

#### 4.2.3 Comparative Bioavailability and Bioequivalence Studies

Sponsor conducted several pilot BA/BE studies to evaluate the performance of different formulations during the formulation development. Synopses/descriptions of the studies with reviewer's comments are presented below:

##### Study M04-712:

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug: Fenofibric Acid (ABT-335, A-770335) and Fenofibrate (ABT-799, A-52799)</b>		
<b>Name of Active Ingredient: Fenofibric Acid</b>		
<b>Title of Study: A Comparison of the Bioavailability of Fenofibric Acid from Two Fenofibric Acid Choline Salt Formulations Relative to that from the Micronized Fenofibrate Capsule Formulation</b>		
<b>Investigator: Timi Edeki, MD, PhD</b>		
<b>Study Site: Abbott Clinical Pharmacology Research Unit 1324 North Sheridan Road Waukegan, IL 60085</b>		
<b>Publications: Not applicable.</b>		
<b>Studied Period:</b> <b>First Subject First Visit: 23 August 2004</b> <b>Last Subject Last Visit: 09 November 2004</b>		<b>Phase of Development: 1</b>
<b>Objectives: The primary objective of this study was to compare the bioavailability of two test formulations of fenofibric acid choline salt with that of a reference fenofibrate capsule. A secondary objective is to assess the food effect for each of the two test formulations.</b>		

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<p><b>Methodology:</b> This Phase I, single-dose, open-label study was conducted according to a three-period, randomized crossover design. Subjects were randomly assigned in equal numbers to receive one of six sequences of the following regimens.</p>	
Regimen A	One 200 mg micronized fenofibrate capsule administered following a low-fat breakfast (reference).
Regimen B	One capsule containing fenofibric acid choline salt micro-tablets equivalent to 130 mg fenofibric acid, administered following a high-fat breakfast (test).
Regimen C	One capsule containing fenofibric acid choline salt micro-tablets equivalent to 130 mg fenofibric acid, administered under fasting conditions (test).
Regimen D	One single-unit tablet containing fenofibric acid choline salt equivalent to 130 mg fenofibric acid, administered following a high-fat breakfast (test).
Regimen E	One single-unit tablet containing fenofibric acid choline salt equivalent to 130 mg fenofibric acid, administered under fasting conditions (test).
<p>Each dose of study drug was taken orally with approximately 240 mL of water. A washout interval of 14 days separated the doses of the three study periods.</p>	
<p>Blood samples for fenofibric acid analysis were collected into 2 mL collection tubes containing potassium oxalate plus sodium fluoride prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing in each study period. Sufficient blood was collected to provide approximately 1 mL plasma from each sample.</p>	
<p>Plasma concentrations of fenofibric acid were determined using a validated liquid chromatography method with tandem mass spectrometric detection at Abbott Laboratories, Abbott Park, IL. The lower limit of quantification for fenofibric acid was established at 0.017 µg/mL using a 0.05 mL plasma sample. Samples were analyzed between the dates of 26 October 2004 and 17 November 2004.</p>	
<p><b>Number of Subjects (Planned and Analyzed):</b></p>	
<p>Planned: 42; Entered: 42; Completed: 41; Evaluated for Safety: 42; Evaluated for Pharmacokinetics: 42</p>	
<p>For the 42 subjects who participated in the study, the mean age was 37 years (ranging from 20 to 55 years), the mean weight was 73.1 kg (ranging from 52 to 95 kg) and the mean height was 172.5 cm (ranging from 156 to 193 cm).</p>	
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal, sterile or were not pregnant or breast-feeding and were practicing at least one of the acceptable methods of birth control specified in the protocol.</p>	

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**Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:**

	Formulation		
	Regimen A: Fenofibrate (Reference)	Regimens B and C: Fenofibric Acid Choline Salt (Test)	Regimens D and E: Fenofibric Acid Choline Salt (Test)
Dosage Form	Capsules	Capsules (micro-tablets)	Tablets (single-unit tablets)
Formulation	NA	5	6
Strength (mg)	200	130*	130*
Bulk Product Lot Number	12-539-AR	19-568-AR	19-569-AR

\* Dosage form contains fenofibric acid choline salt equivalent to 130 mg fenofibric acid.  
NA – Not Applicable/Available

**Duration of Treatment:** Single doses of fenofibrate or fenofibric acid choline salt were administered on 20 September 2004, 04 October 2004 and 18 October 2004.

**Criteria for Evaluation:**

**Pharmacokinetic:** The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), the terminal phase elimination rate constant ( $\lambda_z$ ), terminal phase elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration ( $AUC_t$ ), the AUC from time 0 to infinite time ( $AUC_{\infty}$ ) and the apparent oral clearance (CL/F).

**Safety:** Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECGs and laboratory tests assessments.

**Statistical Methods:**

**Pharmacokinetic:** The following regimen comparisons were made for  $T_{max}$ , the terminal phase elimination rate constant, and the natural logarithms of  $C_{max}$ ,  $AUC_t$  and  $AUC_{\infty}$ : Regimen C vs. Regimen A, Regimen E vs. Regimen A, Regimen B vs. Regimen C, and Regimen D vs. Regimen E.

An analysis of variance (ANOVA) was performed for  $T_{max}$ , the terminal phase elimination rate constant, and the natural logarithms of  $C_{max}$  and  $AUC_{\infty}$ . The data of subjects assigned to Sequences I, II, and III were analyzed separately from the data of the subjects assigned to Sequences IV, V, and VI due to a variance difference between the two test formulations. This ANOVA model included effects for sequence, subject nested within sequence, period and regimen. The effect of subject was considered to be random, while all other effects were fixed. Within the framework of the ANOVA, each regimen comparison was made with a significance level of 0.05.

For each of the above regimen comparisons, for  $C_{max}$  and  $AUC_{\infty}$  a relative bioavailability assessment was performed by means of the two one-sided test procedure at significance level 0.05. This was done using a 90% confidence interval for the relative bioavailability. These confidence intervals were obtained by exponentiation the endpoints of confidence intervals for the difference of mean logarithms in the framework of the ANOVA model described above.

**Safety:** All subjects who received at least one dose of study medication were included in the safety analyses.

Adverse events were coded using the Medical Dictionary for Regulatory Activities Analyses (MedDRA). Treatment-emergent adverse events (i.e., any event which begins or worsens in severity after initiation of randomized study drug) were tabulated by System Organ Class (SOC) and MedDRA preferred term for each treatment group. A summary of the severity and relationship to study drug of all treatment-emergent adverse events, tabulated by MedDRA preferred term and SOC, were presented for each treatment group. Subjects reporting more than one adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

**Summary/Conclusions:**

**Pharmacokinetic Results:** Mean  $\pm$  standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the five regimens are listed in the following table.

Pharmacokinetic Parameters (units)	Regimens <sup>‡</sup>				
	A: Reference, Fenofibrate, Low-Fat Meal (N = 41)	B: Test Micro-Tablets, High-Fat Meal (N = 21)	C: Test Micro-Tablets, Fasting (N = 21)	D: Test Single-Unit Tablet, High-Fat Meal (N = 21)	E: Test Single-Unit Tablet, Fasting (N = 21)
T <sub>max</sub> (h)	4.6 $\pm$ 1.3	12.8 $\pm$ 4.5 <sup>§</sup>	5.0 $\pm$ 2.1	18.5 $\pm$ 14.2 <sup>†</sup>	7.9 $\pm$ 3.3
C <sub>max</sub> ( $\mu$ g/mL)	8.53 $\pm$ 2.27	5.51 $\pm$ 1.54 <sup>§</sup>	6.40 $\pm$ 0.93 <sup>*</sup>	4.04 $\pm$ 2.49 <sup>*</sup>	4.03 $\pm$ 1.46 <sup>*</sup>
AUC <sub>t</sub> ( $\mu$ g $\cdot$ h/mL)	154.4 $\pm$ 43.2	136.1 $\pm$ 34.2 <sup>*</sup>	143.5 $\pm$ 41.1	106.9 $\pm$ 52.3 <sup>*</sup>	108.4 $\pm$ 34.0 <sup>*</sup>
AUC <sub>∞</sub> <sup>§</sup> ( $\mu$ g $\cdot$ h/mL)	159.6 $\pm$ 46.7	140.3 $\pm$ 35.6 <sup>*</sup>	148.4 $\pm$ 44.5	115.2 $\pm$ 56.9 <sup>*</sup>	110.4 $\pm$ 34.9 <sup>*</sup>
t <sub>1/2</sub> <sup>†§</sup> (h)	22.27 $\pm$ 6.50	20.47 $\pm$ 5.98 <sup>*</sup>	21.34 $\pm$ 7.36	19.27 $\pm$ 5.27 <sup>*</sup>	18.71 $\pm$ 5.14 <sup>*</sup>
CL/F (L/h)	NA	0.99 $\pm$ 0.29	0.95 $\pm$ 0.29	1.36 $\pm$ 0.54	1.29 $\pm$ 0.38

<sup>‡</sup> Regimens B and C were administered as a single capsule containing fenofibric acid choline salt micro-tablets equivalent to 130 mg fenofibric acid. Regimens D and E were administered as a single-unit tablet containing fenofibric acid choline salt equivalent to 130 mg fenofibric acid. Regimen A was administered as a 200 mg fenofibrate capsule.

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

<sup>§</sup> Statistically significantly different from Regimen C (ANOVA, p < 0.05).

<sup>†</sup> Statistically significantly different from Regimen E (ANOVA, p < 0.05).

<sup>†§</sup> Harmonic mean and pseudo-standard deviation. Harmonic mean evaluations of t<sub>1/2</sub> were based on statistical tests for  $\lambda_2$ .

<sup>§</sup> For Regimen D, N = 20 for AUC<sub>∞</sub> and t<sub>1/2</sub>.

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The bioequivalence/bioavailability results are listed in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
<b>Fenofibric Acid Micro-Tablets</b>					
C vs. A	C <sub>max</sub>	6.331	7.618	0.831	0.727 – 0.950
	AUC <sub>t</sub>	137.997	145.208	0.950	0.888 – 1.017
	AUC <sub>∞</sub>	142.217	150.384	0.946	0.883 – 1.012
<b>Fenofibric Acid Single-Unit Tablets</b>					
E vs. A	C <sub>max</sub>	3.793	8.777	0.432	0.352 – 0.531
	AUC <sub>t</sub>	103.596	152.353	0.680	0.588 – 0.787
	AUC <sub>∞</sub>	105.384	156.528	0.674	0.600 – 0.756

\* Antilogarithm of the least squares means for logarithms.

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

The effect of food is presented in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
<b>Fenofibric Acid Micro-Tablets</b>					
B vs. C	C <sub>max</sub>	5.324	6.331	0.841	0.736 – 0.961
	AUC <sub>t</sub>	131.904	137.977	0.956	0.894 – 1.023
	AUC <sub>∞</sub>	135.867	142.217	0.955	0.892 – 1.023
<b>Fenofibric Acid Single-Unit Tablets</b>					
D vs. E	C <sub>max</sub>	3.390	3.793	0.894	0.731 – 1.093
	AUC <sub>t</sub>	96.394	103.596	0.930	0.806 – 1.074
	AUC <sub>∞</sub>	106.713	105.423	1.012	0.902 – 1.135

\* Antilogarithm of the least squares means for logarithms.

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

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**Safety Results:** The proportion of subjects reporting at least one treatment-emergent adverse event was similar among subjects who received Regimen C (14.3%), Regimen D (14.3%) and Regimen E (14.3%). The proportion of subjects reporting at least one treatment-emergent adverse event appeared lower for Regimen A (9.8%) and Regimen B (4.8%). The most common treatment-emergent adverse event (reported by at least three subjects in any regimen) was headache. The majority of adverse events were assessed by the investigator as not related to study drug and mild in severity.

No deaths or other serious adverse events were reported in this study. Results of other safety analyses including individual subject changes and individually clinically significant values for vital signs, ECG and laboratory measurements were unremarkable for each treatment group.

**Conclusions:** The test capsule formulation containing fenofibric acid choline salt micro-tablets equivalent to 130 mg fenofibric acid administered under fasting conditions (Regimen C) met bioequivalence criteria with respect to fenofibric acid AUC relative to the reference 200 mg micronized fenofibrate capsule administered following a low-fat meal (Regimen A). The fenofibric acid  $C_{max}$  was 17% lower for the test capsule containing choline salt micro-tablets compared to the reference fenofibrate capsule, and the entire 90% confidence interval for the log-transformed  $C_{max}$  was below unity.

The test single-unit tablet formulation containing fenofibric acid choline salt equivalent to 130 mg fenofibric acid administered under fasting conditions (Regimen E) produced lower bioavailability of fenofibric acid than the reference fenofibrate capsule formulation administered following a low-fat meal (Regimen A). The fenofibric acid  $C_{max}$  and  $AUC_{0-\infty}$  were 57% and 33% lower for the test single-unit choline salt tablets than the reference fenofibrate capsules, respectively, and the entire 90% confidence intervals for the log-transformed  $C_{max}$  and  $AUC_{0-\infty}$  were below unity.

When the test capsule formulation containing fenofibric acid choline salt micro-tablets equivalent to 130 mg fenofibric acid was administered with a high-fat meal (Regimen B), bioequivalence criteria were met with respect to fenofibric acid AUC compared to that under fasting conditions (Regimen C). However, fenofibric acid  $C_{max}$  was 16% lower for the test capsule containing choline salt micro-tablets administered with a high-fat meal, and the entire 90% confidence interval for log-transformed  $C_{max}$  was below unity.

When the test single-unit tablet formulation containing fenofibric acid choline salt equivalent to 130 mg fenofibric acid was administered with a high-fat meal (Regimen D), bioequivalence criteria were met with respect to fenofibric acid AUC compared to that under fasting conditions (Regimen E). However, fenofibric acid  $C_{max}$  was 10% lower for the test single-unit tablet containing choline salt administered with a high-fat meal, and the lower limit of the 90% confidence interval for log-transformed  $C_{max}$  extended below 0.80.

The regimens tested were generally well tolerated by the subjects. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.

**Reviewer's Comments:**

- The 130 mg choline fenofibrate micro-tablets were equivalent to 200 mg micronized fenofibrate but fenofibric acid  $C_{max}$  from the micro-tablet formulation tend to be lower and were further reduced by high-fat meal.
- Single-unit tablet was not successful in meeting the BE criterion with or without food.
- The Guidance Document on Food-Effect Bioavailability and Fed Bioequivalence Studies recommends that "A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150 (15%), 250 (25%), and 500-600 (50-60%) calories from protein, carbohydrate, and fat, respectively." Sponsor used appropriate high-fat meal 890.2 Cal (Note: Tables in the report mention Kcal and it is same as Cal); delivering 55.8% calories from fat, 30.7% calories from carbohydrates and 13.8% calories from protein.

**Study M04-715:**

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug: Fenofibric Acid (ABT-335, A-770335) and Fenofibrate (ABT-799, A-52799)</b>		
<b>Name of Active Ingredient:</b>		
<b>Title of Study: A Comparison of the Bioavailability of Fenofibric Acid from Two Fenofibric Acid Formulations Relative to that from the Micronized Fenofibrate Capsule Formulation</b>		
<b>Investigator:</b> _____		
<b>Study Site:</b> <input type="checkbox"/> _____ <input type="checkbox"/> _____  <input type="checkbox"/> _____ <input type="checkbox"/> _____		
<b>Publications: Not applicable.</b>		
<b>Studied Period:</b> <b>First Subject First Visit: 04 November 2004</b> <b>Last Subject Last Visit: 22 December 2004</b>		<b>Phase of Development: 1</b>
<p><b>Objectives:</b> The primary objective of this study was to compare the bioavailability of fenofibric acid from two fenofibric acid formulations with that of a reference fenofibrate capsule. A secondary objective was to assess the food effect for each of the two test formulations.</p> <p><b>Methodology:</b> This Phase 1, single-dose, open-label study was conducted according to a three-period, randomized crossover design. Subjects were randomly assigned in equal numbers to receive one of six sequences of the following regimens.</p> <p><b>Regimen A</b> One 200 mg micronized fenofibrate capsule administered following a low-fat breakfast (reference).</p> <p><b>Regimen B</b> One capsule containing fenofibric acid granules equivalent to 130 mg fenofibric acid administered following a high-fat breakfast (test).</p> <p><b>Regimen C</b> One capsule containing fenofibric granules equivalent to 130 mg fenofibric acid administered under fasting conditions (test).</p> <p><b>Regimen D</b> One capsule containing fenofibric acid micro-tablets equivalent to 130 mg fenofibric acid administered following a high-fat breakfast (test).</p> <p><b>Regimen E</b> One capsule containing fenofibric acid micro-tablets equivalent to 130 mg fenofibric acid administered under fasting conditions (test).</p>		

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Each dose of study drug was taken orally with approximately 240 mL of water. A washout interval of 14 days separated the doses of the three study periods.

Blood samples for fenofibric acid analysis were collected into 2 mL collection tubes containing potassium oxalate plus sodium fluoride prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing in each study period. Sufficient blood was collected to provide approximately 1 mL plasma from each sample.

Plasma concentrations of fenofibric acid were determined using a validated liquid chromatography method with tandem mass spectrometric detection at Abbott Laboratories, Abbott Park, IL. The lower limit of quantitation (LLOQ) for fenofibric acid was established at 0.017 µg/mL using a 0.050 mL plasma sample. Samples were analyzed between the dates of 05 January 2005 and 31 January 2005.

**Number of Subjects (Planned and Analyzed):**

Planned: 42; Entered: 42; Completed: 38; Evaluated for Safety: 42;  
Evaluated for Pharmacokinetics: 39

For the 42 subjects who participated in the study, the mean age was 25.6 years (ranging from 18 to 54 years), the mean weight was 74.2 kg (ranging from 51 to 98 kg) and the mean height was 174.1 cm (ranging from 160 to 188 cm). For the 39 subjects included in the pharmacokinetic analyses, the mean age was 26.0 years (ranging from 18 to 54 years), the mean weight was 74.9 kg (ranging from 51 to 98 kg) and the mean height was 174.7 cm (ranging from 160 to 188 cm).

**Diagnosis and Main Criteria for Inclusion:** Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal, sterile or were not pregnant or breast-feeding and were practicing at least one of the acceptable methods of birth control specified in the protocol.

**Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:**

	Formulation		
	Micronized Fenofibrate (Reference)	Fenofibric Acid Granules (Test)	Fenofibric Acid Micro-Tablets (Test)
Dosage Form	Capsule	Capsule	Capsule
Formulation	NA	7	8
Strength (mg)	200	130	130
Bulk Product Lot Number	12-539-AR	21-573-AR	21-576-AR

NA = Not Applicable/Available

**Duration of Treatment:** Single doses of fenofibrate or fenofibric acid were administered on 17 November 2004, 01 December 2004 and 15 December 2004.

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**Criteria for Evaluation:**

**Pharmacokinetic:** The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), the terminal phase elimination rate constant ( $\lambda_z$ ), terminal phase elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration ( $AUC_t$ ), the AUC from time 0 to infinite time ( $AUC_{\infty}$ ) and the apparent oral clearance (CL/F).

**Safety:** Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, 12-lead electrocardiograms (ECGs) and laboratory profiles.

**Statistical Methods:**

**Pharmacokinetic:** The following regimen comparisons were made for  $T_{max}$ ,  $\lambda_z$  and the natural logarithms of  $C_{max}$ ,  $AUC_t$  and  $AUC_{\infty}$ : Regimen C vs. Regimen A, Regimen E vs. Regimen A, Regimen B vs. Regimen C, and Regimen D vs. Regimen E.

An analysis of variance (ANOVA) was performed for  $T_{max}$ , the terminal phase elimination rate constant, and the natural logarithms of  $C_{max}$  and  $AUC_{\infty}$ . The data of subjects assigned to Sequences I, II, and III were analyzed separately from the data of the subjects assigned to Sequences IV, V, and VI due to a variance difference between the two test formulations. This ANOVA model included effects for sequence, subject nested within sequence, period and regimen. The effect of subject was considered to be random, while all other effects were fixed. Within the framework of the ANOVA, each regimen comparison was made with a significance level of 0.05.

For each of the above regimen comparisons, for  $C_{max}$  and  $AUC_{\infty}$  a relative bioavailability assessment was performed by means of the two one-sided test procedure at significance level 0.05. This was done using a 90% confidence interval for the relative bioavailability. These confidence intervals were obtained by exponentiation of the endpoints of the confidence intervals for the difference of mean logarithms within the framework of the ANOVA model described above.

**Safety:** The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and primary system organ class with a breakdown by regimen. Laboratory test values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were identified.

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**Summary/Conclusions:**

**Pharmacokinetic Results:** Mean  $\pm$  standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the five regimens are listed in the following table.

Pharmacokinetic Parameters (units)	Regimens <sup>‡</sup>				
	A: Reference, Fenofibrate, Low-Fat Meal (N = 39)	B: Test Granules, High-Fat Meal (N = 19)	C: Test Granules, Fasting (N = 19)	D: Test Micro-Tablets, High-Fat Meal (N = 20)	E: Test Micro-Tablets, Fasting (N = 18)
T <sub>max</sub> (h)	4.8 $\pm$ 0.9	9.9 $\pm$ 1.4 <sup>§</sup>	4.7 $\pm$ 2.0	9.7 $\pm$ 2.6 <sup>*</sup>	9.8 $\pm$ 3.6 <sup>*</sup>
C <sub>max</sub> ( $\mu$ g/mL)	7.53 $\pm$ 2.44	4.16 $\pm$ 1.28 <sup>*</sup>	4.89 $\pm$ 1.22 <sup>*</sup>	5.77 $\pm$ 2.12 <sup>††</sup>	3.68 $\pm$ 1.13 <sup>*</sup>
AUC <sub>t</sub> ( $\mu$ g·h/mL)	149.5 $\pm$ 47.7	122.3 $\pm$ 47.3 <sup>*</sup>	121.2 $\pm$ 38.1 <sup>*</sup>	120.3 $\pm$ 38.7 <sup>*</sup>	114.4 $\pm$ 30.5 <sup>*</sup>
AUC <sub>∞</sub> ( $\mu$ g·h/mL)	156.3 $\pm$ 54.2	131.8 $\pm$ 58.6 <sup>*</sup>	128.9 $\pm$ 50.8 <sup>*</sup>	123.3 $\pm$ 41.7 <sup>*</sup>	117.6 $\pm$ 32.6 <sup>*</sup>
t <sub>1/2</sub> <sup>§</sup> (h)	20.29 $\pm$ 6.50	20.18 $\pm$ 8.22	20.18 $\pm$ 8.79	18.73 $\pm$ 4.27 <sup>††</sup>	19.91 $\pm$ 4.33
CL/F (L/h)	NA	1.18 $\pm$ 0.53	1.15 $\pm$ 0.46	1.18 $\pm$ 0.40	1.19 $\pm$ 0.33

‡ Regimens B and C were administered as one capsule of fenofibric acid granules equivalent to 130 mg fenofibric acid. Regimens D and E were administered as one capsule of fenofibric acid micro-tablets equivalent to 130 mg fenofibric acid. Regimen A was administered as a 200 mg fenofibrate capsule.

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

§ Statistically significantly different from Regimen C (ANOVA, p < 0.05).

† Statistically significantly different from Regimen E (ANOVA, p < 0.05).

‡ Harmonic mean and pseudo-standard deviation. Harmonic mean evaluations of t<sub>1/2</sub> were based on statistical tests for  $\lambda_z$ .

NA = Not applicable.

The bioequivalence/bioavailability results are listed in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>†</sup>	90% Confidence Interval
<b>Fenofibric Acid Granules</b>					
C vs. A	C <sub>max</sub>	4.68	7.05	0.664	0.561 - 0.787
	AUC <sub>t</sub>	107.28	140.57	0.763	0.710 - 0.821
	AUC <sub>∞</sub>	110.93	145.84	0.761	0.710 - 0.814
<b>Fenofibric Acid Micro-Tablets</b>					
E vs. A	C <sub>max</sub>	3.67	7.05	0.521	0.438 - 0.619
	AUC <sub>t</sub>	121.61	140.57	0.865	0.803 - 0.932
	AUC <sub>∞</sub>	126.64	145.84	0.868	0.810 - 0.931

\* Antilogarithm of the least squares means for logarithms.

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

The effect of food is presented in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
<b>Fenofibric Acid Granules</b>					
B vs. C	$C_{max}$	3.93	4.68	0.839	0.708 - 0.994
	$AUC_t$	105.68	107.28	0.985	0.916 - 1.059
	$AUC_{\infty}$	110.91	110.93	1.000	0.934 - 1.071
<b>Fenofibric Acid Micro-Tablets</b>					
D vs. E	$C_{max}$	5.55	3.67	1.513	1.273 - 1.797
	$AUC_t$	121.71	121.61	1.001	0.930 - 1.077
	$AUC_{\infty}$	125.39	126.64	0.990	0.924 - 1.061

\* Antilogarithm of the least squares means for logarithms.

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

**Safety Results:** The overall incidence rate of treatment-emergent adverse event was slightly higher among subjects who received Regimen B (47.4%) than those who received Regimen A (31.7%), Regimen C (30%), Regimen D (30%) and Regimen E (26.3%). The only adverse event reported by two or more subjects in any regimen was dizziness in Regimen A. No serious adverse events were reported in this study.

No clinically significant changes in vital signs, ECG or laboratory measurements were observed during the course of the study.

**Conclusions:** The test capsule formulation containing 130 mg fenofibric acid as granules administered under fasting conditions (Regimen C) produced 34% lower fenofibric acid  $C_{max}$  and 24% lower  $AUC_{\infty}$  compared to the reference, 200 mg micronized fenofibrate capsule administered with a moderate-fat meal (Regimen A); bioequivalence criteria were not met with respect to fenofibric acid  $C_{max}$  and  $AUC_{\infty}$ .

When the test capsule formulation containing fenofibric acid granules was administered following a high-fat meal (Regimen B), the fenofibric acid  $AUC_{\infty}$  was bioequivalent to that under fasting conditions (Regimen C) because the 90% confidence interval was contained within the 0.80 to 1.25 range. The bioequivalence criterion was not met with respect to fenofibric acid  $C_{max}$  comparing Regimens B vs. C because the entire 90% confidence interval was below unity, and the lower limit extended below 0.80.

The test capsule formulation containing 130 mg fenofibric acid as micro-tablets administered under fasting conditions (Regimen E) produced 48% lower fenofibric acid  $C_{max}$  and 13% lower  $AUC_{\infty}$  compared to the reference fenofibrate formulation (Regimen A); bioequivalence criteria were not met with respect to fenofibric acid  $C_{max}$ .

Administration of the test capsule formulation containing fenofibric acid micro-tablets following a high-fat meal (Regimen D) increased fenofibric acid  $C_{max}$  by 51% compared to that under fasting conditions (Regimen E). The entire 90% confidence interval for the ratio of the central values of log-transformed  $C_{max}$  was above 1.25. Fenofibric acid  $AUC_{0-\infty}$  met the bioequivalence criterion comparing the micro-tablet formulation administered after a high-fat meal and under fasting conditions.

The regimens tested were generally well tolerated by the subjects.

The overall incidence rate of treatment-emergent adverse event was slightly higher among subjects who received Regimen B (47.4%) than those who received Regimen A (31.7%), Regimen C (30.0%), Regimen D (30.0%) and Regimen E (26.3%). The only adverse event reported by two or more subjects in any regimen was dizziness in Regimen A. No serious adverse events were reported in this study.

No clinically significant changes in vital signs, ECG or laboratory measurements were observed during the course of the study.

**Reviewer's Comments:**

- This study was identical to M04-712 except that a capsule formulation containing 130 mg fenofibric acid as granules was evaluated instead of the single-unit tablet.
- Capsule formulation containing 130 mg fenofibric acid as granules was not successful in meeting the BE criterion with or without food.
- Results from the 130 mg choline fenofibrate micro-tablets were inconsistent to those observed in study M04-712 as it failed to show BE to 200 mg micronized fenofibrate.

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**Study M03-636:**

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of the Dossier</b>  Volume:  Page:	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug: Fenofibric Acid (ABT-335, A-770335) and Fenofibrate (ABT-799, A-52799)</b>		
<b>Name of Active Ingredient: Fenofibric Acid</b>		
<b>Title of Study: Comparison of Bioavailability of Two Fenofibric Acid Formulations Relative to the Micronized Fenofibrate Capsule Formulation</b>		
<b>Investigator: Barbara Freyer-Kern, MD, PhD</b>		
<b>Study Site: Clinical Pharmacology Abbott GmbH &amp; Co. KG 67008 Ludwigshafen Germany</b>		
<b>Publications: Not applicable.</b>		
<b>Studied Period:</b> First Screening Procedure: 13 October 2003 Date First Subject Dosed: 21 October 2003 Date Last Subject Completed Dosing: 25 November 2003 Date of Last Study Procedure: 30 November 2003		<b>Phase of Development: 1</b>
<b>Objective: The objective of this study was to compare the bioavailability of two test capsule regimens of fenofibric acid with that of a reference fenofibrate capsule regimen.</b>		
<p><b>Methodology:</b> This Phase I, single-dose, open-label study was conducted according to a three-period, randomized, partial-crossover design. Forty-eight subjects were separated into two cohorts of 24 subjects each. Subjects within each cohort were randomly assigned to one of nine sequences of Regimen A (reference, 200 mg fenofibrate, low-fat meal), Regimen B (Formulation 1, test, 130 mg fenofibric acid, high-fat meal), Regimen C (Formulation 1, test, 130 mg fenofibric acid, fasting), Regimen D (Formulation 2, test, 130 mg fenofibric acid, high-fat meal), and Regimen E (Formulation 2, test, 130 mg fenofibric acid, fasting). A washout interval of 14 days separated the doses of the three study periods.</p> <p>Blood samples were collected into evacuated collection tubes containing potassium oxalate plus sodium fluoride prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 48, 72, 96 and 120 hours after dosing in each study period. Sufficient blood was collected to provide approximately 2 mL plasma from each sample.</p> <p>Plasma concentrations of fenofibric acid were determined using a validated analytical method with mass spectral detection at Abbott Laboratories, Abbott Park, IL. The lower limit of quantitation for fenofibric acid was 0.019 µg/mL using a 150 µL plasma sample. Samples were analyzed between the dates of 18 December 2003 and 10 February 2004.</p>		

<b>Number of Subjects (Planned and Analyzed):</b>			
Planned: 48; Entered: 48; Completed: 48; Evaluated for Safety: 48; Evaluated for Pharmacokinetics: 48			
For the 48 subjects who participated in the study, the mean age was 38.7 years (ranging from 21 to 50 years), the mean weight was 74.3 kg (ranging from 57 to 101 kg) and the mean height was 175.9 cm (ranging from 155 to 197 cm).			
<b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were male and female volunteers between 18 and 50 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal, sterile or were not pregnant or breast-feeding and were practicing at least one of the acceptable methods of birth control specified in the protocol.			
<b>Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:</b>			
	<b>Reference Formulation</b>	<b>Test Formulation</b>	<b>Test Formulation</b>
Dosage Form	Normalip Pro	Extended-release capsule	Extended-release capsule
Formulation	Micronized	1	2
Strength (mg)	200	130	130
Bulk Product Lot Number	091379S	08061HB	07-525-AR
Bulk NPRO	NA	NA	1035N
Potency (% of Label Claim)	NA	97.1	100.3
Manufacturing Site	Laboratories Fournier	Ludwigshafen, Germany	PARD <sup>†</sup>
Expiration/Retest Date	31 March 2004	NA	NA
<sup>†</sup> PARD = Pilot Plant, Abbott, North Chicago, IL. NA = Not Applicable/Available.			
<b>Duration of Treatment:</b> A single dose of fenofibric acid was administered to Cohort 1 on 21 October 2003, 04 November 2003 and 18 November 2003, and to Cohort 2 on 28 October 2003, 11 November 2003 and 25 November 2003, in Periods 1, 2 and 3, respectively. Subjects receiving the reference formulation were administered a 200 mg dose of fenofibrate; all test formulations were administered as a 130 mg dose of fenofibric acid.			
<b>Criteria for Evaluation:</b>			
<b>Pharmacokinetic:</b> The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum plasma concentration ( $C_{max}$ ) and time to $C_{max}$ ( $T_{max}$ ), the terminal phase elimination rate constant ( $\lambda_z$ ), terminal phase elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration (AUC <sub>t</sub> ), the AUC from time 0 to infinite time (AUC <sub>∞</sub> ).			
<b>Safety:</b> Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECGs and laboratory tests.			

**Statistical Methods:**

**Pharmacokinetic:** An analysis of variance (ANOVA) that utilized only intra-subject information was applied to  $T_{max}$ ,  $\lambda_z$ , and the natural logarithms of  $C_{max}$  and  $AUC_{0-\infty}$ . Within the ANOVA the following regimen comparisons were made: Regimen C vs. Regimen A, Regimen E vs. Regimen A, Regimen B vs. Regimen C, Regimen D vs. Regimen E, and Regimen C vs. Regimen E. For each regimen comparison, a test of the hypothesis of the equality of regimens was performed at the 0.05 level (not adjusted for multiple comparisons).

For each of the above regimen comparisons, for  $C_{max}$  and  $AUC_{0-\infty}$ , a relative bioavailability assessment was performed by means of a two one-sided tests procedure at significance level 0.05. This was done by means of 90% confidence intervals for the relative bioavailability.

**Safety:** The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by the MedDRA preferred term and system organ class with a breakdown by regimen. Laboratory test values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were identified.

**Summary/Conclusions:**

**Pharmacokinetic Results:** Mean  $\pm$  standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the five regimens are listed in the following table.

Pharmacokinetic Parameters (units)	Regimen <sup>z</sup>				
	A: Reference Low-Fat Meal	B: Test Formulation 1, High-Fat Meal	C: Test Formulation 1, Fasting	D: Test Formulation 2, High-Fat Meal	E: Test Formulation 2, Fasting
	(N = 48)	(N = 18)	(N = 30)	(N = 18)	(N = 30)
$T_{max}$ (h)	4.8 $\pm$ 2.0	5.9 $\pm$ 1.5	4.5 $\pm$ 2.9 <sup>†</sup>	9.6 $\pm$ 3.9 <sup>†</sup>	6.1 $\pm$ 3.8
$C_{max}$ ( $\mu$ g/mL)	5.89 $\pm$ 1.67	7.62 $\pm$ 1.32 <sup>§</sup>	3.92 $\pm$ 1.55 <sup>**†</sup>	5.03 $\pm$ 1.74 <sup>†</sup>	2.96 $\pm$ 1.59 <sup>‡</sup>
$AUC_{0-\infty}$ ( $\mu$ g $\cdot$ h/mL)	112.2 $\pm$ 41.3	111.3 $\pm$ 31.4 <sup>§</sup>	99.6 $\pm$ 37.4 <sup>**†</sup>	97.7 $\pm$ 40.3 <sup>†</sup>	71.7 $\pm$ 43.3 <sup>‡</sup>
$t_{1/2}$ <sup>§</sup> (h)	15.9	14.4	14.8 <sup>*</sup>	14.4	15.1

<sup>z</sup> Regimens B, C, D and E were administered as a 130 mg fenofibric acid capsule. Regimen A was administered as a 200 mg fenofibrate capsule.

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

<sup>§</sup> Statistically significantly different from Regimen C (ANOVA,  $p < 0.05$ ).

<sup>†</sup> Statistically significantly different from Regimen E (ANOVA,  $p < 0.05$ ).

<sup>‡</sup> Harmonic mean, evaluations of  $t_{1/2}$  were based on statistical tests for  $\lambda_z$ .

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The bioavailability results are listed in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Values <sup>*</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
C vs. A	C <sub>max</sub> (µg/mL)	3.59	5.68	0.63	0.56 - 0.72
	AUC <sub>∞</sub> (µg·h/mL)	89.48	105.44	0.85	0.79 - 0.92
E vs. A	C <sub>max</sub> (µg/mL)	2.52	5.68	0.44	0.39 - 0.50
	AUC <sub>∞</sub> (µg·h/mL)	60.91	105.44	0.58	0.54 - 0.62
C vs. E	C <sub>max</sub> (µg/mL)	3.59	2.52	1.42	1.21 - 1.67
	AUC <sub>∞</sub> (µg·h/mL)	89.48	60.91	1.47	1.34 - 1.61

\* Antilogarithm of the least squares means for logarithms.

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

The food effect results are listed in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Values <sup>*</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
B vs. C	C <sub>max</sub> (µg/mL)	7.94	3.59	2.21	1.88 - 2.61
	AUC <sub>∞</sub> (µg·h/mL)	109.36	89.48	1.22	1.11 - 1.35
D vs. E	C <sub>max</sub> (µg/mL)	4.89	2.52	1.95	1.65 - 2.29
	AUC <sub>∞</sub> (µg·h/mL)	95.77	60.91	1.57	1.43 - 1.73

\* Antilogarithm of the least squares means for logarithms.

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

**Safety Results:** Seven (7/48, 15%) subjects reported at least one treatment-emergent adverse event: One subject each reported headache, dyspepsia and nausea in Regimen A, cervical radiculopathy and phlebitis superficial in Regimen B, headache and premenstrual syndrome in Regimen C, and headache and premenstrual syndrome in Regimen E. No adverse events were reported in Regimen D. The majority of the treatment-emergent adverse events were assessed by the investigator as not related to the study drug and mild in severity.

The proportion of subjects reporting at least one treatment-emergent adverse event was slightly higher among subjects who received Regimen B (11%) than those who received Regimen A (6%), Regimen C (7%) and Regimen E (7%). There were no adverse events reported in Regimen D.

No deaths or other serious adverse events were reported in this study. Results of other safety analyses including individual subject changes, and individual clinically significant values for vital signs, ECG and laboratory measurements were unremarkable for each treatment group.

**Conclusions:** Fenofibric acid exposure following administration of Formulation 1 under fasting conditions (130 mg fenofibric acid capsule, Regimen C) was approximately 37% less for  $C_{max}$  and 15% less for  $AUC_{0-\infty}$  relative to the reference Regimen A (200 mg fenofibrate capsule, low-fat meal). Fenofibric acid exposure following administration of Formulation 2 under fasting conditions (130 mg fenofibric acid capsule, Regimen E) was approximately 56% less for  $C_{max}$  and 42% less for  $AUC_{0-\infty}$  relative to the reference Regimen A.

Under fasting conditions, fenofibric acid exposure from Formulation 1 (130 mg fenofibric acid capsule, Regimen C) was approximately 42% greater for  $C_{max}$  and 47% greater for  $AUC_{0-\infty}$  than Formulation 2 (130 mg fenofibric acid capsule, Regimen E).

The effect of food on Formulation 1 (130 mg fenofibric acid capsule, Regimen B vs. Regimen C) did not meet the criteria to document lack of food effect for  $C_{max}$  or  $AUC_{0-\infty}$ . The upper limit of the 90% confidence interval for log-transformed  $AUC_{0-\infty}$  was above 1.25 and the entire confidence interval for log-transformed  $C_{max}$  was above 1.25. The effect of food on Formulation 2 (130 mg fenofibric acid capsule, Regimen D vs. Regimen E) did not meet the criteria to document lack of food effect for  $C_{max}$  or  $AUC_{0-\infty}$  since the entire confidence intervals for log-transformed  $C_{max}$  and  $AUC_{0-\infty}$  were above 1.25. The fenofibric acid elimination rate constants and half-lives were similar whether fenofibrate or fenofibric acid was administered to the subjects.

The regimens tested were generally well tolerated by the subjects with no clinically relevant differences among the regimens with regard to safety. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.

**Reviewer's Comments:**

- This study was first study that evaluated extended release formulations of fenofibric acid (not choline fenofibrate) and was conducted prior to M04-712 and M04-715.
- The test formulations evaluated in the study though failed to show BE to 200 mg micronized fenofibrate and lack of food effect.

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**Study M05-732:**

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of the Dossier</b>  Volume:  Page:	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Fenofibric acid (ABT-335)		
<b>Name of Active Ingredient:</b> Fenofibric acid		
<b>Title of Study: Bioavailability of Fenofibric Acid from Three Fenofibric Acid Choline Salt Formulations with Various Compositions Relative to Fenofibrate</b>		
<b>Investigator: Timi Edeki, MD, PhD</b>		
<b>Study Site:</b> Abbott Clinical Pharmacology Research Unit 1324 North Sheridan Road Waukegan, IL 60085		
<b>Publications: None.</b>		
<b>Studied Period:</b> First Screening Procedure: 15 May 2005. Date of last study procedure: 11 July 2005.	<b>Phase of Development: 1</b>	
<b>Objective: The objective of this study was to determine the bioavailability of fenofibric acid from three fenofibric acid choline salt formulations with various compositions relative to micronized fenofibrate.</b>		
<b>Methodology: This Phase I, single-dose, open-label study was conducted according to a four-period, randomized, complete crossover design. Adult male and female subjects (N = 40) in general good health were selected to participate in the study according to the selection criteria.</b>  <b>After meeting the selection criteria, the subjects were randomly assigned in equal numbers to four sequences of Regimens A (One 200 mg micronized fenofibrate capsule), B (one capsule containing fenofibric acid choline salt micro-tablets [Formulation 9] equivalent to 135 mg fenofibric acid), C (one capsule containing fenofibric acid choline salt micro-tablets [Formulation 10] equivalent to 135 mg fenofibric acid) and D (one capsule containing fenofibric acid choline salt micro-tablets [Formulation 11] equivalent to 135 mg fenofibric acid). Drug/polymer ratios for the formulations were _____ or Formulations 9, 10 and 11, respectively. Regimen A was administered following a low-fat breakfast; regimens B, C and D were administered under fasting conditions. All regimens were administered on Study Day 1 of each period. A washout interval of at least 14 days separated the doses of the four study periods.</b>		

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**Methodology (Continued):**

Blood samples for fenofibric acid assay were collected by venipuncture prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing in each study period. The blood samples were collected in 2 mL collection tubes containing potassium oxalate plus sodium fluoride. Sufficient blood was collected to provide approximately 1 mL plasma from each sample.

Plasma concentrations of fenofibric acid were determined using a validated liquid chromatography method with LC/MS/MS detection at Abbott Laboratories Drug Analysis department. The lower limit of quantitation for fenofibric acid was established at 0.017 µg/mL using a 0.050 mL plasma sample. Samples were analyzed between the dates of 14 July 2005 and 29 July 2005.

**Number of Subjects (Planned and Analyzed):**

Planned: 40; Entered: 40; Completed: 40; Evaluated for Safety: 40; Evaluated for Pharmacokinetics: 40

For the 40 subjects who participated in the study, the mean age was 32.7 years (ranging from 18 to 55 years), the mean weight was 72.4 kg (ranging from 51 to 103 kg) and the mean height was 168.7 cm (ranging from 154 to 192 cm).

**Diagnosis and Main Criteria for Inclusion:** Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal, sterile and were not pregnant or breast-feeding and were practicing at least one of the acceptable methods of birth control specified in the protocol.

**Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:**

	Reference		Test	
	A	B	C	D
<b>Formulation</b>	Micronized Fenofibrate	Fenofibric acid Choline Salt Formulation 9	Fenofibric acid Choline Salt Formulation 10	Fenofibric acid Choline Salt Formulation 11
<b>Dosage Form</b>	Capsule	Capsule	Capsule	Capsule
<b>Strength (mg)</b>	200	135 <sup>a</sup>	135 <sup>a</sup>	135 <sup>a</sup>
<b>Bulk Product Lot Number</b>	12-539-AR	26-579-AR	27-580-AR	27-581-AR
<b>Finishing Sublot Number</b>	107487	27-009-S2	27-010-S2	27-011-S2
<b>Manufacturer</b>	Fournier	Abbott	Abbott	Abbott

a. Dosage forms B, C and D contained fenofibric acid choline salt equivalent to 135 mg fenofibric acid.

**Duration of Treatment:** Four single doses were administered on 16 May 2005, 06 June 2005, 20 June 2005 and 07 July 2005.

**Criteria for Evaluation**

**Pharmacokinetic:** The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), the terminal phase elimination rate constant ( $\lambda_z$ ), terminal phase elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration ( $AUC_t$ ) and the AUC from time 0 to infinity ( $AUC_{\infty}$ ). The apparent oral clearance (CL/F) was calculated for the test regimens.

**Safety:** Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECGs and laboratory tests.

**Statistical Methods**

**Pharmacokinetic:** An analysis of variance (ANOVA) was performed for  $T_{max}$ , elimination rate constant ( $\lambda_z$ ) and the natural logarithms of  $C_{max}$ ,  $AUC_t$  and  $AUC_{\infty}$ . The model included effects for sequence, subject nested within sequence, period and regimen. The effect for subject was random and all other effects were fixed. For the test on sequence effects, the denominator sum of squares for the F statistic was the sum of squares for subjects nested within sequence. For the tests on other effects, the denominator sum of squares was the sum of squares for error. Within the ANOVA modeling framework, the test regimens (Regimens B, C and D) were compared to the reference (Regimen A) using tests with significance levels of 0.05 (not adjusted for multiple comparisons).

The bioavailability of each test regimen (Regimens B, C and D) relative to that of the reference regimen (Regimen A) was assessed by a two one-sided tests procedure via 90% confidence intervals obtained from the analyses of the natural logarithms of  $C_{max}$  and  $AUC_{\infty}$ . These confidence intervals were obtained by exponentiating the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. The point estimate of the relative bioavailability was likewise obtained by exponentiating the least squares estimate of the difference of mean logarithms, and the population central value for each regimen was estimated by exponentiating the least squares mean for the logarithm. Bioequivalence between a test regimen and the reference regimen was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC and  $C_{max}$  were within the 0.80 to 1.25 range.

**Safety:** The number and percentage of subjects reporting adverse events were tabulated by MedDRA preferred term. Laboratory test values that were Very High or Very Low were identified. Urinalysis values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were identified.

**Summary/Conclusions**

**Pharmacokinetic Results:** Mean  $\pm$  standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the four regimens are listed in the following table.

Pharmacokinetic Parameters (units)	Regimens <sup>‡</sup>			
	A: Reference Capsules (N = 40)	B: Test Capsules (N = 40)	C: Test Capsules (N = 40)	D: Test Capsules (N = 40)
T <sub>max</sub> (h)	4.7 $\pm$ 1.2	4.6 $\pm$ 1.5	4.3 $\pm$ 1.2	4.3 $\pm$ 1.3
C <sub>max</sub> ( $\mu$ g/mL)	9.86 $\pm$ 2.44	7.56 $\pm$ 1.97*	8.08 $\pm$ 2.37*	9.14 $\pm$ 2.78*
AUC <sub>t</sub> ( $\mu$ g $\cdot$ h/mL)	163.4 $\pm$ 49.4	141.1 $\pm$ 43.6*	142.2 $\pm$ 45.4*	143.3 $\pm$ 44.9*
AUC <sub>∞</sub> ( $\mu$ g $\cdot$ h/mL)	166.1 $\pm$ 50.9	143.2 $\pm$ 45.1*	144.3 $\pm$ 46.7*	145.2 $\pm$ 46.6*
t <sub>1/2</sub> <sup>§</sup> (h)	19.34 $\pm$ 4.92	17.51 $\pm$ 3.89*	17.89 $\pm$ 4.16*	17.32 $\pm$ 3.69*
CL/F <sup>†</sup> (L/h)	--	1.03 $\pm$ 0.32	1.04 $\pm$ 0.34	1.03 $\pm$ 0.35

‡ Regimen A = one 200 mg micronized fenofibrate capsule following low-fat breakfast; Regimens B, C and D = one capsule containing fenofibric acid choline salt micro-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions (different formula for each regimen).

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

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

† Parameter was not tested statistically.

The bioequivalence/bioavailability results are listed in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>+</sup>	90% Confidence Interval
B vs. A	C <sub>max</sub>	7.31	9.55	0.765	0.712 - 0.822
	AUC <sub>t</sub>	134.85	156.64	0.861	0.831 - 0.892
	AUC <sub>∞</sub>	136.64	159.08	0.859	0.829 - 0.890
C vs. A	C <sub>max</sub>	7.72	9.55	0.808	0.752 - 0.868
	AUC <sub>t</sub>	135.28	156.64	0.864	0.833 - 0.895
	AUC <sub>∞</sub>	137.14	159.08	0.862	0.832 - 0.893
D vs. A	C <sub>max</sub>	8.70	9.55	0.911	0.848 - 0.979
	AUC <sub>t</sub>	136.51	156.64	0.871	0.841 - 0.903
	AUC <sub>∞</sub>	138.11	159.08	0.868	0.838 - 0.900
C vs. B	C <sub>max</sub>	7.72	7.31	1.056	0.982 - 1.135
	AUC <sub>t</sub>	135.28	134.85	1.003	0.968 - 1.040
	AUC <sub>∞</sub>	137.14	136.64	1.004	0.968 - 1.040
D vs. B	C <sub>max</sub>	8.70	7.31	1.191	1.108 - 1.280
	AUC <sub>t</sub>	136.51	134.85	1.012	0.977 - 1.049
	AUC <sub>∞</sub>	138.11	136.64	1.011	0.975 - 1.047
D vs. C	C <sub>max</sub>	8.70	7.72	1.128	1.049 - 1.212
	AUC <sub>t</sub>	136.51	135.28	1.009	0.974 - 1.046
	AUC <sub>∞</sub>	138.11	137.14	1.007	0.972 - 1.044

\* Antilogarithm of the least squares means for logarithms.

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

**Safety Results:** Twenty three (23/40, 57.5%) subjects reported at least one treatment-emergent adverse event: 9/40 (22.5%) in Regimen A; 7/40 (17.5%) in Regimen B; 10/40 (25%) in regimen C; 7/40 (17.5%) in Regimen D. Adverse event reported by three or more subjects was headache (2/40 subjects, 5% in Regimen A; (3/40 subjects, 7.5%) in Regimen B; (3/40 subjects, 7.5%) in Regimen C and (4/40 subjects, 10%) in Regimen D. All remaining adverse events were reported by a maximum of 5% of subjects (two subjects).

The proportion of subjects reporting at least one treatment-emergent adverse event was slightly higher among subjects who received Regimens A (22.5%) and C (25%) than those who received Regimens B (17.5%) and Regimen D (17.5%). The most common treatment-emergent adverse event (reported by three or more subjects in any regimen) was headache. The majority of adverse events were assessed by the investigator as not related to study drug and mild in severity.

No deaths or other serious adverse events were reported in this study. Results of other safety analyses including individual subject changes, and individually clinically significant values for ECG and laboratory measurements were unremarkable for each treatment group.

**Conclusions:** Test Regimens B, C and D met bioequivalence criteria to the reference Regimen A with respect to fenofibric acid AUC because the 90% confidence intervals for comparing the log-transformed AUC between regimens were contained within 0.80 to 1.25. Regimen D was also bioequivalent to the reference Regimen A with respect to fenofibric acid  $C_{min}$ . The lower limits of the 90% confidence intervals for comparing the log-transformed  $C_{min}$  of test Regimens B and C to Regimen A extended below 0.80.

The ratio of drug to polymer was approximately 1.6, 2.4 and 3.4 for Regimens B, C, and D, respectively. Comparing the relative bioavailability of the three test formulations to the reference (Regimen A) suggest that fenofibric acid AUC was insensitive to the drug/polymer ratio, whereas the  $C_{min}$  increased with increasing drug to polymer ratio. *In vitro* dissolution profiles suggest the fastest rate of dissolution for Regimen D followed by Regimen C and Regimen B. The dissolution rate *in vitro* is reflective of the rank order of  $C_{min}$  observed *in vivo*.

Test Regimen C was bioequivalent to Regimens B and D with respect to the  $C_{min}$  and AUC of fenofibric acid because the 90% confidence intervals for comparing the log-transformed parameters between regimens were contained within 0.80 to 1.25. Bioequivalence criteria were also met with respect to fenofibric acid AUC between test Regimens B and D. However, the upper limit of the 90% confidence interval for comparing log-transformed fenofibric acid  $C_{min}$  between Regimens B and D extended above 1.25.

The regimens tested were generally well tolerated by the subjects. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.

**Reviewer's Comments:**

- This study evaluated three test formulations containing choline fenofibrate micro-tablets equivalent to 135 mg fenofibric acid and micro-tablets differed in their drug-polymer ratio (#9 ~~\_\_\_\_\_~~ #10 ~~\_\_\_\_\_~~ #11 ~~\_\_\_\_\_~~)
- All test formulations showed BE to 200 mg micronized fenofibrate with regards to AUC and only formulation 11 showed BE with regards to both  $C_{max}$  and AUC. Sponsor selected formulation 10 for further optimization.

**Study M05-743:**

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of the Dossier</b>  Volume:  Page:	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug: Fenofibric Acid (ABT-335, A-770335) and Fenofibrate (ABT-799, A-52799)</b>		
<b>Name of Active Ingredient: Fenofibric Acid</b>		
<b>Title of Study: Comparison Fenofibric Acid Bioavailability from a Fenofibric Acid Choline Salt Formulation Relative to that from the Micronized Fenofibrate Capsule Formulation and Assessment of Food Effect on Fenofibric Acid Bioavailability from the Choline Salt Formulation</b>		
<b>Investigator: Timi Edeki, MD, PhD</b>		
<b>Study Site: Abbott Clinical Pharmacology Research Unit 1324 North Sheridan Road Waukegan, IL 60085</b>		
<b>Publications: Not applicable.</b>		
<b>Studied Period: Approximately 2 months</b>		<b>Phase of Development: 1</b>
<b>First Subject First Visit: 03 August 2005</b>		
<b>Last Subject Last Visit: 03 October 2005</b>		
<b>Objectives: The objectives of this study were to compare the bioavailability of a test fenofibric acid choline salt formulation from a scale-up lot with that of a reference fenofibrate capsule, and to assess the food effect on the bioavailability of fenofibric acid from the test formulation.</b>		
<b>Methodology: This Phase I, single-dose, open-label study was conducted according to a three-period, randomized, crossover design. Subjects were randomly assigned in equal numbers to receive one of six sequences of Regimens A, B and C as follows.</b>		
<b>Regimen A</b>	<b>One capsule containing fenofibric acid choline salt mini-tablets (Formulation 10) equivalent to 135 mg fenofibric acid administered following a high-fat breakfast (test).</b>	
<b>Regimen B</b>	<b>One capsule containing fenofibric acid choline salt mini-tablets (Formulation 10) equivalent to 135 mg fenofibric acid administered under fasting conditions (test).</b>	
<b>Regimen C</b>	<b>One 200 mg micronized fenofibrate capsule administered following a low-fat breakfast (reference).</b>	
<b>A washout interval of at least 14 days separated the doses of the three study periods.</b>		

**Methodology (Cont.):**

Blood samples for fenofibric acid assay were collected into 2 mL collection tubes containing potassium oxalate plus sodium fluoride prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing in each study period. Sufficient blood was collected to provide approximately 1 mL plasma from each sample.

Plasma concentrations of fenofibric acid were determined using a validated liquid chromatography method with tandem mass spectrometric detection at Abbott Laboratories, Abbott Park, IL. The lower limit of quantitation for fenofibric acid was established at 0.017 µg/mL using a 0.050 mL plasma sample. Samples were analyzed between the dates of 05 October 2005 and 17 October 2005.

**Number of Subjects (Planned and Analyzed):**

Planned: 24; Entered: 24; Completed: 24; Evaluated for Safety: 24; Evaluated for Pharmacokinetics: 24

For the 24 subjects who participated in the study, the mean age was 38.9 years (ranging from 19 to 55 years), the mean weight was 74.4 kg (ranging from 53 to 100 kg) and the mean height was 171.9 cm (ranging from 146 to 193 cm).

**Diagnosis and Main Criteria for Inclusion:** Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were not pregnant or breast-feeding. Females were either surgically sterile, postmenopausal, or practicing at least one of the acceptable methods of birth control specified in the protocol.

**Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:**

	Test	Reference
Formulation	Fenofibric Acid Choline Salt Formulation 10	Fenofibrate
Dosage Form	Capsule	Capsule
Strength (mg)	135*	200
Bulk Product Lot Number	30-589-AR	12-539-AR

\* Dosage form contains fenofibric acid choline salt equivalent to 135 mg fenofibric acid.

**Duration of Treatment:** Three single doses were administered on 26 August 2005, 14 September 2005 and 28 September 2005.

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### Criteria for Evaluation

**Pharmacokinetic:** The pharmacokinetic parameters of fenofibric acid were estimated using noncompartmental methods. These included: the maximum plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), the terminal phase elimination rate constant ( $\lambda_z$ ), terminal phase elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration ( $AUC_t$ ), the AUC from time 0 to infinite time ( $AUC_{\infty}$ ), and for Regimens A and B only, the apparent oral clearance (CL/F).

**Safety:** Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECGs and laboratory tests.

### Statistical Methods

**Pharmacokinetic:** An analysis of variance (ANOVA) with fixed effects for sequence, period, regimen, and with random effects for subjects nested within sequence, were performed for  $T_{max}$ ,  $\lambda_z$ , and the natural logarithms of  $C_{max}$ ,  $AUC_t$  and  $AUC_{\infty}$ . Within the ANOVA modeling framework, the test regimens (Regimens A and B) were compared to the reference (Regimen C) and test Regimen A was compared with test Regimen B using tests with significance levels of 0.05 (not adjusted for multiple comparisons).

The bioavailability of each test regimen (Regimens A and B) relative to that of the reference regimen (Regimen C) and the bioavailability of Regimen A to Regimen B were assessed by the two one-sided tests procedure *via* 90% confidence intervals obtained from the analysis of the natural logarithms of  $AUC_t$  and  $AUC_{\infty}$ . The confidence intervals were obtained by exponentiating the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. Bioequivalence was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC were within the 0.80 to 1.25 range.

**Safety:** The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and primary system organ class with a breakdown by regimen. Laboratory test values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were identified.

### Summary/Conclusions

**Pharmacokinetic Results:** Mean  $\pm$  standard deviation pharmacokinetic parameters of fenofibric acid after administration of the three regimens are listed in the following table.

Pharmacokinetic Parameters (units)	Regimen <sup>f</sup>		
	A (Test)	B (Test)	C (Reference)
	Fenofibric Acid Choline Salt Formulation 10 High-Fat Breakfast (N = 24)	Fenofibric Acid Choline Salt Formulation 10 Fasting (N = 24)	Fenofibrate Low-Fat Breakfast (N = 24)
$T_{max}$ (h)	10.3 $\pm$ 4.8 <sup>g</sup>	4.3 $\pm$ 1.2	4.6 $\pm$ 0.9
$C_{max}$ ( $\mu$ g/mL)	6.85 $\pm$ 1.91 <sup>g</sup>	8.01 $\pm$ 2.02 <sup>*</sup>	9.82 $\pm$ 2.21
$AUC_t$ ( $\mu$ g-h/mL)	140.4 $\pm$ 38.1 <sup>*</sup>	137.8 $\pm$ 46.1 <sup>*</sup>	159.2 $\pm$ 47.5
$AUC_{\infty}$ ( $\mu$ g-h/mL)	143.0 $\pm$ 40.1 <sup>*</sup>	139.9 $\pm$ 47.6 <sup>*</sup>	162.3 $\pm$ 49.6
$t_{1/2}$ <sup>h</sup> (h)	18.44 $\pm$ 4.87	17.98 $\pm$ 4.60	18.96 $\pm$ 5.09
CL/F <sup>†</sup> (L/h)	1.01 $\pm$ 0.26	1.08 $\pm$ 0.40	NA

<sup>f</sup> Regimens A and B were administered as one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid. Regimen C was administered as a 200 mg fenofibrate capsule.

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

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

<sup>h</sup> Harmonic mean  $\pm$  pseudo standard deviation; evaluations of  $t_{1/2}$  were based on statistical tests for  $\lambda_z$ .

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

NA – Not applicable.

The bioequivalence/bioavailability results are listed in the following table.

Regimens <sup>f</sup> Test vs. Reference	Pharmacokinetic Parameter	Central Values <sup>g</sup>		Relative Bioavailability	
		Test	Reference	Point <sup>h</sup> Estimate	90% Confidence Interval
<b>Bioequivalence</b>					
B vs. C	$C_{max}$ (µg/mL)	7.787	9.572	0.8135	0.7536 – 0.8781
	$AUC_0-t$ (µg·h/mL)	130.841	152.259	0.8593	0.8160 – 0.9050
	$AUC_{0-\infty}$ (µg·h/mL)	132.717	154.892	0.8568	0.8135 – 0.9025
<b>Food Effect</b>					
A vs. B	$C_{max}$ (µg/mL)	6.581	7.787	0.8452	0.7830 – 0.9124
	$AUC_0-t$ (µg·h/mL)	135.907	130.841	1.0387	0.9863 – 1.0939
	$AUC_{0-\infty}$ (µg·h/mL)	138.127	132.717	1.0408	0.9881 – 1.0962

<sup>f</sup> Regimens A and B were administered as one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid. Regimen C was administered as a 200 mg fenofibrate capsule. Regimen A was administered after a high-fat breakfast, Regimen B under fasting conditions and Regimen C after a low-fat breakfast.

<sup>g</sup> Antilogarithm of the least squares means for logarithms.

<sup>h</sup> Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

**Safety Results:** Five (5/24, 20.8%) subjects reported at least one treatment-emergent adverse event: 1/24 (4.2%) in Regimen A; 2/24 (8.3%) in Regimen B and 3/24 (12.5%) in Regimen C. Except for the mild nausea which was possibly related to the study drug, all the remaining adverse events were assessed by the investigator as not related to study drug and all were mild in severity. No serious adverse events were reported in this study. No subjects were discontinued from the study.

No clinically significant changes in vital signs, ECG or laboratory measurements were observed during the course of the study.

**Conclusions:** This study was designed to evaluate the bioequivalence between the test formulation (Formulation 10) containing fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions and the reference formulation (200 mg fenofibrate capsule) administered following a low-fat meal on the basis of AUC only. The expectation for the  $C_{max}$  for the test formulation was to be no greater than that for the reference formulation. Additionally, this study was also designed to evaluate the food effect on the test formulation.

Formulation 10 under fasting conditions (Regimen B) met the bioequivalence criteria with respect to fenofibric acid AUC relative to the reference 200 mg micronized fenofibrate capsule administered following a low-fat meal (Regimen C). The fenofibric acid  $C_{max}$  was about 19% lower on average for

**Conclusions (Cont.):**

Regimen B than the reference Regimen C, and the upper limit of the 90% confidence interval comparing Regimen B to Regimen C was less than 1.25 suggesting that the  $C_{max}$  of Formulation 10 was no greater than that of the reference.

Formulation 10 administered with a high-fat meal (Regimen A) was bioequivalent to Regimen B with respect to fenofibric acid AUC. The fenofibric acid  $C_{max}$  was about 15% lower on average for Regimen A, and the lower limit of the 90% confidence interval comparing Regimen A to Regimen B was slightly below 0.80.

The regimens tested were generally well tolerated by the subjects. No clinically significant changes in vital signs, physical examination results, ECG or laboratory measurements were observed during the course of the study.

**Reviewer's Comments:**

- This study evaluated BE of test formulation 10 from a scale-up lot containing choline fenofibrate mini-tablets (instead of micro-tablets) equivalent to 135 mg fenofibric acid to the 200 mg micronized fenofibrate.
- The test formulation 10 from this scale-up lot did not show BE to 200 mg micronized fenofibrate with regards to  $C_{max}$  with or without high-fat meal.
- The Guidance Document on Food-Effect Bioavailability and Fed Bioequivalence Studies recommends that "A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 Calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150 (15%), 250 (25%), and 500-600 (50-60%) calories from protein, carbohydrate, and fat, respectively." Sponsor used appropriate high-fat meal 847.8 Kcal; 51.7% calories from fat, 33.7% calories from carbohydrates and 14.2% calories from protein.

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