

Figure 12 Mean fenofibric acid plasma concentrations from 135 mg ABT-335 formulations given with or without meal

Table 15 Study M06-831: Mean \pm SD Pharmacokinetic Parameters of Fenofibric Acid.

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} (µg/mL)	6.683 \pm 1.547*	6.091 \pm 1.606*	7.725 \pm 1.462
AUC_{0-1} (µg·h/mL)	152.7 \pm 47.1	143.1 \pm 47.2*	156.3 \pm 46.7
$AUC_{0-\infty}$ (µg·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, $p < 0.05$).

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

† Parameter was not tested statistically.

Results of the two one-sided tests procedure from the analysis of log-transformed C_{max} , AUC_{0-1} and $AUC_{0-\infty}$ are presented in the following table.

Table 16 Study M06-831: Relative Bioavailability and 90% Confidence Intervals for Food Effect Assessment.

Regimens [‡] Test vs. Reference	Pharmacokinetic Parameter	Central Values ⁺		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
A vs. C	C _{max} (µg/mL)	6.356	7.476	0.850	0.806 – 0.897
High-Fat vs. Fasting	AUC ₀₋₄ (µg·h/mL)	140.108	144.172	0.972	0.942 – 1.002
	AUC _{0-∞} (µg·h/mL)	144.021	147.356	0.977	0.947 – 1.009
B vs. C	C _{max} (µg/mL)	5.830	7.476	0.780	0.739 – 0.823
Low-Fat vs. Fasting	AUC ₀₋₄ (µg·h/mL)	131.516	144.172	0.912	0.884 – 0.941
	AUC _{0-∞} (µg·h/mL)	135.532	147.356	0.920	0.891 – 0.950

* Antilogarithm of the least squares means for logarithms.

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

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

- When the ABT-335 formulation was administered after high-fat, high-calorie meal, the C_{max}, AUC₀₋₄ and AUC_{0-∞} of fenofibric acid were bioequivalent to those under fasting conditions (Regimen C) as the 90% confidence intervals for comparing the three pharmacokinetic parameters (C_{max}, AUC₀₋₄ and AUC_{0-∞}) between the two conditions were contained within the 0.80 to 1.25 range. However, there was a definitive mean reduction in fenofibric acid C_{max} by 15% (20 to 10% low and upper 90% CIs), thus the rate of absorption was affected, which was also evident from the prolonged T_{max}.
- A low-fat meal (422.7 Kcal with 25.1% of calories from fat) was used in Regimen B (Note: regulatory guidance has no recommendations for the composition of a low-fat meal). When the ABT-335 formulation was administered after this low-fat meal, the AUC₀₋₄ and AUC_{0-∞} of fenofibric acid were bioequivalent to those under fasting conditions because the 90% confidence intervals for comparing the AUC least square mean values between the two conditions were contained within the 0.80 to 1.25 range. The low-fat meal decreased fenofibric acid C_{max} by 22%, on average, and the lower bound of the 90% confidence interval for C_{max} extended below 0.80.
- The mean T_{max} values for Regimens A and B occurred significantly later than that for Regimen C. The delay in mean T_{max} was up to 6 hours for the high-fat, high-calorie meal in Regimen A. However, the observed reduction in rate of absorption and delay in onset of absorption resulted in essentially no change in overall bioavailability of fenofibric acid as demonstrated by the AUC values from both Regimens A and B meeting the bioequivalence criteria relative to those from Regimen C.

Based on this data it can be concluded that Trilipix™ can be administered without regards to food.

2.4.2 Drug-Drug Interaction

The sponsor conducted two separate clinical studies to assess the potential drug interactions between ABT-335 and rosuvastatin and to evaluate the effects of increased gastric pH following omeprazole administration on the absorption of fenofibric acid from the ABT-335 formulation. The sponsor referred to previously conducted (NDA 21-656) or published (simvastatin) clinical drug interaction studies between fenofibrate and drugs that are likely to be taken concomitantly by dyslipidemia patients. These drugs included six lipid-lowering agents and three antihyperglycemic agents.

2.4.2.1 What is the CYP inhibition potential of fenofibric acid?

The effects of fenofibrate and fenofibric acid on selected cytochrome P-450 (CYP)-dependent enzyme activities were evaluated using human liver microsomes and the highlights of the findings are:

- At concentrations of 20 and 200 μM , neither fenofibrate nor fenofibric acid demonstrated significant ($> 10\%$) inhibition of the CYP3A-dependent oxidation of terfenadine, the CYP2D6-mediated O-demethylation of dextromethorphan, the CYP1A2-mediated O-deethylation of phenacetin, or the CYP2E1-mediated 6-hydroxylation of chlorzoxazone.
- Fenofibrate inhibited CYP2C19-mediated 4-hydroxylation of S-mephenytoin by 4.1% and 20.4% at 20 and 200 μM , respectively. Inhibition by fenofibric acid was 12% and 25.5% at these concentrations.
- Both fenofibrate and fenofibric acid demonstrated concentration dependent inhibition of the CYP2C9-mediated methylhydroxylation of tolbutamide. The concentrations at which fenofibrate and fenofibric acid inhibited 50% of the CYP2C9-mediated enzyme activity (IC_{50}) were 127 and 139 μM , respectively. The IC_{50} values were between 4 and 6-times higher than the average circulating plasma concentrations of fenofibric acid in humans (20-30 μM).

We agree to sponsors conclusions that fenofibrate and fenofibric acid are unlikely to inhibit CYP3A-, CYP2D6-, CYP1A2-, CYP2E1-, CYP2C9- or CYP2C19-mediated metabolism at clinically relevant plasma concentrations.

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Table 17 Summary of Fenofibrate and Fenofibric Acid Effects on Selected CYP Activities in Human Liver Microsome

CYP Isoform	Assay	% Control Activity ^a			
		[Fenofibrate]		Fenofibric Acid	
		20 μ M	200 μ M	20 μ M	200 μ M
1A2	Phenacetin <i>O</i> -deethylation	99.9 \pm 1	115 \pm 18	102 \pm 2	110 \pm 23
2A6	Coumarin 7-hydroxylation	92.8 \pm 3	87.5 \pm 2	90.1 \pm 3	85.5 \pm 1
2C9	Tolbutamide hydroxylation	81.7 \pm 1	42.0 \pm 1	78.8 \pm 10	32.6 \pm 6
2C19	S-Mephenytoin 4'-hydroxylation	95.9 \pm 6	79.6 \pm 6	88.0 \pm 2	74.5 \pm 7
2D6	Dextromethorphan <i>O</i> -demethylation	101 \pm 1	101 \pm 3	103 \pm 3	101 \pm 3
2E1	Chlorzoxazone 6-hydroxylation	95.7 \pm 6	92.6 \pm 3	98.5 \pm 1	98.3 \pm 10
3A	Terfenadine hydroxylation/	97.3 \pm 1	102 \pm 2	96.0 \pm 5	103 \pm 3

a. Data presented as Mean \pm SD.

- The effect of fenofibric acid on human hepatic microsomal paclitaxel 6 α -hydroxylase activity, as a selective marker for CYP2C8, was also investigated. The calculated IC₅₀ values for fenofibric acid were 293.1 and 153.3 μ M, when the assay was performed in competitive and preincubation (10 min) modes, respectively. Based on these results, fenofibric acid is unlikely to inhibit CYP2C8-mediated metabolism at clinically relevant plasma concentrations (20-30 μ M).

2.4.2.2 What is the effect of other drugs on pharmacokinetics of ABT-335 and vice versa?

Statins

The summary of ABT-335/statin and referred fenofibrate/statin drug interaction study designs are presented in Table 18 below.

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Table 18 Summary of ABT-335/Statin and Fenofibrate/Statin Pharmacokinetic Interaction Study Designs

Statin	Design	Dose	Dosing Duration	N*
Rosuvastatin	Open-label, Randomized, Crossover, Multiple-dose	Rosuvastatin: 40 mg QD, ABT-335: 135 mg QD fenofibric acid equivalent	10 days rosuvastatin; 10 days ABT-335; 10 days combination	18/16
Atorvastatin	Open-label, Randomized, Crossover, Multiple-dose	Atorvastatin: 20 mg QD, Fenofibrate: 160 mg QD	10 days atorvastatin; 10 days fenofibrate; 10 days combination	24/22
Pravastatin	Open-label, Randomized, Crossover, Single-dose	Pravastatin: 40 mg, Fenofibrate: 3 x 67 mg	1 dose pravastatin; 1 dose fenofibrate; 1 dose combination	23/23
	Open-label, Sequential, Multiple-dose	Pravastatin: 40 mg QD, Fenofibrate: 160 mg QD	5 days pravastatin, 10 days combination	24/23
Fluvastatin	Open-label, Randomized, Crossover, Single-dose	Fluvastatin: 40 mg, Fenofibrate: 160 mg	1 dose fluvastatin; 1 dose fenofibrate; 1 dose combination	24/22
Simvastatin	Open-label, Randomized, Crossover, Multiple-dose	Simvastatin: 80 mg QD, Fenofibrate: 160 mg QD	7 days simvastatin; 7 days fenofibrate + 7 days combination	13/12

* Number of subjects enrolled/number of subjects included in pharmacokinetic analysis.
QD = daily.

Study M06-811 was a Phase 1, multiple-dose, open-label, three-period, randomized, crossover study assessing the pharmacokinetic interactions between ABT-335 and rosuvastatin. Having met the selection criteria, the subjects were randomly assigned in equal numbers to one of six sequences of Regimens A, B and C.

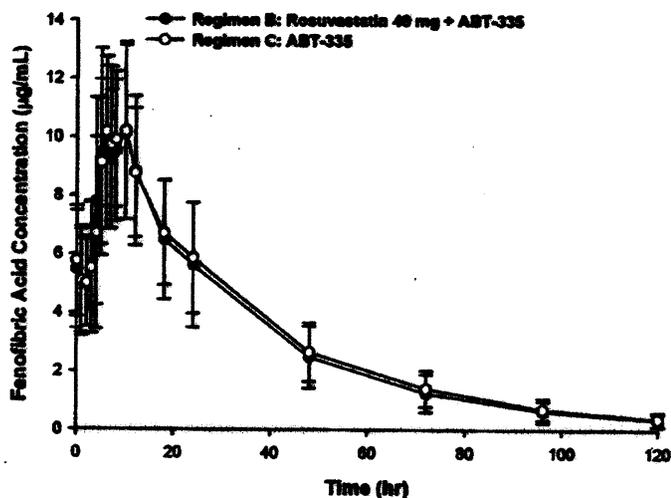
- Regimen A: One Crestor® 40 mg tablet containing rosuvastatin calcium equivalent to 40 mg rosuvastatin, once daily for 10 consecutive days, administered under non-fasting conditions.
- Regimen B: One Crestor® 40 mg tablet containing rosuvastatin calcium equivalent to 40 mg rosuvastatin, plus one capsule containing ABT-335 (fenofibric acid choline salt) mini-tablets equivalent to 135 mg of fenofibric acid, once daily for 10 consecutive days, administered under non-fasting conditions.
- Regimen C: One capsule containing ABT-335 (fenofibric acid choline salt) mini-tablets equivalent to 135 mg of fenofibric acid, once daily for 10 consecutive days, administered under non-fasting conditions.

Each dose of study drug was taken orally with approximately 240 mL of water 30 minutes after starting a low-fat breakfast. The sequences of the treatment regimens were such that each subject had received all three regimens upon completion of the study. The washout interval of at least 14 days separated the last dose of a treatment period from the first dose of any subsequent treatment period.

The results showed that co-administration of ABT-335 had no significant effects on the C_{min} or AUC_{0-24} of rosuvastatin at steady state. The rosuvastatin C_{max} least square mean value was

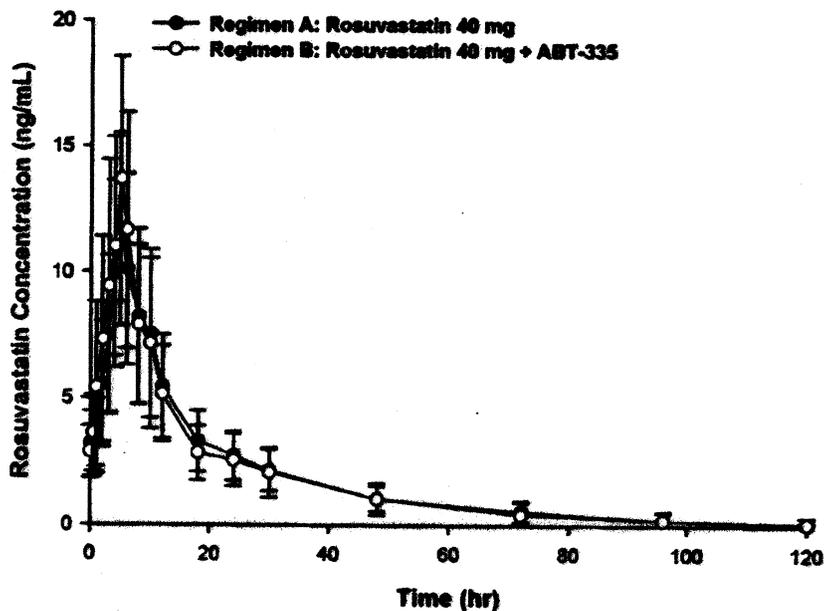
increased by about 20%. However, this effect on C_{max} is not considered to be clinically significant.

Figure 13 Mean (\pm SD) fenofibric acid plasma concentration-time profiles after study day 10 dosing.



Note: Regimens B and C contained one capsule of ABT-335 equivalent to 135 mg fenofibric acid.

Figure 14 Mean (\pm SD) rosuvastatin plasma concentration-time profiles after study day 10 dosing.



Note: Regimen B contained one capsule of ABT-335 equivalent to 135 mg fenofibric acid.

Table 19 Effects of Statins on Pharmacokinetic Parameters of Fenofibric Acid

Study Drugs	Analyte	Point Estimate [§] (90% Confidence Interval)		Study
		C _{max}	AUC	
ABT-335 and Rosuvastatin	Fenofibric acid	0.978 (0.915 – 1.046)	0.982 (0.927 – 1.041)	Study M06-811
Fenofibrate and Atorvastatin	Fenofibric acid	0.960 (0.91 – 1.02)	0.977 (0.92 – 1.04)	K178P0201KH (Fournier, K178P0201KH)
Fenofibrate and Pravastatin	Fenofibric acid	0.975 (0.878 – 1.086) ⁻	0.994 (0.931 – 1.060) ⁺	M98-898 (R&D/98/595)
Fenofibrate and Fluvastatin	Fenofibric acid	0.896 (0.831 – 0.966)	0.982 (0.931 – 1.036)	M02-525 (R&D/04/062)
Fenofibrate and Simvastatin [*]	Fenofibric acid	0.89 (0.77 – 1.02)	0.95 (0.88 – 1.04)	Bergman, et al., 2004 (Bergman AJ, 2004)

§ Point estimates (90% confidence interval) comparing the central values of fenofibric acid pharmacokinetic parameters after the co-administration with statins to that after ABT-335 or fenofibrate administered alone.

+ 95% confidence interval.

* Data presented as geometric mean ratios (90% confidence interval).

Figure 15 Effect of fenofibric acid co-administration on mean peak and total exposures of statins.

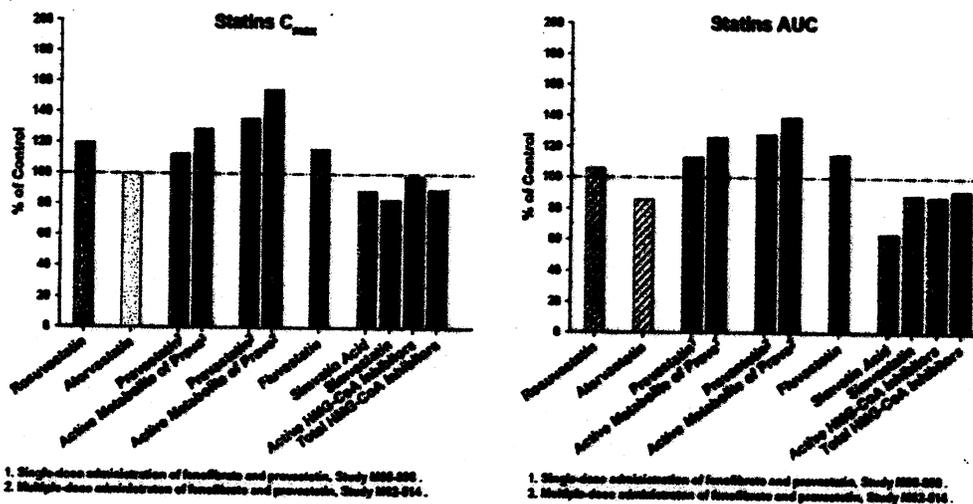


Table 20 Effects of Fenofibric Acid on Pharmacokinetic Parameters of Statins

Study Drugs	Analyte(s)	Point Estimate ^S (90% Confidence Interval)		Study
		C _{max}	AUC	
ABT-335 and Rosuvastatin	Rosuvastatin	1.196 (1.119 – 1.278)	1.058 (0.998 – 1.121)	Study M06-811
Fenofibrate and Atorvastatin	Atorvastatin	1.000 (0.85 – 1.18)	0.830 (0.74 – 0.93)	K178P0201KH (Fournier, K178P0201KH)
Fenofibrate and Pravastatin	Pravastatin	1.130 (0.854 – 1.496)*	1.129 (0.912 – 1.397)*	M06-898 (R&D/98/595)
	3 α -Hydroxyl-iso-pravastatin	1.291 (1.033 – 1.613)*	1.264 (1.019 – 1.568)*	
	Pravastatin	1.360 (1.108 – 1.670)	1.277 (1.092 – 1.493)	M02-514 (R&D/03/207)
	3 α -Hydroxyl-iso-pravastatin	1.546 (1.290 – 1.853)	1.389 (1.193 – 1.613)	
Fenofibrate and Fluvastatin	(+)-3R, 5S-Fluvastatin	1.160 (0.974 – 1.378)	1.150 (1.052 – 1.248)	M02-525 (R&D/04/062)
Fenofibrate and Simvastatin	Simvastatin Acid	0.89 (0.79 – 1.02)	0.64 (0.58 – 0.70)	Bergman, et al., 2004
	Simvastatin	0.83 (0.64 – 1.08)	0.89 (0.78 – 1.01)	(Bergman AJ, 2004)
	Active HMG-CoA Inhibitors	0.99 (0.86 – 1.14)	0.88 (0.80 – 0.95)	
	Total HMG-CoA Inhibitors	0.90 (0.72 – 1.11)	0.92 (0.82 – 1.03)	

^S Point estimates (90% confidence interval) comparing the central values of fenofibric acid pharmacokinetic parameters after the co-administration with statins to that after ABT-335 or fenofibrate administered alone.

• Data presented as geometric mean ratios (90% confidence interval).

- Concomitant administration of fenofibrate with atorvastatin (20 mg) once daily for 10 days resulted in a decrease of approximately 17% (range from 67% decrease to 44% increase) in atorvastatin AUC. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid was not significantly affected by concomitantly administered atorvastatin.
- Concomitant administration of fenofibrate and pravastatin (40 mg) had little or no effect on the pharmacokinetics of fenofibric acid or pravastatin. While the C_{max} and AUC_{0-∞} least square mean values for 3 α -hydroxy-iso-pravastatin were statistically significantly increased, the modest increase (less than 30%) in the formation of this metabolite was not expected to be clinically important. The 3 α -hydroxy-iso-pravastatin metabolite has 2.5 to 10% of the HMG-CoA reductase activity of parent pravastatin.
- The second study evaluated the effects of fenofibrate (160 mg tablet) on the pharmacokinetics of pravastatin and its metabolite, 3 α -hydroxy-iso-pravastatin after multiple doses of pravastatin (40 mg QD). The C_{max} and AUC₂₄ for pravastatin and 3 α -hydroxy-iso-pravastatin on Study Day 15 (pravastatin + fenofibrate) were compared to those on Study Day 5 (pravastatin alone). Concomitant administration of fenofibrate increased the mean C_{max} and AUC values for pravastatin by 36% (range from a 69% decrease to a 321% increase) and 28% (range from a 54% decrease to a 128% increase),

respectively, and for 3 α -hydroxy-isopravastatin by 55% (range from a 32% decrease to a 314% increase) and 39% (range from a 24% decrease to a 261% increase).

- Co-administration of a single-dose fenofibrate had minimal on the pharmacokinetics of the active enantiomer of fluvastatin, (+)-3R,5S-fluvastatin. (+)-3R,5S-fluvastatin exposure was increased 15 to 16%, on average upon co-administration. Co-administration of a single 40 mg dose of fluvastatin had no significant effect on fenofibric acid pharmacokinetics.
- A published study evaluated the potential pharmacokinetic interactions after multiple-dose administration of fenofibrate (160 mg tablet) and simvastatin 80 mg once daily in 12 healthy subjects (9 males and 3 females). The steady-state pharmacokinetic parameters for active and total HMG-CoA reductase inhibitors, simvastatin acid, and simvastatin were determined following simvastatin administration with and without fenofibrate. Also, fenofibric acid steady-state pharmacokinetics was evaluated with and without simvastatin. Co-administration of fenofibrate had no significant effect on the exposure of active or total HMG-CoA reductase inhibitors. Fenofibric acid pharmacokinetics was not affected significantly by simvastatin co-administration.

Cholesterol Absorption Inhibitor – Ezetimibe

A Phase 1, open-label, multiple-dose, three-period randomized crossover study was conducted to evaluate the potential pharmacokinetic interaction between fenofibrate (145 mg tablet) and ezetimibe. Eighteen healthy subjects (12 males and 6 females) received fenofibrate 145 mg alone for 10 days, ezetimibe 10 mg alone for 10 days, and the combination of the two study drugs for 10 days. All the doses were administered under non-fasting conditions. A washout interval of at least 14 days separated the last dose of a period from the first dose of any subsequent period.

Concomitant administration of fenofibrate resulted in increases in total ezetimibe AUC, C_{max} and C_{min} of approximately 43%, 33% and 56%, respectively, and increases in ezetimibe glucuronide AUC, C_{max} and C_{min} of approximately 49%, 34% and 62%, respectively. The pharmacokinetics of fenofibric acid was not significantly affected by ezetimibe and the multiple-dose pharmacokinetics of free (unconjugated) ezetimibe was not significantly affected by fenofibrate.

Antihyperglycemic Agents

Three studies evaluated the pharmacokinetic interactions between fenofibrate and glimepiride, metformin and rosiglitazone, respectively.

- Co-administration of fenofibrate resulted in a modest increase in the mean AUC of glimepiride of 35%. The glimepiride C_{max} was not significantly affected by fenofibrate co-administration. The increase in overall exposure of glimepiride was not associated with an increased occurrence of hypoglycemia based on scheduled monitoring of blood glucose levels. Glimepiride had no significant effect on the pharmacokinetics of fenofibric acid.
- Concomitant administration of fenofibrate 54 mg and metformin 850 mg TID for 10 days resulted in no significant changes in the pharmacokinetics of fenofibric acid or metformin when compared with fenofibrate and metformin administered alone.
- Multiple-dose pharmacokinetic interaction between fenofibrate and rosiglitazone in 25 healthy male subjects showed that concomitant administration of fenofibrate with

rosiglitazone, resulted in no significant changes in the pharmacokinetics of fenofibric acid or rosiglitazone when compared with the two drugs administered alone in healthy subjects.

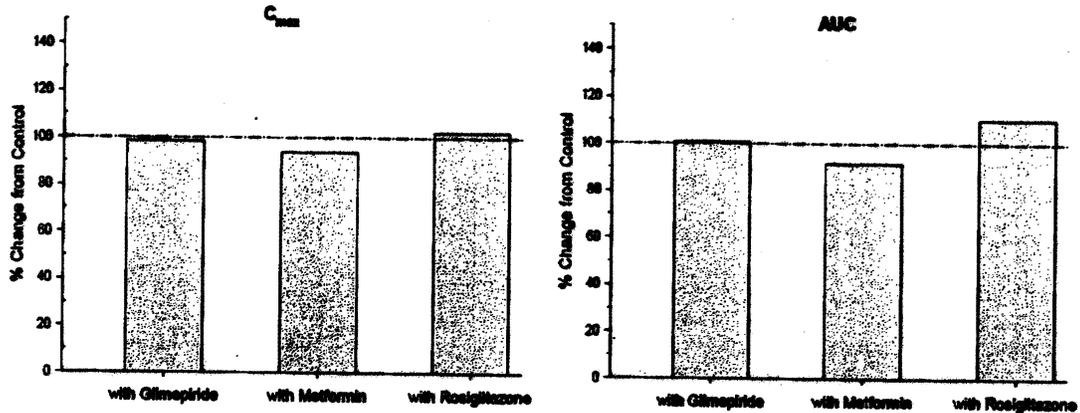


Figure 16 Effects of Antihyperglycemic Agents on the Pharmacokinetics of Fenofibric Acid.

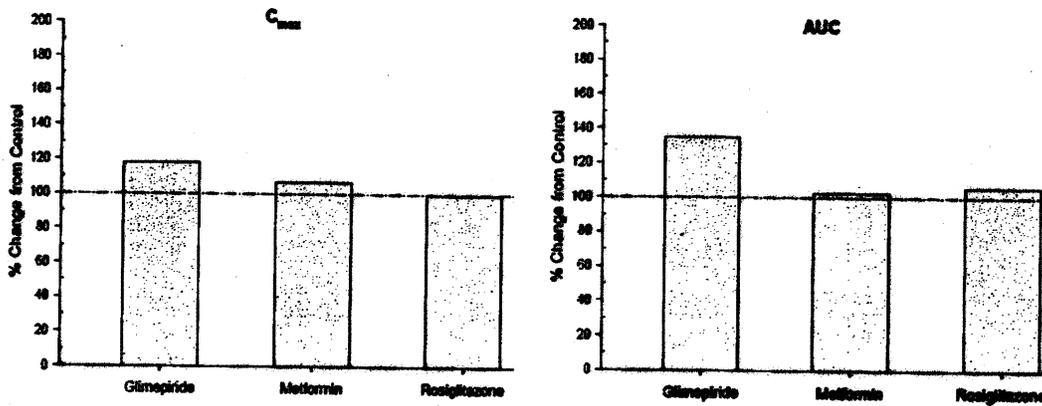


Figure 17 Effects of Fenofibrate on the Pharmacokinetics of Co-administered Anti-hyperglycemic Agents.

Omeprazole

Study M06-804 was a Phase 1, open-label, three-period, randomized, crossover study evaluating the effects of omeprazole on the absorption of fenofibric acid from the ABT-335 formulation administered under fasting conditions and after a high-fat meal. Thirty-six healthy subjects (23 males and 13 females) were enrolled and were to receive three regimens as follows: a single dose of ABT-335 equivalent to 135 mg fenofibric acid alone under fasting conditions; omeprazole 40 mg once daily under fasting conditions for 5 days with a single dose of ABT-335 on Study Day 5 under fasting conditions; omeprazole 40 mg once daily under fasting conditions for 5 days with a

single dose of ABT-335 on Study Day 5 after a high-fat meal. The dosing times of ABT-335 in the two combination regimens were kept similar relative to the dosing of omeprazole on Study Day 5. Administered with or without a meal, the co-administration of the ABT-335 formulation with omeprazole had no significant effect on fenofibric acid pharmacokinetics.

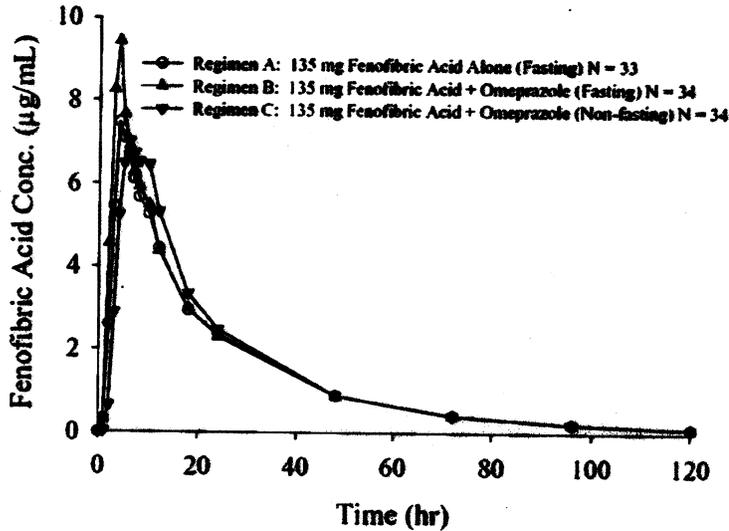


Figure 18 Effects of Omeprazole on the Pharmacokinetics of Fenofibrate.

Table 21 Effects of Omeprazole on Pharmacokinetic Parameters of Fenofibric Acid

Regimens [§] Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate [†]	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.

2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response)?

There was no systemic exposure-response data available under current submission. Phase 3 efficacy studies involving combination therapy utilized combination therapy of 135 mg ABT-335 with low and moderate dose statin. The effect of addition of 135 mg ABT-335 on the primary efficacy measurements (HDL-C, TG and LDL-C) was evaluated. The mean percent change from baseline to the final value in HDL-C, TG, and LDL-C based on the controlled studies analysis set and based on all randomized subjects is presented in Tables 22 and 23, respectively below:

Table 22 Mean percent change from baseline to the final value in HDL-C, TG, and LDL-C (Controlled Studies Analysis Set)

	ABT-335 + Low-dose statin				ABT-335 + Moderate-dose statin			High-dose statin (N=245)
	ABT-335 (N=490)	Low-dose statin (N=493)	Low-dose statin (N=490)	p-value	Moderate- dose statin (N=491)	Moderate- dose statin (N=490)	p-value	
HDL-C	(N=420)	(N=455)	(N=423)		(N=430)	(N=422)		(N=217)
BL mean	38.4	38.4	38.2		38.4	38.1		38.0
Final mean	44.3	40.7	44.8		41.1	44.3		40.6
Mean % Δ	16.3%	7.4%	18.1%	< 0.001 ^a	8.7%	17.5%	< 0.001 ^a	7.9%
TG	(N=459)	(N=477)	(N=470)		(N=472)	(N=462)		(N=235)
BL mean	280.7	286.1	282.1		287.9	286.1		282.5
Final mean	177.3	217.6	146.7		202.5	147.5		186.1
Mean % Δ	-31.0%	-16.8%	-43.9%	< 0.001 ^a	-23.7%	-42.0%	< 0.001 ^a	-28.1%
LDL-C	(N=427)	(N=463)	(N=436)		(N=439)	(N=434)		(N=225)
BL mean	158.4	153.8	155.7		158.0	156.4		156.1
Final mean	146.1	100.6	101.9		91.6	99.1		81.7
Mean % Δ	-5.1%	-33.9%	-33.1%	< 0.001 ^b	-40.6%	-34.6%	< 0.001 ^b	-47.1%

a. ABT-335 in combination with statin vs. corresponding statin monotherapy

b. ABT-335 in combination with statin vs. ABT-335 monotherapy

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Table 23 Mean percent change from baseline to the final value in HDL-C, TG, and LDL-C Worst-Case Analysis (Controlled Studies Analysis Set-All Randomized Subjects)

Treatment Group	N	HDL-C (mg/dL)			p-value
		BL Mean	Final Mean	Mean % Δ	
Low-dose statin	499	38.4	41.5	9.2%	
ABT-335 + low-dose statin	491	38.4	44.3	16.0%	< 0.001 ^a
Moderate-dose statin	495	38.3	41.8	10.4%	
ABT-335 + moderate-dose statin	491	38.4	44.3	16.8%	< 0.001 ^a
TG (mg/dL)					
Low-dose statin	499	283.6	206.1	-21.1%	
ABT-335 + low-dose statin	491	281.0	158.5	-40.8%	< 0.001 ^a
Moderate-dose statin	495	289.6	198.3	-26.1%	
ABT-335 + moderate-dose statin	491	288.5	156.1	-40.7%	< 0.001 ^a
LDL-C (mg/dL)					
ABT-335	492	158.6	138.2	-10.7%	
ABT-335 + low-dose statin	491	153.9	111.0	-27.7%	< 0.001 ^b
ABT-335	492	158.6	137.8	-11.0	
ABT-335 + moderate-dose statin	491	156.5	108.6	-29.1	< 0.001 ^b

Note: P-value from an ANCOVA with corresponding baseline lipid value as the covariate, and with effects for treatment group, diabetic status, screening TG level and interaction of diabetic status by screening TG level.

- a. ABT-335 in combination with statin vs. corresponding statin monotherapy
- b. ABT-335 in combination with statin vs. ABT-335 monotherapy

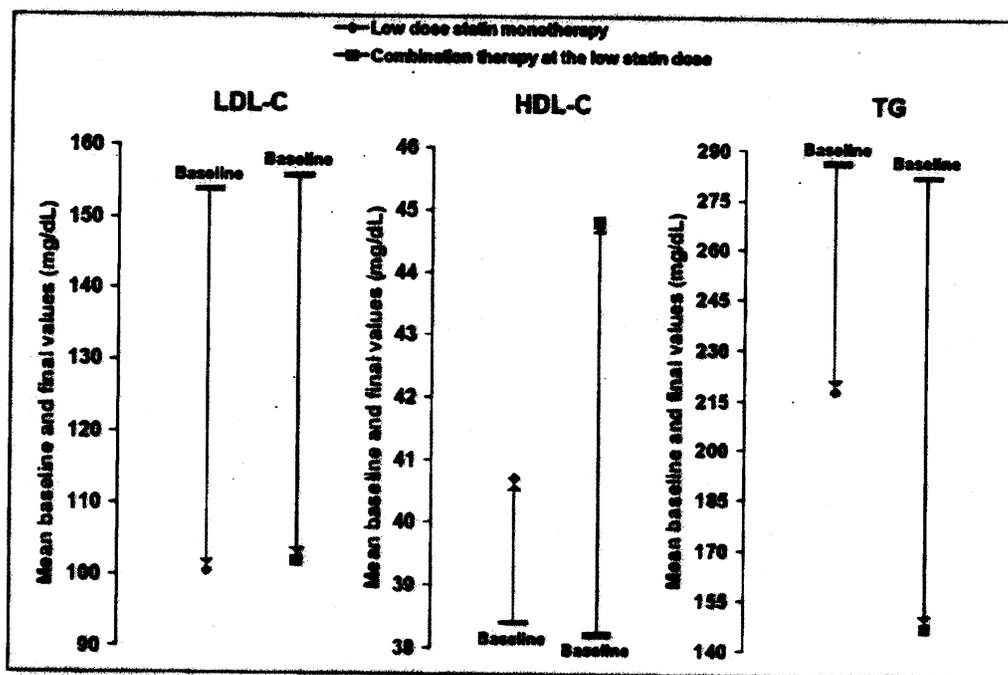


Figure 19 Mean Baseline and Final Values for HDL-C, TG, and LDL-C with ABT-335 in Combination with Low-Dose Statins and Low-Dose Statin Monotherapy

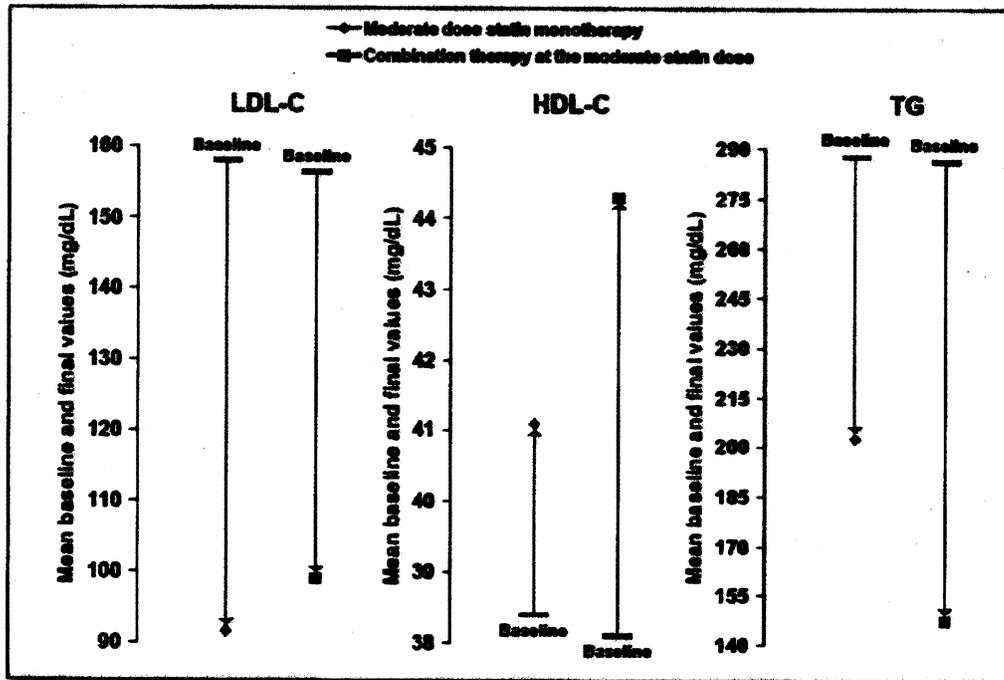


Figure 20 Mean Baseline and Final Values for HDL-C, TG, and LDL-C with ABT-335 in Combination with Moderate-Dose Statins and Moderate-Dose Statin Monotherapy

- The difference in mean percent change from baseline in HDL-C and TGs was statistically significant between combination therapies versus statin monotherapy; however, low and moderate doses of statins in combination with ABT-335 did not differ from each other in their effect on HDL-C and TG.
- Mean percent change from baseline in LDL was significantly greater in combination arm versus ABT-335 monotherapy arm; however, low and moderate doses of statins in combination with ABT-335 did not appear to differ from each other in their effect on LDL-C.

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2.6 General Biopharmaceutics

2.6.1 What is absolute bioavailability and absorption behavior of fenofibric acid and how does it relate to development of ABT-335 formulation?

Comparison of absolute and relative bioavailability of both fenofibrate and fenofibric acid formulations following oral dose or delivery at different sites of the gastro-intestinal tract was evaluated in an exploratory Phase 1 clinical study. Both fenofibrate and fenofibric acid were administered as NanoCrystal dispersion (NCD) suspensions

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145 mg fenofibrate NCD suspension or 130 mg fenofibric acid NCD suspension were delivered to the ascending colon, distal small bowel, proximal small bowel or to the stomach in first Phase of the study. Phase two of this study was open, randomized, 2-way crossover design with fenofibrate tablet and fenofibric acid as IV infusion, where 50 mg of fenofibric acid as 10 mL sterile phosphate buffer pH 7.2 solution was administered at 5 mg/mL over 10-minute IV infusion. The primary endpoint was the comparison of the absolute bioavailability between fenofibrate and fenofibric acid NCD suspensions at each GI tract site.

On average, absolute bioavailability of fenofibrate NCD suspension was approximately 22% at colon, 66% at distal small bowel, 73% at proximal small bowel and 69% at stomach; absolute bioavailability of fenofibric acid NCD suspension was approximately 78% at colon, 84% at distal small bowel, 88% at proximal small bowel and 81% at stomach. For fenofibric acid, the analysis did not show any significant difference between GI tract sites. The results on the fenofibric acid molecule thus show it has good absorption characteristics throughout the GI tract from the stomach to the colon. The C_{max} values were lower in the colon (see Fig. 21), but not so low as to impact the bioavailability from this absorption site (as shown in the table below).

Table 24 Absolute bioavailability (%) of 130 mg fenofibric acid at each GI site

FA 130 mg NCD	F (colon)	F (distal)	F (proximal)	F (stomach)
N	7	5	6	7
Mean \pm SD	78.9 \pm 11.0	86.0 \pm 10.3	90.5 \pm 10.8	78.1 \pm 8.1
(CV%)	(14 %)	(12 %)	(12 %)	(10 %)

FA=fenofibric acid

F=Bioavailability

In comparison to the fenofibrate data, the higher C_{max} values, more rapid T_{max} values and higher bioavailability results for the fenofibric acid molecule at all regions of the GI tract showed that fenofibric acid presented improved absorption characteristics over the fenofibrate molecule.

This evaluation provided the information that the development of immediate release and modified release formulations of fenofibric acid were both plausible. However, to develop a formulation bioequivalent to the 145 mg fenofibrate tablet (Sponsor did not mention 200 mg micronized fenofibrate as reference here), the release characteristics of the formulation were needed to be slowed down in order to match the slower absorption properties of fenofibrate in the GI tract.

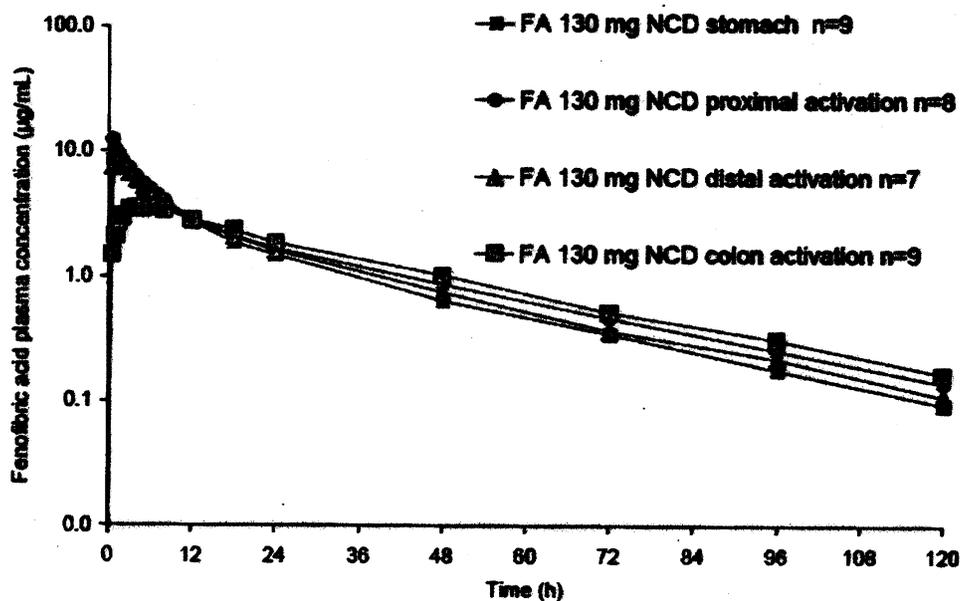


Figure 21 Mean plasma fenofibric acid profiles after 130 mg fenofibric acid NCD at colon, distal small bowel, proximal small bowel and stomach on semi-logarithmic scale

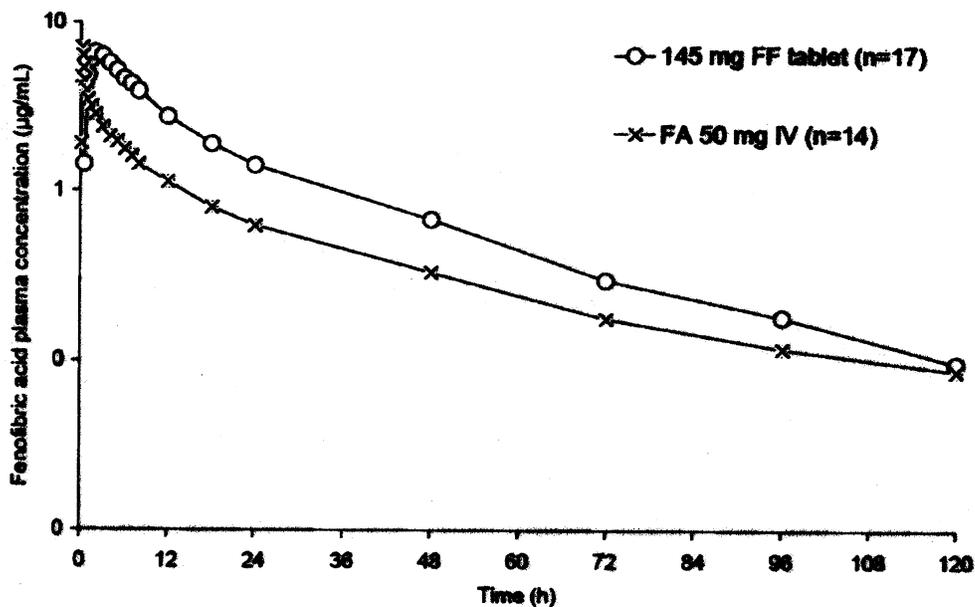


Figure 22 Mean plasma fenofibric acid profiles after 50 mg fenofibric acid 10-minute IV infusion and 145 mg fenofibrate tablet on semi-logarithmic scale

2.6.2 Is bioequivalence established between the to-be-marketed formulation and the Phase 3 trial formulation?

The bioequivalence between the to-be-marketed and the Phase 3 trial formulations was established in the definitive bioequivalence study (Study M06-830). The study was designed to evaluate the bioavailability of fenofibric acid from the to-be-marketed ABT-335 formulation manufactured at full production scale at the Abbott Puerto Rico facility relative to the bioavailability of the ABT-335 Phase 3 formulation manufactured at the Abbott Park facility, and the 200 mg micronized fenofibrate capsule.

This was a Phase 1, single-dose, open-label, three-period, randomized, crossover design study. Sixty-six (66) healthy adult male and female subjects were selected to participate in the study and 65 subjects received study drug. The study was carried out in two cohorts of subjects, with 30 subjects in Cohort 1 and 35 subjects in Cohort 2. The subjects in each cohort were randomly assigned in equal numbers to six sequences of Regimens A, B and C. Regimen A was the to-be-marketed formulation manufactured in Puerto Rico administered under fasting conditions (test); Regimen B was the Phase 3 formulation administered under fasting conditions (reference); and Regimen C was the 200 mg micronized fenofibrate capsule administered following a low-fat breakfast (reference).

Study drug was administered in the morning on Study Day 1 of each period with approximately 240 mL of water. Regimens A and B were administered after a fast of approximately 10 hours and 4 hours before lunch. Subjects who received Regimen C were served a low-fat breakfast 30 minutes prior to dosing. Washout intervals of 14 days separated the doses of any two consecutive periods. Blood samples were collected for 120 hours after dosing. Plasma concentrations of fenofibric acid were determined using a validated LC-MS/MS method. Six-three (63) subjects completed all three periods of the study. Pharmacokinetic parameters including C_{max} , T_{max} , λ_z , $t_{1/2}$, AUC_{0-4} , $AUC_{0-\infty}$ were determined using noncompartmental methods. The CL/F was determined for ABT-335 regimens only. Log-transformed C_{max} and AUC values were statistically analyzed via ANOVA and the two-one sided test procedure.

The summary of bioequivalence assessment using pharmacokinetic parameters of fenofibric acid after administration of each of the three regimens is presented in Table 25.

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Table 25 Results of bioequivalence analysis (Study M06-830)

Regimens [£] 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 – 1.088
	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

* Antilogarithm of the least squares means for logarithms.

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

£ 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.

Based on the statistical analysis

- 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 also bioequivalent to the 200 mg micronized fenofibrate capsule with regard to both the C_{max} and AUC of fenofibric acid.

This pivotal bioequivalence study (Study M06-830) was audited by the Division of Scientific Investigation (DSI), and based on their review the clinical study and bioanalytical study were acceptable. Please see the memo by Dr. Jacqueline O'Shaughnessy dated 09/12/2008 for details.

2.6.3 What is the appropriate dissolution test condition and specification?

A dual stage method was used to test the drug release of the to-be-marketed ABT-335 formulation because the formulation contains enteric-coated mini-tablets. The test method used United States Pharmacopoeia (USP) Apparatus 2 rotating at 50 rpm with an initial 2 hour acid stage at pH 3.5 followed by a drug release stage at pH 6.8. The general parameters of the drug release method are presented in Table below.

Table 26 The proposed dissolution test conditions.

Parameter	Condition
Apparatus	USP Apparatus 2
Agitation	50 rpm
Medium	Two Stages: Acid stage: 500 mL of 0.05M sodium phosphate pH 3.5 ± 0.05 maintained at 37 ± 0.5°C for 2 hours; Buffer Stage: 400mL of 0.05M sodium phosphate concentrate added to the Acid Stage media for a total volume of 900 mL and a final pH 6.8 maintained at 37 ± 0.5°C.
Sampling Time Points*	2.5, 3, 3.5, 4, 5, 6, 8, 10 hours
Filter	35 micron polyethylene
Analytical Finish	HPLC analysis with UV detection at 286 nm

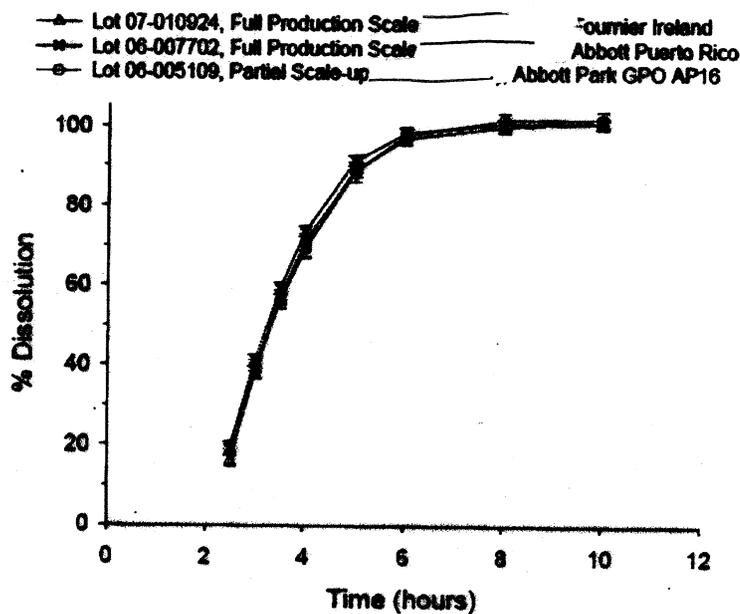
USP = United States Pharmacopeia

* The proposed compendial drug release method has sampling time-points at 2.5, 3.5 and 6 hours.

In vitro drug release test profiles for ABT-335 Formulation 10 lots manufactured at full production scale (approximately _____ batch size) at the Abbott Puerto Rico Limited plant and at the Fournier Pharma facility in Ireland, or at Abbott Park facility (approximately _____ batch size) for use in Phase 3 trials are presented in Figure below. These _____ lots were assessed in the definitive bioequivalence Study M06-830 (Lot 06-007702 and Lot 06-005109), Study M06-831 (Lot 06-007702) and Study M06-886 (Lot 06-007702 and Lot 07-010924).

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Drug Release Profiles for ABT-335 Formulation 10



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Figure 23 Drug Release profile for ABT-335 Formulations Mean ± SD (N = 12).

2.6.4 Has dosage form equivalence been established among the tablet strengths?

Two ABT-335 capsule strengths were developed containing ABT-335 equivalent to 135 mg and 45 mg fenofibric acid. The only difference between the 135 mg and 45 mg strengths is that the 135 mg capsule strength contains mini-tablets, whereas the 45 mg capsule strength contains mini-tablets. The to-be-marketed 135 mg strength has been tested in the definitive bioequivalence study (Study M06-830).

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Based on the data presented in the reports, the composition of the mini-tablets seemed identical for the two strengths. To demonstrate dissolution similarity, thirty-six 45 mg and 135 mg capsules from three batches with 12 capsules per batch were tested using the drug release method described above under response to Question 3. The three batches for 45 mg and 135 mg capsules were Lots 06-007370, 06-007371 and 06-007372, and Lots 06-005108, 06-005109 and 06-005111, respectively (Please refer to CMC's review for details on the acceptability of this data).

Mean \pm SD percent of drug release versus time profiles for the two capsule strengths are illustrated in Figure 24 below.

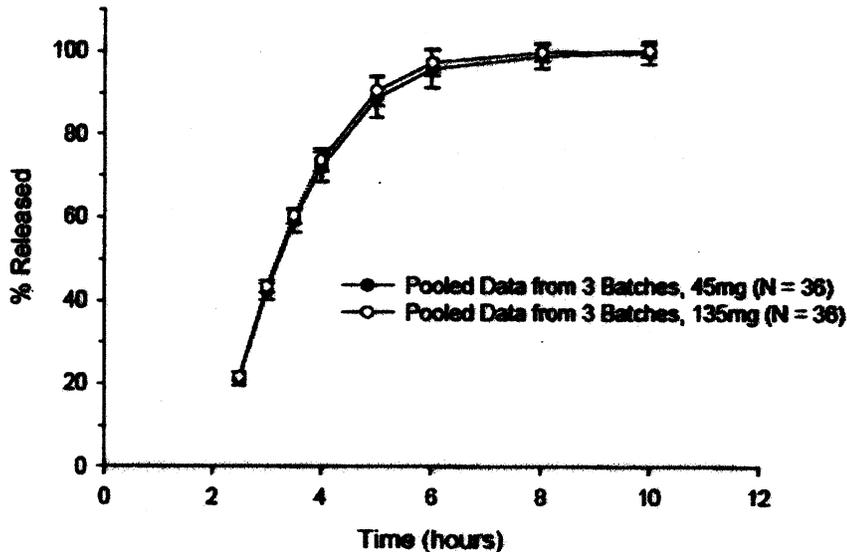


Figure 24 Mean \pm SD percent of drug release versus time profiles for the two capsule strengths

An f_2 test using drug release data up to 5 hours (approximately 90% release) was performed to compare the profiles for the two strengths. The f_2 value was 88.6 indicating similar in vitro drug release profiles for the two strengths.

The sponsor, however, has not done any study of which the objective is to establish dosage form equivalence between 45 mg and 135 mg strengths of ABT-335 formulation. To support the dosage form equivalence sponsor has relied on compositional similarity, dissolution similarity and referred to the results of the clinical pharmacology studies conducted with fenofibrate doses and their equivalence to subsequently developed products.

Based on the historical BE demonstrations;

- (i) between original dosage form of fenofibrate; non-micronized 100 mg hard gelatin capsule (NDA 19-304) and micronized capsule formulations containing 67 mg fenofibrate (NDA 19-304/S005)
- (ii) between three capsules containing 67 mg micronized fenofibrate and a single 200 mg micronized capsule
- (iii) between 54 mg or 160 mg of micronized fenofibrate tablet (NDA 21-203) and 67 and 200 mg capsules, respectively,
- (iv) and between most recent 3 x 48 mg or 145 mg of NanoCrystal fenofibrate tablet (NDA 21-656) and one 200 mg micronized capsule (also see Table 1 section 2.1),

the sponsor presented the argument that "Fenofibric acid is the only pharmacologically active moiety circulating in plasma following administration of either ABT-335 or fenofibrate. In Study M06-830, the 200 mg fenofibrate capsule was shown to be bioequivalent to the to-be-marketed ABT-335 formulation of dose equivalent to 135 mg fenofibric acid. A fenofibrate dose of 300 mg as non-micronized capsules is equivalent to the 200 mg micronized fenofibrate capsule or the currently marketed 145 mg TriCor tablet. Thus, the observed dose-proportionality over the fenofibrate dose range of 100 to 300 mg as non-micronized capsules also demonstrates the dose-proportionality over the fenofibric acid dose range of 45 to 135 mg"

The argument for demonstration of dose proportionality in fenofibric acid pharmacokinetics is not convincing due to the following limitations:

- The sponsors have not presented data based on a statistical analysis demonstrating dose-proportionality across 100-300 mg non-micronized fenofibrate given under non-fasting condition. Empirically, the figure presented by sponsor (Fig. 25) does indicate linearity in C_{max} and $AUC_{0-\infty}$. However, upon dose normalization both mean $AUC_{0-\infty}$ and C_{max} (Fig. 26) indicate less than dose proportional increase.
- Translation of the dose-proportionality across 100-300 mg non-micronized fenofibrate to 45-135 mg choline fenofibrate is strictly based on the demonstration of bioequivalence between 100 mg non-micronized fenofibrate, 67 mg of micronized fenofibrate and proposed 45 mg fenofibric acid choline salt formulations, and/or on the demonstration of bioequivalence between 300 mg non-micronized fenofibrate, 200 mg of micronized fenofibrate, 145 mg TriCor™ Tablet and proposed 135 mg fenofibric acid choline salt formulations under fasted conditions. No data is presented that demonstrates equivalence of 300 mg non-micronized dose and 200 mg micronized fenofibrate to support the argument "A fenofibrate dose of 300 mg as non-micronized capsules is equivalent to the 200 mg micronized fenofibrate capsule or the currently marketed 145 mg TriCor™ tablet".
- Historically, during each subsequent modification in fenofibrate formulation, the approval of low and high strengths have been supported by BE evaluation of both strengths and sponsor could have followed the same approach for the current application.

Table 27 Mean \pm SD Pharmacokinetic Parameters of Fenofibric Acid After Single Oral Doses of Non-micronized Fenofibrate

Pharmacokinetic Parameters (units)	Fenofibrate Dose (mg) ^g			
	100 (N = 12)	200 (N = 12)	300* (N = 12)	500 (N = 12)
T _{max} (h)	4.8 \pm 0.8	5.2 \pm 1.2	5.2 \pm 1.4	4.5 \pm 1.2
C _{max} (μ g/mL)	4.80 \pm 9.12	8.64 \pm 2.41	12.70 \pm 3.37	15.04 \pm 3.48
AUC ₀₋₉₆ [†] (μ g·h/mL)	90.0 \pm 46.0	148.1 \pm 92.4	192.4 \pm 74.0	208.8 \pm 65.3
AUC _∞ (μ g·h/mL)	97.6 \pm 54.0	160.0 \pm 109.4	221.2 \pm 69.4	228.0 \pm 80.9
t _{1/2} [‡] (h)	20.8 \pm 5.9	22.5 \pm 4.6	21.0 \pm 5.2	23.6 \pm 7.5
Urine excretion as free+conjugated FA (% of dose)	27.6 \pm 12.5	15.9 \pm 3.5	17.6 \pm 8.6	10.9 \pm 5.0
Urine excretion as free+conjugated benzhydrol metabolite (% of dose)	3.9 \pm 1.1	1.9 \pm 0.6	1.9 \pm 0.8	1.7 \pm 0.7

FA = fenofibric acid.

^g Administered as 100 mg capsules under non-fasting conditions.

* Equivalent to 200 mg fenofibrate as the micronized capsule or 145 mg as the currently marketed TriCor tablet. In Study M06-830, the 200 mg micronized fenofibrate capsule was shown to be bioequivalent to the to-be-marketed ABT-335 formulation of 135 mg of fenofibric acid equivalent.

[†] AUC from 0 to 96 hours post-dose.

[‡] Harmonic mean \pm pseudo standard deviation.

Cross Reference: [Formier, FR/001/84/001](#).

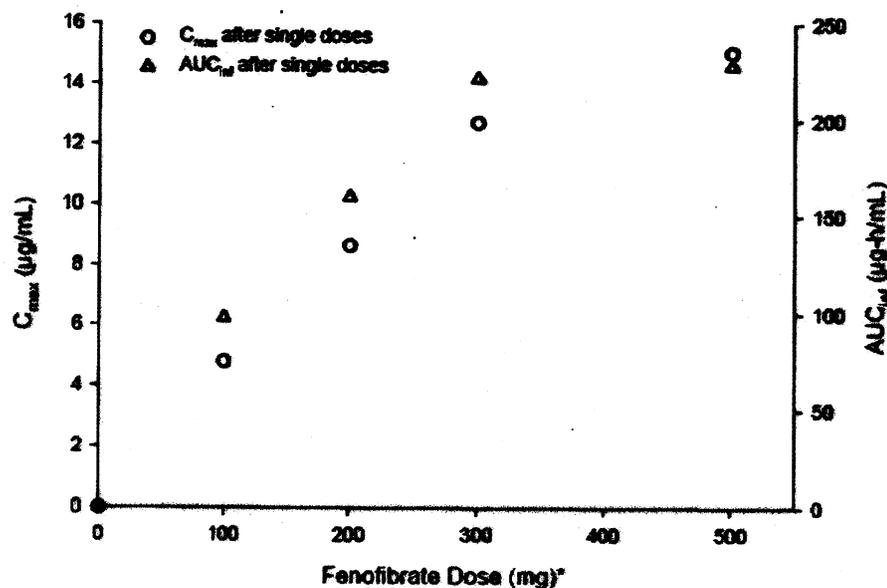


Figure 25 Mean C_{max} and AUC_∞ versus dose for non-micronized fenofibrate

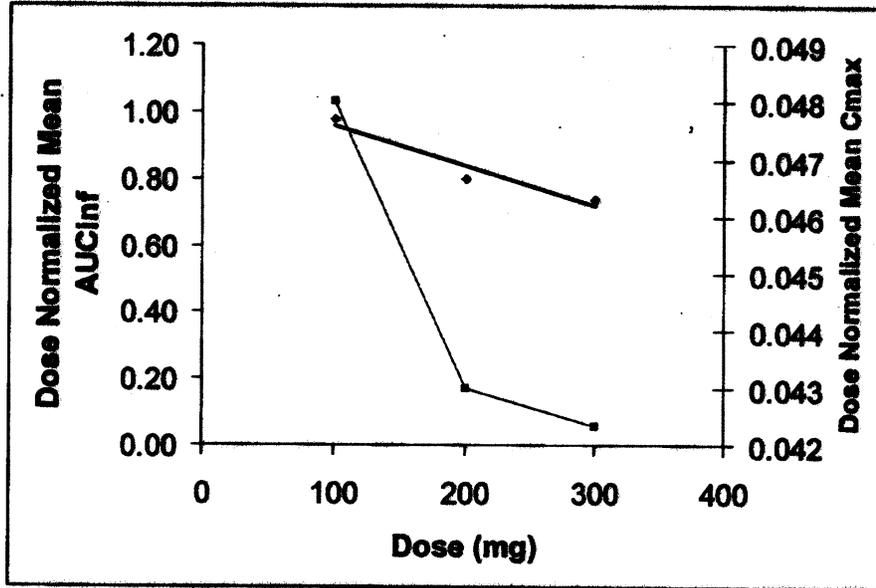


Figure 26 Dose normalized mean AUCinf and Cmax versus dose for non-micronized fenofibrate

2.6.5 Can we consider that different manufacturing sites and scale-up will produce equivalent tablets?

The definitive bioequivalence study (Study M06-830) as described in section 2.6.2 above compared the fenofibric acid bioavailability from ABT-335 Formulation 10 capsules manufactured at full production scale at the Abbott Puerto Rico Limited plant (to-be-marketed) to that from the Formulation 10 capsules manufactured at the Abbott Park facility and used in Phase 3 clinical trials.

Study M06-886 compared fenofibric acid bioavailability from the to-be-marketed formulation manufactured at the Fournier Pharma facility in Ireland to that from the Formulation 10 capsules manufactured at the Abbott Puerto Rico Limited Manufacturing Facility. This was a Phase 1, single-dose, open-label two-period, randomized, crossover design study. Forty-two healthy adult male and female subjects were enrolled in the study and were randomly assigned in equal numbers to two sequences of Regimens A and B. Regimen A was the Fournier product (test), and Regimen B was the Abbott Puerto Rico product (reference). Study drug was administered on Study Day 1 of each study period with approximately 240 mL of water after a fast of approximately 10 hours and 4 hours before lunch. A washout interval of 14 days separated the doses of the two study periods.

Blood samples were collected for 120 hours after each dosing. Plasma concentrations of fenofibric acid were determined using a validated LC-MS/MS method. Pharmacokinetic parameters including C_{max} , T_{max} , λ_z , $t_{1/2}$, AUC_{0-6} , $AUC_{0-\infty}$ and CL/F were determined using noncompartmental methods. Log-transformed C_{max} , AUC_{0-6} , and $AUC_{0-\infty}$ values were statistically analyzed via ANOVA and the two-one sided test procedure. The to-be-marketed ABT-335

formulation manufactured at Fournier Ireland is bioequivalent to that manufactured at Abbott Puerto Rico with respect to fenofibric acid C_{max} and AUC because the 90% confidence intervals for comparing the C_{max} and AUC between the two regimens were contained within the 0.80 to 1.25 range.

Table 28 Results of bioequivalence analysis (M06-886)

Regimens [‡] Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate [†]	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
	$AUC_{0-\infty}$	167.612	171.757	0.976	0.943 – 1.010

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

* Antilogarithm of the least squares means for logarithms.

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

The two studies demonstrated that ABT-335 Formulation 10 capsules manufactured at different sites and/or batch sizes were bioequivalent with respect to both the C_{max} and AUC of fenofibric acid because the 90% confidence intervals comparing the least square mean values of C_{max} and AUC between regimens were within the 0.80 to 1.25 range.

Table 29 Mean ± SD Pharmacokinetic Parameters of Fenofibric Acid After Single Oral Doses of Non-micronized Fenofibrate

Study	Manufacturing Site	Production Scale	N*	Pharmacokinetic Parameter	Relative Bioavailability	
					Point Estimate	90% Confidence Interval
M06-830	Abbott Puerto Rico Limited	Plant vs. Abbott, Abbott Park, IL (GPO AP16)	63	C_{max}	1.031	0.977 – 1.088
				AUC_t	1.010	0.986 – 1.035
				$AUC_{0-\infty}$	1.013	0.989 – 1.039
M06-836	Fournier Pharma facility in Ireland vs. Abbott Puerto Rico Limited		41	C_{max}	0.960	0.911 – 1.013
				AUC_t	0.971	0.938 – 1.005
				$AUC_{0-\infty}$	0.976	0.943 – 1.010

* Number of subjects included in pharmacokinetic analyses.

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2.7 Analytical

2.7.1 Is the analytical methods appropriately validated?

A liquid/liquid extraction HPLC method with tandem mass spectrometric detection (LC-MS/MS) was used to determine plasma concentrations of fenofibric acid for the pharmacokinetic studies. The analytical method was developed and validated at Abbott for the quantitative determination of fenofibric acid in plasma under the applicable guidance's and regulations. In brief, calibration standards, quality control (QC) standards, blank plasma, and unknown plasma samples (0.05 mL) were mixed with internal standar

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Quantitation was achieved by a mass spectrometric detector _____ using the electrospray ion source _____ and monitoring the precursor-to-product ion reaction channels: m/z 317 \rightarrow 231 for fenofibric acid and m/z 267 \rightarrow 195 for the internal standard _____. Analytes were ionized in the negative ion mode. The mass spectrometer was operated under MS/MS conditions and data were acquired in the multiple reaction-monitoring mode. The analyte/internal

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standard peak area ratios from the calibration standard samples were subjected to weighted linear least squares regression. The concentrations of fenofibric acid in unknown plasma samples were calculated by interpolation, using the regression parameters of the calibration curve.

Sensitivity

The lower limit of quantitation (LLOQ) using 0.05 mL plasma samples was 0.016 µg/mL (Note: summary report has a typographical error of concentration units as ng/mL) of fenofibric acid in plasma. The precision and accuracy of the assay at the LLOQ are summarized in Table below.

Table 30 Precision and Accuracy of Fenofibric Acid Plasma Concentration Assay at the LLOQ

Intra-Assay (N = 6)	
Mean Analytical Recovery (%)	%CV Range
103.8 – 109.9	5.6 - 5.9
Inter-Assay (N = 18)	
Mean Analytical Recovery (%)	%CV
103.8	5.9

Linearity

In plasma, the standard curves of peak area ratios (analyte/internal standard) versus concentrations of analyte were linear over the fenofibric acid concentration range of 0.016 to 5.486 µg/mL. Correlation coefficients were greater than 0.9966 during the method validation.

Precision and Accuracy

The precision and accuracy of the assay were measured from the average of four replicate measurements on each of three days. The precision and accuracy at four QC concentrations ranging from 0.044 to 4.552 µg/mL are summarized in Table below.

Table 31 Precision and Accuracy of Fenofibric Acid Plasma Concentration Assay at the QC

Intra-Assay (N = 6)	
Mean Analytical Recovery (%)	%CV Range
99.2 – 105.4	2.2 – 5.9
Inter-Assay (N = 18)	
Mean Analytical Recovery (%)	%CV Range
101.1 – 103.1	3.8 – 5.2

Stability

QC samples were stable for at least 44 hours at room temperature and at least seven freeze/thaw cycles. Frozen storage stability at approximately -20°C was established for at least 129 days.

Table 32 Summary of analytical methods used for the CPB studies

Matrix	Analyte	Extraction	Separation	Detection	Linear Range	LLOQ	Study	Report RAB Number
Plasma	Fenofibric acid	Liquid	HPLC	MS/MS	0.019-3.300 µg/mL	0.019 µg/mL	303-696	R&D/04/073
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.017-5.419 µg/mL	0.017 µg/mL	304-712	R&D/04/093
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.017-5.420 µg/mL	0.017 µg/mL	304-715	R&D/05/021
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.017-5.333 µg/mL	0.017 µg/mL	305-732	R&D/05/518
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.017-5.433 µg/mL	0.017 µg/mL	305-737	R&D/06/006
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.017-5.433 µg/mL	0.017 µg/mL	305-743	R&D/06/005
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.017-5.333 µg/mL	0.017 µg/mL	305-801	R&D/06/008
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.016-5.469 µg/mL	0.016 µg/mL	306-830	R&D/06/752
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.016-5.399 µg/mL	0.016 µg/mL	306-831	R&D/07/001
Plasma	Fenofibric acid	Solid	HPLC	MS/MS	0.017-5.340 µg/mL	0.017 µg/mL	306-896	R&D/07/311

All analyses were conducted by the Drug Analysis Department, Abbots, Abbots Park, E. 60064.

The results presented are acceptable to the current recommendation by the Agency.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

4.2 Individual Study Reviews

4.2.1 Initial Human PK and Tolerability Study (M02-513)

Title of Study: A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Ascending Single Oral Doses of Fenofibric Acid in Subjects in General Good Health

Study Site: Clinical Pharmacology, Abbott GmbH & Co KG, 67008 Ludwigshafen, Germany

Studied Period:

First Screening Procedure: 11 February 2003

Date First Subject Dosed: 24 February 2003

Date Last Subject Completed Dosing: 23 April 2003

Date of Last Study Procedure: 28 April 2003

Objective: The primary objective of this study was to evaluate the safety, tolerability, and pharmacokinetics of ascending single oral doses of fenofibric acid in healthy subjects. The effect of food on the 100 mg dose was also evaluated.

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

Blood samples were collected into 5 mL evacuated collection tubes containing potassium oxalate plus sodium fluoride prior to dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48, 72, 96, and 120 hours after dosing (Study Day 1) in each period. Additional blood samples were collected at 0.75 and 1.5 hours after dosing in Period 3. Sufficient blood was collected to provide approximately 2 mL plasma from each sample. Plasma concentrations of fenofibric acid were determined using a validated liquid chromatographic method with mass spectral detection at Abbott Laboratories, Abbott Park, IL. The lower limit of quantitation of fenofibric acid was 0.018 µg/mL using a 150 µL plasma sample. Samples were analyzed between the dates of 05 March 2003 and 12 May 2003.

Number of Subjects (Planned and Analyzed): Planned: 20; Entered: 20; Completed: 20; Evaluated for Safety: 20; Evaluated for Pharmacokinetics: 15. For the 20 subjects who participated in the study, the mean age was 38.5 years (ranging from 24 to 47 years), the mean weight was 77.3 kg (ranging from 55 to 95 kg) and the mean height was 175.0 cm (ranging from 164 to 187 cm). For the 15 subjects included in the pharmacokinetic analyses, the mean age was 38.9 years (ranging from 24 to 47 years), the mean weight was 78.5 kg (ranging from 55 to 95 kg) and the mean height was 176.1 cm (ranging from 165 to 187 cm).

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

	Fenofibric Acid Formulation	
	hard gelatin capsule	hard gelatin capsule
Dosage Form	hard gelatin capsule	hard gelatin capsule
Formulation	neat drug in capsule	neat drug in capsule
Strength (mg)	50	100
Bulk Product Lot Number	95-621-ZW-00	95-621-ZW-00
Lot Number(s)	02180HT	02181HT, 02182HT
Potency (% of Label Claim)	98.6	98.6
Manufacturing Site [†]	PARD-Pilot plant, LU	PARD-Pilot plant, LU
Manufacturing Date(s) [‡]	17 February 2003	17 March 2003, 10 April 2003
Retest Date [*]	31 December 2003	31 December 2003

[†] LU = Ludwigshafen, Germany.

[‡] Capsules were manufactured for each study period.

^{*} Reflects most current retest date.

Pharmacokinetic Assessment: The pharmacokinetic parameter values of fenofibric acid were estimated using noncompartmental methods. These included: the maximum observed 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 infinity (AUC_∞) and the apparent oral clearance (CL/F).

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

Statistical Methods:

Pharmacokinetic: To address the issue of dose proportionality and linearity of pharmacokinetics, paired t-tests were performed for dose-normalized C_{max}, dose-normalized AUC_∞, T_{max} and λ_z of the fasting regimens. For C_{max} and AUC_∞, point estimates and 95% confidence intervals were calculated for the ratio of the dose-normalized least square mean values in order to assess the degree of non-linearity. The point estimates were obtained by exponentiating the differences of mean logarithms, and the dose-normalized population least square mean value for each regimen was estimated by exponentiating the mean for the logarithm. The 95% confidence intervals were obtained by exponentiating the endpoints of the confidence intervals for the difference of mean logarithms.

To assess the effect of food on the pharmacokinetics of fenofibric acid, paired t-tests were performed for C_{max}, AUC_∞, T_{max} and λ_z of the 100 mg doses. The pharmacokinetic parameters for Period 3 were calculated both including and excluding the data from the 0.75 h and 1.5 h sampling times. The primary analysis of the food effect used the Period 3 pharmacokinetic parameters calculated excluding the 0.75 h and 1.5 h sampling time data.

The bioavailability of the nonfasting 100 mg fenofibric acid regimen relative to the fasting 100 mg regimen was assessed by a two one-sided tests procedure via 90% confidence intervals

obtained from the analyses of the natural logarithms of C_{max} and AUC_{∞} . These confidence intervals were obtained by exponentiating the endpoints of a confidence interval for the difference of mean logarithms. The point estimate of the relative bioavailability was likewise obtained by exponentiating the difference of mean logarithms, and the population least square mean value for each regimen was estimated by exponentiating the mean for the logarithm.

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		
	50 mg Capsule Fasting (N = 15)	100 mg Capsule Fasting (N = 15)	100 mg Capsule Nonfasting [‡] (N = 15)
T_{max} (h)	1.7 \pm 0.6	2.0 \pm 1.1	3.8 \pm 1.2 [‡]
C_{max} (μ g/mL)	3.673 \pm 0.846	8.086 \pm 2.440	5.491 \pm 1.058 [‡]
AUC_{∞} (μ g·h/mL)	41.8 \pm 11.2	76.3 \pm 15.8*	75.2 \pm 16.4
$t_{1/2}$ [§] (h)	11.8	12.6	13.2
CL/F [†] (L/h)	1.3 \pm 0.4	1.4 \pm 0.3	1.4 \pm 0.3

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

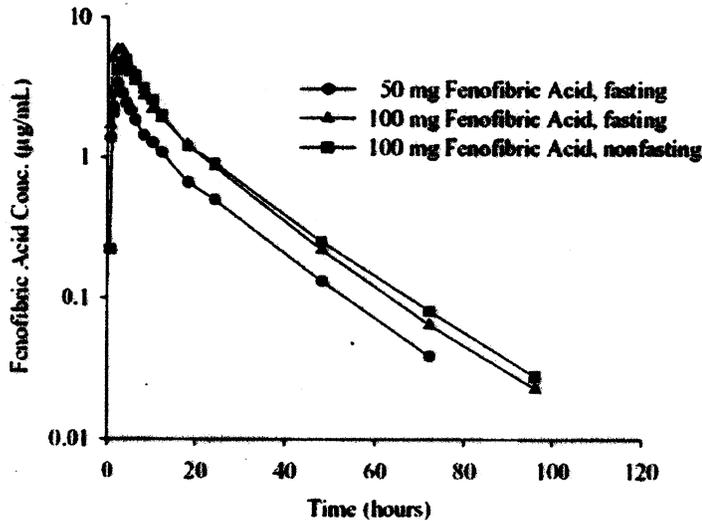
‡ Statistically significantly different from 100 mg capsule, fasting (paired t-test, $p < 0.05$).

§ Harmonic mean; evaluations of $t_{1/2}$ were based on statistical tests for λ_z .

† Parameter was not tested statistically.

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

Mean Fenofibric Acid Plasma Concentration-Time Profiles, Log-Linear Scale



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

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval [£]
Dose Proportionality Evaluation [†]					
100 mg capsule (fasting) vs. 50 mg capsule (fasting)	C _{max} (µg/mL)	3.85	3.58	1.0755	0.8709 – 1.3280
	AUC _∞ (µg·h/mL)	37.37	40.31	0.9272	0.8614 – 0.9980
Food Effect Evaluation					
100 mg capsule (nonfasting) [‡] vs. 100 mg capsule (fasting)	C _{max} (µg/mL)	5.40	7.71	0.7011	0.6109 – 0.8047
	AUC _∞ (µg·h/mL)	73.59	74.75	0.9845	0.9565 – 1.0132

* Antilogarithm of the least squares means for logarithms.

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

† Dose proportionality evaluation based upon analysis of dose-normalized data.

£ 95% confidence intervals were used for evaluating dose proportionality; 90% confidence intervals were used for evaluating food effect.

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

Safety Results: The treatments tested were generally well tolerated by the subjects. No clinically significant physical examination results, or vital signs, ECG or laboratory measurements were observed during the course of the study. With 50 mg fenofibric acid, three (3/15, 20%) subjects randomized to receive the active drug and one (1/5, 20%) subject randomized to receive placebo reported at least one treatment-emergent adverse event. No adverse events were reported with either of the 100 mg fenofibric acid administrations, fasting and nonfasting. There were no apparent differences among the treatments with respect to safety.

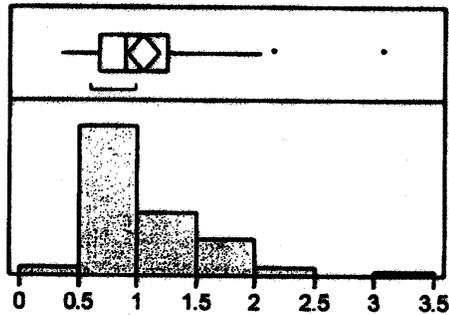
Four subjects reported a total of seven treatment-emergent adverse events. Only three (3/7) of the treatment-emergent adverse events were assessed by the investigator as possibly or probably related to the study drug and the majority of adverse events were mild in severity. All adverse events judged to be probably related to study drug were reported with placebo. No deaths or other serious adverse events were reported during the study. Results of other safety analyses, including vital signs, ECGs and physical examinations, were unremarkable for each treatment.

Sponsor's Conclusions: The pharmacokinetics of fenofibric acid appeared approximately linear. Fenofibric acid AUC_∞ was slightly less than proportional for fasting doses of 50 and 100 mg. However, T_{max} and elimination rate constant were independent of dose, and C_{max} increased proportionally with dose.

Administration of 100 mg fenofibric acid with food reduced the C_{max} least square mean value by approximately 30% and nearly doubled the T_{max} mean compared to fasting administration. However, the extent of absorption, based upon analysis of AUC_∞, was not affected by food.

All regimens tested were generally well tolerated by the subjects with no apparent differences among the regimens with respect to safety. No clinically significant physical examination results, or vital signs, ECGs or laboratory measurements were observed during the course of the study.

Reviewer's Comments: The pharmacokinetics of single rising doses of fenofibric acid was adequately characterized. The AUC_{∞} was appropriately estimated with less than 4% contribution from the extrapolation (see figure below).



Distribution of %Extrapolation in AUC_{∞} values

In the context of the current application, this exploratory study only indicated that exposure was approximately dose-proportional and was not adequate to confirm the dose-proportionality in fenofibric acid exposure from proposed ABT-335 formulations.

The study, however, provided useful information that pharmacokinetics (rate of absorption) of fenofibric acid given as neat drug is affected by food.

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4.2.2 Absolute and Relative Bioavailability Study (K LF178P 03 03 KH 05 02)

NAME OF COMPANY: FOURNIER Laboratories Ireland Limited NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT: Fenofibrate/Fenofibric acid	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	<i>(FOR NATIONAL AUTHORITY USE ONLY)</i>
Title of the study: Comparison of absolute and relative bioavailability of fenofibrate and fenofibric acid formulations following oral dose or delivery at different sites of the gastro-intestinal tract (protocol number: K LF178P 03 03 KH)		
Investigators: H. Wray, MB, ChB, FEPM (Pharmaceutical Profiles)		
Study center (s): _____		
Publication (reference): Not applicable		
Studied period (years): Date of first screening visit: 05 Apr 2004 Date of last subject assessment: 31 Jul 2004	Phase of development: I	
Objectives: Primary objective: - to compare the absolute bioavailability of FF and FA as NCD suspensions when delivered at different GI tract sites in healthy male subjects. Secondary objective: - to assess the optimal site of GI tract absorption for both FF and FA BCD suspensions; - to determine the relative bioavailabilities of FF and FA NCD suspensions at each intestinal site compared to stomach; - to determine the relative bioavailability of FF NCD suspension at each GI tract site compared to 145 mg FF tablet as oral reference; - to determine the absolute bioavailability of the 145 mg FF tablet; - to assess the general safety.		
Methodology: This study was conducted according to 2 successive phases: Phase 1: open, randomized in 2 groups of 10 subjects (Group X and Group Y). Group X received FF and Group Y received FA. Each subject was to receive 4 treatments, each separated by at least a 10-day washout period according to the same sequence from ascending colon to stomach. Phase 2: open, randomized, 2-way crossover design, with at least a 10-day washout period, composed of one group of 20 subjects (Group XY) with 10 subjects from Group X (FF) and 10 subjects from Group Y (FA). Each subject was to receive 2 treatments as FA IV reference (10-minute IV infusion of FA 50 mg) and FF oral reference (145 mg FF tablet). Phase 1 and Phase 2 were separated by at least a 10-day washout period. Each subject was to receive the 6 treatments according to their group allocation. The study schedule is illustrated in the following scheme.		

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NAME OF COMPANY: FOURNIER Laboratories Ireland Limited NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT: Fenofibrate/Fenofibric acid	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)																		
<div style="display: flex; justify-content: space-around;"> <div style="width: 45%;"> <p style="text-align: center;">Phase 1</p> <p>Group X n=10 planned Fenofibrate (FF)</p> <p>FF NCD 145 mg orally once daily XA → FF NCD 145 mg orally small amount XB → FF NCD 145 mg orally small amount XC → FF NCD 145 mg orally once daily XD</p> <p>Group Y n=10 planned Fenofibrate acid (FA)</p> <p>FA NCD 145 mg orally once daily YA → FA NCD 145 mg orally small amount YB → FA NCD 145 mg orally small amount YC → FA NCD 145 mg orally once daily YD</p> <p style="text-align: center;">← Treat. allocation non-randomized order →</p> </div> <div style="width: 45%;"> <p style="text-align: center;">Phase 2</p> <p>Group XV n=20 planned Fenofibrate and fenofibric acid</p> <p>(At least 12 complete subjects - 6 from group X & 6 from group Y)</p> <p>145 mg FF NCD XV → 145 mg FF acid Y</p> <p style="text-align: center;">← Open, randomized 2-way cross-over →</p> </div> </div> <p style="text-align: center; font-size: small;">At least 10 days between</p>																				
Number of subjects (planned and analyzed): <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Number of subjects</th> <th>FAS</th> <th>PK Set 1</th> <th>PK Set 2</th> <th>PK Set 3</th> <th>PK Set 4</th> </tr> </thead> <tbody> <tr> <td>Planned</td> <td>10 FF + 10 FA</td> <td>6 FF + 6 FA</td> <td>6 FF + 6 FA</td> <td>6 FF + 6 FA</td> <td>-</td> </tr> <tr> <td>Analyzed</td> <td>10 FF + 10 FA</td> <td>8 FF + 4 FA</td> <td>8 FF + 4 FA</td> <td>10 FF + 7 FA</td> <td>7 FF + 7 FA</td> </tr> </tbody> </table>			Number of subjects	FAS	PK Set 1	PK Set 2	PK Set 3	PK Set 4	Planned	10 FF + 10 FA	6 FF + 6 FA	6 FF + 6 FA	6 FF + 6 FA	-	Analyzed	10 FF + 10 FA	8 FF + 4 FA	8 FF + 4 FA	10 FF + 7 FA	7 FF + 7 FA
Number of subjects	FAS	PK Set 1	PK Set 2	PK Set 3	PK Set 4															
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Analyzed	10 FF + 10 FA	8 FF + 4 FA	8 FF + 4 FA	10 FF + 7 FA	7 FF + 7 FA															
Diagnosis and main criteria for inclusion: Healthy male volunteers (18 - 55 years old)																				
Test product, dose and mode of administration, batch no:																				
Phase 1: fenofibrate or fenofibric acid NCD suspension administered at different levels of the GI tract																				
Group X/145 mg FF NCD suspension batch No. RD-04-0002																				
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Treatments</th> <th>Description</th> <th>Dosing Instructions</th> </tr> </thead> <tbody> <tr> <td>Treatment XA</td> <td></td> <td>swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵Tc-DTPA) in 30 ml. water</td> </tr> <tr> <td>Treatment XB</td> <td></td> <td>swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵Tc-DTPA) in 30 ml. water</td> </tr> <tr> <td>Treatment XC</td> <td></td> <td>swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵Tc-DTPA) in 30 ml. water</td> </tr> <tr> <td>Treatment XD</td> <td>145 mg of FF as NCD suspension orally</td> <td>Swallowed with 240 ml. of still ingested to be delivered to the stomach water</td> </tr> </tbody> </table>	Treatments	Description	Dosing Instructions	Treatment XA		swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵ Tc-DTPA) in 30 ml. water	Treatment XB		swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵ Tc-DTPA) in 30 ml. water	Treatment XC		swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵ Tc-DTPA) in 30 ml. water	Treatment XD	145 mg of FF as NCD suspension orally	Swallowed with 240 ml. of still ingested to be delivered to the stomach water					
Treatments	Description	Dosing Instructions																		
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Treatment XB		swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵ Tc-DTPA) in 30 ml. water																		
Treatment XC		swallowed with 210 ml. water followed by a radiolabeled drink containing 4 MBq (¹²⁵ Tc-DTPA) in 30 ml. water																		
Treatment XD	145 mg of FF as NCD suspension orally	Swallowed with 240 ml. of still ingested to be delivered to the stomach water																		

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Group Y/130 mg FA NCD suspension batch No. RD-04-0001

Treatments	Description	Dosing Instructions
Treatment YA		Swallowed with 210 mL water followed by a radiolabeled drink containing 4 MBq (¹²⁵ I)-DTPA in 30 mL water
Treatment YB		Swallowed with 210 mL water followed by a radiolabeled drink containing 4 MBq (¹²⁵ I)-DTPA in 30 mL water
Treatment YC		Swallowed with 210 mL water followed by a radiolabeled drink containing 4 MBq (¹²⁵ I)-DTPA in 30 mL water
Treatment YD	130 mg of FA as NCD suspension orally ingested to be delivered to the stomach	Swallowed with 240 mL of still water

Phase 2: FF tablet (oral reference) and FA 10-minute IV infusion

Group XY/145 mg fenofibrate tablet (batch No. 317/03) and 50 mg fenofibric acid IV infusion (batch No. 317/04)

Treatments	Description	Dosing Instructions
Treatment E	50 mg of FA as 10 mL sterile phosphate buffer pH 7.2 solution at 5 mg/mL - 10-minute IV infusion at an infusion rate of 1 mL/min	10-minute IV infusion using a syringe driver
Treatment F	145 mg nanoparticle FF tablet - per os	Swallowed with 240 mL of still water

Duration of treatment: Not applicable: all treatments were administered as single doses.

Reference therapy, dose and mode of administration, batch no: IV 50 mg FA (absolute reference) and 145 mg FF tablet (FF oral reference).

Criteria for evaluation:

Primary criteria

Pharmacokinetics of fenofibric acid

Following treatments with Enterion™ capsules: Blood samples (4 mL at each collection-time) were to be collected at time 0 (pre-dose), 0 (pre-activation), 30 minutes, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 18, 24, 48, 72, 96 and 120 hours post-activation (n = 19 per period i.e. 228 mL for 3 periods).

Following all the other oral treatments: Blood samples (4 mL at each collection-time) were collected at time 0 (pre-dose), 30 minutes, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 18, 24, 48, 72, 96 and 120 hours post-dose (n = 18 per period i.e. 144 mL for 2 periods).

Following IV treatment: Blood samples (4 mL at each collection-time) were collected at time 0 (pre-dose), 3, 6, 10 (just before of the end of infusion), 15, 20, 30, 40, 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 18, 24, 48, 72, 96 and 120 hours post-dose (n = 25 i.e. 100 mL for 1 period).

The following pharmacokinetic parameters were determined using a non-compartmental method: AUC, AUC_{0-t}, C_{max}, t_{max}, absolute bioavailability expressed in raw value (f) and as a percentage (F).

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<p>The following pharmacokinetic parameters were determined using a non-compartmental method: AUC, AUC_t, C_{max}, t_{max}, absolute bioavailability expressed in raw value (f) and as a percentage (F).</p> <p>Secondary criteria</p> <ul style="list-style-type: none"> - Pharmacokinetics of fenofibric acid <p>t_{1/2}, L_z, C_{1/2} and V_d/f were considered as secondary variables following oral route. t_{1/2}, L_z, C₁ and V_d were considered as secondary variables following intravenous route.</p> <ul style="list-style-type: none"> - General safety assessed by means of vital signs, electrocardiogram (EKG), laboratory investigations at screening, during treatment periods, and at follow-up and by the collection of adverse events (AEs). 		
<p>Statistical methods:</p> <p>Descriptive statistics for plasma concentration at each time point as well as for all pharmacokinetic parameters (n, mean, SD, CV%, min, max and median).</p> <p>Primary analysis</p> <ul style="list-style-type: none"> - Comparison of the absolute bioavailability of NCD suspension fenofibrate and NCD suspension fenofibric acid when delivered at each GI tract site: <p>Individual data and descriptive statistics of the absolute bioavailability of FF and FA NCD suspensions at each GI tract sites were provided. A 2-way (subject-group (FA or FF)) repeated measures (GI tract sites) analysis of variance was performed. In case of a significant group effect or significant subject-group x GI tract site interaction, a one-way analysis of variance by GI tract sites was to be done.</p> <p>Secondary analysis</p> <ul style="list-style-type: none"> - Assessment of the optimal site of GI tract absorption for both FF and FA <p>Following the previous 2-way repeated measures analysis, in case of a "GI tract sites" effect, a one-way analysis of variance by group was to be done. In case of significant test, the optimal site of GI tract absorption for each formulation (FF and FA NCD suspensions) was to be determined by using comparisons of absolute bioavailabilities between GI tract sites by the Tukey's studentized range test. - Determination of the relative bioavailability of FF and FA NCD suspensions at each intestinal site versus stomach <p>Individual data and descriptive statistics of the relative bioavailability.</p> <ul style="list-style-type: none"> - Determination of the relative bioavailability of FF NCD suspension at each GI tract site versus 145 mg FF tablet as oral reference <p>Individual data and descriptive statistics of the relative bioavailability.</p> <ul style="list-style-type: none"> - Determination of the absolute bioavailability of 145 mg FF tablet <p>Individual data and descriptive statistics, including 95% confidence interval, of the absolute bioavailability of 145 mg fenofibrate tablet.</p> <ul style="list-style-type: none"> - Comparisons of t_{0.5} in Phase 1 <p>Statistical comparison of FA t_{0.5} between FF and FA NCD suspensions performed using the non parametric Wilcoxon's test between fenofibrate and fenofibric acid NCD suspensions.</p> <p>Statistical comparison of FA t_{0.5} between GI tract sites for FF and FA NCD suspensions separately, performed using the global Friedman test for multiple non parametric data, followed by the non parametric Wilcoxon's for pair-wise comparisons.</p> </p>		

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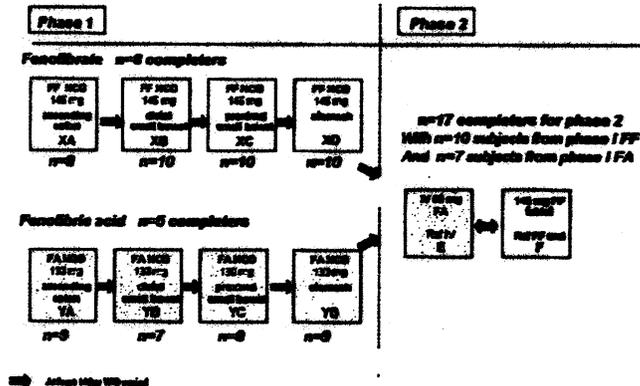
- Comparisons of $t_{1/2}$ in Phase 2
 Statistical comparison of FA $t_{1/2}$ performed using the non parametric Wilcoxon's test between 145 mg FF tablet and FA IV to confirm that the elimination rate of FA is not limited by the transformation of FF into FA.
 - Safety and tolerability was assessed using summary statistics.
- Complementary analysis**
- Determination of the relative bioavailabilities of FF and FA NCD suspension at each intestinal site versus stomach
 Individual data and descriptive statistics of the relative bioavailability.

Summary - Conclusion:

Subject disposition:

Twenty (20) subjects were enrolled into the study and treated. Their mean age was 34.2 ± 7.5 years, with a range from 18 to 45 years. One subject withdrew following Treatment YA (130 mg FA NCD suspension delivered at colon) and 2 subjects were withdrawn prior to Treatment E (50 mg FA 10-minute IV infusion). The remaining 17 subjects completed the study. Twelve subjects received the 6 treatments.

The number of subjects for each treatment is presented below.



Safety:

The FF and FA NCD formulations delivered to the GI tract sites, as well as the 145 mg FF tablet were well tolerated. The 50 mg FA given as a 10-minute IV infusion appeared irritant in 16 of the 17 treated subjects who reported pain in the infused arm. Two subjects received a partial IV dose due to a premature infusion discontinuation. Nevertheless, the absolute bioavailability was calculated after adjustment to the real dose in these 2 subjects. This local reaction was not unexpected as already observed in rabbits. This IV formulation was tested for the first time only for the determination of absolute bioavailability and is not intended to be used in current practice. Furthermore, no systemic side effect was observed following this route of administration. There were no serious adverse events and only 1 subject withdrew prematurely from the study due to an AE, a CK increase, which was attributed to volunteer's job and considered not related to the study medication by the investigator. Individual changes in laboratory parameters were considered clinically significant in 5 subjects. Only the case of CK elevation, which led to study withdrawal was reported as an AE. None of the abnormal vital sign values and none of the abnormal EKG assessments were considered to be clinically relevant.

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Fenofibrate/Fenofibric acid		

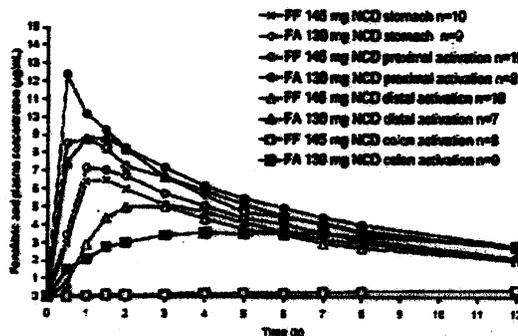
Analytical results:

The method for measuring fenofibric acid concentrations in plasma fully complies with US FDA requirements. The results of the QCs assessed during the study (accuracy and precision lower than 4% and 8%, respectively) showed that the method is reliable and robust, and provide a good level of confidence in the accuracy and precision of data used for pharmacokinetic assessment. Two successive administrations were separated by a washout of 10 days (> 6 fenofibric acid t_{1/2}), which was long enough to eliminate the first dose from the body. Indeed, all the pre-dose samples were found below the LLOQ and no carry-over effect was observed. All the 120-hour post-dose samples were found below or close to the LLOQ.

Pharmacokinetics:

The determination of PK parameters as well as the absolute and relative bioavailability obtained both on FAS and the appropriate PK Sets gave similar results. Although some PK Sets included a small number of subjects, they were representative of the randomized population.

Whatever the GI tract site, FA plasma levels following 130 mg FA NCD suspension were systematically higher than after 145 mg FF NCD suspension, as illustrated below.



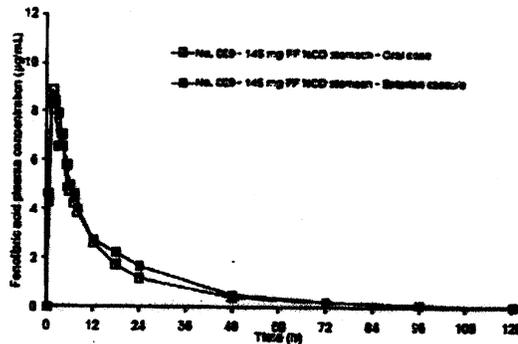
On an equimolar basis, AUC obtained for stomach (FF: 92 µg/mL.h; FA: 133 µg/mL.h), proximal (FF: 105 µg/mL.h; FA: 158 µg/mL.h) and distal small bowel (FF: 94 µg/mL.h; FA: 143 µg/mL.h) were ca. 1.5 times higher after 130 mg FA NCD suspension than after 145 mg FF NCD suspension while for colon (FF: 29 µg/mL.h; FA: 142 µg/mL.h), the exposure was ca. 5 times higher.

For FF NCD suspension, C_{max} values increased from colon (0.6 µg/mL) to proximal small bowel and stomach (3 and 7 µg/mL, respectively) and were associated with decreasing t_{max} (20.3 hours to 1.8 and 1.4 hours, respectively). For FA NCD suspension, C_{max} values increased from colon (3.9 µg/mL) to proximal small bowel and stomach (11.8 and 10.2 µg/mL, respectively) and were associated with decreasing t_{max} (4.3 hours to 0.6 and 0.8 hours, respectively).

For FF NCD suspension, t_{1/2} values were similar between GI tract sites (24, 24, 22, 26 hours, respectively for stomach, proximal, distal small bowel and colon). For FA NCD suspension, t_{1/2} values were similar between GI tract sites (20, 21, 20, 19 hours, respectively for stomach, proximal, distal small bowel and colon).

In the current study, the Entenion™ capsule was not used to assess the delivery at the stomach site. Actually, the NCD formulations were orally administered to test the GI tract site. In 1 subject (No. 009), the activation of Entenion™ capsule at stomach instead of proximal small bowel allowed to confirm this hypothesis. FA plasma profiles obtained following 145 mg FF NCD suspension administered orally and 145 mg FF NCD suspension delivered using Entenion™ capsule were superimposable as illustrated below.

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The primary endpoint was the comparison of the absolute bioavailability between FF and FA NCD suspensions at each GI tract site. On average, absolute bioavailability of FF NCD suspension was approximately 22% at colon, 66% at distal small bowel, 73% at proximal small bowel and 69% at stomach; absolute bioavailability of FA NCD suspension was approximately 78% at colon, 84% at distal small bowel, 88% at proximal small bowel and 81% at stomach. The statistical analysis led to conclude that absolute bioavailability of FA NCD suspension was higher (at colon and distal small bowel) or tended to be higher (at proximal small bowel and stomach) than the absolute bioavailability of FF NCD suspension.

As a secondary endpoint, the absolute bioavailability was compared between GI tract sites for both FF and FA NCD suspensions.

The results on FF showed that the absolute bioavailability at colon was significantly lower than at any other GI tract sites, indicating that the FF molecule is well absorbed from the stomach through to the distal small bowel. However, analysis of the C_{max} and t_{max} data (see table below) shows the rate of absorption starting to diminish at the distal small bowel, which is often a prelude to reduced colonic uptake.

FF	Stomach	Proximal SB	Distal SB	Colon
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
AUC (µg·ml·h)	91.1 ± 34.0	99.8 ± 46.3	89.3 ± 42.2	28.0 ± 17.1
C _{max} (µg/ml)	7.48 ± 1.46	7.84 ± 2.44	8.08 ± 2.03	0.698 ± 0.260
t _{max} (h)	28.4 ± 7.7	21.8 ± 6.9	2.3 ± 1.0	28.3 ± 5.3

The lower absorption of FA following delivery of FF NCD suspension at colon is consistent with the lower percentage of unionized drug at this site as presented in the following table.

Theoretically	pH	pKa	pKa-pH	antilog (pKa-pH)	% ionization	% unionized	surface
Stomach	1.50	3.14	1.6	5.1552	18	83.75	1 m ²
Proximal	6.90	3.14	-3.8	0.0233	98	2.28	
Distal	7.60	3.14	-4.5	0.0116	99	1.14	200 to 300
Colon	8.00	3.14	-4.9	0.0078	99	0.77	

% ionization = 100 / (1 + antilog (pKa-pH)) with pKa of FA equal to 3.14

The absorption of FA at colon level could be limited by the intestinal esterase-mediated transformation of FF into FA.

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The dramatic decrease in absorption of FF at the colon would prevent the development of a modified release dosage form with an in-vivo release time of longer than 4 hours.

For FA, the analysis did not show any significant difference between GI tract sites. The results on the FA molecule thus show it has excellent absorption characteristics throughout the GI tract from the stomach to the colon. The C_{max} values are depressed in the colon (as shown in the table below), but not so low as to impact the bioavailability from this absorption site. In comparison to the FF data, the higher C_{max} values, more rapid t_{max} values and higher bioavailability results for the FA molecule at all regions of the GI tract shows that FA presents improved absorption characteristics over the FF molecule. From this information, the development of immediate release and modified release formulations of FA are both plausible.

FA	Stomach	Proximal SB	Distal SB	Colon
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
AUC (µg/ml.h)	144 ± 66.2	160 ± 85.1	162 ± 70.8	140 ± 67.4
C _{max} (µg/ml)	10.9 ± 1.09	12.8 ± 2.01	9.40 ± 1.41	4.19 ± 1.60
t _{max} (h)	0.9 ± 0.5	0.8 ± 0.0	0.8 ± 0.5	3.9 ± 3.0

The relative bioavailability of 145 mg FF NCD suspension when delivered to small bowel (distal and proximal) versus stomach was very high (ca. 103% and 115%) while it was markedly lower when NCD suspension was delivered to colon (around 32%). For FA, relative bioavailability of NCD was high for all intestinal sites including colon (98%). Note that it was higher (above 100%) for the proximal and distal small bowel (ca. 112% and 111%).

The relative bioavailability of 145 mg FF NCD suspension versus 145 mg FF tablet was comparable between distal, proximal and stomach (ca. 80%, 89% and 80%) except when the NCD suspension was delivered to colon (around 26%). From these results, the better bioavailability of FF tablet compared to FF NCD suspension, which was previously observed in pilot studies, is confirmed.

On the other hand, a longer residence time of the tablet could participate to the absorption improvement.

The mean absolute bioavailability of the 145 mg FF tablet was 85% with a very low intersubject variability (CV% = 11%). A reduction of dose for a subsequent FF formulation bioequivalent to the current 145 mg FF tablet appears very challenging. The absolute bioavailability could theoretically be improved by 15%, leading to a dose of approximately 120 mg of FF i.e. 100% absolute bioavailability.

Finally, the comparison of t_{1/2} between the 145 mg FF tablet and 50 mg FA IV infusion did not show any statistically significant effect. From this, the terminal half-life following oral administration of 145 mg FF tablet can be considered as the elimination half-life of FA, the active moiety. Thus, the FA elimination rate does not seem to be limited by the transformation of FF into FA.

Conclusion:

For a FF formulation:

From these results, no optimal site of absorption was identified. Absorption appeared comparable from stomach to distal small bowel while colon was the worst absorption site.

A reduction of dose for a subsequent FF formulation bioequivalent to the current 145 mg FF tablet appears very challenging. The absolute bioavailability could theoretically be improved by 15% leading to a dose of approximately 120 mg of FF i.e. 100% absolute bioavailability. An oral dose of 130 mg would be more realistic.

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For a FA emulsion: From these results, it can be concluded that absorption from FA NCD formulation was high throughout the GI tract from stomach to colon. FA seems an ideal candidate for any form of product enhancement strategy. However, to develop a formulation bioequivalent to the 145 mg FF tablet, the release characteristics of the formulation requires to be slowed down in order to match the slower absorption properties of FF in the GI tract. Date of report: 15 Mar 2005		

Reviewer's Comments: Sponsor only submitted the study report for this early exploratory study. Based on the information provided in the report, the assessment of absolute bioavailability of fenofibric acid after single oral doses of fenofibric acid or fenofibrate from different regions of gastro-intestinal tract seems adequate. Sponsor's conclusions regarding fenofibric acid formulation development were also reasonable.

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