M05-737:

Abbott Laboratories	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Study Drug: Fenofibric Acid (ABT-335, A-770335) and Fenofibrate (ABT-799, A-52799)	Volume:	
Name of Active Ingredient: Fenofibric Acid	Page:	

Title of Study: Comparison of *In Vivo* Performance of Three Modified-Release Formulations of Fenofibric Acid Choline Salt with Various *In Vitro* Dissolution Rates

Investigator: Timi Edeki, MD, PhD

Study Site: Abbott Clinical Pharmacology Research Unit
1324 North Sheridan Road
Waukegan, IL 60085

Publications: Not applicable.

Studied Period: Approximately 2 months First Subject First Visit: 17 August 2005 Last Subject Last Visit: 10 October 2005	Phase of Development: 1

Objective: The objective was to explore any correlation observed between *in vitro* dissolution and *in vivo* performance of fenofibric acid from three modified-release formulations that differ in release rates. An immediate release formulation was used as a reference. This report presents only the bioavailability and safety results. The analysis comparing the *in vitro* dissolution data and *in vivo* pharmacokinetic data (IVIVC) is reported separately.

Methodology: This Phase 1, single-dose, open-label study was conducted according to a four-period, randomized, crossover design. Subjects were randomly assigned in equal numbers to receive one of four sequences of the following regimens.

Regimen A	One immediate-release capsule of fenofibric acid, 135 mg, administered under fasting conditions (reference).
Regimen B	One capsule containing fenofibric acid choline salt mini-tablets (Formulation 12), equivalent to 135 mg fenofibric acid, administered under fasting conditions (test).
Regimen C	One capsule containing fenofibric acid choline salt mini-tablets (Formulation 10), equivalent to 135 mg fenofibric acid, administered under fasting conditions (test).
Regimen D	One capsule containing fenofibric acid choline salt mini-tablets (Formulation 13), equivalent to 135 mg fenofibric acid, administered under fasting conditions (test).

A washout interval of at least 14 days separated the doses of the four study periods.

Blood samples for fenofibric acid assay were collected into 2 mL collection tubes containing potassium oxalate plus sodium fluoride. For Regimen A, blood samples were collected prior to dosing (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing. For Regimens B, C and D, blood samples were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing. 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 18 October 2005 and 21 October 2005.

Number of Subjects (Planned and Analyzed):

Planned: 24; Entered: 24; Completed: 23; Evaluated for Safety: 24; Evaluated for Pharmacokinetics: 24

For the 24 subjects who participated in the study, the mean age was 37.0 years (ranging from 18 to 55 years), the mean weight was 75.1 kg (ranging from 59 to 97 kg) and the mean height was 170.9 cm (ranging from 155 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 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:

	Regimen			
	Reference	Test		
	A	B	C	D
Formulation	Fenofibric Acid Immediate-release	Fenofibric Acid Choline Salt Formulation 12	Fenofibric Acid Choline Salt Formulation 10	Fenofibric Acid Choline Salt Formulation 13
Dosage Form	Capsule	Capsule	Capsule	Capsule
Strength (mg)	135	135*	135*	135*
HPMC Amount (%)	0	27	27	27
HPMC molecular weight (MW) grades used	NA	Both Low and High MW	High MW only	High MW only
Size of mini-tablets in the capsules	NA	3 mm	3 mm	4 mm
Bulk Product Lot Number	29-585-AR	29-587-AR	30-589-AR	29-588-AR

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

HPMC = hydroxypropylmethyl-cellulose.

NA = Not applicable.

Duration of Treatment: Four single doses were administered on 18 August 2005, 07 September 2005, 21 September 2005 and 05 October 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 (λ_z), terminal phase elimination half-life ($t_{½}$), 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_∞) 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.

Statistical Methods:

Pharmacokinetic: An ANOVA was performed for T_{max}, the elimination rate constant (λ_z) and the natural logarithms of C_{max}, AUC_t and AUC_∞. 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. 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 of 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}, AUC_t and AUC_∞. Bioequivalence between the fenofibric acid choline salt formulation and the reference fenofibric acid immediate-release capsule formulation was concluded if the 90% confidence interval for relative bioavailability was within the 0.80 to 1.25 range.

The bioavailability between each pair combination among Regimens B, C, and D was also assessed using the two one-sided tests procedure *via* 90% confidence intervals obtained from the analysis of the natural logarithms of C_{max}, AUC_t and AUC_∞. Bioequivalence was concluded if the 90% confidence interval for relative bioavailability was within the 0.80 to 1.25 range.

Safety: The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by 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 ± standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the four regimens are listed in the following table.

Pharmacokinetic Parameters (units)		Regimens[#]			
		Reference	Test		
		A	B	C	D
		Fenofibric Acid Immediate-release (N = 24)	Fenofibric Acid Choline Salt Formulation 12 (N = 24)	Fenofibric Acid Choline Salt Formulation 10 (N = 24)	Fenofibric Acid Choline Salt Formulation 13 (N = 24)
T_{max}	(h)	2.6 ± 0.9	4.1 ± 1.6*£	3.9 ± 0.8*£	6.0 ± 2.5*
C_{max}	(µg/mL)	11.24 ± 2.24	8.70 ± 2.38*£	8.01 ± 1.59*£	5.59 ± 1.31*
AUC_t	(µg•h/mL)	166.0 ± 57.3	156.3 ± 47.6£	161.6 ± 50.1£	147.9 ± 45.5*
AUC_∞	(µg•h/mL)	168.9 ± 59.7	159.5 ± 50.2£	165.6 ± 53.9£	152.0 ± 48.2*
$t_{½}$¢	(h)	19.42 ± 4.66	19.58 ± 4.47	19.60 ± 4.24	20.27 ± 4.86
CL/F†	(L/h)	0.89 ± 0.27	0.92 ± 0.26	0.90 ± 0.29	0.99 ± 0.33

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

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

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

¢ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for λ_z.

† Parameter was not tested statistically.

The relative bioavailability results are listed in the following table.

Regimens[#] Test *vs.* Reference	Pharmacokinetic Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate[+]	Relative Bioavailability 90% Confidence Interval
B *vs.* A	C_{max} (µg/mL)	8.379	11.044	0.7586	0.6984 – 0.8241
	AUC_t (µg•h/mL)	149.968	157.717	0.9509	0.9116 – 0.9919
	AUC_∞ (µg•h/mL)	152.656	160.068	0.9537	0.9139 – 0.9952
C *vs.* A	C_{max} (µg/mL)	7.852	11.044	0.7110	0.6545 – 0.7723
	AUC_t (µg•h/mL)	154.430	157.717	0.9792	0.9387 – 1.0214
	AUC_∞ (µg•h/mL)	157.621	160.068	0.9847	0.9437 – 1.0275
D *vs.* A	C_{max} (µg/mL)	5.428	11.044	0.4915	0.4525 – 0.5339
	AUC_t (µg•h/mL)	141.193	157.717	0.8952	0.8582 – 0.9338
	AUC_∞ (µg•h/mL)	144.589	160.068	0.9033	0.8657 – 0.9426
B *vs.* C	C_{max} (µg/mL)	8.379	7.852	1.0671	0.9824 – 1.1591
	AUC_t (µg•h/mL)	149.968	154.430	0.9711	0.9310 – 1.0130
	AUC_∞ (µg•h/mL)	152.656	157.621	0.9685	0.9281 – 1.0106
B *vs.* D	C_{max} (µg/mL)	8.379	5.428	1.5435	1.4210 – 1.6766
	AUC_t (µg•h/mL)	149.968	141.193	1.0622	1.0183 – 1.1079
	AUC_∞ (µg•h/mL)	152.656	144.589	1.0558	1.0118 – 1.1017
C *vs.* D	C_{max} (µg/mL)	7.852	5.428	1.4465	1.3317 – 1.5712
	AUC_t (µg•h/mL)	154.430	141.193	1.0938	1.0486 – 1.1409
	AUC_∞ (µg•h/mL)	157.621	144.589	1.0901	1.0447 – 1.1375

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

* 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 proportion of subjects reporting at least one treatment-emergent adverse event was slightly higher among subjects who received Regimens B (16.7%) and D (12.5%) than those who received Regimens A (8.3%) and C (8.3%). The most common treatment-emergent adverse event was headache. The majority of adverse events were assessed by the investigator as not related to the study drug and mild in severity. 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: This study was designed to explore the potential for an *in vivo/in vitro* correlation. Three modified-release formulations of fenofibric acid choline salt along with an immediate-release formulation were tested. The immediate-release formulation was used as the reference (Regimen A). Formulation 10 (Regimen C) was the target formulation. Formulation 12 (Regimen B, fast-release formulation) and Formulation 13 (Regimen C, slow-release formulation) were selected to cover a relatively broad range of *in vitro* dissolution profiles and to bracket the *in vitro* dissolution profile of Formulation 10.

When evaluated by the 90% confidence interval method, Regimens B, C and D had equivalent AUC_t and AUC_∞ when compared to Regimen A. The C_{max} values for Regimens B, C and D were lower than that for Regimen A.

Regimen B had equivalent AUC_t and AUC_∞ and C_{max} compared to Regimen C. Regimen D showed equivalent AUC_t and AUC_∞ compared to Regimens B and C. However, the C_{max} value for Regimen D was significantly lower than that for Regimen B and Regimen C.

In brief, Regimen B had a similar *in vivo* plasma concentration profile as Regimen C. Regimen D had significantly lower AUC_t, AUC_∞ and C_{max} compared to Regimens B and C. The rank order of the *in vitro* dissolution profiles evaluated with Method 2 (Apparatus 2, pH 1 to 6.8) and Method 3 (Apparatus 2, pH 3.5 to 6.8) was consistent with the *in vivo* performance.

The regimens tested were generally well tolerated by the subjects.

Reviewer's Comments:

- This study was conducted to develop IVIVC correlation using different release formulations (11, 10, 12) and also evaluated BE of test formulations containing choline fenofibrate mini-tablets equivalent to 135 mg fenofibric acid to the 200 mg micronized fenofibrate formulation.
- The test formulations did not show BE to 200 mg micronized fenofibrate with regards to C_{max}, which were consistently lower than the reference formulation.
- For adequacy of the results of IVIVC model development please refer to the CMC review.

M05-801:

Abbott Laboratories	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Study Drug: Fenofibric Acid (ABT-335, A-770335)	**Volume:**	
Name of Active Ingredient: Fenofibric Acid	**Page:**	

Title of Study: Bioavailability of Fenofibric Acid from a Fenofibric Acid Choline Salt Formulation Relative to that from Fenofibrate Capsule

Investigator: Timi I. Edeki, MD, PhD

Study Site: Abbott Clinical Pharmacology
Research Unit
1324 North Sheridan Road
Waukegan, IL 60085

Publications: None.

Studied Period:	Phase of Development: 1
First Subject First Visit: 05 February 2006 Last Subject Last Visit: 22 February 2006	

Objective: The objective of this study was to determine the bioavailability of fenofibric acid from a fenofibric acid choline salt formulation relative to that from micronized fenofibrate capsule. The fenofibric acid choline salt formulation was manufactured at the scale used for the manufacture of Phase 3 clinical study supplies.

Methodology: This Phase 1, single-dose, open-label study was conducted according to a two-period, randomized crossover design. Subjects were randomly assigned in equal numbers to two sequences of Regimen A (one 200 mg micronized fenofibrate capsule, reference), and Regimen B (one capsule containing fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid, test). A washout interval of 10 days separated the doses of the two study periods.

Blood samples for plasma fenofibric acid concentration assay were collected prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 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 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 0.050 mL plasma sample. Samples were analyzed between the dates of 07 March 2006 and 10 March 2006.

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 36.3 years (ranging from 20 to 51 years), the mean weight was 75.2 kg (ranging from 55 to 90 kg) and the mean height was 174.2 cm (ranging from 158 to 189 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 practicing at least one of the acceptable methods of birth control specified in the protocol. Females were not pregnant or breast-feeding.

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

	Regimen	
	A (Reference)	B (Test)
Formulation	Micronized Fenofibrate	Fenofibric Acid Choline Salt
Dosage Form	Fenofibrate Capsules	Capsule
Strength (mg)	200	135†
Bulk Product Lot Number	05-001067 (12-539-AR)	05-002449
Bulk MMID Number*	PTB0500188	D0500081
Finishing Lot Numbers	06-004108	06-003996
Potency (% of Label Claim)	97.8	98.4
Manufacturer	Fournier	Abbott
Manufacturing Date	23 October 2003	November 2005
Expiration/Retest Date	01 October 2006 (expires)	01 November 2006 (retest)

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

* Material master identification number.

Duration of Treatment: Two single doses were administered on 06 February 2006 and 17 February 2006.

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, λ_z, terminal phase elimination half-life ($T_{½}$), 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_∞).

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 a random effect for subject nested within sequence, was performed for T_{max}, λ_z, and the natural logarithms of C_{max}, AUC_t and AUC_∞. Within the framework of the ANOVA, the test regimen was compared to the reference with a test at significance level of 0.05.

The bioavailability of the test regimen relative to that of the reference regimen was assessed by the two one-sided tests procedure via 90% confidence intervals. Bioequivalence with respect to AUC between the test regimen and the reference regimen was concluded if the 90% confidence intervals from the analysis of the natural logarithm of AUC was within the 0.80 to 1.25 range. For C_{max}, a one-sided test at significance level 0.05 was performed. The hypothesis that the ratio of the test regimen C_{max} central value to the reference regimen C_{max} value is ≥ 1.25 was tested against the alternative hypothesis that the ratio is < 1.25. For the sake of uniformity, this test was also performed using a 90% confidence interval. The null hypothesis was rejected in favor of the alternative hypothesis if the upper endpoint of the 90% confidence interval for the ratio was < 1.25.

Safety: The number and percentage of subjects reporting adverse events were tabulated by 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 ± standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the two regimens are listed in the following table.

Pharmacokinetic Parameters (units)		Regimen£ A: Reference, Low-Fat Meal (N = 24)	Regimen£ B: Test, Fasting (N = 24)
T_{max}	(h)	4.7 ± 1.3	4.2 ± 0.8
C_{max}	(µg/mL)	9.75 ± 2.05	8.20 ± 1.78*
AUC_t	(µg•h/mL)	182.3 ± 69.1	159.1 ± 53.6*
AUC_∞	(µg•h/mL)	187.7 ± 74.1	162.8 ± 57.6*
$t_{½}$¢	(h)	19.49 ± 7.88	18.80 ± 6.61

£ Regimen A was administered as a 200 mg fenofibrate capsule. Regimen B was administered as a single capsule containing fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid.

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

¢ Harmonic mean ± pseudo standard deviation; evaluations of $t_{½}$ were based on statistical tests for λ_z.

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

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
B *vs.* A	C_{max}	7.976	9.569	0.834	0.762 – 0.912
	AUC_t	150.273	170.572	0.881	0.846 – 0.918
	AUC_∞	153.218	174.699	0.877	0.841 – 0.914

* Antilogarithm of the least squares means for logarithms.

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

Safety Results: All treatment-emergent adverse events were reported in Regimen A (2/24, 8.3 % in Regimen A and 0/24, 0% in Regimen B). All of the treatment-emergent adverse events were assessed by the investigator as not related to the study drug and mild in severity. No serious adverse events were reported in this study. No subjects were discontinued from the study. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.
Conclusions: The test Regimen B (one capsule containing fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions) was bioequivalent to the reference Regimen A (one 200 mg micronized fenofibrate capsule administered with a low-fat meal) with regard to fenofibric acid AUC because the 90% confidence intervals for log-transformed AUC_t and AUC_∞ were contained within the 0.80 to 1.25 range. The central value of fenofibric acid C_{max} was 17% lower for the test regimen than the reference. The upper limit of the 90% confidence interval for the ratio of the C_{max} central value of Regimen B to that of Regimen A was less than 1.25, indicating that the C_{max} of the test fenofibric acid choline salt formulation was not significantly greater than that of the reference fenofibrate capsule. 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. All treatment-emergent adverse events were reported in the reference Regimen A (2/24, 8.3% in Regimen A and 0/24, 0% in the test Regimen B). All of the treatment-emergent adverse events were assessed by the investigator as not related to the study drug and mild in severity. No serious adverse events were reported in this study. No subjects were discontinued from the study.

Reviewer's Comments:

- This study was conducted to evaluate BE of formulation containing choline fenofibrate mini-tablets equivalent to 135 mg fenofibric acid to the 200 mg micronized fenofibrate formulation. The fenofibric acid choline salt formulation was manufactured at the scale used for the manufacture of Phase 3 clinical study supplies.
- The study results, as observed in all other BE studies, revealed that choline fenofibrate formulation does not show BE to 200 mg micronized fenofibrate with regards to C_{max}, which were consistently lower than the reference formulation.

4.2.4 Bioequivalence Study M06-830 (Full production Scale)

Title of Study: Evaluation of the Relative Bioavailability of Fenofibric Acid from Fenofibric Acid Choline Salt Formulations Manufactured at Two Different Sites and Batch Sizes, and 200 mg Micronized Fenofibrate Capsule.

Study Site: Abbott Clinical Pharmacology Research Unit at Vista Medical Center East, 1324 North Sheridan Road, Waukegan, IL 60085

First Subject First Visit: 22 August 2006

Last Subject Last Visit: 16 October 2006

Objective: The objective of this study was to evaluate the bioavailability of fenofibric acid from the ABT-335 (fenofibric acid choline salt) formulation manufactured at full production scale at the Abbott Puerto Rico facility relative to the bioavailability of fenofibric acid from:

- The ABT-335 Phase 3 formulation manufactured at the Abbott Park facility, and
- 200 mg micronized fenofibrate capsule.

Methodology: This Phase 1, single-dose, open-label study was conducted according to a three-period, randomized crossover design. The study was carried out in two cohorts of subjects, 30 in one cohort and 35 in the other cohort. Subjects in a cohort went through the study procedures at the same time. The subjects in each cohort were randomly assigned in equal numbers to six sequences of Regimens A, B and C.

> Regimen A: One capsule containing ABT-335 (fenofibric acid choline salt) mini-tablets equivalent to 135 mg fenofibric acid manufactured in Puerto Rico, administered under fasting conditions (test).
>
> Regimen B: One capsule containing ABT-335 (fenofibric acid choline salt) mini-tablets equivalent to 135 mg fenofibric acid manufactured at Abbott Park, administered under fasting conditions (reference).
>
> Regimen C: One 200 mg micronized fenofibrate capsule administered following a low-fat breakfast (reference).

A washout interval of 14 days separated the doses of any two consecutive periods. 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 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing on Study Day 1 of each 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, Abbott Park, IL. The lower limit of quantitation for fenofibric acid was established at 0.016 µg/mL using a 50 µL plasma sample. Samples were analyzed between the dates of 18 October 2006 and 16 November 2006. The in-study calibration contained ten standards ranging from 0.016 to 5.465 µg/mL. All calibration curves had

coefficient of determination (r2) values greater than or equal to 0.9959. Samples quantified above the highest standard were diluted with blank plasma and re-assayed. Samples quantified below the lowest standard were reported as zero. In-study quality control (QC) samples, supplemented with concentrations of 0.047, 0.234, 1.169 and 4.869 µg/mL fenofibric acid, were analyzed with the unknowns. The coefficient of variation (CV) values for the data ranged from 3.1 to 5.6%; the mean bias values were between –0.7 and 1.0%. Dilution QC samples were also evaluated at two times (2x) and ten times (10x).

Number of Subjects (Planned and Analyzed): 66 subjects were planned. 65 subjects entered the study and 63 completed. 63 completers were evaluated for safety and all 65 were evaluated for pharmacokinetics.

For the 65 subjects who participated in the study, the mean age was 38.1 years (ranging from 19 to 55 years), the mean weight was 74.7 kg (ranging from 52 to 106 kg) and the mean height was 171.2 cm (ranging from 148 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 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:

	Regimens		
	A (Test)	B (Reference)	C (Reference)
Formulation	ABT-335	ABT-335	Micronized Fenofibrate
Dosage Form	Capsule	Capsule	Capsule
Strength (mg)	135*	135*	200
Manufacturing Site	Abbott Barceloneta, PR (Abbott Puerto Rico Limited Plant)	Abbott Abbott Park, IL (GPO AP 16 Site)	Fournier Laboratories Dijon, France
Bulk Product Lot Number	06-007702	06-005109	06-007493

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

GPO = Global Pharmaceutical Operations.

AP = Abbott Park.

Criteria for Evaluation

Pharmacokinetic: The pharmacokinetic parameter values of fenofibric acid were estimated using non-compartmental methods. These included: the maximum plasma concentration (Cmax) and time to Cmax (Tmax), the terminal phase elimination rate constant (λz), terminal phase elimination half-life (t½), the area under the plasma

concentration-time curve (AUC) from time 0 to time of the last measurable concentration (AUCt), the AUC from time 0 to infinite time (AUC∞), 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) was performed for Tmax, λz, and the natural logarithms of Cmax, AUCt and AUC∞. The model included effects for cohort, sequence, subjects nested within combination of cohort and sequence, period, regimen and the interaction of cohort and period. The effect for subject was random and all other effects were fixed. Within the ANOVA modeling framework, the test regimen was compared to each of the two references by a test with a significance level of 0.05.

The bioavailability of the test regimen (Regimen A) relative to that of the reference Regimen B was assessed by a two one-sided tests procedure via 90% confidence intervals obtained from the analyses of the natural logarithms of Cmax, AUCt, and AUC∞. 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. Bioequivalence between Regimen A and Regimen B was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC and Cmax were within the 0.80 to 1.25 range, which is the standard regulatory criterion for bioequivalence.

In the same way, the bioavailability of test Regimen A relative to that of reference Regimen C was assessed by a two one-sided tests procedure via 90% confidence intervals obtained from the analyses of the natural logarithms of AUCt, and AUC∞. Bioequivalence between Regimen A and Regimen C with respect to AUC was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUCt, and AUC∞ were within the 0.80 to 1.25 range. For Cmax, a one-sided test was performed at significance level 0.05. The hypothesis that the ratio of the Cmax least square mean value of Regimen A to that of Regimen C is ≥ 1.25 was tested against the alternative hypothesis that the ratio is < 1.25. For the sake of uniformity, the test was also conducted via a 90% confidence interval with the null hypothesis rejected if the upper endpoint of the 90% confidence interval was < 1.25. The bioavailability of Regimen B relative to that of Regimen C was assessed in the same way as test Regimen A was evaluated relative to reference Regimen C.

Safety: The number and percentage of subjects reporting treatment-emergent adverse events was tabulated by 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 ± standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the three regimens are listed in the following table.

Pharmacokinetic Parameters (units)		Regimen£ A (Test) ABT-335 (N = 63)	Regimen£ B (Reference) ABT-335 (N = 65)	Regimen£ C (Reference) Fenofibrate (N = 65)
T_{max}	(h)	4.2 ± 1.3	4.4 ± 1.9	4.6 ± 1.4
C_{max}	(µg/mL)	8.234 ± 2.224*	7.979 ± 2.075*	9.281 ± 2.667
AUC_t	(µg•h/mL)	152.8 ± 48.1*	149.8 ± 41.7*	168.9 ± 55.5
AUC_∞	(µg•h/mL)	157.2 ± 52.9*	153.5 ± 44.8*	175.0 ± 59.5
$t_{½}$#	(h)	19.20 ± 7.49*	19.79 ± 6.10*	21.82 ± 7.43
CL/F†	(L/h)	0.96 ± 0.35	0.96 ± 0.33	NA

£ Regimens A and B were administered as one capsule of ABT-335 equivalent to 135 mg fenofibric acid. Regimen A was manufactured in Puerto Rico; Regimen B was manufactured at Abbott Park. Regimen C was administered as one 200 mg fenofibrate capsule.

* Statistically significantly different from reference Regimen C (ANOVA, $p < 0.05$).

\# Harmonic mean ± pseudo standard deviation; evaluations of $t_{½}$ were based on statistical tests for λ_z.

† Parameter was not tested statistically.

NA = Not applicable.

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

Regimens£ Test vs. Reference	Pharmacokinetic Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
A vs. B	C_{max}	7.966	7.725	1.031	0.977 – 1.088
	AUC_t	145.270	143.772	1.010	0.986 – 1.035
	AUC_∞	148.795	146.854	1.013	0.989 – 1.039
A vs. C	C_{max}	7.966	8.914	0.894	0.847 – 0.943
	AUC_t	145.270	160.087	0.907	0.886 – 0.930
	AUC_∞	148.795	165.298	0.900	0.878 – 0.923
B vs. C	C_{max}	7.725	8.914	0.867	0.822 – 0.914
	AUC_t	143.772	160.087	0.898	0.877 – 0.920
	AUC_∞	146.854	165.298	0.888	0.867 – 0.910

£ Regimens A and B were administered as one capsule of ABT-335 equivalent to 135 mg fenofibric acid. Regimen A was manufactured in Puerto Rico; Regimen B was manufactured at Abbott Park. Regimen C was administered as one 200 mg fenofibrate capsule.

* Antilogarithm of the least squares means for logarithms.

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

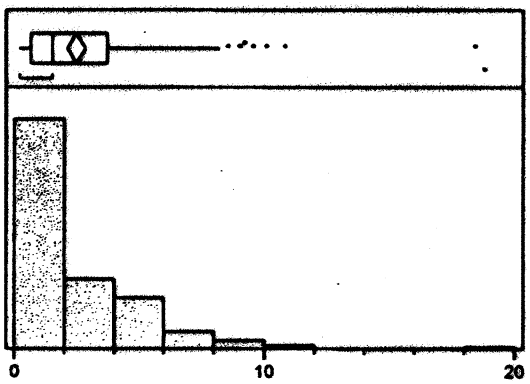
Safety Results: Overall, the most common treatment-emergent adverse events (reported by two or more subjects for any one regimen) were back pain, diarrhea, headache, dizziness, nasal congestion, and viral upper respiratory tract infection. There were no clinically significant changes observed in clinical laboratory or vital signs values, in the ECGs or in the physical examination findings during the study.

Sponsor's Conclusions:

- The ABT-335 formulation manufactured at full production scale at the Abbott Puerto Rico facility (Regimen A) was bioequivalent to the Phase 3 formulation manufactured at Abbott Park (Regimen B) with regard to both the Cmax and AUC of fenofibric acid.
- The ABT-335 formulation manufactured at Abbott Puerto Rico facility (Regimen A) was bioequivalent to the 200 mg micronized fenofibrate capsules (Regimen C) with regard to both the Cmax and AUC of fenofibric acid.
- The Phase 3 ABT-335 formulation manufactured at Abbott Park (Regimen B) was bioequivalent to the 200 mg micronized fenofibrate capsule (Regimen C) with regard to both the Cmax and AUC of fenofibric acid.
- All three regimens were generally well tolerated by the subjects.

Reviewer's Comments:

Overall, the study assessments and conduct seemed appropriate and the concentration data was well supported by the bioanalytical method. The half-life and thus the AUC_{0-inf} estimation was also appropriate with reasonable extrapolation for all the time profile except in one case with 20% extrapolation (see Figure below). There were no major protocol violations affecting the study outcome. The sponsor's interpretation of the results was also reasonable.



Distribution of % Extrapolation in AUC_{0-inf} values

The sponsor's BE results were confirmed by reviewer's analysis (see Table below) and the conclusions drawn from the study are acceptable. It is interesting to note that this was the first study that showed successful BE for all the ABT-335 formulations, possibly due to large sample size used in the study. However, even though the BE criteria was satisfied, the pattern of lower C_{max} remained consistent for the ABT-335 formulation when compared against the reference 200 mg micronized fenofibrate.

AUC_{0-inf}				
Test	Reference	Difference Between Means	90% Confidence Limits	
A	B	101.14	98.72	103.61
A	C	90.81	88.64	93.03
B	C	89.79	87.67	91.96
C_{max}				
Test	Reference	Difference Between Means	90% Confidence Limits	
A	B	103.22	97.82	108.93
A	C	89.38	84.70	94.32
B	C	86.59	82.08	91.35

Abbott Puerto Rico facility (Regimen A)
Phase 3 formulation manufactured at Abbott Park (Regimen B)
200 mg micronized fenofibrate capsule (Regimen C)

This pivotal bioequivalence study was audited by the Division of Scientific Investigation (DSI), and based on their review the data was recommended to be accepted for review. Please see the memo by Dr. Jacqueline O'Shaughnessy dated 09/12/2008 for details. Based on the findings of DSI review and the review of BE analysis mentioned above, from the clinical pharmacology perspective, the results of the pivotal BE study were acceptable.

4.2.5 Bioequivalence Study M06-886

Title of Study: Evaluation of the Bioavailability of Fenofibric Acid From ABT-335 Formulation Manufactured at Fournier Site Relative to ABT-335 Formulation Manufactured at Abbott Laboratories.

Studied Period:
First Subject First Visit: 12 February 2007
Last Subject Last Visit: 29 March 2007

Objective: The objective of this study was to evaluate the bioavailability of fenofibric acid from a formulation of ABT-335 manufactured at a Fournier Pharma facility in Ireland ("Fournier") relative to the same formulation of ABT-335 manufactured at the Abbott Puerto Rico Limited plant ("Abbott Puerto Rico").

Methodology: This Phase 1, single-dose, open-label study was conducted according to a two-period, randomized crossover design. Subjects were randomly assigned in equal numbers to receive one of two sequences of Regimens A and B.

- Regimen A: One capsule containing ABT-335 mini-tablets equivalent to 135 mg fenofibric acid manufactured at a Fournier Pharma facility in Ireland, administered under fasting conditions (test).

- Regimen B: One capsule containing ABT-335 mini-tablets equivalent to 135 mg fenofibric acid manufactured at the Abbott Puerto Rico Limited plant, administered under fasting conditions (reference).

A washout interval of 14 days separated the doses of the two study periods.

Blood samples for fenofibric acid plasma assay were collected into 2 mL collection tubes containing potassium oxalate plus sodium fluoride prior to dosing (0-hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing on Study Day 1 of each study period. Sufficient blood was collected to provide approximately 1 mL plasma from each sample. Plasma concentrations of fenofibric acid were determined using validated liquid chromatography method with tandem mass spectrometric detection at Abbott, Abbott Park, IL. The lower limit of quantitation for fenofibric acid was established at 0.017 µg/mL using a 50 µL plasma sample. Pestanal (2-(2, 4, 5- trichlorophenoxy)-propionic acid) was used as an internal standard. The analysis of the samples began on 29 March 2007 and was completed on 09 April 2007. Samples were analyzed by subject. The in-study calibration contained eight standards ranging from 0.017 to 5.340 µg/mL. All calibration curves had coefficient of determination (r2) values greater than 0.9966. Samples quantified above the highest standard were diluted with blank plasma and reassayed. Samples quantified below the lowest standard were reported as zero. In-study quality control (QC) samples, supplemented with concentrations of 0.050, 0.499, and 4.995 µg/mL fenofibric acid, were analyzed with the unknowns. The coefficient of variation (CV) values for the data ranged from 4.2 to 6.0%; the mean bias values were between –0.9 and 3.9%. Dilution QC samples were also evaluated at two times (2x) and ten times (10x).

Number of Subjects (Planned and Analyzed):

Planned: 42; Entered: 42; Completed: 40; Evaluated for Safety: 42; Evaluated for Pharmacokinetics: 41

For the 42 subjects who participated in the study, the mean age was 35.6 years (ranging from 21 to 54 years), the mean weight was 73.1 kg (ranging from 56 to 95 kg) and the mean height was 171.3 cm (ranging from 153 to 190 cm). For the 41 subjects included in the pharmacokinetic analyses, the mean age was 35.8 years (ranging from 21 to 54 years), the mean weight was 72.9 kg (ranging from 56 to 95 kg) and the mean height was 170.9 cm (ranging from 153 to 190 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:

	Regimens	
	A (Test)	B (Reference)
Formulation	ABT-335	ABT-335
Dosage Form	Capsule	Capsule
Strength (mg)	135*	135*
Manufacturing Site	Fournier Laboratories County Cork, Ireland	Abbott Barceloneta, PR (Abbott Puerto Rico Limited Plant)
Bulk Product Lot Number	07-010924	06-007702

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

Criteria for Evaluation

Pharmacokinetic: The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum observed plasma concentration (Cmax) and time to Cmax (Tmax), the terminal phase elimination rate constant (λz), terminal phase elimination halflife ($t_{1/2}$), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration (AUCt), the AUC from time 0 to infinite time (AUC_∞) 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.

Statistical Methods

Pharmacokinetic: An ANOVA was performed for Tmax, λz and the natural logarithms of Cmax, AUCt and AUC_∞. 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. Within the ANOVA modeling framework, the test regimen was compared to the reference by a test with a significance level of 0.05.

The bioavailability of the test Regimen A relative to that of the reference Regimen B was assessed by a two one-sided tests procedure via 90% confidence intervals obtained from the analyses of the natural logarithms of Cmax, AUCt and AUC_∞. Bioequivalence between the test regimen and the reference regimen was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC and Cmax were within the 0.80 to 1.25 range, which are the standard regulatory criteria for bioequivalence.

Safety: The number and percentage of subjects reporting treatment-emergent adverse events were tabulated. Laboratory test values and vital signs measurements that are Very High or Very Low according to predefined criteria were identified.

Summary/Conclusions

Pharmacokinetic Results: Mean ± standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the two regimens are listed in the following table.

Pharmacokinetic Parameters (units)		Regimen£ A (Test) Fournier Pharma, Ireland (N = 41)	Regimen£ B (Reference) Abbott, Puerto Rico (N = 41)
T_{max}	(h)	4.1 ± 1.4	4.2 ± 1.6
C_{max}	(µg/mL)	8.897 ± 2.205	9.129 ± 1.646
AUC_t	(µg•h/mL)	174.0 ± 68.4	176.2 ± 58.4
AUC_∞	(µg•h/mL)	178.8 ± 72.5	179.9 ± 61.9
$t_{½}$#	(h)	20.62 ± 5.59*	19.38 ± 5.38
CL/F†	(L/h)	0.85 ± 0.27	0.82 ± 0.22

£ Both regimens were administered as one capsule of ABT-335 equivalent to 135 mg fenofibric acid under fasting conditions. Regimen A was manufactured at Fournier Pharma, Ireland; Regimen B was manufactured at Abbott, Puerto Rico.

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

Harmonic mean ± pseudo standard deviation; evaluations of $t_{½}$ were based on statistical tests for λ_z.

† Parameter was not tested statistically.

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

Regimens£ Test *vs.* Reference	Pharmacokinetic Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
A vs. B	C_{max}	8.622	8.978	0.960	0.911 – 1.013
	AUC_t	163.732	168.699	0.971	0.938 – 1.005
	AUC_∞	167.612	171.757	0.976	0.943 – 1.010

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

* Antilogarithm of the least squares means for logarithms.

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

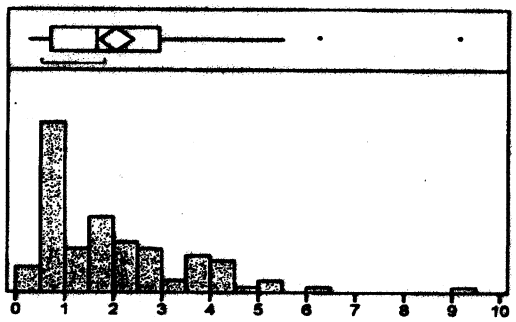
Safety Results: Overall, the most common treatment-emergent adverse events (reported by two or more subjects for any one regimen) were headache and fatigue. One subject was discontinued from the study due to an adverse event (elevated aspartate aminotransferase (AST) level) on Study Day -1 of Period 2, which was assessed by the investigator as mild in severity and probably not related to study drug, but due to exercise. With the exception of the elevated AST level observed in one subject, there were no other clinically significant changes observed in clinical laboratory and vital signs values, in the ECGs or in the physical examination findings during the study.

Sponsor's Conclusions: The ABT-335 capsules manufactured at Fournier Pharma Ireland and at Abbott Puerto Rico are bioequivalent as the 90% confidence intervals for comparing the fenofibric acid Cmax, AUCt and AUC∞ values between the capsules from the two manufacturing sites were contained within the 0.80 to 1.25 range.

Both regimens were generally well tolerated by the subjects. With the exception of the elevated AST level observed in one subject, which was assessed by the investigator as mild in severity and probably not related to study drug, there were no clinically significant safety observations.

Reviewer's Comments:

Overall, the study assessments and conduct were appropriate and the concentration data was well supported by the bioanalytical method. The half-life and thus the $AUC_{0\text{-}inf}$ estimation was also appropriate with reasonable extrapolation (see Figure below). There were no major protocol violations affecting the study outcome. The sponsor's interpretation of the results was also reasonable.



Distribution of % Extrapolation in $AUC_{0\text{-}inf}$ values

The sponsor's BE results were confirmed by reviewer's analysis (see Table below) and the conclusions drawn from the study are acceptable. Formulation containing ABT-335 mini-tablets equivalent to 135 mg fenofibric acid manufactured at a Fournier Pharma facility in Ireland, administered under fasting conditions were bioequivalent to the formulation containing ABT-335 mini-tablets equivalent to 135 mg fenofibric acid manufactured at the Abbott Puerto Rico Limited plant, administered under same fasting conditions.

$AUC_{0\text{-}inf}$				
Test	Reference	Difference Between Means	90% Confidence Limits	
A	B	97.6	94.3	101.0
$AUC_{0\text{-}t}$				
Test	Reference	Difference Between Means	90% Confidence Limits	
A	B	97.1	93.8	100.5
C_{max}				
Test	Reference	Difference Between Means	90% Confidence Limits	
A	B	96.0	91.1	101.3

ABT-335 formulation manufactured at a Fournier Pharma facility in Ireland (Regimen A)
Formulation manufactured at Abbott Puerto Rico facility (Regimen B)

4.2.6 DDI Study With Omeprazole (M06-804)

Title of Study: Effect of Omeprazole on the Absorption of Fenofibric Acid from a Modified-release Formulation of Fenofibric Acid Choline Salt in Healthy Subjects

First Subject First Visit: 22 March 2006 **Last Subject Last Visit:** 20 May 2006

Objective: The objective of this study was to evaluate the effects of omeprazole on the absorption of fenofibric acid from a capsule formulation containing the choline salt of fenofibric acid administered under both fasting and non-fasting (high-fat) meal conditions.

Methodology: This Phase 1, 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.

- Regimen A: One capsule containing fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions on Study Day 5.

- Regimen B: Omeprazole magnesium, equivalent to 40 mg of omeprazole (two 20 mg tablets of Prilosec OTC®) administered once daily under fasting conditions on Study Days 1 through 5 plus one capsule containing fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions on Study Day 5.

- Regimen C Omeprazole magnesium, equivalent to 40 mg of omeprazole (two 20 mg tablets of Prilosec OTC®) administered once daily under fasting conditions on Study Days 1 through 5 plus one capsule containing fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered with a high-fat meal on Study Day 5.

A washout interval of at least 14 days separated the last dose of a period and the first dose of any subsequent period.

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 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing. 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 Abbot Laboratories, Abbott Park, IL. The lower limit of quantitation for fenofibric acid was established at 0.017 µg/mL usingba 50 µL plasma sample. Samples were analyzed between the dates of 24 May 2006 and 08 June 2006. The in-study calibration contained ten standards ranging from approximately 0.017 to 5.472 µg/mL. All calibration curves had coefficient of determination (r2) values greater than or equal to 0.9977. Samples quantified above the highest standard were diluted with blank plasma and re-assayed. Samples quantified below the lowest standard were reported as zero. In-study quality control (QC) samples, supplemented with concentrations of 0.041, 0.203, 1.014 and 4.224 µg/mL of fenofibric acid, were analyzed with the unknowns. The coefficient of variation (CV) values for the data ranged from 3.2 to 4.9%; the mean bias values were between 0.2 and 1.1%. Dilution QC samples were also evaluated. For dilution QC samples diluted 10 times (10x) and 2 times (2x), the CV% were 1.7 and 4.1%, respectively; the mean biases were 5.8 and –0.7%, respectively.

Number of Subjects (Planned and Analyzed):

Planned: 36; Entered: 36; Completed: 33; Evaluated for Safety: 36; Evaluated for Pharmacokinetics: 34

For the 36 subjects who participated in the study, the mean age was 36.4 years (ranging from 20 to 55 years), the mean weight was 73.5 kg (ranging from 52 to 100 kg) and the mean height was 173.4 cm (ranging from 155 to 193 cm). For the 34 subjects included in the pharmacokinetic analyses, the mean age was 36.6 years (ranging from 20 to 55 years), the mean weight was 74.1 kg (ranging from 52 to 100 kg) and the mean height was 174.0 cm (ranging from 155 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:

	Regimen
	A, B, C
Dosage Form	Capsule
Formulation	Fenofibric Acid Choline Salt
Strength (mg)	135†
Bulk Product Lot Number	05-002449

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

Omeprazole magnesium equivalent to 40 mg omeprazole (two 20 mg tablets of Prilosec OTC®) was administered in Regimens B and C. The tablets were manufactured by AstraZeneca (Sweden) as Lot #5192171971, NDC #37000-455-04; expiration date 29 February 2008.

Criteria for Evaluation:

Pharmacokinetic: The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum plasma concentration (Cmax) and time to Cmax (Tmax), the terminal phase elimination rate constant (λz), 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 (AUCt), the AUC from time 0 to infinity (AUC_∞) 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.

Statistical Methods:

Pharmacokinetic: An analysis of variance (ANOVA) was performed for Tmax, λz, and the natural logarithms of Cmax, AUCt and AUC∞ of fenofibric acid. The model included effects for sequence, subject nested within sequence, period and regimen. Within the ANOVA modeling framework, each of the regimens with omeprazole (B and C) were compared to the regimen consisting of fenofibric acid alone (A) by a test with a significance level of 0.05. Regimen B was also compared with Regimen C with a significance level of 0.05.

The bioavailability of each test regimen (Regimens B and C) relative to that of the reference regimen (Regimen A), and the bioavailability of Regimen C 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 AUCt and AUC∞. 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 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 ± standard deviation (SD) pharmacokinetic parameters of fenofibric acid after administration of the three regimens are listed in the following table.

Pharmacokinetic Parameters (units)		Regimens[£] A: Fenofibric Acid Choline Salt (Fasting) (N = 33)	B: Omeprazole + Fenofibric Acid Choline Salt (Fasting) (N = 34)	C: Omeprazole + Fenofibric Acid Choline Salt (High-Fat Meal) (N = 34)
T_{max}	(h)	4.6 ± 1.7	3.8 ± 1.0*	6.3 ± 2.1*#
C_{max}	(µg/mL)	8.41 ± 1.79	9.93 ± 2.81*	8.17 ± 1.49#
AUC_t	(µg•h/mL)	163.5 ± 49.0	170.8 ± 45.4*	168.4 ± 46.3
AUC_∞	(µg•h/mL)	167.4 ± 52.4	174.9 ± 49.2*	172.6 ± 49.5
$t_{½}$[¢]	(h)	20.45 ± 4.64	21.05 ± 5.00	21.25 ± 5.21
CL/F[†]	(L/h)	0.88 ± 0.27	0.83 ± 0.22	0.85 ± 0.24

£ Regimen A: one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions on Study Day 5.
Regimen B: 40 mg of omeprazole administered as two 20 mg tablets of Prilosec OTC™ under fasting conditions on Study Days 1 through 5 plus one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions on Study Day 5.
Regimen C: 40 mg of omeprazole administered as two 20 mg tablets of Prilosec OTC™ under fasting conditions on Study Days 1 through 5 plus one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered with a high-fat meal on Study Day 5.

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

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

¢ Harmonic mean ± pseudo standard deviation; evaluations of $t_{½}$ were based on statistical tests for λ_z.

† Parameter was not tested statistically.

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

Regimens[£] Test *vs.* Reference	Pharmacokinetic Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate[+]	Relative Bioavailability 90% Confidence Interval
B *vs.* A	C_{max} (µg/mL)	9.597	8.207	1.169	1.096 - 1.247
	AUC_t (µg•h/mL)	165.476	156.357	1.058	1.022 - 1.096
	AUC_∞ (µg•h/mL)	168.894	159.560	1.058	1.022 - 1.096
C *vs.* A	C_{max} (µg/mL)	8.059	8.207	0.982	0.921 - 1.047
	AUC_t (µg•h/mL)	162.736	156.357	1.041	1.005 - 1.078
	AUC_∞ (µg•h/mL)	166.296	159.560	1.042	1.006 - 1.079
C *vs.* B	C_{max} (µg/mL)	8.059	9.597	0.840	0.788 - 0.895
	AUC_t (µg•h/mL)	162.736	165.476	0.983	0.950 - 1.018
	AUC_∞ (µg•h/mL)	166.296	168.894	0.985	0.951 - 1.019

£ Regimen A: one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions on Study Day 5.
Regimen B: 40 mg of omeprazole administered as two 20 mg tablets of Prilosec OTC™ under fasting conditions on Study Days 1 through 5 plus one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions on Study Day 5.
Regimen C: 40 mg of omeprazole administered as two 20 mg tablets of Prilosec OTC™ under fasting conditions on Study Days 1 through 5 plus one capsule of fenofibric acid choline salt mini-tablets equivalent to 135 mg fenofibric acid administered with a high-fat meal on Study Day 5.

* Antilogarithm of the least squares means for logarithms.

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

Safety Results: Overall, the most common treatment-emergent adverse events (reported by two or more subjects who received fenofibric acid and omeprazole) were diarrhea, headache and nausea.

Two subjects were discontinues from the study due to adverse events: Subject 107 was discontinued from the study due to elevated alanine aminotransferase (ALT); and Subject 110 was discontinued from the study due to a serious adverse event of hemorrhoids requiring hospitalization.

With the exception of the elevated ALT, there were no other clinically significant changes observed in the clinical laboratory values and in addition no clinically significant changes were observed in vital signs, ECGs and physical examinations during the study.

Sponsor' Conclusions:

Administered with or without a meal, the co-administration of the new modified-release fenofibric acid formulation with omeprazole had no significant effect on fenofibric acid pharmacokinetics. The 90% confidence intervals for the Cmax and AUC values assessing the drug interaction under fasting and non-fasting conditions were contained within the 80 - 125% goal posts.

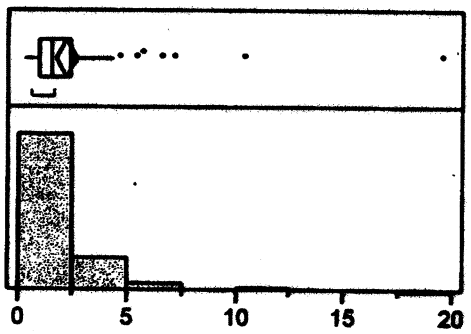
In the presence of omeprazole, a high-fat meal slightly decreased fenofibric acid Cmax by 16%, but had no significant effect on its AUC (Regimen C versus B). These food effect results are very

similar to those previously seen when the modified-release formulation was given under fasting and high-fat meal conditions in the absence of omeprazole.

All three regimens were generally well tolerated by the subjects. Overall, the most common treatment-emergent adverse events (reported by two or more subjects who received fenofibric acid and omeprazole) were diarrhea, headache and nausea.

Reviewer's Comments:

Overall, the study conduct was appropriate and the concentration data was well supported by the analytical method. The half-life and thus the AUC_{0-inf} estimation was also appropriate with reasonable extrapolation for all the time profile except in one case with 20% extrapolation (see Figure below). There were no major protocol violations affecting the study outcome. The sponsor's interpretation of data was also reasonable and acceptable.



Distribution of % Extrapolation in AUC_{0-inf} values

4.2.7 DDI Study with Rosuvastatin (M06-811)

Title of Study: Multiple-Dose Pharmacokinetic Interaction Between Fenofibric Acid and Rosuvastatin

Study Site: Abbott Clinical Pharmacology Research Unit, Victory Memorial Hospital, 1324 North Sheridan Road, Waukegan, IL 60085

Studied Period:

First Subject First Visit: 20 May 2006, **Last Subject Last Visit:** 20 July 2006

Objectives: The primary objective of this study was to evaluate the potential pharmacokinetic interaction between fenofibric acid and rosuvastatin after multiple-dose coadministration of ABT-335, a fenofibric acid choline salt formulation (choline fenofibrate) and rosuvastatin calcium. The secondary objective was to assess time linearity in fenofibric acid pharmacokinetics following the administration of the ABT-335 formulation alone. Safety and tolerability were also assessed.

Methodology: This Phase 1, multiple-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 Regimen A (one Crestor® 40 mg tablet containing rosuvastatin calcium equivalent to 40 mg rosuvastatin), Regimen B (one Crestor® 40 mg tablet containing rosuvastatin calcium equivalent to 40 mg rosuvastatin, plus one capsule containing ABT-335 [fenofibric acid choline salt] mini-tablets equivalent to 135 mg of fenofibric acid) and Regimen C (one capsule containing ABT-335 [fenofibric acid choline salt] mini-tablets equivalent to 135 mg of fenofibric acid) under non-fasting conditions. A washout interval of 14 days separated the last dose of a treatment period from the first dose of any subsequent treatment period.

Blood samples for rosuvastatin plasma concentration assay were collected within 5 minutes prior to dosing (0 hour) on Study Days 1, 5, 7, 8, 9 and 10 of Regimens A and B, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 72, 96 and 120 hours after the dosing on Study Day 10 of Regimens A and B. The blood samples were collected in 6 mL evacuated edetic acid (EDTA)-containing collection tubes. Sufficient blood was collected to provide approximately 3 mL plasma from each sample.

Blood samples for fenofibric acid plasma concentration assay were collected within 5 minutes prior to dosing (0 hour) on Study Days 1, 5, 7, 8, 9 and 10 of Regimens B and C; at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18 and 24 hours after dosing on Study Day 1 of Regimen C only; and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72, 96 and 120 hours after the dosing on Study Day 10 of Regimens B and C. The blood samples were collected in 2 mL evacuated potassium oxalate plus sodium fluoride-containing collection tubes. Sufficient blood was collected to provide approximately 1 mL plasma from each sample.

Plasma concentrations of rosuvastatin were determined using a validated liquid chromatography method with tandem mass spectrometric detection at [redacted] The lower limit of quantitation for fenofibric acid was established at 0.100 ng/mL using a 200 µL plasma sample. Samples were analyzed between the dates of 22 August 2006 and 07 September 2006. b(4)

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 0.019 µg/mL using a 50 µL plasma sample.

Samples were analyzed between the dates of 26 July 2006 and 02 August 2006. Plasma concentrations of fenofibric acid were determined using a validated liquid chromatography method with tandem mass spectrometric detection. Pestanal® was used as an internal standard. The analysis of the samples began on 26 July 2006 and was completed on 02 August 2006. Samples were analyzed by subject. The LLOQ for fenofibric acid was established at 0.019 µg/mL using a 50 µL plasma sample.

The in-study calibration contained ten standards ranging from approximately 0.019 to 5.3 µg/mL. All calibration curves had r2 values greater than or equal to 0.9948. Samples quantified above the highest standard were diluted and assayed with a set of QC samples with the same dilution factor. Samples quantified below the lowest standard were reported as zero. In-study QC samples, supplemented with concentrations of 0.05, 0.3, 1.3 and 4.2 µg/mL of fenofibric acid, were analyzed with the unknowns. The CV values ranged from 2.7 to 5.8%; the mean bias values ranged from –1.2 to 4.9%.

The lower limit of quantitation (LLOQ) for rosuvastatin was established at 0.100 ng/mL using a 200 µL plasma sample. The in-study calibration contained eight standards ranging from approximately 0.100 to 100 ng/mL. All calibration curves had correlation coefficient (R) values greater than or equal to 0.9991. Samples quantified above the highest standard were diluted and assayed with a set of quality control (QC) samples with the same dilution factor. Samples quantified below the lowest standard were reported as < 0.1. In-study QC samples, supplemented with concentrations of 0.300, 0.750, 3.00, 12.5 and 75.0 ng/mL of rosuvastatin, were analyzed with the unknowns. The coefficient of variation (CV) values ranged from 2.86 to 7.68%; the mean bias values ranged from –7.11 to –4.39%. The analysis of the samples began on 22 August 2006 and was completed on 07 September 2006.

Number of Subjects (Planned and Analyzed):

Planned: 18; Entered: 18; Completed: 15; Evaluated for Safety: 18; Evaluated for Pharmacokinetics: 16

For the 18 subjects who participated in the study, the mean age was 40.1 years (ranging from 21 to 55 years), the mean weight was 82.7 kg (ranging from 67 to 101 kg) and the mean height was 177.8 cm (ranging from 164 to 190 cm). For the 16 subjects included in the pharmacokinetic analyses, the mean age was 40.6 years (ranging from 21 to 55 years), the mean weight was 82.7 kg (ranging from 67 to 101 kg) and the mean height was 178.2 cm (ranging from 165 to 190 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 Formulation
Dosage Form	Capsule
Formulation (MMID No.)*	D0500081
Strength (mg)†	135
Bulk Product Lot Number	05-002449
Bulk NPRO [redacted] Lot No.)#	06-006526
Potency (% of Label Claim)	98.4
Manufacturing Site	Abbott Park
Manufacturing Date	November 2005
Retest Date	01 March 2008

b(4)

† Dosage form contains fenofibric acid choline salt equivalent to 135 mg fenofibric acid.
* Material master identification number.
# NPRO = New product research order.

The Crestor® 40 mg tablets used in this study contained rosuvastatin calcium equivalent to 40 mg rosuvastatin and were manufactured by manufactured by IPR Pharmaceuticals, Inc. for AstraZeneca Pharmaceuticals, as bulk product lot number 06-006126; the expiration date was 31 December 2008.

Criteria for Evaluation

Pharmacokinetic: The pharmacokinetic parameter values of fenofibric acid were estimated using non-compartmental and compartmental methods. For Study Day 10 data for both analytes, pharmacokinetic parameters for non-compartmental analysis included: the maximum plasma concentration (Cmax), the time to Cmax (Tmax), the terminal phase elimination rate constant (λz), terminal phase elimination half-life ($t_{½}$), the area under the plasma concentration-time curve (AUC) from time 0 to 24 (AUC24), and the apparent oral clearance (CL/F). For Study Day 1 data for Regimen C, fenofibric acid Cmax, Tmax, and AUC24 were determined. The accumulation ratio (AR), and the fluctuation index (FI) of fenofibric acid were determined by comparing Study Day 10 and Study Day 1 exposure from Regimen C.

Compartmental model analyses were performed on fenofibric acid concentrations for Regimen C to assess the time linearity in fenofibric acid pharmacokinetics. Serial concentration data on Study Days 1 and 10, and the trough concentrations on Study Days 5, 7, 8, and 9 in Regimen C were simultaneously modeled for each individual subject. One and two compartment models with different weighing schemes were evaluated to determine the best-fit model.

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

Statistical Methods

Pharmacokinetic: For fenofibric acid and rosuvastatin pharmacokinetics, an analysis of variance

(ANOVA) was performed for Tmax, λz, and the natural logarithms of Cmax, Cmin and AUC24 determined from the data following the last dose of study drug on Study Day 10. The effects of period and regimen were fixed, while the effect of subject was random. Within the framework of these analyses for the logarithms of Cmax, Cmin and AUC24, 90% confidence intervals for the bioavailability of the combination regimen relative to that of the single agent regimens were

provided. The confidence intervals were used to perform the two one-sided tests procedure for assessing bioequivalence with 0.80 to 1.25 as the range of equivalence.

For Regimen C (ABT-335 alone), an analysis was performed on the natural logarithms of Cmax and AUC24 to estimate the ratio of the Study Day 10 least square mean value to that of the Study Day 1 least square mean value.

That is, the point estimate of the ratio was the ratio of geometric means. A 95% confidence interval was also provided.

Safety: The number and percentage of subjects reporting adverse events grouped by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class were tabulated 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 ± standard deviation (SD) pharmacokinetic parameters of fenofibric acid on Study Day 10 after administration of Regimens B and C are listed in the following table.

Pharmacokinetic Parameters (units)		Regimens£ C: ABT-335 Alone, Non-fasting (N = 16)	Regimens£ B: ABT-335 + Rosuvastatin, Non-fasting (N = 15)
T_{max}	(h)	6.9 ± 2.1	6.9 ±2.5
C_{max}	(µg/mL)	12.13 ± 2.83	11.89 ± 2.83
C_{min}	(µg•h/mL)	4.59 ± 1.41	4.64 ± 1.45
AUC_{24}	(µg•h/mL)	182.6 ± 44.0	180.4 ± 47.3
$t_{½}$¢	(h)	23.44 ± 3.78	23.33 ± 3.67
CL/F†	(L/h)	0.79 ± 0.21	0.80 ± 0.22

£ Regimen B was administered as 40 mg rosuvastatin and ABT-335 equivalent to 135 mg fenofibric acid. Regimen C was administered as ABT-335 equivalent to 135 mg fenofibric acid.

¢ Harmonic mean ± pseudo-SD; evaluations of $t_{½}$ were based on statistical tests for λ_z.

† Parameter was not tested statistically.

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

Regimens Test *vs.* Reference	Pharmacokinetic Parameter (units)	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
B *vs.* C	C_{max} (µg/mL)	11.59	11.85	0.978	0.915 – 1.046
	C_{min} (µg/mL)	4.47	4.40	1.016	0.927 – 1.113
	AUC_{24} (µg•h/mL)	175.1	178.2	0.982	0.927 – 1.041

* Antilogarithm of the least squares means for logarithms.

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

Mean ± SD pharmacokinetic parameters of rosuvastatin on Study Day 10 after administration of Regimens B and C are listed in the following table.

Pharmacokinetic Parameters (units)		Regimens£ A: Rosuvastatin Alone, Non-fasting (N = 17)	Regimens£ B: Rosuvastatin + ABT-335, Non-fasting (N = 15)
T_{max}	(h)	5.1 ± 0.9	4.9 ± 1.1
C_{max}	(ng/mL)	11.95 ± 3.76	14.02 ± 4.77*
C_{min}	(ng•h/mL)	2.57 ± 0.96	2.48 ± 0.98
AUC_{24}	(ng•h/mL)	136.3 ± 45.7	141.1 ± 51.0
$t_{½}$¢	(h)	17.45 ± 4.30	17.86 ± 5.50
CL/F†	(L/h)	0.32 ± 0.10	0.31 ± 0.10

£ Regimen A was administered as 40 mg rosuvastatin. Regimen B was administered as 40 mg rosuvastatin and ABT-335 equivalent to 135 mg fenofibric acid.

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

¢ Harmonic mean ± pseudo-SD evaluations of $t_{½}$ were based on statistical tests for λ_z.

† Parameter was not tested statistically.

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

Regimens Test *vs.* Reference	Pharmacokinetic Parameter (units)	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
B *vs.* A	C_{max} (µg/mL)	13.69	11.45	1.196	1.119 – 1.278
	C_{min} (µg/mL)	2.35	2.43	0.969	0.924 – 1.015
	AUC_{24} (µg•h/mL)	137.4	129.9	1.058	0.998 – 1.121

* Antilogarithm of the least squares means for logarithms.

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

Safety Results: 55.6% (10/18) of subjects reported at least one treatment-emergent adverse event. The most common treatment-emergent adverse event (reported by two subjects who

received ABT-335 and rosuvastatin) was stomach discomfort. One subject was discontinued from the study due to a mild urinary tract infection.

The proportion of subjects reporting at least one treatment-emergent adverse event was higher among subjects who received Regimen B (6/16, 37.5%) than those who received Regimen A (3/17, 17.6%) and Regimen C (2/16, 12.5%). All adverse events in Regimens A, B and C were either not related or probably not related to fenofibric acid and/or rosuvastatin. All adverse events were assessed by the investigator as mild in severity.

No deaths, other serious adverse events or other significant adverse events were reported in this study.

With the exception of a small number of subjects with clinical laboratory and vital signs values that met the Abbott-defined potentially clinically significant criteria, there were no other clinically significant changes observed in clinical laboratory and vital signs values, and in addition, no clinically significant changes were observed in the ECGs and physical examination findings during the study.

Sponsor's Conclusions: Co-administering rosuvastatin 40 mg QD, the highest approved dose, with ABT-335 equivalent to 135 mg fenofibric acid had no significant effects on the steady-state pharmacokinetics of fenofibric acid. Co-administration of ABT-335 equivalent to 135 mg fenofibric acid QD had no significant effects on the Cmin or AUC24 of rosuvastatin at steady state. The rosuvastatin Cmax least square mean value was increased by about 20% and the upper bound of the 90% confidence interval for the ratio of the combined regimen least square mean value to the rosuvastatin alone least square mean value extended slightly above the goal post of 1.25 to 1.278. The slight increase in rosuvastatin Cmax is unlikely to be clinically significant.

After multiple-dose administration of ABT-335 (fenofibric acid choline salt formulation), the mean accumulation ratio expressed as the arithmetic mean of the ratio of the Study Day 10 AUC24 to the Study Day 1 AUC24 among individuals, was 2.60. The estimated accumulation of fenofibric acid following multiple dosing of ABT-335 was similar to that obtained after the administration of fenofibrate. The degree of fluctuation in steady-state fenofibric acid concentration following the administration of ABT-335 was also similar to that obtained after the administration of fenofibrate.

All three regimens were generally well tolerated by the subjects. While a small number of subjects had clinical laboratory and vital signs values that met the Abbott-defined potentially clinically significant criteria, there were no clinically significant changes observed in clinical laboratory and vital signs values. No clinically significant changes were observed in the ECGs and physical examination findings during the study.

Reviewer's Comment:

- Overall, the study conduct and assessments were appropriate and the concentration data was well supported by the analytical method. There were no major protocol violations affecting the study outcome. Sponsors interpretation of results is also reasonable and acceptable.