On Day 57, subject's CPK was > 5 × ULN. Concomitant medications at time of CPK elevation was acetylsalicylic acid and ibuprofen. A recut of CPK on Day 88 indicated that the CPK had returned to normal. Subject completed the study and enrolled in the M05-758 Safety Study.
40 mg Simvastatin Monotherapy					
(33275)/24210[#]	55/M	198	4558 / 57	435 / 84 (27)	See narrative above.
(11288)/24076	43/M	198	4654 / 29	218 / 88 (1)	See narrative above.
80 mg Simvastatin Monotherapy					
(33304)/24216	54/F	169	1135 / 88 (1)	1135 / 88 (1)	Subject's CPK was > 5 × ULN on Day 88 which was the subject's final study visit. No additional information is available and the subject did not enroll in the M05-758 Safety Study.

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

Study M05-750

No cases of rhabdomyolysis were reported.

Table 7.3.5.BB. Muscle 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)
Muscle events	5 (4.5)	6 (5.3)	6 (5.5)	10 (9.2)	7 (6.4)	5 (9.1)
Musculoskeletal discomfort	0	1 (0.9)	0	0	0	0
Musculoskeletal pain	2 (1.8)	0	0	2 (1.8)	2 (1.8)	0
Myalgia	3 (2.7)	5 (4.4)	2 (1.8)	8 (7.3)	5 (4.5)	3 (5.5)
Blood CPK increased	0	0	4 (3.6)	1 (0.9)	0	2 (3.6)

'Myalgia' was the only muscle event that led to discontinuation in this study.

Comment: Although muscle events are more frequent with the higher doses of atorvastatin, it is reassuring that the combination of ABT-335 and atorvastatin 40 mg did

not increase their incidence as compared to ABT-335 and moderate- and high-dose atorvastatin monotherapy.

Table 7.3.5.CC. Muscle events leading to discontinuation, 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)
Myalgia	2 (1.8)	0	1 (0.9)	3 (2.8)	2 (1.8)	1 (1.8)

No subject in this study had a CK > 10x ULN. None of the subjects who had an AE of 'blood CPK increased' had a CK > 5x ULN. No subject who discontinued the study prematurely for an AE of 'myalgia' experienced a CK value > 5x ULN.

One subject (33183, atorvastatin 20 mg monotherapy group) experienced a CK that met potentially clinically significant criteria of ≥ 1000 U/L (M). This was a 49-year-old male who on Day 55 was noted to have a CK 1237 U/L and on Day 85 have a CK of 1591 U/L.

Study M05-758

Although no cases of rhabdomyolysis were reported in the study report, a review of narratives revealed a case of unreported "rhabdomyolysis". The narrative is presented here:

Subject 13028 is a 55-year-old black male who was hospitalized for vomiting, diarrhea, dehydration, and "passing out." His randomization in Study M05-748 was rosuvastatin 20 mg, and then he was treated with ABT-335 + rosuvastatin 20 mg in the open-label study. Medical history includes hypertension, "trivial" carotid artery disease, diverticulitis, mixed dyslipidemia, seasonal allergies, lichen planus, and toenail fungus. Concomitant medications at the time of the event included amlodipine, hydrochlorothiazide, atenolol, loratadine, hydrocortisone, acetylsalicylic acid, and terbinafine. He is a non-smoker and non-drinker.

On Day 207, the subject presented to the Emergency Room with vomiting, diarrhea, dehydration, and reported he had "passed out twice" and "hit his head." On Day 208, the subject was admitted to the hospital with a principal diagnosis of syncope and additional diagnosis of gastroenteritis, increased lipids, and rhabdomyolysis. A computed tomography of the head was normal. An abdominal x-ray showed nonspecific bowel gas pattern. An ECG revealed normal sinus rhythm with a rate of 87 bpm; poor R-wave progression in leads V1 to V3, and non-specific T-wave abnormalities. The event of syncope was considered resolved on Day 208. The subject's creatine phosphokinase was elevated and thought to be consistent with rhabdomyolysis. The investigator reported the subject has a history of elevated creatine phosphokinase for several years. Creatine phosphokinase (CPK) values are provided in the table below. The study drug was interrupted on Day 208. The subject was treated intravenously with sodium chloride and ondansetron. On Day 210, an echocardiogram revealed the left ventricle was normal in size and LV ejection fraction was 65%. On Day 211, a carotid ultrasound revealed "no hemodynamically significant stenosis in the bilateral carotid artery system." On Day 211, the event of

gastroenteritis was considered resolved and the subject was discharged. On Day 212, the study drug was re-introduced.

Table 7.3.5.DD.

Subject #13028 Fasting Laboratory Data

Treatment Day	CPK Reference Range < 18-198 U/L	Creatinine Reference Range 0.8-1.3 mg/dL	BUN Reference Range 4-24 mg/dL	Creatinine clearance Reference Range 88-128 mL/min
Screening (M05-748)	340	1.3	14	99
Baseline (M05-748)	394	1.5	17	86
Day 27 (M05-748)	282	1.3	18	96
Day 57 (M05-748)	298	1.5	22	90
Day 1 (M05-758)	526	1.5	13	89
Day 29 (M05-758)	347	1.5	15	89
Day 57 (M05-758)	386	1.8	18	72
Day 86 (M05-758)	222	1.5	15	88
Day 113 (M05-758)	294	1.8	17	74
Day 194 (M05-758)	337	1.7	15	75
Day 278 (M05-758)	260	1.8	14	72
Day 369 (M05-758)	632	1.5	18	84

Table 7.3.5.EE.

Subject # 13028 Hospital Laboratory Data

Treatment Day	CPK Hospital Reference Range < 180 U/L	Creatinine Hospital Reference Range 0.5-1.2 mg/dL	BUN Hospital Reference Range 6-19 mg/dL
Day 208 Hospital	350	1.6	19
Day 211 Hospital	558	1.3	8

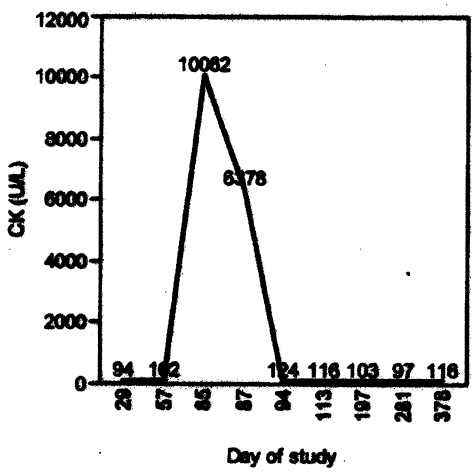
The investigator considered the event of gastroenteritis viral to be not related to study drug but rather to a viral infection and the event of syncope to be not related to study drug but rather to a vasovagal response secondary to severe vomiting.

Comment: Rhabdomyolysis was not mentioned on the case report form, and the investigator specifically denied that the elevated CK was an adverse event when asked.

This subject did have a baseline elevated CK, and this reviewer would agree that the CK elevation to the degree seen in the hospital is unlikely to be the culprit for the acute renal failure; creatinine elevations had been noted throughout the open-label portion of the study and are consistent with changes seen with ABT-335 treatment. CK elevation above baseline could have been consistent with the report of a fall. Reassuringly, the subject remained on study drug without further adverse events reported, although it is noted that CK increased to 632 U/L on Day 369. However, BUN, creatinine, and creatinine clearance returned to baseline levels.

To evaluate CK excursions during therapy and after medication discontinuation during the open-label period, the CK timecourse is presented for each subject with CK > 10x ULN in Study M05-758. Narratives, if available because of study discontinuation, are included below.

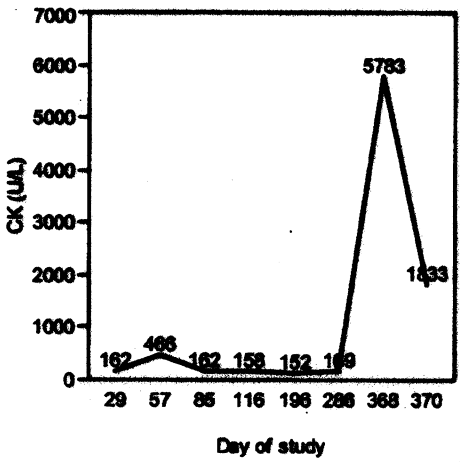
Figure 7.3.5.A. Subject 14162 (ABT-335 + rosuvastatin 20 mg)



Day 378 (CK value=116 U/L) is 1 day off study.

Comment: The CK value decreased to normal while still on therapy.

Figure 7.3.5.B. Subject 13203 (ABT 335 + rosuvastatin 20 mg)



Day 368 (maximum CK value=5783 U/L) is 1 day off study.

Comment: The CK began decreasing after therapy was stopped. No further CK values were provided.

Subject 13218 (ABT-335 + rosuvastatin 20 mg) did not develop elevated CK due to skeletal myopathy, but rather due to a myocardial infarction. This was a 78-year-old female with hypertension, diabetes mellitus, pacemaker, stroke, mixed dyslipidemia, osteoarthritis, acid reflux, and hypothyroidism who presented with a myocardial infarction on Day 246. On Day 247, her laboratory values were CK 2090 and CK-MB 138. Cardiac catheterization revealed a right coronary artery stenosis. On Day 248 the subject was discontinued from the study.

Comment: This case is not relevant to a skeletal myopathy evaluation. Myocardial infarction is not unexpected in a 78-year-old female with multiple risk factors.

Subject 14284 (ABT-335 + rosuvastatin 20 mg) was a 51-year-old white female who was prematurely discontinued study drug on Day 28 due to an elevated CK value. Medical history included seasonal allergies, sleep apnea, chronic cough, hypertension, obesity, and mixed dyslipidemia. Concomitant medications at the time of the event included ibuprofen, triamterene/hydrochlorothiazide, loratadine, phentermine, and losartan. The subject is an ex-smoker of cigarettes (10 pack years) and an ex-light-drinker.

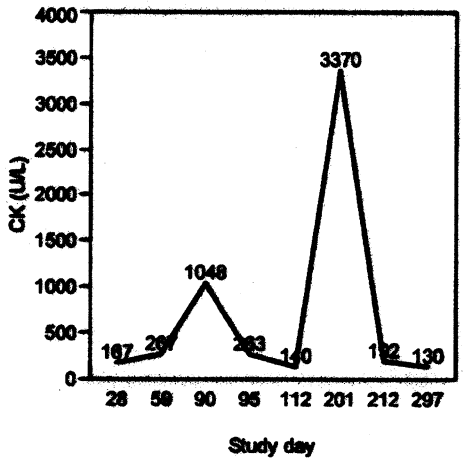
On Day 28, the subject was reported to have an increased CK, as seen in the table below. Study drug was discontinued on Day 28. The event was considered resolved on Day 32 (Post Treatment Day 4). The subject did not report any intercurrent events. No further information was provided.

Table 7.3.5.FF.

Subject #14284 Fasting Laboratory Data

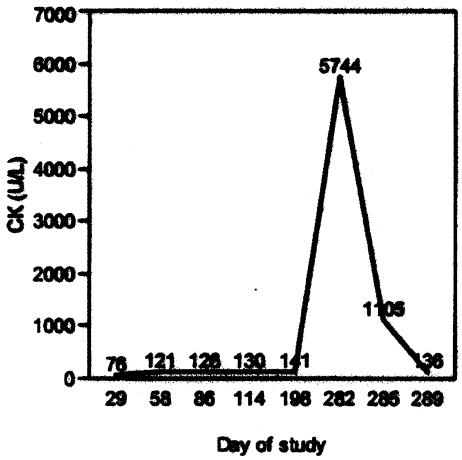
Treatment Day	CPK Reference Range < 18-169 U/L
Baseline (M05-748)	72
Day 86/Final Visit (M05-748)	64
Day 28 (M05-758)	2645
Day 32 (4 days post study drug)/Final Visit (M05-758)	175

Figure 7.3.5.C. Subject 14262 (ABT-335 + rosuvastatin 20 mg)



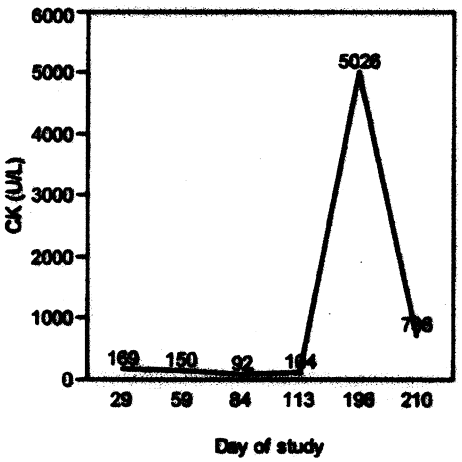
Day 297 (CK value=130 U/L) was 21 days off study.

Figure 7.3.5.D. Subject 32041 (ABT-335 + atorvastatin 40 mg)



Day 282 (maximum CK value=5744 U/L) was 1 day off study.

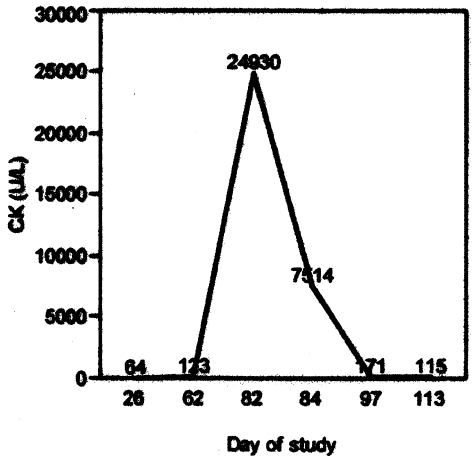
Figure 7.3.5.E. Subject 24104 (ABT-335 + simvastatin 40 mg)



AEs of elevated ALT (139 U/L), AST (202 U/L), and CK (5026 U/L) led to this subject's discontinuation. On the CRF the investigator stated that the subject had recently bought a farm and was doing a lot of physical labor.

Day 210 (CK value=736 U/L) was 13 days off study.

Figure 7.3.5.F. Subject 24017 (ABT-335 + simvastatin 40 mg)



Subject 24017 is a 53-year-old white Hispanic male who prematurely discontinued study drug on Day 83 due to "elevated liver functions," and elevated creatine phosphokinase (CK). Medical history included hepatitis A and mixed dyslipidemia. Concomitant medications at the time of the event included glucosamine/chondroitin and acetaminophen. The subject is a current 3-pack-year smoker and light drinker.

The subject was previously treated with ABT-335 135 mg in the M05-749 study, during which time he sustained fractures of the right leg and right hand, with surgical repair of right wrist, infection of the right foot, and open reduction and internal fixation of right talus.

On Day 82, the subject was reported to have elevated liver enzymes and an elevated CK. The investigator reported that the subject was experiencing post-surgical pain that had begun in the M05-749 study and was still ongoing. Laboratory values are provided in the table below. The study drug was discontinued on Day 83. On Day 113 (Post Treatment Day 30), the investigator considered the events of elevated liver enzymes and elevated CK resolved. No further information was provided.