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*APPLICATION NUMBER:*

**22-224**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

9/26/08

### ONDQA BIOPHARMACEUTICS REVIEW

NDA Number, submission date and related submission dates	NDA 022-224, December 7, 2007 June 23 2008, September 2008
Sponsor	Abbott Laboratories, Abbott Park, IL
Product name, generic name, dosage form and strength	TriLipix® (fenofibric acid) Delayed-Release Capsules, choline fenofibrate oral extended release capsules, 45-mg and 135-mg
Clinical Division	Division of Metabolism and Endocrinology Products
Primary Quality Reviewer	Yvonne Yang, Ph.D.
Biopharmaceutics Reviewer	Arzu Selen, Ph.D.

### EXECUTIVE SUMMARY AND RECOMMENDATION

The Sponsor is submitting this NDA as a 505(b)(2) application for TriLipix® (fenofibric acid Delayed-Release Capsules) containing 45 mg or 135 mg fenofibric acid as choline salt (ABT-335: choline fenofibrate). The reference listed drug for this application is fenofibrate (TriCor® oral tablets); also manufactured by Abbott in 48 mg and 145 mg strengths. The TriCor NDA (NDA 21-656) was approved in November 2004 for fenofibrate tablets with an indication for the treatment of hypertriglyceridemia, hypercholesterolemia and mixed dyslipidemia.

To improve solubility of fenofibrate and thereby, enhance its absorption, and to reduce the effect of food on its bioavailability, fenofibrate formulations have undergone significant changes since the approval of the original dosage form. The first dosage form, non-micronized 100 mg fenofibrate hard gelatin capsule (NDA 19-304, Lipidil®, Fournier Res. Inc.) was approved in 1993. The highest approved dose was 300 mg. A subsequent improvement was development of the micronized fenofibrate capsules (containing 67 mg micronized fenofibrate) followed by additional micronized fenofibrate capsule strengths (134 mg and 200 mg). The micronized fenofibrate capsules were introduced under the trade name of TriCor and the highest approved micronized fenofibrate capsule formulation was 200 mg. This was followed by development of a tablet formulation containing 54 mg or 160 mg of fenofibrate (NDA 21-203). The approved labeling of these fenofibrate formulations instructed that fenofibrate should be taken with food to maximize its oral absorption, as fenofibric acid exposure was shown to be 35% higher based on AUC (area under plasma fenofibric acid concentration-time curve) under fed conditions compared to that under fasted conditions. The next fenofibrate NDA (NDA 21-656) was approved in 2004 for the currently marketed 48 mg or 145 mg of fenofibrate tablets developed using NanoCrystal technology. The exposure to fenofibric acid from the new nanocrystal formulation is not increased by food. The labeling states that exposure to fenofibric acid in plasma is not significantly different when a single 145 mg dose of fenofibrate is administered under fed or fasting conditions. Furthermore, it is also stated in the label that following administration of TriCor tablets, three 48 mg or one 145 mg tablets, fenofibric acid exposure is equivalent to that from TriCor 200-mg micronized fenofibrate capsules when given with a low fat meal.

Following approval of the nanocrystal fenofibrate tablets (48-mg and 145-mg strengths), the Sponsor discontinued manufacture of the previous 54 mg and 160 mg micronized

TriCor tablets, and the trade name remained the same for the nanocrystal tablets. Although Abbott has discontinued manufacturing micronized fenofibrate tablets, there are other companies (such as Oscient, Teva and Impax) manufacturing micronized fenofibrate capsules.

In this submission, choline salt of fenofibric acid (ABT-335: choline fenofibrate), is formulated as 45-mg and 135-mg capsules with improved bioavailability compared to the previous fenofibrate formulations. Fenofibric acid, active metabolite of fenofibrate, has higher aqueous solubility than fenofibrate at alkaline pH, and has high permeability. As a result, it is likely to be more readily absorbed than fenofibrate and its absorption should be less affected by food.

The proposed to be marketed formulation of ABT-335 consists of enteric-coated, modified-release mini-tablets filled into a capsule shell.

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Please see Dr. Yvonne Yang's Quality review for full CMC assessment of this product. This Biopharmaceutics Review is specific for determining whether the requested biowaiver may be granted for the lower strength (45-mg) of the choline fenofibrate capsules.

#### **Biowaiver for the 45-mg strength:**

The pre-NDA Meeting (7/20/2007) minutes reflect the discussion regarding the biowaiver that may apply for the low dose 45-mg capsules and the Sponsor's reference to the 2003 FDA guidance to support their biowaiver request. In the following section from the minutes of this meeting, it is evident that the areas of focus for the review were identified as information characterizing the product (dissolution, composition similarity and proportionality) and linearity in drug PK.

*Biopivalence Studies for Orally Administered Drug Products — General Considerations (March 2003)*, Abbott believes that the *in vivo* bioequivalency requirement for the 45 mg strength can be waived based on the *in vitro* dissolution data generated using the recommended dissolution method. Further information is provided in Section 13.0 of this Information Package.

**Does the Agency agree that a Biowaiver can be granted for the 45 mg dose strength of ABT-335?**

*Agency Response: A waiver of the *in vivo* bioequivalency requirement for the 45 mg strength dose is based on the following:*

- composition similarity and proportionality*
- data to demonstrate linear PK*
- in vitro dissolution data*

*Meeting Discussion: The firm said that this information would be provided from cross study comparison and historical information from early development formulations. The agency said this was acceptable.*

The rationale for requesting data to show pharmacokinetic linearity for the 45-mg low dose capsule formulation is unclear, and is not consistent with the principles outlined in the Guidance referenced above. Linearity in pharmacokinetics becomes a consideration when the proposed dose is higher than the highest strength. In this case, this should not have been a concern for supporting the low dose (45-mg strength) capsules.

The FDA request at the pre-NDA meeting may be due to a general interest for a broader review of the submitted fenofibrate information. The data for pharmacokinetic non-linearity for the lower dose strength can not be a specific requirement for the biowaiver assessment for the lower strength.

The Clinical Pharmacology Team indicated in their review (9/23/2008) that there is insufficient data to comment on dose proportionality/pharmacokinetic linearity over the 45-mg to 135-mg dose range (page 18).

For completeness of this review, pharmacokinetic linearity for the 45-mg dose is addressed in detail in the review section of this document. Briefly, the Sponsor has submitted data obtained following administration of neat 50-mg and 100-mg fenofibric acid doses and has established linearity in fenofibric acid pharmacokinetics over the doses studied (as also confirmed by the clinical pharmacology review). The Sponsor has also included data from multiple studies to provide information on linearity of fenofibric acid pharmacokinetics. Based on all submitted information including that fenofibric acid metabolism does not involve a complex scheme and is mainly by glucuronidation, additional data to support fenofibric acid linearity at 45-mg dose is not scientifically necessary.

The following points support granting the biowaiver requested by the Sponsor for the 45-mg strength capsules:

- 1) The same formulation is used for the 45-mg and the 135-mg capsules, the difference between the two capsule strengths is in the difference of number of enteric-coated, modified-release (MR) mini-tablets filled into a capsule shell (there are ~~mini-tablets and~~ mini-tablets for the 45-mg and 135-mg capsules, respectively).
- 2) In vitro dissolution profiles are superimposable for the two strengths
- 3) The high strength (135-mg capsule) is well-characterized.

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These points are consistent with the following section in the FDA Guidance "Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations", March 2003.

"Waiver of in vivo studies for different strengths of a drug product can be granted under § 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is *proportionally similar* in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate in vivo study; and (3) the new strength meets an appropriate in vitro dissolution test."

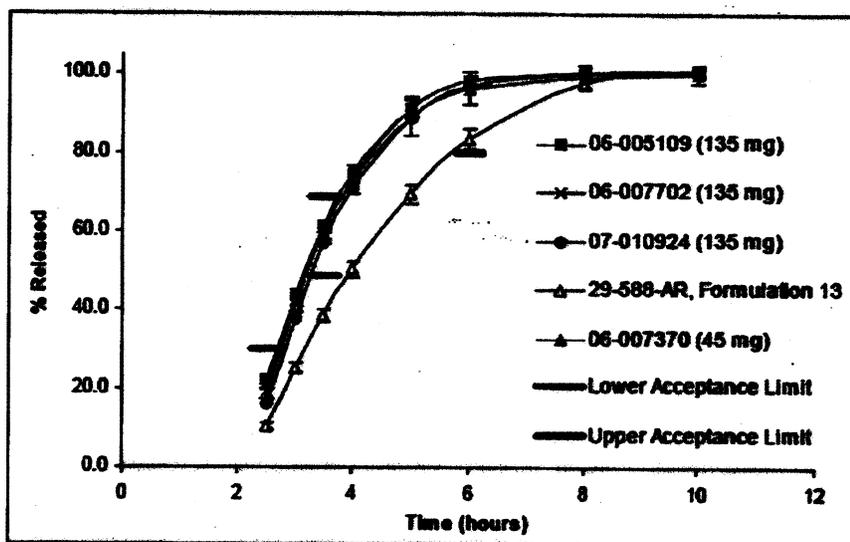
The Sponsor has provided in vitro dissolution/release data collected with acid stage testing carried out at pH 1 and pH 3.5. Of the two approaches, in past and recent communications, the Agency and the Sponsor have agreed that the dissolution/release testing is more informative with acid stage testing at pH 3.5. In the remainder of this

review, mainly data generated with acid stage testing at pH 3.5 are presented and discussed.

In the following figure (Figure 1), similarity in the in vitro release profile from 135-mg and 45-mg capsule dosage form is further illustrated. This figure also contains the dissolution/release profile from Formulation 13 which was studied for exploring IVVC relationships.

Figure 1

Figure 1. Drug Release Profiles of Choline Fenofibrate Capsule Formulations Evaluated During Development



With this dissolution method, the Sponsor is proposing the dissolution upper and lower boundaries as displayed in Figure 1. Please see Dr. Yang's review for the final in vitro dissolution/release specification for this product.

As presented above, the Sponsor has provided adequate data to support their biowaiver request for the low strength, 45-mg TriLipix capsules.

**In-Vitro and In-Vivo Correlation Efforts:**

37 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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BIOPHARMACEUTICS

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**CLINICAL PHARMACOLOGY REVIEW**

NDA: 22-224	Submission Date(s): 12/07/2007
Brand Name	TRILIPIX™
Generic Name	Fenofibric Acid Choline Salt (ABT-335)
Reviewer	Manoj Khurana, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolic and Endocrine Products
Sponsor	Abbott Laboratories
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Encapsulated enteric coated extended release mini-tablets; Encapsulate <sup>d</sup> mini-tablets containing fenofibric acid choline salt equivalent to 45 mg fenofibric acid Encapsulate <sup>d</sup> mini-tablets containing fenofibric acid choline salt equivalent to 135 mg fenofibric acid
Proposed Indication	Treatment of dyslipidemia (mixed dyslipidemia [in combination with HMG-CoA reductase inhibitors (statins), or as monotherapy], primary hypercholesterolemia [as monotherapy], or hypertriglyceridemia [as monotherapy])

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## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted in support of approval of 135 mg strength Trilipix™ (Fenofibric acid choline salt) formulation under NDA 22-224 submitted on December 07, 2007. NDA-22-224 is acceptable provided that the Agency and the Sponsor agree on the labeling. The biowaiver assessment for the 45 mg strength formulation is deferred to the Office of New Drug Quality Assessment (ONDQA).

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology Findings

Abbott Laboratories is seeking an approval of Trilipix™ (ABT-335; fenofibric acid choline salt) capsule for the treatment of dyslipidemia. The proposed indications are dyslipidemia (mixed dyslipidemia [in combination with HMG-CoA reductase inhibitors (statins), or as monotherapy], primary hypercholesterolemia [as monotherapy], or hypertriglycerdemia [as monotherapy]).

ABT-335 formulation for oral use has been manufactured at two dose strengths that contain ABT-335 equivalent to 45 mg and 135 mg fenofibric acid. The formulation is comprised of a capsule that contains multiple mini-tablets. Each compositionally identical mini-tablet contains a hypromellose (HPMC) matrix to extend the release of ABT-335, and has an enteric coating to prevent the release of ABT-335 in the acidic environment in the stomach. The 135 mg strength contains 3 mini-tablets, whereas the 45 mg strength contains 1 mini-tablet. In this application, the 135 mg ABT-335 capsule was used in all the clinical studies. Abbott is requesting a biowaiver for the 45 mg strength based on composition proportionality, *in vitro* drug release data, and dose proportionality in fenofibric acid pharmacokinetics. The biowaiver is being assessed by ONDQA.

Clinical pharmacology of ABT-335 under this 505(b)(2) submission (NDA 22-224) was supported with 14 clinical pharmacology studies including two bioequivalence trials, seven relative bioavailability studies for the pilot formulations conducted during the formulation development, one Phase 1 pharmacokinetic study, one definitive food effect study, two drug-drug interaction studies and one *in vitro in vivo* correlation (IVIVC) study. The sponsor referred to the mass balance study, renal impairment study, drug-interaction studies with statins, antihypertensives, and anti-diabetics conducted with the previously approved fenofibrate product, TriCor™ (NDA 21-656).

The bioequivalence was appropriately demonstrated between the to-be-marketed ABT-335 135 mg formulation (encapsulated mini-tablets) and previously approved 200 mg micronized fenofibrate reference formulation. This pivotal bioequivalence study (Study M06-830) was audited by the Division of Scientific Investigation (DSI), and the clinical study and bioanalytical study were acceptable. Please see the memo by Dr. Jacqueline O'Shaughnessy dated 09/12/2008 for details. In addition, the sponsor has demonstrated the bioequivalence between the to-be-marketed 135 mg formulation and the formulations used in Phase 3 clinical trials, and between to-be-marketed 135 mg formulation manufactured at two different sites. Dose proportionality in pharmacokinetics was demonstrated between 50 and 100 mg neat fenofibric acid doses, which did not cover the dose range submitted for approval and the ABT-335 formulation was not evaluated.

The additional assessments the sponsor presented did not demonstrate the dose-proportionality over the proposed formulation strengths of 45 and 135 mg fenofibric acid.

Single oral administration of 135 mg ABT-335 formulation in healthy subjects resulted in mean peak exposure ( $C_{max}$ ) of approximately 9  $\mu\text{g/mL}$ , which occurred at a  $T_{max}$  of around 4 hour post-dose. The total exposure ( $AUC_{0-\infty}$ ) was approximately 180  $\mu\text{g}\cdot\text{hr/mL}$  and fenofibric acid was eliminated with a half-life of about 19 hours. The apparent oral clearance ( $CL/F$ ) was 0.85 L/hour. There was no standalone evaluation of pharmacokinetics of ABT-335 in patient population as the application relied on the clinical pharmacology studies conducted with the previously approved fenofibrate products and demonstration of bioequivalence between ABT-335 formulation and the 200 mg micronized fenofibrate reference product.

Absolute bioavailability ranged between 78-90% from different regions of GI tract after oral administration of 130 mg fenofibric acid as NanoCrystal dispersion (NCD) suspension

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The total exposures were compared against those resulting from 50 mg intravenous infusion of fenofibric acid administered over 10 minutes.

There was a significant accumulation after multiple daily oral doses of 135 mg fenofibric acid and mean accumulation ratio was about 2.6, which was similar to the value, 2.3, which was reported previously after administration of fenofibrate (TriCor™ 145 mg tablets).

Following a single therapeutic dose (66  $\mu\text{Ci}$ /subject) of  $^{14}\text{C}$ -fenofibrate orally, a total of 84% of the orally administered radioactivity was recovered in 7 days with 59% of the dose being recovered in the urine and 25% being recovered in the feces. The renally recovered radioactivity was composed of free fenofibric acid (9% of total dose), fenofibric acid ester glucuronide (45%), free benzhydrol metabolite (1%) and its glucuronide (3%). Fecal metabolites were not profiled. Based on these data, Phase-2 hepatic glucuronidation and renal excretion of both conjugated and free drug appeared to be the major elimination pathway for fenofibric acid. Fenofibric acid seemed to be neither an inhibitor nor an inducer of P450s at therapeutic concentrations. Fenofibric acid was highly bound to plasma protein (99% bound).

High fat, high calorie food did not significantly affect bioavailability of 135 mg ABT-335 formulation; though the mean peak exposures were lowered by 15%. The low-fat meal lowered the mean peak exposure by 22% without impacting the total AUC. The effect of food on ABT-335 pharmacokinetics is not clinically relevant.

ABT-335 did not show clinically relevant pharmacokinetic interaction with rosuvastatin and omeprazole in the drug interaction studies conducted under the current application.

After oral administration of previously approved fenofibrate, the exposure of fenofibric acid was significantly higher in patients with severe renal impairment compared to that of healthy subjects. With very limited data in mild and moderate renally impaired patients, the reduced dose of 45 mg in these patients is an acceptable approach. The pharmacokinetics of ABT-335 was not evaluated in hepatic impaired subjects and it is acceptable contraindicating the use of Trilipix™ and fenofibrate in both severe renal impairment and hepatic impairment patients.

In conclusion, the clinical pharmacology aspects of ABT-335 at 135 mg dose strength were appropriately characterized and this NDA 22-224 is acceptable.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes

Trilipix™ is an oral formulation of ABT-335, the choline salt of fenofibric acid, for the treatment of dyslipidemia. Fenofibric acid is the active metabolite of fenofibrate, the active ingredient in currently marketed TriCor™ tablets (NDA 21-656). Since, fenofibrate is rapidly converted to fenofibric acid *in vivo*, it is fenofibric acid that is found circulating in plasma and is responsible for the clinical effect and is, therefore, the active moiety of fenofibric acid choline salt as well.

The proposed indications are:

- (1) in combination with statins as an adjunctive therapy to diet for the reduction of elevated triglycerides, LDL-C, non-HDL-C, VLDL-C, Apo B and Total-C, and to increase HDL-C in adult patients with mixed dyslipidemia (Fredrickson Type IIb), when combination therapy is appropriate,
- (2) as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, triglycerides and Apo B, and to increase HDL-C in adults with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb) and
- (3) as adjunctive therapy to diet for treatment of adults with hypertriglyceridemia (Fredrickson Types IV and V).

Historically, the original dosage form of fenofibrate developed (NDA 19-304) was a non-micronized 100 mg hard gelatin capsule, and the highest dose approved was 300 mg. As part of a formulation improvement, micronized capsule formulations containing 67 mg, 134 mg or 200 mg fenofibrate were developed (NDA 19-304/S005). A single capsule containing 67 mg of the micronized fenofibrate was bioequivalent to a non-micronized 100 mg capsule. Three capsules containing 67 mg micronized fenofibrate were bioequivalent to a single 200 mg micronized capsule. The highest dose approved for the micronized capsule formulation was 200 mg.

Subsequently, a tablet formulation containing 54 mg or 160 mg of fenofibrate was developed (NDA 21-203), which was bioequivalent to the 67 and 200 mg capsules, respectively. Most recently, the currently marketed tablet formulation (TriCor™) containing 48 mg or 145 mg of fenofibrate was developed using NanoCrystal technology (NDA 21-656). Both three 48 mg and one 145 mg tablets are bioequivalent to one 200 mg micronized capsule.

Table 1 Summary of BE assessments during fenofibrate and ABT-335 development

Non-micronized fenofibrate capsule	Micronized Capsule	Micronized Tablet	NanoCrystal Tablet	Choline salt of Fenofibric acid
			48	45
200 mg	134			
300 mg				
	200*	(67 x 3)	48 x 3	
*Reference				
**Reference				
Shaded cells indicate the BE assessments across products and doses				

Under the current application, ABT-335 capsules are developed for oral use and the to-be-marketed modified-release formulation is manufactured at two dose strengths that contain ABT-

335 equivalent to 45 mg and 135 mg fenofibric acid. The formulation is comprised of a capsule  
 Each mini-tablet contains a hypromellose (HPMC) matrix to extend the release of ABT-335, and has an enteric coating to prevent the release of ABT-335 in the acidic environment in the stomach. The composition of the mini-tablets filled into the 45 mg and 135 mg strength capsules are identical.

The 135 mg strength contain 3 mini-tablets, whereas the 45 mg strength contain 1 mini-tablet. For this application, the 135 mg ABT-335 capsule was used in all the clinical studies and biowaiver is requested for the 45 mg strength formulation.

b(4)

**2.1.1 What are the highlights of the physicochemical properties of ABT-335 as they relate to clinical pharmacology review?**

- ABT-335 is choline salt of fenofibric acid. ABT-335 has the chemical structure illustrated in Figure 1 below:

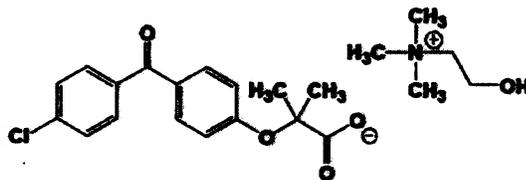
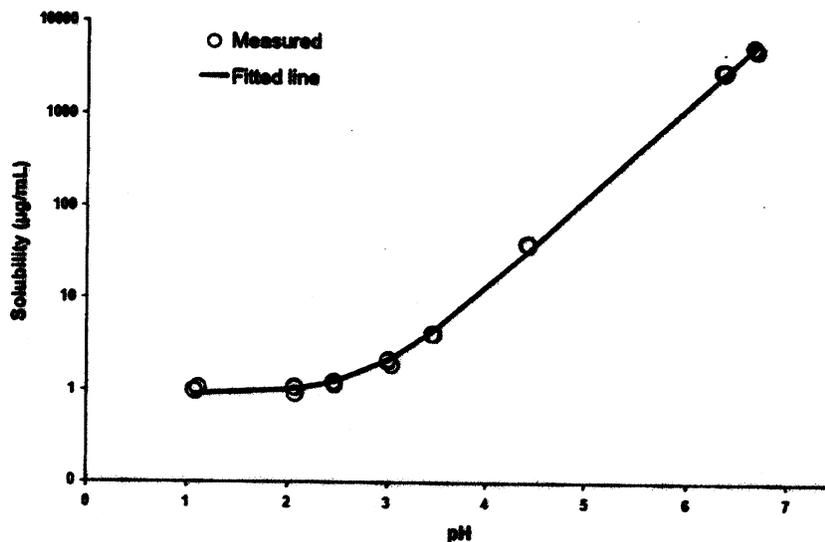


Figure 1 Chemical Structure of ABT-335.

Table 2 Physicochemical Properties of ABT-335

<b>Chemical Name</b>	2 [4-(4-chloro benzoyl) phenoxy] 2-methyl propanoic acid, (2-hydroxyethyl) trimethylammonium salt
<b>Mol. Wt. (Daltons)</b>	421.92
<b>pKa</b>	2.9
<b>Solubility in water</b>	exceeding 300 mg/mL at 25°C
<b>Physical properties</b>	crystalline solid; melting/decomposition temperature of 210.3°C

- ABT-335 (Choline salt of fenofibric acid) is freely soluble in water. Sponsor proposed that in acidic pH solutions (or at gastric pH), the choline salt will convert to the free fenofibric acid and thus the saturation solubility at equilibrium for ABT-335 is expected to follow the pH-solubility profile of fenofibric acid, but they have not presented any data to support their proposal. However, the pH-solubility profile of fenofibric acid was provided and is illustrated in Figure 2 below.



Note: Fitted line based on solubility expression for an acid with a single ionizable site

Figure 2 pH-solubility profile of fenofibric acid.

- Fenofibric acid exhibits good solubility at intestinal pH (approximately 7.8 mg/mL at pH 6.8) but low solubility at gastric pH (1.01 µg/mL at pH 1.1). The intrinsic dissolution rate of ABT-335 is exceedingly high, greater than 10 mg/min/cm<sup>2</sup> in at pH 4.5 and 6.8. At this rate, the absorption of fenofibric acid will not be dissolution rate limited.
- Fenofibric acid is a lipophilic compound with a logarithmic distribution coefficient between n-octanol and aqueous buffer at pH 7.4 (logD) value of 0.23.
- In vitro Caco-2 cell permeability measurements have shown that the absorptive (apical to basolateral) apparent permeability (P<sub>app</sub>) values over a concentration range of 200 to 800 µg/mL ranged from 35 to 97 × 10<sup>-6</sup> cm/sec at pH 7.4.

#### 2.1.2 What is the composition of to be marketed formulation of ABT-335?

Abbott developed and tested several prototype formulations in pilot clinical pharmacology studies (Study M03-636, Study M04-712, Study M04-715 and Study M05-732), which facilitated the selection and development of the to-be-marketed formulation, Formulation 10. The proposed commercial products have been manufactured at Abbott Puerto Rico Limited plant and at the Fournier Pharma facility in Ireland. The quantitative composition of the to-be-marketed ABT-335 formulations is presented in Table 3 below.

**Table 3 Quantitative Composition of To-Be-Marketed ABT-335 Capsule (Formulation 10; 45 and 135 mg Strengths)**

Component	Amount (mg/capsule)	
	45 mg Strength	135 mg Strength
<b>Mini-tablet Cores</b>		
<b>Components</b>		
Fenofibric Acid Choline Salt	100	300
Hypromellose	100	100
Povidone	100	100
water	100	100
<b>Components</b>		
Hydroxypropyl cellulose	100	100
Colloidal silicon dioxide	100	100
Sodium stearyl fumarate	100	100
<b>Methacrylic Acid Copolymer, NF</b>	100	100
Talc	100	100
Triethyl citrate	100	100
water	100	100
<b>Encapsulation</b>		
	1 Capsule shell, Gelatin, Yellow opaque body and Red opaque cap	1 Capsule shell, Gelatin, Yellow opaque body and Blue opaque cap

b(4)

\* Target amount; actual amount may vary.

b(4)

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Table 4 Composition of Choline Fenofibrate Mini-Tablet

Component	Quality Standard	Function	Amount/unit
<b>Mini-Tablet Core</b>			
_____ components			
Choline fenofibrate	DMF <sup>b</sup>		
Hypromellose	USP		
Povidone	USP		
Water, r	USP or EP		
_____ components			
Hydroxypropyl cellulose	NF		
Colloidal silicon dioxide	NF		
Sodium stearyl fumarate	NF		
Total core mini-tablet weight			
_____			
Methacrylic Acid Copolymer	USP		
Talc	USP		
Triethyl citrate	NF		
Water	USP or EP		
Total coated mini-tablet weight			

b(4)

b(4)

a Corresponds to 11.25 mg fenofibric acid.

The two ABT-335 capsule formulations differing in number of mini-tablets appeared to be compositionally proportional. However, refer to the CMC review for further details.

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Table 5 Lots of the 135 mg Strength of Formulation 10 Used in Clinical Studies in ABT-335 Development Program

b(4)

Lot*	Manufacturing Site	Batch Scale	Lot Size	Study
27-580-AR	Abbott, North Chicago, IL			<u>M05-732</u>
30-589-AR	Abbott, North Chicago, IL			<u>M05-743, M05-737</u>
05-002449	Abbott, Abbott Park, IL (GPO AP16)			<u>M06-804, M06-811, M05-801, M05-748, M05-749, M05-750</u>
05-002450	Abbott, Abbott Park, IL (GPO AP16)			<u>M05-748, M05-749, M05-750</u>
06-005109	Abbott, Abbott Park, IL (GPO AP16)			<u>M06-830</u>
05-003336, 06-004932, 06-005437, 06-005591, 06-008198, 06-008199, 06-008200, 06-008201, 06-008202	Abbott, Abbott Park, IL (GPO AP16)			<u>M05-758</u>
06-007702	Abbott Barceloneta, PR (Abbott Puerto Rico Limited)			<u>M06-830, M06-831, M06-886</u>
07-010924	Fournier Laboratories County Cork, Ireland			<u>M06-886</u>

b(4)

\* Bulk product lot numbers.

GPO = Global Pharmaceutical Operations.

AP = Abbott Park.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the basic pharmacokinetic characteristics of ABT-335?

Basic pharmacokinetics of ABT-335 after single oral administration of the to-be-marketed formulations under fasting conditions is presented in Figure 3 and summarized in Table 6 below:

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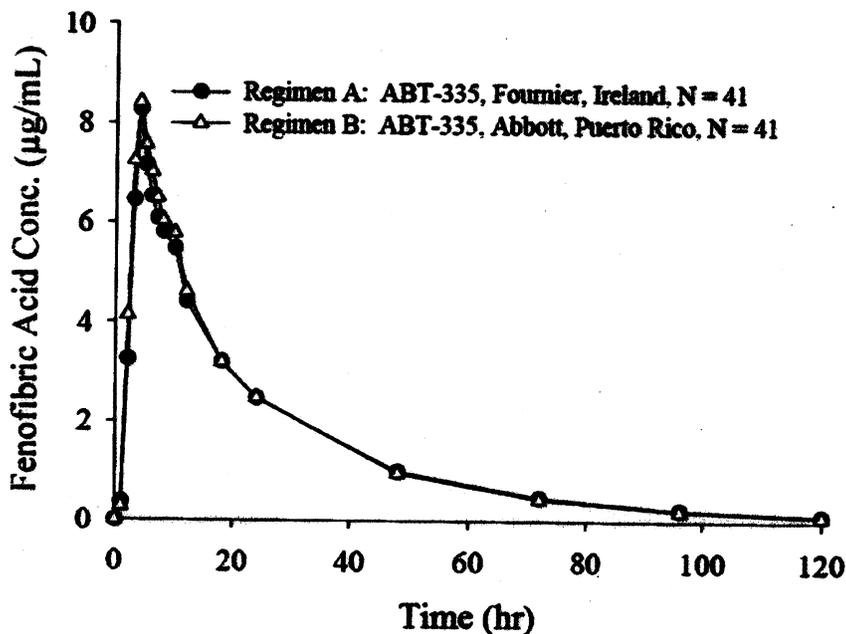


Figure 3 Mean Fenofibric Acid Plasma Concentration-Time Profile after Single Oral Administration of to-be-marketed 135 mg ABT-335 formulations from two manufacturing sites- Linear Scale.

Table 6 Mean ( $\pm$  SD) Pharmacokinetic Parameters of Fenofibric Acid after Single Oral Dose Administration of To-Be-Marketed ABT-335 Formulations from Two Different Manufacturing Sites

Pharmacokinetic Parameters (units)	Regimen <sup>‡</sup>	
	A (Test) Fournier (N = 41)	B (Reference) Abbott, Puerto Rico (N = 41)
T <sub>max</sub> (h)	4.1 $\pm$ 1.4	4.2 $\pm$ 1.6
C <sub>max</sub> ( $\mu$ g/mL)	8.897 $\pm$ 2.205	9.129 $\pm$ 1.646
AUC <sub>t</sub> ( $\mu$ g $\cdot$ h/mL)	174.0 $\pm$ 68.4	176.2 $\pm$ 58.4
AUC <sub><math>\infty</math></sub> ( $\mu$ g $\cdot$ h/mL)	173.8 $\pm$ 72.5	179.9 $\pm$ 61.9
t <sub>1/2</sub> <sup>‡</sup> (h)	20.62 $\pm$ 5.59 <sup>*</sup>	19.38 $\pm$ 5.38
CL/F <sup>†</sup> (L/h)	0.85 $\pm$ 0.27	0.82 $\pm$ 0.22

<sup>‡</sup> Both regimens were administered as one capsule containing ABT-335 equivalent to 135 mg fenofibric acid under fasting conditions. Regimen A was manufactured at Fournier, Ireland; Regimen B was manufactured at Abbott, Puerto Rico.

<sup>\*</sup> Statistically significantly different from reference Regimen B (ANOVA,  $p < 0.05$ ).

<sup>‡</sup> Harmonic mean = pseudo standard deviation: evaluations of t<sub>1/2</sub> were based on statistical tests for  $\lambda_2$ .

<sup>†</sup> Parameter was not tested statistically.

Administration of 135 mg ABT-335 formulation resulted in mean peak exposure of about 9  $\mu\text{g/mL}$ , which occurred at 4 hour post-dose. The total exposure ( $\text{AUC}_{0-\infty}$ ) was approximately 180  $\mu\text{g}\cdot\text{hr/mL}$  and elimination half-life was 20 hours. The apparent oral clearance was 0.8 L/hr.

The pharmacokinetics of ABT-335 (fenofibric acid choline salt) given as immediate release formulation has not been evaluated. However, pharmacokinetics of fenofibric acid given as immediate release formulation was available from Study M05-737, which was actually conducted to explore potential correlations between in vitro drug release and in vivo performance. The study evaluated pharmacokinetics of fenofibric acid given as one IR capsule containing 135 mg fenofibric acid and other developmental formulations of ABT-335.

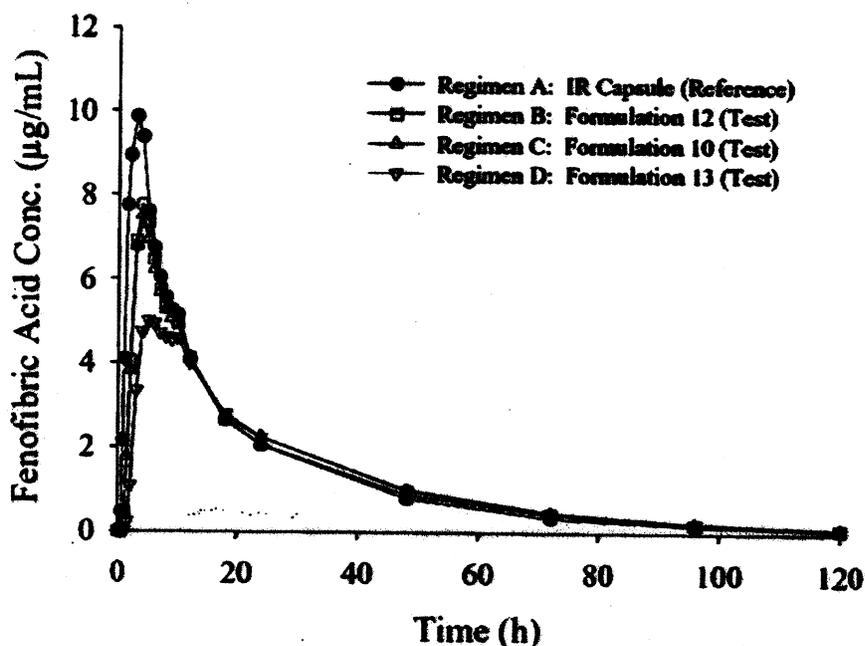


Figure 4 Mean Fenofibric Acid Plasma Concentration-Time Profile after Single Oral Administration of Different Formulations- Linear Scale.

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Table 7 Mean (SD) Pharmacokinetic Parameters of Fenofibric Acid from Different Formulations

Pharmacokinetic Parameters (units)	Regimens <sup>#</sup>			
	Reference	Test		
	A	B	C	D
	Fenofibric Acid Immediate-release (N = 24)	Fenofibric Acid Choline Salt Formulation 12 (N = 24)	Fenofibric Acid Choline Salt Formulation 10 (N = 24)	Fenofibric Acid Choline Salt Formulation 13 (N = 24)
T <sub>max</sub> (h)	2.6 ± 0.9	4.1 ± 1.6 <sup>*‡</sup>	3.9 ± 0.8 <sup>*‡</sup>	6.0 ± 2.5 <sup>*</sup>
C <sub>max</sub> (µg/mL)	11.24 ± 2.24	8.70 ± 2.38 <sup>*‡</sup>	8.01 ± 1.59 <sup>*‡</sup>	5.59 ± 1.31 <sup>*</sup>
AUC <sub>t</sub> (µg·h/mL)	166.0 ± 57.3	156.3 ± 47.6 <sup>‡</sup>	161.6 ± 50.1 <sup>‡</sup>	147.9 ± 45.5 <sup>*</sup>
AUC <sub>∞</sub> (µg·h/mL)	168.9 ± 59.7	159.5 ± 50.2 <sup>‡</sup>	165.6 ± 53.9 <sup>‡</sup>	152.0 ± 48.2 <sup>*</sup>
t <sub>1/2</sub> <sup>‡</sup> (h)	19.42 ± 4.66	19.58 ± 4.47	19.60 ± 4.24	20.27 ± 4.86
CL/F <sup>†</sup> (L/h)	0.89 ± 0.27	0.92 ± 0.26	0.90 ± 0.29	0.99 ± 0.33

# Regimens B, C and D were administered as one capsule of fenofibric acid choline salt equivalent to 135 mg fenofibric acid. Regimen A was administered as one 135 mg fenofibric acid immediate-release capsule.

\* Statistically significantly different from the reference regimen (Regimen A, ANOVA, p < 0.05).

‡ Statistically significantly different from the slow release formulation (Regimen D, ANOVA, p < 0.05).

‡ Harmonic mean ± pseudo-standard deviation; evaluations of t<sub>1/2</sub> were based on statistical tests for λ<sub>z</sub>.

† Parameter was not tested statistically.

Pharmacokinetics of fenofibric acid was also evaluated in a Phase 1, randomized, three-period, double-blind, placebo-controlled single-center study (Trial M02-513) in which ascending single doses of fenofibric acid were administered to healthy male and female subjects. Subjects were randomly assigned to receive fenofibric acid or placebo. Fifteen subjects received 50 mg and 100 mg of fenofibric acid under fasting conditions in Periods 1 and 2, respectively, and 100 mg of fenofibric acid under nonfasting conditions in Period 3. A washout interval of at least 28 days separated the doses in each of the three study periods.

Plasma concentration-time profiles are shown in the following figure and pharmacokinetic parameters are summarized in the following table. Upon oral administration of fenofibric acid a C<sub>max</sub> of 4 µg/mL and 8 µg/mL was reached at about 2 hours after 50 and 100 mg dose, respectively under fasting conditions. Pharmacokinetic parameters were estimated using non-compartmental analysis and AUC<sub>0-inf</sub> was reasonably estimated with % extrapolation not exceeding 10% of the AUC. The terminal half-life was about 12 hours, shorter than that observed in all other trials (19-20 hrs), and the difference could not be explained.

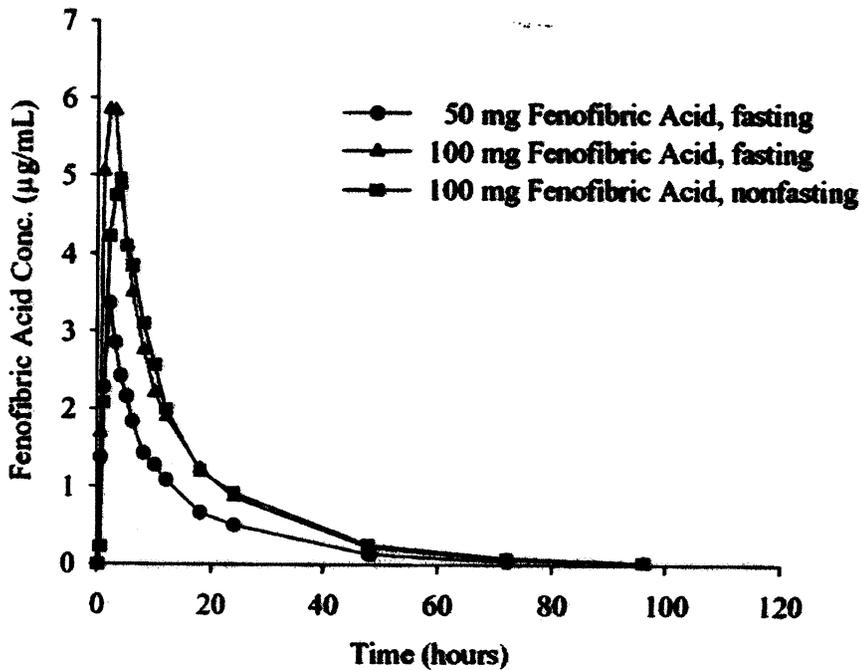


Figure 5 Plasma concentration-time profile of fenofibric acid after oral administration.

Table 8 (Mean  $\pm$  SD) Pharmacokinetic parameters of fenofibric acid after oral administration of three regimens

Pharmacokinetic Parameters (units)	Regimen		
	50 mg Capsule Fasting (N = 15)	100 mg Capsule Fasting (N = 15)	100 mg Capsule Nonfasting <sup>‡</sup> (N = 15)
T <sub>max</sub> (h)	1.7 $\pm$ 0.6	2.0 $\pm$ 1.1	3.8 $\pm$ 1.2 <sup>‡</sup>
C <sub>max</sub> (µg/mL)	3.673 $\pm$ 0.846	8.086 $\pm$ 2.440	5.491 $\pm$ 1.058 <sup>‡</sup>
AUC <sub>∞</sub> (µg·h/mL)	41.8 $\pm$ 11.2	76.3 $\pm$ 15.8*	75.2 $\pm$ 16.4
t <sub>1/2</sub> <sup>§</sup> (h)	11.8	12.6	13.2
CL/F <sup>†</sup> (L/h)	1.3 $\pm$ 0.4	1.4 $\pm$ 0.3	1.4 $\pm$ 0.3

\* Statistically significantly different from 50 mg capsule (paired t-test on dose-normalized data,  $p < 0.05$ ).

‡ Statistically significantly different from 100 mg capsule, fasting (paired t-test,  $p < 0.05$ ).

§ Harmonic mean; evaluations of t<sub>1/2</sub> were based on statistical tests for  $\lambda_z$ .

† Parameter was not tested statistically.

‡ Pharmacokinetic parameters presented above were calculated excluding the plasma concentration values for the 0.75 and 1.5-hour timepoints.

### 2.2.2 Is dose proportionality of ABT-335 established?

A formal consult to review the dose-proportionality in fenofibric acid PK was submitted by CMC as the sponsor mentioned it as one of the criteria for biowaiver request for the 45 mg strength formulation. The observations are as follows:

The dose proportionality of fenofibric acid exposure from ABT-335 formulation has not been demonstrated.

Dose proportionality of fenofibric acid administered as neat drug in capsule was evaluated in a Phase 1 study (Trial M02-513) as mentioned above. For  $C_{max}$  and  $AUC_{0-\infty}$ , point estimates and 95% confidence intervals were calculated for the ratio of the dose-normalized least-square mean values in order to assess the degree of non-linearity. Based on the results of this comparison, the pharmacokinetic parameters for fenofibric acid appeared to be dose proportional from 50 to 100 mg dose.

Table 9 Dose-proportionality of fenofibric acid after oral administration of two regimens

Regimens Test vs. Reference	Pharmacokinetic Parameter	Relative Bioavailability			
		Central Value*		Point Estimate†	95% Confidence Interval
		Test	Reference		
100 mg capsule (fasting) vs. 50 mg capsule (fasting)	$C_{max}$	3.85	3.58	1.0755	0.8709 – 1.3280
	$AUC_{0-\infty}$	37.37	40.31	0.9272	0.8614 – 0.9980

\* Antilogarithm of the least squares means for logarithms.

† Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

The dose normalized  $C_{max}$  and  $AUC_{0-\infty}$  were comparable between 50 and 100 mg fenofibric acid doses.

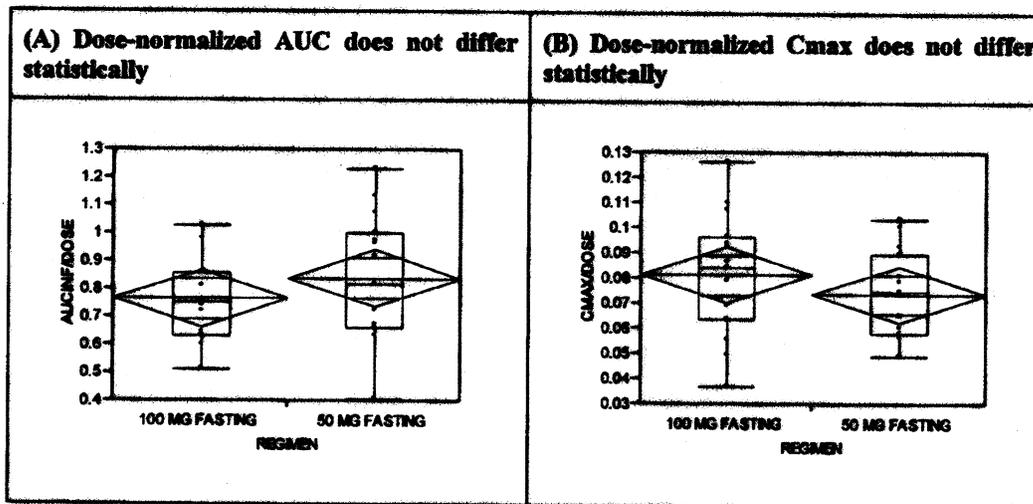


Figure 6 Comparison of dose-normalized AUC (A) or  $C_{max}$  (B) in Trial M02-513.

**(B) Dose-normalized Cmax does not differ statistically**

**Analysis of Variance**

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
REGIMEN	1	0.0408259	0.040826	1.0800	0.3076
Error	28	1.0584555	0.037802		
C. Total	29	1.0992814			

**Means for One-way Anova**

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
100 MG FASTING	15	0.762742	0.05020	0.65991	0.86557
50 MG FASTING	15	0.836522	0.05020	0.73369	0.93935

Std Error uses a pooled estimate of error variance

**(B) Dose-normalized Cmax does not differ statistically**

**Analysis of Variance**

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
REGIMEN	1	0.00041040	0.000410	0.9308	0.3429
Error	28	0.01234521	0.000441		
C. Total	29	0.01275562			

**Means for One-way Anova**

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
100 MG FASTING	15	0.080861	0.00542	0.06976	0.09197
50 MG FASTING	15	0.073464	0.00542	0.06236	0.08457

Std Error uses a pooled estimate of error variance

Apart from this dose-proportionality assessment for fenofibric acid, the sponsor also conducted dose-linearity assessment for fenofibric acid pharmacokinetics, which in this reviewer's opinion is inconclusive for the following reasons:

- Sponsor has not exclusively evaluated different doses of ABT-335 in either neat or in the form of modified release formulation in any of the pharmacokinetic studies to generate the dose-linearity data over the range of proposed doses.
- The cross-study and cross-formulation comparison approach to determine dose-linearity, using pooled pharmacokinetic data from immediate release and modified release formulations (Table 10), was inadequate for the limitations no different than those cited by the sponsor themselves (see footnote to table 10) as the formulations used in these pharmacokinetic studies not only were different from the to-be-marketed formulation but also differed in their release characteristics resulting in in-comparable Cmax values. Moreover, the CL/F was inconsistent among the studies making comparison of AUC data difficult.

Overall, the data is, therefore, considered insufficient to comment on the dose-proportionality/linearity over the proposed 45 mg and 135 mg extended release formulation strengths in the current application.

Table 10 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)
Following Fenofibric acid Administration <sup>c</sup>						
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
Following 200 mg Fenofibrate Reference Capsule Administration <sup>f</sup>						
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.

### 2.2.3 Do pharmacokinetic parameters of ABT-335 change with time following chronic dosing ?

Study M06-811 evaluated the time-dependence of fenofibric acid pharmacokinetics after multiple-dose administration of ABT-335 Formulation 10. Once-daily ABT-335 equivalent to fenofibric acid 135 mg was administered under non-fasting conditions for 10 days. Linear mixed effect modeling was used to assess steady state attainment, which indicated that fenofibric acid trough plasma concentrations appeared to reach steady state around Study Day 8. The mean  $\pm$  SD fenofibric acid pharmacokinetic parameters determined following a single dose of ABT-335 (Study Day 1) and at steady-state (Study Day 10) are presented in Table 11 below. The mean plasma concentration-time profile of fenofibric acid on Study Day 1 through Study Day 10 is illustrated in the Figure 7 below.

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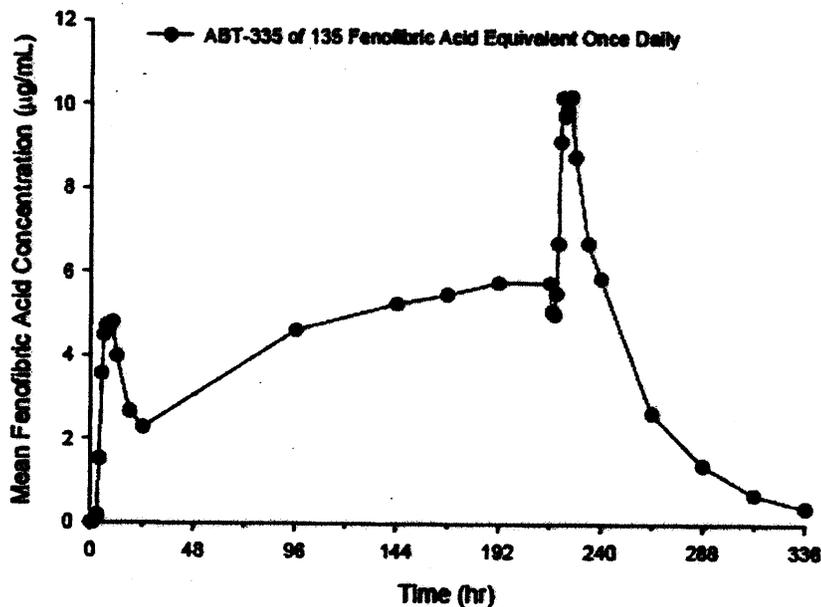


Figure 7 Mean plasma concentrations of fenofibric acid following multiple daily doses of 135 mg choline fenofibrate

There was a significant accumulation of fenofibric acid after multiple daily doses for 135 mg (Table 11).

Table 11 Pharmacokinetic parameters of fenofibric acid at Day 1 and Day 10 after daily doses of 135 mg choline fenofibrate.

Pharmacokinetic Parameters (units)	Regimen C: ABT-335 Alone <sup>‡</sup>	
	Study Day 1 (N = 16)	Study Day 10 (N = 16)
$T_{max}$ (h)	7.8 ± 2.1	6.9 ± 2.1
$C_{max}$ (µg/mL)	5.60 ± 0.90	12.13 ± 2.83
$C_{min}$ <sup>†</sup> (µg/mL)	— <sup>£</sup>	4.59 ± 1.41
AUC <sub>24</sub> (µg·h/mL)	70.8 ± 13.4	182.6 ± 44.0
$t_{1/2}$ <sup>£</sup> (h)	— <sup>£</sup>	23.44 ± 3.78
CL/F <sup>†</sup> (L/h)	— <sup>£</sup>	0.79 ± 0.21
AR <sup>†</sup>	— <sup>£</sup>	2.60 ± 0.45
FI <sup>†</sup>	— <sup>£</sup>	1.01 ± 0.16

<sup>‡</sup> Regimen C was administered as ABT-335 equivalent to 135 mg fenofibric acid QD.

<sup>£</sup> Harmonic mean ± pseudo-SD; evaluations of  $t_{1/2}$  were based on statistical tests for  $\lambda_z$ .

<sup>†</sup> Parameter was not tested statistically.

<sup>£</sup> Parameter not determined.

AR: Accumulation ratio.

FI: Fluctuation index.

Overall, by Day 10 the peak and total exposure was increased by 90-180% after multiple daily doses of 135 mg compared to that of single dose.

Table 12 Comparison of pharmacokinetic parameters at Day 1 and Day 10 after daily doses of 135 mg choline fenofibrate.

Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	95% Confidence Interval
Study Day 10 vs. Study Day 1	C <sub>max</sub>	11.73	5.51	2.128	1.913 – 2.366
	AUC <sub>24</sub>	176.52	68.89	2.563	2.358 – 2.785

\* Geometric means.

+ The ratio of the geometric means (Study Day 10/Study Day 1).

#### 2.2.4 Is major route of elimination identified?

The elimination fate of ABT-335 has not been evaluated. However, the sponsor has referred to an earlier mass balance study in which metabolic fate of <sup>14</sup>C-fenofibrate was evaluated in vivo following oral administration in humans. In this study eight healthy volunteers (four male, four female) received a single therapeutic dose (66 µCi/subject) of <sup>14</sup>C-fenofibrate orally. Urine and feces were collected for up to 7 days after dosing. A total of 84% of the orally administered radioactivity was recovered in 7 days with 59% of the dose being recovered in the urine and 25% being recovered in the feces. The entire renally recovered radioactivity was composed of 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, indicating 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.

In vitro metabolism study showed that the conversion of fenofibrate to fenofibric acid is driven by microsomal enzymes. In the presence of human liver microsomes, the conversion of fenofibrate (5 and 30 mM) to fenofibric acid was complete in < 2 minutes, suggesting that fenofibrate is likely converted to fenofibric acid in the intestine and via a single pass through the liver after oral administration.

Considering that fenofibrate is completely and rapidly converted into fenofibric acid, we agree to the sponsor's interpretation that the metabolic pathway of fenofibric acid determined in humans following <sup>14</sup>C-fenofibrate administration in humans is applicable to that following the oral administration of ABT-335, as illustrated in Figure 8 below. Though, in this reviewer's opinion, a renal excretion assessment in PK or BE studies would have further generated hard evidence in support of the elimination of fenofibric acid.

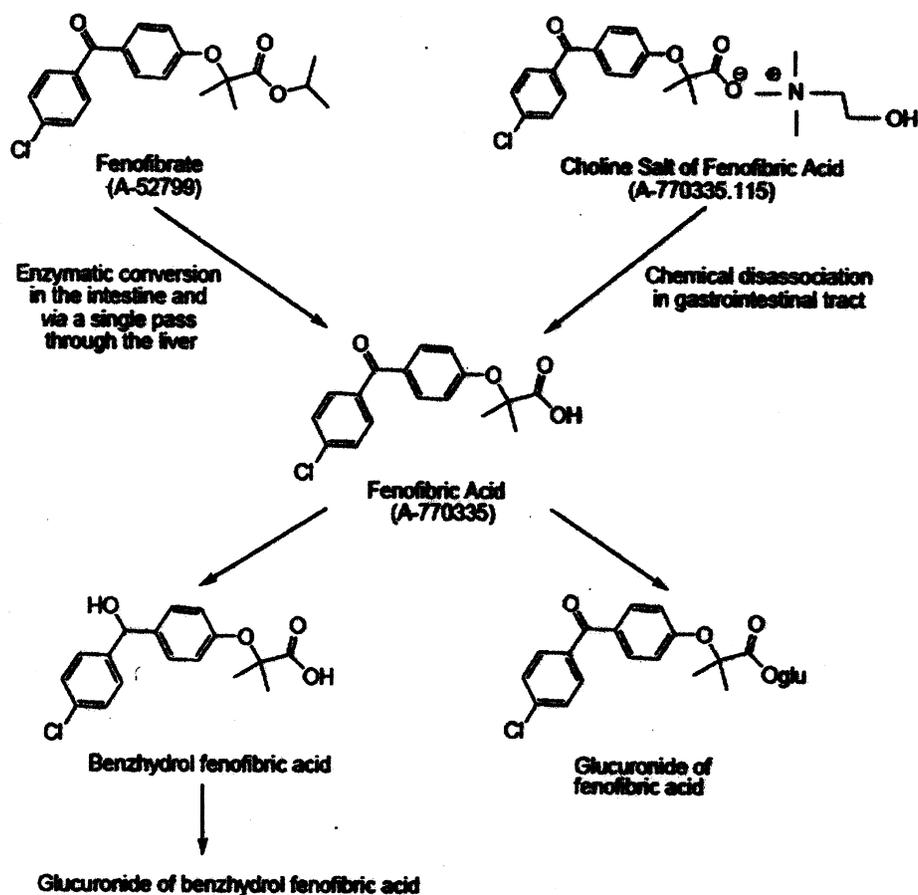


Figure 8 Proposed metabolic pathways of fenofibrate and fenofibric acid.

## 2.3 Intrinsic Factors

### 2.3.1 Is there age, weight, gender or race effect on ABT-335 pharmacokinetics?

**Age:** There have been no studies or analyses carried out to assess fenofibric acid pharmacokinetics after ABT-335 administration in elderly subjects. The pharmacokinetics of fenofibric acid after oral administration of either ABT-335 or fenofibrate has not been investigated in pediatric subjects.

In Study M06-830, Study M06-831 and Study M06-886, single 135 mg doses of the to-be-marketed ABT-335 formulation manufactured at full production scale were administered to 182 healthy volunteers between the ages of 18 and 55 years. The  $C_{max}$  and  $AUC_{0-\infty}$  values of fenofibric acid from each subject after the administration of the to-be-marketed ABT-335

formulation manufactured at full production scale at Abbott Puerto Rico did not change with age over the age range of 18 to 55 years (Figure 9).

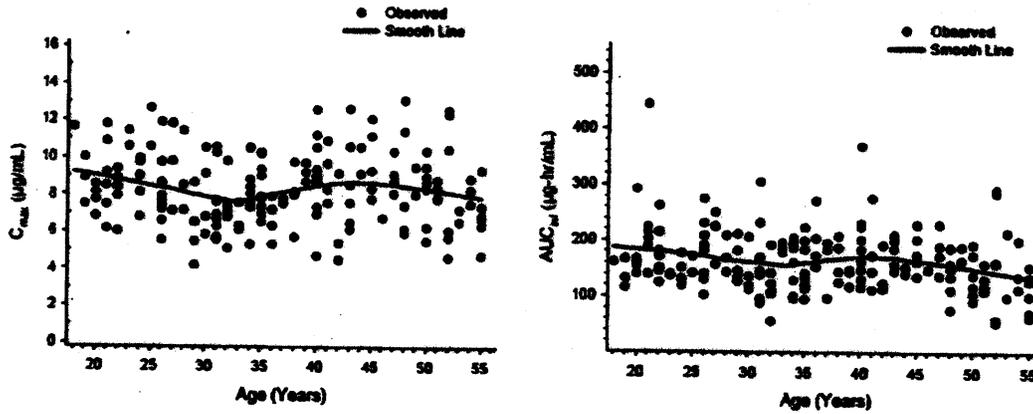


Figure 9 No effect of age on fenofibric acid peak and total exposure from 135 mg dose over the age range of 18 to 55 years.

**Body Weight:** In Study M06-830, Study M06-831 and Study M06-886, 182 healthy volunteers with the body weight ranging from 52 to 106 kg were administered single 135 mg doses of the to be marketed ABT-335 formulation manufactured at full production scale at Abbott Puerto Rico under fasting conditions. The  $C_{max}$  and  $AUC_{0-\infty}$  values of fenofibric acid versus body weight are illustrated in Figure 10 below.

The  $C_{max}$  shows increasing trend with decreasing body weight. However, body weight appears to have no effect on fenofibric acid AUC over the range of 52 to 106 kg. Thus, the apparent trend of increasing  $C_{max}$  with decreasing body weight after single doses of ABT-335 is not clinically relevant.

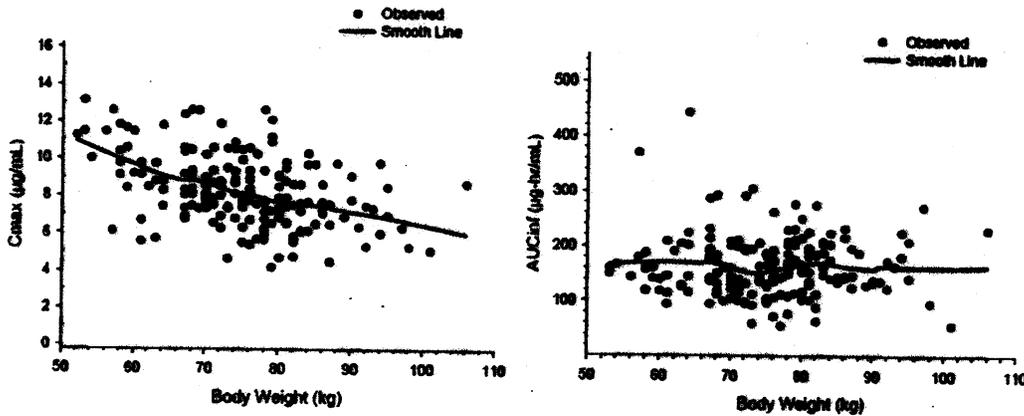


Figure 10 Effect of body weight on fenofibric acid pharmacokinetics.

**Gender:** The mean (+ SD)  $C_{max}$  and  $AUC_{0-\infty}$  values of fenofibric acid observed for 182 healthy volunteers (113 Males and 69 Females) after single-dose administration of the to-be-marketed ABT-335 formulation manufactured at full production scale at Abbott Puerto Rico from Study M06-830, Study M06-831 and Study M06-886 are illustrated in Figure 11 below. No differences were apparent in fenofibric acid pharmacokinetics between males and females.

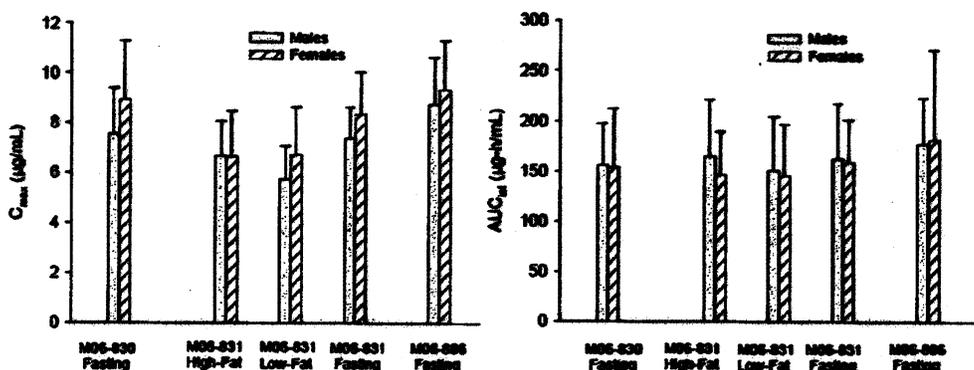


Figure 11 No effect of gender on fenofibric acid pharmacokinetics.

**Race:** Studies or analyses have not been conducted to evaluate the pharmacokinetics of fenofibric acid after the administration of ABT-335 to patients of varying races. The prescribing information for fenofibrate (TriCor) (TriCor® [Package Insert], 2004) states that "The influence of race on the pharmacokinetics of fenofibrate has not been studied; however fenofibrate is not metabolized by enzymes known for exhibiting interethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely."

Although sponsor concluded that since the fenofibric acid is the circulating moiety in plasma after oral administration of fenofibrate and ABT-335 undergoes negligible first-pass metabolism, no race or ethnicity effects on the pharmacokinetics of fenofibric acid following ABT-335 administration are expected. There is no information on the enzymes responsible for glucuronidation of fenofibric acid. Considering that the ethnic differences in glucuronidation (UGT1A1-mediated) are well documented in literature, the sponsor's conclusion regarding no race or ethnicity effects on the pharmacokinetics of fenofibric acid need to be supported by data.

### 2.3.2 Does the renal function affect ABT-335 pharmacokinetics?

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

However, the sponsor referred to two pharmacokinetic studies (Fournier, K 178 79 01 KH 80 02 and Fournier, K 178 85 03 KH 89 02) evaluating the pharmacokinetics of fenofibric acid in subjects with renal impairment after oral administration of fenofibrate. The first study (Fournier, K 178 79 01 KH 80 02) included subjects with end-stage renal disease on hemodialysis. The second study (Fournier, K 178 85 03 KH 89 02) included subjects with varying degrees of renal impairment, but none of the subjects were on hemodialysis.

In the renal impairment study, (Fournier, K 178 85 03 KH 89 02) 15 renally impaired subjects received a single oral dose of fenofibrate 100 mg as the non-micronized capsule, which is 1/3 of the full approved dose, under non-fasting conditions. Sponsor conducted and presented the re-analysis of data from this study as it was conducted before the issuance of FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling, May 1998, (FDA, 1998) or the guideline by National Kidney Foundation on Definition and Classification of Stages of Chronic Kidney Disease (referred to as Kidney Dialysis Outcomes and Quality Initiative (K/DOQI) Chronic Kidney Disease (CKD) guidelines hereafter), February 2002 (American Journal of Kidney Diseases, 2002). The classification of patients in this study was different from either guidance's recommended groupings.

Upon reanalysis of the data from this study, (Fournier, K 178 85 03 KH 89 02) subjects were categorized into mild, moderate, and severe renal impairment groups based on the classifications described in the two guidance documents. Summary statistics for fenofibric acid pharmacokinetic parameters were calculated for each group. All individual pharmacokinetic parameters were taken directly from the existing study report. As in the original study report, this re-analysis of renal clearance estimates used fenofibric acid pharmacokinetics in healthy young adults from a separate study as the control group (Fournier, K 178 85 03 KH 89 02).

Table 13 The FDA and K/DOQI classifications of renal impairment groups

Group or Stage	FDA Guidance		K/DOQI Guideline	
	Description	CrCl (mL/min) <sup>a</sup>	Description	eGFR (mL/min/1.73 m <sup>2</sup> ) <sup>b</sup>
1	Normal renal function	> 80	Kidney damage with normal or ↑ GFR	≥ 90
2	Mild renal impairment	50 – 80	Kidney damage with mild ↓ GFR	60 – 89
3	Moderate renal impairment	30 – 50	Moderate ↓ GFR	30 – 59
4	Severe renal impairment	< 30	Severe ↓ GFR	15 – 29
5	ESRD	Requiring dialysis	Kidney failure	< 15 (or dialysis)

<sup>a</sup> Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{plasma creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female}).$$

<sup>b</sup> The estimated glomerular filtration rate (eGFR) was calculated using the equation derived from the Modification of Diet in Renal Disease (MDRD) Study:

$$\text{eGFR} = 136 \times \text{plasma creatinine (mg/dL)}^{-1.154} \times \text{age (years)}^{-0.203} \quad (\times 0.742 \text{ for female}).$$

Pharmacokinetic parameters are summarized in the following table.

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Table 14 Pharmacokinetic parameters of fenofibric acid after 100 mg fenofibrate in healthy and renally impaired subjects

Pharmacokinetic Parameter (unit)	Renal Impairment			Healthy Young Adults <sup>a</sup> (N = 12)
	Mild <sup>a</sup> (N = 3)	Moderate <sup>a</sup> (N = 3)	Severe <sup>a</sup> (N = 9)	
C <sub>max</sub> (µg/mL)	1.879 ± 1.720	1.747 ± 0.987	1.804 ± 0.902	4.8 ± 0.9
T <sub>max</sub> (h)	10.7 ± 11.6	3.7 ± 1.2	7.8 ± 6.5	4.8 ± 0.8
t <sub>1/2</sub> (h)	22.24 ± 17.10	31.32 ± 28.27	116.56 ± 154.91	20.8 ± 5.9
AUC (µg·h/L)	42.64 ± 18.44	45.67 ± 8.24	265.39 ± 348.39	97.6 ± 54.0
CL/F (L/h)	2.30 ± 0.80	1.97 ± 0.32	0.72 ± 0.53	1.07 ± 0.49
V <sub>z</sub> /F (L)	82.56 ± 78.78	93.30 ± 89.68	61.40 ± 28.16	30.3 ± 8.5
f <sub>u</sub> (%)	2.01 ± 0.5	1.51 ± 0.11	1.98 ± 0.43	1.00 ± 0.20
CL <sub>R2</sub> (L/h)	1.160 ± 1.159	0.475 ± 0.272	0.062 ± 0.054	0.38 ± 0.23
Ae <sub>2</sub> (mg)	45.02 ± 36.45	21.96 ± 8.57	4.71 ± 3.25	27.6 ± 12.5
Ae <sub>2</sub> /Ae <sub>1</sub>	3.06 ± 1.86	2.16 ± 0.55	1.95 ± 1.34	- <sup>b</sup>

CL<sub>R</sub> = renal clearance of total (free + conjugated) fenofibric acid.

Ae<sub>2</sub> = amount of total fenofibric acid excreted in the urine at infinite time.

Ae<sub>2</sub>/Ae<sub>1</sub> = the ratio of total to free amounts of fenofibric acid excreted in the urine at infinite time.

AUC = area under the plasma concentration-time curve from zero to infinite time

f<sub>u</sub> = free fraction of fenofibric acid.

a. Single oral dose of fenofibrate 100 mg as a non-micronized capsule, which is 1/3 of the full approved dose, was administered to all dose groups under non-fasting conditions.

b. No value reported.

Data presented as Mean ± SD.

The sponsor concluded that:

- None of the subjects in the mild and moderate renal impairment groups demonstrated higher C<sub>max</sub> or AUC values than the means observed in healthy young adults.
- Mean t<sub>1/2</sub> observed in the mild renal impairment group was comparable to that observed in the healthy group, while the mean t<sub>1/2</sub> in the moderate renal impairment group was somewhat longer than the healthy group (one subject with moderate renal impairment had a t<sub>1/2</sub> of 63.90 hours, which was approximately three times longer than the mean t<sub>1/2</sub> in the healthy group).
- Compared to the healthy subjects, the % unbound drug in plasma was higher in renally impaired patients. The observed increases in volume of distribution (V<sub>z</sub>/F) in the renally impaired patients are likely a result of the increase in free fraction of fenofibric acid.
- The apparent oral clearance (CL/F) and renal clearance (CL<sub>R2</sub>) in the mild and moderate renal impairment groups were somewhat higher than those seen in the healthy group suggesting that the elimination of fenofibric acid was not compromised in these two renal impairment groups.
- The AUC was higher in the severe renal impairment group compared to that observed in healthy adults. Patients with severe renal impairment also demonstrated a prolonged t<sub>1/2</sub>,

a decreased CL/F, a decreased CLR<sub>2</sub>, and a decreased total amount of fenofibric acid excreted in the urine (A<sub>e2</sub>) compared to the healthy group.

The hemodialysis study (Fournier, K 178 79 01 KH 80 02) evaluated the effect of hemodialysis on plasma pharmacokinetics of fenofibric acid in patients with end-stage renal disease (ESRD). Six patients on hemodialysis and 9 patients not on hemodialysis received a single oral dose of the non-micronized fenofibrate 300 mg, which is the full-approved therapeutic dose under non-fasting conditions. Additionally, five other patients undergoing hemodialysis received oral doses of 100 mg, which is one-third of the full-approved therapeutic dose, once daily for 14 days.

Pharmacokinetic results from this study suggested that after a single dose, the elimination t<sub>1/2</sub> was between 54 and 362 hours in patients not on hemodialysis, and between 56 and 257 hours in the patients undergoing hemodialysis. In patients receiving multiple doses of 100 mg once daily, fenofibric acid plasma concentrations were similar to those inpatients with normal renal function given 300 mg once daily, however, steady state had not been achieved at the end of the 14-day dosing period.

Based on the findings from the two renal impairment studies, current fenofibrate (TriCor®) prescribing information recommends that the use of fenofibrate should be avoided in patients who have severe renal impairment.

Sponsor proposed that:

- (1) treatment with fenofibrate should be initiated at one-third of the full therapeutic dose in patients having mildly or moderately impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose,
- (2) Given that fenofibric acid is the circulating moiety in plasma after oral administration of fenofibrate, that ABT-335 undergoes negligible first-pass metabolism, and that relative bioavailability studies in the ABT-335 program have established bioequivalence between ABT-335 administration and the micronized 200 mg fenofibrate capsule, similar labeling recommendations for ABT-335 in patients with impaired renal function are appropriate.

From a clinical pharmacology perspective, although there is limited information available on fenofibric acid exposure in mild and moderate renal impairment subjects from existing data, the reduced dose of 45 mg based on the 3 times higher exposure seen in severely impaired subjects, seems an acceptable conservative approach.

### 2.3.3 Does the hepatic function affect ABT-335 pharmacokinetics?

Based on the information that:

- fenofibric acid is the circulating moiety in plasma after oral administration of fenofibrate or ABT-335,
- neither ABT-335 nor fenofibric acid undergoes oxidative metabolism (e.g., cytochrome P450) to a significant extent,
- and that the <sup>14</sup>C-fenofibrate mass balance study showed that renal excretion is the dominant elimination pathway for fenofibric acid,

the sponsor proposed that impaired hepatic function is not expected to have significant effects on ABT-335 pharmacokinetics. As a result, no pharmacokinetic studies were conducted in patients having hepatic insufficiency after oral administration of fenofibrate or ABT-335. They also mentioned that this approach is consistent with the Agency's Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (FDA, 2003b).

However, it should be noted that majority of the renally excreted radioactivity (60% of the administered radioactivity) in the mass balance study was due to the glucuronidated fenofibric acid (45%) and only 9% was due to free fenofibric acid, 25% of the administered radioactivity was excreted through feces (possibly includes unabsorbed and bile excreted radioactivity) and 15% was unrecovered. Although renal excretion was dominant pathway for the elimination of radioactivity, major role of hepatic Phase 2 elimination cannot be ignored in this case. Therefore, sponsor's conclusion that impaired hepatic function is not expected to have significant effects on ABT-335 pharmacokinetics will require a formal clinical evaluation. This further becomes significant as the hepatic impairment also has implications on the renal function and fenofibric acid and its glucuronide are renally excreted.

However, the existing TriCor® and proposed labeling language recommends that Trilipix™ is contraindicated in subjects with Hepatic Impairment. The approach seems reasonable from a clinical pharmacology perspective in absence of a formal evaluation.

## **2.4 Extrinsic Factors**

### **2.4.1 What is the effect of food on the bioavailability of ABT-335?**

Food effect on ABT-335 was assessed in study M06-831, which was conducted to compare the pharmacokinetics of fenofibric acid after administration of the to-be-marketed ABT-335 formulation after a high-fat/high-calorie meal (Regimen A) and after a low-fat meal (Regimen B) conditions to that under fasting conditions (Regimen C). Healthy adult male and female subjects (N=75) were enrolled and received study drug in two cohorts; 70 subjects completed all three periods, and 74 subjects were included in the pharmacokinetic analysis. The mean fenofibric acid plasma concentrations and mean ( $\pm$  SD) pharmacokinetic parameters of fenofibric acid after administration of each of the three regimens are presented in Figure 12 and Table 14 below, respectively.

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