

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-418

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

CLINICAL PHARMACOLOGY REVIEW

6/8/09

NDA: 22-418 Submission Date(s): 08/15/08
Brand Name Fibricor™
Generic Name Fenofibric acid
Reviewer Immo Zdrojewski, Ph.D.
Team Leader (Acting) Wei Qiu, Ph.D.
OCP Division Clinical Pharmacology 2
OND Division Metabolic and Endocrine Products
Sponsor Mutual Pharmaceutical Company, Inc.
Submission Type 505 (b)(2)
Formulation; Strength(s) Immediate release tablets 35 mg and 105 mg
Indication Treatment of hypercholesterolemia, specifically as
 adjunctive therapy to diet, Treatment of
 hypertriglyceridemia, specifically as adjunctive therapy to
 diet

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1. Executive Summary

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted in support of NDA 22-418 and found that the 105 mg fenofibric acid tablets manufactured by Mutual Pharmaceutical Company, Inc. are bioequivalent to the 145 mg fenofibrate tablets manufactured by Abbott. In addition, a dose of 3 x 35 mg tablets is found to be bioequivalent to a 105 mg tablet. NDA 22-418 is acceptable provided that the Agency and the Sponsor agree on the labeling. The biowaiver assessment for the 35 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

Mutual Pharmaceutical Company, Inc. is developing an immediate release tablet containing fenofibric acid, the active moiety of fenofibrate. Fenofibrate is currently approved as adjunctive therapy to diet to reduce elevated LDL-cholesterol (LDL-C), total-C, Triglycerides and ApoB, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia.

On December 15th, 2008, Trilipix was approved for the same indication as Tricor. Similarly, Trilipix's active ingredient is fenofibric acid choline salt. Trilipix is available as 45 and 135 mg tablets. For detailed information of Trilipix approval, please see the review from Dr. Manoj Khurana for NDA 22-224, finalized on 09/22/2008.

Mutual's fenofibric acid tablets are manufactured in two strengths, 35 mg, and 105 mg. In this application, the sponsor evaluated the bioequivalence of the 105 mg tablet compared to the reference product, Abbott's Tricor® 145 mg. The bioequivalence between 3 x 35 mg and 105 mg were also evaluated. Mutual requested a biowaiver for the 35 mg tablet based on the compositional proportionality of the two strengths, in vitro drug dissolution data, and dosage form proportionality in the fenofibric acid pharmacokinetics. The biowaiver was assessed by ONDQA. Dr. Houda Mahayni reviewed the biowaiver application for ONDQA (DFS date: 05/13/09) and found that the dissolution method used is not acceptable. She recommends using a different rotation speed, since the data provided is not discriminative at the speed chosen.

Clinical development of the fenofibric acid tablets under this 505(b)(2) submissions is supported by 15 clinical pharmacology studies. The clinical pharmacology program consists of one dose proportionality study, 5 in vitro and 1 in vivo drug-drug interaction studies and 8 biopharmaceutics studies, including a fasted, and a fed BE study, and a food effect study. The sponsor refers to the previously approved fenofibrate product Tricor® for safety and efficacy findings. According to Kim Quaintance, Associate Director for Regulatory Affairs, Office of New Drugs, Mutual has cited reliance on all of the Tricor applications. Please note, that the Tricor NDAs 19-304 and 21-203 were not discontinued for reasons due to safety or efficacy.

The Office of Clinical Pharmacology focused its review on the bioequivalence study (MPC-028-07-1007) entitled, "A single-dose, bioequivalence study of 105 mg fenofibric acid tablets versus 145 mg Tricor® (fenofibrate) tablets under fasting conditions," as well as on the bioequivalence study under fed conditions (MPC-028-07-1008), the food-effect study (MPC-028-07-1009), and the study evaluating the dosage form proportionality (MPC-028-07-1017).

Bioequivalence:

The bioequivalence is appropriately demonstrated between Mutual's 105 mg tablet and the reference listed drug under fasting (Table 1) and fed conditions (Table 2).

Table 1 Study MPC-028-07-1007: Statistical Summary (Geometric means, ratio of means, and 90% confidence intervals) Ln-transformed data (N=49)

Parameter	Fenofibric Acid Tablets (105 mg)	TriCor [®] Tablets (145 mg)	% Ratio	90% CI
AUC _{0-∞} (µg·hr/mL)	148.59371	158.70070	93.63	(91.28, 96.05)
AUC _{0-t} (µg·hr/mL)	162.95683	173.93396	93.69	(91.67, 95.75)
C _{max} (µg/mL)	12.00135	10.65025	112.69	(107.99, 117.59)

The results from Study MPC-028-07-1007 (n=49) demonstrate that Mutual's 105 mg fenofibric acid tablets are bioequivalent to Abbott's Tricor[®] 145 mg tablets under fasted conditions. The geometric mean ratios of AUC_{inf}, AUC_{0-last}, and C_{max}, and the 90% confidence intervals for these ratios meet the bioequivalence criteria. An audit of the pivotal bioequivalence study by the Division of Scientific Investigation was requested. The Division of Scientific Investigation concluded that

- it is objectionable that PRACS Institute-Cetero Research failed to report subjects #04's miscarriage to the IRB and,
- it is objectionable, that the firm changes 50 of the 54 subjects' case report forms from being study eligible to being ineligible without clarification, more than 8 month after study completion.

Additional information, as well as the sponsor's justification for the inclusion of the subjects has been requested, and the sponsor submitted the requested data. This reviewer, and the medical officer, Dr. Ifat Chowdhury, agree that the protocol deviations were unlikely to impact the pharmacokinetics of fenofibric acid in study MPC-028-07-1007.

The sponsor also evaluated the bioequivalence of the 105 mg fenofibric acid tablets to the reference product under fed conditions (Study MPC-028-07-1008). In this randomized, single dose, two-way crossover study, 54 subjects were enrolled and the bioequivalence of test and reference was evaluated under standardized meal conditions. The standardized meal did not meet the requirements of an FDA high fat high calorie meal. Compared to Tricor, the geometric mean ratios for AUC_{0-inf}, AUC_{0-last}, and C_{max}, and the 90% confidence interval fall wholly within 80-125%. (Table 2). The rate and extent of exposure was approximately 10% lower in the test product compared to the reference product.

Table 2 Study MPC-028-07-1008: Summary Statistics of fenofibric acid tablets vs. Tricor[®] following a standard breakfast

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=47				
Parameter	Fenofibric Acid Tablets (105 mg)	TriCor [®] Fenofibrate Tablets (145 mg)	% Ratio	90% CI
AUC _{0-∞} (µg·hr/mL)	113.62538	123.91562	91.70	(89.73, 93.7)
AUC _{0-t} (µg·hr/mL)	124.88596	137.01609	91.15	(89.08, 93.26)
C _{max} (µg/mL)	8.36916	9.30079	89.98	(86.78, 93.31)

Food Effect:

Mutual's fenofibric acid tablets pharmacokinetics are influenced by food. When administered with a low fat meal, the C_{max} is approximately 20% lower, when administered with a high fat/high calorie meal; the C_{max} is approximately 35% lower. However, the decrease in maximum exposure with a lack of difference in total exposure may not be clinically relevant.

Dosage Form Proportionality:

Mutual's 35 mg tablets showed dosage form proportionality to the 105 mg tablets when pharmacokinetic parameters are evaluated dose adjusted to 105 mg, and when the 35 mg tablets are given as 3x35mg (Study MPC-028-07-1017).

The 90% confidence intervals for the geometric mean ratios for the 1x35 mg adjusted to 105 mg and the 3x35 mg fall within the bioequivalence criteria of 80-125% when compared to the 105 mg tablet.

Drug-Drug Interaction:

Mutual's 105 mg fenofibric acid tablet did not show a clinically relevant interaction with a CYP 2B6 substrate efavirenz, total exposure of efavirenz when administered with fenofibric acid at steady state are approximately 10 to 11 % lower than efavirenz administered alone.

REVIEWER'S COMMENT:

- The efavirenz label does not recommend a dose adjustment when administered with nelfinavir, which leads to decreases in AUC of efavirenz of 12%. A similar decrease (10%) is demonstrated in the drug-drug interaction study MPC-028-07-1018.

2. Question Based Review

2.1 General Clinical Pharmacology

2.1.1 Is the dose proportionality of Mutual's 105 mg fenofibric acid tablet established? Is the dosage form proportionality demonstrated?

Yes. Study MPC-028-07-1017, an open label, single dose, three arm cross over study enrolled 54 healthy subjects (36 males and 18 females) and showed, that Mutual's 35 mg tablets are bioequivalent to the 105 mg tablets when pharmacokinetic parameters are evaluated dose adjusted to 105 mg, and when the 35 mg tablets are given as 3x35mg. The study was conducted under fasting conditions and consisted of three arms: 1 x 35 mg, 3 x 35 mg, and 1 x 105 mg fenofibric acid tablet.

The geometric mean ratios for the 1x35 mg adjusted to 105 mg and the 3x35 mg fall within the bioequivalence criteria of 80-125% when compared to the 105 mg tablet (Tables 3 and 4).

Table 3 Fenofibric Acid Tablets, 35 mg (3 x 35 mg) vs. Fenofibric Acid Tablets, 105 mg – N=53

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=53				
Parameter	Fenofibric Acid 3 x 35-mg Tablets	Fenofibric Acid 1 x 105-mg Tablet	% Ratio	90% CI
AUC ₀₋₄ (µg-hr/mL)	125.79	128.70	97.74	(95.54, 99.99)
AUC _{0-∞} (µg-hr/mL)	136.03	139.90	97.23	(95.18, 99.32)
C _{max} (µg/mL)	10.84	10.93	99.19	(96.67, 101.77)

Table 4 Fenofibric Acid Tablets, 35 mg (Dose Normalized to 105 mg) vs. Fenofibric Acid Tablets, 105 mg – N=53

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=53				
Parameter	Fenofibric Acid, 1 x 35-mg Tablet (Dose Adjusted to 105 mg)	Fenofibric Acid 1 x 105-mg Tablet	% Ratio	90% CI
AUC ₀₋₄ (µg-hr/mL)	138.97	128.70	107.97	(105.54, 110.46)
AUC _{0-∞} (µg-hr/mL)	164.33	139.90	117.46	(114.99, 119.98)
C _{max} (µg/mL)	10.50	10.93	96.04	(93.61, 98.54)

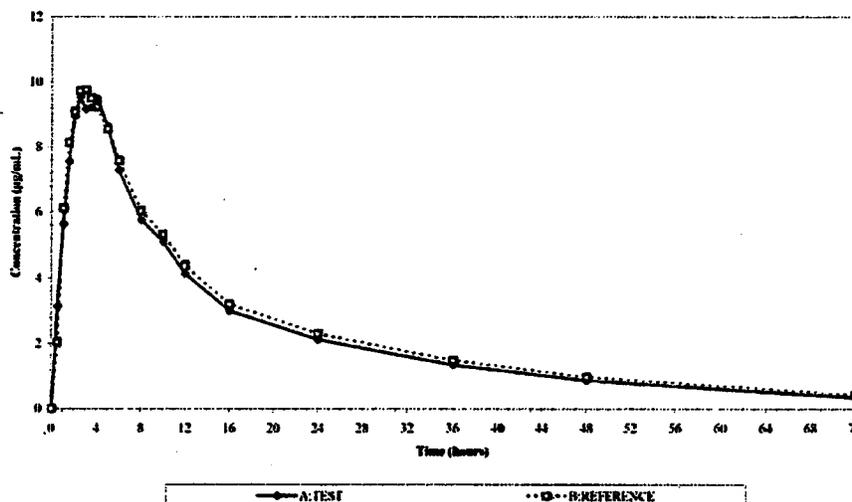
2.1.2 Are Mutual's 105 mg fenofibric acid tablets bioequivalent to the reference listed drug?

Yes. A randomized, single dose, two way crossover study (Study MPC-028-07-1007) in which 54 subjects were enrolled, shows that Mutual's 105 mg fenofibric acid tablets are bioequivalent when compared to the reference listed drug (Abbott's Tricor 145 mg tablets). 49 subjects completed the study. Compared to Tricor the geometric mean ratios for AUC_{0-inf} , AUC_{0-last} , and C_{max} , and the 90% confidence interval fall wholly within 80-125% (Table 5). A plasma concentration vs. time profile of both test and reference product is illustrated in Figure 1.

Table 5 Statistical Summary Statistical Summary (Geometric means, ratio of means, and 90% confidence intervals) Ln-transformed data

Parameter	Fenofibric Acid Tablets (105 mg)	TriCor [®] Tablets (145 mg)	% Ratio	90% CI
AUC_{0-inf} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	148.59371	158.70070	93.63	(91.28, 96.05)
AUC_{0-last} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	162.95683	173.93396	93.69	(91.67, 95.75)
C_{max} ($\mu\text{g}/\text{mL}$)	12.00135	10.65025	112.69	(107.99, 117.59)

Figure 1 Mean Fenofibric Acid Plasma Concentration *versus* Time Profile (N=49)



Note: Test: A single, 105-mg dose (1 x 105-mg tablet of the fenofibric acid formulation) given in the fasting state

Reference: A single, 145-mg dose (1 x 145-mg tablet of the TRICOR® [fenofibrate] commercial formulation) given in the fasting state

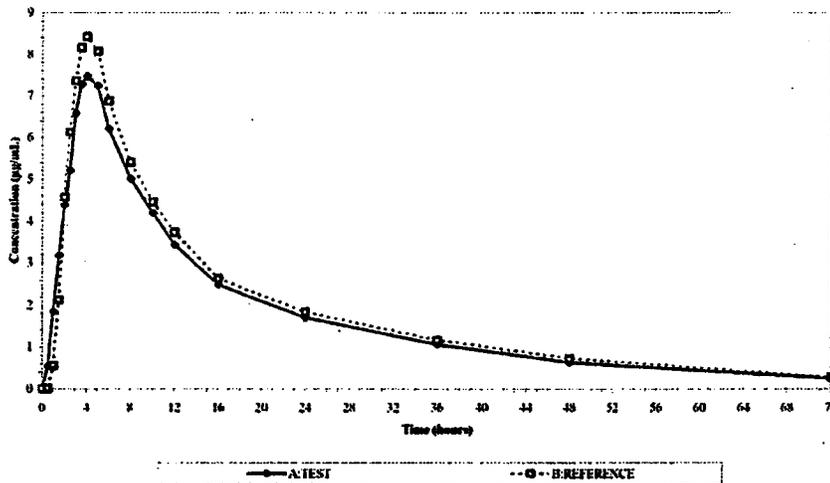
The sponsor also evaluated the bioequivalence of the 105 mg fenofibric acid tablets to the reference product under fed conditions (Study MPC-028-07-1008). In this randomized, single dose, two-way crossover study, 54 subjects were enrolled and the bioequivalence of test and reference was evaluated under standardized meal conditions. The standardized meal did not meet the requirements of an FDA high fat high calorie meal. It consisted of 55% carbohydrates, 9% protein and 36% fat with 316, 2, and 207 calories respectively. The total caloric content of this meal was 575 calories. 47 subjects completed the study. Compared to Tricor, the geometric mean ratios for AUC_{0-inf} , AUC_{0-last} , and C_{max} , and the 90% confidence interval fall wholly within 80-125% (Table 6). A plasma concentration vs.

time profile of both test and reference product is illustrated in Figure 2. The rate and extent of exposure was approximately 10% lower in the test product compared to the reference product.

Table 6 Study MPC-028-07-1008: Summary Statistics of fenofibric acid tablets vs. Tricor® following a standard breakfast

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=47				
Parameter	Fenofibric Acid Tablets (105 mg)	TriCor® Fenofibrate Tablets (145 mg)	% Ratio	90% CI
AUC _{0-∞} (µg·hr/mL)	113.62538	123.91562	91.70	(89.73, 93.7)
AUC _{0-t} (µg·hr/mL)	124.88596	137.01609	91.15	(89.08, 93.26)
C _{max} (µg/mL)	8.36916	9.30079	89.98	(86.78, 93.31)

Figure 2 Mean Fenofibric Acid Plasma Concentration versus Time Profile (N=47)



Note: Test: A single, 105-mg dose (1 x 105-mg tablet of the fenofibric acid formulation) given under standardized meal conditions

Reference: A single, 145-mg dose (1 x 145-mg tablet of the TRICOR® [fenofibrate] commercial formulation) given under standardized meal conditions

2.1.3 What is the in-vitro metabolism of fenofibric acid?

An in-vitro study (Study MPC-028-06-0001) determining the metabolism of fenofibric acid was conducted in human liver microsomes and expressed recombinant human microsomes, containing one of the following CYP isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

Incubations of 5.7 and 57 µM in the presence and absence of CYP-isoform specific inhibitors and in presence of human liver microsomes, and recombinant human microsomes containing a single

expressed recombinant human CYP-isoform indicate that the CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 do not play a role in the metabolism of fenofibric acid.

2.1.4 What is the CYP P450 inhibition potential of fenofibric acid in vitro?

An in-vitro study (MPC-028-06-0002) determining the potential for fenofibric acid to inhibit the activities of CYP2B6 and CYP2C8 in human liver microsomes was conducted. Significant concentration-dependent inhibition of CYP2B6 and CYP2C8 activities by fenofibric acid was observed. The calculated IC₅₀ values for inhibition of CYP2B6 activity were 820 µM for co-incubation and 741 µM for pre-incubation. The calculated IC₅₀ values for inhibition of CYP2C8 activity were 282 µM for co-incubation and 441 µM for pre-incubation.

A separate determination of the K_i values for inhibition of CYP2B6 and CYP 2C8 was conducted — In Vitro Inc Reference Number 0305-122-05). The calculated K_i value for inhibition of CYP2B6 activity was 208 µM. The calculated K_i value for inhibition of CYP2C8 activity was 201 µM.

b(4)

As a conclusion of this study, an in-vivo drug interaction study with efavirenz to assess the interaction potential of fenofibric acid with CYP 2B6 substrates was conducted under study # MPC-028-08-1018.

2.1.5 What is the CYP P450 induction potential of fenofibric acid in vitro?

Two in vitro studies were conducted to assess the induction potential of fenofibric acid on CYP enzymes. Study MPC-028-06-1003 evaluated the induction potential of fenofibric acid on the activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 and the cytotoxic potential of fenofibric acid in human hepatocytes at concentrations of 34, 57, 114, 284, 568, and 1135 µM.

Fenofibric acid showed induction of the CYP2C8 enzyme activities. The CYP2C8 enzyme activities were >200% of vehicle control activities for two of the three donors at concentrations ranging from 100–500 µM. The enzyme activities at these concentrations were also >40% of reference control activities (10 µM rifampin). Fenofibric acid showed cytotoxic potential at concentrations ≥ 500 µM for Donor 4 and ≥ 1000 µM for Donor 5. Fenofibric acid did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP 2C19, CYP2D6, CYP2E1, or CYP 3A4.

A subsequent study MPC-028-07-0002 was conducted at fenofibric acid concentrations of 5.7, 57, and 570 µM. No apparent cytotoxicity was observed after treatment with fenofibric acid in the cultures of hepatocytes. The percent increases in enzyme activity ranged between 6.1 and 34.0 % of the adjusted positive control response for CYP 2C8 across all hepatocyte cultures treated with fenofibric acid, and were thus below the set cutoff of ≥40 % increase of the positive control. In this study, fenofibric acid did not induce CYP1A2, CYP2A6, CYP2B6, CYP 2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP 3A4 (Table 7).

Overall concentrations of 5.7, 57 and 570 µM represent plasma concentrations of 1.8, 18, and 180 µg/mL, and concentrations above 100 µM represent plasma concentrations above 31.8 µg/ml. which is approximately 2.5 fold higher than the peak plasma concentration reported in the pivotal bioequivalence study MPC-028-07-1007. The in-vitro study results are inconclusive with regards to the CYP2C8 induction.

Table 7 Summary of Enzyme Activity (% Adjusted Positive Control) after Treatment with Fenofibric acid (Study MPC-028-07-0002)

Treatment	CYP1A2			CYP2A6			CYP2B6		
	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702
3-MC (2 µM)	100	100	100	-10.4	-22.5	-20.5	1.6	1.0	3.4
Phenobarbital (1000 µM)	4.6	3.6	2.6	100	100	100	100	100	100
Rifampicin (10 µM)	3.9	4.2	2.1	73.5	74.2	51.7	35.1	50.2	37.6
Dexamethasone (50 µM)	2.3	1.4	1.1	1.3	-20.6	2.2	6.0	1.8	1.6
Fenofibric acid (5.7 µM)	0.47	0.20	-0.23	-7.6	-16.6	-3.7	0.90	4.5	0.17
Fenofibric acid (57 µM)	-0.25	0.05	-0.29	-26.2	-21.9	-15.1	0.23	-0.04	0.39
Fenofibric acid (570µM)	-0.17	0.63	-0.39	-74.1	-40.6	-38.8	6.4	13.0	4.7
Treatment	CYP2C8			CYP2C9			CYP2C19		
	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702
3-MC (2 µM)	3.1	-4.2	-2.2	21.6	-5.8	13.2	15.7	-1.1	9.2
Phenobarbital (1000 µM)	76.9	65.9	86.3	75.8	79.2	94.0	21.8	20.5	-23.8
Rifampicin (10 µM)	100	100	100	100	100	100	100	100	100
Dexamethasone (50 µM)	13.4	1.3	9.2	9.0	-23.0	5.3	-5.8	-5.5	-28.8
Fenofibric acid (5.7 µM)	6.1	9.2	13.7	-1.4	-9.5	10.3	11.4	7.5	5.7
Fenofibric acid (57 µM)	6.5	13.5	22.3	-46.5	-35.8	-31.5	-7.4	-1.6	-17.8
Fenofibric acid (570µM)	16.8	23.2	34.0	-62.0	-48.6	-47.0	-18.7	-1.4	-25.3
Treatment	CYP2D6			CYP2E1			CYP3A4		
	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702
3-MC (2 µM)	NA*	NA*	NA*	NA*	NA*	NA*	-2.5	-8.2	-5.7
Phenobarbital (1000 µM)	NA*	NA*	NA*	NA*	NA*	NA*	85.2	88.2	83.0
Rifampicin (10 µM)	NA*	NA*	NA*	NA*	NA*	NA*	100	100	100
Dexamethasone (50 µM)	NA*	NA*	NA*	NA*	NA*	NA*	9.2	-1.2	3.3
Fenofibric acid (5.7 µM)	NA*	NA*	NA*	NA*	NA*	NA*	-0.21	0.38	-0.52
Fenofibric acid (57 µM)	NA*	NA*	NA*	NA*	NA*	NA*	0.40	4.1	1.5
Fenofibric acid (570µM)	NA*	NA*	NA*	NA*	NA*	NA*	10.2	19.9	16.4

NA*: No Recommended Positive Controls

2.2. Extrinsic Factors

2.2.1. What is the effect of food on the pharmacokinetics of the 105 mg fenofibric acid tablet?

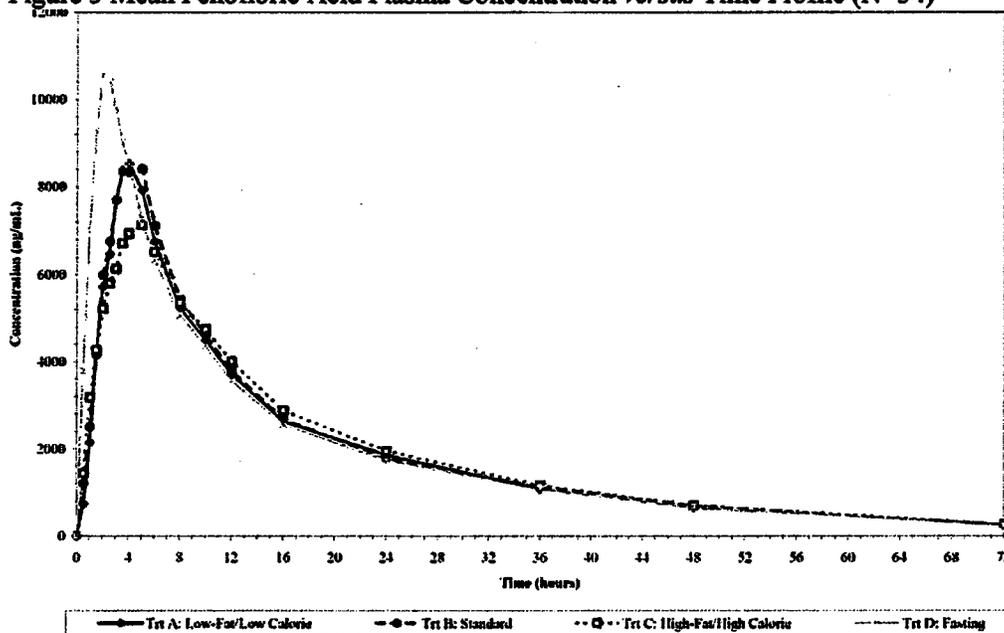
To evaluate the effect of food on Mutual's 105 mg fenofibric acid tablets a four arm, single-dose, food effect study with 105 mg fenofibric acid tablets administered in a fasted state and three different fed conditions, low-fat meal, standard meal, and high fat/ high calorie meal (Study MPC-028-07-1009). A comparison of the meal composition is illustrated in Table 8.

Meal type		Total calories	Carbohydrates	Protein	Fat
Low fat breakfast	Total %		81%	10%	9%
	Total calories	497	400	52	45
Standardized breakfast	Total %		55%	9%	36%
	Total calories	575 (per protocol) (524 actual)	316	2	207
High fat breakfast	Total %		30%	15%	55%
	Total calories	923.6	280	136	507.6

The C_{max} of fenofibric acid is significantly lower when administered under fed conditions. When administered with a low fat meal, the C_{max} is approximately 20% lower, when administered with a high fat/high calorie meal; the C_{max} is approximately 35% lower. The overall extent of exposure is unaffected. Since there is insufficient data to suggest that the response to fenofibric acid is not exposure driven, we cannot conclude that a decrease in C_{max} is likely to result in a clinical significant difference in response. Mutual's 105 mg fenofibric acid tablets are bioequivalent to the reference listed drug under fasted (MPC-028-07-1007) and standardized fed conditions (MPC-028-07-1008). Median T_{max} was increased from 1.5 h under fasting conditions to 3.75, 3.5, and 4 h when administered after a low, standardized, and high fat meal respectively. A comparison of the test product under fasted conditions vs. all the meal conditions is illustrated in Table 9 and Figure 3.

Parameter	Treatment A vs. D		Treatment B vs. D		Treatment C vs. D	
	% Ratio	90 % CI	% Ratio	90 % CI	% Ratio	90 % CI
AUC_{0-t} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	94.06	(91.06, 97.16)	95.37	(92.32, 98.52)	96.36	(93.29, 99.54)
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	94.53	(91.49, 97.67)	95.64	(92.57, 98.82)	96.88	(93.77, 100.1)
C_{max} ($\mu\text{g}/\text{mL}$)	80.78	(76.7, 85.08)	81.85	(77.71, 86.2)	65.42	(62.11, 68.9)
Treatment A: Fenofibric Acid Tablets, 105 mg – following a low-fat breakfast Treatment B: Fenofibric Acid Tablets, 105 mg – following a standard meal Treatment C: Fenofibric Acid Tablets, 105 mg – following a high-fat/high-calorie meal Treatment D: Fenofibric Acid Tablets, 105 mg – fasted state						

Figure 3 Mean Fenofibric Acid Plasma Concentration *versus* Time Profile (N=34)



2.2.2 What is the interaction potential on CYP 2B6 substrates?

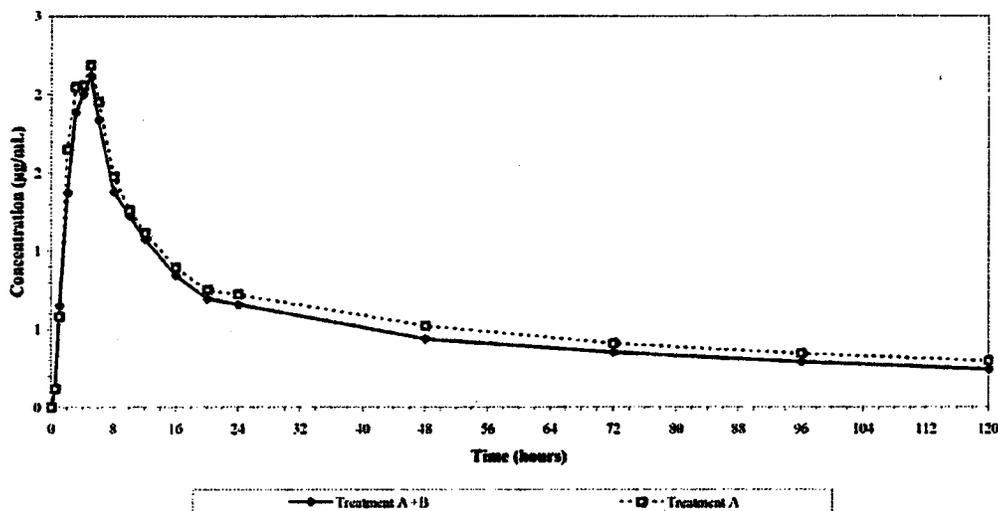
In an open-label drug interaction study to investigate the effects of steady state fenofibric acid on the single-dose pharmacokinetics of efavirenz in healthy volunteers, efavirenz was given while fenofibric acid was at steady state concentrations (MPC-028-08-1018). There was no significant effect on peak efavirenz plasma concentration compared to efavirenz alone (Table 10, Figure 4). However, the total exposure of efavirenz was lowered by approximately 10-11%. The efavirenz label does not recommend a dose adjustment when efavirenz exposure is lowered by 12% when given concomitantly with nelfinavir. No dose adjustment is necessary.

Table 10 Study MPC-028-08-1018: Ln-Transformed Geometric Mean Efavirenz Pharmacokinetic Parameter Values When Administered Alone *versus* Efavirenz Pharmacokinetic Parameter Values When Co-Administered with Steady-State Fenofibric Acid in Healthy Adults, N=24

Parameter	Efavirenz 600-mg Tablet + Fenofibric Acid 105-mg Tablet (Test)	Efavirenz 600 mg Tablet (Reference)	% Ratio	90% CI
Ln-AUC _{0-∞}	60.97	68.06	89.59	79.18, 101.38
Ln-AUC _{0-t}	91.76	103.35	88.79	77.44, 101.80
Ln-C _{max}	2.32	2.38	97.62	86.32, 110.40

Source: Table 14.2.8

Figure 4 Comparative Efavirenz Plasma Concentration *versus* Time Profiles Day 1 (Efavirenz alone – Treatment A) and Day 31 (Efavirenz + Fenofibric Acid, - Treatment A+B) (N=24)



2.3 Analytical

2.3.1 Are the analytical methods appropriately validated?

Yes, both analytical method for fenofibric acid and efavirenz were adequately validated.

Fenofibric acid:

The interday coefficient of variation (%CV) for the 70, 900 and 1800 ng/mL QCs are 6.1%, 4.3%, and 5.2% respectively. All intraday %CV's are below 4.8%. Deviations of the measured concentration from the nominal concentrations of fenofibric acid are within 10.2%. The assay is sensitive to quantify concentrations of 25 ng/ml.

Short-term stability is 6 hours at room temperature and fenofibric acid is stable over three freeze/thaw cycles.

In the partial validation report, FL06-MUT-TR032A2 the dynamic range is expanded from 25-2500 ng/ml to 250 to 25000 ng/ml. Intraday precision (%CV) for this dynamic range is less than 3.5%.

Efavirenz:

The intraday coefficient of variation (%CV) for the 730.00, 400.0, and 6000 ng/ml QCs is between 2.0 and 5.6%. The intraday accuracy for the quality controls is within the range of 90.2 to 102%. Interday coefficient of variation for the calibration standards is within the range of 2.2-5.1% and accuracy is within the range of 96.5 to 1.3%. For the QC samples, interday precision is within the range of 3.8-5.6%. A validation addendum includes the long-term stability at -20°C, which was determined to be at least 86 days

3. Preliminary Labeling Recommendations

Labeling statements to be removed are shown in ~~red strikethrough~~ and suggested labeling to be included is shown in underline blue font.

b(4)

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b(4)

4. Appendix

4.1. INDIVIDUAL STUDY REVIEW

4.1.1. Fasted Bioequivalence Study: MPC-028-07-1007

TITLE: "A single-dose, bioequivalence study of 105 mg fenofibric acid tablets versus 145 mg Tricore (fenofibrate) tablets under fasting conditions."

CLINICAL FACILITY: PRACS Institute, Ltd. - Cetero Research, 4801 Amber Valley Parkway, Fargo, ND, USA

BIOANALYTICAL FACILITY: _____

b(4)

STUDY PERIOD: October 27 to November 06, 2007

OBJECTIVE: To compare the bioequivalence of Mutual's 105 mg fenofibric acid tables to Abbott's 145 mg Tricor® tablets.

STUDY DESIGN:

- Randomized single dose, two way cross over
- 7 day washout between dosing

Table 11 Treatment Sequences

Sequence (Group)	N	Treatment	
		Period 1	Period 2
1	27	A	B
2	27	B	A

Treatment A: A single, 105-mg dose (1 x 105-mg tablet of the fenofibric acid formulation) given in the fasting state (test)

Treatment B: A single, 145-mg dose (1 x 145-mg tablet of the TRICOR® [fenofibrate] commercial formulation) given in the fasting state (reference)

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hour post-dose.

SUBJECTS: 54 healthy-non smoking subjects (19 men and 35 women) were enrolled. The demographic characteristics for all enrolled subjects are summarized in the following Table.

Table 12 Demographic Characteristics

Parameters	All Subjects (N=54)	Males (N=19)	Females (N=35)
Mean Age (years), range	23.8 (18-43)	23.9 (18-43)	23.7 (18-38)
Mean Weight (lbs), range	155.2 (103.0-267.0)	181.1 (138.0-267.0)	141.1 (103.0-192.0)
Mean Height (in.), range	67.0 (59.0-80.0)	70.8 (67.0-80.0)	65.0 (59.0-72.0)
Mean BMI (units), range	24.1 (17.8-29.5)	25.3 (20.4-29.4)	23.5 (17.8-29.5)
Race¹ [n (%)]			
American Indian or Alaskan Native:	1 (1.85%)	0 (0%)	1 (2.86%)
Black or African American:	1 (1.85%)	1 (5.26%)	0 (0%)
Asian:	2 (3.70%)	1 (5.26%)	1 (2.86%)
White, American Indian or Alaskan Native:	2 (3.70%)	2 (10.53%)	0 (0%)
White:	48 (88.89%)	15 (78.95%)	33 (94.29%)

¹Mean (percentage)

ANALYTICAL METHOD:

A validated high performance liquid chromatography (HPLC) assay with MS/MS detection was employed for the detection of fenofibric acid in human plasma. The assay used protein precipitation out of human plasma containing K2EDTA as anticoagulant.

Results of the quality control of this bioanalytical report are represented in the following Table.

Table 13 Results of Quality Control

Analyte / Parameter	Curve range (ng/mL)	Calibration		Quality control (between batch)	
		LLOQ (ng/mL)	%CV	%CV	%Bias
Fenofibric acid	250-25000	250	1.1-3.2%	3.1-3.4%	-5.6 to -8%

A set of eight calibration standards were used covering a range from 250 to 25000 ng/mL. Three quality controls were used during the batch runs: 700, 9000, and 18000 ng/mL. The lower limit of quantification was 250 ng/mL.

RESULTS:

- 49 subjects completed the study and were included in the analysis
- 5 subjects had one missing blood sample
- The summary of the pharmacokinetic parameters for fenofibric acid and their geometric least squares mean values are given in the following Tables:

Table 14 Summary Statistics by Treatment Arm and Pharmacokinetic Parameter

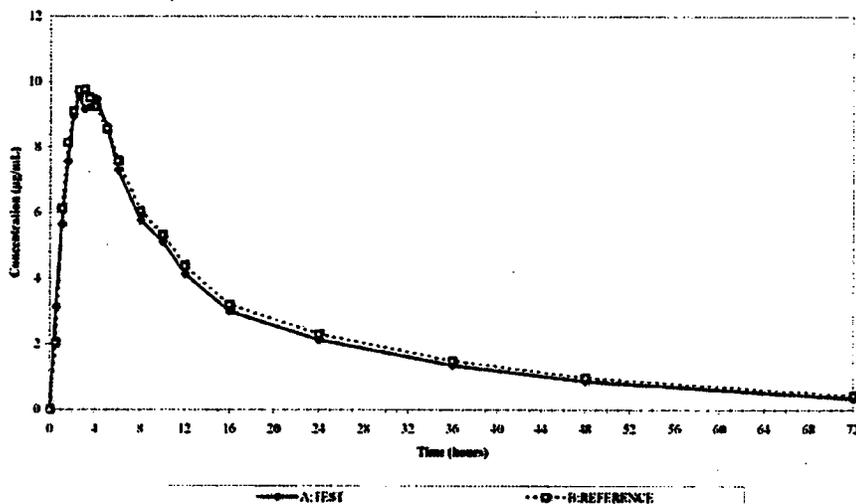
Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T _{max}	
	Fenofibric Acid 105 mg (N=49)	Fenofibrate (TriCor [®]) 145 mg (N=49)
AUC _{0-∞} (μg·hr/mL)	159.86623 (39.94)	170.7271 (38.81)
AUC _{0-t} (μg·hr/mL)	176.81678 (42.98)	188.33149 (41.52)
C _{max} (μg/mL)	12.344 (24.57)	10.94005 (23.55)
T _{max} (hr)	2.50 (1.00 – 5.00)	2.50 (1.00 – 5.00)
K _d (1/hr)	0.0403 (37.23)	0.0377 (27.17)
T _{1/2} (hr)	18.93 (28.62)	19.69 (26.15)
V _d /F (L)	17.30 (22.54)	17.17 (28.04)
CL/F (mL/hr)	700.75 (43.29)	656.01 (43.34)
Weight-adjusted CL/F (mL/hr/kg)	10.06 (41.41)	9.41 (41.00)

Table 15 Statistical Summary Statistical Summary (Geometric means, ratio of means, and 90% confidence intervals) Ln-transformed data

Parameter	Fenofibric Acid Tablets (105 mg)	TriCor [®] Tablets (145 mg)	% Ratio	90% CI
AUC _{0-∞} (μg·hr/mL)	148.59371	158.70070	93.63	(91.28, 96.05)
AUC _{0-t} (μg·hr/mL)	162.95683	173.93396	93.69	(91.67, 95.75)
C _{max} (μg/mL)	12.00135	10.65025	112.69	(107.99, 117.59)

The following plot of mean fenofibric acid plasma concentrations versus time by treatment on linear scale was submitted by the sponsor:

Figure 5 Mean Fenofibric Acid Plasma Concentration *versus* Time Profile (N=49)



Note: Test: A single, 105-mg dose (1 x 105-mg tablet of the fenofibric acid formulation) given in the fasting state

Reference: A single, 145-mg dose (1 x 145-mg tablet of the TRICOR[®] [fenofibrate] commercial formulation) given in the fasting state

SAFETY:

Fourteen (14) subjects (25.9%) experienced twenty-nine (29) adverse events (AEs) over the course of the study. One serious adverse event (SAE), a pregnancy that resulted in miscarriage, was reported over the course of this study. Overall, the most common AE was headache occurring in 9/54 (16.7%) subjects. Adverse events were mild or moderate in intensity.

CONCLUSION:

The results from Study MPC-028-07-1007 (n=49) demonstrated that Mutual's 105 mg fenofibric acid tablet compared to the RLD Abbott's Tricor® 145 mg fenofibrate tablet shows comparable AUC_{0-inf}, AUC_{0-last}, and C_{max}, and that the confidence intervals for the ratio of adjusted geometric means for both AUC_{inf}, AUC_{0-last}, and C_{max} fell within the bioequivalence interval of 80% to 125%. Thus, Mutual's fenofibric acid tablets are bioequivalent to Abbott's fenofibrate tablets.

REVIEWER'S COMMENT:

- This reviewer re-analyzed the BE datasets using WinNonlin and SAS program and got the same results as the sponsor.
- The test product met the bioequivalence criteria when administered in fasted state.

4.1.2. Food Effect Study: MPC-028-07-1009

TITLE: "A four arm, single-dose, food effect evaluation with 105 mg fenofibric acid tablets administered in a fasted state and three different fed conditions, low-fat meal, standard meal, and high fat/ high calorie meal."

OBJECTIVE: To compare the rate and extent of absorption of fenofibric acid when administered as a single 105-mg dose to healthy volunteers with a low-fat meal, standard meal, and high fat/ high-calorie meal compared to the fasted state.

STUDY DESIGN:

- Open-label, single-dose, randomized, four-period crossover
- 7 day washout between dosing
- Meal composition as follows:

Table 16 Caloric Breakdown of the Standardized Low-Fat Breakfast (Treatment A)

Menu Item	Total Calories	Carbohydrates (Grams)	Protein (Grams)	Fat (Grams)
1 Lowfat muffin	208	48	4	0
1 Margarine	45	---	---	5
1 Individual box of Cornflakes	76	18	1	---
6 oz Apple juice	84	21	---	---
8 fluid oz. (1 x 240 mL) skim milk	84	13	8	---
---	---	Total: 100	Total: 13	Total: 5
Total Percent		81%	10%	9%
Total Calories	497	400	52	45

Table 17 Caloric Breakdown of the Standardized Breakfast (Treatment B)

Menu Item	Total Calories	Carbohydrates (Grams)	Protein (Grams)	Fat (Grams)
6 oz Orange juice	84	21	---	---
1 Blueberry Muffin	257	32	3	13
1 Margarine	45	---	---	5
1 Individual box of Cheerios	60	13	2	---
8 fluid oz. (1 × 240 mL) 2% milk	129	13	8	5
---	---	Total: 79	Total: 13	Total: 23
Total Percent		55%	9%	36%
Total Calories	575	316	2	207

Table 18 Caloric Breakdown of the Standardized High-Fat Breakfast (Treatment C)

Menu Item	Total Calories	Carbohydrates (Grams)	Protein (Grams)	Fat (Grams)
2 medium eggs	151	---	13	11
-fried in 1 pat (2 tsp) of butter	72	---	---	8
2 strips of bacon	68.6	---	5	5.4
2 slices of toast	144	30	6	---
-with 1 pat (2 tsp) butter	72	---	---	8
4 oz. hash brown potatoes	264	28	2	16
8 fluid oz. (1 × 240 mL) whole milk	152	12	8	8
---	---	Total: 70	Total: 34	Total: 56.4
Total Percent		30 %	15%	53%
Total Calories	923.6	280	136	507.6

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected predose and at 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 36, 48, and 72 hours.

SUBJECTS: 37 healthy, non-smoking subjects (16 men and 21 women) were enrolled. The demographic characteristics for all enrolled subjects are summarized in the following Table.

Table 19 Demographic Characteristics

Parameters	All Subjects (N=37)	Males (N=16)	Females (N=21)
Mean Age (years), Range	23.9 (18-45)	25.0 (19-45)	23.0 (18-43)
Mean Weight (lbs), Range	153.4 (108-222)	168.9 (124-222)	141.6 (108-179)
Mean Height (in.), Range	66.7 (60-74)	68.8 (62-74)	65.1 (60-69)
Mean BMI (units), Range	24.1 (18.5-29.8)	25.1 (21.1-28.5)	23.5 (18.5-29.8)
Race [n (%)]			
African American:	1 (2.7%)	1 (6.3%)	0.0%
Asian:	2 (5.4%) ¹	2 (12.5%) ¹	0.0%
Caucasian:	33 (89.2%) ¹	13 (81.3%)	20 (95.2%) ¹
American Indian:	1 (2.7%)	0.0%	1 (4.7%)

¹ One of whom was Hispanic

ANALYTICAL METHOD:

A validated high performance liquid chromatography (HPLC) assay with MS/MS detection was employed for the detection of fenofibric acid in human plasma. The assay used protein precipitation out of human plasma containing K2EDTA as anticoagulant.

Results of the quality control of this bioanalytical report are represented in the following Table.

Table 20 Results of Quality Control

Analyte / Parameter	Curve range (ng/mL)	Calibration		Quality control (between batch)	
		LLOQ (ng/mL)	%CV	%CV	%Bias
Fenofibric acid	250-25000	250	1.1-2.3	3.5-4.5	0.0-2.4%

A set of eight calibration standards were used covering a range from 250 to 25000 ng/mL. Three quality controls were used during the batch runs: 700, 9000, and 18000 ng/mL. The lower limit of quantification was 250 ng/mL.

RESULTS:

- 34 subjects completed the study and were included in the analysis
- The summary of the pharmacokinetic parameters for fenofibric acid and their geometric least squares mean values are given in the following Tables:

Table 21 Summary Statistics by Treatment Arm and Pharmacokinetic Parameters: Arithmetic Means (% CV) of Non-Transformed Data for Fenofibric Acid

Parameter (unit)	Treatment A Low-fat (9%)/ Calorie (497 kcal) Meal (N=34)	Treatment B Standard Fat (36%) Calorie (575 kcal) Meal (N=34)	Treatment C High-fat (55%) High-Calorie (924 kcal) Meal (N=34)	Treatment D Fasting (N=34)
AUC _{0-t} (µg·hr/mL)	132.64 (35.91)	134.93 (37.25)	134.81 (34.96)	139.98 (34.88)
AUC _{0-∞} (µg·hr/mL)	145.83 (38.50)	148.37 (39.65)	148.49 (37.68)	152.57 (36.09)
C _{max} (µg/mL)	9.81 (21.63)	9.85 (20.10)	7.95 (24.16)	12.06 (18.58)
T _{max} (hr) ¹	3.75 (1.50 – 6.00)	3.50 (1.50 – 5.13)	4.00 (1.00 – 6.00)	1.50 (1.00 – 5.00)
K _e (1/hr)	0.0434 (35.17)	0.0444 (32.92)	0.0447 (34.34)	0.0454 (34.63)
t _{1/2} (hr)	17.29 (36.46)	17.25 (31.65)	17.38 (34.66)	16.83 (29.80)
V _{zss} /F (L)	18.57 (21.90)	18.41 (19.27)	18.34 (24.36)	17.16 (14.07)
CL/F (mL/hr)	833.47 (39.24)	822.15 (38.41)	802.56 (34.45)	779.47 (35.69)
Weight-adjusted CL/F (mL/hr/kg)	12.12 (42.63)	11.96 (41.95)	11.63 (37.02)	11.35 (39.94)

¹Median (Range)

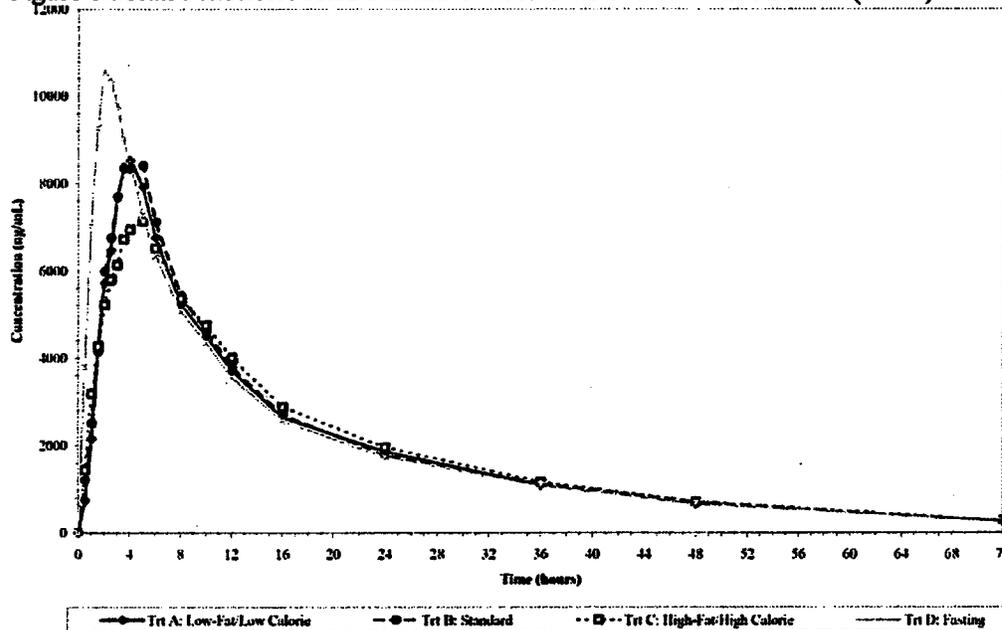
Table 22 Study MPC-028-07-1009: Statistical Summary Statistical Summary (Geometric means, ratio of means, and 90% confidence intervals) Ln-transformed data

Parameter	Treatment A vs. D		Treatment B vs. D		Treatment C vs. D	
	% Ratio	90 % CI	% Ratio	90 % CI	% Ratio	90 % CI
AUC _{0-t} (µg·hr/mL)	94.06	(91.06, 97.16)	95.37	(92.32, 98.52)	96.36	(93.29, 99.54)
AUC _{0-∞} (µg·hr/mL)	94.53	(91.49, 97.67)	95.64	(92.57, 98.82)	96.88	(93.77, 100.1)
C _{max} (µg/mL)	80.78	(76.7, 85.08)	81.85	(77.71, 86.2)	65.42	(62.11, 68.9)

Treatment A: Fenofibric Acid Tablets, 105 mg – following a low-fat breakfast
 Treatment B: Fenofibric Acid Tablets, 105 mg – following a standard meal
 Treatment C: Fenofibric Acid Tablets, 105 mg – following a high-fat/high-calorie meal
 Treatment D: Fenofibric Acid Tablets, 105 mg – fasted state

The following plot of mean fenofibric acid plasma concentrations versus time by treatment on linear scale was submitted by the sponsor:

Figure 6 Mean Fenofibric Acid Plasma Concentration *versus* Time Profile (N=34)



The BE criteria are met concerning exposure, when fenofibric acid is given under different meal conditions. However, the criteria are not met with regard to C_{max} under any of the meal conditions. C_{max} is approximately 9% lower when administered with a low fat meal and 35% lower when administered with a high fat high calorie meal.

SAFETY:

Ten (10) subjects (27.0%) experienced 19 adverse events (AEs) over the course of the study. Adverse events were mild to moderate in severity. One (1) resulted in discontinuation. The AE that led to discontinuation of subject 23 (vomiting, diarrhea, dizziness) was deemed unrelated to the study article.

CONCLUSION:

The results from Study MPC-028-07-1009 (n=34) demonstrates that Mutual's 105 mg fenofibric acid tablet administered under different meal condition was comparable to the RLD Abbott's Tricor® 145 mg fenofibrate tablet regarding AUC_{0-inf} and AUC_{0-last} . The ratio of adjusted geometric means for treatment C (high fat/high calorie meal) and the confidence interval for all three treatments with regards to C_{max} were outside the bioequivalence interval of 80% to 125%.

REVIEWER'S COMMENT:

- The actual caloric content of the standardized breakfast was only 524 kcal rather than the stated 575 kcal.
- The product did not meet the BE criteria under any of the meal conditions.
- The C_{max} of fenofibric acid is significantly lower when administered under fed conditions. When administered with a low fat meal, the C_{max} is approximately 10% lower, when

administered with a high fat/high calorie meal; the C_{max} is approximately 35% lower. The overall extent of exposure is unaffected. Since there is insufficient data to suggest that the response to fenofibric acid is not exposure driven, we cannot conclude that a decrease in C_{max} is likely to result in a clinical significant difference in response.

4.1.3. Fed Bioequivalence Study: MPC-028-07-1008

TITLE: "A single-dose, bioequivalence study of 105 mg fenofibric acid tablets versus 145 mg Tricore® (fenofibrate) tablets under fed conditions (standard meal)."

OBJECTIVE: To characterize the pharmacokinetic profile of fenofibric acid when administered as a single 105-mg dose to healthy volunteers in a fed state (standard meal).

STUDY DESIGN:

- Randomized, single-dose, two-way crossover study
- 54 healthy subjects were enrolled
- 7 day washout between dosing
- Meal composition as follows:

Table 23 Caloric Breakdown of the Standardized Breakfast

	Calories	Carbohydrates (g)	Protein (g)	Fat (g)
6 oz. Orange juice	84	21	-	-
1 Blueberry muffin	257	32	3	13
1 Margarine	45	-	-	5
1 Individual box of Cheerios	60	13	2	-
8 oz. 2% milk	129	13	8	5
Total content (g)	-	79	13	23
Total calories	575	316	2	207
Percent of total calories	100%	55%	9%	36%

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected predose and at 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours.

ANALYTICAL METHOD:

A validated high performance liquid chromatography (HPLC) assay with MS/MS detection was employed for the detection of fenofibric acid in human plasma. The assay used protein precipitation out of human plasma containing K2EDTA as anticoagulant.

Results of the quality control of this bioanalytical report are represented in the following Table.

Table 24 Results of Quality Control

Analyte / Parameter	Curve range (ng/mL)	Calibration		Quality control (between batch)	
		LLOQ (ng/mL)	%CV	%CV	%Bias
Fenofibric acid	250-25000	250	0.9-5.3	4.1-9.3	7.9-4.3%

A set of eight calibration standards were used covering a range from 250 to 25000 ng/mL. Three qualities controls were used during the batch runs: 700, 9000, and 18000 ng/mL. The lower limit of quantification was 250 ng/mL.

RESULTS:

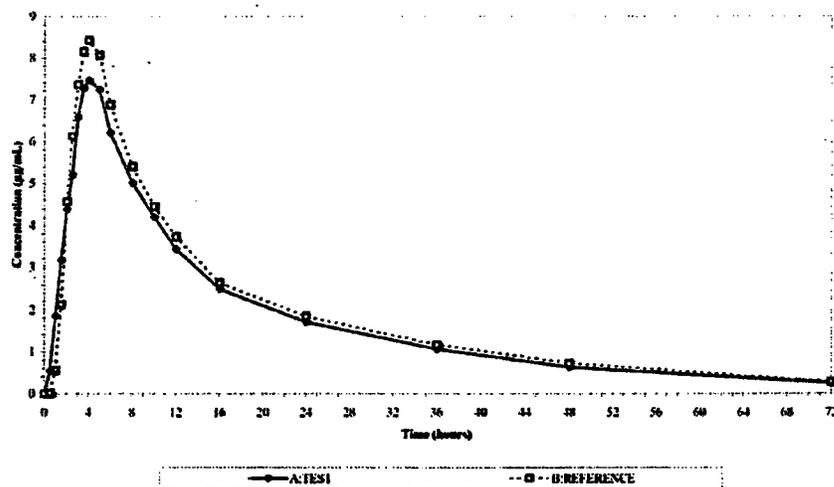
- 47 subjects completed the study and were included in the analysis
- The summary of the pharmacokinetic parameters for fenofibric acid and their geometric least squares mean values are given in the following Tables:

Table 25 Study MPC-028-07-1008: Summary Statistics of fenofibric acid tablets vs. Tricor® following a standard breakfast

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=47				
Parameter	Fenofibric Acid Tablets (105 mg)	TriCor® Fenofibrate Tablets (145 mg)	% Ratio	90% CI
AUC _{0-∞} (µg·hr/mL)	113.62538	123.91562	91.70	(89.73, 93.7)
AUC _{0-t} (µg·hr/mL)	124.88596	137.01609	91.15	(89.08, 93.26)
C _{max} (µg/mL)	8.36916	9.30079	89.98	(86.78, 93.31)

The following plot of mean fenofibric acid plasma concentrations versus time by treatment on linear scale was submitted by the sponsor:

Figure 7 Mean Fenofibric Acid Plasma Concentration *versus* Time Profile (N=47)



Test: fenofibric acid tablets 105 mg

Reference: Tricor® 145 mg

The test product met the bioequivalence criteria for AUC and C_{max}. The rate and extent of exposure was approximately 10% lower than the reference product.

REVIEWER'S COMMENT:

- Five subjects were dropped out by the medical investigator due to AE's. One subject had an increased white blood cell count; four subjects had increased creatine phosphokinase levels.

- The meal composition is similar to one of the meals administered in study 1009. Study 1009 however compared the test product i.e. Mutual's 105 mg fenofibric acid tablets under fasted and three different fed conditions, whereas this study compared test (Mutual's 105 mg fenofibric acid tablet) and reference product (Tricor® 145 mg fenofibrate tablet) under fed conditions.

4.1.4. Extrinsic Factor Study: MPC-028-08-1018

TITLE: "An open-label drug interaction study to investigate the effects of steady state fenofibric acid on the single-dose pharmacokinetics of efavirenz in healthy volunteers."

OBJECTIVE: to determine the effect of multiple doses of fenofibric acid (steady state) on the pharmacokinetics of single-dose efavirenz in healthy adult subjects

STUDY DESIGN:

- open label, non randomized, single center, one sequence drug interaction study
- 30 healthy subjects were enrolled
 - day 1: single dose efavirenz 600 mg
 - 21 day washout
 - day 22 to 30 single daily dose 105 mg fenofibric acid
 - day 31 efavirenz 600 mg plus 105 mg fenofibric acid

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected predose and at 0.5, 1.0, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, and 120 hours post-dose administration.

ANALYTICAL METHOD:

A validated high performance liquid chromatography (HPLC) assay with MS/MS detection was employed for the detection of efavirenz in human plasma. The analysis was performed by an API 4000 LC/MS/MS using _____ as the internal standard (IS). The assay used protein precipitation out of human plasma containing K2EDTA as anticoagulant. Results of the quality control of this bioanalytical report are represented in the following Table.

b(4)

Table 26 Results of Quality Control

Analyte / Parameter	Curve range (ng/mL)	Calibration	%CV	Quality control (between batch)	
		LLOQ (ng/mL)		%CV	%Bias
efavirenz	10-8000 ng/mL	10 ng/mL	1.2 to 5.5%	3.3 to 5.0%	-0.8 to 1.6%

A set of 10 calibration standards were used covering a range from 10.0 to 8000ng/mL. Three qualities controls were used during the batch runs: 30.0, 4000, and 6000 ng/mL. The lower limit of quantification was 10.0 ng/mL.

RESULTS:

- 24 subjects completed the study and were included in the analysis
- The summary of the pharmacokinetic parameters for fenofibric acid and their geometric least squares mean values are given in the following Tables:

Table 27 Mean (%CV) Pharmacokinetic Parameters of Efavirenz (n=24)

Treatment	C _{max} (µg/mL)	AUC ₀₋₁ (µg·hr/mL)	AUC _{0-∞} (µg·hr/mL)	t _{1/2} (hr)	T _{max} * (hr)	K _{e1} (hr)	CL/F (mL/hr)	Vd _{dss} /F (L)
Efavirenz (Day 1)	2.46 (26.61)	70.14 (25.67)	106.69 (25.47)	84.97 (28.22)	3.5 (2.0-6.0)	0.0089 (32.77)	6005.10 (27.85)	711.0 (28.60)
Efavirenz + fenofibric acid (Day 31)	2.38 (24.06)	63.31 (33.87)	96.38 (36.78)	90.75 (33.90)	4.5 (1.0-6.0)	0.0085 (31.99)	6798.05 (25.85)	850.8 (28.98)

Source: Table 14.2.4 and Table 14.2.3

* Median values (range) reported for T_{max}

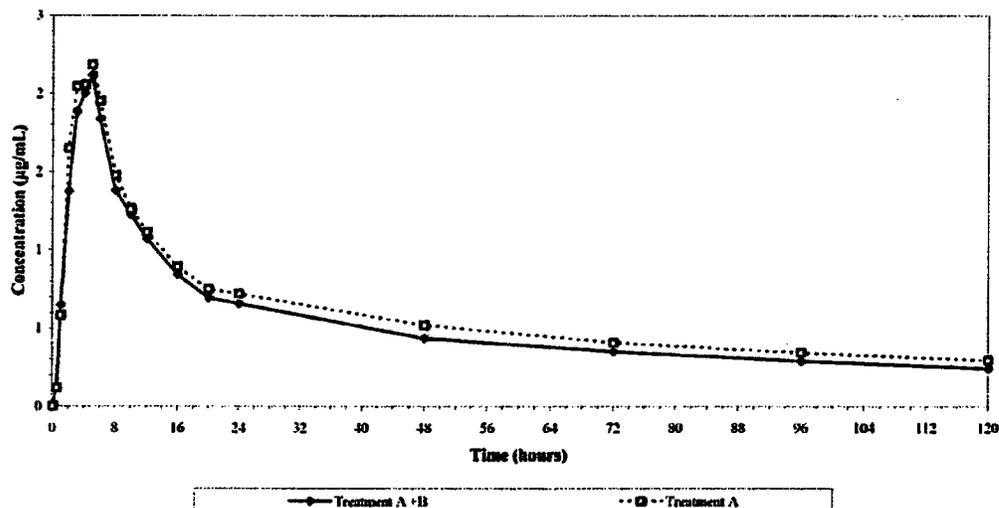
Table 28 Study MPC-028-08-1018: Ln-Transformed Geometric Mean Efavirenz Pharmacokinetic Parameter Values When Administered Alone *versus* Efavirenz Pharmacokinetic Parameter Values When Co-Administered with Steady-State Fenofibric Acid in Healthy Adults, N=24

Parameter	Efavirenz 600-mg Tablet + Fenofibric Acid 105-mg Tablet (Test)	Efavirenz 600 mg Tablet (Reference)	% Ratio	90% CI
Ln-AUC ₀₋₁	60.97	68.06	89.59	79.18, 101.38
Ln-AUC _{0-∞}	91.76	103.35	88.79	77.44, 101.80
Ln-C _{max}	2.32	2.38	97.62	86.32, 110.40

Source: Table 14.2.8

The following plot of mean efavirenz plasma concentrations versus time by treatment on linear scale was submitted by the sponsor:

Figure 8 Comparative Efavirenz Plasma Concentration *versus* Time Profiles Day 1 (Efavirenz alone – Treatment A) and Day 31 (Efavirenz + Fenofibric Acid - Treatment A+B, (N=24)



The total exposure of efavirenz when administered with fenofibric acid at steady state is approximately 10 to 11 % lower than efavirenz administered alone. The maximal exposure (C_{max}) is similar under either administration conditions.

REVIEWER'S COMMENT:

- The efavirenz label does not recommend dose adjustment for an AUC and C_{max} decrease in efavirenz when administered with nelfinavir. Coadministration of efavirenz and nelfinavir results in a decrease in AUC and C_{max} of 12%.
- The interaction potential of fenofibric acid on CYP2B6 substrates is minor.
- 10 out of 24 subjects have measurable concentrations at day 0 of the second period. Concentrations ranged from 11.71 to 44.18 ng/ml mean C_{max} on day 1 and day 31 was 2.46 and 2.38 mcg/ml respectively.
- Carryover of small amounts has little impact on the overall results of the study.

4.1.5. Dosage form proportionality Study: MPC-028-07-1017

TITLE: "An open-label, randomized, single-dose, 3-arm, crossover pharmacokinetic and bioequivalence study of a single 35-mg fenofibric acid tablet (single-dose pharmacokinetics) and three 35-mg fenofibric acid tablets (105-mg total dose) versus one 105-mg fenofibric acid tablet (105-mg total dose) bioequivalence evaluation under fasting conditions."

OBJECTIVE: To evaluate the dose proportionality of fenofibric acid over the 35- to 105-mg dose range when administered to healthy adult volunteers under fasted conditions.

STUDY DESIGN:

- open-label, single-dose, randomized, 3-period, 3-treatment crossover study
- 54 healthy-non smoking subjects (36 males and 18 females) were enrolled
- 7 day washout between dosing

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post dosing.

ANALYTICAL METHOD:

A validated high performance liquid chromatography (HPLC) assay with MS/MS detection was employed for the detection of fenofibric acid in human plasma. The assay used protein precipitation out of human plasma containing K2EDTA as anticoagulant.

Results of the quality control of this bioanalytical report are represented in the following Table

Table 29 Results of Quality Control

Analyte / Parameter	Calibration Curve range (ng/mL)	Calibration		Quality control (between batch)	
		LLOQ (ng/mL)	%CV	%CV	%Bias
Fenofibric acid	250-25000	250	-3.7 to 1.5%	5.9-6.5%	-3.5 to 0.7%%

A set of eight calibration standards were used covering a range from 250 to 25000 ng/mL. Three quality controls were used during the batch runs: 700, 9000, and 18000 ng/mL. The lower limit of quantification was 250 ng/mL.

RESULTS:

- 53 subjects were included in the analysis. One subject was dropped due to the use of concomitant medication.
- The summary of the pharmacokinetic parameters for fenofibric acid and their geometric least squares mean values are given in the following tables:

Table 30 Summary Statistics by Treatment Arm and Pharmacokinetic Parameter

Parameter (unit)	Fenofibric Acid, 35 mg (1 × 35 mg) (N=53)	Fenofibric Acid, 35 mg (35 mg Dose Adjusted to 105 mg) (N=53)	Fenofibric Acid, 35 mg (3 × 35 mg) (N=53)	Fenofibric Acid 105 mg (1 × 105 mg) (N=53)
AUC ₀₋₂₄ (µg·hr/mL)	49.42 (36.80)	148.26 (36.8)	131.98 (31.13)	135.12 (31.33)
AUC _{0-∞} (µg·hr/mL)	58.30 (35.81)	174.91 (35.81)	142.86 (31.89)	147.56 (33.2)
C _{max} (µg/mL)	3.57 (19.19)	10.71 (19.19)	11.01 (18.47)	11.20 (22.05)
T _{max} (hr) ¹	2.50 (1.00 – 8.00)	2.50 (1.00 – 8.00)	2.00 (1.00 – 6.00)	2.50 (1.00 – 5.08)
K _a (1/hr)	0.045 (48.07)	0.045 (48.07)	0.046 (42.77)	0.0445 (44.50)
T _{1/2} (hr)	17.65 (31.87)	17.65 (31.87)	16.92 (29.55)	17.53 (30.76)
V _{dss} /F (L)	15.72 (22.15)	15.72 (22.15)	18.31 (21.27)	18.41 (20.42)
CL/F (mL/hr)	682.73 (38.04)	682.73 (38.04)	811.22 (32.97)	793.53 (34.10)
Weight-adjusted CL/F (mL/hr/kg)	9.21 (43.04)	9.21 (43.04)	10.88 (36.36)	10.65 (37.28)

¹Median (Range)

Source: Table 14.2.5, 14.2.6, 14.2.7, 14.2.8

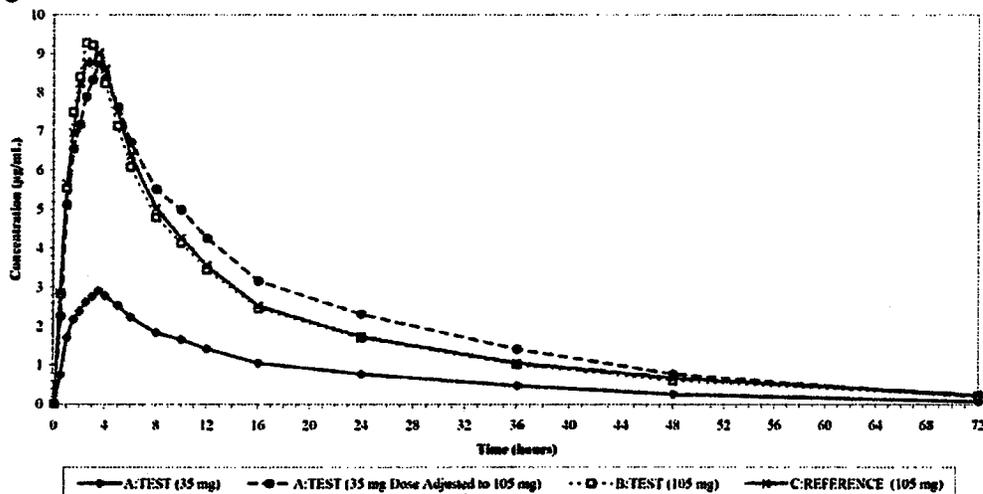
Table 31 Study MPC-028-07-1017: Statistical Summary

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=53				
Parameter	Fenofibric Acid, 1 × 35-mg Tablet (Dose Adjusted to 105 mg)	Fenofibric Acid 1 × 105-mg Tablet	% Ratio	90% CI
AUC ₀₋₂₄ (µg·hr/mL)	138.97	128.70	107.97	(105.54, 110.46)
AUC _{0-∞} (µg·hr/mL)	164.33	139.90	117.46	(114.99, 119.98)
C _{max} (µg/mL)	10.50	10.93	96.04	(93.61, 98.54)

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=53				
Parameter	Fenofibric Acid 3 × 35-mg Tablets	Fenofibric Acid 1 × 105-mg Tablet	% Ratio	90% CI
AUC ₀₋₂₄ (µg·hr/mL)	125.79	128.70	97.74	(95.54, 99.99)
AUC _{0-∞} (µg·hr/mL)	136.03	139.90	97.23	(95.18, 99.32)
C _{max} (µg/mL)	10.84	10.93	99.19	(96.67, 101.77)

The following plot of mean fenofibric acid plasma concentrations versus time by treatment on linear scale was submitted by the sponsor:

Figure 9 Mean Fenofibric Acid Plasma Concentration *versus* Time Profile N=53



The geometric mean ratios for the 1x35 mg adjusted to 105 mg and the 3x35 mg fall within the bioequivalence criteria of 80-125% when compared to the 105 mg tablet.

4.1.6 *In-Vitro* Metabolism: Study MPC-028-06-0001

TITLE: "Determination of fenofibric acid metabolism in human liver microsomes and expressed recombinant human enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4"

OBJECTIVE: The objective of this study was to determine the metabolism of fenofibric acid in human liver microsomes and expressed recombinant human microsomes containing one of the following CYP isoforms; CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

EXPERIMENTAL METHODS:

Two sets of incubations were conducted.

- Set 1: Fenofibric acid in presence and absence of CYP-isoform specific inhibitors
- Set 2: recombinant human microsomes containing a single expressed recombinant human CYP-isoform in presence of fenofibric acid.
- Final concentrations:
 - Fenofibric acid concentrations were final concentrations of 5.7 and 57 μ M.

RESULTS: The metabolism of fenofibric acid was evaluated at 5.7 and 57 μ M. The data from these experiments indicate that CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 do not play a role in the metabolism of fenofibric acid.

REVIEWER'S COMMENT:

- The reviewer agrees with the results

4.1.7 In-Vitro Inhibition: Study MPC-028-06-0002

TITLE: "Determination of the potential for fenofibric acid to inhibit the activities of CYP2B6 and CYP2C8 in human liver microsomes."

OBJECTIVE: The objective of this study was to determine the potential for fenofibric acid to inhibit the activities of cytochrome P450 isoforms CYP2B6 and CYP2C8 in human liver microsomes.

EXPERIMENTAL METHODS:

Two sets of incubations were conducted.

- Set 1 was a co-incubation of fenofibric acid and a selective substrate with microsomes.
- Set 2 was a pre-incubation of fenofibric acid with microsomes for 30 minutes followed by the addition of a selective substrate.
- Incubation concentrations for fenofibric acid were 11, 34, 114, 341, and 1,135 μM

CYP isoform	Isoform-selective substrate	Substrate concentration	Solvent
CYP2B6	Bupropion	150 μM	acetonitrile
CYP2C8	Paclitaxel	5 μM	acetonitrile
CYP3A4*	Testosterone	100 μM	acetonitrile

* CYP3A4 was evaluated as a positive control only.

RESULTS: Significant concentration-dependent inhibition of CYP2B6 and CYP2C8 activities by fenofibric acid was observed. The calculated IC_{50} values for inhibition of CYP2B6 activity were 820 μM for co-incubation and 741 μM for pre-incubation. The calculated IC_{50} values for inhibition of CYP2C8 activity were 282 μM for co-incubation and 441 μM for pre-incubation

A separate determination of the K_i values for inhibition of CYP2B6 and CYP 2C8 was conducted as In Vitro Inc Reference Number 0305-122-05. The calculated K_i value for inhibition of CYP2B6 activity was 208 μM . The calculated K_i value for inhibition of CYP2C8 activity was 201 μM . b(4)

CYP 2B6: $[i]/\text{K}_i = 38.6\mu\text{M}/208\mu\text{M} = 0.189$

CYP 2C8: $[i]/\text{K}_i = 38.6\mu\text{M}/201\mu\text{M} = 0.19$

REVIEWER'S COMMENT:

- The reviewer agrees with the results
- An in vivo drug interaction study with efavirenz to assess the interaction potential of fenofibric acid with CYP 2B6 substrates was conducted under study # MPC-028-08-1018.

4.1.8 In-Vitro Induction: Study MPC-028-07-0002

TITLE: "In vitro assessment of the induction potential of fenofibric acid in primary cultures of human hepatocytes"

OBJECTIVE: To evaluate the potential of fenofibric acid to induce liver microsomal cytochrome P450 (CYP) enzymes.

EXPERIMENTAL METHODS:

- Fenofibric acid concentrations of 5.7, 57 and 570 μM were used
- Fenofibric acid and known CYP inducers were incubated in cultures of human hepatocytes from three separate donors for three consecutive days.
- activities and mRNA of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 were determined
- mRNA of MDR-1 was also determined

RESULTS: The results from this study suggest that there appears to be low potential for drug-drug interactions with fenofibric acid due to enzyme induction of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 at the concentrations examined.

In contrast, these results also indicate that fenofibric acid has the potential to induce MDR1 mRNA expression at 570 μM as showed in all three donors.

No apparent cytotoxicity was observed after treatment with fenofibric acid in the cultures of hepatocytes.

Table 32 Summary of Enzyme Activity (% Adjusted Positive Control) after Treatment with Fenofibric acid (Study MPC-028-07-0002)

Treatment	CYP1A2			CYP2A6			CYP2B6		
	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702
3-MC (2 μM)	100	100	100	-10.4	-22.5	-20.5	1.8	1.0	3.4
Phenobarbital (1000 μM)	4.8	3.8	2.8	100	100	100	100	100	100
Rifampicin (10 μM)	3.9	4.2	2.1	73.5	74.2	51.7	35.1	50.2	37.6
Dexamethasone (50 μM)	2.3	1.4	1.1	1.3	-20.8	2.2	8.0	1.8	1.8
Fenofibric acid (5.7 μM)	0.47	0.20	-0.23	-7.6	-18.6	-3.7	0.90	4.5	0.17
Fenofibric acid (57 μM)	-0.25	0.05	-0.29	-28.2	-21.9	-15.1	0.23	-0.04	0.39
Fenofibric acid (570 μM)	-0.17	0.63	-0.39	-74.1	-40.8	-38.8	8.4	13.0	4.7
Treatment	CYP2C8			CYP2C9			CYP2C19		
	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702
3-MC (2 μM)	3.1	-4.2	-2.2	21.6	-5.8	13.2	15.7	-1.1	9.2
Phenobarbital (1000 μM)	78.9	65.9	88.3	75.8	79.2	94.0	21.8	20.5	-23.8
Rifampicin (10 μM)	100	100	100	100	100	100	100	100	100
Dexamethasone (50 μM)	13.4	1.3	9.2	9.0	-23.0	5.3	-5.8	-5.5	-28.8
Fenofibric acid (5.7 μM)	8.1	9.2	13.7	-1.4	-9.5	10.3	11.4	7.5	5.7
Fenofibric acid (57 μM)	8.5	13.5	22.3	-48.5	-35.8	-31.5	-7.4	-1.8	-17.8
Fenofibric acid (570 μM)	18.8	23.2	34.0	-82.0	-48.8	-47.0	-18.7	-1.4	-25.3
Treatment	CYP2D6			CYP2E1			CYP3A4		
	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702	Hu695	Hu700	Hu702
3-MC (2 μM)	NA*	NA*	NA*	NA*	NA*	NA*	-2.5	-8.2	-5.7
Phenobarbital (1000 μM)	NA*	NA*	NA*	NA*	NA*	NA*	85.2	88.2	83.0
Rifampicin (10 μM)	NA*	NA*	NA*	NA*	NA*	NA*	100	100	100
Dexamethasone (50 μM)	NA*	NA*	NA*	NA*	NA*	NA*	9.2	-1.2	3.3
Fenofibric acid (5.7 μM)	NA*	NA*	NA*	NA*	NA*	NA*	-0.21	0.38	-0.52
Fenofibric acid (57 μM)	NA*	NA*	NA*	NA*	NA*	NA*	0.40	4.1	1.5
Fenofibric acid (570 μM)	NA*	NA*	NA*	NA*	NA*	NA*	10.2	19.9	16.4

NA*: No Recommended Positive Controls

REVIEWER'S COMMENT:

- CYP 2A6 could not be induced by dexamethasone, however analysis of mRNA content showed that phenobarbital was able to induce CYP2A6 as positive control.

4.1.9 *In-Vitro* Induction: Study MPC-028-06-0003:

TITLE: "Evaluation of the Induction Potential of Fenofibric Acid on the Activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 and the Cytotoxic Potential of Fenofibric Acid in Human Hepatocytes."

OBJECTIVES: To evaluate the potential of fenofibric acid to induce the catalytic activities and expression of cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 and to evaluate the cytotoxic potential of fenofibric acid in human hepatocytes following *in vitro* exposure.

EXPERIMENTAL METHODS:

Three sets of incubations were conducted.

- Set 1 incubations examined the induction of enzyme activities by fenofibric acid and fenofibrate in human hepatocytes.
- Set 2 incubations examined the induction of gene expression by fenofibric acid and fenofibrate in human hepatocytes.
- Set 3 incubations examined the cytotoxicity potential of fenofibric acid and fenofibrate in human hepatocytes.

RESULTS:

Fenofibric acid and fenofibrate did not induce CYP3A4 enzyme activities. Fenofibric acid, at concentrations up to 1,135 μM , did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 enzyme activities. Fenofibric acid and fenofibrate showed induction of the CYP2C8 enzyme activities. The CYP2C8 enzyme activities were >200% of vehicle control activities for two of the three donors at concentrations ranging from 100–500 μM . The enzyme activities at these concentrations were also >40% of reference control activities (10 μM rifampin).

REVIEWER'S COMMENT:

- Fenofibric acid showed cytotoxic potential at concentrations $\geq 500 \mu\text{M}$ for Donor 4 and $\geq 1000 \mu\text{M}$ for Donor 5.
- CYP2C8 mRNA was increased in one of the three donors after incubation with fenofibric acid.

4.1.10 *Caco-2* permeability: Study 6MUTUP1:

TITLE: "Bi-directional apparent permeability (P_{app}) across *caco-2* cell monolayers"

OBJECTIVE: to determine the bi-directional apparent permeability of fenofibric acid across *Caco-2* cell monolayers.

EXPERIMENTAL METHODS:

- Dosing Concentration: 10 μM
- Replicates: 2
- Direction: apical-to-basolateral and basolateral-to-apical
- Time Points: 1 and 2 hours

RESULTS:

According to the sponsor, fenofibric acid exhibits a high absorption potential and no significant efflux. Low diffusion rate from apical to the basolateral site however indicates a lack of free diffusion.

Table 1.1 Recovery and Permeability of Fenofibric Acid (10^{-6} cm/s)

Test Article Identification	Percent Recovery ⁽¹⁾			P _{app} ⁽²⁾ Blank	P _{app} A-to-B			P _{app} B-to-A			E _{app} ⁽³⁾ P _{app} ⁽⁴⁾ Ratio ⁽⁵⁾	Absorption Potential ⁽⁶⁾	Significant Efflux ⁽⁷⁾
	Blank	A-to-B	B-to-A		Rep. 1	Rep. 2	Avg	Rep. 1	Rep. 2	Avg			
Fenofibric Acid	99	88	102	30.7	10.7	10.0	10.4	25.8	23.7	24.8	2.1	High	No

⁽¹⁾ Absorption Potential Classification:

P_{app} (A-to-B) ≥ 1.0 × 10⁻⁶ cm/s High
 P_{app} (A-to-B) ≥ 0.5 × 10⁻⁶ cm/s, P_{app} < 1.0 × 10⁻⁶ cm/s Medium
 P_{app} (A-to-B) < 0.5 × 10⁻⁶ cm/s Low

⁽²⁾ Efflux considered significant if:

P_{app} (B-to-A) ≥ 1.0 × 10⁻⁶ cm/s and Ratio P_{app} (B-to-A) / P_{app} (A-to-B) ≥ 3.0

⁽³⁾ Low recoveries caused by non-specific binding, etc. can affect the measured permeability.

⁽⁴⁾ A low rate of diffusion (< 20 × 10⁻⁶ cm/s) through the cell-free membrane indicates a lack of free diffusion, which may affect the measured permeability.

REVIEWER'S COMMENT:

- Based on the limited data provided, the study was not adequately designed to characterize fenofibric acid as a high permeability drug as claimed by the sponsor.

4.2. ANALYTICAL METHOD VALIDATION

4.2.1 Fenofibric acid method validation: FL06-MUT-TR032

The validation titled "Determination of Fenofibric Acid in Human Plasma by LC/MS/MS" was conducted at the following site: _____

b(4)

SUMMARY

An adequately validated LC/MS/MS method is established to analyze the human plasma concentration of fenofibric acid. The calibration curve is based on four separately analyzed curves with calibration standards of 25, 50, 100, 500, 1000, 150, 2000, 2500 ng/mL. Six pooled quality controls (QC) of 70, 900 and 1800 ng/mL are included in each calibration curve run.

The interday coefficient of variation (%CV) for the 70, 900 and 1800 ng/mL QCs are 6.1%, 4.3%, and 5.2% respectively. All intraday %CV's are below 4.8%. Deviations of the measured concentration from the nominal concentrations of fenofibric acid are within 10.2%.

The retention time is about 2.3 minutes and no significant interference in six different lots of human plasma was detected. The assay is sensitive to quantify concentrations of 25 ng/ml.

Short-term stability is 6 hours at room temperature and fenofibric acid is stable over three freeze/thaw cycles.

In the validation addendum, FL06-MUT-TR032A1 the long-term stability at -20°C is determined to be at least 52 days and benchtop stability at room temperature at least 15 h.

In the partial validation report, FL06-MUT-TR032A2 the dynamic range is expanded from 25-2500 ng/ml to 250 to 25000 ng/ml. Intraday precision (%CV) for this dynamic range is less than 3.5%.

REVIEWER'S COMMENT:

The bioanalytical report and the validation report for the BE study MPC-028-07-1007 are acceptable.

4.2.2 Efavirenz method validation: AP LC/MS/MS 200.100

The validation titled: "The method validation of efavirenz in human plasma" was conducted at the following site: _____

b(4)

SUMMARY:

An adequately validated LC/MS/MS method is established for the detection of efavirenz in human plasma with detection in the range of 10.00 to 8000 ng/mL. The method is validated using one calibration curve and six sets of QC samples in three different batch runs. The calibration curve consists of ten non-zero concentrations (i.e. 10.00, 20.00, 50.00, 100.0, 200.0, 500.0, 1000, 3000, 6500, and 8000 ng/mL) the quality control samples are 30.00, 400.0, and 6000 ng/mL.

The intraday coefficient of variation (%CV) for the 730.00, 400.0, and 6000 ng/ml QCs is between 2.0 and 5.6%. The intraday accuracy for the quality controls is within the range of 90.2 to 102%. Interday coefficient of variation for the calibration standards is within the range of 2.2-5.1% and accuracy is within the range of 96.5 to 1.3%. For the QC samples, interday precision is within the range of 3.8-5.6%. A validation addendum includes the long-term stability at -20°C, which was determined to be at least 86 days

REVIEWER'S COMMENT:

The bioanalytical report and the validation report for the DDI study *MPC-028-08-1018* are acceptable.

4.3 OCP FILING MEMO

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-418	Brand Name	to be determined
OCP Division	2	Generic Name	Fenofibrate acid
Medical Division	DMEP	Drug Class	
OCP Reviewer	Immo Zdrojewski, Ph.D.	Indication(s)	Treatment of hypercholesterolemia
OCP Team Leader	Sally Choe, Ph.D.	Dosage Form	35/105 mg tablets
		Proposed Dosing Regimen	35 or 105 mg per day without regard to food
Date of Submission	08/15/08	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Mutual Pharmaceutical Company Inc.
PDUFA Due Date	06/15/09	Priority Classification	Standard
	03/15/09	Submission Type	505 (b) (2)
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isosyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1		
In-vitro:	X	3		
In-vitro permeability:	X	1		
In-vitro metabolism:	X	1		
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
ii. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X		4	
Bioequivalence studies -				
traditional design; single / multi dose:	X		2	
replicate design; single / multi dose:				
Food-drug interaction studies:	X		2	
Dissolution:				
(IVVC):				
Bio-wavier request based on BCS				
BCS class	2			
iii. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies			15	
Fiability and QBR comments				
	X if yes	Comments		
Application fiable ?	X	Yes, it is fiable.		
Comments sent to firm ?		Please submit the SAS transport data files for the BE study MPC-028-07-1007 (or if submitted, indicate where the files are located).		
QBR questions (key issues to be considered)	Is the fenofibric acid product bioequivalent to the reference product and what is the food effect?			
Other comments or information not included above	DSI inspection is requested for the BE studyMPC-028-07-1007.			
Primary reviewer Signature and Date	Immo Zdrojewski, Ph.D.			
Secondary reviewer Signature and Date	Sally Choe, Ph.D.			

Summary:

The sponsor (Mutual Pharmaceutical Company Inc.) submitted NDA _____ to seek approval for fenofibric acid tablets intended for the treatment of hypercholesterolemia. The submission type of this NDA is 505 (b) (2) and the sponsor references to Tricor® (fenofibrate NDA 21-656) and also references to studies performed under sponsor's IND 76,749. Fenofibric acid is the main metabolite of fenofibrate; however fenofibrate cannot be detected in plasma after oral administration. The sponsor states that since the parent drug (fenofibrate) is not present in plasma, the pharmacokinetic as well as pharmacodynamic properties of fenofibrate drug products are characterized by fenofibric acid levels and the pharmacological response to this active metabolite.

b(4)

Batch size / Formulation:

- The sponsor states that they manufactured three cGMP registration batches at a pilot scale for the intended commercial production size of _____ tablets.
- Pilot batch sizes _____ tablets for 35/105 mg) seem adequate for BE evaluation according to the guidance labeled "Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation."
- According to the sponsor, the registration formulations were manufactured by the same process and on equipment of the same design and operating principles as the ones intended for commercial production.

b(4)

Biowaiver:

This biowaiver request is for the pivotal BE study for their fenofibric acid lowest strength (35 mg) tablet. The biowaiver request will be reviewed by ONDQA/Biopharm.

- According to sponsor:
 - the composition is proportional,
 - the in-vitro dissolution profiles are similar and
 - the pharmacokinetics are similar over the proposed dose range (35-105 mg)*.

* The PK similarity over the proposed dose range of 35-105 mg will be reviewed by this reviewer as well.

Studies:

- 10 clinical studies in healthy volunteers and 5 non-clinical studies consist of the following:
 - bioequivalence at 105 mg [sponsor claims bioequivalence between fenofibric acid and Tricor®],
 - food-effect [sponsor claims no food effect],
 - dose proportionality [sponsor claims dose proportionality],
 - metabolism [sponsor claims CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 do not play a role in the metabolism of fenofibric acid], and

- o drug-drug interaction [sponsor claims no clinically significant interaction of fenofibric acid steady state concentration on a single dose of efavirenz].

A tabular overview of the performed clinical studies is shown in attachment 1.

DSI Inspection:

- DSI inspection is requested for the BE study MPC-028-07-1007 titled "A Single-Dose, Bioequivalence Study of 105 mg Fenofibric Acid Tablets Versus 145 mg TriCor® (Fenofibrate) Tablets Under Fasting Conditions." Details are as follows:

CLINICAL FACILITY:

PRACS Institute, Ltd. - Cetero Research
4801 Amber Valley Parkway
Fargo, ND, USA

BIOANALYTICAL FACILITIES:

[REDACTED] b(4)

Application is filable from the Clinical Pharmacology perspective.

Attachment 1.

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative B/BE	MPC-028-07-1005	CSR	Section 3.3.1.2	To compare the relative BA of a single oral dose of fenofibric acid tablets, 90 mg (Munual) after low-fat and standardized meals with that of a single oral dose of 145-mg TriCor® tablets (Abbott) after a standardized meal.	Three-period, crossover	1 tablet; 90 mg; oral	18	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 3.3.1.4							
		Datasets	Datasets							
Comparative B/BE	MPC-028-07-1006	CSR	Section 3.3.1.2	To compare the rate and extent of absorption of 130-mg fenofibric acid tablets (Munual) under fed and fasted conditions with that of fenofibrate 145-mg tablets (TriCor®, Abbott Laboratories) under fasted conditions.	Three-period, crossover, open-label	1 tablet; 130 mg; oral	18	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 3.3.1.4							
		Datasets	Datasets							

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative BA/BE	MPC-028-07-1007	CSR	Section 5.3.1.2	To evaluate the bioequivalence of fenofibric acid tablets, 105 mg (Mutual) relative to Tricor® Tablets (145 mg by Abbott Pharmaceuticals, Inc.) in healthy adult volunteers when each is administered under fasted conditions.	Two-period, crossover	1 tablet; 105 mg; oral	54	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							
Comparative BA/BE	MPC-028-07-1008	CSR	Section 5.3.1.2	To evaluate the bioequivalence of fenofibric acid tablets, 105 mg (Mutual) relative to Tricor® Tablets (145 mg, Abbott) when each was administered following a break fast of standard composition.	Two-period, crossover	1 tablet; 105 mg; oral	47	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative BA/BE	MPC-028-07-1016	CSR	Section 5.3.1.2	To compare the rate and extent of absorption of a single 105-mg fenofibric acid capsule (Mutual) to the rate and extent of absorption of a single 145-mg TRICOR® tablet (Abbott Laboratories) under standard fasting conditions.	Three-period, crossover	1 tablet; 105 mg; oral	18	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							
Comparative BA/BE and Pharmacokinetic	MPC-028-07-1017	CSR	Section 5.3.1.2	To evaluate the pharmacokinetic linearity and bioequivalence of fenofibric acid over a single dose range of 35 to 105 mg when administered to healthy adult volunteers under fasted conditions.	Three-period, crossover	1 tablet; 35 and 105 mg; oral	54	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							
Pharmacokinetic	MPC-028-06-0001	Study report	Section 5.3.2.2	To determine the metabolism of fenofibric acid in human liver microsomes and expressed recombinant human microsomes.	<i>In Vitro</i>	--	--	--	Complete	

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pharmacokinetic	MPC-028-06-0002	Study report	Section 3.3.2.2	The objective of this study was to determine the potential for fenofibric acid to inhibit the activities of cytochrome P450 isoforms CYP2B6 and CYP2C8 in human liver microsomes.	<i>In Vitro</i>	--	--	--	--	Complete
Pharmacokinetic	MPC-028-06-1003	Study report	Section 3.3.2.2	The objectives of this study were to evaluate the potential of fenofibric acid to induce the catalytic activities and expression of certain cytochrome P450 isoforms and to evaluate the cytotoxic potential of fenofibric acid in human hepatocytes following <i>in vitro</i> exposure.	<i>In Vitro</i>	--	--	--	--	Complete
Pharmacokinetic	MPC-028-07-0002	Study report	Section 3.3.2.2	To utilize primary cultures of human hepatocytes to evaluate the potential of fenofibric acid to induce liver microsomal cytochrome P450 (CYP) enzymes.	<i>In Vitro</i>	--	--	--	--	Complete
Pharmacokinetic	6MUTUPI	Study report	Section 3.3.2.2	To determine the bi-directional apparent permeability of fenofibric acid across Caco-2 cell monolayers.	<i>In Vitro</i>	--	--	--	--	Complete

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Extrinsic factor	MPC-028-08-1018	CSR	Section 5.3.3.4	To determine the effect of multiple doses of fenofibric acid (steady-state) on the pharmacokinetics of single-dose efavirenz in healthy adult subjects.	One-sequence, open-label, drug-interaction study	Single daily dose of fenofibric acid (1 x 105-mg tablet) for 10 days	24	Healthy subjects	Ten days	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							

11 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Immo Zdrojewski
6/8/2009 03:51:56 PM
BIOPHARMACEUTICS

Wei Qiu
6/8/2009 03:57:18 PM
BIOPHARMACEUTICS

5/13/09

NDA:	22-418
Submission Date:	August 15, 2008, March 4, 2009
Type of Submission:	Original under section 505(b)(2)
Product name	Fenofibric Acid
Dosage Form:	Tablet
Dosage Strengths:	35 mg, and 105 mg
Sponsor:	URL Mutual

Recommendation

Although the 35 mg fenofibric acid tablet is compositionally proportional to the 105 mg fenofibric acid tablet, the comparative dissolution results of fenofibric acid tablets (35 mg vs. 105 mg) in three media show similarity in only one media (0.1 N HCl), $f_2 > 50$. The dissolution profile were not similar in the other two media tested (water and pH 4.5 acetate buffer), $f_2 < 50$. Therefore, the information provided in this submission on its own merit does not support the biowaiver request. However, the sponsor submitted a clinical study report (MPC-028-08-1017) to evaluate the pharmacokinetic linearity of fenofibric acid over a single dose range of 35 to 105 mg, and to compare drug composition proportionality of three 35 mg fenofibric acid tablets (total 105 mg single dose) to a single 105 mg fenofibric acid tablet in healthy adult volunteers when each is administered under fasted conditions. According to the Clinical Pharmacology reviewer, Dr. Immo Zdrojewski, the sponsor demonstrated that comparison of three Mutual's fenofibric acid tablets, 35 mg to a one Mutual's fenofibric acid tablets, 105 mg in the fasting state are bioequivalent. Administration of three of Mutual's fenofibric acid tablets, 35 mg and one of Mutual's fenofibric acid tablets, 105 mg resulted in C_{max} and AUC for which the 90% confidence intervals (CI) were within the bioequivalence interval of 80 to 125% which indicates the two treatments are bioequivalent.

The dissolution method is not acceptable. The data provided at the speed chosen is not discriminative. It is recommended that a rotation speed of 50 rpm be used instead of 75 rpm. Another option is to try to use a different media in order to achieve slower release and provide a discriminative method.

Background

Fenofibrate, the prodrug for the active moiety fenofibric acid, was first approved in 1993 and is currently available in a number of tablet and capsule formulations. The fenofibrate reference listed drug (RLD) for this NDA, submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act, is a noncrystal formulation (TriCor® Tablets, NDA 21-656), which gained FDA approval on 05 November 2004. TriCor® Tablets are available in two tablet strengths, 48 mg and 145 mg; the recommended dose is 48 mg to 145 mg once daily without regard to food.

Mutual is developing fenofibric acid for the same indications as those approved for the RLD. The proposed drug product, fenofibric acid tablets, will be available in two strengths, 35 mg and 105 mg. Three registration batches of each strength of drug product were manufactured by Mutual in June-July 2007 at a pilot scale of _____, b(4)

and _____ tablets (35 mg and 105 mg, respectively); this is a representative pilot scale of the intended commercial production (_____ tablets). One batch of each strength, Batch BB 787 0307 (35 mg) and batch BB 788 0318 (105 mg), was used in the pharmacokinetic and/or clinical pharmacology studies in support of the NDA. b(4)

The information to support a biowaiver was a topic of discussion in the pre-NDA briefing package (IND 76,749 Serial No. 013, submitted 4 December 2007, Question #9). Specifically, Mutual proposed to support the biowaiver request of the 35 mg fenofibric acid tablets based on composition proportionality and similar dissolution profiles. The official pre-NDA meeting responses, dated 15 January 2008 stated that the proposal was acceptable if pharmacokinetic linearity of fenofibric acid was demonstrated over the proposed dose range.

According to Mutual, bioequivalence of the 105 mg fenofibric acid tablet with the RLD, TriCor® 145 mg, was demonstrated in two single-dose studies performed in healthy adult subjects under fasted and fed conditions. Additionally, pharmacokinetic linearity was demonstrated over the dose range 35-105 mg. Therefore, Mutual is requesting a "biowaiver" of any further in vivo studies for the 35 mg fenofibric acid tablet based on the 35 mg fenofibric acid tablet being compositionally proportional to the 105 mg fenofibric acid tablet, and the in vitro dissolution profiles of both strengths being similar using suitable methodology.

Assessing Proportional Similarity:

The dosage form is an immediate-release tablet that is fast disintegrating. Batches of the two strengths were manufactured using the same proposed process and from equivalent common blends using different blend weights and tablet sizes/thickness to produce the desired strengths. As seen in Table 1 below, the active and inactive are in exactly the same proportion between both strengths. Therefore, both 35 mg and 105 mg tablet strengths are dose proportional.

Table 1: Composition of Fenofibric Acid Tablets Intended for Commercialization

Ingredient	% w/w	Tablet Strength	
		35 mg	105 mg
		mg/Tablet	
Fenofibric acid		35.0	105.0
Microcrystalline cellulose, NF			
Croscopollose, NF			
Croscopollose, NF			
Magnesium stearate, NF			
Total			

b(4)

Assessing Dissolution Similarity:

Solubility was assessed using three different dissolution medium, 0.1 N HCl, Acetate buffer pH 4.5 and phosphate buffer pH 6.8. It was found that the solubility of fenofibric acid depends on the pH of the dissolution medium. The results of the solubility studies are shown in Table 2 below.

Table 2: Solubility of Fenofibric Acid in Different Medium

Buffer	pH	Solubility (mg/mL)
0.1 N HCl	1	0.03
Acetate	4.5	0.12
	5.0	0.15
	5.5	0.18
Phosphate	6.0	0.30
	6.5	0.74
	7.0	1.39
	7.5	1.65

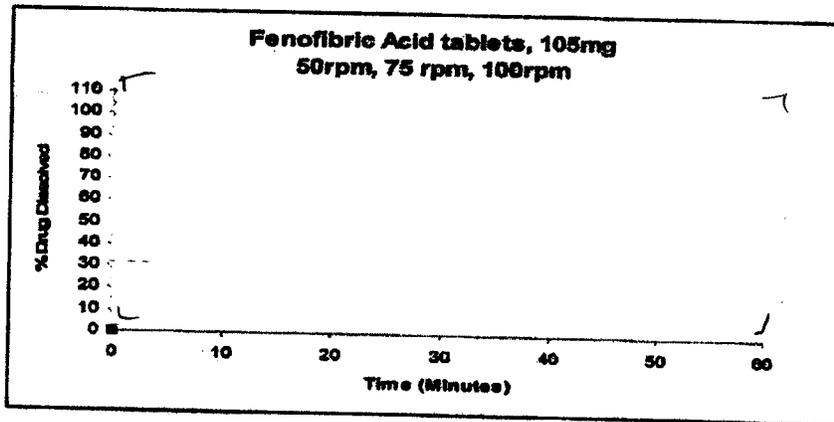
Based on the solubility information, the total amount of drug that dissolves in 900 mL of pH 4.5 acetate buffers is 108 mg (900 mL x 0.12 mg/mL). The sponsor stated that this quantity is less than the acceptable upper limit of drug content in a 105 mg tablet, as the upper limit of drug content could be up to _____ of fenofibric acid. This is based on _____ of the label claimed. Therefore, the sponsor selected 900 mL of phosphate buffer at pH 6.8 to be the medium to ensure complete solubility of the drug substance.

b(4)

b(4)

Fenofibric acid tablets, 105 mg (Lot # BB7880318) were tested under dissolution media of pH 6.8 with different paddle speeds. The paddle speeds studied were 50, 75, and 100 rpm. The dissolution medium volume was 900 mL. The sampling points were 5, 10, 15, 30, 45, and 60 minutes. Figure 1 below shows the dissolution profiles under each paddle speed.

Figure 1: Dissolution profile for Fenofibric acid tablets under different paddle speeds



b(4)

The final dissolution parameters proposed for the NDA are summarized in Table 3 below. These parameters are the same for the two tablet strengths 35 mg and 105

mg. The proposed specification is NLT (Q) of the labeled amount of fenofibric acid dissolved in 15 minutes.

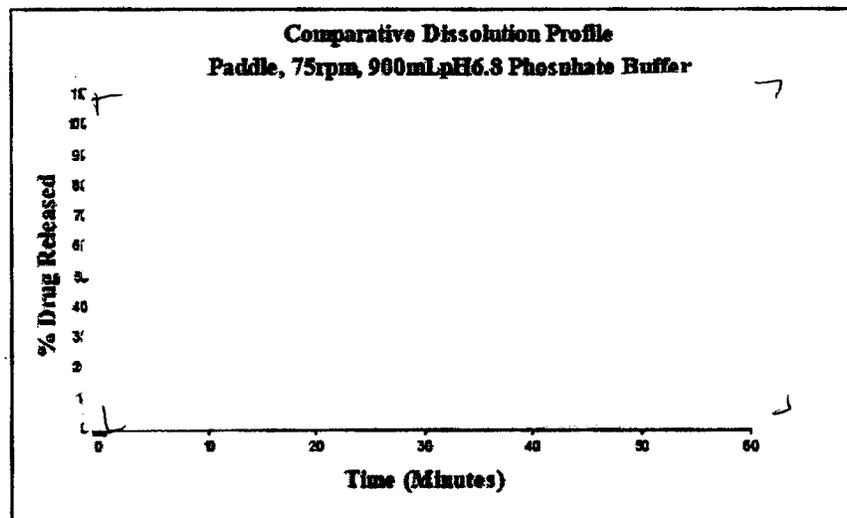
b(4)

Table 3: In vitro Dissolution Parameters for Proposed Dissolution Method

Medium:	pH 6.8 phosphate buffer
Volume:	900 mL
Apparatus:	2 (Paddle)
Speed:	75 rpm
Temperature:	37 ± 0.5°C
Time Period:	15 minutes
For Profile:	5, 15, 30, 45, and 60 minutes

Figure 2 shows the in vitro dissolution profiles in 12 units tested from each of the three bio-batches for each of the tablet strength.

Figure 2: Comparative Dissolution Profiles for 35 mg and 105 mg Fenofibric Acid Tablets



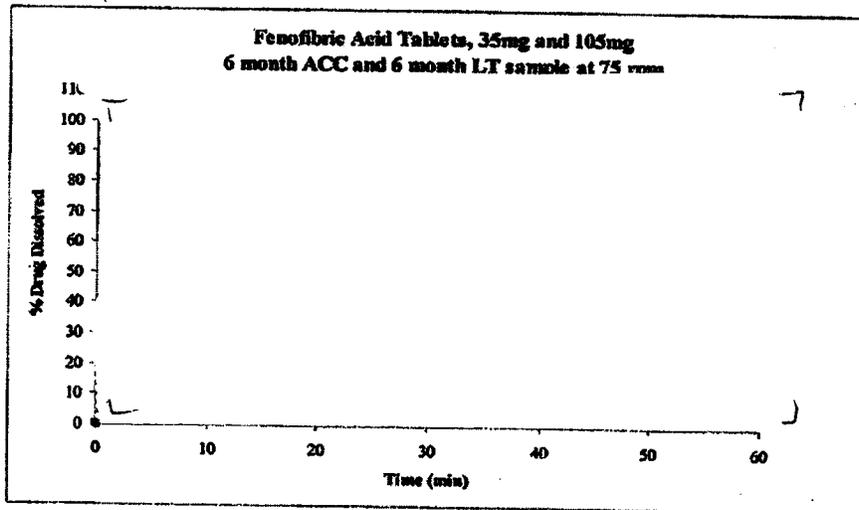
b(4)

Reviewer's Note:

The dissolution method at the speed chosen is not discriminative. To obtain a discriminative method, it is recommended that a rotation speed of 50 rpm be used instead of 75 rpm, or to try using a different media.

Figure 3 below shows the dissolution profile of fenofibric acid tablets under six month accelerated stability and under 6 month long term stability using 75 rpm paddle speeds.

Figure 3: Dissolution profile for fenofibric acid tablets under 6 month accelerated and 6 month ICH long term stability at 75 rpm paddle speeds



b(4)

On February 9th, 2009, after a cursory review of the information submitted to support the biowaiver request, FDA requested that the sponsor provide dissolution data in multiple media (3 media) for both strength, and provide data comparing the similarity of dissolution profiles obtained of both strengths in all media tested.

On March 4th, 2009, the sponsor submitted dissolution profiles in water, 0.1 N HCl, and pH 4.5 acetate buffer for fenofibric acid tablets, 35 mg and 105 mg. Dissolution profiles were performed using apparatus 2 (paddles) at 75 rpm with sampling time points, 5, 15, 30, 45, 60, 120 and 150 minutes. The sponsor provided comparative dissolution tables and profiles (shown in the appendix Tables 7-12 and Figures 3-5) for 12 fenofibric acid tablets, 35 mg (Lot # BB787 0307), and 105 mg (Lot BB 788 0320). The sponsor did not provide the calculations of the similarity factor (f_2). However, this reviewer performed the similarity factor f_2 calculations for fenofibric acid tablets comparing both strengths (35 mg vs. 105 mg) in three media. The results of the calculations are shown in Table 4 below.

Table 4: f_2 Statistics for Fenofibric Acid Tablets Comparing Both Strengths (35 mg vs. 105 mg) in three media

Media pH	Fenofibric Acid Tablets		f_2 Statistic
0.1N HCl	35 mg Tablet Lot# BB787 0307	Vs. 105 mg Tablet Lot# BB788 0320	87.3
Water	35 mg Tablet Lot# BB787 0307	Vs. 105 mg Tablet Lot# BB788 0320	35.5
pH 4.5 Acetate Buffer	35 mg Tablet Lot# BB787 0307	Vs. 105 mg Tablet Lot# BB788 0320	36.9

Reviewer's Note:

Fenofibric acid tablets when comparing both strengths (35 mg vs. 105 mg) in three media show similarity only with one media (0.1 N HCl), $f_2 > 50$. The dissolution profile were not similar in the other two media tested (water and pH 4.5 acetate buffer), $f_2 < 50$.

Analytical Method:

The drug product is assayed by HPLC with UV detection at 286 nm; the method was validated for testing of drug substance and drug product for fenofibric acid tablets 50 mg, 75 mg, 90 mg, and 130 mg. The parameters listed below are from Method Validation Report (ARD 2006-159).

Method Validation	
<i>Lower Limit Quantitation (LOQ)</i>	_____
<i>Sample Linearity</i>	0.001 mg/mL to 0.03 mg/mL
<i>Mean Accuracy%</i>	100.5%-101.3%
<i>Precision (%RSD)</i>	_____
<i>Ruggedness (%RSD)</i>	0.2%
<i>Recovery</i>	_____
<i>Stability</i>	Stable up to 2 days when stored under Normal Laboratory Environmental Conditions

b(4)

b(4)

b(4)

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.
Biopharmaceutics Expert
Office of New Drug Quality Assessment

Appendix

In-vitro dissolution data of fenofibric acid tablets, 35 mg Lot # BB787 030307, BB787 0308, and BB787 0309 are shown in Tables 1-3 below.

Table 1: In-Vitro Dissolution Data of Fenofibric Acid Tablets, 35 mg Lot BB787 0307

FENOFIBRIC ACID TABLETS 35mg Lot# BB787 0307 (Reference: ARD-1699 Pg. 44)					
Sample No.	5 min	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	94	100	100	100	100
% R.S.D.	2.8	1.5	1.5	1.5	1.4
Min.					
Max.					

b(4)

b(4)

**Table 2: In-Vitro Dissolution Data of Fenofibric Acid Tablets, 35 mg
Lot BB787 0308**

FENOFIBRIC ACID TABLETS 35mg Lot# 787 0308 (Reference: ARD 1699 Pg. 45)					
Sample No.	5 min	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	93	100	100	100	100
% R.S.D.	1.9	1.6	1.7	1.7	1.9
Min.					
Max.					

b(4)

b(4)

b(4)

**Table 3: In-Vitro Dissolution Data of Fenofibric Acid Tablets, 35 mg
Lot BB787 0309**

FENOFIBRIC ACID TABLETS 35mg Lot# BB787 0309 (Reference: ARD-1699 Pg.40)					
Sample No.	5 min	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	94	100	101	101	101
% R.S.D.	2.9	2.2	2.2	2.1	2.1
Min.					
Max.					

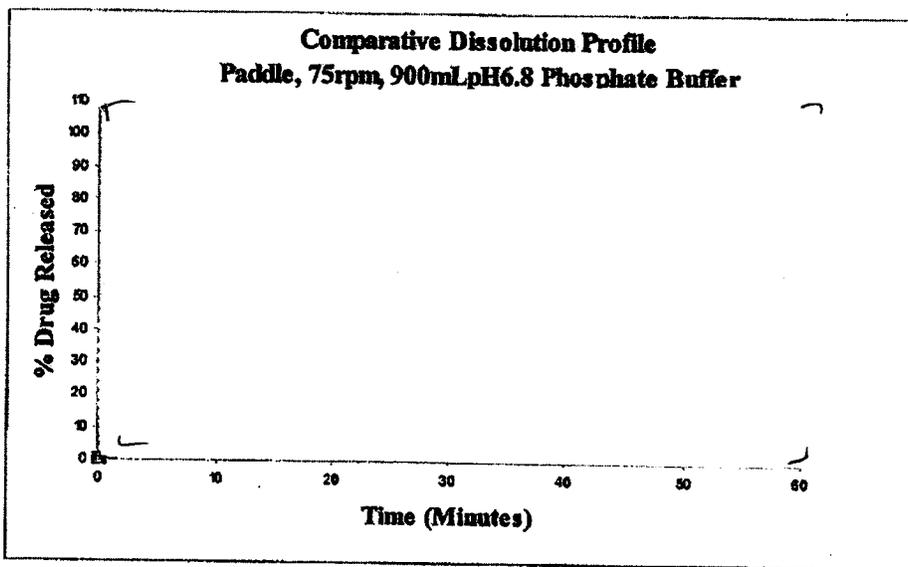
b(4)

b(4)

b(4)

The comparative dissolution profiles for the three Lots of fenofibric acid tablets 35 mg (Average of 12 tablets) are shown in Figure 1 below.

Figure 1: Comparative Dissolution Profiles for Three Lots Fenofibric Acid Tablets 35 mg (Average of 12 tablets)



b(4)

b(4)

In-vitro dissolution data of fenofibric acid tablets, 105 mg Lot # BB788 0318, BB788 0319, and BB788 0320 are shown in Tables 4-6 below.

Table 4: In-Vitro Dissolution data of Fenofibric Acid Tablets, 105 mg, Lot BB788 0318

FENOFIBRIC ACID TABLETS 105mg Lot # BB7880318 (Reference: ARD 1649 Pg. 55)					
Sample No.	5 min	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	98	100	101	101	102
% R.S.D.	3.3	2.1	1.8	1.7	1.6
Min.					
Max.					

b(4)

b(4)

b(4)

**Table 5: In-Vitro Dissolution Data of Fenofibric Acid Tablet, 105 mg,
Lot BB788 0319**

FENOFIBRIC ACID TABLETS 105mg Lot/ BB788 0319 (Reference: ARD-1649 Pg. 55)					
Sample No.	5 min	15 min	30 min	45 min	60 min
1	[REDACTED]				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	94	102	104	104	104
% R.S.D.	2.2	1.5	1.4	1.4	1.4
Min.	[REDACTED]				
Max.					

b(4)

b(4)

b(4)

**Table 6: In-Vitro Dissolution Data of Fenofirbric Acid Tablets, 105 mg
Lot BB788 0320**

FENOIRBRIC ACID TABLETS 105mg Lot BB788 0320 (Reference: AND-1649 Pg.46)					
Sample No.	5 min	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	91	99	100	101	101
% R.S.D.	2.6	2.0	1.4	1.2	1.0
Min.					
Max.					

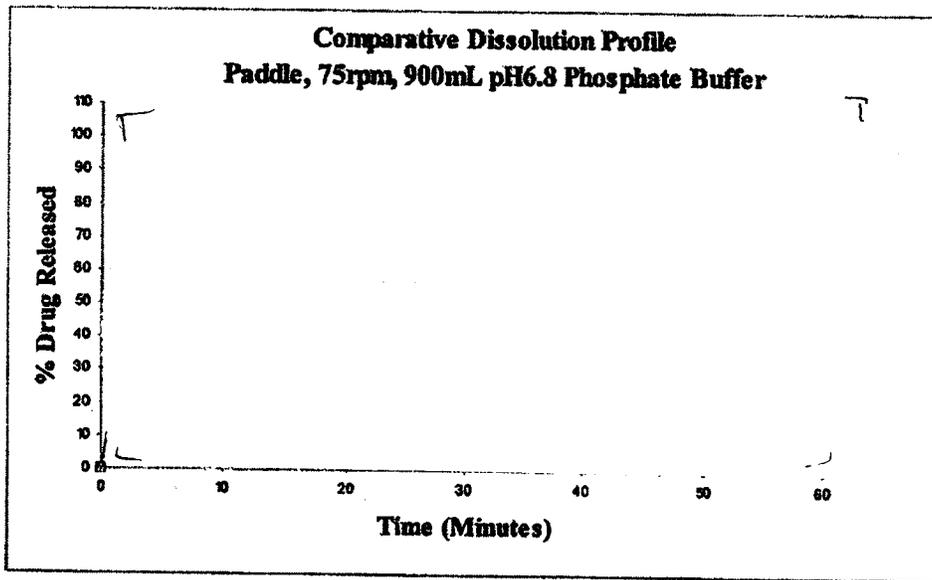
b(4)

b(4)

b(4)

The comparative dissolution profiles for the three Lots of fenofibric acid tablets 105 mg (Average of 12 tablets) are shown in Figure 2 below.

Figure 2: Comparative Dissolution Profiles for Three Lots Fenofibric Acid Tablets, 105 mg (Average of 12 tablets)



b(4)

b(4)

Table 7-9 below show the in-vitro data of fenofibric acid tablets 35 mg in three dissolution media (0.1 N HCl, Water, and Acetate Buffer pH 4.5) submitted on March 4, 2008 upon FDA request.

Table 7: In Vitro Dissolution Data for Fenofibric Acid Tablets, 35 mg in 0.1 N HCl

Sample No.	5 minutes	15 minutes	30 minutes	45 minutes	60 minutes	120 minutes	150 minutes
1							7
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
mean	2.1	2	2	3	3	3	3
% R.S.D.	17.6	13.2	13.3	8.8	7.7	11.2	11.3
Min.							
Max.							

b(4)

b(4)

b(4)

**Table 8: In Vitro Dissolution Data for Fenofibric Acid Tablets,
35 mg in Purified Water**

Sample No.	5 minutes	15 minutes	30 minutes	45 minutes	60 minutes	120 minutes	150 minutes
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
mean	26	36	43	47	50	56	59
% R.S.D.	2.2	1.7	1.2	1.3	1.5	1.2	1.2
Min.							
Max.							

b(4)

b(4)

b(4)

**Table 9: In Vitro Dissolution Data for Fenofibric Acid Tablets,
35 mg in 0.1 N HCl in pH 4.5 Acetate Buffer**

Sample No.	5 minutes	15 minutes	30 minutes	45 minutes	60 minutes	120 minutes	150 minutes
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	25	40	52	59	66	77	80
% R.S.D.	2.9	1.5	1.9	1.9	1.8	1.9	1.9
Min.							
Max.							

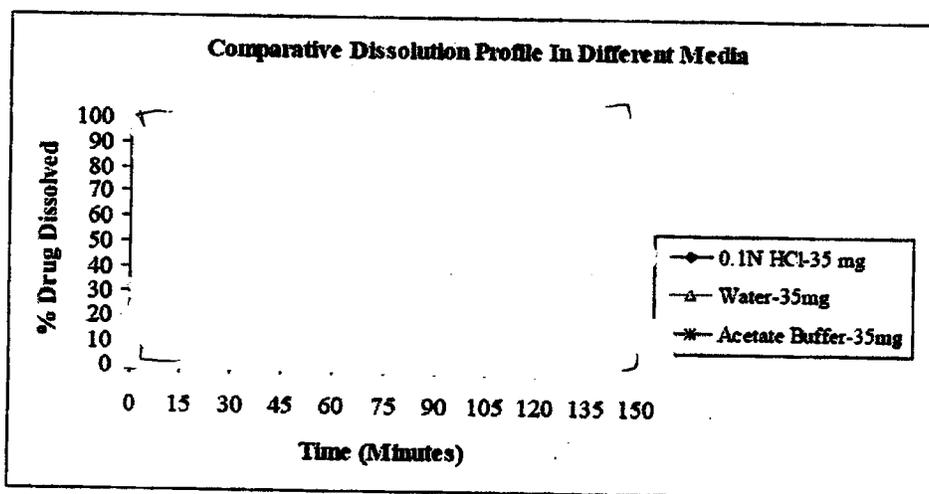
b(4)

b(4)

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Figures 3 below shows the comparative dissolution profiles of fenofibric acid tablets 35 mg in three dissolution media (0.1 N HCl, Water, and Acetate Buffer pH 4.5) submitted on March 4, 2008 upon FDA request.

Figure 3: Comparative Dissolution Profiles of Fenofibric Acid Tablets, 35 mg Lot # BB787 0307 in Three Different Media (Average of 12 Tablets)



b(4)

Table 10-12 below show the in-vitro data of fenofibric acid tablets 105 mg in three dissolution media (0.1 N HCl, Water, and Acetate Buffer pH 4.5) submitted on March 4, 2008 upon FDA request.

Table 10: In Vitro Dissolution Data for Fenofibric Acid Tablets, 105 mg in 0.1 N HCl

Sample No.	5 minutes	15 minutes	30 minutes	45 minutes	60 minutes	120 minutes	150 minutes
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	0	7.8	15.0	8.3	7.9	12.4	12.9
% R.S.D.	0	7.8	15.0	8.3	7.9	12.4	12.9
Min.							
Max.							

b(4)

b(4)

b(4)

**Table 11: In Vitro Dissolution Data for Fenofibric Acid Tablets,
105 mg in Purified Water**

Sample No.	5 minutes	15 minutes	30 minutes	45 minutes	60 minutes	120 minutes	150 minutes
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
mean	18	21	23	24	24	24	26
% R.S.D.	3.1	2.1	1.5	1.0	1.1	2.4	2.6
Min.							
Max.							

b(4)

b(4)

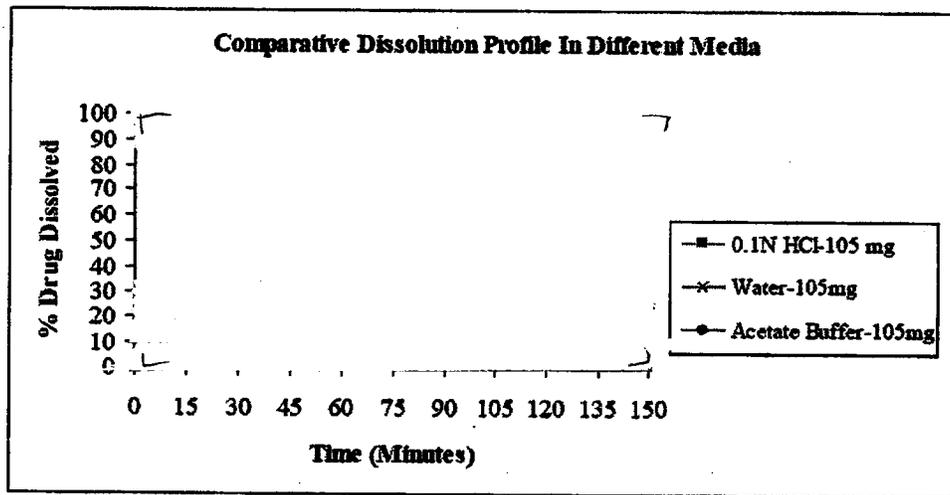
b(4)

**Table 12: In Vitro Dissolution Data for Fenofibric Acid Tablets,
105 mg in pH 4.5 Acetate Buffer**

Sample No.	5 minutes	15 minutes	30 minutes	45 minutes	60 minutes	120 minutes	150 minutes
1	b(4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
mean	15	27	34	38	41	46	49
% R.S.D.	2.5	2.1	1.7	1.5	1.5	1.5	1.0
Min.	b(4)						
Max.							

Figures 4 below shows the comparative dissolution profiles of fenofibric acid tablets 105 mg in three dissolution media (0.1 N HCl, Water, and Acetate Buffer pH 4.5) submitted on March 4, 2008 upon FDA request.

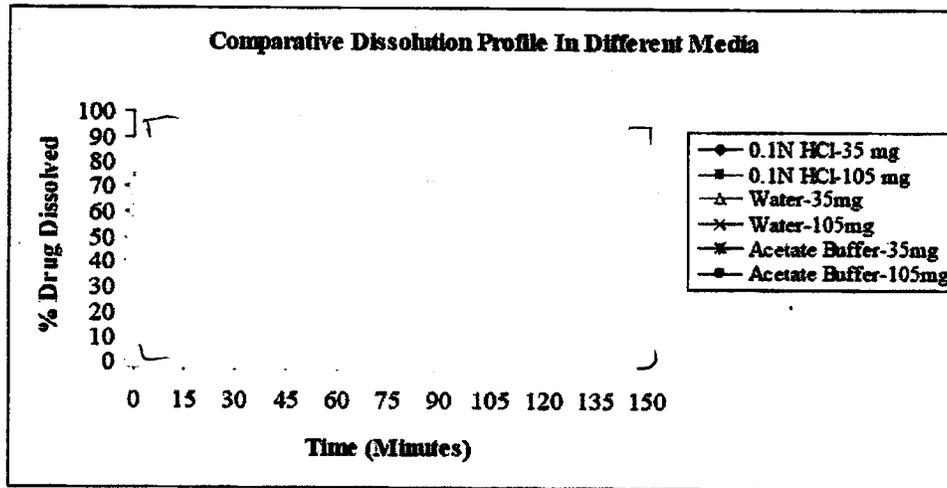
Figure 4 : Comparative Dissolution Profiles of Fenofibric Acid Tablets, 105 mg, Lot # BB7880320 in Three Different Media (Average of 12 Tablets)



b(4)

Figures 5 below shows the comparative dissolution profiles of fenofibric acid tablets 35 mg and 105 mg in three dissolution media (0.1 N HCl, Water, and Acetate Buffer pH 4.5) submitted on March 4, 2008 upon FDA request.

Figure 5: Comparative Dissolution Profiles of Fenofibric Acid Tablets, 35 mg (Lot # BB787 0307) and Fenofibric Acid Tablet, 105 mg (Lot #BB788 0320) (Average of 12 Tablets)



b(4)

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/s/

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5/13/2009 11:09:45 AM
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Patrick Marroum
5/13/2009 12:09:12 PM
BIOPHARMACEUTICS

10/21/08

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission				
	Information		Information	
NDA Number	22-418	Brand Name	to be determined	
OCF Division	2	Generic Name	Fenofibric acid	
Medical Division	DMEP	Drug Class		
OCF Reviewer	Immo Zdrojewski, Ph.D.	Indication(s)	Treatment of hypercholesterolemia	
OCF Team Leader	Sally Choe, Ph.D.	Dosage Form	35/105 mg tablets	
		Proposed Dosing Regimen	35 or 105 mg per day without regard to food	
Date of Submission	08/15/08	Route of Administration	Oral	
Estimated Due Date of OCPB Review		Sponsor	Mutual Pharmaceutical Company Inc.	
PDUFA Due Date	06/15/09	Priority Classification	Standard	
Division Due Date	03/15/09	Submission Type	505 (b) (2)	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1		
In-vitro:	X	3		
In-vitro permeability:	X	1		
In-vitro metabolism:	X	1		

Subpopulation studies -			
ethnicity:			
gender:			
pediatrics:			
geriatrics:			
renal impairment:			
hepatic impairment:			
PD:			
Phase 2:			
Phase 3:			
PK/PD:			
Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:			
Population Analyses -			
Data rich:			
Data sparse:			
II. Biopharmaceutics	1	1	
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:	x	4	
Bioequivalence studies -			
traditional design; single / multi-dose:	X	2	
replicate design; single / multi dose:			
Food-drug interaction studies:	X	2	
Dissolution:			
(IVVC):			
Bio-waiver request based on BCS			
BCS class	2		
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References	X		
Total Number of Studies		15	
Fiability and QBR comments			
	"X" if yes	Comments	
Application filable ?	X	Yes, it is filable.	
Comments sent to firm ?		Please submit the SAS transport data files for the BE study MPC-028-07-1007 (or if submitted, indicate where the files are located).	
QBR questions (key issues to be considered)	Is the fenofibric acid product bioequivalent to the reference product and what is the food effect?		
Other comments or information not included above	DSI inspection is requested for the BE study MPC-028-07-1007.		
Primary reviewer Signature and Date	Immo Zdrojewski, Ph.D.		
Secondary reviewer Signature and Date	Sally Choe, Ph.D.		

Summary:

The sponsor (Mutual Pharmaceutical Company Inc.) submitted NDA _____, to seek approval for fenofibric acid tablets intended for the treatment of hypercholesterolemia. The submission type of this NDA is 505 (b) (2) and the sponsor references to TriCor (fenofibrate NDA 21-656) and also references to studies performed under sponsor's IND 76,749. Fenofibric acid is the main metabolite of fenofibrate; however fenofibrate cannot be detected in plasma after oral administration. The sponsor states that since the parent drug (fenofibrate) is not present in plasma, the pharmacokinetic as well as pharmacodynamic properties of fenofibrate drug products are characterized by fenofibric acid levels and the pharmacological response to this active metabolite.

b(4)

Batch size / Formulation:

- The sponsor states that they manufactured three cGMP registration batches at a pilot scale for the intended commercial production size of _____ tablets.
- Pilot batch sizes of _____ tablets for 35/105 mg seem adequate for BE evaluation according the guidance labeled "Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation."
- According to the sponsor, the registration formulations were manufactured by the same process and on equipment of the same design and operating principles as the ones intended for commercial production.

b(4)

b(4)

Biowaiver:

This biowaiver request is for the pivotal BE study for their fenofibric acid lowest strength (35 mg) tablet. The biowaiver request will be reviewed by ONDQA/Biopharm.

- According to sponsor:
 - the composition is proportional,
 - the in-vitro dissolution profiles are similar and
 - the pharmacokinetics are similar over the proposed dose range (35-105 mg)*.

* The PK similarity over the proposed dose range of 35-105 mg will be reviewed by this reviewer as well.

Studies:

- 10 clinical studies in healthy volunteers and 5 non-clinical studies consist of the following:
 - bioequivalence at 105 mg [sponsor claims bioequivalence between fenofibric acid and TriCor],
 - food-effect [sponsor claims no food effect],
 - dose proportionality [sponsor claims dose proportionality],

Attachment 1.

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative BA/BE	MPC-028-07-1005	CSR	Section 5.3.1.2	To compare the relative BA of a single oral dose of fenofibric acid tablets, 90 mg (Mutual) after low-fat and standardized meals with that of a single oral dose of 145-mg TriCor® tablets (Abbott) after a standardized meal.	Three-period, crossover	1 tablet; 90 mg; oral	18	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							
Comparative BA/BE	MPC-028-07-1006	CSR	Section 5.3.1.2	To compare the rate and extent of absorption of 130-mg fenofibric acid tablets (Mutual) under fed and fasted conditions with that of fenofibrate 145-mg tablets (TriCor®, Abbott Laboratories) under fasted conditions.	Three-period, crossover; open-label	1 tablet; 130 mg; oral	18	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimes; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative BA/BE	MPC-028- 07-1007	CSR	Section 5.3.1.2	To evaluate the bioequivalence of fenofibric acid tablets, 105 mg (Mutual) relative to TriCor® Tablets (145 mg by Abbott Pharmaceuticals, Inc.) in healthy adult volunteers when each is administered under fasted conditions.	Two-period, crossover	1 tablet; 105 mg; oral	54	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							
Comparative BA/BE	MPC-028- 07-1008	CSR	Section 5.3.1.2	To evaluate the bioequivalence of fenofibric acid tablets, 105 mg (Mutual) relative to TriCor® Tablets (145 mg, Abbott) when each was administered following a breakfast of standard composition.	Two-period, crossover	1 tablet; 105 mg; oral	47	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative BA/BE	MPC-028-07-1016	CSR	Section 5.3.1.2	To compare the rate and extent of absorption of a single 105-mg fenofibric acid capsule (Munial) to the rate and extent of absorption of a single 145-mg TRICOR® tablet (Abbott Laboratories) under standard fasting conditions.	Three-period, crossover	1 tablet; 105 mg; oral	18	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							
Comparative BA/BE and Pharmacokinetic	MPC-028-07-1017	CSR	Section 5.3.1.2	To evaluate the pharmacokinetic linearity and bioequivalence of fenofibric acid over a single dose range of 35 to 105 mg when administered to healthy adult volunteers under fasted conditions.	Three-period, crossover	1 tablet; 35 and 105 mg; oral	54	Healthy subjects	Single dose	Complete
		Bioanalytical Report	Section 5.3.1.4							
		Datasets	Datasets							
Pharmacokinetic	MPC-028-06-0001	Study report	Section 5.3.2.2	To determine the metabolism of fenofibric acid in human liver microsomes and expressed recombinant human microsomes.	<i>In Vitro</i>	--	--	--	Complete	

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pharmacokinetic	MPC-028-06-0002	Study report	Section 5.3.2.2	The objective of this study was to determine the potential for fenofibric acid to inhibit the activities of cytochrome P450 isoforms CYP2B6 and CYP2C8 in human liver microsomes.	<i>In Vitro</i>	--	--	--	--	Complete
Pharmacokinetic	MPC-028-06-1003	Study report	Section 5.3.2.2	The objectives of this study were to evaluate the potential of fenofibric acid to induce the catalytic activities and expression of certain cytochrome P450 isoforms and to evaluate the cytotoxic potential of fenofibric acid in human hepatocytes following <i>in vitro</i> exposure.	<i>In Vitro</i>	--	--	--	--	Complete
Pharmacokinetic	MPC-028-07-0002	Study report	Section 5.3.2.2	To utilize primary cultures of human hepatocytes to evaluate the potential of fenofibric acid to induce liver microsomal cytochrome P450 (CYP) enzymes.	<i>In Vitro</i>	--	--	--	--	Complete
Pharmacokinetic	6MUTU1	Study report	Section 5.3.2.2	To determine the bidirectional apparent permeability of fenofibric acid across Caco-2 cell monolayers.	<i>In Vitro</i>	--	--	--	--	Complete

Type of Study	Study Identifier	File	Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Extrinsic factor	MPC-028-08-1018	CSR Bioanalytical Report Datasets	Section 5.3.1.4 Section 5.3.1.4 Datasets	To determine the effect of multiple doses of fenofibric acid (steady-state) on the pharmacokinetics of single-dose efavirenz in healthy adult subjects.	One-sequence, open-label, drug-drug interaction study	Single daily dose of fenofibric acid (1 x 105-mg tablet) for 10 days	24	Healthy subjects	Ten days	Complete

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/s/

Immo Zdrojewski
10/20/2008 03:33:09 PM
BIOPHARMACEUTICS

Sally Choe
10/21/2008 03:58:14 PM
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