

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-224**

**MEDICAL REVIEW**

12/15/08

## CLINICAL REVIEW

**Application Type** NDA  
**Submission Number** 22-224  
**Submission Code** N

**Letter Date** December 7, 2007  
**Stamp Date** December 7, 2007  
**PDUFA Goal Date** October 7, 2008

**Reviewer Name** Julie Golden, M.D.  
**Review Completion Date** December 15, 2008

**Established Name** Fenofibric acid  
**Proposed Trade Name** Trilipix  
**Therapeutic Class** Lipid Altering Agent  
**Applicant** Abbott Laboratories

**Priority Designation** S

**Formulation** Capsule  
**Dosing Regimen** 135 mg QD, 45 mg QD  
**Indication** ↓TG, ↓LDL-C, ↓non-HDL-C,  
↓VLDL-C, ↓Apo B, ↓Total-C,  
↑HDL-C  
**Intended Population** Fredrickson Types IIa, IIb,  
IV, V

**TABLE OF CONTENTS**

**1 RECOMMENDATIONS/RISK BENEFIT ANALYSIS ..... 4**

1.1 RECOMMENDATION ON REGULATORY ACTION .....4

1.2 RISK BENEFIT ANALYSIS.....4

1.3 RECOMMENDATIONS FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES .....6

1.4 RECOMMENDATION FOR OTHER POSTMARKETING STUDY COMMITMENTS.....6

**2 INTRODUCTION AND REGULATORY BACKGROUND ..... 7**

2.1 PRODUCT INFORMATION .....7

2.2 CURRENTLY AVAILABLE TREATMENTS FOR PROPOSED INDICATIONS.....7

2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES .....8

2.4 IMPORTANT ISSUES WITH CONSIDERATION TO RELATED DRUGS.....8

2.5 SUMMARY OF PRESUBMISSION REGULATORY ACTIVITY RELATED TO THIS SUBMISSION.....10

2.6 OTHER RELEVANT BACKGROUND INFORMATION.....11

**3 ETHICS AND GOOD CLINICAL PRACTICES..... 11**

3.1 SUBMISSION QUALITY AND INTEGRITY .....11

3.2 COMPLIANCE WITH GOOD CLINICAL PRACTICES.....11

3.3 FINANCIAL DISCLOSURES.....13

**4 SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES  
14**

4.1 CHEMISTRY, MANUFACTURING, AND CONTROLS .....14

4.2 CLINICAL MICROBIOLOGY .....14

4.3 PRECLINICAL PHARMACOLOGY/TOXICOLOGY .....15

4.4 CLINICAL PHARMACOLOGY .....16

4.4.1 Mechanism of Action .....16

4.4.2 Pharmacodynamics .....16

4.4.3 Pharmacokinetics .....16

**5 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY ..... 22**

5.1 TABLES OF CLINICAL STUDIES .....22

5.2 REVIEW STRATEGY .....23

5.3 DISCUSSION OF INDIVIDUAL STUDIES .....24

**6 INTEGRATED REVIEW OF EFFICACY ..... 24**

SUMMARY OF EFFICACY RESULTS AND CONCLUSIONS.....24

6.1 PROPOSED INDICATION .....27

6.1.2 METHODS/STUDY DESIGN .....27

6.1.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS .....34

6.1.4 PATIENT DISPOSITION .....41

6.1.5 ANALYSIS OF THE PRIMARY ENDPOINTS.....46

6.1.6 SECONDARY ENDPOINTS .....62

6.1.7 SUBPOPULATIONS .....80

6.1.8 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS .....88

6.1.9 DISCUSSION OF PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS .....88

6.1.10 ADDITIONAL EFFICACY ISSUES/ANALYSES.....91

**7. INTEGRATED REVIEW OF SAFETY ..... 91**

SUMMARY OF SAFETY RESULTS AND CONCLUSIONS .....91

7.1 METHODS.....93

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety .....93

7.1.2	Adequacy of Data .....	93
7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence .....	94
7.2	ADEQUACY OF SAFETY ASSESSMENTS .....	96
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	96
7.2.2	Explorations for Dose Response .....	99
7.2.3	Special Animal and/or In Vitro Testing .....	100
7.2.4	Routine Clinical Testing .....	100
7.2.5	Metabolic, Clearance, and Interaction Workup .....	100
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .....	101
7.3	MAJOR SAFETY RESULTS AND DISCUSSION .....	103
7.3.2	Serious Adverse Events .....	108
7.3.3	Dropouts and/or Discontinuations .....	112
7.3.4	Significant Adverse Events .....	119
7.3.5	Submission Specific Primary Safety Concerns .....	119
7.4	SUPPORTIVE SAFETY RESULTS AND DISCUSSION .....	166
7.4.1	Common Adverse Events .....	166
7.4.2	Laboratory Findings .....	170
7.4.3	Vital Signs .....	180
7.4.4	Electrocardiograms (ECGs) .....	181
7.4.5	Special Safety Studies .....	183
7.4.6	Immunogenicity .....	184
7.5	OTHER SAFETY EXPLORATIONS .....	184
7.5.1	Dose Dependency for Adverse Findings .....	184
7.5.2	Time Dependency for Adverse Findings .....	184
7.5.3	Drug-Demographic Interactions .....	186
7.5.4	Drug-Disease Interactions .....	190
7.5.5	Drug-Drug Interactions .....	195
7.6	ADDITIONAL SAFETY EVALUATIONS .....	196
7.6.1	Human Carcinogenicity .....	196
7.6.2	Human Reproduction and Pregnancy Data .....	196
7.6.3	Pediatrics and Assessment and/or Effects on Growth .....	196
7.6.4	Overdose, Drug Abuse Potential/ Withdrawal and Rebound .....	198
7.7	ADDITIONAL SUBMISSIONS .....	198
8.	POSTMARKETING EXPERIENCE .....	217
9.	APPENDICES .....	218
9.1	LITERATURE REVIEW AND OTHER IMPORTANT RELEVANT MATERIALS/REFERENCES .....	218
9.2	LABELING RECOMMENDATIONS .....	223
9.3	ADVISORY COMMITTEE MEETING .....	223

Appears This Way  
On Original

## **1 RECOMMENDATIONS/RISK BENEFIT ANALYSIS**

### **1.1 Recommendation on Regulatory Action**

ABT-335 (the investigational name for fenofibric acid or Trilipix) should be approved for use in combination with a statin for treatment of high-risk patients with mixed dyslipidemia pending labeling changes and agreement on a postmarketing study and Risk Evaluation and Mitigation Strategy (REMS) to address the risk of rhabdomyolysis with ABT-335 and statin co-administration.

Based on the review of the clinical data, and given the availability of other treatments, the use of ABT-335 as monotherapy has not been adequately demonstrated as first-line for treatment of primary hypercholesterolemia and mixed dyslipidemia. ABT-335 monotherapy should be approved as second-line therapy for treatment of primary hypercholesterolemia and mixed dyslipidemia in patients who are intolerant of statins.

The use of ABT-335 for severe hypertriglyceridemia should be approved based on bioequivalence to fenofibrate.

### **1.2 Risk Benefit Analysis**

The primary consideration in this application was to determine whether ABT-335 is safe and effective for the treatment of mixed dyslipidemia (i.e., raising HDL-C and lowering LDL-C and TG) when administered in combination with a statin. In this clinical program the combination of ABT-335 135 mg and up to a "moderate dose" of a statin (the equivalent of rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) was effective in raising HDL-C and lowering TG as compared to the equivalent dose of monotherapy statin and effective in lowering LDL-C as compared to ABT-335 135 mg monotherapy. The combination was generally not as effective as statin monotherapy for LDL-lowering, and therefore, the clinician will have to weigh the potential loss of some LDL-C efficacy against additional improvements in TG and HDL-C, as well as non-HDL-C and atherogenic lipoproteins such as VLDL and apoB, when considering adding ABT-335 to a statin. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines recommend targeting atherogenic triglyceride-rich lipoproteins, reflected in non-HDL-C concentrations, by intensifying LDL-lowering (i.e., statin) therapy or adding a TG-lowering therapy such as fenofibrate.<sup>1</sup> Labeling should indicate that the incremental cardiovascular benefit of the combination of ABT-335 and a statin is unknown. The risk-benefit equation may be favorably altered by limiting the combination to patients with coronary heart disease (CHD) or a CHD-equivalent.

In terms of efficacy with ABT-335 monotherapy, the LDL-lowering was notably low at approximately -5%, overall. This is considerably less LDL-lowering than was seen in the studies supporting Tricor for an LDL-lowering indication for Fredrickson Types IIa: -31.4% and IIb: -20.1% (not placebo-corrected changes). Because there was no head-to-head comparison of

---

<sup>1</sup> The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2002). National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. NIH Publication No. 02-5215.

ABT-335 and fenofibrate, and no placebo group in the studies in this clinical program, the true difference between the two drugs, if any, is unknown. The treatment effects may be influenced by background lifestyle interventions and other patient characteristics: subjects in the ABT-335 program had higher TG and lower LDL-C at baseline, both of which can contribute to diminished fenofibrate LDL-lowering. In fact, LDL-raising by fenofibrate in patients with very high TG is described in the fenofibrate package insert and likely explains the attenuation of LDL-lowering seen in this program when ABT-335 was added to a statin.<sup>2,3,4</sup>

Of some interest is that the highest dose of statin, specifically rosuvastatin and atorvastatin, appeared to have similar TG-lowering efficacy as compared to ABT-335. Maximizing statin therapy for this indication may be a reasonable therapeutic option for some patients with mixed dyslipidemia. Ultimately, the clinician can determine the best approach for his or her patient based on the lipid profile and risk status.

The primary safety concern of the combination of ABT-335 and a statin is rhabdomyolysis, which was not convincingly demonstrated in this clinical program (although there were two reports in the clinical studies, neither case met criteria based on myoglobinuria). Because of the rarity of the event, the risk of rhabdomyolysis to a large extent is unknown, but theoretically increased as compared to the known risk of either statin or fenofibrate monotherapy. Given the likelihood for widespread use of the combination, a postmarketing study evaluating statins in combination with fenofibrate/ABT-335 should be conducted to evaluate the risk of muscle toxicity, and a Medication Guide (MedGuide) describing this potential risk to patients and information regarding early muscle symptoms should be distributed as part of a REMS.

In terms of the safety of ABT-335 monotherapy, pharmacokinetic bioequivalence has been established with fenofibrate, and therefore the experience with fenofibrate guided the safety review. In particular, liver and renal safety in addition to muscle safety described above was highlighted.

Liver findings were seen in the ABT-335 program preclinically (coagulative necrosis and hypertrophy down to the lowest dose of ABT-335 in rats) and clinically (elevations in transaminases in all groups treated with ABT-335 in the clinical trials; these elevations were seen less frequently even at the highest statin doses). Reassuringly, transaminase elevations appeared to decrease or normalize after the drug was discontinued. There were no cases of hepatic failure. These findings appear unlikely to represent a safety profile distinct from that of fenofibrate. Transaminase monitoring is recommended with fenofibrate use and will be recommended with ABT-335 use and hepatic safety should be followed postmarketing.

---

2 Durrington PN, Tuomilehto J, Hamann A, Kallend D and Smith K. Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. *Diabetes Res Clin Pract.* 2004;64:137-151.

3 Vega GL, Ma PTS, Cator NB, Filipchuk N, Meguro S, Garcia-Garcia AB, Grundy SM. Effects of adding fenofibrate (200 mg/day) to simvastatin (10 mg/day) in patients with combined hyperlipidemia and metabolic syndrome. *Am J Cardiol.* 2003;91:956-960.

4 Koh KK, Quon MJ, Han SH, Chung W-J, Ahn JY, Seo Y-H, Choi IS Shin EK. Additive beneficial effects of fenofibrate combined with atorvastatin in the treatment of combined hyperlipidemia. *J Am Coll Cardiol.* 2005;45:1649-1653.

Although changes in renal laboratory parameters are a known effect of fenofibrate therapy, there is some debate in the literature about whether these changes reflect a true decrease in glomerular filtration rate (GFR). The clinical program suggested that renal failure associated with ABT-335 occurred infrequently. Those with a calculated creatinine clearance > 60 mL/min had fewer renal events overall associated with ABT-335 therapy than those with more impaired renal function. Renal dysfunction, as reflected by elevations in BUN and creatinine, is monitorable. In individuals with preexisting renal insufficiency, ABT-335 should be administered as a lower dose and renal function should be monitored. Severe renal insufficiency is a contraindication to ABT-335 use.

In summary, based on the LDL-lowering in the clinical studies, ABT-335 should not be first-line for treatment of primary hypercholesterolemia and mixed dyslipidemia. It is difficult to ascertain if the differential LDL-lowering effects as compared to those historically obtained with fenofibrate are a true drug difference, or, as this reviewer suspects, are based on different baseline characteristics of the populations studied in the two programs. However, the data highlight the change in practice guidelines and approach to lipid-altering for cardiovascular prevention since fenofibrate was originally introduced to the market. Based on efficacy for cardiovascular outcomes, statins are considered first-line therapy for LDL-lowering.

If further TG-lowering/HDL-raising is desired in high-risk patients with mixed dyslipidemia already on statin therapy, combination therapy with ABT-335 could be considered. Hepatic and renal laboratories should be monitored and creatinine kinase should be measured in case of muscle symptoms. In order to improve the risk-benefit equation, a REMS to address the risk of muscle toxicity should be implemented, and a postmarketing study evaluating the risk of rhabdomyolysis should be conducted.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

Labeling is the primary approach to risk management. Implementing a REMS, which will include the distribution of a MedGuide and its follow-up, will ensure the benefits of the combination of ABT-335 and a statin outweigh the risk of muscle toxicity. Furthermore, renal monitoring in patients with or at risk for renal insufficiency is being recommended in the ABT-335 prescribing information.

Due to an increase in the incidence of transaminitis seen with ABT-335 in the clinical trials, the liver safety of this compound should be monitored closely postmarketing; particular attention should be paid to liver events in the Periodic Safety Update Reports.

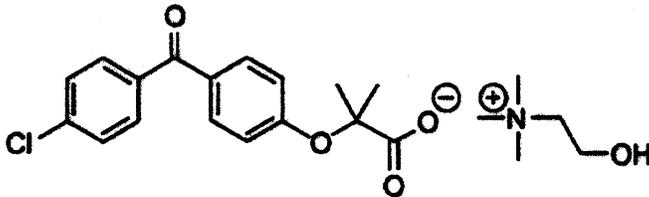
### **1.4 Recommendation for other Postmarketing Study Commitments**

Although muscle injury was not found to be more prevalent in the combination therapy groups as compared to the respective monotherapies in the clinical trials, the risk of rhabdomyolysis with combination therapy is a rare event and therefore remains a serious theoretical concern. A postmarketing requirement (PMR) is recommended to evaluate the relative risk of rhabdomyolysis when fenofibric acid or fenofibrate is administered in combination with a statin in order to fully characterize this risk.

## 2 INTRODUCTION AND REGULATORY BACKGROUND

### 2.1 Product Information

The drug substance is the choline salt of fenofibric acid (ABT-335). Its chemical name is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid choline salt, its empirical formula is  $C_{22}H_{29}ClNO_5$ , and the molecular weight is 421.91. The structural formula is:



The dosage form is a modified release capsule formulation containing 45 mg or 135 mg free acid equivalent. Each 45 mg and 135 mg capsule contains enteric coated fenofibric acid mini-tablets, respectively, inside a gelatin capsule shell. The excipients are: hypromellose, povidone, water, hydroxypropyl cellulose, colloidal silicone dioxide, sodium steryl fumarate, methacrylic acid copolymer, talc, triethyl citrate, and gelatin.

b(4)

The proposed trade name is Trilipix. It is being submitted under 505(b)(2) regulations, with Tricor (fenofibrate) as the reference listed drug.

The pharmacological class is peroxisome proliferator activated receptor alpha ( $PPAR\alpha$ ), also known as a fibrate.

The sponsor has proposed the following indications: co-administration therapy with statins for the treatment of mixed/atherogenic dyslipidemia, treatment of primary hypercholesterolemia or mixed dyslipidemia, and treatment of hypertriglyceridemia.

### 2.2 Currently Available Treatments for Proposed Indications

- Indication 1: Co-administration therapy with statins for the treatment of mixed/atherogenic dyslipidemia
  - Niacin extended-release (Niaspan, Advicor, Simcor)
  - Omega-3-acid ethyl esters (Lovaza)
  - Ezetimibe (as a component of Vytorin only)
  
- Indication 2: Treatment of primary hypercholesterolemia or mixed dyslipidemia
  - Statins (lovastatin, rosuvastatin, fluvastatin, atorvastatin, pravastatin, simvastatin)
  - Ezetimibe (Zetia, Vytorin)
  - Fibrates (fenofibrate, gemfibrozil)
  - Bile acid sequestrants (cholestyramine, colestevlam, colestipol)
  - Niacin

- Indication 3: Treatment of hypertriglyceridemia
  - Fibrates
  - Niacin
  - Omega-3-acid ethyl esters

### 2.3 Availability of Proposed Active Ingredient in the United States

Fenofibric acid is the active ingredient of fenofibrate (Tricor, others), an approved drug in the United States.

### 2.4 Important Issues with Consideration to Related Drugs

- **Rhabdomyolysis:** Current fibrate labeling (gemfibrozil and fenofibrate) warns against the co-administration with a statin due to concerns of severe myopathy and rhabdomyolysis. This concern has primarily been driven by the pharmacokinetic interaction (competition for glucuronidation enzymes) between gemfibrozil and the statins. In particular, the combination of gemfibrozil and cerivastatin (now withdrawn from the market) demonstrated an incidence rate of approximately 1000 cases of rhabdomyolysis per 10,000 patient years in one series.<sup>5</sup> This epidemiological study also found that the incidence rate for hospitalized rhabdomyolysis for patients treated with atorvastatin + a fenofibrate was 22.45 per 10,000 person-years (CI: 0.57-125), while the incidence rate for monotherapy with atorvastatin was 0.54 per 10,000 person-years (CI: 0.22-1.12) and the incidence rate for monotherapy with fenofibrate was 0 (CI: 0-14.58). Nevertheless, combination use of fenofibrate and statins has become more widespread in order to address both LDL-lowering and treatment of atherogenic dyslipidemia, despite the labeling recommendations to avoid the joint use. Furthermore, large trials in which a substantial number of subjects were treated with combination therapy (e.g., the Fenofibrate Intervention and Event Lowering in Diabetes study, FIELD<sup>6</sup>) have not heightened the muscle safety concern with this particular combination. Therefore, a more updated and rigorous appraisal of this issue is warranted in light of the proposed new indication.
- **Mortality:** Fibrates that have been studied in large mortality trials include clofibrate, bezafibrate, gemfibrozil, and fenofibrate. Results have not consistently shown a mortality benefit, and in some cases have even suggested mortality increases, as shown in the following table adapted from the FIELD study report, submitted to FDA under Tricor IND 68,742:

---

5 Graham DJ, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004 Dec 1;292(21):2585-90.

6 Keech A, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005 Nov 26; 366(9500): 1849-61.

Table 2.4.A. Mortality Endpoints in Fibrate Clinical Trials

	Non-Diabetics		Diabetics	
	Fenofibrate	Other Fibrates	Fenofibrate	Other Fibrates
CHD Mortality	NA	No significant change	Non-significant ↑ (FIELD)	↓ (gemfibrozil: VA-HIT subset analysis)
All-Cause Mortality	NA	↑ (clofibrate: WHO study) No significant change (clofibrate: Coronary Drug Project; gemfibrozil: Helsinki Heart Study, VA-HIT; bezafibrate: Bezafibrate Infarction Prevention trial)	Non-significant ↑ (FIELD)	No significant change

Cancer mortality with fibrate use has been debated in the literature.<sup>7</sup> There has been recent attention with respect to other lipid-altering compounds and cancer association.<sup>8</sup> Some authors have focused instead on the positive association between LDL-lowering and cancer,<sup>9</sup> but this area remains controversial.

- **Formulation changes and food effect:** The clinical studies supporting approval of fenofibrate utilized a 100 mg non-micronized formulation; however, this formulation was never marketed in the United States. In 1998, a supplemental new drug application (NDA 19-304/S-001) was submitted for a micronized formulation of fenofibrate. The 67 mg micronized capsule was found to be bioequivalent to 100 mg of non-micronized fenofibrate; subsequently, the micronized formulation was approved and marketed in the US as 67 mg and 200 mg capsules under the trade name, Tricor.

However, because of the marked food effect of this Tricor formulation (under high fat conditions, bioavailability increased ~35%) the drug was again reformulated with the intention of increasing bioavailability and decreasing the food effect. In 1999, the 54 and 160 mg doses of a new Tricor formulation (tablet) were approved (NDA 21-203) for the same indications; however, a food effect was still observed. Labeling, therefore, still included the recommendation that Tricor be taken with meals.

In 2003, a new formulation of Tricor, which was not found to have a food effect, was submitted in two dosage strengths: 48 mg and 145 mg tablets (NDA 21-656). The current formulation, Tricor (fenofibrate) 48 and 145 mg tablets, was approved August 20, 2004.

A second fenofibrate product, Antara™ Capsules, manufactured by Oscient, approved under NDA 21-695, has exclusivity for no food effect. NDA 21-695/S-001 was approved October 20, 2005, which allowed for inclusion of efficacy data in the Clinical Studies section of the Antara label. Antara is the only fenofibrate with clinical data specific to the approved and marketed product in its label. These clinical data also supported the approval of the

<sup>7</sup> A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate: report from the Committee of Principal Investigators. *Br Heart J* 1978;40:1069-1118.

<sup>8</sup> Rossebo AB, et al. Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. *N Engl J Med*. 2008 Sep 2. [Epub ahead of print]

<sup>9</sup> Alsheikh-Ali AA, et al. Statins, Low-Density Lipoprotein Cholesterol, and Risk of Cancer. *J. Am. Coll. Cardiol.* published online Aug 20, 2008.

statement in the Dosage and Administration section that Antara fenofibrate can be taken without regard to meals, given that Antara 130 mg under fed and fasted conditions demonstrated similar efficacy despite not finding bioequivalence in a PK study. A 505(b)(2) fenofibrate, Fenoglide, was approved using Antara as the RLD; however, because of patent issues, Fenoglide's label requires a "take with food" statement.

## **2.5 Summary of Presubmission Regulatory Activity Related to this Submission**

A preIND meeting was held on May 25, 2004 under PIND 69,680. The sponsor was informed that for a co-administration indication for ABT-335 with any statin, PK studies would need to be conducted with all approved statins. Literature describing DDI with statins and fenofibrate would be acceptable to support this indication; the application would then be submitted as a 505(b)(2). The sponsor was told that three years of exclusivity for a co-administration indication could be granted. A monotherapy indication referencing Tricor (fenofibrate) was found to be acceptable, without exclusivity. A food effect study was requested. The sponsor was notified that the drug was not likely to be considered a new molecular entity (NME).

IND 70,345 was opened September 8, 2004 with a single-dose vs. 200 mg micronized fenofibrate capsule bioavailability study.

A Special Protocol Assessment for the Phase 3, 12-week study M05-748 (ABT-335 + rosuvastatin) was completed September 13, 2005. Key agreements included the choice of endpoints, doses of statins, and substitution of the placebo arm for an arm with the highest marketed dose of statin. Of note was the reviewer's comment to the sponsor that:

*Assuming adequate safety and effectiveness established in your clinical development program, labeling is intended to emphasize that single agent therapy is the preferred initial treatment approach with combination therapy to be considered only if LDL-C and non-HDL-C goals are not reached with either statin monotherapy or fenofibrate monotherapy. A disclaimer regarding the unknown effects of combination therapy on cardiovascular risk reductions will also be included in labeling.*

On April 9, 2007, the Division informed the sponsor that their proposal to submit a sizable amount of long-term patient-exposure data in the 4-month safety update of their planned NDA submission for ABT-335 was unacceptable. The Division requested that the company delay submission of the NDA so that sufficient patient exposure information would be included in the original submission and less would appear in the 4-month safety update. In a correspondence dated May 1, 2007, the sponsor provided a counter-proposal for the patient exposures that would be included in their planned NDA submission and the 4-month safety update. This was found to be acceptable given that the NDA would contain all data on subjects exposed out to 9 months.

A preNDA meeting was held July 20, 2007. The following key issues were addressed:

1. The sponsor was referred to the Advicor (Niaspan + lovastatin) label for co-administration labeling language.

2. The sponsor was told that monotherapy labeling language would follow that of Tricor (fenofibrate, the RLD), pending review of the biopharmaceutics data.
3. A partial waiver was granted for pediatric monotherapy and co-administration studies for patients younger than 10 years. A deferral was not granted for patients 10-18 years until more information regarding the number of pediatric patients in the U.S. with triglycerides in the 400-700 mg/dL range was provided.
4. PK data appeared to support administration without regard to meals.
5. [

b(4)

6. The sponsor was informed that it was acceptable to refer to clinical data from the RLD without submitting those data in the NDA for review.
7. The application was determined to be a 505(b)(2) application due to the referencing of fenofibrate-simvastatin drug-drug interaction study in the literature.

The sponsor was informed February 20, 2008 that the proposed tradename was found acceptable. However, this initial acceptability was based on the name "Trilipix" versus "TriLipix", a more updated version submitted with proposed cartons and other labeling. Because of the potential for confusion that could lead to medication errors with TriLipix: that is with a capital "L" and different color for "Tri" and "Lipix", the medication error prevention staff recommended that Trilipix be presented with a lower case "l" and all one color on cartons and labels in a consult to the Division dated August 19, 2008.

## 2.6 Other Relevant Background Information

None.

## 3 ETHICS AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Integrity

In general, the application was well-organized and navigable. It was submitted in the eCTD format. The sponsor did not include analysis datasets that included all of the variables of interest so some merging was required. The sponsor was asked to provide additional information infrequently during the course of the review and did so in a timely fashion.

### 3.2 Compliance with Good Clinical Practices

The review division consulted with the Division of Scientific Investigations to conduct site inspections. Two sites from each controlled study were selected for DSI consideration. The site selection rationale in the consult request, written by this reviewer, was as follows:

*There are no specific concerns with any particular investigative site.*

*Individual sites were not evaluated for site-specific efficacy. Study M05-748 had 203 sites. A total of 1445 subjects were randomized. Study M05-749 had 117 sites. A total of 657 subjects were randomized. Study M05-750 had 102 sites. A total of 613 subjects were randomized. There are 6 study arms and 3 primary efficacy variables. It is unlikely that any one site would drive the efficacy results. The number of subjects randomized and proportion discontinued in a*

*particular site was taken into account in selecting sites for auditing ... (only investigators who randomized  $\geq 10$  subjects [were considered]).*

*Financial disclosures were reported for the following investigators and subinvestigators:*

*Study 748*

- *Michael Davidson – enrolled 7 pts*

*Study 749*

- *Kenneth Cusi – enrolled 8 pts*
- *Carl Pepine (+ subinvestigator \_\_\_\_\_ - enrolled 2 pts*

*Study 750*

- *Roy Fleischmann (+ subinvestigator \_\_\_\_\_ - enrolled 4 pts*
- *Henry Punzi – enrolled 15 pts*

b(4)

*Again, given the size of these studies, the number of investigators, and the nature of the study design (multiple arms, multiple primary efficacy analyses) it is unlikely that any one study site is driving the results.*

*The proportion of subjects with protocol violations from individual sites was taken into account when selecting sites for auditing...*

*Finally, all selected sites enrolled subjects into the open-label extension study (M05-758):*

- *Fraser: 14 subjects*
- *Farrington: 12 subjects*
- *Jones: 4 subjects*
- *Pietri: 6 subjects*
- *Koren: 18 subjects*
- *Gottschlich: 9 subjects*

**The inspection of Dr. Neil Fraser's site by DSI received a No Action Indicated (NAI) review. An audit of 26 subjects' records was conducted revealing no regulatory violations. The data generated from the site were deemed acceptable.**

**The inspection of Dr. Cecil Farrington's site by DSI received a NAI review. An audit of 20 subjects' records was conducted revealing no regulatory violations. The data generated from the site were deemed acceptable.**

**The inspection of Dr. Timothy Jones' site by DSI received a NAI review. An audit of 16 subjects' records was conducted revealing no regulatory violations. The data generated from the site were deemed acceptable.**

**The inspection of Dr. Michael Koren's site by DSI received a NAI review. At this site, 82 subjects were screened, 31 subjects were randomized, and 28 subjects completed the study. Audits of all subjects' consent forms and efficacy endpoints sent from the laboratory to the site were conducted. No unreported adverse events were found when subjects' records were compared against the adverse event data listing. No regulatory violations were noted. The data generated from the site were deemed acceptable.**

The inspection of Dr. Angel Pietri's site by DSI received a voluntary action indicated (VAI) review, and issued a Form FDA 483. At this site, 48 subjects were screened, 16 subjects were randomized, and 12 subjects completed the study. There was one SAE reported. An audit was conducted of 100% of subjects' consent forms for the screened subjects. An audit of 75% (9/12 of randomized subjects completing the study) of case report forms, source documents and data listings and an audit of 69% (11/16 of all randomized subjects) of the baseline laboratory values was conducted. The inspection found that the clinical investigator did not maintain adequate and accurate case histories that record all observations and data pertinent to the investigation. However, it was concluded that the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

The inspection of Gr. Gregory Gottschlich's site by DSI received a NAI review. A full record audit was conducted for all 23 subjects enrolled in the trial. No regulatory violations were noted. The data generated from the site were deemed acceptable.

On November 30, 2006, FDA was notified that an investigator for studies M05-748 and -758 (Dr. Keith Pierce, Livonia, MI) was disqualified for lack of oversight over the study, inappropriate delegation of study activities, a lack of study drug accountability, and non-compliance with protocol requirements. This investigator had 15 subjects in study M05-748 and 10 subjects in study M05-758 who were excluded from efficacy analyses. The data from these subjects were included in sensitivity analyses conducted by the sponsor.

An inspection of the contract research organization (CRO) was conducted by DSI to verify the primary efficacy data endpoints of HDL-C, TG, and LDL-C for protocols M05-748, -749, and -750. The inspection was focused on the following investigators: Neil Fraser, Cecil Farrington, Angel Pietri, Timothy J. Jones, Michael Koren, and Gregory Gottschlich. A comparison of the source data for approximately 700 baseline and final data points for the primary endpoints with the data listing submitted in the NDA, with an audit of 94 subjects' records was conducted. DSI reported that no significant observations of noncompliance were noted and the study appears to have been conducted adequately.

### 3.3 Financial Disclosures

A Form 3454 was completed with a list of clinical investigators certified not to have engaged in financial interests or engagements.

Financial disclosures were reported for the following clinical investigators and subinvestigators via Form 3455. All investigators described the financial interest as *any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria*, with the exception of \_\_\_\_\_ who described his financial interest as *any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study*.

b(6)

Study \_\_\_\_\_

- \_\_\_\_\_ - Disclosed payments in excess of \$25,000; enrolled \_\_\_\_\_

b(6)

- \_\_\_\_\_ - Disclosed honoraria for speaking and consulting in excess of \$25,000; enrolled \_\_\_\_\_ in \_\_\_\_\_

b(6)

Study \_\_\_\_\_

- \_\_\_\_\_ Disclosed payments in excess of \$25,000; in \_\_\_\_\_
- \_\_\_\_\_ + subinvestigator \_\_\_\_\_ who disclosed payments in excess of \$25,000) - Disclosed payments in excess of \$25,000 for consulting and a grant for an investigator-initiated study: \_\_\_\_\_
- \_\_\_\_\_ (subinvestigator; PI \_\_\_\_\_ - Disclosed grants in excess of \$25,000 for ongoing investigator-initiated studies; \_\_\_\_\_

b(4) b(6)

Study \_\_\_\_\_

- \_\_\_\_\_ + subinvestigator \_\_\_\_\_ who disclosed payments in excess of \$25,000) - Disclosed significant equity interest in the form of common stock to the amount of approximately \$100,000; \_\_\_\_\_
- \_\_\_\_\_ - Disclosed payments in excess of \$25,000 for speaking engagements and a grant for an investigator-initiated study \_\_\_\_\_  
\_\_\_\_\_ was also an investigator in study \_\_\_\_\_

b(4)

b(6)

A financial disclosure was also submitted for \_\_\_\_\_, a subinvestigator in study \_\_\_\_\_ a \_\_\_\_\_ He disclosed significant equity interest in the form of shares, to the amount of approximately \$100,000. The PI \_\_\_\_\_, is an \_\_\_\_\_ employee.

b(4)

Given the size of these studies, the number of investigators, and the nature of the study design (multiple arms, multiple primary efficacy analyses) it is unlikely that any one study site is driving the results. These financial disclosures do not lead this reviewer to question the integrity of the data.

#### **4 SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES**

##### **4.1 Chemistry, Manufacturing, and Controls**

The CMC reviewer recommends approval, and there are no issues from her review that require specific clinical consideration. Please refer to the clinical pharmacology and biopharmaceutics reviews for discussion of the 45 mg biowaiver. It appears that although a dose proportionality study for the 45 mg dose was not conducted, pharmacokinetic linearity was demonstrated between a 50 mg and 100 mg dose. The formulation is the same and components are proportional between the 45 mg and 135 mg doses. A post-approval Trilipix PK dose equivalence study (of 3 x 45 mg capsules vs. 1 x 135 mg capsule) will be conducted.

##### **4.2 Clinical Microbiology**

Not applicable. Trilipix (fenofibric acid) is not an injectable.

### **4.3 Preclinical Pharmacology/Toxicology**

The sponsor conducted a 5-week bridging study in rats with fenofibrate and fenofibric acid as well as 3-month toxicity studies with fenofibric acid choline salt in rats and dogs. FDA agreed at the pre-IND meeting May 25, 2004 that preclinical toxicology would be bridged to fenofibrate and no further preclinical studies would be required.

The pharmacology/toxicology reviewer reported that both fenofibrate (100-300 mg/kg/day) and fenofibric acid (75-150 mg/kg/day) produced similar decreases in body weights, food consumption and changes in hematological (decreases in hematocrit and increases in RDW) and clinical chemistry parameters (ALT/AST/ALP were increased by up to 2-fold in males). Target organs of toxicity with both fenofibrate (100-300 mg/kg/day) and fenofibric acid (75-150 mg/kg/day) were liver (centrilobular hypertrophy), skeletal muscle (myofiber degeneration), and heart (lesions with myofiber degeneration). This bridging study did note differences in gross findings in the stomach (red foci in the glandular mucosa less than 1 mm diameter), which were seen with fenofibric acid, but not with fenofibrate.

In all subsequent studies in rats, no ulcerogenic effects were found following oral (gavage) administration of the choline salt of fenofibric acid. In these studies, the exposure levels of fenofibric acid were  $\geq$  80-fold higher than the clinical exposure at the 135 mg dose.

In the pharmacology/toxicology reviewer's assessment of a 3-month oral toxicity study of fenofibric acid choline salt in rats (0, 10, 30, 100 mg/kg/day), target organs of toxicity were determined to be liver (centrilobular hypertrophy of mild to moderate severity at all doses), skeletal muscle, pituitary gland in males, kidneys in females, and thymus in both sexes. No drug free recovery period was assessed in this rat study. The NOAEL or tolerated dose of the drug in the 3-month oral toxicity study in rats is  $<$  10 mg/kg/day based on the liver findings, which provides safety margin of  $<$  3x human exposures. The heart and muscle toxicity was noted in rats at approximately 15X and 60X the human exposures respectively.

In the pharmacology/toxicology reviewer's assessment of a 3-month oral toxicity study of fenofibric acid choline salt in dogs (0, 25, 50, 100 mg/kg/day), followed by a 6-week drug free recovery period, target organs of toxicity were determined to be liver (cell necrosis and/or mixed inflammatory cell infiltrates at MD/HD), ovaries/testis (all doses), thymus (lymphoid atrophy, MD/HD) and stomach (atrophy, MD/HD), heart (HD), and skeletal muscle (mononuclear cell infiltration, MD/HD). During recovery, no toxicity was noted in the stomach, testis and ovaries in dogs, but was still present in the heart and liver. The liver, stomach, heart, and thymus toxicity was noted in dogs at 5-12X the human exposures.

The pharm/tox reviewer concludes that the safety margin for the heart, stomach, and muscle toxicity in rats and dogs is sufficient. Again, liver and pituitary gland (males) toxicity was noted in rats at  $<$  3x the human doses, based on exposures.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Fenofibric acid is a peroxisome proliferator activated receptor alpha (PPAR $\alpha$ ) agonist, the activity of which increases lipolysis and decreases triglyceride-rich lipoproteins by activating lipoprotein lipase and reducing production of apolipoprotein (apo) CIII (an inhibitor of lipoprotein lipase activity). The decrease in TG alters the size and composition of LDL from small and dense to large and buoyant. Large, buoyant LDL particles are thought to be less atherogenic and more rapidly cleared from the circulation than small, dense LDL particles. Activation of PPAR $\alpha$  also induces an increase in the synthesis of HDL-C and apo AI and AII.

### 4.4.2 Pharmacodynamics

The pharmacodynamic effect of fenofibric acid is demonstrated by its effects on lipid parameters. This is discussed in full in Section 6, Efficacy.

### 4.4.3 Pharmacokinetics

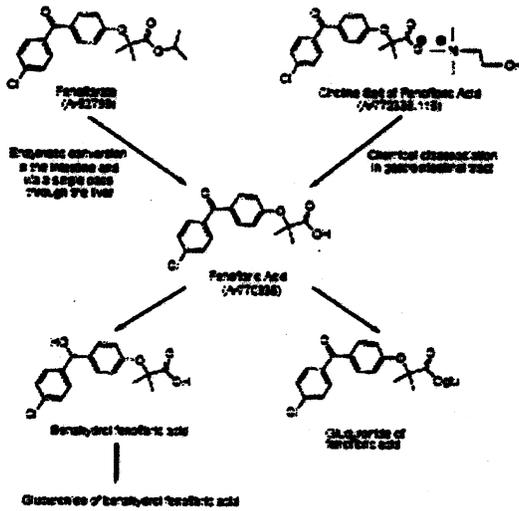
#### *ADME*

Fenofibric acid is rapidly absorbed with a mean  $T_{max}$  of 2.6 hours. The absolute bioavailability of fenofibric acid is approximately 81% in humans. The molecule is well absorbed throughout the gastrointestinal tract. The absolute bioavailability after site-specific delivery of fenofibric acid is consistently in the range of approximately 78 to 88% from the stomach to the ascending colon.

Fenofibric acid is highly bound (99.17%) to human plasma proteins and the binding is constant over the concentration range (mean  $C_{max}$  of 12.13  $\mu\text{g/mL}$  to a mean  $C_{min}$  of 4.59  $\mu\text{g/mL}$ ). In subjects with mild ( $\text{CrCl} \geq 50 \text{ mL/min}$ ), moderate ( $\text{CrCl} 30\text{-}49 \text{ mL/min}$ ), or severe ( $\text{CrCl} \leq 29 \text{ mL/min}$ ) renal impairment, or with end stage renal disease on dialysis, the mean fractions bound were 97.99, 98.49, 98.02, and 99.45%, respectively. The value was 99.00% in a control group of normal young adult volunteers.

Eight healthy volunteers received a single therapeutic dose (66  $\mu\text{Ci}$ /subject) of  $^{14}\text{C}$ -fenofibrate orally. Urine and feces were collected for up to seven days after dosing. A total of 84.4% of the total radioactivity was excreted in seven days with 59.3% of the dose recovered in the urine and 25.0% recovered in the feces. Virtually the entire urinary radioactivity dose was accounted for as free fenofibric acid (9% of total dose), fenofibric acid ester glucuronide (45%), free benzhydrol metabolite (1%), and its glucuronide (3%). Fecal metabolite patterns were not characterized. No unchanged fenofibrate was detected in plasma. Plasma levels for total radioactivity and free fenofibric acid were essentially superimposable, demonstrating that no more than minor amounts of conjugated fenofibric acid or other metabolites were present in plasma. Low levels of the benzhydrol metabolite were found in plasma and accounted for 5% of the total plasma radioactivity. The proposed metabolic pathways of fenofibrate and fenofibric acid are illustrated in Figure 4.4.3.A.

Figure 4.4.3.A. Proposed Metabolic Pathway for Fenofibrate and Fenofibric Acid in Humans



**Bioequivalence**

The definitive bioequivalence study (Study M06-830) demonstrated that the to-be-marketed ABT-335 formulation manufactured at full production scale as well as the formulation used in Phase 3 clinical trials was bioequivalent to the 200 mg micronized fenofibrate reference capsules with regard to both  $C_{max}$  and AUC of fenofibric acid.

Appears This Way  
On Original

Table 4.4.3.A. Mean  $\pm$  SD Pharmacokinetic Parameters for Fenofibric Acid from Various Studies for Dose-Linearity Assessment

Study No.	Dose <sup>a</sup> (mg)	N	C <sub>max</sub> ( $\mu$ g/mL)	AUC <sub>0-<math>\infty</math></sub> ( $\mu$ g $\cdot$ h/mL)	t <sub>1/2</sub> <sup>b</sup> (h)	CL/F (L/h)
<b>Following Fenofibric acid Administration<sup>c</sup></b>						
M02-513	50	15	3.67 $\pm$ 0.85	41.8 $\pm$ 11.2	11.8	1.3 $\pm$ 0.4
M02-513	100	15	8.09 $\pm$ 2.44	76.3 $\pm$ 15.8	12.6	1.4 $\pm$ 0.3
M03-636	130	30	NA <sup>d</sup>	99.6 $\pm$ 37.4	14.8	1.51 $\pm$ 0.67
M05-737	135	24	11.24 $\pm$ 2.24	168.9 $\pm$ 59.7 <sup>e</sup>	19.4	0.89 $\pm$ 0.27
<b>Following 200 mg Fenofibrate Reference Capsule Administration<sup>f</sup></b>						
M03-636	--	48	5.89 $\pm$ 1.67	112.2 $\pm$ 41.3	15.9	ND
M06-830	--	65	9.28 $\pm$ 2.67	168.9 $\pm$ 55.5	21.8	ND

a. Dose of fenofibric acid.

b. Harmonic mean.

c. Administered as fenofibric acid neat drug in capsule.

d. Not applicable for dose-proportionality analysis because Formulation 1 from Study M03-636 was designed to have lower C<sub>max</sub> and delayed T<sub>max</sub>.

e. Not applicable for dose-proportionality analysis as the t<sub>1/2</sub> and CL/F estimates from Study M05-737 were different than those observed in Study M02-513 and Study M03-636.

f. In Study M06-830 the 200 mg fenofibrate capsule was shown to be bioequivalent to the to-be-marketed ABT-335 formulation of 135 mg fenofibric acid equivalent.

ND = not determined. CL/F was not determined for the 200 mg fenofibrate capsule regimen because a different molecule, fenofibric acid, is circulating in plasma.

The steady-state pharmacokinetics of fenofibric acid are similar following multiple administrations of ABT-335 and fenofibrate at doses providing equivalent fenofibric acid exposures. Similar to that following fenofibrate administration, the concentrations of fenofibric acid at steady state following ABT-335 administration are slightly higher than those expected based on concentrations following single dose and time-independent pharmacokinetics.

#### Food effect

Study M06-831 used a high-fat, high-calorie meal to evaluate the effect of food on bioavailability. Analyses of C<sub>max</sub> and AUC showed that the meal had no effect on the bioavailability of fenofibric acid from the ABT-335 formulation (90% CI were within the 0.80 to 1.25 range). The mean T<sub>max</sub> values of fenofibric acid under non-fasting conditions occurred up to six hours later than that under fasting conditions.

The effect of a low-fat meal on fenofibric acid bioavailability from the ABT-335 formulation was also evaluated in Study M06-831. The study showed that the 90% CI for AUC<sub>t</sub> and AUC<sub>∞</sub> were within the 0.80 to 1.25 range. The low-fat meal reduced fenofibric acid C<sub>max</sub> by 22%, with the lower bound of the 90% CI for C<sub>max</sub> extending below 0.80.

Table 4.4.3.B. Summary of Food Effect Assessment on Fenofibric Acid Bioavailability from the To-Be-Marketed ABT-335 Formulation, Studies M05-743, M06-804 and M06-831

Study	Test Meal	N*	Pharmacokinetic Parameter	Relative Bioavailability	
				Point Estimate	90% Confidence Interval
M05-743	A high-fat meal (847.8 Kcal; 51.7% calories from fat)	34	C <sub>max</sub>	0.845	0.783 – 0.912
			AUC <sub>t</sub>	1.039	0.986 – 1.094
			AUC <sub>∞</sub>	1.041	0.988 – 1.096
M06-804 (Omeprazole 40 mg QD co-administered)	A high-fat meal (847.8 Kcal; 51.7% calories from fat)	34	C <sub>max</sub>	0.840	0.788 – 0.895
			AUC <sub>t</sub>	0.983	0.950 – 1.018
			AUC <sub>∞</sub>	0.985	0.951 – 1.019
M06-831	A high-fat meal (1075.9 Kcal; 47.3% calories from fat)	71	C <sub>max</sub>	0.850	0.806 – 0.897
			AUC <sub>t</sub>	0.972	0.942 – 1.002
			AUC <sub>∞</sub>	0.977	0.947 – 1.009
	A low-fat meal (422.7 Kcal; 25.1% calories from fat)	71	C <sub>max</sub>	0.780	0.739 – 0.823
			AUC <sub>t</sub>	0.912	0.884 – 0.941
			AUC <sub>∞</sub>	0.920	0.891 – 0.950

\* Number of subjects included in pharmacokinetic analyses.

### Drug-Drug Interactions

#### In vitro studies

*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.

#### Statins

In the September 13, 2004 Special Protocol Assessment (SPA) response, the Division recommended that Abbott should conduct studies evaluating pharmacokinetic interactions between the highest proposed dose of ABT-335 and the highest proposed dose of all marketed statins. It was agreed that available interaction data between fenofibrate and statins were acceptable; therefore, only Study M06-811 (ABT-335 and rosuvastatin) was conducted under the ABT-335 IND 70,345.

The following two tables display the results of statins on fenofibric acid PK, and fenofibrate/ABT-335 on statin PK, respectively.

Table 4.4.3.C. Effects of Statins on Pharmacokinetic Parameters of Fenofibric Acid

Study Drugs	Analyte	Point Estimate <sup>S</sup> (90% Confidence Interval)		Study
		C <sub>max</sub>	AUC	
ABT-335 and Rosuvastatin	Fenofibric acid	0.978 (0.915 – 1.046)	0.982 (0.927 – 1.041)	Study M06-811
Fenofibrate and Atorvastatin	Fenofibric acid	0.960 (0.91 – 1.02)	0.977 (0.92 – 1.04)	K178P0201KH (Counter, K178P0201KH)
Fenofibrate and Pravastatin	Fenofibric acid	0.975 (0.878 – 1.086) <sup>+</sup>	0.994 (0.931 – 1.060) <sup>+</sup>	M98-898 (R&D/98/595)
Fenofibrate and Fluvastatin	Fenofibric acid	0.896 (0.831 – 0.966)	0.982 (0.931 – 1.036)	M02-525 (R&D/04/062)
Fenofibrate and Simvastatin <sup>+</sup>	Fenofibric acid	0.89 (0.77 – 1.02)	0.95 (0.88 – 1.04)	Bergman, <i>et al.</i> , 2004 (Bergman AJ, 2004)

<sup>S</sup> Point estimates (90% confidence interval) comparing the central values of fenofibric acid pharmacokinetic parameters after the co-administration with statins to that after ABT-335 or fenofibrate administered alone.

<sup>+</sup> 95% confidence interval.

<sup>\*</sup> Data presented as geometric mean ratios (90% confidence interval).

Appears This Way  
On Original

Table 4.4.3.D. Effect of ABT-335 or Fenofibrate on Pharmacokinetic Parameters of Co-Administered Statins

Study Drugs	Analyte(s)	Point Estimate <sup>S</sup> (90% Confidence Interval)		Study
		C <sub>max</sub>	AUC	
ABT-335 and Rosuvastatin	Rosuvastatin	1.196 (1.119 - 1.273)	1.058 (0.998 - 1.121)	Study M06-811
Fenofibrate and Atorvastatin	Atorvastatin	1.000 (0.85 - 1.18)	0.830 (0.74 - 0.93)	K178P0201KH (Fommar, K178P0201KH)
Fenofibrate and Pravastatin	Pravastatin	1.130 (0.854 - 1.496)*	1.129 (0.912 - 1.397)*	M98-898 (R&D/98/595)
	3α-Hydroxy-iso-pravastatin	1.291 (1.033 - 1.613)*	1.264 (1.019 - 1.568)*	
	Pravastatin	1.360 (1.108 - 1.670)	1.277 (1.092 - 1.493)	M02-514 (R&D/03/207)
Fenofibrate and Fluvastatin	3α-Hydroxy-iso-pravastatin	1.546 (1.290 - 1.853)	1.389 (1.195 - 1.613)	
	(-)-3R, 5S-Fluvastatin	1.160 (0.974 - 1.378)	1.150 (1.052 - 1.248)	M02-525 (R&D/04/062)
Fenofibrate and Simvastatin	Simvastatin Acid	0.89 (0.79 - 1.02)	0.64 (0.58 - 0.70)	Bergman, et al., 2004
	Simvastatin	0.83 (0.64 - 1.08)	0.89 (0.78 - 1.01)	(Bergman AJ, 2004)
	Active HMG-CoA Inhibitors	0.99 (0.86 - 1.14)	0.88 (0.80 - 0.99)	
	Total HMG-CoA Inhibitors	0.90 (0.72 - 1.11)	0.92 (0.82 - 1.03)	

<sup>S</sup> Point estimates (90% confidence interval) comparing the central values of fenofibric acid pharmacokinetic parameters after the co-administration with statins to that after ABT-335 or fenofibrate administered alone.

\* Data presented as geometric mean ratios (90% confidence interval).

**Comment:** This reviewer agrees that the changes in statin exposure with concomitant ABT-335 for rosuvastatin, atorvastatin, and simvastatin are unlikely to be clinically significant given that these combinations have been tested in the Phase 3 studies and shown to be safe and effective at the studied doses. The increase in pravastatin exposure (parent and metabolite 13-38% depending on the study) is unlikely to be clinically relevant, particularly since the highest statin dose in combination with Trilipix will be contraindicated.

### Omeprazole

Study M06-804 was conducted under the ABT-335 IND 70,345 to assess the interaction between ABT-335 and omeprazole. This study showed that administered with or without a meal, the co-administration of ABT-335 with omeprazole had no significant effect on fenofibric acid pharmacokinetics. In the presence of omeprazole, a high-fat meal slightly decreased fenofibric acid C<sub>max</sub> by 16%, but had no significant effect on its AUC.

### *Intrinsic Factors*

Pharmacokinetics by age group, gender, race, and renal function are discussed under the Clinical Safety Sections 7.5.3 and 7.5.4.

### Body weight

Body weight appears to have no effect on fenofibric acid AUC over the range of 52 to 106 kg. The  $C_{max}$  shows an increasing trend with decreasing body weight.

### Hepatic impairment

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency after oral administration of fenofibrate or ABT-335. The sponsor notes that because neither ABT-335 nor fenofibric acid undergoes oxidative metabolism to a significant amount and because renal excretion is the dominant elimination pathway, impaired hepatic function is not expected to have significant effects on ABT-335 pharmacokinetics.

**Comment:** Given the potential for hepatic toxicity with ABT-335, this reviewer agrees that its use should be avoided in patients with hepatic insufficiency.

## 5 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

### 5.1 Tables of Clinical Studies

Table 5.1.A. Phase 1 Studies

Trial	Design	N	Dose/Duration
M06-831	BA: OL, crossover	75	ABT-335 135 mg Single dose
K LF178P 03 03 KH	BA: OL	20	130 mg fenofibric acid as Nano Crystal® dispersion suspension or via site-specific Esterion™ capsule; oral 50 mg fenofibric acid (1 mL/min IV x 10 min) 145 mg fenofibrate nanoparticle tablet; oral Single dose
M04-712	BA: OL, crossover	42	Fenofibrate 200 mg Fenofibric acid choline salt capsule (2 formulations) 130 mg Single dose
M04-715	BA: OL, crossover	42	Fenofibrate 200 mg Fenofibric acid (2 formulations) 130 mg Single dose
M03-636	BA: OL, partial-crossover	48	Fenofibrate 200 mg Fenofibric acid (2 formulations) 130 mg Single dose
M03-732	BA: OL, crossover	40	Fenofibrate 200 mg Fenofibric acid choline salt capsule (3 formulations) 135 mg Single dose
M03-743	BA: OL, crossover	24	Fenofibrate 200 mg

Trial	Design	N	Dose/Duration
			Fenofibric acid 135 mg Single dose
M05-801	BA: OL, crossover	24	Fenofibrate 200 mg Fenofibric acid 135 mg Single dose
M06-830	BE: OL, crossover	65	Fenofibrate 200 mg Fenofibric acid 135 mg Single dose
M06-886	BE: OL, crossover	42	ABT-335 135 mg (2 facilities) Single dose
M05-737	IVIVC: OL, crossover	24	Fenofibric acid neat drug in capsule 135 mg Fenofibric acid choline salt (3 formulations) 135 mg Single dose
M02-313	PK: DB, placebo- controlled	20	Fenofibric acid neat drug in capsules 50 mg Fenofibric acid neat drug in capsules 100 mg Single dose
M06-804	DDI: OL, crossover	36	Single dose ABT-335 135 mg Multiple dose omeprazole 40 mg x 5 d
M06-811	DDI: OL, crossover	18	135 mg ABT-335 x 10 d 40 mg rosuvastatin x 10 d

Table 5.1.B. Phase 3 Studies

Trial	Design	Dose	N	Duration
M05-748	Randomized, double-blind, active controlled	135 mg ABT-335 QD 10 mg rosuvastatin QD 20 mg rosuvastatin QD 40 mg rosuvastatin QD 135 mg ABT-335 + 10 mg rosuvastatin QD 135 mg ABT-335 + 20 mg rosuvastatin QD	1445	12 weeks
M05-749	Randomized, double-blind, active controlled	135 mg ABT-335 QD 20 mg simvastatin QD 40 mg simvastatin QD 80 mg simvastatin QD 135 mg ABT-335 + 20 mg simvastatin QD 135 mg ABT-335 + 40 mg simvastatin QD	657	12 weeks
M05-750	Randomized, double-blind, active controlled	135 mg ABT-335 QD 20 mg atorvastatin QD 40 mg atorvastatin QD 80 mg atorvastatin QD 135 mg ABT-335 + 20 mg atorvastatin QD 135 mg ABT-335 + 40 mg atorvastatin QD	613	12 weeks
M05-758	Open-label	135 mg ABT-335 + statin (20 mg rosuvastatin or 40 mg simvastatin or 40 mg atorvastatin) QD	1911	52 weeks

## 5.2 Review Strategy

The efficacy review focused on the clinical studies, M05-748, M05-749, and M05-750, which were 12-week randomized, controlled studies assessing the primary and secondary efficacy measures. The 52-week extension study, M05-758, in which subjects who completed the 12-week studies were eligible to continue taking ABT-335 + the moderate-dose of statin from their

respective clinical trial, was evaluated for durability of response and for the results of the primary and secondary efficacy variable changes in those who were switched from statin and ABT-335 monotherapy to the moderate-dose statin combination therapy.

The safety review primarily focused on the adverse events and laboratory data from the three controlled trials and the extension trial. The 4-month safety update included updated safety data from the ongoing extension trial and two smaller ongoing trials. The update was reviewed separately. The Phase 1 trials were evaluated for any deaths, serious adverse events, and AEs leading to discontinuation. Literature and postmarketing data describing fenofibrate and statin co-administration were reviewed where available.

All data are reviewed in Sections 6 and 7; that is, individual study data are incorporated into the integrated reviews of efficacy and safety.

### **5.3 Discussion of Individual Studies**

The three controlled studies in this NDA (M05-748, -749, and -750) had essentially the same design and all fed into the open-label extension study. Therefore, the results of all three studies are discussed together in Sections 6 and 7.

## **6 INTEGRATED REVIEW OF EFFICACY**

### **Summary of Efficacy Results and Conclusions**

The primary efficacy comparisons of combination therapy (ABT-335 + statin) vs. statin monotherapy for HDL-C and TG and combination therapy vs. ABT-335 for LDL-C were statistically significant in all three 12-week randomized controlled trials. Mean percent changes among the statin and combination groups varied by study due to differential effects of the studied statins. In general, rosuvastatin demonstrated greater lipid changes than simvastatin or atorvastatin as monotherapy and in combination with ABT-335.

The results from the three controlled trials are summarized as follows:

Appears This Way  
On Original

Table 6.A. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C (Controlled Studies Analysis Set)

	ABT-335 (N=490)	Low-dose statin (N=493)	ABT-335 + Low-dose statin (N=490)	p-value	Moderate- dose statin (N=491)	ABT-335 + Moderate- dose statin (N=489)	p-value	High-dose statin (N=245)
<b>HDL-C</b>	(N=420)	(N=455)	(N=423)		(N=430)	(N=422)		(N=217)
BL mean	38.4	38.4	38.2		38.4	38.1		38.0
Final mean	44.3	40.7	44.8		41.1	44.3		40.6
Mean % Δ	16.3%	7.4%	18.1%	< 0.001 <sup>a</sup>	8.7%	17.5%	< 0.001 <sup>a</sup>	7.9%
<b>TG</b>	(N=459)	(N=477)	(N=470)		(N=472)	(N=462)		(N=235)
BL mean	280.7	286.1	282.1		287.9	286.1		282.5
Final mean	177.3	217.6	146.7		202.5	147.5		196.1
Mean % Δ	-31.0%	-16.8%	-43.9%	< 0.001 <sup>a</sup>	-23.7%	-42.0%	< 0.001 <sup>a</sup>	-29.1%
<b>LDL-C</b>	(N=427)	(N=463)	(N=436)		(N=439)	(N=434)		(N=225)
BL mean	158.4	153.8	155.7		158.0	156.4		156.1
Final mean	146.1	109.6	101.9		91.6	99.1		81.7
Mean % Δ	-5.1%	-33.9%	-33.1%	< 0.001 <sup>b</sup>	-40.6%	-34.6%	< 0.001 <sup>b</sup>	-47.1%

a. ABT-335 in combination with statin vs. corresponding statin monotherapy

b. ABT-335 in combination with statin vs. ABT-335 monotherapy

Based on these findings, it is difficult to support the use of ABT-335 as monotherapy for LDL-C lowering. LDL-lowering with ABT-335 is less than has historically been seen in fenofibrate trials, although baseline LDL-C was lower and TG was higher than was seen in the studies described in the Tricor label. The sponsor has demonstrated bioequivalence of ABT-335 with fenofibrate, and it seems likely, given the inverse relationship between baseline TG and LDL-lowering (internal data review) that the inclusion of patients with higher baseline TG is the likely cause for the discrepancy with results in Tricor labeling. However, this hypothesis is conjecture without a direct head-to-head study. The LDL-C results obtained in these studies are described in ABT-335 labeling.

The lipid results (LDL-lowering) confirm the usefulness of the statin as first-line paradigm, particularly with the known cardiovascular benefits statins provide. ABT-335 is effective as add-on therapy to statins to improve TG-lowering and HDL-raising.

Of note, subgroup analyses suggest that patients with high TG might experience a *worsening* of LDL-C on ABT-335, even with combination therapy (this is a described effect of fenofibrate<sup>10</sup>). Therefore, careful thought should be given to the rationale for treatment: if primarily for LDL-C lowering and cardiovascular prevention, statins should take precedence. Patients at risk for pancreatitis because of severe hypertriglyceridemia could benefit from ABT-335 as monotherapy.

In essence, combination therapy improves TG and HDL-C over that of statin monotherapy, with the potential for some decrease in LDL-C efficacy. Therefore, the lipid targets should be defined

10 Tricor package insert.

for each patient individually, with the lipid profile monitored according to NCEP guidelines for those started on combination therapy.

The following table describes the results of the analyses of secondary endpoints:

Table 6.B. Mean Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, ApoB, and hsCRP (Controlled Studies Analysis Set)

Primary Endpoints	ABT-335 +				ABT-335 +			
	ABT-335 (N=490)	Low-dose statin (N=493)	low-dose statin (N=490)	p-value	Moderate-dose statin (N=491)	moderate-dose statin (N=489)	p-value	High-dose statin (N=245)
<b>Non-HDL-C</b>	(N=420)	(N=454)	(N=422)		(N=431)	(N=420)		(N=217)
BL mean	222.5	217.6	219.9		222.4	218.9		220.2
Final mean	181.4	140.9	129.7	< 0.001 <sup>a</sup>	127.0	125.7	< 0.001 <sup>a</sup>	115.5
Mean % Δ	-17.3%	-34.9%	-40.4%	< 0.001 <sup>b</sup>	-42.4%	-42.0%	0.710 <sup>b</sup>	-47.3%
<b>VLDL-C</b>	(N=449)	(N=463)	(N=455)		(N=458)	(N=449)		(N=232)
BL mean	65.0	66.0	65.5		67.8	64.5		66.1
Final mean	38.1	40.2	28.4	< 0.001 <sup>b</sup>	36.7	26.8	< 0.001 <sup>b</sup>	33.6
Mean % Δ	-34.2%	-32.1%	-50.0%	< 0.001 <sup>b</sup>	-38.9%	-51.2%	< 0.001 <sup>b</sup>	-42.1%
<b>Total-C</b>	(N=459)	(N=477)	(N=469)		(N=472)	(N=462)		(N=235)
BL mean	260.9	257.0	258.6		261.3	257.3		258.5
Final mean	225.8	182.4	175.4	0.001 <sup>b</sup>	168.2	170.3	0.093 <sup>b</sup>	155.8
Mean % Δ	-12.4%	-28.7%	-31.5%	0.001 <sup>b</sup>	-34.7%	-33.3%	0.093 <sup>b</sup>	-39.5%
<b>ApoB</b>	(N=455)	(N=470)	(N=465)		(N=468)	(N=455)		(N=229)
BL mean	146.2	145.0	146.1		147.1	145.0		146.0
Final mean	122.1	99.1	92.0	< 0.001 <sup>b</sup>	91.6	90.7	0.817 <sup>b</sup>	83.6
Mean % Δ	-15.6%	-31.1%	-36.3%	< 0.001 <sup>b</sup>	-36.9%	-36.7%	0.817 <sup>b</sup>	-42.4%
<b>hsCRP</b>	(N=457)	(N=471)	(N=467)		(N=470)	(N=457)		(N=231)
BL mean	0.52	0.47	0.53		0.58	0.59		0.48
Final mean	0.53	0.37	0.41	0.603 <sup>b</sup>	0.40	0.33	0.622 <sup>b</sup>	0.34
Mean % Δ	87.4%	24.0%	13.0%	0.603 <sup>b</sup>	7.8%	-2.7%	0.622 <sup>b</sup>	0.1%

a. ABT-335 in combination with statin vs. ABT-335 monotherapy

b. ABT-335 in combination with statin vs. corresponding statin monotherapy

Although the NCEP guidelines state that non-HDL-C should be the lipid target once LDL-C goals are met in the setting of high TG, the data from these three studies suggest that combination therapy does not necessarily improve non-HDL-C as compared to increasing the statin monotherapy dose. Combination therapy is beneficial for reducing TG beyond statin monotherapy. Ultimately, the decision to add-on additional therapy should be based on the lipid goals for an individual patient.

In subjects who had ABT-335 added after an initial 12-week treatment with a moderate-dose statin (Initial Moderate Dose Statin Analysis Set), there was a mean percent increase in LDL-C of 10.4% to a mean value of 100.0 mg/dL after 12-weeks of combination therapy. However, there was also an additional mean percent decrease in TG (-22.2%), non-HDL-C (-1.5%), ApoB (-5.0%), and VLDL-C (-19.3%), and a mean percent increase in HDL-C (+6.8%).

A combination therapy indication should be granted with the implication that a statin is first-line therapy for LDL-lowering and that the cardiovascular benefit of combination therapy is unknown. ABT-335 can be added when additional TG-lowering/HDL-raising is needed. ABT-335 monotherapy should be reserved for use in patients with hypercholesterolemia or mixed dyslipidemia who are statin-intolerant, or in those with severe hypertriglyceridemia.

### **6.1 Proposed Indication**

TRILIPIX is a peroxisome proliferator receptor alpha (PPAR $\alpha$ ) activator that is indicated as adjunctive therapy to diet:

- when co-administered with an HMG-CoA reductase inhibitor to reduce elevated triglycerides, LDL-C, non-HDL-C, VLDL-C, Apo B, and Total-C, and to increase HDL-C in adult patients with mixed/atherogenic dyslipidemia (Fredrickson Type IIb).
- to reduce elevated LDL-C, Total-C, triglycerides, and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb).
- to treat patients with hypertriglyceridemia (Fredrickson Types IV and V).

#### **6.1.2 Methods/Study Design**

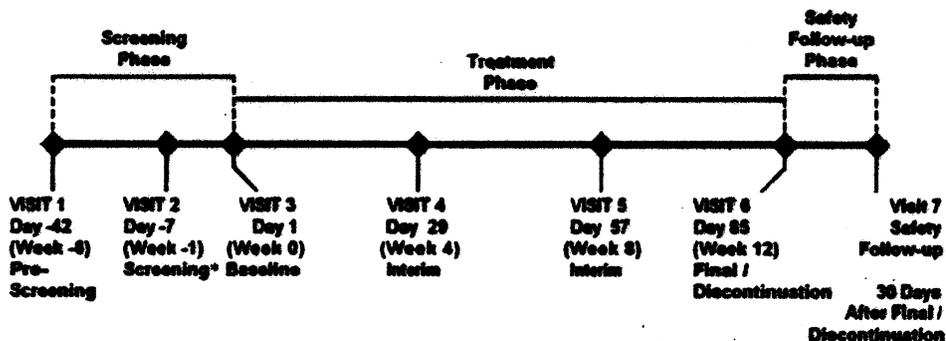
Three double-blind, controlled Phase 3 studies (M05-748, M05-749, and M05-750) and one long-term, open-label extension study (M05-758) were conducted in support of the proposed indication. The study design of the controlled trials was reviewed under a Special Protocol Assessment (SPA), dated September 12, 2005. Selected information conveyed in the SPA is presented under Section 2.5 of this review.

The three double-blind studies had similar designs, differing primarily in the statin used for combination therapy/monotherapy, excluded concomitant medications, and the number of subjects. All were multi-center, randomized, double-blind, prospective, comparative studies in mixed dyslipidemic adults (Fredrickson Type IIb) conducted at sites in the United States, Canada, and Puerto Rico. All studies assessed the efficacy and safety of once daily treatment with ABT-335 (equivalent to 135 mg fenofibric acid) in combination with either a low or a moderate dose of a statin compared to ABT-335 monotherapy and statin monotherapy on the primary lipid parameters associated with increased risk of CHD in a population of subjects with mixed dyslipidemia. The statins in the three Phase 3 studies were rosuvastatin calcium (equivalent to 10 mg, 20 mg, and 40 mg rosuvastatin) in Study M05-748, simvastatin (20 mg, 40 mg, and 80 mg) in Study M05-749, and atorvastatin calcium (equivalent to 20 mg, 40 mg, and 80 mg atorvastatin) in Study M05-750.

Planned enrollment in Study M05-748 was approximately 1,250 subjects at approximately 250 sites; planned enrollment in Study M05-749 and Study M05-750 was approximately 560 subjects at approximately 115 sites in each study.

The planned duration of each double-blind study was approximately 22 weeks, consisting of a 42-day diet run-in/hypolipidemic washout period (Screening Period), a 12-week Treatment Period, and a 30-day Safety Follow-up Period (only if not entering the open-label safety extension study). The schematic of the controlled studies is presented below:

Figure 6.1.2.A. Schematic of Study Timeline, Controlled Studies



\* An optional second Screening Visit (Visit 2.1) may be necessary for subjects who are within 30% of the lab cut off criteria for a specific laboratory parameter(s).

### Screening Phase

Forty-two (42) days or more prior to the Baseline Visit at the Pre-screening Visit (Visit 1, Day -42), subjects received an explanation of the study, provided written informed consent, had a blood sample drawn for a lipid profile, and began the diet run-in/hypolipidemic washout period (Screening Phase). During this phase, subjects stopped any existing hypolipidemic therapy and received instruction on and start to follow the diet recommended by the American Heart Association (AHA).

At Visit 2, Day -7 ( $\pm 3$  days) prior to the Day 1/Baseline Visit and during the diet run-in/hypolipidemic washout period, each subject's fasting lipid profile was obtained to determine eligibility. Subjects that did not meet all the laboratory eligibility criteria, but were within 30% of the lab cut-off value (or at the principal investigator's discretion) could return for an optional second Screening Visit within one week from the original Screening Visit date, which could extend the screening period beyond 42 days (but was not considered a protocol deviation). During this visit subjects had blood only re-drawn for the specific laboratory parameter(s).

Enrollment criteria are as follows, and taken from the Study M05-748 protocol (that of M05-749 and M05-750 were similar):

### Inclusion Criteria

1. Subject or their legally authorized representative has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject has had the opportunity to ask questions and receive answers. The informed consent must be signed at the Pre-screening Visit, prior to the performance of any study-specific procedure.
2. Subject is  $\geq 18$  years of age and any gender at the time of the Pre-screening Visit.
3. Subjects must have the following fasting lipid results following  $\geq 12$  hour fasting period before the Baseline Visit (measured at the Screening Visit):