

**Table 7.7.G. Updated Treatment-Emergent Adverse Events of Special Interest (Muscle Events - Changes in Laboratory Tests) for the All Combination Therapy Analysis Set**

Subjects with:	Treatment Group n (%)			n (%)	n (%)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 801)	Total (23 Dec 07) (N = 2201)	ISS Total (01 Sep 07) (N = 2201)
Muscle Events - Changes in Laboratory Tests <sup>a</sup>	44 (3.7)	21 (4.1)	17 (3.4)	82 (3.7)	80 (3.6)
Led to discontinuation	10	7	5	22	21
Met CPK criterion <sup>b</sup>	11	4	3	18	17 <sup>c</sup>

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

a. Includes adverse events of blood CPK abnormal and blood CPK increased.

b. CPK post-baseline value > 5 x ULN on any occasion

c. The number 18 presented in the ISS was incorrect and should have been 17.

### **Renal**

The percentage of subjects with renal adverse events in the *All Combination Therapy* analysis set was 3.6% overall. Greater percentages of subjects in the ABT-335 + rosuvastatin (4.0%) and ABT-335 + atorvastatin (4.0%) treatment groups had renal adverse events compared with subjects in the ABT-335 + simvastatin treatment group (2.3%). The most common renal-related adverse events were reported adverse events of blood creatinine increased (1.5% overall) and creatinine renal clearance decreased (1.7% overall).

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

Subjects with:	Treatment Group n (%)			n (%)	n (%)
	ABT-335 + rosuva (N = 1146)	ABT-335 + simva (N = 814)	ABT-335 + atorva (N = 801)	Total (28 Dec 07) (N = 2261)	ISS Total (01 Sep 07) (N = 2201)
Any AE of special interest	211 (17.3)	90 (17.5)	100 (20.0)	401 (18.2)	376 (17.1)
Renal Events	47 (4.0)	12 (2.3)	20 (4.0)	79 (3.6)	74 (3.4)
Blood creatinine increased	22 (1.9)	5 (1.0)	7 (1.4)	34 (1.5)	30 (1.4)
Discontinuations	5 (0.4)	2 (0.4)	2 (0.4)	9 (0.4)	7 (0.3)
Creatinine renal clearance decreased	22 (1.9)	3 (0.6)	12 (2.4)	37 (1.7)	36 (1.6)
Discontinuations	5 (0.4)	1 (0.2)	1 (0.2)	7 (0.3)	6 (0.3)
Renal failure	2 (0.2)	2 (0.4)	2 (0.4)	6 (0.3)	6 (0.3)
Discontinuations	0	1 (0.2)	1 (0.2)	2 (< 0.1)	2 (< 0.1)
Renal failure acute	2 (0.2)	1 (0.2)	0	3 (0.1)	3 (0.1)
Discontinuations	1 (< 0.1)	0	0	1 (< 0.1)	1 (< 0.1)
Renal failure chronic	1 (< 0.1)	0	1 (0.2)	2 (< 0.1)	2 (< 0.1)
Discontinuations	0	0	0	0	0
Renal impairment	2 (0.2)	2 (0.4)	2 (0.4)	6 (0.3)	5 (0.2)
Discontinuations	1 (< 0.1)	0	2 (0.4)	3 (0.1)	2 (< 0.1)

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

Since the ISS, two additional subjects were discontinued due to the reported adverse event of blood creatinine increased, one of whom was also discontinued due to the reported event of creatinine renal clearance decreased. The narratives for these subjects are presented below.

Subject 22061 (ABT-335 + simvastatin 40 mg) was a 52-year-old white male who prematurely discontinued study drug on Day 225 due to elevated creatinine and elevated triglycerides. Relevant medical history included hyperlipidemia, hypertension, diabetes mellitus, gastroesophageal reflux disease, seizure, anxiety, broken ankle, and ankle intermittent swelling. Concomitant medications at the time of the event included alprazolam, lorazepam, lisinopril, and glibenclamide. The subject is a current smoker and a current moderate drinker.

On Day 196, the subject was reported to have elevated creatinine and elevated triglyceride levels. Laboratory values are provided in Tables 7.7.I and 7.7.J. Study drug was discontinued on Day 225. The subject was treated with fenofibrate and simvastatin on Day 229. The events of elevated creatinine and elevated triglycerides were considered ongoing as of Day 231.

Table 7.7.I.

**Subject #22061 Fasting Laboratory Data**

Treatment Day	Creatinine Clearance Reference Range 88-128 mL/min	Creatinine Reference Range 0.4-1.3 mg/dL	BUN Reference Range 4-24 mg/dL	Triglycerides Reference Range 88-320 mg/dL
Screening (M05-749)	81	1.0	9	Blinded
Baseline (M05-749)	97	0.9	9	Blinded
Day 29 (M05-749)	77	1.1	14	Blinded
Day 58 (M05-749)	77	1.1	10	Blinded
Day 85 (M05-749)	82	1.0	13	Blinded
Day 28 (M05-758)	67	1.2	13	327
Day 55 (M05-758)	75	1.1	14	471
Day 84 (M05-758)	64	1.3	14	691
Day 112 (M05-758)	63	1.4	12	565
Day 196 (M05-758)	47	1.8	21	1026
Day 222/Retest (M05-758)	49	1.7	Not performed	850
Day 231/Final Visit (6 days post study drug)	53	1.6	13	764

Table 7.7.J. Subject 22061's Triglyceride Values during Study M05-749 (simvastatin 40 mg)

Day	TG (mg/dL)
Baseline	668
29	595
58	880
85	1220

**Comment:** Because no other blood tests are available, it is unknown if the decrease from 1.8 to 1.6 mg/dL in creatinine was a trend towards a decrease upon drug discontinuation, or if the elevation was ongoing (the patient was started on fenofibrate on Day 229).

Subject 34226 (ABT-335 + atorvastatin 40 mg) was a 69-year-old white male who prematurely discontinued study drug on Day 3 of Study M05-758 due to elevated creatinine and decreased creatinine clearance. Medical history included transient renal insufficiency, coronary artery disease status post coronary artery bypass graft, hypertension, two strokes, peripheral vascular disease status post thrombectomy and balloon angioplasty with stent placement right popliteal artery, carotid artery disease, mixed hyperlipidemia, right hip replacement, and diverticulitis. Concomitant medications at the time of the event included doxycycline, multivitamin, acetylsalicylic acid, and atenolol. The subject is an ex-smoker (4-5 packs per day) and an ex-drinker of alcohol.

On Day 30 in Study M05-750, the subject was reported to have elevated creatinine and decreased creatinine clearance. Laboratory values are provided in Table 7.7.K. The event was considered resolved on Day 2 in Study M05-758. Study drug was discontinued on Day 3.

Table 7.7.K.

**Subject #34226 Fasting Laboratory Data**

Treatment Day	Creatinine Reference Range 0.5-1.3 mg/dL	BUN Reference Range 4-24 mg/dL	Calculated Creatinine Clearance Reference Range 98-128 mL/min
Screening (M05-750)	1.0	17.0	82.0
Baseline (M05-750)	1.0	27.0	81.0
Day 30 (M05-750)	1.3	26.0	66.0
Day 58 (M05-750)	1.4	29.0	56.0
Day 86 (M05-750)	1.2	26.0	143.0
Day 6 (3 days post study drug) (M05-758)	1.2	25.0	66.0
Day 41 (38 days post study drug) (M05-758)	1.2	Not Performed	69.0

**Comment: The Day 86 calculated creatinine clearance appears to be an error.**

One additional subject discontinued due to renal impairment. The event of renal impairment was a serious adverse event reported in a subject with a medical history of known impaired renal function that predated participation in the ABT-335 program. The event occurred in a setting of a gastrointestinal illness and dehydration that resulted in "slightly worsened" renal insufficiency.

Subject 14379 (ABT-335 + rosuvastatin 20 mg) was a 63-year-old white male with medical history of peripheral neuropathy, mixed dyslipidemia, hypertension, kidney stones, gastroesophageal reflux disease, headache, "temper", and drug allergy to "sulfur". Concomitant medications at the time of the event included acetylsalicylic acid, ranitidine, sertraline, topiramate, hydrocodone/acetaminophen, mometasone, meloxicam, diltiazem, and valsartan. He is a non-smoker and a light drinker.

On Day 213, the subject was reported to have numbness and limpness of his legs and lisinopril was discontinued. On Day 321, the subject was reported to have severe leg pain, numbness and weakness. On Day 324, the subject was reported to have decreased creatinine clearance. Laboratory values are provided in Table 7.7.L. Study drug was discontinued on Day 324. The events of severe leg pain, numbness, weakness and decreased creatinine clearance were considered ongoing as of Day 364.

Table 7.7.L.

**Subject #14379 Fasting Laboratory Data**

Treatment Day	Creatinine Clearance Reference Range 88-128 mL/min	Creatinine Reference Range 0.8-1.3 mg/dL	BUN Reference Range 4-24 mg/dL	CPK Reference Range 18-198 U/L
Screening (M05-748)	59	1.4	16	122
Baseline (M05-748)	74	1.1	22	127
Day 29 (M05-748)	66	1.3	14	158
Day 61 (M05-748)	65	1.3	18	171
Day 89/Final Visit (M05-748)	64	1.3	21	151
Day 28 (M05-758)	59	1.5	21	162
Day 56 (M05-758)	55	1.6	19	146
Day 85 (M05-758)	53	1.6	17	200
Day 113 (M05-758)	50	1.8	20	156
Day 185 (M05-758)	46	1.8	21	179
Day 273 (M05-758)	49	1.7	19	164
Day 364/Final Visit (M05-758) (40 days post study drug)	57	1.5	23	126

**Comment:** The sponsor stated that the event of renal impairment leading to discontinuation was a serious adverse event reported in a subject with a medical history of known impaired renal function that predated participation in the ABT-335 program and that the event occurred in a setting of a gastrointestinal illness and dehydration that resulted in "slightly worsened" renal insufficiency. This reviewer could not find a discontinuation in the safety update due to renal impairment that was also a SAE and fit this description.

No additional subjects discontinued due to renal failure, renal failure acute, or renal failure chronic.

Of the two additional subjects who discontinued due to a renal laboratory adverse event since the ISS, neither had a post-baseline creatinine value > 2 mg/dL or increased  $\geq$  100% from baseline.

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**Table 7.7.M. Updated Treatment-Emergent Adverse Events of Special Interest (Renal Events - Changes in Laboratory Tests) for the All Combination Therapy Analysis Set**

Subjects with:	Treatment Group n (%)			n (%)	n (%)
	ABT-335 + rosuvu (N = 1196)	ABT-335 + simva (N = 814)	ABT-335 + atorva (N = 901)	Total (28 Dec 07) (N = 2201)	ISS Total (01 Sep 07) (N = 2201)
Renal Events - Changes in Laboratory Tests <sup>a</sup>	40 (3.4)	7 (1.4)	15 (3.0)	62 (2.8)	58 (2.6)
Led to discontinuation	9	3	2	14	12
Met creatinine criteria <sup>b</sup>	4	1	3	8	8

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

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

a. Includes adverse events of blood creatinine increased and creatinine renal clearance decreased

b. Creatinine post-baseline value > 2 mg/dL or ≥ 100% increase from baseline value

No additional subjects since the ISS had renal parameters that met PCS criteria (serum creatinine ≥ 3 mg/dL [F], ≥ 3.5 mg/dL [M], BUN ≥ 40 mg/dL, or calculated CrCl ≤ 30 mL/min) or were characterized as a renal laboratory result of special interest (creatinine > 2 mg/dL or ≥ 100% increase from baseline).

### Hepatic

The percentage of subjects with hepatic adverse events in the *All Combination Therapy* analysis set was 5.4% overall. As in the ISS, the percentage of subjects experiencing hepatic adverse events was greatest in the ABT-335 + atorvastatin treatment group (7.4%), compared with the ABT-335 + rosuvastatin (4.8%) and ABT-335 + simvastatin (4.7%) treatment groups. The incidence of discontinuations due to ALT increased was 1.0% overall and that of AST increased was 0.9% overall.

There were no events of hepatic/liver failure. Although one subject had a reported adverse event of jaundice, available laboratory data revealed normal total bilirubin and AST throughout the study, with a maximal elevation in ALT to 90 U/L; this subject was subsequently diagnosed with cholelithiasis and discontinued the study. This subject's narrative was presented in Section 7.3.5.

Reported adverse events of hepatic enzyme increased and liver function test abnormal led to discontinuation in 0.6% and 0.4% of subjects overall. No subject in the *All Combination Therapy* analysis set discontinued due to blood bilirubin increased. Since the ISS, one additional subject discontinued treatment due to a hepatic adverse event (the reported event of hepatic enzyme increased). The subject was treated with ABT-335 + atorvastatin 40 mg, with a maximum ALT of 124 U/L. Fifteen days after study discontinuation, the transaminase elevations were decreasing.

Table 7.7.N describes the hepatic events seen in the updated dataset.

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

Subjects with:	Treatment Group n (%)			Total (28 Dec 07) (N = 2201)	ISS Total (01 Sep 07) (N = 2201)
	ABT-335 + rosuva (N = 1186)	ABT-335 + simva (N = 514)	ABT-335 + atorva (N = 501)		
Any AE of special interest	211 (17.8)	90 (17.5)	100 (20.0)	401 (18.2)	376 (17.1)
Hepatic Events	57 (4.8)	24 (4.7)	37 (7.4)	118 (5.4)	108 (4.9)
ALT increased	31 (2.6)	11 (2.1)	15 (3.0)	57 (2.6)	51 (2.3)
Discontinuations	15 (1.3)	2 (0.4)	5 (1.0)	22 (1.0)	22 (1.0)
AST increased	29 (2.4)	10 (1.9)	15 (3.0)	54 (2.5)	50 (2.3)
Discontinuations	14 (1.2)	2 (0.4)	4 (0.8)	20 (0.9)	20 (0.9)
Blood bilirubin increased	0	1 (0.2)	2 (0.4)	3 (0.1)	3 (0.1)
Discontinuations	0	0	0	0	0
Hepatic enzyme increased	9 (0.8)	3 (0.6)	17 (3.4)	29 (1.3)	27 (1.2)
Discontinuations	4 (0.3)	0	10 (2.0)	14 (0.6)	13 (0.6)
Hepatic function abnormal	0	0	1 (0.2)	1 (<0.1)	1 (<0.1)
Discontinuations	0	0	1 (0.2)	1 (<0.1)	1 (<0.1)
Hepatic steatosis	1 (<0.1)	3 (0.6)	0	4 (0.2)	2 (<0.1)
Discontinuations	0	0	0	0	0
Jaundice	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)
Discontinuations	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)
Liver function test abnormal	13 (1.1)	6 (1.2)	5 (1.0)	24 (1.1)	24 (1.1)
Discontinuations	2 (0.2)	2 (0.4)	4 (0.8)	8 (0.4)	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

**Comment:** As in the ISS, the incidence of hepatic events was greater in the ABT-335 + atorvastatin group, mostly due to AEs of 'hepatic enzyme increased'.

#### Ongoing Studies

Study M06-884 is a Phase 3, multicenter, long-term, open-label safety study in subjects with mixed dyslipidemia who completed one of three ABT-335/statin efficacy studies (M05-748, M05-749, or M05-750) and the M05-758 safety study at selected study sites. This safety study was designed to further assess the safety of once daily 135 mg ABT-335 in combination with either 20 mg rosuvastatin QD, 40 mg simvastatin QD, or 40 mg atorvastatin QD for an additional year. Approximately 300 subjects who completed the M05-758 study were to enter M06-884: approximately 150 subjects receiving ABT-335 + rosuvastatin, 75 subjects receiving ABT-335 + simvastatin, and 75 subjects receiving ABT-335 + atorvastatin. All subjects enrolled in this

study received the same treatment they received in Study M05-758. The Baseline Visit of M06-884 corresponded to the Final Visit of M05-758. Subjects were allowed to enroll into Study M06-884 study up to seven days after the Final Visit of Study M05-758.

As of December 28, 2007, a total of 310 subjects were enrolled and received at least one dose of study drug in M06-884 (174 subjects received ABT-335 + rosuvastatin 20 mg, 50 subjects received ABT-335 + simvastatin 40 mg, and 86 subjects received ABT-335 + atorvastatin 40 mg).

As of December 28, 2007, 304 subjects remained active and six subjects had discontinued. Two subjects discontinued due to adverse events, two withdrew consent, one was lost to follow-up, and one subject discontinued due to two reasons, adverse event and lost to follow-up.

The study is ongoing. Adverse events and serious adverse events have not been included in the *All Combination Therapy* analysis set and, therefore, are not presented in the updated review of Study M05-758, above. As of September 1, 2007, treatment-emergent serious adverse events were reported for the following five subjects:

Table 7.7.O. Serious Adverse Events, Study M06-884

Subject Number	Serious Adverse Event
12062	Foot ulcer
14017	Hyperparathyroidism, goiter nodular
14049	Total knee replacement
14282	Subarachnoid hemorrhage
31008	Mental status changes, occipital headache, chest pain

Study M06-844 is a Phase 3, multicenter, randomized, prospective, double-blind, active-controlled (double-dummy), comparative study in subjects with primary hypercholesterolemia or mixed dyslipidemia, conducted under IND 75,154. This study was designed to assess the safety and efficacy of once daily ABT-335 dosed at 135 mg in combination with rosuvastatin, dosed at 5 mg QD, compared to the individual monotherapy components (5 mg rosuvastatin monotherapy QD or 135 mg ABT-335 monotherapy QD) for a 12-week Treatment Phase.

Approximately 675 subjects were planned to be randomized at approximately 170 investigative sites in the United States. Subjects were randomized in a double blind fashion to one of three treatment regimens defined below, in a ratio of 1:1:1.

Table 7.7.P. Treatment Groups, Study M06-844

Treatment Group	Planned No.	Study Drug (administered orally, QD)
ABT-335 and rosuvastatin calcium	225	135 mg ABT-335, 5 mg rosuvastatin calcium
ABT-335 monotherapy	225	135 mg ABT-335, rosuvastatin calcium placebo
Rosuvastatin calcium monotherapy	225	ABT-335 placebo, 5 mg rosuvastatin calcium

This is designed as a 12-week study with two interim visits at Weeks 4 and 8, and a 30-day follow-up visit.

A total of 760 subjects were randomized and received at least one dose of study drug. As of December 28, 2007, 92 subjects had prematurely discontinued and 12 subjects were ongoing. Of the subjects who discontinued, all reasons for discontinuation (subjects could have had more than one reason) were adverse event in 41 subjects, withdrawal of consent in 37 subjects, lost to follow-up in eight subjects, noncompliance in two subjects, and "other" reasons in 11 subjects.

The study is ongoing and data remain blinded. As of September 1, 2007, treatment-emergent serious adverse events were reported for the following 16 subjects:

Table 7.7.Q. Serious Adverse Events, Study M06-844

Subject Number	Serious Adverse Event
1028	Sixth nerve paralysis
1074	Coronary artery disease
2043	Anxiety aggravated
2059	Pituitary adenoma
2086	Aphasia, mental status changes
3059	Uterovaginal prolapse, complete
3100	Acute exacerbation of chronic bronchitis
3165	Acute myocardial infarction, of other anterior wall; cardiogenic shock
3205	Claudication
4016	Coronary artery disease, apical myocardial infarction, myocardial ischemia
4043	Intracranial hemorrhage
4119	Transient ischaemic attack
4146	Rhabdomyolysis
4150	Nephrolithiasis, renal cell cancer, acute pancreatitis
4186	Cerebrovascular accident
4260	Coronary artery disease

As listed in the table above, one of the reported events is of rhabdomyolysis (subject 4146). The sponsor notes that although there was an elevation of CPK to approximately 14x ULN associated with myalgias, there was no reported associated creatinine elevation and urine was negative for blood/hemoglobin. This subject's narrative is presented below:

On Treatment Day 61, the subject reported leg pain, calf pain that radiated to the abdomen and chest, and body aches. On Day 63, the subject went to the ER, where relevant labs included a CPK of 2306 ng/ml (reference range 45-234) and a CK-MB of 64.3 ng/ml (reference range 0.0-4.7). The study drug was discontinued. A CXR was normal. A venous Doppler ultrasound of the lower extremities showed no evidence of DVT. An ECG showed sinus rhythm with first degree AV block, left axis deviation, and non-specific intraventricular block. A CT of the chest showed mild cardiomegaly, atherosclerotic changes of the thoracic aorta, no evidence of a pulmonary embolus, and no evidence of an aortic aneurysm. The subject was treated with glyceryl trinitrate, heparin-fraction, and olmesartan. On Day 64, the subject was admitted to the hospital for further evaluation. A stress test and echocardiogram showed normal left ventricular

size and systolic function, mild left ventricular hypertrophy, mild to moderate mitral regurgitation, aortic valve sclerosis with trace aortic insufficiency, and mild tricuspid regurgitation with mild pulmonary hypertension. The subject was treated with acetylsalicylic acid, pantoprazole, tamsulosin, and IV fluids with sodium bicarbonate. The subject was diagnosed with rhabdomyolysis. Peak CPK value (3308 ng/ml) occurred on Day 64. CPK was 571 ng/dL on Day 68 and 56 U/L (performed at different laboratory) on Day 83. On Day 65, an ultrasound on the kidney showed a 1 cm stone in the left renal pelvis without hydronephrosis, possible tiny right calyceal stones, a 5 cm cystic structure to the right of the urinary bladder that might represent a bladder diverticulum or possibly a prior post operative hematoma. The subject's urinalysis showed 1+ leukocytes, 25-50 WBCs, 1-5 RBCs, and moderate bacteria, but was negative for blood/hemoglobin. The subject was referred to a nephrologist for further evaluation. On Day 68, a myocardial perfusion SPECT scan was considered to be normal and the subject was discharged from the hospital. The event of rhabdomyolysis was considered resolved on Day 83. The investigator considered the event of rhabdomyolysis to be probably related to study drug.

**Comment:** Regardless of whether this case meets the strict definition for rhabdomyolysis, it can still be considered to be a case of severe myopathy, with CK > 10x ULN, myalgias, and hospitalization. (It is unclear if the CK-MB was considered significant because although it was elevated, it remained < 5% of total CK). Because this case remains blinded, its relation to ABT-335 as monotherapy or in combination with rosuvastatin is unknown (but suspect). Fortunately, the CK elevation resolved upon discontinuation of study drug, similar to other adverse events of elevated CK that occurred in the Phase 3 program, and in addition, there was no reported myoglobinuria, and renal function was not compromised.

## 8. POSTMARKETING EXPERIENCE

Postmarketing experience exists with fenofibrate, the pro-drug for fenofibric acid (ABT-335). The following publications described in the Appendix, Section 9.1, discuss 1) FDA AERS reports of fenofibrate using gemfibrozil as a comparator, and 2) the incidence of rhabdomyolysis with fibrates as monotherapy and in combination with statins in a paper written by reviewers in FDA's then Office of Safety and Epidemiology.

Postmarketing data provided by the sponsor in the NDA were limited; an analysis submitted later in the review cycle described the occurrence of rhabdomyolysis with fibrate and statin use in a retrospective cohort study in the \_\_\_\_\_ Patients who had been dispensed at least one statin or at least one fibrate from January 2001 through June 2007 were identified from the database. Patients who had ever been prescribed cerivastatin or clofibrate were excluded.

b(4)

The incidence rate of rhabdomyolysis in the statin group was \_\_\_\_\_, for fenofibrate the incidence rate was \_\_\_\_\_ and for gemfibrozil the incidence rate was \_\_\_\_\_. The adjusted incidence rate ratio for fenofibrate was \_\_\_\_\_, and for gemfibrozil \_\_\_\_\_ relative to statins. When fenofibrate was combined with statin therapy, the adjusted incidence rate ratio was \_\_\_\_\_. Combination therapy of statin and gemfibrozil was associated with an adjusted incidence rate ratio of \_\_\_\_\_.

b(4)

**Comment:** Although the fenofibrate + statin incidence rate ratio was not statistically significant in the sponsor's analysis, the point estimate of the adjusted incidence rate ratio still demonstrates a possible increase in risk. The DDI with gemfibrozil and statin is a known effect and does not exonerate the possibility of an increase in risk with the combination of fenofibrate/fenofibric acid and a statin.

## 9. APPENDICES

### 9.1 Literature Review and other Important Relevant Materials/References

#### *FIELD Study*

The full study report for the FIELD study was submitted to the Agency December 4, 2006 under IND 68,742 (Tricor). This was an investigator-initiated study evaluating cardiovascular outcomes in patients with diabetes randomized to fenofibrate or placebo. The sponsor of Tricor (Abbott Labs) did not submit an efficacy supplement based on these findings (the primary endpoint was NS). Mortality and some of the safety information from that study was included in the Tricor label. Because a significant number of patients in this 5-year trial were concomitantly treated with statins, the safety of the combination in certain events of interest was evaluated post-hoc.

Table 9.1.A. FIELD Study: Selected Clinical and Biological Adverse Events Observed with Combination Therapy Reported During the Randomized Period – Number (%) of Subjects

	Placebo (N=4989*) n (%*)	Fenofibrate (N=4895*) n (%*)
<b>Statins</b>	<b>N=1649</b>	<b>N=684</b>
Elevated CK ≤ 5x ULN	258 (15.6)	169 (19.1)
5 < CK ≤ 10x ULN	2 (0.1)	1 (0.1)
CK > 10x ULN	1 (<0.1)	2 (0.2)
Myositis	0 (0)	1 (0)
Rhabdomyolysis	1 (<0.1)	1 (0)
ALT > 3x ULN	8 (0.2)	7 (0.8)
Hepatitis	2 (0.1)	0 (0)
Pancreatitis	9 (0.5)	13 (1.9)
Creatinine > 200 µmol/L	26 (1.6)	21 (2.4)
Need for dialysis	9 (0.5)	4*** (0.3)
<b>Other lipid-lowering drugs**</b>	<b>N=119</b>	<b>N=52</b>
Elevated CK ≤ 5x ULN	21 (17.6)	12 (23.1)
5 < CK ≤ 10x ULN	0 (0)	0 (0)
CK > 10x ULN	1 (0.8)	0 (0)
Myositis	0 (0)	0 (0)
Rhabdomyolysis	0 (0)	0 (0)
ALT > 3x ULN	0 (0)	0 (0)
Hepatitis	0 (0)	0 (0)
Pancreatitis	2 (1.7)	1 (1.9)
Creatinine > 200 µmol/L	2 (1.7)	0 (0)
Need for dialysis	1 (0.8)	0 (0)

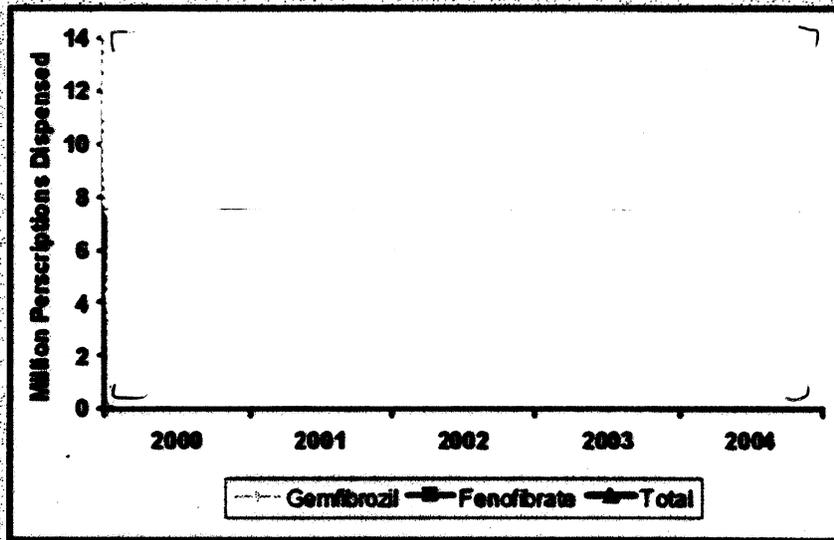
	Placebo (N=4900 <sup>a</sup> ) n (%) <sup>*</sup>	Fenofibrate (N=4895 <sup>b</sup> ) n (%) <sup>*</sup>
<b>Study medication only</b>	<b>N=3099</b>	<b>N=3917</b>
Elevated CK ≤ 5x ULN	442 (14.3)	694 (17.7)
5 < CK ≤ 10x ULN	5 (0.2)	10 (0.3)
CK > 10x ULN	1 (<0.1)	2 (<0.1)
Myositis	1 (0)	1 (0)
Rhabdomyolysis	0 (0)	2 (0)
ALT > 3x ULN	29 (0.6)	15 (0.3)
Hepatitis	6 (0.2)	7 (0.2)
Pancreatitis	12 (0.4)	26 (0.7)
Creatinine > 200 μmol/L	20 (0.6)	52 (1.3)
Need for dialysis	11 (0.4)	13 (0.3)
<sup>*</sup> percentages calculated for each lipid-lowering treatment (LLT) category <sup>**</sup> other LLT include resins, fibrates, and other drugs <sup>***</sup> includes 1 subject found to receive hemodialysis after database closure a 33 missing data for CK, 31 missing data for ALT and creatinine b 42 missing data for CK, 39 missing data for ALT and creatinine		

### Literature

Holoshitz, et al.<sup>27</sup> conducted a review of FDA AERS cases of adverse events with gemfibrozil relative to fenofibrate in the post-cerivastatin era (gemfibrozil had previously been associated with a high number of adverse events, primarily rhabdomyolysis, due to an important drug-drug interaction with cerivastatin, now-removed from the market). Gemfibrozil is the other approved fibrate in the U.S. for treatment of dyslipidemia, and it serves as a reasonable control to assess discordant adverse event reporting between the two drugs. The paper presented the prescription trends in the following figure:

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Figure 9.1.A. Fibrate Prescription Trends in the United States, 2000 to 2004<sup>9</sup>



b(4)

The table from this publication demonstrates that rates of AERS and serious AERS were higher for fenofibrate than gemfibrozil. While liver AERS were higher with fenofibrate, muscle-related AERS were higher with gemfibrozil.

Table 9.1.B. Comparative rates of reported adverse events associated with gemfibrozil and fenofibrate (excluding reports with concomitant cerivastatin use) submitted to the US Food and Drug Administration from January 2000 to December 2004<sup>9</sup>

	Rates per Million Prescriptions		OR	95% CI	p Value
	Gemfibrozil	Fenofibrate			
All AERs			0.76	0.69 – 0.83	<0.001
Serious AERs			0.72	0.65 – 0.81	<0.001
Rhabdomyolysis AERs			2.67	2.11 – 3.39	<0.001
Muscle-related AERs with no rhabdomyolysis			1.36	1.12 – 1.71	0.002
Liver AERs			0.37	0.28 – 0.50	<0.001

b(4)

The authors note that according to their analyses in a previous publication,<sup>44</sup> the rates of fibrate-associated AERs (after excluding reports with concomitant cerivastatin use) are within the range reported for the commonly used statins: e.g., rates of serious AERs for the statins atorvastatin,

44 Alsheikh-Ali A and Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone (from the United States Food and Drug Administration adverse event reporting system). *Am J Cardiol* (2007). 99:379-81.

simvastatin, and pravastatin are \_\_\_\_\_ prescriptions; observed rates for  
rhabdomyolysis AERs are \_\_\_\_\_ prescriptions and liver AERs are \_\_\_\_\_  
prescriptions. These higher findings of liver AERS and comparable muscle AERS are  
consistent with the AE profile that was seen in the clinical trials in this NDA.

b(4)

Graham DJ, et al (JAMA 2004)<sup>5</sup> conducted an analysis of the incidence rates and relative risk of  
rhabdomyolysis in patients treated with different statins and fibrates, alone and in combination,  
in the ambulatory setting.

The findings from this paper are described in the following two tables:

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Table 9.1.C<sup>5</sup>



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Table 9.1.D<sup>5</sup>



b(4)

**Comment: Although the point estimate for gemfibrozil and fenofibrate in combination with a statin (minus the outlier cerivastatin estimates) with respect to rhabdomyolysis are similar, the confidence intervals are wide and the estimate for fenofibrate is based on one case reported in combination with atorvastatin. No cases were seen with fenofibrate administered as monotherapy.**

## 9.2 Labeling Recommendations

A listing of major labeling recommendations is included here. Line-by-line labeling changes are ongoing and will be sent to the sponsor separately.

- In general, Trilipix labeling in the PLR format should be consistent with labeling for fenofibrate.
- Indications should be changed to the following:
  - In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.
  - As monotherapy to reduce TG in patients with severe hypertriglyceridemia.
  - As monotherapy to reduce LDL-C, Total-C, TG and Apo B, and increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia who are intolerant of statin therapy.
- The following statement should be added as a "limitations of use statement" under Indications: No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.
- Under Impaired Renal Function (2.5), a statement should be included that the use of Trilipix should be avoided in patients with severely impaired renal function.
- Add increases in transaminases seen in the statin monotherapy groups to Section 5.1, Liver Function.
- Under Section 5.2, Serum Creatinine, add information regarding monitoring renal function.
- AE tables need to be revised to reflect all AEs, not just those considered related to drug by the investigator.
- Under Geriatric Use (8.5), monitoring renal function should be discussed.
- Under the Clinical Studies Section, only one table of primary efficacy results is necessary; preferably the table describing the three controlled studies' results in combination.
- In both the primary and secondary efficacy tables, \_\_\_\_\_ and the change in the mean percent change for each tested lipid parameter should be presented.
- The high-dose statin efficacy data should be presented.
- P-values can be removed from the secondary efficacy table.

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## 9.3 Advisory Committee Meeting

Not applicable; no advisory committee meeting was held.

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