

4.2.8 Food Effect Study (M06-831)

Title of Study: Assessment of the Effect of Food on ABT-335 Bioavailability from the Choline Salt Formulation

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

Studied Period: Approximately 3 months

First Subject First Visit: 27 December 2006

Last Subject Last Visit: 06 April 2007

Objective: The objective of this study was to assess the effect of food on the bioavailability of fenofibric acid from a formulation of the choline salt of ABT-335 (choline fenofibrate).

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, with 39 subjects in Cohort 1 and 36 subjects in Cohort 2. Subjects within a cohort were to go through the study procedures at the same time. The subjects in each cohort were randomly assigned in approximately equal numbers to receive one of six sequences of Regimens A, B and C.

- Regimen A: One capsule containing ABT-335 mini-tablets equivalent to 135 mg fenofibric acid administered following a high-fat breakfast.
- Regimen B: One capsule containing ABT-335 mini-tablets equivalent to 135 mg fenofibric acid administered following a low-fat breakfast.
- Regimen C: One capsule containing ABT-335 mini-tablets equivalent to 135 mg fenofibric acid administered under fasting conditions.

A washout interval of 20 to 21 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, 9, 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 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. The lower limit of quantitation (LLOQ) for fenofibric acid was established at 0.016 µg/mL using a 50 µL plasma sample. The in-study calibration contained eight standards ranging from 0.016 to 5.399 µg/mL. All calibration curves had coefficient of determination (r^2) values ≥ 0.9917 . 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, 0.345 and 5.180 µg/mL fenofibric acid, were analyzed with the unknowns. The coefficient of variation (CV)

values for the data ranged from 4.9 to 5.9%; the mean bias values were between -3.0 and -1.1%. Dilution QC samples were also evaluated at two times (2x) and ten times (10x). Samples were analyzed between the dates of 27 February 2007 and 15 March 2007.

Number of Subjects (Planned and Analyzed):

Planned: 75; Entered: 75; Completed: 70; Evaluated for Safety: 75; Evaluated for Pharmacokinetics: 72 For the 75 subjects who participated in the study, the mean age was 35.1 years (ranging from 18 to 55 years), the mean weight was 76.1 kg (ranging from 53 to 101 kg) and the mean height was 173.4 cm (ranging from 151 to 191 cm). For the 72 subjects included in the pharmacokinetic analyses, the mean age was 34.9 years (ranging from 19 to 55 years), the mean weight was 76.7 kg (ranging from 53 to 101 kg) and the mean height was 173.8 cm (ranging from 151 to 191 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	ABT-335
Strength (mg)	135[†]
Bulk Product Lot Number	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 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_{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_∞) 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 T_{max} , the elimination rate constant (λ_z) and the natural logarithms of C_{max} , AUC_t and AUC_{∞} . The model included effects for cohort, sequence, subject nested within combination of cohort and sequence, period, regimen and the interaction of cohort and period. The effect of subject was random, and all other effects were fixed.

Within the ANOVA modeling framework, the test regimens (A and B) were compared to the reference regimen (C) by a test with a significance level of 0.05.

The bioavailability of each test regimen (A and B) relative to that of the reference regimen (Regimen C) 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 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, which are the standard regulatory criteria for bioequivalence.

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 \pm standard deviation (SD) pharmacokinetic parameters of ABT-335 after administration of the three regimens are listed in the following table.

Pharmacokinetic Parameters (units)	Regimen [‡]		
	A (Test)	B (Test)	C (Reference)
	ABT-335 High-Fat Meal (N = 71)	ABT-335 Low-Fat Meal (N = 71)	ABT-335 Fasting (N = 72)
T_{max} (h)	10.2 \pm 4.3*	7.5 \pm 3.9*	4.5 \pm 2.7
C_{max} (μ g/mL)	6.683 \pm 1.547*	6.091 \pm 1.606*	7.725 \pm 1.462
AUC_t (μ g·h/mL)	152.7 \pm 47.1	143.1 \pm 47.2*	156.3 \pm 46.7
AUC_{∞} (μ g·h/mL)	158.6 \pm 53.0	148.9 \pm 52.8*	161.1 \pm 51.3
$t_{1/2}$ [#] (h)	19.86 \pm 6.89	19.86 \pm 6.77	19.46 \pm 6.95
CL/F [†] (L/h)	0.96 \pm 0.36	1.04 \pm 0.45	0.94 \pm 0.37

‡ All regimens were administered as one capsule of ABT-335 equivalent to 135 mg fenofibric acid.

* Statistically significantly different from reference Regimen C (ANOVA, $p < 0.001$).

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

† Parameter was not tested statistically.

The results of the assessment of food effect are listed in the following table.

Regimens [‡] Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate [†]	90% Confidence Interval
A vs. C	C _{max}	6.356	7.476	0.850	0.806 – 0.897
High-Fat vs. Fasting	AUC _t	140.108	144.172	0.972	0.942 – 1.002
	AUC _∞	144.021	147.356	0.977	0.947 – 1.009
B vs. C	C _{max}	5.830	7.476	0.780	0.739 – 0.823
Low-Fat vs. Fasting	AUC _t	131.516	144.172	0.912	0.884 – 0.941
	AUC _∞	135.532	147.356	0.920	0.891 – 0.950

[‡] All regimens were administered as one capsule of ABT-335 equivalent to 135 mg fenofibric acid.

* 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 three or more subjects in any one regimen) were viral upper respiratory tract infection and headache.

One subject was discontinued from the study due to a serious adverse event (car accident, non-life-threatening traumas) that was judged by the investigator to be not related to study drug.

One subject withdrew from the study due to a mild adverse event (viral upper respiratory tract infection) that was judged by the investigator to be not related to study drug.

There were no clinically significant changes observed in clinical laboratory and vital signs values, in the ECGs or in the physical examination findings during the study.

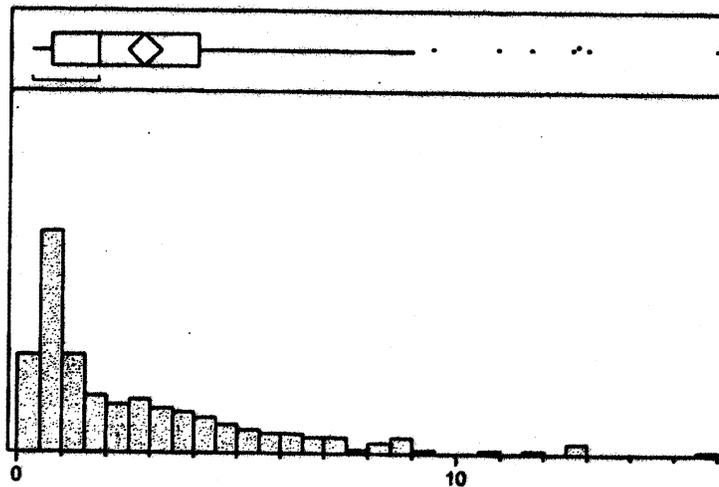
Sponsor's Conclusions: The two one-sided tests procedure based on the analyses of log-transformed C_{max} and AUC showed that the high-fat, high-calorie meal had no effect on the bioavailability of fenofibric acid from the ABT-335 formulation because the 90% confidence intervals for evaluating food effect were within the 0.80 to 1.25 range. The low-fat meal had no effect on the AUC of fenofibric acid from the ABT-335 formulation because the 90% confidence intervals evaluating low-fat meal food effect for AUC_t and AUC_∞ were within the 0.80 to 1.25 range. The low-fat meal decreased fenofibric acid C_{max} by 22%, on average. When administered under non-fasting conditions, the mean T_{max} for fenofibric acid from the ABT-335 formulation was delayed by up to 6 hours.

The observed slower rate of absorption following administration of the ABT-335 formulation under either high-fat or low-fat meal conditions resulted in essentially no change in the overall extent of bioavailability of fenofibric acid as measured by AUC_t and AUC_∞. The delayed mean T_{max} after meals and the reduced mean C_{max} after the low-fat meal are unlikely to be clinically important for a chronically administered drug such as ABT-335. Furthermore, successful treatment of mixed dyslipidemia in the Phase 3 program, where patients were instructed to take the study medication without regard to meals, further supports the conclusion that ABT-335 can be administered without regard to meals.

All three regimens were generally well tolerated by the subjects. There were no clinically significant changes observed in clinical laboratory and vital signs values, in the ECGs or in the physical examination findings during the study.

Reviewer's Comment:

- Overall, the study conduct and assessments were appropriate and the concentration data was supported by the analytical method. The half-life and thus the AUC_{0-inf} estimation was also appropriate with reasonable extrapolation for majority of the time profiles (see Figure below). There were no major protocol violations affecting the study outcome.
- Although the results of statistical analysis showed that the high-fat, high-calorie meal had no effect on the bioavailability of fenofibric acid from the ABT-335 formulation because the 90% confidence intervals for evaluating food effect were within the 0.80 to 1.25 range, the absolute values of the 90% lower and upper bounds were contained within 80-90% indicating that there was around 15% reduction in C_{max} with high-fat meal. Therefore, food does affect the rate of absorption of fenofibric acid, though not the extent of absorption to raise any concern.
- 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 1075.9 Kcal; 47.3% calories from fat, 37.1% calories from carbohydrates and 15.9% calories from protein.



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

4.3 OCP Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
Information	Information	Information	Information	
NDA Number	22-224	Brand Name	Choline Fenofibrate (ABT-335)	
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Fenofibric acid choline salt	
Medical Division	DMEP	Drug Class		
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	For treatment of patients with dyslipidemia (mixed dyslipidemia [in combination with HMG-CoA reductase inhibitors, or as monotherapy], primary hypercholesterolemia [as monotherapy], or hypertriglyceridemia [as monotherapy])	
OCP Pharmacometrics Reviewer	-	Dosage Form	Tablet	
OCPB Team Leader	Sally Choo, Ph.D.	Dosing Regimen		
Date of Submission	December 10, 2007	Route of Administration	Oral	
Estimated Due Date of OCP Review	09/05/2008	Sponsor	Abbott Laboratories	
PD/LFA Due Date	10/07/2008	Priority Classification	Standard	
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	X			
Biosimilarity:				
enzyme characterization:				
blood/plasma ratio:				
plasma protein binding:				
Pharmacokinetics (e.g., Phase II -				
Healthy Volunteers-				
single dose:	X	1	1	Study # M02-513*
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies				
In-vivo effects on primary drug:	X	2	2	Study # M06-804*, M06-811*
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1	1	Study # KLF178P03 03 KH
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	5		BA studies (Study # M04-712, M04-715, M03-636, M05-732*, M05-801)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	X	2	2	Two BE studies (Study # M06-830*, M06-886*), M06-830 is pivotal BE study
Food-drug interaction studies:	X	2	2	BA studies (Study # M06-831*, M05-743)
Dissolution:				
(MVC):	X	1		Study # M05-737*
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		14	8	
Fiability				
	"X" if yes	Comments		
Application fiabile?	X	Comments to the Sponsor: None		
Submission in Brief: See the details below.	Reviewer's Comments: Clinical Pharmacology Review will focus on pivotal BE study, other clinical pharmacology study results and the proposed labeling. The PK linearity will be reviewed to address the biowaiver aspect of 45 mg formulation based on the formal consult received from CMC. DSI inspection will be requested for the pivotal BE study (M06-830) trial site and its analytical site. *Studies submitted with Analysis Data sets			

Submission in Brief:

The sponsor, Abbott Laboratories, has submitted NDA 22-224 requesting approval of two strengths of Choline fenofibrate capsules: 45 and 135 mg as a 505(b)(2) application. Choline fenofibrate capsules are an oral capule formulation containing choline fenofibrate equivalent to 45 and 135 mg of fenofibric acid, which has been developed for the treatment of patients with dyslipidemia (mixed dyslipidemia [in combination with HMG-CoA reductase inhibitors, or as

monotherapy], primary hypercholesterolemia [as monotherapy], or hypertriglyceridemia [as monotherapy].

The reference listed drug for the 505(b)(2) categorization of this application, as mentioned in the cover letter, is fenofibrate (TriCor® oral tablets, 48 and 145 mg, approved under NDA 21-656 and marketed by Abbott). Approval for the TriCor® Oral Tablets was based on the demonstration of BE (NDA 21-656) against the approved micronized fenofibrate 200 mg capsules (NDA 21-656). Abbott requested a biowaiver for the 45 mg strength of choline fenofibrate capsules.

Under the current NDA application, sponsor submitted 18 clinical studies, including 14 Phase 1 and three Phase 3 studies of the co-administration of choline fenofibrate with statins and a Phase 3 open-label, long-term safety extension study (See Attachment 1 for details). Out of 14 Phase 1 clinical studies, a pivotal BE clinical pharmacology study evaluated the bioequivalence of choline fenofibrate 135 mg capsules with micronized fenofibrate 200 mg capsules. This request for a waiver for the 45 mg strength is made based on formulation composition proportionality, the similarity in the in vitro drug release profiles between the 45 mg and 135 mg strengths, and dose proportionality in fenofibric acid pharmacokinetics. The supporting information for this request was also submitted with this application.

The results of the pivotal BE study, Study No. M06-830, are described below:

Study No. M06-830:

Title: 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

Trial and Analytical Sites:

The investigator and site for this study were:
Brendan J Smyth, PhD, MD, Associate Medical Director
Abbott Clinical Pharmacology Research Unit at
Vista Medical Center East
1324 North Sheridan Road, Wankegan, IL 60085

Primary 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.

Study Design:

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.

Investigational Products:

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.

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Study Results:
Analytical Details:

Scope	Analysis of A-770335 in human plasma with sodium fluoride/potassium oxalate
Sample Volume	50 µL
Calibration Standards	10 Standard levels ranging from 0.016 µg/mL to 5.465 µg/mL A-770335
Sample Storage	Approximately -20°C
Sample Container	Polypropylene cryogenic tubes
Analytical Method	On-line solid phase extraction with partial protein precipitation followed by LC/MS/MS
Analysis Site	Abbott Laboratories, R46W
Blinding	Yes
Assayed by	Subject
Chromatograms for Regulatory Submission	All chromatograms associated with the first 14 subjects.
Lower Limit of Quantitation for sample analysis	0.016 µg/mL
Number of samples received	3293
Number of samples analyzed	3293

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 (Test) ABT-335 (N = 63)	B (Reference) ABT-335 (N = 65)	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 _{0-∞} (µg·h/mL)	152.8 ± 48.1*	149.8 ± 41.7*	168.9 ± 55.5
AUC _{0-t} (µg·h/mL)	157.2 ± 52.9*	153.5 ± 44.8*	175.0 ± 59.5
t _{1/2} [#] (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_{1/2} 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 ^f Test vs. Reference	Pharmacokinetic Parameter	Central Values ^g		Relative Bioavailability	
		Test	Reference	Point Estimate ^h	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

^f 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.

^g Antilogarithm of the least squares means for logarithms.

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

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 C_{max} 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 with regard to both the C_{max} 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 with regard to both the C_{max} and AUC of fenofibric acid.
- All three regimens were generally well tolerated by the subjects.

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Attachment 1: Tabular Listing of Clinical Studies

Table 1. Tabular Listing of Clinical Studies

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I RA	M06-031	5.3.1.1	Assess the effect of food on famotidine acid bioavailability from the to-be-marketed ABT-335 capsules	Single-dose, open-label, three-period, randomized, crossover	125 mg ABT-335 capsule (Formulation 10) oral	75	Healthy Subjects	Single dose	Complete; Full
Phase I RA	E LF12P 03 03 KH	5.3.1.1	Determine the absolute RA of famotidine acid from famotidine and famotidine acid NCD suspensions delivered to different GI sites; vs. from famotidine acid IV infusion and to assess the optimal site of GI tract absorption for famotidine acid.	Randomized, open-label, controlled of two successive phases	145 mg famotidine and 130 mg famotidine acid as Nano Crystal [®] dispersion (NCD) suspension delivered orally or via site-specific Entonox [™] capsule and 50 mg famotidine acid (10 minute infusion at a rate of 1 mL/min); IV and 145 mg famotidine nanoparticle tablet, oral	20	Healthy Subjects	Single dose	Complete; Full
Phase I RA	M04-712	5.3.1.2	Compare famotidine acid bioavailability from two test famotidine acid choline salt formulations with that from a 200 mg famotidine capsule and to assess the food effect on the two test formulations	Single-dose, open-label, three-period, randomized, crossover design	200 mg famotidine capsule and two famotidine acid choline salt capsule formulations containing 130 mg famotidine acid equivalent; oral	42	Healthy Subjects	Single dose	Complete; Full
Phase I RA	M04-715	5.3.1.2	Compare famotidine acid bioavailability from two test formulations with that from a 200 mg famotidine capsule and to assess the food effect on the two test formulations	Single-dose, open-label, three-period, randomized, crossover	200 mg famotidine capsule and two capsule formulations of 130 mg famotidine acid; oral	42	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 BA	M01-416	5.3.1.2	Compare fenofibrate acid bioavailability from two test capsule formulations with that from a 200 mg fenofibrate capsule	Single-dose, open-label, three-period, randomized, partial-crossover	200 mg fenofibrate capsule and two capsule formulations of 130 mg fenofibrate acid, oral	48	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 BA	M05-732	5.3.1.2	Compare fenofibrate acid bioavailability from three fenofibrate acid choline salt formulations with various compositions relative to that from a 200 mg fenofibrate capsule	Single-dose, open-label, four-period, randomized, complete crossover	200 mg fenofibrate capsule and three fenofibrate acid choline salt capsule formulations containing 135 mg of fenofibrate acid equivalent (Formulations 9, 10 and 11); oral	48	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 BA	M05-743	5.3.1.2	Compare fenofibrate acid bioavailability from a 15-kg manufacturing lot ABT-335 capsule with that from a 200 mg fenofibrate capsule, and to assess the food effect on the ABT-335 capsule	Single-dose, open-label, three-period, randomized, crossover	200 mg fenofibrate capsule and 135 mg of ABT-335 capsule (Formulation 10); oral	24	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 BA	M05-801	5.3.1.2	Compare fenofibrate acid bioavailability from ABT-335 capsules used in Phase 1 clinical trials relative to that from a 200 mg fenofibrate capsule	Single-dose, open-label, two-period, randomized, crossover	200 mg fenofibrate capsule and 135 mg ABT-335 capsule (Formulation 10); oral	36	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I BE	M04-830	5.3.1.2	Compare fexofenadine acid bioavailability from the to-be-manufactured ABT-335 capsules relative to that from the ABT-335 capsules used in Phase 3 clinical trial and that from a 200 mg fexofenadine capsule	Single-dose, open-label, three-period, randomized, crossover	200 mg fexofenadine capsule and 135 mg ABT-335 capsule (Formulation 10); oral	65	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I BE	M06-886	5.3.1.2	Compare fexofenadine acid bioavailability from the to-be-manufactured ABT-335 capsules manufactured at Formier Pharma facility in Ireland vs. those manufactured at Abbott Puerto Rico facility	Single-dose, open-label, two-period, randomized, crossover	135 mg ABT-335 capsule (Formulation 10); oral	42	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I TVTC	M05-737	5.3.1.3	Explore the correlation between <i>in vitro</i> drug release and <i>in vivo</i> performance of three modified-release fexofenadine acid choline salt formulations that differ in drug release rate	Single-dose, open-label, four-period, randomized, crossover design	135 mg of fexofenadine acid next drug in capsule, three fexofenadine acid choline salt formulations. (Formulation 10, 12 and 13); oral	24	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I PK	M07-513	5.3.3.1	Evaluate the safety, tolerability, and PK of ascending single oral doses of fexofenadine acid and to assess the effect of food on the 100 mg dose	Randomized, three-period, double-blind, placebo-controlled, single-center study	50 mg and 100 mg of fexofenadine acid next drug in capsule; oral	20	Healthy Subjects	Single dose	Complete; Full
Phase I Drug Interaction	M06-804	5.3.3.4	Evaluate the effects of omeprazole on fexofenadine acid absorption from ABT-335 capsule	Open-label, three-period, randomized, crossover	135 mg ABT-335 capsule, single dose, 40 mg omeprazole tablet once daily for 5 days; oral	36	Healthy Subjects	Single dose ABT-335, multiple dose omeprazole for 5 days	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 Drug Interaction	3005-811	3.3.3.4	Evaluate PK interaction between fenofibric acid and roxarsoxacin and assess time linearity in fenofibric acid PK	Multiple-dose, open-label, three-period, randomized crossover	135 mg ABT-335 capsule, 40 mg roxarsoxacin tablet, once daily for 10 days; oral	18	Healthy Subjects	10 days	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2 Efficacy and Safety	3005-748	3.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and roxarsoxacin monotherapy with ABT-335 and roxarsoxacin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 10 mg roxarsoxacin, 20 mg roxarsoxacin, 40 mg roxarsoxacin, 135 mg ABT-335 + 10 mg roxarsoxacin or ABT-335 + 20 mg roxarsoxacin	1465	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full
Phase 2 Efficacy and Safety	3005-749	3.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and roxarsoxacin monotherapy with ABT-335 and roxarsoxacin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 20 mg roxarsoxacin, 40 mg roxarsoxacin, 80 mg roxarsoxacin, 135 mg ABT-335 + 20 mg roxarsoxacin or ABT-335 + 40 mg roxarsoxacin	657	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2 Efficacy and Safety	3005-750	3.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and roxarsoxacin monotherapy with ABT-335 and roxarsoxacin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 20 mg roxarsoxacin, 40 mg roxarsoxacin, 80 mg roxarsoxacin, 135 mg ABT-335 + 20 mg roxarsoxacin or ABT-335 + 40 mg roxarsoxacin	613	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full
Phase 2 Efficacy and Safety	3005-750	3.3.5.2	Long Term Safety and Efficacy	Open-label	Once daily oral doses of: 135 mg ABT-335 + roxacin (20 mg roxarsoxacin or 40 mg roxarsoxacin or 40 mg roxarsoxacin)	1911	Patients with mixed dyslipidemia (Fredrickson Type IIb)	52 weeks	Ongoing; interim report with 9/3/2007 data cut-off utilized for the FDA submission

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

/s/

Manoj Khurana
9/22/2008 05:35:39 PM
BIOPHARMACEUTICS

Sally Choe
9/23/2008 08:40:14 AM
BIOPHARMACEUTICS

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Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
Information		Information		
NDA Number	22-224	Brand Name	Choline Fenofibrate (ABT-335)	
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	fenofibric acid choline salt	
Medical Division	DMEP	Drug Class		
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	For treatment of patients with dyslipidemia (mixed dyslipidemia [in combination with HMG-CoA reductase inhibitors, or as monotherapy], primary hypercholesterolemia [as monotherapy], or hypertriglyceridemia [as monotherapy])	
OCP Pharmacometrics Reviewer	-	Dosage Form	Tablet	
OCPB Team Leader	Sally Choo, Ph.D.	Dosing Regimen		
Date of Submission	December 10, 2007	Route of Administration	Oral	
Estimated Due Date of OCP Review	09/05/2008	Sponsor	Abbott Laboratories	
PDUFA Due Date	10/07/2008	Priority Classification	Standard	
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	X			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	Study # M02-513*
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies				
in-vivo effects on primary drug:	X	2	2	Study # M06-804*, M08-811*
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

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pediatric:				
geriatric:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1	1	Study # KLF178P03 03 KH
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	5		BA studies (Study # M04-712, M04-715, M03-636, M05-732*, M05-801)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	X	2	2	Two BE studies (Study # M06-830*, M06-886*), M06-830 is pivotal BE study
Food-drug interaction studies:	X	2	2	BA studies (Study # M06-831*, M05-743)
Dissolution:				
(IVC):	X	1		Study # M05-737*
Bio-waiver request based on BCS				
BCS class				
III. Other CPE Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		14	8	
Fitability				
	"X" if yes	Comments		
Application fileable?	X	Comments to the Sponsor: None		
Submission in Brief: See the details below.	Reviewer's Comments: Clinical Pharmacology Review will focus on pivotal BE study, other clinical pharmacology study results and the proposed labeling. The PK linearity will be reviewed to address the biowaiver aspect of 45 mg formulation based on the formal consult received from CMC. DSI inspection will be requested for the pivotal BE study (M06-830) trial site and its analytical site. *Studies submitted with Analysis Data sets			

Submission in Brief:

The sponsor, Abbott Laboratories, has submitted NDA 22-224 requesting approval of two strengths of Choline fenofibrate capsules: 45 and 135 mg as a 505(b)(2) application. Choline fenofibrate capsules are an oral capsule formulation containing choline fenofibrate equivalent to 45 and 135 mg of fenofibric acid, which has been developed for the treatment of patients with dyslipidemia (mixed dyslipidemia [in combination with HMG-CoA reductase inhibitors, or as

monotherapy], primary hypercholesterolemia [as monotherapy], or hypertriglyceridemia [as monotherapy].

The reference listed drug for the 505(b)(2) categorization of this application, as mentioned in the cover letter, is fenofibrate (TriCor® oral tablets, 48 and 145 mg, approved under NDA 21-656 and marketed by Abbott). Approval for the TriCor® Oral Tablets was based on the demonstration of BE (NDA 21-656) against the approved micronized fenofibrate 200 mg capsules (NDA 21-656). Abbott requested a biowaiver for the 45 mg strength of choline fenofibrate capsules.

Under the current NDA application, sponsor submitted 18 clinical studies, including 14 Phase 1 and three Phase 3 studies of the co-administration of choline fenofibrate with statins and a Phase 3 open-label, long-term safety extension study (See Attachment 1 for details). Out of 14 Phase 1 clinical studies, a pivotal BE clinical pharmacology study evaluated the bioequivalence of choline fenofibrate 135 mg capsules with micronized fenofibrate 200 mg capsules. This request for a waiver for the 45 mg strength is made based on formulation composition proportionality, the similarity in the in vitro drug release profiles between the 45 mg and 135 mg strengths, and dose proportionality in fenofibric acid pharmacokinetics. The supporting information for this request was also submitted with this application.

The results of the pivotal BE study, Study No. M06-830, are described below:

Study No. M06-830:

Title: 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

Trial and Analytical Sites:

The investigator and site for this study were:

Brendan J Smyth, PhD, MD, Associate Medical Director
Abbott Clinical Pharmacology Research Unit at
Vista Medical Center East
1324 North Sheridan Road, Waukegan, IL 60085

Primary 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.

Study Design:

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.

Investigational Products:

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.

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Study Results:
Analytical Details:

Scope	Analysis of A-770335 in human plasma with sodium fluoride/potassium oxalate
Sample Volume	50 μ L
Calibration Standards	10 Standard levels ranging from 0.016 μ g/mL to 5.465 μ g/mL. A-770335
Sample Storage	Approximately -20°C
Sample Container	Polypropylene cryogenic tubes
Analytical Method	On-line solid phase extraction with partial protein precipitation followed by LC/MS/MS
Analysis Site	Abbott Laboratories, R46W
Blinding	Yes
Assayed by	Subject
Chromatograms for Regulatory Submission	All chromatograms associated with the first 14 subjects.
Lower Limit of Quantitation for sample analysis	0.016 μ g/mL
Number of samples received	3293
Number of samples analyzed	3293

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

Pharmacokinetic Parameters (units)	Regimen ^f		
	A (Test)	B (Reference)	C (Reference)
	ABT-335 (N = 63)	ABT-335 (N = 65)	Fenofibrate (N = 65)
T _{max} (h)	4.2 \pm 1.3	4.4 \pm 1.9	4.6 \pm 1.4
C _{max} (μ g/mL)	8.234 \pm 2.224*	7.979 \pm 2.075*	9.281 \pm 2.667
AUC _t (μ g \cdot h/mL)	152.8 \pm 48.1*	149.8 \pm 41.7*	168.9 \pm 55.5
AUC _{∞} (μ g \cdot h/mL)	157.2 \pm 52.9*	153.5 \pm 44.8*	175.0 \pm 59.5
t _{1/2} [*] (h)	19.20 \pm 7.49*	19.79 \pm 6.10*	21.82 \pm 7.43
CL/F [†] (L/h)	0.96 \pm 0.35	0.96 \pm 0.33	NA

^f 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 \pm pseudo standard deviation; evaluations of t_{1/2} were based on statistical tests for λ_e .

[†] Parameter was not tested statistically.

NA = Not applicable.

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

Regimens ^f Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
A vs. B	C _{max}	7.966	7.725	1.031	0.977 – 1.083
	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

^f 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.

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 C_{max} 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 with regard to both the C_{max} 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 with regard to both the C_{max} and AUC of fenofibric acid.
- All three regimens were generally well tolerated by the subjects.

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Attachment 1: Tabular Listing of Clinical Studies

Table 1. Tabular Listing of Clinical Studies

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I BA	M06-831	5.3.1.1	Assess the effect of food on fenofibric acid bioavailability from the to-be-marketed ABT-335 capsules	Single-dose, open-label, three-period, randomized, crossover	135 mg ABT-335 capsule (Foundation 10); oral	75	Healthy Subjects	Single dose	Complete; Full
Phase I BA	K LF178P 03 03 KH	5.3.1.1	Determine the absolute BA of fenofibric acid from fenofibrate and fenofibric acid NCD suspensions delivered to different GI sites vs. from fenofibric acid IV infusion and to assess the optimal site of GI tract absorption for fenofibric acid	Randomized, open-label, consisted of two successive phases	145 mg fenofibrate and 130 mg fenofibric acid as Nano Crystal [®] dispersion (NCD) suspension delivered orally or via site-specific Euteron [™] capsule and 50 mg fenofibric acid (10 minute infusion at a rate of 1 mL/min); IV and 145 mg fenofibrate nanoparticle tablet; oral	20	Healthy Subjects	Single dose	Complete; Full
Phase I BA	M04-712	5.3.1.2	Compare fenofibric acid bioavailability from two test fenofibric acid choline salt formulations with that from a 200 mg fenofibrate capsule and to assess the food effect on the two test formulations	Single-dose, open-label, three-period, randomized, crossover design	200 mg fenofibrate capsule and two fenofibric acid choline salt capsule formulations containing 130 mg fenofibric acid equivalent; oral	42	Healthy Subjects	Single dose	Complete; Full
Phase I BA	M04-715	5.3.1.2	Compare fenofibric acid bioavailability from two test formulations with that from a 200 mg fenofibrate capsule and to assess the food effect on the two test formulations	Single-dose, open-label, three-period, randomized, crossover	200 mg fenofibrate capsule and two capsule formulations of 130 mg fenofibric acid; oral	42	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I BA	M03-636	5.3.1.2	Compare fenofibric acid bioavailability from two test capsule formulations with that from a 200 mg fenofibrate capsule	Single-dose, open-label, three-period, randomized, partial-crossover	200 mg fenofibrate capsule and two capsule formulations of 130 mg fenofibric acid, oral	48	Healthy Subjects	Single dose	Complete; Full
Phase I BA	M05-732	5.3.1.2	Compare fenofibric acid bioavailability from three fenofibric acid choline salt formulations with various compositions relative to that from a 200 mg fenofibrate capsule	Single-dose, open-label, four-period, randomized, complete crossover	200 mg fenofibrate capsule and three fenofibric acid choline salt capsule formulations containing 135 mg of fenofibric acid equivalent (Formulations 9, 10 and 11); oral	40	Healthy Subjects	Single dose	Complete; Full
Phase I BA	M05-743	5.3.1.2	Compare fenofibric acid bioavailability from a 15-kg manufacturing lot ABT-335 capsule with that from a 200 mg fenofibrate capsule, and to assess the food effect on the ABT-335 capsule	Single-dose, open-label, three-period, randomized, crossover	200 mg fenofibrate capsule and 135 mg of ABT-335 capsule (Formulation 10); oral	24	Healthy Subjects	Single dose	Complete; Full
Phase I BA	M05-801	5.3.1.2	Compare fenofibric acid bioavailability from ABT-335 capsules used in Phase 3 clinical trials relative to that from a 200 mg fenofibrate capsule	Single-dose, open-label, two-period, randomized, crossover	200 mg fenofibrate capsule and 135 mg ABT-335 capsule (Formulation 10); oral	24	Healthy Subjects	Single dose	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I BE	M06-830	5.3.1.2	Compare fenofibric acid bioavailability from the to-be-marketed ABT-335 capsules relative to that from the ABT-335 capsules used in Phase 3 clinical trial and that from a 200 mg fenofibrate capsule	Single-dose, open-label, three-period, randomized, crossover	200 mg fenofibrate capsule and 135 mg ABT-335 capsule (Formulation 10); oral	65	Healthy Subjects	Single dose	Complete; Full
Phase I BE	M06-886	5.3.1.2	Compare fenofibric acid bioavailability from the to-be-marketed ABT-335 capsules manufactured at Fournier Pharma facility in Ireland vs. those manufactured at Abbott Puerto Rico facility	Single-dose, open-label, two-period, randomized, crossover	135 mg ABT-335 capsule (Formulation 10); oral	42	Healthy Subjects	Single dose	Complete; Full
Phase I IV/VC	M05-737	5.3.1.3	Explore the correlation between <i>in vitro</i> drug release and <i>in vivo</i> performance of three modified-release fenofibric acid choline salt formulations that differ in drug release rate	Single-dose, open-label, four-period, randomized, crossover design	135 mg of fenofibric acid neat drug in capsule, three fenofibric acid choline salt formulations, (Formulation 10, 12 and 13); oral	24	Healthy Subjects	Single dose	Complete; Full
Phase I PK	M02-513	5.3.3.1	Evaluate the safety, tolerability, and PK of ascending single oral doses of fenofibric acid and to assess the effect of food on the 100 mg dose	Randomized, three-period, double-blind, placebo-controlled, single-center study	50 mg and 100 mg of fenofibric acid neat drug in capsules; oral	20	Healthy Subjects	Single dose	Complete; Full
Phase I Drug Interaction	M06-804	5.3.3.4	Evaluate the effects of omeprazole on fenofibric acid absorption from ABT-335 capsule	Open-label, three-period, randomized, crossover	135 mg ABT-335 capsule, single dose, 40 mg omeprazole tablet once daily for 5 days; oral	36	Healthy Subjects	Single dose ABT-335; multiple dose omeprazole for 5 days	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 Drug Interaction	M06-811	5.3.3.4	Evaluate PK interaction between fenofibric acid and rosuvastatin and assess time linearity in fenofibric acid PK.	Multiple-dose, open-label, three-period, randomized, crossover	135 mg ABT-335 capsule, 40 mg rosuvastatin tablet, once daily for 10 days; oral	18	Healthy Subjects	10 days	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M05-748	5.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and rosuvastatin monotherapy with ABT-335 and rosuvastatin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 10 mg rosuvastatin, 20 mg rosuvastatin, 40 mg rosuvastatin, 135 mg ABT-335 + 10 mg rosuvastatin or ABT-335 + 20 mg rosuvastatin	1445	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full
Phase 3 Efficacy and Safety	M05-749	5.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and simvastatin monotherapy with ABT-335 and simvastatin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 20 mg simvastatin, 40 mg simvastatin, 80 mg simvastatin, 135 mg ABT-335 + 20 mg simvastatin or ABT-335 + 40 mg simvastatin	657	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy and Safety	M05-750	5.3.5.1	Compare the efficacy and safety of ABT-335 monotherapy and rosuvastatin monotherapy with ABT-335 and rosuvastatin combination therapy	Randomized, double-blind, active controlled	Once daily oral doses of: 135 mg ABT-335, 20 mg atorvastatin, 40 mg atorvastatin, 80 mg atorvastatin, 135 mg ABT-335 + 20 mg atorvastatin or ABT-335 + 40 mg atorvastatin	613	Patients with mixed dyslipidemia (Fredrickson Type IIb)	12 weeks	Complete; Full
Phase 3 Efficacy and Safety	M05-758	5.3.5.2	Long Term Safety and Efficacy	Open-label	Once daily oral doses of: 135 mg ABT-335 + statin (20 mg atorvastatin or 40 mg rosuvastatin)	1911	Patients with mixed dyslipidemia (Fredrickson Type IIb)	52 weeks	Ongoing; interim report with 9/1/2007 data cut-off utilized for the NDA submission

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/s/

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