

Comments: Mean increases in ALT and AST reflect adverse events and categorical increases as described in the analysis of hepatic events in Section 7.3.5. Other changes associated with ABT-335 therapy include decreases in alkaline phosphatase, increases in BUN and creatinine, decreases in inorganic phosphate, increases in serum calcium, and decreases in uric acid. With the exception of uric acid, none of these mean changes associated with ABT-335 therapy are compounded with the addition of a statin in these 12-week studies.

Mean changes in serum calcium are consistent with proportions of subjects with normal or low baseline calcium concentrations who experienced elevations in serum calcium concentrations during the controlled studies (4.9-7.6% in ABT-335-treated groups vs. 1.9-3.8% in statin monotherapy groups), and the proportions of subjects who developed serum calcium \geq 11 mg/dL during the course of the study (1.6-2.2% in ABT-335-treated groups vs. 0.6-1.2% in statin monotherapy groups. Adverse events of hypercalcemia or serum calcium increased were seen in six subjects in the controlled trials (one each in the ABT-335 monotherapy, ABT-335 + atorvastatin 40 mg, ABT-335 + rosuvastatin 10 mg, ABT-335 + rosuvastatin 20 mg, ABT-335 + simvastatin 20 mg, and rosuvastatin 40 mg monotherapy groups) and in 14 subjects (0.6%) in the open-label trial (6 each in the ABT-335 + atorvastatin and rosuvastatin and 2 in the ABT-335 + simvastatin groups). Only one subject was discontinued due to hypercalcemia, and she had elevations in ALT and CK as well:

Subject 13497 was a 59-year-old white female who prematurely discontinued study drug on Day 4 due to an elevated CK, calcium, and ALT. She was treated with ABT-335 and rosuvastatin 20 mg in the M05-748 study. Medical history included headache, coronary artery disease, hypertension, possible cardiac arrhythmia, mixed dyslipidemia, hysterectomy, and sinus infection. Concomitant medications at the time of the event included amlodipine, irbesartan, calcium citrate/vitamin D, acetaminophen, and cefdinir. She is a non-smoker and a non-drinker. On Day 85 of the M05-748 study, the subject was reported to have an elevated CPK, calcium, and ALT. Laboratory values are provided in the table below. On Day 4 of the M05-758 study, study drug was discontinued. The events were reported to be resolved on Day 31 (Post Treatment Day 27).

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Table 7.4.2.I.

Subject #13497 Fasting Laboratory Data

Treatment Day	CPK Reference Range <18-169 U/L	Calcium Reference Range 8.3-10.6 mg/dL	ALT Reference Range 6-34 U/L	AST Reference Range 9-34 U/L	Total Bilirubin Reference Range 0.2-1.2 mg/dL
Screening (M05-748)	80	10.7	23	17	0.4
Baseline (M05-748)	90	10.0	19	17	0.4
Day 29 (M05-748)	94	10.5	35	23	0.5
Day 57 (M05-748)	99	10.1	39	28	0.3
Day 85 (M05-748)	226	11.5	42	28	0.4
Day 2/Reass (M05-758)	1134	10.4	39	33	0.4
Day 5 (1 day post study drug)/Final Visit (M05-758)	977	10.3	45	35	0.4

The CK and ALT elevations could be related to drug; how they relate to the calcium elevation in this subject who is taking calcium and vitamin D supplementation is unclear. It appears that if these calcium findings translate into clinically important events, their incidence is relatively infrequent. To the knowledge of this reviewer, this finding has not been described previously with fenofibrate treatment.

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Table 7.4.2.J. Mean Change from Baseline to Final Value for Selected Chemistry Parameters for the All Combination Therapy Analysis Set

	ABT-338 + rosurva (N = 1166)	ABT-338 + simva (N = 514)	ABT-338 + atorva (N = 493)	Total (N = 2288)
Chemistry Parameter	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
SGPT/ALT (U/L)	(N = 1166)	(N = 508)	(N = 493)	(N = 2166)
Baseline mean	27.2	25.4	27.9	26.9
Mean Δ to Final Value	1.2 (17.59)	1.6 (10.84)	2.5 (18.49)	1.5 (16.46)
SGOT/AST (U/L)	(N = 1166)	(N = 508)	(N = 493)	(N = 2166)
Baseline mean	24.1	22.8	24.1	23.8
Mean Δ to Final Value	2.0 (12.30)	1.6 (7.20)	1.9 (10.79)	1.9 (10.99)
Alkaline Phosphatase (U/L)	(N = 1166)	(N = 508)	(N = 493)	(N = 2166)
Baseline mean	78.7	77.5	83.6	79.4
Mean Δ to Final Value	-17.6 (19.81)	-17.3 (17.29)	-19.0 (23.09)	-17.9 (20.05)
CPK (U/L)	(N = 1167)	(N = 509)	(N = 492)	(N = 2168)
Baseline mean	133.2	125.9	127.6	130.2
Mean Δ to Final Value	12.6 (119.39)	9.1 (113.15)	9.9 (118.41)	11.1 (117.69)
Creatinine (mg/dL)	(N = 1166)	(N = 508)	(N = 492)	(N = 2166)
Baseline mean	0.93	0.92	0.93	0.92
Mean Δ to Final Value	0.11 (0.150)	0.12 (0.149)	0.11 (0.165)	0.11 (0.152)
BUN (mg/dL)	(N = 1166)	(N = 508)	(N = 492)	(N = 2166)
Baseline mean	16.36	16.06	16.40	16.30
Mean Δ to Final Value	1.50 (4.369)	1.79 (4.228)	1.99 (4.519)	1.67 (4.372)
Fasting Glucose (mg/dL)	(N = 1166)	(N = 508)	(N = 492)	(N = 2166)
Baseline mean	104.868	105.848	107.073	105.599
Mean Δ to Final Value	2.731 (21.6359)	2.245 (21.2389)	1.696 (22.3739)	2.257 (21.6936)
Calculated CrCl (mL/min)	(N = 1166)	(N = 508)	(N = 492)	(N = 2166)
Baseline mean	113.173	113.621	111.804	112.967
Mean Δ to Final Value	-11.656 (16.6352)	-12.219 (16.4396)	-12.399 (17.9409)	-12.064 (16.8657)

Note: Include data from Studies M05-748, M05-749, M05-750, and M05-751.

Note: Baseline was defined as the last value before the first dose of combination therapy, whether in the double-blind or open-label study.

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

7.4.3 Vital Signs

The following vital signs were collected in the Phase 1 and Phase 3 studies: systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, weight, and body temperature. In the Phase 1 studies, no vital sign value was considered clinically significant, nor was any vital sign value associated with adverse events or premature discontinuation.

In the Phase 3 controlled studies, mean differences and values that reached potential clinical significance were evaluated. Mean changes/differences were not clinically significant. A summary of potentially clinically vital sign values is presented in Table 7.4.3.A. These results are unlikely to be clinically relevant.

Table 7.4.3.A. Number of Subjects Meeting Criteria After Baseline for Potentially Clinically Significant Vital Sign Values for the Controlled Studies Analysis Set

Vital Sign Parameter Criteria ^a	Treatment Group n/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)
SBP (mmHg)						
> 180 mmHg	0/474	5/486 (1.0)	0/481	4/482 (0.8)	1/474 (0.2)	0/239
DBP (mmHg)						
< 40 mmHg	0/474	0/486	0/481	0/482	1/474 (0.2)	0/239
> 110 mmHg	1/474 (0.2)	0/486	1/481 (0.2)	0/482	2/474 (0.4)	0/239
Pulse (bpm)						
< 50 bpm	8/474 (1.7)	5/486 (1.0)	6/481 (1.2)	5/482 (1.0)	10/474 (2.1)	2/239 (0.8)
> 110 bpm	0/474	0/486	0/481	2/482 (0.4)	0/474	1/239 (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.

bpm = beats per minute

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

7.4.4 Electrocardiograms (ECGs)

As ABT-335 references Tricor (NDA 21-656), for which no known QT signal exists (this reviewer conducted a Medline search of the terms 'fenofibrate' or 'Tricor' and 'QT', and did not find any relevant references), ABT-335 is not required to be formally evaluated for a QT signal. A QT signal would not be predicted based on either the preclinical data or the clinical experience with fenofibrate.

In the clinical trials, ECGs were collected at baseline and at the end of the study. In the Controlled Studies Analysis Set, a total of six subjects (five from Study M05-748 and one from Study M05-749) had ECG results that shifted from normal or abnormal, not clinically significant at baseline to abnormal, clinically significant (Table 7.4.4.A).

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Table 7.4.4.A. Shifts in ECG Findings from Normal or Abnormal, Not Clinically Significant, at Baseline to Abnormal, Clinically Significant for the Controlled Studies Analysis Set

ECG Shift from Baseline	Treatment Group n (%)						Total (N = 2690)
	ABT-335 (N = 490)	ABT-335 + Low-dose Statin		ABT-335 + Moderate-dose Statin		High-dose Statin (N = 245)	
		Low-dose Statin (N = 493)	+ Low-dose Statin (N = 490)	Moderate-dose Statin (N = 491)	+ Moderate-dose Statin (N = 489)		
Normal to Abnormal, CS	1	0	0	0	0	0	1
Abnormal, NCS to Abnormal, CS	2	0	0	2	1	0	5
Normal to Abnormal, NCS	39	40	39	33	44	18	213

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.

CS = clinically significant; NCS = not clinically significant

Additional detail for these six subjects is provided below:

- Subject 13487 (Study M05-748, ABT-335) had a normal ECG at baseline. On the Final Visit ECG the investigator described inferior and "antiseptal" ST-T changes. This was reported as an adverse event of abnormal ECG. A stress test was planned to further evaluate the subject, who did not enroll in Study M05-758.
- Subject 14383 (Study M05-748, ABT-335) had an abnormal, not clinically significant ECG at baseline with first-degree atrioventricular block, right ventricular hypertrophy and abnormal anterior Q waves noted. On the Final Visit ECG sinus bradycardia, first-degree atrioventricular block, right ventricular hypertrophy, and possible anteroseptal myocardial ischemia were noted. The subject had a history of first-degree atrioventricular block. No adverse event was reported for this subject who enrolled in Study M05-758.
- Subject 11105 (Study M05-748, ABT-335 + rosuvastatin 20 mg) had an abnormal, not clinically significant ECG at baseline with poor R wave progression noted. On the Final Visit ECG the investigator described premature ventricular contraction and left bundle branch block. The subject had a history of left bundle branch block. No adverse event was reported for this subject who did not enroll in Study M05-758.
- Subject 12158 (Study M05-748, rosuvastatin 20 mg) had an abnormal, not clinically significant ECG at baseline with T wave abnormality in high lateral leads noted. On the Final Visit ECG abnormal T waves were noted although it was confirmed by the PI that the abnormality was not changed from the baseline ECG. No adverse event was reported for this subject who enrolled in Study M05-758.
- Subject 13309 (Study M05-748, rosuvastatin 20 mg) had an abnormal, not clinically significant ECG at baseline with abnormal T waves noted. On the Final Visit ECG ST segment depression and abnormal T waves with lateral ischemia was noted. This was reported as an adverse event of lateral ischemia. The subject enrolled in Study M05-758.
- Subject 21011 (Study M05-749, ABT-335) had an abnormal, not clinically significant ECG at baseline with mild non-specific ST changes noted. In the Final Visit ECG (which was

obtained just nine days after baseline ECG) worsened anterior ST-T changes were noted. An adverse event of abnormal ECG changes was reported for the subject. A serious adverse event of unstable angina was also reported for the subject, who subsequently underwent coronary revascularization (four vessel coronary artery bypass grafting). The subject did not enroll in Study M05-758.

Comment: These ECG changes are likely due to these individuals' underlying comorbidities.

ECGs were conducted at Baseline and End-of-Study in Study M05-758. Results were not summarized, but this reviewer investigated the datasets for prolonged QTc (Bazett's correction) and highlighted those follow-up values of interest (all deemed not clinically significant by the investigator).

Table 7.4.4.B. Abnormal QTc Findings, Study M05-758

Subject ID	Treatment Group	Study Day	Baseline QTc (msec)	Visit QTc (msec)	Investigator Assessment
14182	ABT-335 + rosuvastatin 20 mg	1 day after D/C	469	474	Abnormal - Clinically Significant
14176	ABT-335 + rosuvastatin 20 mg	1 day after D/C	459	495	Abnormal - Not Clinically Significant
13258	ABT-335 + rosuvastatin 20 mg	1 day after D/C	470	526	Abnormal - Not Clinically Significant
13070	ABT-335 + rosuvastatin 20 mg	1 day after D/C	413	483	Abnormal - Not Clinically Significant
33084	ABT-335 + atorvastatin 40 mg	364	458	457	Abnormal - Clinically Significant
14208	ABT-335 + rosuvastatin 20 mg	1 day after D/C	471	479	Abnormal - Not Clinically Significant
12069	ABT-335 + rosuvastatin 20 mg	364	430	417	Abnormal - Clinically Significant
13177	ABT-335 + rosuvastatin 20 mg	370	437	438	Abnormal - Clinically Significant
24159	ABT-335 + simvastatin 40 mg	1 day after D/C	410	482	Abnormal - Not Clinically Significant

Comment: No adverse events related to QT were reported, and the subject (13258) with the QTc = 526 msec was a 56-year-old non-diabetic female, on multiple COPD medications (bronchodilators, antiinflammatories, antihistamine), anxiolytics, and a SSRI. The subject was started on varenicline (Chantix) on Day 288 for smoking cessation. It is unknown when any of these ECGs were taken in relation to the timing of ABT-335 or statin C_{max}.

7.4.5 Special Safety Studies

No special safety studies were done.

7.4.6 Immunogenicity

Not applicable; ABT-335 is not a therapeutic protein.

7.5 Other Safety Explorations

For the *Controlled Studies, All Combination Therapy at the Moderate Statin Dose, and All Combination Therapy* analysis sets, adverse events (frequencies and percentages by SOC and Preferred Term) were summarized by the following subgroups:

- Age (< 65 years, ≥ 65 years)
- Gender (male, female)
- Race (White, Black, Other)
- Ethnicity (Hispanic: yes, no)
- Body weight (< 70 kg, ≥ 70 kg)
- Baseline diabetic status (diabetic, non-diabetic)
- Lipid therapy within 30 days prior to Pre-screening Visit of double-blind, controlled studies (yes, no) for the Controlled Studies analysis set only
- Baseline creatinine clearance (< 60 mL/min, ≥ 60 mL/min)
- Baseline estimated glomerular filtration rate (eGFR) (< 60 mL/min/1.73 m², ≥ 60 mL/min/1.73 m²). Estimated GFR was calculated as follows: $eGFR (mL/min/1.73 m^2) = 186 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$.

7.5.1 Dose Dependency for Adverse Findings

ABT-335 was only studied at the 135 mg dose, so dose-dependency for ABT-335 could not be assessed in the Phase 3 trials.

Most adverse events were not seen at a greater incidence in combination than in the respective statin monotherapies, and in particular were not dose-dependent based on statin dose (i.e., there was no indication of additional adverse effects with the moderate-dose combination relative to the low-dose combination).

7.5.2 Time Dependency for Adverse Findings

Evaluating time-dependency is most meaningfully done when the drug is studied over a relatively long period of time – particularly in the case of chronically-administered drugs. Therefore, the All Combination Analysis Set, which included patients followed for a year of treatment is a reasonable analysis set from which to evaluate adverse events over time. The sponsor focused on muscle, renal, and hepatic events for the time-dependency evaluation.

The following tables demonstrate that the first occurrence of these adverse events of interest generally is seen early on, with the majority of the first events occurring in the first 12-26 weeks of therapy.

Table 7.5.2.A. Incidence of First Occurrence of Muscle Adverse Events over Time for the All Combination Therapy Analysis Set

Treatment Group	Exposure Interval n (%)				
	1-12 Weeks	13-26 Weeks	27-40 Weeks	41-54 Weeks	55-68 Weeks
ABT-335 - rosuvastatin	62 (5.2)	32 (3.1)	16 (1.9)	8 (1.1)	1 (0.2)
ABT-335 - simvastatin	33 (6.4)	14 (3.1)	6 (1.8)	2 (0.9)	0
ABT-335 - atorvastatin	30 (6.0)	12 (2.8)	6 (1.7)	6 (2.2)	0

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

Table 7.5.2.B. Incidence of First Occurrence of Renal Adverse Events over Time for the All Combination Therapy Analysis Set

Treatment Group	Exposure Interval n (%)				
	1-12 Weeks	13-26 Weeks	27-40 Weeks	41-54 Weeks	55-68 Weeks
ABT-335 - rosuvastatin	26 (2.2)	10 (0.9)	4 (0.4)	4 (0.5)	0
ABT-335 - simvastatin	5 (1.0)	3 (0.6)	2 (0.5)	1 (0.4)	0
ABT-335 - atorvastatin	15 (3.0)	3 (0.7)	1 (0.3)	0	0

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

rosuvastatin = 10 or 20 mg rosuvastatin; simvastatin = 20 or 40 mg simvastatin; atorvastatin = 20 or 40 mg atorvastatin

Table 7.5.2.C. Incidence of First Occurrence of Hepatic Adverse Events over Time for the All Combination Therapy Analysis Set

Treatment Group	Exposure Interval n (%)				
	1-12 Weeks	13-26 Weeks	27-40 Weeks	41-54 Weeks	55-68 Weeks
ABT-335 - rosuvastatin	33 (2.8)	11 (1.0)	6 (0.7)	2 (0.3)	0
ABT-335 - simvastatin	16 (3.1)	2 (0.4)	1 (0.3)	1 (0.4)	0
ABT-335 - atorvastatin	28 (5.6)	7 (1.6)	1 (0.3)	0	0

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

rosuvastatin = 10 or 20 mg rosuvastatin; simvastatin = 20 or 40 mg simvastatin; atorvastatin = 20 or 40 mg atorvastatin

The sponsor goes on to note that the prevalence of individual adverse events of interest generally decreases or are stable over time.

Comment: Adverse events that lead to greater discontinuation can bias these estimates by disproportionately causing subjects who would typically continue to report such events to drop out.

7.5.3 Drug-Demographic Interactions

Age

There have been no studies or analyses carried out to assess fenofibric acid pharmacokinetics after ABT-335 administration in geriatric subjects. One study evaluated the pharmacokinetics of fenofibric acid after oral administration of fenofibrate in five subjects aged 77-87 years (mean \pm SD; 83.2 \pm 3.7 years) free of severe cardiovascular, digestive, renal or hepatic diseases. This study was reviewed under NDA 21-656/S-004 (Tricor).³⁸ It demonstrated that fenofibrate exposure was not increased in the elderly as compared to healthy young adults.

Although in the sponsor's analysis of the controlled studies no consistent age-related pattern in the incidence of treatment-emergent adverse events was observed, older subjects treated with ABT-335 + moderate dose statin demonstrated a greater incidence of blood creatinine increased (5%) as compared to younger subjects (0%):

Table 7.5.3.A. Renal-Related Treatment-Emergent Adverse Events by Age Group for Which Statistically Significant Differences Were Observed for the Controlled Studies Analysis Set

	ABT-335		Low-dose statin		ABT-335 + low statin		Moderate-dose statin		ABT-335 + moderate statin	
	< 65 (N=492)	\geq 65 (N=88)	< 65 (N=419)	\geq 65 (N=74)	< 65 (N=394)	\geq 65 (N=96)	< 65 (N=408)	\geq 65 (N=83)	< 65 (N=389)	\geq 65 (N=100)
Blood creatinine increased ^a	2 (0.5)	0	0	0	3 (0.8)	1 (1.0)	0	0	0	5 (5.0)
^a Statistically significant heterogeneity in odds ratio (ABT-335 in combination with moderate statin vs. ABT-335) ($p \leq 0.05$) based on Breslow-Day test for homogeneity of odds ratios.										

Comment: Older subjects might be more susceptible to increased creatinine with the combination of ABT-335 + moderate dose statin as compared to younger subjects (5% vs. 0%); this finding was not seen in the other treatment groups.

This reviewer looked at the events of special interest for the age group \geq 65 years old only in the sponsor's datasets, and came up with the following event rates:

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Table 7.5.3.B. Events of Special Interest, Controlled Studies, Age Group ≥ 65 Years

	ABT-335 N=88	low-dose statin N=74	ABT-335 + low- dose statin N=96	mod-dose statin N=83	ABT-335 + mod- dose statin N=100	high-dose statin N=50
Hepatic Events	3 (3.4)	0	6 (6.3)	0	1 (1.0)	0
Muscle Events	6 (6.8)	6 (8.1)	4 (4.2)	4 (4.8)	6 (6.0)	4 (8.0)
Renal Events	5 (5.7)	1 (1.4)	4 (4.2)	0	8 (8.0)	2 (4.0)

Comment: The incidences of adverse events of interest do not appear to be greatly different in this subgroup from those of the overall dataset, with the exception of renal events: rates are higher in all treatment groups except the moderate-dose statin group. Combination therapy does not appear to increase the risk of events of interest in this subgroup.

In the long-term evaluation (All Combination Therapy Analysis Set), 'Blood creatinine increased' and 'Creatinine renal clearance decreased' occurred more frequently in subjects ≥ 65 years of age versus subjects < 65 years of age across all treatment groups:

Table 7.5.3.C. Renal-Related Treatment-Emergent Adverse Events by Age Group for the All Combination Therapy Analysis Set Occurring in at Least 2.0% in Any Treatment Group Overall

	ABT-335 + rosuva (N=1186)		ABT-335 + simva (N=314)		ABT-335 + atorva (N=301)		Total (N=2201)	
	< 65 (N=965)	≥ 65 (N=221)	< 65 (N=440)	≥ 65 (N=74)	< 65 (N=398)	≥ 65 (N=103)	< 65 (N=1803)	≥ 65 (N=398)
Blood creatinine increased	12 (1.2)	8 (3.6)	3 (0.7)	1 (1.4)	4 (1.0)	2 (1.9)	19 (1.1)	11 (2.8)
Creatinine renal clearance decreased	6 (0.6)	15 (6.8)	2 (0.5)	1 (1.4)	4 (1.0)	8 (7.8)	12 (0.7)	24 (6.0)

Comment: The extension trial of the moderate-dose combinations, while demonstrating a greater incidence of renal AEs than the younger subjects, has no comparator group, so it may be that this finding is a reflection of changes in renal function occurring over time in elderly patients. Nevertheless, renal function in elderly patients should be monitored while on ABT-335 treatment.

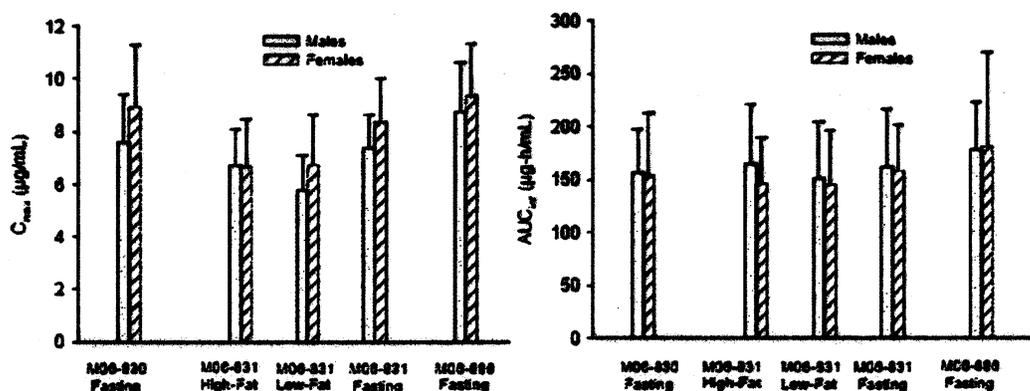
With respect to hepatic and muscle events, no significant differences were reported in the incidence between the younger and older groups in these adverse events in either the controlled or long-term studies.

Sex

The mean (+SD) C_{max} and $AUC_{0-\infty}$ values of fenofibric acid observed for 182 healthy volunteers (113 males and 69 females) after single-dose administration of ABT-335 are illustrated in Figure

7.5.3.A. There appear to be no significant differences in fenofibric acid pharmacokinetics between males and females.

Figure 7.5.3.A. Mean + SD Pharmacokinetic Parameters of Fenofibric Acid Observed for Male and Female Healthy Subjects after Single-Dose Administration of the To-Be-Marketed ABT-335 Formulation



Overall in each treatment group in the clinical trials, the percentage of female subjects with any adverse event was greater than that of males. The sponsor provided a reference³⁹ that had described this observation as a known phenomenon.

The following table describes this reviewer's analysis of adverse events of special interest by sex:

Table 7.5.3.D. Events of Special Interest, Controlled Studies, By Sex

Sex	ABT-335		LD statin		ABT-335 + LD statin		MD statin		ABT-335 + MD statin		HD statin	
	F	M	F	M	F	M	F	M	F	M	F	M
N	277	213	234	259	263	227	245	246	249	240	125	120
Hepatic Events	17 (6.1)	2 (0.9)	0	3 (1.2)	20 (7.6)	11 (4.8)	1 (0.4)	3 (1.2)	16 (6.4)	6 (2.5)	5 (4.0)	1 (0.8)
Muscle Events	15 (5.4)	12 (5.6)	14 (6.0)	18 (6.9)	23 (8.7)	15 (6.6)	19 (7.8)	22 (8.9)	14 (5.6)	12 (5.0)	8 (6.4)	17 (14.2)
Renal Events	3 (1.1)	6 (2.8)	0	2 (0.8)	4 (1.5)	6 (2.6)	0	0	4 (1.6)	4 (1.7)	2 (1.6)	1 (0.8)

Comment: Females appear to be more sensitive to the hepatic effects of ABT-335 (as discussed in Section 7.3.5, this was primarily events of transaminase increase) than males. Although the numbers overall are fewer, the sex-based discrepancy is also seen in the high-dose statin group. A sex-based discrepancy was only seen for muscle events in the high-

³⁹ Montastruc J-L, et al. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. *Fundam Clin Pharmacol.* 2002;16:343-346.

dose statin group (males > females). The incidences of renal events are inconsistent between groups with an apparent imbalance in the ABT-335 monotherapy and in combination with low-dose statin groups, but the numbers of these events are few overall.

In the sponsor's analyses of individual preferred terms, of the most frequent ($\geq 2.0\%$ in any treatment group overall) treatment-emergent adverse events and adverse events of special interest, a statistically significant heterogeneity in odds ratio of the ABT-335 in combination with moderate-dose statin group and moderate-dose statin monotherapy group was observed between males and females for adverse event of hepatic enzyme increased. In the moderate-dose statin monotherapy group, this adverse event was more common among males than females; in the ABT-335 in combination with moderate-dose statin group, no males had this adverse event reported. For other hepatic adverse events, females had greater incidences compared to males of the events of AST increased and ALT increased in the ABT-335 and both combination therapy groups. However, the relative difference in incidence between males and females was similar across treatment groups.

Statistically significant heterogeneity in odds ratios of the ABT-335 in combination with low-dose statin group versus both the ABT-335 monotherapy and corresponding statin monotherapy groups was observed for myalgia. In the ABT-335 in combination with low-dose statin group, a greater incidence was observed among females compared to males. In the low-dose statin monotherapy group, a greater incidence was observed among males compared to females. In the ABT-335 monotherapy group, the incidence was similar in males and females.

Males had a greater incidence of blood CPK increased than females in each treatment group. Muscle spasms were reported for a greater percentage of female subjects compared with male subjects across each of the treatment groups. Statistically significant heterogeneity in odds ratios for muscle spasms was observed between ABT-335 in combination with moderate-dose statin therapy and moderate dose statin monotherapy.

A greater percentage of males than females had an adverse event of blood creatinine increased. No apparent difference by gender was observed for the adverse event of creatinine renal clearance decreased.

Race

Studies or analyses have not been conducted to evaluate the pharmacokinetics of fenofibric acid after the administration of ABT-335 to patients of varying races. The Tricor package insert states that fenofibrate is not metabolized by enzymes known for exhibiting interethnic variability and as bioequivalence for ABT-335 and fenofibrate has been established, no race or ethnicity effects on the pharmacokinetics of fenofibric acid following ABT-335 administration are expected.

Due to the small number of subjects in the race groups of Black and Other in each treatment group compared with Whites, no meaningful conclusions were made regarding treatment-emergent adverse events or change from baseline in laboratory variables by race group in either

the controlled or long-term studies. No consistent race-related pattern in the incidence of treatment-emergent adverse events was observed.

7.5.4 Drug-Disease Interactions

Renal Impairment

A stand-alone pharmacokinetic study of ABT-335 administration in subjects with renal impairment has not been conducted.

Two pharmacokinetic studies were conducted evaluating the pharmacokinetics of fenofibric acid in subjects with renal impairment after oral administration of fenofibrate. The first study included subjects with end-stage renal disease on hemodialysis. The second study included subjects with varying degrees of renal impairment, but none of the subjects were on hemodialysis. In the renal impairment study, 15 renally-impaired subjects received a single oral dose of fenofibrate 100 mg as the non-micronized capsule, which is 1/3 of the full approved dose, under non-fasting conditions. Because the classification of patients in this study was different from either FDA or K/DOQI guidance's recommended groupings, this study was reanalyzed and subjects were categorized into mild, moderate, and severe renal impairment groups. None of the subjects in the mild and moderate renal impairment groups demonstrated higher C_{max} or AUC values than the means observed in healthy young adults. The apparent oral clearance (CL/F) and renal clearance (CL_{R2}) in the mild and moderate renal impairment groups were somewhat higher than those seen in the healthy group suggesting that the elimination of fenofibric acid was not compromised in these two renal impairment groups.

The AUC was higher in the severe renal impairment group compared to that observed in healthy adults. Patients with severe renal impairment also demonstrated a prolonged $t_{1/2}$, a decreased CL/F, a decreased CL_{R2}, and a decreased total amount of fenofibric acid excreted in the urine (A_{e2}) compared to the healthy group.

The hemodialysis study evaluated the effect of hemodialysis on plasma pharmacokinetics of fenofibric acid in patients with end-stage renal disease (ESRD). Six patients on hemodialysis and 9 patients not on hemodialysis received a single oral dose of the non-micronized fenofibrate 300 mg. Additionally, five other patients undergoing hemodialysis received oral doses of 100 mg once daily for 14 days. Pharmacokinetic results from this study suggested that after a single dose, the elimination $t_{1/2}$ was between 54 and 362 hours in patients not on hemodialysis, and between 56 and 257 hours in the patients undergoing hemodialysis. In patients receiving multiple doses of 100 mg once daily, fenofibric acid plasma concentrations were similar to those in patients with normal renal function given 300 mg once daily, however, steady state had not been achieved at the end of the 14-day dosing period.

Based on the findings from the two renal impairment studies, current fenofibrate prescribing information recommends that the use of fenofibrate should be avoided in patients who have severe renal impairment and treatment with fenofibrate should be initiated at one-third of the full therapeutic dose in patients having mildly or moderately impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose.

Comment: This reviewer agrees that similar labeling recommendations for initial dosing of ABT-335 monotherapy in patients with impaired renal function are appropriate.

In the clinical trials, subjects were excluded for a calculated creatinine clearance < 50 mL/min. There were relatively few subjects in the controlled or long-term trials with baseline calculated creatinine clearance < 60 mL/min or likewise, baseline calculated eGFR < 60 mL/min/1.73 m².

Comment: Due to the small number of these subjects, no meaningful conclusions were drawn by the sponsor regarding individual treatment-related adverse events or changes in laboratory variables from baseline. However, it does appear that subjects with renal impairment are more susceptible to the serum creatinine increasing effects of ABT-335. For example, 4 of 20 subjects (20%) with baseline calculated creatinine clearance < 60 mL/min treated with ABT-335 had an adverse event of 'Creatinine renal clearance decreased' compared to 0 of 470 of subjects with baseline creatinine clearance ≥ 60 mL/min. One of 20 renally-impaired subjects (5%) in the ABT-335-treatment group had an adverse event of 'Renal impairment' and none of the subjects in this group had adverse events of renal failure. The combination of ABT-335 + statin did not seem to increase the risk of renal events in this population; nevertheless, with so few subjects, conclusions regarding renal safety in subjects with renal impairment are limited. K/DOQI guidelines recommend avoiding the use of a fibrate together with a statin, at least until additional studies are conducted in patients with chronic kidney disease to establish the safety of this combination.⁴⁰ Based on these limited data, ABT-335 alone or in combination did not appear to increase the risk of adverse events of myopathy or increases in CK in patients with renal impairment.

This reviewer conducted a separate analysis of adverse events of special interest in the group of subjects with eGFR < 60 mL/min/1.73 m², as shown in the table below:

Table 7.5.4.A. Events of Special Interest, Controlled Studies, Subjects with eGFR < 60

	ABT-335	LD statin	ABT-335 + LD statin	MD statin	ABT-335 + MD statin	HD statin
N	38	29	27	32	33	17
Hepatic Events	1 (2.6)	0	2 (7.4)	0	2 (6.1)	0
Muscle Events	1 (2.6)	6 (20.7)	3 (11.1)	1 (3.1)	1 (3.0)	1 (5.9)
Renal Events	5 (13.2)	1 (3.4)	2 (7.4)	0	4 (12.1)	1 (5.9)

The sponsor provided mean creatinine changes in subjects with eGFR < and ≥ 60. The following table demonstrates these changes, and also illustrates that the creatinine increases with ABT-335 occur within the first four weeks and do not continue to appreciably increase beyond eight weeks.

40 K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease (2003). Accessed from http://www.kidney.org/professionals/KDOQI/guidelines_lipids/iii.htm#guide4.

Table 7.5.4.B. Mean Change From Baseline In Chemistry Values in Controlled Studies By Baseline eGFR

	ABT-335		Low-dose statin		ABT-335 + low statin		Moderate-dose statin		ABT-335 + moderate statin		High-dose statin	
	< 60	≥ 60	< 60	≥ 60	< 60	≥ 60	< 60	≥ 60	< 60	≥ 60	< 60	≥ 60
Baseline eGFR (mL/min/1.73 m ²)	37	433	28	454	26	449	32	447	33	435	17	221
N												
Mean Δ creatinine, week 4 (mg/dL)	0.16	0.12	-0.05	0.00	0.15	0.12	0.00	0.00	0.20	0.12	-0.08	0.03
N	34	394	27	434	27	415	31	426	30	412	17	199
Mean Δ creatinine, week 8 (mg/dL)	0.17	0.14	-0.04	0.02	0.22	0.14	-0.06	0.01	0.17	0.13	-0.01	0.02
N	31	375	25	423	25	391	30	401	30	384	16	196
Mean Δ creatinine, week 12 (mg/dL)	0.17	0.14	-0.02	0.01	0.18	0.15	-0.06	0.01	0.20	0.13	-0.09	0.02
N	37	436	28	456	27	452	32	448	33	439	17	221
Final visit	0.17	0.13	-0.03	0.01	0.17	0.14	-0.06	0.00	0.19	0.12	-0.09	0.02

Comment: With the exception of the imbalance of events seen in the low-dose statin groups for muscle events, the incidence of these adverse events of special interest appear similar to the group as a whole. The incidence of renal events is higher overall in all treatment groups with the exception of the moderate-dose statin group (where there were no events). As noted above, patients with diminished renal function at baseline might be more susceptible to the creatinine-increasing effect of ABT-335, and therefore monotherapy treatment should be initiated in these patients at a lower dose. This reviewer does not believe that there are enough safety data to make a conclusion on the safety of the combination in patients with calculated creatinine clearance < 60 mL/min.

Diabetes Mellitus

Overall, the controlled studies suggest an increase in adverse events in the combination groups as compared to their respective monotherapy groups in subjects with diabetes as compared to non-diabetics. However, review of most individual adverse events by diabetes status did not reveal a particular pattern. Certain gastrointestinal disorders is an exception: diabetic subjects treated with ABT-335 + moderate dose of statin appeared somewhat more likely to have nausea and/or vomiting adverse events as compared to the monotherapy treatment groups than non-diabetics. (Although subjects with diabetes treated with the combination of ABT-335 + a moderate statin dose were more likely to have nervous system disorders than those treated with the respective monotherapies, the Preferred Terms under the nervous system SOC is broad and there was no group of terms that fit a particular syndrome or concern.) Subjects with diabetes treated with the combination did not have a greater occurrence of muscle, or hepatic adverse events than those treated with the respective monotherapies as compared with their non-diabetic counterparts. Because renal events were of particular interest in this population, these adverse events are presented separately in Table 7.5.4.D.

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Table 7.5.4.C. Treatment-Emergent Adverse Events by Baseline Diabetic Status for Which Statistically Significant Differences Were Observed for the Controlled Studies Analysis Set Among Adverse Events of Special Interest and Those Occurring in at Least 2.0% in Any Treatment Group Overall

System Organ Class	Treatment Group 2 (%)									
	ABT-335		Low-dose Statin		ABT-335 + low Statin		Moderate-dose Statin		ABT-335 + moderate Statin	
	Diab (N=105)	Non-diab (N=385)	Diab (N=105)	Non-diab (N=385)	Diab (N=105)	Non-diab (N=385)	Diab (N=107)	Non-diab (N=384)	Diab (N=110)	Non-diab (N=379)
Baseline Diabetic Status										
Any adverse event ^a	70 (66.7)	257 (66.8)	57 (54.3)	241 (62.1)	81 (76.9)	254 (66.1)	72 (67.3)	255 (66.6)	82 (74.5)	241 (63.6)
Gastrointestinal Disorders										
Abdominal pain^a										
	0	10 (2.6)	2 (1.9)	3 (0.8)	3 (2.8)	4 (2.0)	0	5 (1.3)	3 (2.7)	6 (1.6)
Vomiting^a										
	1 (1.0)	7 (1.8)	2 (1.9)	5 (1.3)	1 (0.9)	4 (1.0)	1 (0.9)	3 (0.8)	5 (4.5)	2 (0.5)
Infections and Infestations										
URI^b										
	8 (7.6)	18 (4.7)	0	13 (3.4)	8 (7.5)	10 (2.6)	5 (4.7)	18 (4.7)	7 (6.4)	16 (4.2)
Investigations										
ALT increased^b										
	1 (1.0)	5 (1.3)	0	2 (0.5)	4 (3.8)	11 (2.9)	1 (0.9)	1 (0.3)	0	11 (3.2)
Blood CPK increased^{c,d}										
	2 (1.9)	2 (0.5)	2 (1.9)	2 (0.5)	1 (0.9)	12 (3.1)	2 (1.9)	9 (2.3)	0	8 (1.9)
Nervous System Disorders										
Headache^b										
	10 (9.5)	52 (13.5)	11 (10.5)	53 (13.7)	12 (11.3)	52 (13.5)	9 (8.4)	73 (19.0)	15 (13.6)	43 (11.3)
Respiratory, Thoracic and Medicinal Disorders										
Cough^b										
	3 (2.9)	8 (2.1)	1 (1.0)	9 (2.3)	4 (3.8)	7 (2.5)	5 (4.7)	2 (0.5)	1 (0.9)	11 (2.9)

Note: Includes data from Studies 3403-748, 3403-749, and 3403-750.

Diab = diabetic; Non-diab = non-diabetic; URI = upper respiratory tract infection.

- Statistically significant homogeneity in odds ratio (ABT-335 in combination with low statin vs. low-dose statin) ($p \leq 0.05$) based on Breslow-Day test for homogeneity of odds ratios.
- Statistically significant homogeneity in odds ratio (ABT-335 in combination with moderate statin vs. moderate-dose statin) ($p \leq 0.05$) based on Breslow-Day test for homogeneity of odds ratios.
- Statistically significant homogeneity in odds ratio (ABT-335 in combination with low statin vs. ABT-335) ($p \leq 0.05$) based on Breslow-Day test for homogeneity of odds ratios.
- Statistically significant homogeneity in odds ratio (ABT-335 + moderate statin vs. ABT-335) ($p \leq 0.05$) based on Breslow-Day test for homogeneity of odds ratios.

Table 7.5.4.D. Treatment-Emergent Adverse Events by Baseline Diabetic Status, Renal Events

MedDRA Preferred Term	ABT-335		Low-dose statin		ABT-335 + low statin		Moderate-dose statin		ABT-335 + moderate statin	
	Diab (N=105)	Non-diab (N=385)	Diab (N=105)	Non-diab (N=385)	Diab (N=105)	Non-diab (N=384)	Diab (N=107)	Non-diab (N=384)	Diab (N=110)	Non-diab (N=379)
Renal failure	0	1 (0.3)	1 (1.0)	0	0	1 (0.3)	0	0	0	0
Renal failure acute	1 (1.0)	0	0	1 (0.3)	0	1 (0.3)	0	0	1 (0.9)	0
Renal impairment	1 (1.0)	1 (0.3)	0	0	0	0	0	0	0	0
Creatinine renal clearance decreased	2 (1.9)	2 (0.5)	0	0	2 (1.9)	3 (0.8)	0	0	3 (2.7)	2 (0.5)
Blood creatinine increased	2 (1.9)	0	0	0	1 (0.9)	3 (0.8)	0	0	3 (2.7)	2 (0.5)

Comment: Table 7.5.4.D suggests that diabetic patients might be more prone to elevations in serum creatinine, as reflected by adverse events of calculated creatinine clearance and increased serum creatinine that is seen with ABT-335 treatment. Laboratory data

reviewed (not shown) demonstrated a slightly higher mean increase in serum creatinine in the diabetic subjects in the ABT-335 groups than the non-diabetic subjects; diabetic subjects treated with statin monotherapy also had a slight (but less) mean increase in serum creatinine as compared to the non-diabetic subjects. Reassuringly, renal failure and impairment was not seen to a greater extent in the diabetic subjects. It should be noted that the diabetic subjects in this study were relatively well-controlled with HbA1c criteria for entry $\leq 8.5\%$. Ultimately, renal function should guide the dosing of ABT-335 in diabetic and non-diabetic patients.

The following table is this reviewer's analysis of adverse events of special interest in the diabetic patient population:

Table 7.5.4.E. Events of Special Interest, Controlled Studies, Subjects with Diabetes

	ABT-335	LD statin	ABT-335 + LD statin	MD statin	ABT-335 + MD statin	HD statin
N	101	102	99	99	102	50
Hepatic Events	3 (3.0)	0	6 (6.1)	3 (3.0)	4 (3.9)	0
Muscle Events	5 (5.0)	8 (7.8)	5 (5.1)	5 (5.1)	6 (5.9)	2 (4.0)
Renal Events	4 (4.0)	1 (1.0)	3 (3.0)	0	6 (5.9)	1 (2.0)

Comment: Incidences of hepatic and muscle events are similar to the database as a whole. Subjects with diabetes have higher incidences of renal events, which may be a reflection of an increased incidence of renal dysfunction in this population. See the section above for a discussion of subjects with decreased baseline renal function. Serum creatinine should be monitored in patients with diabetes.

Table 7.5.4.F presents adverse events of special interest by baseline diabetic status in the All Combination Therapy Analysis Set. Diabetic subjects had more adverse renal events than their non-diabetic counterparts.

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Table 7.5.4.F. Treatment-Emergent Adverse Events by Baseline Diabetic Status for the All Combination Therapy Analysis Set among Adverse Events of Special Interest

	ABT-335 + rosuva (N=1186)		ABT-335 + simva (N=514)		ABT-335 + atorva (N=501)		Total (N=2201)	
	Diabetic (N=241)	Non- diabetic (N=945)	Diabetic (N=116)	Non- diabetic (N=398)	Diabetic (N=125)	Non- diabetic (N=376)	Diabetic (N=482)	Non- diabetic (N=1719)
Investigations								
ALT increased	3 (1.2)	24 (2.5)	2 (1.7)	8 (2.0)	2 (1.6)	12 (3.2)	7 (1.5)	44 (2.6)
AST increased	2 (0.8)	24 (2.5)	2 (1.7)	7 (1.8)	3 (2.4)	12 (3.2)	7 (1.5)	43 (2.5)
Blood bilirubin increased	0	0	0	1 (0.3)	1 (0.8)	1 (0.3)	1 (0.2)	2 (0.1)
Blood CPK increased	10 (4.1)	32 (3.4)	4 (3.4)	16 (4.0)	4 (3.2)	13 (3.5)	18 (3.7)	61 (3.5)
Blood creatinine increased	9 (3.7)	11 (1.2)	2 (1.7)	2 (0.5)	2 (1.6)	4 (1.1)	13 (2.7)	17 (1.0)
Creatinine renal clearance decreased	10 (4.1)	11 (1.2)	2 (1.7)	1 (0.3)	2 (1.6)	10 (2.7)	14 (2.9)	22 (1.3)
Hepatic enzyme increased	1 (0.4)	7 (0.7)	1 (0.9)	2 (0.5)	3 (2.4)	13 (3.5)	5 (1.0)	22 (1.3)
Liver function test abnormal	1 (0.4)	13 (1.4)	0	5 (1.3)	2 (1.6)	3 (0.8)	3 (0.6)	21 (1.2)
Musculoskeletal and Connective Tissue Disorders								
Myalgia	10 (4.1)	44 (4.7)	4 (3.4)	17 (4.3)	4 (3.2)	20 (5.3)	18 (3.7)	81 (4.7)
Myositis	0	2 (0.2)	0	0	0	0	0	2 (0.1)
Renal and Urinary Disorders								
Renal failure	1 (0.4)	1 (0.1)	2 (1.7)	0	1 (0.8)	1 (0.3)	4 (0.8)	2 (0.1)
Renal failure acute	1 (0.4)	1 (0.1)	0	1 (0.3)	0	0	1 (0.2)	2 (0.1)
Renal impairment	0	1 (0.1)	1 (0.9)	1 (0.3)	1 (0.8)	1 (0.3)	2 (0.4)	3 (0.2)

Comment: Increased renal events would be expected over the course of a year in this patient population. Adverse events of renal failure and impairment are still < 1%. The majority of the findings are related to changes in serum creatinine, as discussed above with the controlled studies.

7.5.5 Drug-Drug Interactions

Drug-drug interactions (DDI) between statins and fibrates are clearly the most important DDI assessment in this NDA, given the new proposed indication for concomitant administration. Pharmacokinetic interactions are discussed in Section 4.4.3 and safety as assessed by the Phase 3 program is discussed throughout Section 7.

Other DDI studies conducted included that of fenofibrate and ezetimibe, glimepiride, metformin, and rosiglitazone. These studies have been previously reviewed under the fenofibrate NDA. ABT-335 was studied for its pharmacokinetic interaction with omeprazole and the results are summarized in Section 4.4.3.

In vitro studies indicate that fenofibrate and fenofibric acid are unlikely to inhibit CYP3A-, CYP2D6-, CYP1A2-, CYP2E1-, CYP2C8-, CYP2C9-, or CYP2C19-dependent metabolism at clinically relevant plasma concentrations.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Neoplasms developed infrequently in the clinical trials and were from a variety of sites. Human carcinogenicity potential cannot be predicted from the Phase 3 studies.

Carcinogenicity concerns have been raised with other PPAR compounds, including fibrates. The Tricor label describes pancreatic acinar adenomas, hepatocellular carcinoma, hepatic neoplastic nodules, and testicular interstitial cell tumors in carcinogenicity studies in animals with various fibrates. Fenofibrate has been demonstrated to be devoid of mutagenic potential in Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis tests.

7.6.2 Human Reproduction and Pregnancy Data

No adequate and well-controlled studies have been conducted in pregnant women.

Three spontaneous abortions were reported in the trials and were considered to be SAEs: all from study M05-758; one subject in the ABT-335 + atorvastatin group (originally randomized to atorvastatin 80 mg), one from the ABT-335 + rosuvastatin group (originally randomized to ABT-335 + rosuvastatin 10 mg), and one from the ABT-335 + simvastatin group (originally randomized to simvastatin 40 mg). This reviewer determined that no other pregnancies were reported after a search of the adverse event datasets and the integrated review of safety failed to reveal any further pregnancies.

Based on these data, the risk to the pregnant woman or the fetus with exposure to ABT-335 is unknown. Fenofibrate is a Category C and all HMG-CoA reductase inhibitors are Category X.

7.6.3 Pediatrics and Assessment and/or Effects on Growth

Historically, fenofibrate has received waivers for pediatric studies, given that the number of potential patients is small and other drugs are available to treat hypercholesterolemic children (namely, statins). The sponsor cited the increased prevalence of obesity and the metabolic syndrome in children

b(4)

Comment: The sponsor appeared to be targeting cardiovascular risk reduction, rather than prevention of pancreatitis with this proposal, as that is how fenofibrate is currently used in clinical practice.⁴²

_____ The sponsor was informed that because of the known cardiovascular benefit from statin use in adults and the track record of safe

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41 McCrindle BW, et al. Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing. *Circulation* 2007; 115:1948-67.

42 Steinberger J, personal communication.

use in children and adolescents, statins are considered first-line therapy. In addition, neither the treatment of hypertriglyceridemia in adults nor the use of fibrates in children⁴³ has been proven to improve cardiovascular outcomes

b(4)

The sponsor responded September 8, 2008 by requesting a full pediatric study waiver (partial waiver request for the 10-18 year old age group in addition to the partial waiver granted for the < 10 year old age group) because, as they stated, the prevalence estimates for children and

⁴³ Daniels SR, et al. Lipid Screening and Cardiovascular Health in Childhood. *Pediatrics* 2008; 122:198-208.

adolescents with the combined lipid disorder of TG > 400 mg/dL and LDL-C \geq 130 mg/dL is extremely low, indicating that it would be highly impracticable to perform the recommended study as described in section 505B(a)(4)(A)(i) of the Act because the number of patients is so small. The sponsor's submission provided an estimate of the proposed study population of 0.05%, or less than 15,000 children and adolescents in the US. Because these prevalence estimates likely represent a largely untreated population, the sponsor asserted that the persistence of a TG level > 400 mg/dL following treatment with a maximally tolerated dose of a statin would likely be present at an even lower prevalence than 0.05%.

The sponsor was informed that a pediatric trial in the 12-17 year age range studying Trilipix in addition to a statin would be required under PREA. Details of the trial are under negotiation.

7.6.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

Drug abuse potential, withdrawal, and rebound have not been specifically studied, but because of the lack of effect of ABT-335 on the central nervous system, physiological or psychological dependency is not expected to occur with this drug.

Overdose was not reported in the clinical studies. The sponsor notes that there is no specific treatment for overdose with fenofibrate or fenofibric acid. The Tricor package insert recommends general supportive care, and if indicated, elimination of unabsorbed drug by emesis or gastric lavage. Because fenofibric acid is highly bound to plasma proteins, hemodialysis should not be considered in the case of overdose.

7.7 Additional Submissions

The safety update was submitted April 7, 2008, and includes safety data from the ongoing extension study M05-758. The data were collected through December 28, 2007 and integrated with safety data from the NDA ISS (last cut-off date September 1, 2007). The *All Combination Therapy* analysis set was the focus of the safety update, and includes cumulative data from subjects who received at least one dose of ABT-335 in combination with either low-dose or moderate-dose statins in one of the double-blind, controlled studies (Studies M05-748, M05-749, and M05-750) or at least one dose of ABT-335 in combination with moderate-dose statins in the long-term, open-label, safety extension study (Study M05-758).

In addition to Study M05-758, which was included in the original NDA submission, two additional studies were ongoing at the time the safety update was submitted. Study M06-884 is an open-label, long-term safety extension study for subjects who complete M05-758 at a subset of sites. Study M06-844 is a 12-week, double-blind, controlled study of ABT-335 in combination with 5 mg rosuvastatin compared with ABT-335 monotherapy and 5 mg rosuvastatin monotherapy, conducted under a separate IND (75,154).

Table 7.7.A describes updated exposure to combination therapy with the new cut-off date. Median duration ranged from 358 to 364 days across groups. A total of 1682 subjects were treated with combination therapy for \geq 24 weeks, 1041 subjects were treated with combination therapy for \geq 52 weeks, and 391 subjects were treated with combination therapy for \geq 64 weeks. Exposure was shorter in the ABT-335 in combination with simvastatin treatment group,

reflecting a later completion of enrollment of subjects into Study M05-749 and consequently later entry of these subjects into Study M05-758.

Table 7.7.A. Updated Duration of Exposure to Combination Therapy for the All Combination Therapy Analysis Set

Duration Category (weeks)	Treatment Group n (%)			n (%) Total (28 Dec 07) (N = 2201)	n (%) ISS Total (01 Sep 07) (N = 2201)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)		
< 4	31 (2.6)	20 (3.9)	17 (3.4)	68 (3.1)	68 (3.1)
≥ 4	1155 (97.4)	494 (96.1)	484 (96.6)	2133 (96.9)	2133 (96.9)
≥ 8	1093 (92.2)	480 (93.4)	457 (91.2)	2030 (92.2)	2030 (92.2)
≥ 12	1038 (87.5)	456 (88.7)	439 (87.6)	1933 (87.8)	1933 (87.8)
≥ 24	911 (76.8)	386 (75.1)	385 (76.8)	1682 (76.4)	1661 (75.5)
≥ 36	864 (72.8)	367 (71.4)	371 (74.1)	1602 (72.8)	1352 (61.4)
≥ 48	836 (70.5)	274 (53.3)	318 (63.5)	1428 (64.9)	756 (34.3)
≥ 52	613 (51.7)	201 (39.1)	227 (45.3)	1041 (47.3)	568 (25.8)
≥ 64	236 (19.9)	67 (13.0)	88 (17.6)	391 (17.8)	139 (6.3)
Summary Statistics (days)					
Mean (SD)	309.8 (143.63)	285.9 (137.04)	301.2 (140.73)	302.2 (141.72)	254.4 (124.89)
Median	364	358	363	363	279
Min, max	1, 507	1, 484	1, 482	1, 507	1, 482

Note: Duration of treatment = last combination dose date - first combination dose date + 1 in 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
Min, max = minimum, maximum; SD = standard deviation

As seen in Table 7.7.B, of the 2201 treated subjects in the *All Combination Therapy* analysis set, 1457 (66.27%) completed treatment, 534 (24.3%) prematurely discontinued, and 200 subjects were ongoing as of December 28, 2007. As discussed in Section 3.2, site 33087 (Dr. Keith Pierce) was closed prematurely; therefore, study status was unknown for the 10 subjects from this site.

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Table 7.7.B. Updated Summary of Subject Status and Reasons for Discontinuation for the All Combination Therapy Analysis Set

	Treatment Group n (%)			Total (28 Dec 07)	ISS Total (01 Sep 07)
	ABT-335 + rosuva	ABT-335 + simva	ABT-335 + atorva		
Total Treated	1186 ^a	514	501	2201	2201
Ongoing	9	118	73	200	1090
Total Discontinued	292 (24.6)	118 (23.0)	124 (24.8)	534 (24.3)	493 (22.4)
Adverse event	145 (12.2)	53 (10.3)	69 (13.8)	267 (12.1)	254 (11.5)
Withdrew consent	87 (7.3)	35 (6.8)	23 (4.6)	145 (6.6)	136 (6.2)
Lost to follow-up	45 (3.8)	14 (2.7)	18 (3.6)	77 (3.5)	64 (2.9)
Subject noncompliant	8 (0.7)	8 (1.6)	8 (1.6)	24 (1.1)	22 (1.0)
Other	102 (8.6)	46 (8.9)	31 (6.2)	179 (8.1)	166 (7.5)

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

Note: Subjects who discontinued study drug are counted under each reason given for discontinuation. Therefore, the sum of the counts for the reasons may be greater than the overall number of discontinuations.

Demographic and other baseline characteristics of the *All Combination Therapy* analysis set reported in this update were similar to those of subjects in Study M05-758 reported in the ISS.

Study M05-758: Results

Deaths

No additional deaths occurred in the updated dataset.

Serious Adverse Events

In the updated analysis set, a total of 144 (6.5%) subjects had treatment-emergent serious adverse events; see Table 7.7.C. Overall, the most common serious adverse events were osteoarthritis (ten subjects), deep vein thrombosis (six subjects), coronary artery disease, myocardial infarction, and chest pain (five subjects each), and diverticulitis, intervertebral disc protrusion, and syncope (four subjects each). The general issue of fenofibric acid and DVT, in addition to a review of all six cases of DVT were presented under Section 7.3.5.

Table 7.7.C. Updated Summary of Treatment-Emergent Serious Adverse Events Reported in at Least Two Subjects Overall for the All Combination Therapy Analysis Set

System Organ Class MedDRA Preferred Term	Treatment Group n (%)			n (%) Total (28 Dec 07) (N = 2201)	n (%) ISS Total (01 Sep 07) (N = 2201)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)		
Any Serious Adverse Event	84 (7.1)	38 (7.4)	22 (4.4)	144 (6.5)	132 (6.0)
Cardiac Disorders					
Acute myocardial infarction	1 (<0.1)	1 (0.2)	0	2 (<0.1)	2 (<0.1)
Angina pectoris	1 (<0.1)	1 (0.2)	0	2 (<0.1)	2 (<0.1)
Atrial flutter	2 (0.2)	1 (0.2)	0	3 (0.1)	2 (<0.1)
Coronary artery disease	5 (0.4)	0	0	5 (0.2)	5 (0.2)
Myocardial infarction	4 (0.3)	1 (0.2)	0	5 (0.2)	4 (0.2)
Gastrointestinal Disorders					
Pancreatitis	1 (<0.1)	0	1 (0.2)	2 (<0.1)	2 (<0.1)
General Disorders and Administration Site Conditions					
Chest discomfort	1 (<0.1)	0	2 (0.4)	3 (0.1)	2 (<0.1)
Chest pain	2 (0.2)	1 (0.2)	2 (0.4)	5 (0.2)	4 (0.2)
Non-cardiac chest pain	1 (<0.1)	1 (0.2)	0	2 (<0.1)	2 (<0.1)
Hepatobiliary Disorders					
Cholecystitis	2 (0.2)	0	1 (0.2)	3 (0.1)	3 (0.1)
Cholecystitis acute	2 (0.2)	0	0	2 (<0.1)	2 (<0.1)
Cholelithiasis	0	1 (0.2)	1 (0.2)	2 (<0.1)	2 (<0.1)
Infections and Infestations					
Diverticulitis	4 (0.3)	0	0	4 (0.2)	4 (0.2)
Pneumonia	1 (<0.1)	1 (0.2)	0	2 (<0.1)	2 (<0.1)
Injury, Poisoning and Procedural Complications					
Accidental overdose	1 (<0.1)	0	1 (0.2)	2 (<0.1)	2 (<0.1)
Musculoskeletal and Connective Tissue Disorders					
Back pain	1 (<0.1)	1 (0.2)	0	2 (<0.1)	1 (<0.1)
Intervertebral disc protrusion	3 (0.3)	1 (0.2)	0	4 (0.2)	4 (0.2)
Osteoarthritis	6 (0.5)	4 (0.8)	0	10 (0.5)	9 (0.4)

Note: Includes data from Studies M03-748, M03-749, M03-750, and M03-758.

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

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System Organ Class MedDRA Preferred Term	Treatment Group n (%)			n (%)	n (%)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	Total (28 Dec 07) (N = 2201)	ISS Total (01 Sep 07) (N = 2201)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)					
Colon cancer	1 (< 0.1)	1 (0.2)	0	2 (< 0.1)	2 (< 0.1)
Nervous System Disorders					
Syncope	2 (0.2)	1 (0.2)	1 (0.2)	4 (0.2)	3 (0.1)
Pregnancy, Puerperium and Perinatal Conditions					
Abortion spontaneous	1 (< 0.1)	1 (0.2)	1 (0.2)	3 (0.1)	3 (0.1)
Psychiatric Disorders					
Anxiety disorder	1 (< 0.1)	1 (0.2)	0	2 (< 0.1)	2 (< 0.1)
Renal and Urinary Disorders					
Renal colic	1 (< 0.1)	0	1 (0.2)	2 (< 0.1)	2 (< 0.1)
Reproductive System and Breast Disorders					
Uterine prolapse	2 (0.2)	0	1 (0.2)	3 (0.1)	3 (0.1)
Respiratory, Thoracic and Mediastinal Disorders					
Dyspnoea	2 (0.2)	0	0	2 (< 0.1)	2 (< 0.1)
Pulmonary embolism	2 (0.2)	0	1 (0.2)	3 (0.1)	3 (0.1)
Vascular Disorders					
Deep vein thrombosis	4 (0.3)	1 (0.2)	1 (0.2)	6 (0.3)	5 (0.2)
Hypotension	1 (< 0.1)	0	1 (0.2)	2 (< 0.1)	2 (< 0.1)

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

Adverse Events Leading to Discontinuation

A total of 259 (11.8%) subjects had adverse events leading to discontinuation, and were most commonly seen in the Investigations, Musculoskeletal and Connective Tissue Disorders, and Gastrointestinal Disorders SOCs.

Overall, the most common ($\geq 1.0\%$ in any treatment group) adverse events that led to discontinuation were reported adverse events of ALT increased, AST increased, blood CPK increased, hepatic enzyme increased, and myalgia.

Both the overall incidence of adverse events leading to discontinuation and the incidence of specific adverse events leading to discontinuation reported in this update were similar to those reported in the ISS. Adverse events leading to discontinuation in ≥ 2 subjects in any treatment group are presented in Table 7.7.D.

Table 7.7.D. Updated Summary of Treatment-Emergent Adverse Events Leading to Discontinuation in at Least Two Subjects in Any Treatment Group for the All Combination Therapy Analysis Set

System Organ Class MedDRA Preferred Term	Treatment Group n (%)			n (%)	n (%)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	Total (28 Dec 07) (N = 2201)	ISS Total (01 Sep 07) (N = 2201)
Any Adverse Event Leading to Discontinuation	141 (11.9)	51 (9.9)	67 (13.4)	259 (11.8)	246 (11.2)
Cardiac Disorders					
Atrial fibrillation	0	2 (0.4)	0	2 (< 0.1)	1 (< 0.1)
Cardiac failure congestive	2 (0.2)	0	0	2 (< 0.1)	1 (< 0.1)
Coronary artery disease	2 (0.2)	0	0	2 (< 0.1)	1 (< 0.1)
Gastrointestinal Disorders					
Abdominal distension	2 (0.2)	0	2 (0.4)	4 (0.2)	4 (0.2)
Abdominal pain	4 (0.3)	2 (0.4)	3 (0.6)	9 (0.4)	8 (0.4)
Abdominal pain upper	2 (0.2)	1 (0.2)	3 (0.6)	6 (0.3)	5 (0.2)
Constipation	5 (0.4)	0	0	5 (0.2)	5 (0.2)
Diarrhoea	1 (< 0.1)	2 (0.4)	2 (0.4)	5 (0.2)	5 (0.2)
Dyspepsia	5 (0.4)	1 (0.2)	1 (0.2)	7 (0.3)	7 (0.3)
Nausea	2 (0.2)	3 (0.6)	2 (0.4)	7 (0.3)	7 (0.3)
General Disorders and Administration Site Conditions					
Asthenia	1 (< 0.1)	1 (0.2)	2 (0.4)	4 (0.2)	4 (0.2)
Oedema peripheral	4 (0.3)	0	0	4 (0.2)	4 (0.2)
Hepatobiliary Disorders					
Cholelithiasis	1 (< 0.1)	1 (0.2)	2 (0.4)	4 (0.2)	4 (0.2)

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

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System Organ Class MedDRA Preferred Term	Treatment Group n (%)			n (%)	n (%)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)	Total (28 Dec 07 (N = 2201)	ISS Total (01 Sep 07) (N = 2201)
Investigations					
ALT increased	15 (1.3)	2 (0.4)	5 (1.0)	22 (1.0)	22 (1.0)
AST increased	14 (1.2)	2 (0.4)	4 (0.8)	20 (0.9)	20 (0.9)
Blood alkaline phosphatase increased	2 (0.2)	1 (0.2)	1 (0.2)	4 (0.2)	4 (0.2)
Blood CPK increased	10 (0.8)	7 (1.4)	5 (1.0)	22 (1.0)	21 (1.0)
Blood creatinine increased	5 (0.4)	2 (0.4)	2 (0.4)	9 (0.4)	7 (0.3)
Blood glucose increased	1 (< 0.1)	2 (0.4)	0	3 (0.1)	3 (0.1)
Blood triglyceride increased	0	2 (0.4)	0	2 (< 0.1)	1 (< 0.1)
Blood urea increased	4 (0.3)	0	0	4 (0.2)	4 (0.2)
Creatinine renal clearance decreased	5 (0.4)	1 (0.2)	1 (0.2)	7 (0.3)	6 (0.3)
Hepatic enzyme increased	4 (0.3)	0	10 (2.0)	14 (0.6)	13 (0.6)
Liver function test abnormal	2 (0.2)	2 (0.4)	4 (0.8)	8 (0.4)	8 (0.4)
Platelet count increased	2 (0.2)	1 (0.2)	0	3 (0.1)	3 (0.1)
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	5 (0.4)	0	0	5 (0.2)	5 (0.2)
Muscle spasms	5 (0.4)	3 (0.6)	3 (0.6)	11 (0.5)	9 (0.4)
Myalgia	12 (1.0)	1 (0.2)	7 (1.4)	20 (0.9)	20 (0.9)
Pain in extremity	6 (0.5)	1 (0.2)	0	7 (0.3)	6 (0.3)
Rheumatoid arthritis	2 (0.2)	0	0	2 (< 0.1)	2 (< 0.1)
Nervous System Disorders					
Dizziness	3 (0.3)	1 (0.2)	1 (0.2)	5 (0.2)	5 (0.2)
Headache	8 (0.7)	0	1 (0.2)	9 (0.4)	9 (0.4)
Renal and Urinary Disorders					
Renal impairment	1 (< 0.1)	0	2 (0.4)	3 (0.1)	2 (< 0.1)
Skin and Subcutaneous Tissue Disorders					
Urticaria	2 (0.2)	0	1 (0.2)	3 (0.1)	3 (0.1)
Vascular Disorders					
Deep vein thrombosis	4 (0.3)	1 (0.2)	1 (0.2)	6 (0.3)	5 (0.2)

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

Comment: Although no additional subjects discontinued due to hepatobiliary AEs, or AEs under the Investigations SOC such as ALT or AST increased, the disparity in the atorvastatin treatment group as compared to the other statins continues in this safety update with the AE 'hepatic enzyme increased'. Otherwise, the safety profile reflected in discontinuations is similar to the original safety dataset.

Common Adverse Events

As expected, the incidence of adverse events overall and individually increased from the ISS as the denominator remained the same but exposure to drug, and therefore accumulated events, increased in the 4-month safety update. Reassuringly, with additional length of exposure the overall and most individual event rates per 100 PY of exposure were lower in the safety update than rates reported in the ISS. This is illustrated in Table 7.7.E.

Table 7.7.E. Updated Summary of Treatment-Emergent Adverse Events (Preferred Terms with at Least 5.0 Events Per 100 Patient-Years in Any Treatment Group) for the All Combination Therapy Analysis Set

System Organ Class MedDRA Preferred Term	Treatment Group E (E/100PY)			E (E/100PY)	E (E/100PY)
	ABT-338 + rosuva (N = 1186) (PY = 1006.6)	ABT-338 + simva (N = 814) (PY = 482.6)	ABT-338 + atorva (N = 501) (PY = 413.6)	Total (28 Dec 07) (N = 2201) (PY = 1822.6)	ISS Total (01 Sep 07) (N = 2201) (PY = 1834.1)
Total Events	4568 (453.8)	2251 (559.1)	1966 (461.0)	8725 (478.7)	7830 (516.4)
Gastrointestinal Disorders:					
Constipation	61 (6.1)	18 (4.5)	19 (4.6)	98 (5.4)	93 (6.1)
Diarrhoea	64 (6.4)	40 (9.9)	40 (9.7)	144 (7.9)	135 (8.8)
Dyspepsia	46 (4.6)	30 (7.5)	33 (8.0)	109 (6.0)	100 (6.5)
Nausea	72 (7.2)	24 (6.0)	38 (9.2)	134 (7.4)	131 (8.5)
Toothache	24 (2.4)	20 (5.0)	16 (3.9)	60 (3.3)	50 (3.3)
General Disorders and Administration Site Conditions:					
Fatigue	48 (4.8)	20 (5.0)	16 (3.9)	84 (4.6)	75 (4.9)
Pain	38 (3.8)	28 (7.0)	14 (3.4)	80 (4.4)	68 (4.4)
Infections and Infestations:					
Bronchitis	68 (6.8)	30 (7.5)	26 (6.3)	124 (6.8)	110 (7.2)
Influenza	36 (3.6)	21 (5.2)	25 (6.0)	82 (4.5)	76 (5.0)
Nasopharyngitis	133 (13.2)	82 (20.4)	72 (17.4)	287 (15.7)	257 (16.8)
Sinusitis	118 (11.7)	45 (11.2)	46 (11.1)	209 (11.5)	181 (11.8)
Upper respiratory tract infection	171 (17.0)	76 (18.9)	67 (16.2)	314 (17.2)	283 (18.4)
Urinary tract infection	55 (5.5)	12 (3.0)	26 (6.3)	93 (5.1)	87 (5.7)
Investigations:					
Blood CPK increased	48 (4.8)	21 (5.2)	20 (4.8)	89 (4.9)	87 (5.7)

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;

E = events; E/100PY = events per 100 patient-years

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System Organ Class MedDRA Preferred Term	Treatment Group E (E/100PY)			E (E/100PY)	ISS Total E (E/100PY)
	ABT-335 + rosuva (N = 1186) (PY = 1096.5)	ABT-335 + simva (N = 514) (PY = 462.6)	ABT-335 + atorva (N = 501) (PY = 433.5)	Total (28 Dec 07) (N = 2201) (PY = 1822.6)	(91 Sep 07) (N = 2201) (PY = 1834.1)
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	110 (10.9)	62 (15.4)	42 (10.2)	214 (11.7)	193 (12.7)
Back pain	159 (15.5)	66 (16.4)	47 (11.4)	272 (14.9)	243 (15.8)
Muscle spasms	76 (7.6)	38 (9.4)	39 (9.4)	153 (8.4)	135 (8.8)
Musculoskeletal pain	37 (3.7)	28 (7.0)	14 (3.4)	79 (4.3)	74 (4.8)
Myalgia	78 (7.7)	28 (7.0)	32 (7.7)	138 (7.6)	125 (8.1)
Pain in extremity	87 (8.6)	35 (8.7)	38 (9.2)	160 (8.8)	143 (9.3)
Nervous System Disorders					
Dizziness	55 (5.5)	17 (4.2)	27 (6.5)	99 (5.4)	97 (6.3)
Headache	304 (30.2)	150 (37.3)	105 (25.4)	559 (30.7)	519 (33.8)
Psychiatric Disorders					
Insomnia	61 (6.1)	17 (4.2)	18 (4.4)	96 (5.3)	89 (5.8)
Respiratory, Thoracic and Mediastinal Disorders					
Cough	57 (5.7)	42 (10.4)	32 (7.7)	131 (7.2)	112 (7.3)
Nasal congestion	17 (1.7)	27 (6.7)	16 (3.9)	60 (3.3)	49 (3.2)
Pharyngolaryngeal pain	25 (2.5)	28 (7.0)	30 (7.3)	83 (4.6)	73 (4.9)

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;
E = events; E/100PY = events per 100 patients-years

Adverse Events of Special Interest

Muscle

Overall, the incidence of muscle events in the *All Combination Therapy* analysis set was 10.9% (ABT-335 + rosuvastatin, 10.5%; ABT-335 + simvastatin, 11.9%; and ABT-335 + atorvastatin, 11.2%). No cases of rhabdomyolysis or myopathy were reported. The most common treatment-emergent muscle-related adverse event was 'myalgia' occurring in 5.0% of subjects overall.

The percentage of subjects with reported muscle adverse events of blood CPK abnormal or blood CPK increased was 3.7% overall. Since the ISS, one additional subject (ABT-335 + rosuvastatin) discontinued treatment due to any muscle adverse event of special interest; this subject had a post-baseline CPK value > 5x ULN. This 45-year-old female had a maximum CK value of 1270 U/L on Day 288, which returned to normal after drug discontinuation. The investigator reported the subject had a recent change in exercise patterns.

Of the subjects with a reported adverse event of myalgia, three had CPK values > 5x ULN, one of whom had CPK values > 10x ULN. One of these three subjects is discussed above: she was discontinued from the trial; the other two subjects, including the subject whose CK was > 10x ULN with myalgia are briefly described here:

- Subject 14413 (ABT-335 + 20 mg rosuvastatin in M05-758) had a single CPK value > 5x ULN of 1281 U/L on Day 122, and had an adverse event of myalgia on Day 139. Myalgia

was reported to have resolved on Day 155. Testing on Day 203 revealed a CPK of 333 U/L. Study drug was not interrupted for this adverse event, nor was any additional action taken.

- Subject 14162 (ABT-335 + 20 mg rosuvastatin in M05-758) had an adverse event of myalgia reported on Day 83; soon thereafter, two CPK values were > 10x ULN: 10062 U/L on Day 85 and 6378 U/L on Day 87. All other CPK values for this subject ranged from 79 U/L to 124 U/L. Myalgia was reported to have resolved on Day 94. No action was taken by the investigator due to this adverse event, nor was any additional information available concerning the event.

Comment: It is reassuring that both subjects remained on study drug with improvement of CK elevation.

Since the ISS, two additional subjects had a PCS CPK value (≥ 850 U/L [F]; ≥ 1000 U/L [M]).

Table 7.7.F. Updated Treatment-Emergent Adverse Events of Special Interest (Muscle Events) for the All Combination Therapy Analysis Set

Subjects with:	Treatment Group n (%)			n (%) Total (28 Dec 07 (N = 2201)	n (%) ISS Total (01 Sep 07) (N = 2201)
	ABT-335 + rosuva (N = 1180)	ABT-335 + simva (N = 814)	ABT-335 + atorva (N = 601)		
Any Adverse Event of Special Interest	211 (17.9)	90 (17.5)	100 (20.0)	401 (18.2)	376 (17.1)
Muscle Events	124 (10.5)	61 (11.9)	56 (11.2)	241 (10.9)	228 (10.4)
Blood CPK abnormal	1 (< 0.1)	0	0	1 (< 0.1)	1 (< 0.1)
Discontinuations	0	0	0	0	0
Blood CPK increased	43 (3.6)	21 (4.1)	17 (3.4)	81 (3.7)	79 (3.6)
Discontinuations	10 (0.8)	7 (1.4)	5 (1.0)	22 (1.0)	21 (1.0)
Musculoskeletal discomfort	2 (0.2)	0	1 (0.2)	3 (0.1)	3 (0.1)
Discontinuations	0	0	0	0	0
Musculoskeletal pain	30 (2.5)	20 (3.9)	13 (2.6)	63 (2.9)	61 (2.8)
Discontinuations	1 (< 0.1)	0	0	1 (< 0.1)	1 (< 0.1)
Myalgia	60 (5.1)	26 (5.1)	25 (5.0)	111 (5.0)	99 (4.5)
Discontinuations	12 (1.0)	1 (0.2)	7 (1.4)	20 (0.9)	20 (0.9)
Myositis	2 (0.2)	0	0	2 (< 0.1)	2 (< 0.1)
Discontinuations	0	0	0	0	0

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 = 0 or 40 mg atorvastatin;

AE = adverse event

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