

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-695

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

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-695	Submission Date(s): 12/1/2003
Brand Name	RP 1824
Generic Name	Fenofibrate micronized
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE-2
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Reliant Pharmaceuticals
Relevant IND(s)	66,249
Submission Type; Code	505 (b) (2) Standard
Formulation; Strength(s)	Oral capsules; 43, 87, and 130 mg
Indication	Type IIa, IIb, IV, and V hyperlipidemia

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1 Executive Summary

On Dec 1, 2003, Reliant Pharmaceuticals submitted an original NDA 505b(2) for RP 1824 fenofibrate capsules, 43, 87, and 130 mg for the treatment of Type IIa, IIb, IV, and V hyperlipidemia. Fenofibrate is a lipid-lowering agent, which acts primarily by increasing the activity of lipoprotein lipase.

RP-1824 capsules are an oral immediate release encapsulated drug product containing micronized fenofibrate in the form of ~~_____~~ Fenofibrate micronized Tricor[®] 200 mg capsules (Abbott Laboratories) was used as a reference listed drug (approved under NDA 19-304).

The sponsor has submitted 5 PK studies in support of this application. No phase III clinical trial was conducted with this product. Clinical pharmacology section includes the following studies:

FF4C- Single dose BE study under fasting and fed condition

FF3- Multiple-dose BE study under fed condition

FF2- Food effect on RP-1824 capsules

FF4B- Dosage form equivalence study

FF4- Dose proportionality study

A DSI inspection has been requested for the multiple BE study site and the report is pending.

The bioavailability of fenofibrate refers to the rate and extent of absorption of fenofibric acid, the main metabolite. In this NDA submission, only fenofibric acid concentration was measured in all studies.

- Following single dose administration under low fat fed condition, the C_{max} of RP 1824 130 mg capsule was similar to that of Tricor[®] 200 mg capsule however the extent of RP 1824 exposure was less than that of Tricor[®]. RP 1824 130 mg capsules were bioequivalent to Tricor 200 mg capsules following multiple dose administration under low fat fed condition.
- The sponsor is proposing that RP 1824 can be given without regard to meals. However, food increases the rate and extent of fenofibrate absorption from RP 1824 capsules although magnitude of increase for RP 1824 is less than that of Tricor[®]. Bioequivalence was established between RP 1824 130 mg capsules and Tricor[®] 200 mg capsules only under low fat fed condition following multiple doses. Therefore, based on the food effect study and the multiple dose fed bioequivalent study, it is recommended that RP 1824 be given with meal.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-695 and finds it acceptable, pending inspection report from DSI. Recommendation and labeling comments should be conveyed to sponsor as appropriate.

The following dissolution method and specification is recommended:

Based on the limited information provided, we believe that dissolution medium using 0.5% SLS is appropriate since dissolution profiles using 0.5% SLS are not different from those using 0.72% SLS. The dissolution method proposed by the sponsor using 0.72% SLS is acceptable as an interim basis until the method using 0.5% SLS is concurrently validated. However, the specification of NLT \geq (Q) @ 30 min for both methods is recommended.

Medium: 0.72% SLS as an interim and 0.5% SLS
Apparatus: USP Apparatus 2 (Paddles)
Speed: 75 rpm
Tolerance Specifications: NLT \geq (Q) @ 30 minutes.

CPB briefing was held on 9/2/04. The attendees were Drs. Hank Malinowski, John Hunt, Hae-Young Ahn, Mary Parks, Jayabharathi Vaidyanathan, Wei Qiu and Project Manager Patrica Madara.

1.2 Phase IV Commitments

None.

1.3 Summary of CPB findings

Dose proportionality:

The bioavailability of 1 x 43 mg, 1 x 87 mg and 1 x 130 mg RP 1824 capsules were compared under fasting conditions. A power model (regression of ln-transformed data) was used to assess dose proportionality. The 90% confidence intervals for the slope of the ln-transformed $AUC_{(0-t)}$ versus ln-transformed dose was calculated. The slope (90% CI) for $AUC_{(0-t)}$ was 0.798 (0.715-0.881). Since the 90% confidence interval does not include the value of 1, dose proportionality cannot be concluded.

Dosage Form Equivalence:

The bioavailability of two 43 mg RP 1824 versus one 87 mg RP 1824 capsule and three 43 mg RP 1824 versus one 130 mg RP 1824 capsule were compared under fasting conditions. Ratios (two 43 mg RP 1824 capsules/one 87 mg RP 1824 capsule) of least square means of AUC_{inf} and C_{max} of fenofibric acid were 98.1% and 108.5% respectively, while ratios of AUC_{inf} and C_{max} of fenofibric acid from three 43 mg RP 1824 versus one 130 mg RP 1824 capsule were 101.5% and 97.3% respectively. Because the 90% confidence intervals of AUC_{inf} and C_{max} ratios were within 80-125% range, it was concluded that the rate and extent of absorption of RP 1824 capsules were similar when administered either as single 87 or 130 mg or multiple 43 mg capsules under fasting

conditions. Therefore, dosage form equivalence between the three strengths was established.

Food Effects:

The bioavailability of RP 1824 capsule 130 mg was examined under fasting and high fat fed conditions. Food increased the rate and extent of fenofibrate absorption from RP 1824 capsules. Ratios (high fat fed/fasted) of least square means for AUC_{inf} and C_{max} of fenofibric acid were 124.6 and 210.2% respectively. Additionally, the extent and rate of absorption of RP 1824 capsules were much higher in high fat meal as compared to low fat diet.

The bioavailability of Tricor[®] capsule 200 mg was also examined under fasting and high fat fed conditions. Ratios (high fat fed/fasted) of least square means for AUC_{inf} and C_{max} of fenofibric acid were 218.8 and 434.2% respectively, indicating that food increased the rate and extent of absorption of Tricor[®] capsule 200 mg.

Relative Bioavailability Compared to Tricor[®] Capsule after single dose:

Bioavailability of RP 1824 130 mg capsule was compared with Tricor[®] 200 mg capsules under low fat fed and fasting conditions. Under fasting conditions, the extent of absorption of RP 1824 capsule 130 mg was equivalent to that of Tricor[®] 200 mg however RP 1824 130 mg capsules exhibited higher C_{max} of fenofibric acid when compared to Tricor[®]. The ratios (RP 1824 130 mg capsule fasted/ Tricor[®] 200 mg fasted) of least square means of AUC_{inf} and C_{max} of fenofibric acid were 101.93% and 172.3% respectively.

Under low fat meal fed conditions, ratios (RP 1824 130 mg capsule/ Tricor[®] 200 mg) of least square means of AUC_{inf} and C_{max} of fenofibric acid were 83.51% and 105.98% respectively. The 90% confidence interval of AUC_{inf} was lower than the 80-125% range. RP 1824 capsule 130 mg is less bioavailable than Tricor[®]200 mg capsule when administered with a low fat meal.

Relative Bioavailability to Tricor[®] Capsule after multiple doses:

Bioavailability of RP 1824 130 mg capsules was compared to that of Tricor[®] 200 mg capsules after multiple doses after consumption of a low fat meal. The ratio of least square means of (RP 1824 130 mg fed/Tricor[®] 200 mg fed) for AUC_{tss} and $C_{max ss}$ and C_{min} were 88.4%, 91.7% and 88.4% respectively. Because the 90% confidence interval for the AUC_{tss} and $C_{max ss}$ were in the 80-125% range, the RP 1824 130 mg capsules and Tricor[®] 200 mg capsules were concluded to be bioequivalent after multiple dosing, immediately following consumption of a low fat meal.

2 QBR

2.1 General Attributes

Q) What is the formulation of the drug product? What is the proposed mechanism of the drug action and therapeutic indications? What is the proposed dosage and route of administration?

The formulation consists of different capsule shells filled with different fill weights of fenofibrate to produce the 43 mg, 87 mg and 130 mg strengths. The fenofibrate

The quantitative composition is shown in Table 1. The compositions of the finished products are proportional among strengths. The strengths differ only by the amount of excipients and fenofibrate contained in different size capsules, while the ratio of fenofibrate/excipients remains constant.

Table 1: Composition of RP 1824 43, 87, 130 mg

Component	Reference	Function	Unit Dose (mg/capsule)		
			43 mg	87 mg	130 mg
Fenofibrate (micronized)	EP	Active Ingredient	43.00	87.00	130.00
Sugar Spheres	NF or EP				
Hypromellose	USP or EP				
Sodium Lauryl Sulfate	NF or EP				
Dimethicone Emulsion	In-house monograph				
Simethicone Emulsion	USP				
Hypromellose	USP or EP				
Talc	USP or EP				
	USP				
Total					
Hard Gelatin Capsules ^c	In-house monograph	Dosage Form			
Total					

^c 43 mg - light green cap and white body (size 2), 87 mg - white body (size 4), 87 mg - dark green cap and light green body (size 3), 130 mg - dark green cap and white body (size 2)

Fenofibrate is a lipid regulating agent that reduces the plasma triglycerides level in healthy subjects and in patients with hyperlipidemia. The mechanism of fenofibrate action involves the nuclear peroxisome proliferators-activated receptor alpha (PPAR α), which belongs to the nuclear steroid hormone receptor gene super family and has the potential to control the expression of genes involved in intracellular and extracellular lipid metabolism.

The proposed indication of RP 1824 capsules is for the treatment of Type IIa, IIb, IV, and V hyperlipidemia.

The proposed strengths are 43, 87, and 130 mg capsules given orally

Q) Is the dissolution method appropriate for RP1824 capsules?

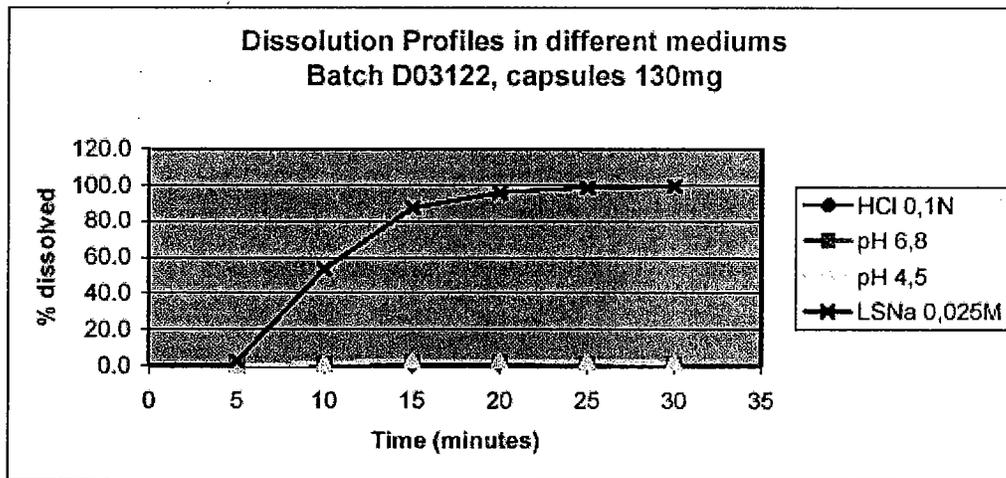
The sponsor has proposed the following dissolution method and specification:

Medium: 0.025 M SLS
Apparatus: USP Apparatus 2 (paddles)
Speed: 75 rpm
Specification: Q= — at 30 minutes.

Justification was provided for the choice of media, speed, and concentration of SLS.

Each strength fenofibrate capsule was tested in the following media (1000 ml) using paddle apparatus at 75 rpm: 0.1 N HCl; pH 4.5 USP buffer; pH 6.8 USP buffer; and 0.025 M SLS. Each sample was tested at 5, 10, 15, 20, 25 and 30- min intervals. The dissolution profiles of the three strengths are similar and the dissolution profiles of fenofibrate 130 mg capsules in various media are shown in the following figure. As shown, fenofibrate is sparingly soluble in the 0.1N HCl, pH 6.8 and pH 4.5 USP buffer. Therefore the 0.025M SLS medium seems to be the most appropriate medium for the dissolution method.

Figure 1:



Note: SLS = LSNa

Dissolution profiles were also generated for the 43 mg, 87 mg and 130 mg capsules using 0.025M SLS with 50, 75 and 100 rpm paddle speeds.

Dissolution results for fenofibrate capsules using different paddle speeds:

A] Table 2: 43 mg

Time (min.)	0	5	10	15	20	25	30
50 rpm	-0.2%	0.5%	32.5%	76.3%	90.0%	93.4%	95.2%
75 rpm	-0.3%	1.5%	56.0%	94.7%	100.9%	102.1%	102.4%
100 rpm	-0.4%	0.0%	48.9%	95.5%	101.2%	101.4%	101.7%

B] Table 3: 87 mg

	50 rpm	75 rpm	100 rpm
	30 minutes		
1			
2			
3			
4			
5			
6			
Mean	103.22%	101.55%	100.00%
Standard Deviation	2.18	2.31	1.91

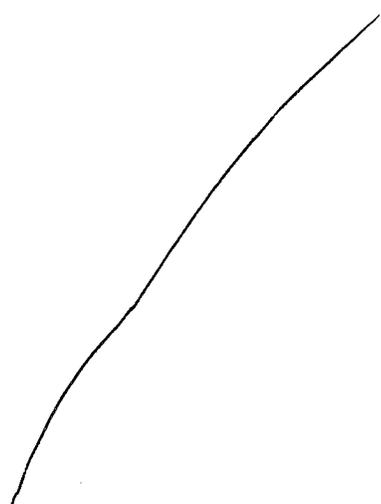
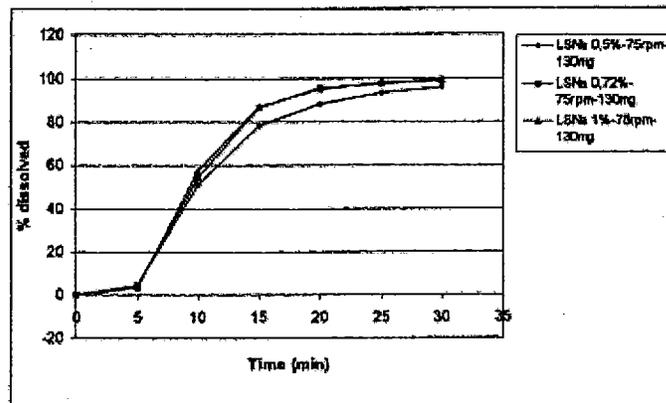
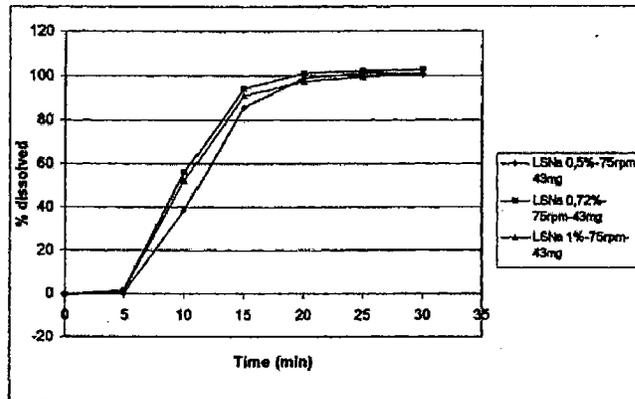
C] Table 4: 130 mg

Time (min.)	0	5	10	15	20	25	30
50 rpm	-0.1%	2.7%	39.6%	75.9%	89.9%	95.5%	97.9%
75 rpm	-0.1%	4.1%	54.0%	86.7%	95.6%	98.0%	99.7%
100 rpm	-0.2%	3.4%	65.2%	92.2%	97.2%	98.8%	99.3%

The dissolution increased with increase in paddle speed. The sponsor has chosen a speed of 75 rpm. The paddle speed of 75 rpm is acceptable provided a low concentration of SLS is used.

In order to justify the use of SLS, sponsor has provided dissolution profiles in 0.5 %, 0.72% and 1.0% SLS (0.72% SLS is equivalent to 0.025M SLS). Figure 2 shows the dissolution profiles for the 43 and 130 mg capsules. The sponsor has provided dissolution results only at 30 min for the 87 mg fenofibrate capsules. The mean dissolution profiles suggest there were no differences at different SLS concentration for the 43 mg fenofibrate capsules. For 87 mg and 130 mg the dissolution was slightly greater at 0.72% than 0.5% SLS. The percent dissolved at 30 min for the 87 mg capsules was 99.23% using 0.5% SLS compared to 101.55% at 0.72% SLS while for the 130 mg capsules 96.2% dissolved at 30 min using 0.5% SLS compared to 99.7% using 0.72%. However, the profiles were similar for 0.72% and 1.0%. The sponsor chose the intermediate concentration of SLS, 0.72% (0.025 M).

Figure 2: Dissolution profile for fenofibrate capsules 43 mg (top panel) and 130 mg (bottom panel), using different SLS concentrations



Reviewer Comments:

1. For quality control purpose, based on dissolution profiles in different conditions, the most appropriate dissolution medium would be SLS.
2. The sponsor was requested to provide dissolution data using 0.25% SLS (information request dated 6/10/04), since there was greater than 95% dissolution using SDS of 0.5%, 0.72% as well as 1.0%. The sponsor provided an amendment (dated 7/7/04) mentioning the reason for using 0.72% SLS that this intermediate SLS concentration provided sink conditions, and this was according to the dissolution parameters referenced in the Patent 6,277,405, which was established in the Tricor[®] NDA 19-304. Sponsor also submitted dissolution profile using 0.25% SLS (dated 8/30/04) for the three strengths. This data shows that there was less than 20% of fenofibrate dissolved in 30 min for the three strengths. Thus, 0.25% SDS is not suitable for dissolution studies. However, based on the provided data the total dissolution using a SLS concentration of 0.5% is not different from that of 0.72%. Therefore, a SLS concentration of 0.5% is recommended for RP 1824, since there is greater than 95% dissolution at the lowest concentration of SLS (0.5%) for all the three strengths.
3. The paddle speed of 75 rpm is acceptable. —
4. There appears to be greater than 95% dissolved at 30min for all the three strengths at the lowest SLS concentration (0.5%, based on the dissolution data provided from 1 lot) The specification of not less than — (Q) in 30 minutes would be appropriate using 0.5% SLS.

2.2 General Clinical Pharmacology

Not available

2.3 Intrinsic Factors

Not available

2.4 Extrinsic Factors

Not available

2.5 General Biopharmaceutics

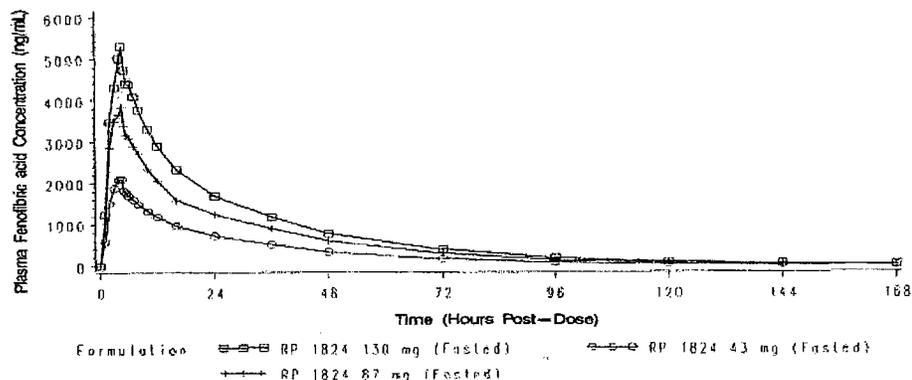
Q) Does the dose-proportionality exist?

A randomized, single-dose, open-label, 3-way crossover study was done to determine the dose proportionality of RP1824 43 mg, 87 mg and 130 mg capsules under fasting

conditions in healthy adult subjects (29 completed, 18-45 yrs). The 3 treatment periods were separated by at least 14 day washout period. The blood sampling was done up to 168 h post-dose.

Dose-proportionality was evaluated for pharmacokinetic parameters AUC_{0-t} and C_{max} using power analysis. The plasma fenofibric acid concentration versus time profile is shown in Figure 3.

Figure 3: Plasma concentration time profiles of RP 1824 capsules.



The pharmacokinetic parameters for the 43, 87 and 130 mg under fasting conditions are summarized in the following table. There appears to be slightly less than dose proportional increase in the AUC and C_{max} .

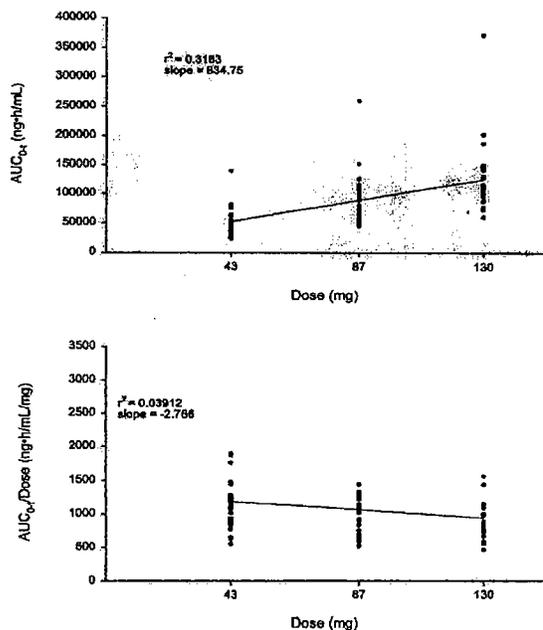
Table 6: Pharmacokinetic parameters for fenofibric acid following single 43 mg, 87 mg, and 130 mg doses under fasted conditions

Parameter	Treatment A: RP 1824 43 mg (Fasted)	Treatment B: RP 1824 87 mg (Fasted)	Treatment C: RP 1824 130 mg (Fasted)
AUC_{0-t} (ng·h/mL)	51333 (\pm 23123)	91167 (\pm 42776)	123932 (\pm 59037)
AUC_{0-inf} (ng·h/mL)	52430 (\pm 23868)	92514 (\pm 44677)	125742 (\pm 61901)
C_{max} (ng/mL)	2242 (\pm 747)	4018 (\pm 1674)	5525 (\pm 2034)
T_{max} (h)	4.16 (\pm 1.73)	4.32 (\pm 1.49)	4.56 (\pm 1.49)
$t_{1/2}$ (h)	20.4 (\pm 4.84)	20.6 (\pm 5.08)	21.8 (\pm 5.78)
K_{el} (1/h)	0.0356 (\pm 0.00721)	0.0352 (\pm 0.00695)	0.0336 (\pm 0.00736)
CL_m/F (L/h)	0.944 (\pm 0.333)	1.09 (\pm 0.395)	1.18 (\pm 0.382)
Vd_m/F (L)	26.3 (\pm 7.00)	30.9 (\pm 9.51)	35.1 (\pm 8.69)

Dose proportionality for the 43 mg, 87 mg and 130 mg doses of RP1824 administered under fasting conditions was assessed by calculating the slope of $\ln AUC_{(0-t)}$ and $\ln AUC_{(0-inf)}$ versus \ln -dose. The slope and the 90% confidence interval were 0.798 (0.715-0.881) and 0.792 (0.723-0.861) for $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ respectively.

The graphic representations of the raw data for the relationship between the individual pharmacokinetic parameters of fenofibric acid and dose of RP 1824 administered are presented in figures 3 & 4.

Figure 4: Relationship between individual AUC_{0-t} of fenofibric acid and dose of RP 1824



Reviewer Comments:

The slope of ln-transformed $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ versus ln-transformed dose of fenofibric acid from the RP 1824 87 mg capsule was significantly different from 1. The slope (90% CI) for $AUC_{(0-t)}$ was 0.798 (0.715-0.881) and 0.792 (0.723-0.861) for $AUC_{(0-inf)}$. Since the 90% confidence interval of the slope does not include the value of 1, dose proportionality cannot be concluded.

Q) Was the dosage form equivalency established?

In order to establish the dose equivalence of multiple RP 1824 43 mg capsules relative to single RP 1824 87 and 130 mg capsules a randomized, single-dose, open-label, 4-way crossover study was conducted. Doses of 43 mg x 2 capsules, 43 mg x 3 capsules, 87 mg x 1 capsule and 130 mg x 1 capsule was administered under fasting conditions to healthy adults (18-45 yrs). There was at least 14 days washout between treatments. Blood samples were collected through 168 h post dose.

The results are summarized in Table 7 and in Table 8. As shown, the AUC and C_{max} of fenofibric acid from RP 1824 43 mg x 2 capsules was similar to that of the RP 1824 87 mg x 1 capsule under fasting conditions. The ratio of LSM of AUC_{0-t} , AUC_{inf} and C_{max}

were 98.4%, 98.1% and 108.5%. Similarly, the AUC and C_{max} of fenofibric acid from RP 1824 43 mg x 3 capsules was similar to that of the RP 1824 130 mg x 1 capsule under fasting conditions. The ratio of LSM of AUC_{0-t} , AUC_{inf} and C_{max} were 101.3%, 101.5% and 97.3%. Therefore, it can be concluded that dosage form equivalency is established.

Table 7:

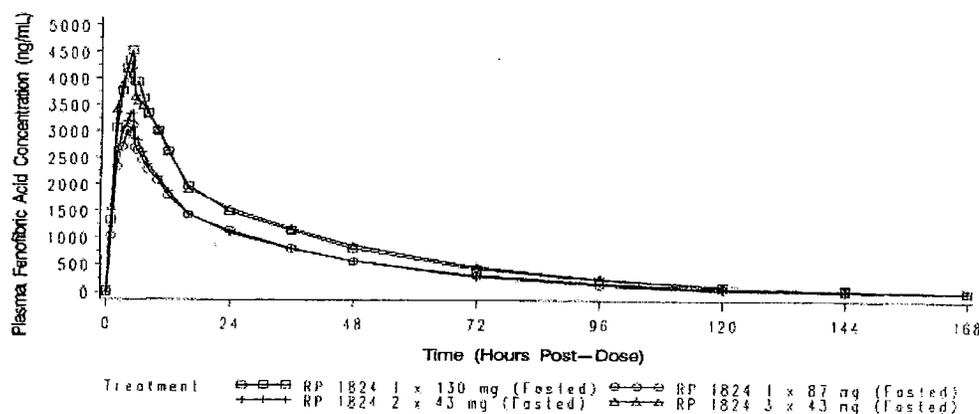
Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted Conditions - Arithmetic Mean (\pm SD)

Parameter	Treatment A: RP 1824 2 x 43 mg (Fasted)	Treatment B: RP 1824 3 x 43 mg (Fasted)	Treatment C: RP 1824 1 x 87 mg (Fasted)	Treatment D: RP 1824 1 x 130 mg (Fasted)
AUC_{0-t} (ng·h/mL)	82917 (\pm 31384)	119906 (\pm 52441)	83221 (\pm 30091)	117368 (\pm 44085)
AUC_{0-inf} (ng·h/mL)	84295 (\pm 32385)	122505 (\pm 55095)	84939 (\pm 31655)	119809 (\pm 46180)
C_{max} (ng/mL)	3699 (\pm 1252)	4722 (\pm 1641)	3343 (\pm 969)	4766 (\pm 1388)
T_{max} (h)	4.65 (\pm 2.04)	4.73 (\pm 1.68)	4.52 (\pm 1.77)	4.66 (\pm 1.08)
$t_{1/2}$ (h)	20.2 (\pm 6.56)	21.8 (\pm 13.4)	20.4 (\pm 6.82)	21.1 (\pm 7.25)
K_{el} (1/h)	0.0376 (\pm 0.0107)	0.0366 (\pm 0.0100)	0.0371 (\pm 0.0106)	0.0360 (\pm 0.0102)
CL_m/F (L/h)	1.18 (\pm 0.491)	1.23 (\pm 0.465)	1.18 (\pm 0.474)	1.25 (\pm 0.476)
Vd_m/F (L)	31.4 (\pm 7.63)	34.7 (\pm 12.0)	31.5 (\pm 7.05)	34.9 (\pm 9.36)

Table 8: Ratios of LSM (90% CI) of RP 1824 2 x 43 mg vs RP 1824 1 x 87 mg and Ratios of LSM (90% CI) of RP 1824 3 x 43 mg vs RP 1824 1 x 130 mg

Parameter	A: RP 1824 2 x 43 mg (Fasted) vs C: RP 1824 1 x 87 mg (Fasted)	B: RP 1824 3 x 43 mg (Fasted) vs D: RP 1824 1 x 130 mg (Fasted)
AUC_{0-t}	98.4% (93.6% - 103.4%)	101.3% (96.4% - 106.3%)
AUC_{0-inf}	98.1% (93.3% - 103.1%)	101.5% (96.5% - 106.7%)
C_{max}	108.5% (98.5% - 119.6%)	97.3% (88.4% - 107.1%)

Figure 5: Mean plasma fenofibric acid concentrations



Q) Is RP 1824 bioequivalent to Tricor[®] after single dose administration?

In order to establish bioequivalence of RP 1824 130 mg capsules to Tricor[®] 200 mg capsules, a relative bioavailability study was conducted under fasting conditions and immediately following consumption of a low fat meal in healthy adults (18-45 yrs, 32 enrolled, 29 completed). This was a randomized, single-dose, open-label (laboratory blinded), 4-way crossover study. A single dose of the study drug was given at the beginning of each treatment period (Day 1), followed by pharmacokinetic sampling up to 168 h post dose. There was a washout of at least 14 days between each treatment.

The 4 treatments were:

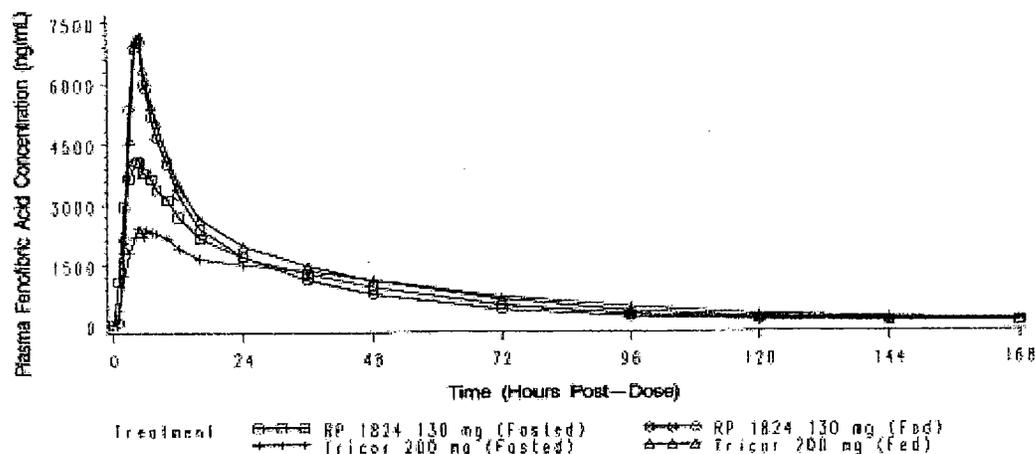
Treatment A: Single dose, 130 mg RP 1824; fasted condition

Treatment B: Single dose, 130 mg RP 1824; fed condition

Treatment C: Single dose, 200 mg Tricor[®]; fasted condition

Treatment D: Single dose, 200 mg Tricor[®]; fed condition

Figure 6: Mean plasma fenofibric acid concentration in fed and fasting conditions.



The pharmacokinetic parameters are summarized in Table 9 and point estimates of different treatment comparisons are provided in table 10. Results indicate that the under fed conditions (low fat meal), the maximum fenofibric acid concentrations (C_{max}) from the RP 1824 130 mg capsules and Tricor[®] 200 mg capsules were similar. The 90% CI was within the interval of 80-125%. However, the AUC for RP 1824 capsules was low as compared to Tricor[®] AUC, the 90% lower CI being slightly below 80% for both AUC_{0-t} and AUC_{0-inf} under fed conditions, (Table 10).

The bioavailability of a single dose RP 1824 130 mg capsule was also compared to single dose of Tricor[®] 200 mg capsules under fasting conditions under the same study. Based on the ln-transformed data, the 90% confidence intervals of the ratios of geometric means (RP 1824 vs Tricor[®]) for AUC were within 80-125% interval. However, the 90% confidence interval for the ratios of geometric means for C_{max} was not within 80-125%. The RP 1824 130mg capsules exhibited 62% higher C_{max} when compared to Tricor[®] (Table 9 & 10).

Table 9: Pharmacokinetic parameters for fenofibric acid following a single dose under fasted and fed (low fat meal) conditions, Arithmetic mean (\pm SD)

Parameter	Treatment A: RP 1824 130 mg (Fasted)	Treatment B: RP 1824 130 mg (Fed)	Treatment C: Tricor® 200 mg (Fasted)	Treatment D: Tricor® 200 mg (Fed)
AUC _{0-t} (ng·h/mL)	126091 (\pm 31875)	130400 (\pm 38928)	123769 (\pm 45252)	159932 (\pm 49760)
AUC _{0-inf} (ng·h/mL)	128020 (\pm 33000)	132387 (\pm 40251)	129798 (\pm 49944)	162332 (\pm 45509)
C _{max} (ng/mL)	4403 (\pm 1303)	7565 (\pm 1593)	2734 (\pm 1312)	7554 (\pm 2934)
T _{max} (h)	4.73 (\pm 1.59)	4.21 (\pm 0.632)	8.37 (\pm 9.68)	4.58 (\pm 0.508)
t _{1/2} (h)	29.1 (\pm 7.32)	23.0 (\pm 6.22)	27.1 (\pm 17.9)	23.3 (\pm 6.81)
K _{el} (1/h)	0.0324 (\pm 0.00913)	0.0324 (\pm 0.00899)	0.0315 (\pm 0.0117)	0.0321 (\pm 0.00870)
CL _{cr} /F (L/h)	1.09 (\pm 0.330)	1.06 (\pm 0.302)	1.89 (\pm 1.28)	1.37 (\pm 0.584)
Vd _{ss} /F (L)	35.6 (\pm 14.4)	34.0 (\pm 11.7)	64.5 (\pm 38.1)	44.5 (\pm 19.4)

Table 10: RP 1824 vs. Tricor under fasted and fed (low fat meal) conditions

Ratios (%) of LSM (90% CI)

Parameter	Formulation	B VS D (fed)		A VS C (fasted)	
		% Ratio	90% CI	% Ratio	90% CI
C _{max}	105.98	90.43-124.2	172.37	147.11-201.96	
AUC _{0-t}	83.62	75.99-92.02	105.99	96.32-116.63	
AUC _{0-inf}	83.51	75.82-91.99	101.93	92.42-112.41	

The results for fed vs fasted comparisons for individual formulations are summarized later in the review under the effect of food.

Reviewer Comments:

The single-dose bioequivalence study was conducted under both fasting and low fat fed conditions. Under either condition, RP 1824 130 mg capsules were not bioequivalent to Tricor® 200 mg capsules. Under fed conditions (low fat meal) the AUC of fenofibric acid from RP 1824 capsules was lower than (17% lower) that from Tricor® capsules.

Q) Is RP 1824 bioequivalent to Tricor[®] after multiple dose administration?

A randomized, multiple-dose, open-label, 2-way crossover study was conducted to compare the bioavailability of RP 1824 130 mg capsules relative to Tricor[®] 200 mg capsules in 28 healthy male and female subjects following consumption of a low fat meal. There was at least 14 days between the two periods. Fenofibric acid has elimination half-life of approximately 20 hours and analysis of trough levels from days 4-8 established that steady-state was attained by day 6 for both treatments. The results are summarized in table 11.

Table 11: Arithmetic mean (\pm SD) pharmacokinetic parameters for fenofibric acid following multiple dosing in healthy subjects on a TLC diet.

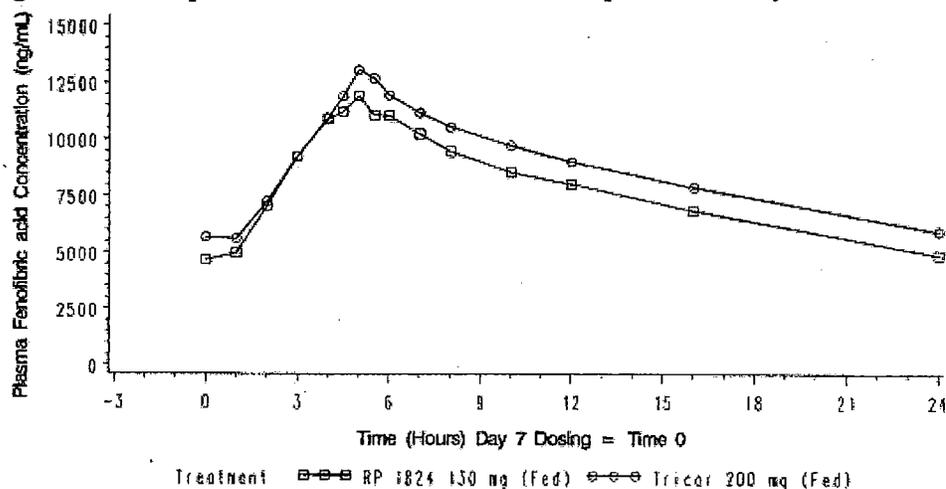
Parameter	Treatment A	Treatment B
	RP 1824 130 mg (Fed)	Tricor [®] 200 mg (Fed)
AUC _{t,ss} (ng-h/mL)	182889 (\pm 53669)	204988 (\pm 50946)
C _{max,ss} (ng/mL)	12864 (\pm 2685)	13810 (\pm 2781)
T _{max,ss} (h)	4.696 (\pm 0.978)	5.343 (\pm 1.281)
C _{av,ss} (ng/mL)	7620 (\pm 2236)	8541 (\pm 2123)
C _{min,ss} (ng/mL)	4859 (\pm 1850)	5878 (\pm 1860)
T _{1/2,ss} (h)	24.0 (\pm 0.0482)	24.0 (\pm 0.0378)
FI (%)	110 (\pm 39.1)	97.6 (\pm 36.1)
Swing (%)	202 (\pm 181)	161 (\pm 120)
CL _{m,ss/F} (L/h)	0.777 (\pm 0.269)	1.04 (\pm 0.293)

The ratios of ln-transformed AUC_{tss} and C_{max,ss} and C_{min} are summarized in the table below. The ratio of least square means of (RP 1824 130 mg fed/Tricor[®] 200 mg fed) for AUC_{tss} and C_{max,ss} and C_{min} were 88.4%, 91.7% and 88.4% respectively. Because the 90% confidence interval for the ratios were in the 80-125% range, the RP 1824 130 mg capsules and Tricor[®] 200 mg capsules were concluded to be bioequivalent after multiple dosing, immediately following consumption of a low fat meal.

Table 12: Statistical analysis of the rate and extent of bioavailability for fenofibric acid

Parameter	Treatment A:	Treatment B:	Ratio of LSM A/B % (90% CI)
	RP 1824 130 mg (Fed) LSM	Tricor [®] 200 mg (Fed) LSM	
AUC _{t,ss} (ng-h/mL)	175127	198058	88.4 (84.0–93.0)
C _{max,ss} (ng/mL)	12426	13555	91.7 (85.1–98.7)
C _{av,ss} (ng/mL)	7297	8252	88.4 (84.0–93.0)

Figure 7: Mean plasma concentration versus time profiles on day 7



Reviewer Comments:

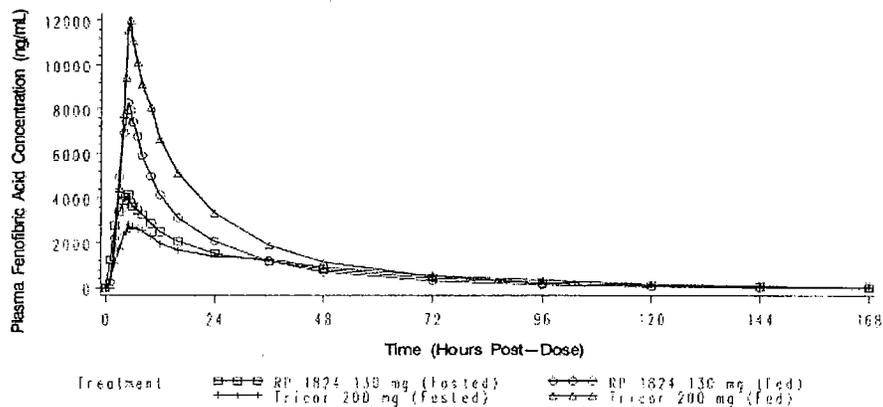
The steady state AUC of fenofibric acid from RP 1824 was 11% lower than that from Tricor[®] after multiple dose administration following a low fat meal. However, the geometric means of both AUC_{ss} and C_{max} after multiple dose administration of RP 1824 pass the bioequivalence criteria and are within the 80-125% interval.

Q) What is the effect of food on the bioavailability of fenofibric acid from RP 1824 and Tricor[®]?

High fat meal increased both AUC and C_{max} of fenofibric acid from both RP 1824 130 mg and Tricor[®] 200 mg capsules.

A randomized, single-dose, open-label, 4-way crossover study was conducted in healthy adults (18-45 yrs; N=32) to determine the effect of food on the bioavailability of fenofibric acid from RP 1824 and Tricor[®] capsules.

Figure 8: Mean fenofibric acid plasma concentration versus time by treatment



The results are summarized in Table 13.

Table 13: Pharmacokinetic parameters for fenofibric acid (Mean \pm SD)

Parameter	Treatment A RP 1824 130 mg (Fasted)	Treatment B RP 1824 130 mg (Fed)	Treatment C Tricor [®] 200 mg (Fasted)	Treatment D Tricor [®] 200 mg (Fed)
AUC _{0-t} (ng·h/mL)	114853 (\pm 37964)	145562 (\pm 48454)	109224 (\pm 53486)	224330 (\pm 78997)
AUC _{0-inf} (ng·h/mL)	116134 (\pm 38773)	146843 (\pm 49315)	111235 (\pm 55135)	226004 (\pm 80699)
C _{max} (ng/mL)	4375 (\pm 1614)	9118 (\pm 2494)	3413 (\pm 2092)	12829 (\pm 3373)
T _{max} (h)	4.84 (\pm 1.26)	4.89 (\pm 1.10)	9.61 (\pm 10.3)	5.65 (\pm 1.29)
t _{1/2} (h)	19.7 (\pm 5.39)	18.3 (\pm 4.80)	21.0 (\pm 7.03)	19.0 (\pm 5.50)
K _{el} (1/h)	0.0378 (\pm 0.0101)	0.0402 (\pm 0.00990)	0.0362 (\pm 0.0106)	0.0392 (\pm 0.0105)
CL _{m/F} (L/h)	1.25 (\pm 0.452)	0.984 (\pm 0.329)	2.27 (\pm 1.25)	0.988 (\pm 0.330)
Vd _{m/F} (L)	33.7 (\pm 10.1)	24.5 (\pm 5.27)	62.1 (\pm 22.9)	25.4 (\pm 6.37)

As shown, there was about 26% increase in AUC and 108% in C_{max} of fenofibric acid from RP 1824. In case of Tricor[®] the food caused a greater increase in both AUC (100%) and C_{max} (276%) than that seen with RP 1824. The point estimates and the confidence interval of the geometric least square means of AUC and C_{max} are shown in table 14.

Table 14: RP 1824 and Tricor[®] under fasted and fed conditions: Ratio (%) of geometric means and confidence interval

Parameter	Formulation RP 1824 fed vs fasted		Formulation Tricor fed vs fasted	
	Ratio (%)	CI	Ratio (%)	CI
AUC(0-t)	124.8	116-134.3	221.1	205.6-237.6
AUC(0-inf)	124.6	115.7-134.1	218.8	203.5-235.2
Cmax	210.2	181.8-242.9	434.2	376.5-500.7

Parameter	Formulation RP 1824 vs Tricor (fed)		Formulation RP 1824 vs Tricor (fasted)	
	Ratio (%)	CI	Ratio (%)	CI
AUC(0-t)	64.7	60.2-69.6	114.6	106.5-123.3
AUC(0-inf)	64.9	60.3-69.8	113.9	105.9-122.6
Cmax	69.6	60.2-80.4	143.7	124.4-166

Low fat meal also increased both the rate and extent of bioavailability of Tricor[®] capsules and the C_{max} for RP 1824 (single dose BE study discussed above). Consumption of a low fat meal did not affect the AUC of fenofibric acid from the RP 1824 capsules, the 90% confidence interval for the ratios of the geometric means were within 80-125%. In presence of food, the C_{max} of RP 1824 130 mg capsules increased by 75%. The 90% CI for the ratio of geometric mean of C_{max} was 149.05-205.33. The exposure to fenofibric acid from Tricor[®] 200 mg capsule was increased under low fat fed condition (~ 30%), while C_{max} increased by 185%.

2.6 Analytical

In each of the five pharmacokinetic studies, venous blood samples were drawn for plasma fenofibric acid assay determination. For single dose administration, samples were collected for 168 h post dose and with repeated dosing, assay was done at trough (days 4-6) and throughout 24 h dosing interval on the 7-day in each treatment.

For all studies the concentrations of fenofibric acid was determined using high performance liquid chromatography with mass spectrometric determination. All assays were performed by — . The lower limit of quantification (LLOQ) for fenofibric acid was 20 ng/ml. Calibration curve standards ranging from 20.0 ng/ml to 20006.7 ng/ml and QC samples at three different concentrations (60.0 ng/ml, 800.3 ng/ml, and 15005.0 ng/ml) were used.

The within and between batch precision and accuracy for fenofibric acid was as follows:
Precision (%CV) for LOQ and low QC ≤ 20%.
Precision (%CV) for medium and high QC ≤ 15%.
Accuracy (%nominal) for LOQ and low QC within 80-120%.
Accuracy (%nominal) for medium and high QC within 85-115%.

3 Labeling Comments

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE-2) has reviewed the package insert labeling for RP1824 and finds it acceptable pending the following revision:

(~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added.)

Under CLINICAL PHARMACOLOGY Section

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after multiple dose administration of TRADENAME 130 mg capsules are

21 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓
_____ § 552(b)(4) Draft Labeling

4.2 Individual Study Reviews

Synopsis: Food Effect Study

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02059 Volume: 1	
RP 1824		
Title of Study:	A Randomized, Single-Dose, 4-Way Crossover Study to Determine and Compare the Relative Bioavailability of RP 1824 130 mg to Tricor [®] 200 mg Under Fasted Conditions and Following Consumption of a Standard High Fat FDA Test Meal in Healthy Adult Subjects	
Investigator:	—	
Study Center:	/	
Publication (Reference):	Not applicable	
Studied period: (Date of first screening) 03 January 2003 (Date of last completed) 01 March 2003	Phase of development: I	
Objectives: The objectives of this study were as follows:	<ul style="list-style-type: none"> • To determine the relative bioavailability of RP 1824 130 mg oral capsules to Tricor[®] 200 mg oral capsules under fasting and fed conditions in healthy adults using a standard high-fat, FDA test meal. • To determine the relative bioavailability RP 1824 130 mg oral capsules following single doses under fasting and fed conditions in healthy adults using a standard high-fat, FDA test meal. • To determine the relative bioavailability of Tricor[®] 200 mg oral capsules following single doses under fasting and fed conditions in healthy adults using a standard high-fat, FDA test meal. 	
Methodology:	This was a randomized, single-dose, open-label (laboratory blinded), 4-way crossover study to determine the relative bioavailability of RP 1824 130 mg oral capsules to Tricor [®] 200 mg oral capsules under fasted and fed conditions in healthy adult subjects. The relative bioavailability of each formulation under fasted and fed conditions was also assessed.	
Number of Subjects (planned and analyzed):	A total of 32 subjects were enrolled in the study, and 30 subjects completed the study. All 32 subjects were included in the safety and pharmacokinetic (PK) analyses.	

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02059	
RP 1824	Volume: I	
<p>Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the investigator to be normal, healthy volunteers who met all inclusion and exclusion criteria.</p>		
<p>Test Product, Dose, Duration, Mode of Administration, and Batch Number: The test product was RP 1824 130 mg capsules, manufactured by Ethypharm S.A., Lot No.: D02357, manufacture date: 10 Nov 2002. Subjects randomized to Treatment A received a single oral dose of one RP 1824 130 mg capsule taken with 240 mL of tap water following a 10-hour fast. Subjects randomized to Treatment B received a single oral dose of one RP 1824 130 mg capsule taken with 240 mL of tap water following a standardized high-fat meal.</p>		
<p>Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The reference product was Tricor[®] (fenofibrate) 200 mg micronized capsules, manufactured by Abbott Laboratories, Lot No.: 751172E21, expiration date: 01 Apr 2003. Subjects randomized to Treatment C received a single oral dose of one Tricor[®] (fenofibrate) 200 mg micronized capsule taken with 240 mL of tap water following a 10-hour fast. Subjects randomized to Treatment D received a single oral dose of one Tricor[®] (fenofibrate) 200 mg micronized capsule taken with 240 mL of tap water following a standardized high-fat meal.</p>		
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics: The AUC_{0-12}, AUC_{0-24}, AUC_{0-48}, AUC_{0-96}, C_{max}, T_{max}, $t_{1/2}$, K_{el}, CL_{cr}/F, and Vd_{m}/F pharmacokinetic parameters were calculated for fenofibric acid from the plasma concentrations from the 32 subjects retained for pharmacokinetic analysis. Descriptive statistics (including arithmetic mean, standard deviation [SD], coefficient of variation [CV], minimum, maximum, median, geometric mean, and number of observations) for plasma fenofibric acid concentrations at each time point and for pharmacokinetic parameters were tabulated by treatment.</p> <p>Safety: Physical examination, medical and drug history, clinical laboratory tests, vital signs, electrocardiogram (ECG), and adverse event assessments were evaluated during this study.</p>		

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02059	
RP 1824	Volume: I	
<p>Statistical Methods:</p> <p>Pharmacokinetics: Relative bioavailabilities were determined using the parameters AUC_{0-12}, AUC_{0-24}, and C_{max} for the following treatments:</p> <p>Treatment B: RP 1824 130 mg (Fed)/Treatment A: RP 1824 130 mg (Fasted),</p> <p>Treatment D: Tricor[®] 200 mg (Fed)/Treatment C: Tricor[®] 200 mg (Fasted),</p> <p>Treatment B: RP 1824 130 mg (Fed)/Treatment D: Tricor[®] 200 mg (Fed),</p> <p>Treatment A: RP 1824 130 mg (Fasted)/Treatment C: Tricor[®] 200 mg (Fasted),</p> <p>Treatment B: RP 1824 130 mg (Fed)/Treatment C: Tricor[®] 200 mg (Fasted), and</p> <p>Treatment A: RP 1824 130 mg (Fasted)/Treatment D: Tricor[®] 200 mg (Fed)</p> <p>The analysis of variance (ANOVA) model included sequence, formulation, and period as fixed effects and subject nested within sequence as a random effect. The 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals (CI) obtained for the difference between drug formulation least squares means (LSM) resulting from the analyses on the ln-transformed parameters AUC_{0-12}, AUC_{0-24}, and C_{max}. If the 90% CI for the ratios of population least-square geometric means (based on ln-transformed parameters) of fed and fasted treatments fell within 80 – 125% for the AUCs and C_{max}, then the presence of a food effect was excluded. If the CI for AUCs and C_{max} fell outside the above limits, then a food effect was assumed.</p>		

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT		
RP 1824	Report No.: AA02059 Volume: 1	
<p>Safety: Descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) were calculated for continuous variables (age, height, weight, and body mass index [BMI]) and frequency counts were tabulated for categorical demographic variables (race) by randomized dosing sequence for each gender and overall.</p> <p>Adverse events (AEs) were coded using MedDRA (Version 5.1) and are summarized by preferred term. Number and percentage of subjects experiencing each coded event, total number of each coded event and as a percentage of total adverse events, and by severity and relationship to study drug are displayed for each treatment.</p> <p>Laboratory values were summarized using descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) for continuous serum chemistry and hematology results at each time point (screening and poststudy) and change from screening to poststudy values. The shift from screen to poststudy was provided for each laboratory test for serum chemistry, hematology, and urinalysis. All out-of-range values were listed by subject for each laboratory parameter. Rechecks were used in determination of screen values. Poststudy values were defined as the first observation obtained at that time point.</p> <p>Sitting vital signs measurements (systolic and diastolic blood pressure and heart rate) were summarized using descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) by time point of collection and change from predose for each treatment group. Predose was defined as the last observation obtained prior to dosing for each period on Day 1 (including rechecks). Rechecks were not included as postdose observations.</p> <p>Shifts from screening to poststudy results for physical examinations were tabulated.</p> <p>ECG values were summarized using descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) at screening and poststudy and change from screening to poststudy values. Rechecks were used in determination of screening values. Poststudy values were defined as the first observation obtained at that time point.</p>		

**APPEARS THIS WAY
ON ORIGINAL**

NAME OF COMPANY		INDIVIDUAL STUDY TABLE SYNOPSIS		(FOR NATIONAL AUTHORITY USE ONLY)	
Reliant Pharmaceuticals, LLC		REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02059 Volume: 1			
NAME OF FINISHED PRODUCT					
RP 1824					
NAME OF ACTIVE INGREDIENT					
RP 1824					
SUMMARY – CONCLUSIONS					
<p>Pharmacokinetic Results: The pharmacokinetic results for all parameters and the ratios of LSM (with the 90% CI) derived from the analyses of the ln-transformed AUC_{0-t}, AUC_{0-∞}, and C_{max} pharmacokinetic parameters for all comparisons of interest are tabulated below.</p> <p>Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Standard High-Fat FDA Test Meal) Conditions - Arithmetic Mean (± SD)</p>					
Parameter	Treatment A RP 1824 130 mg (Fasted)	Treatment B RP 1824 130 mg (Fed)	Treatment C Tricor® 200 mg (Fasted)	Treatment D Tricor® 200 mg (Fed)	
AUC _{0-t} (ng-h/mL)	114853 (±37964)	145562 (±48454)	109224 (±53486)	224330 (±76897)	
AUC _{0-∞} (ng-h/mL)	116134 (±38773)	146843 (±49315)	111235 (±55135)	226004 (±80699)	
C _{max} (ng/mL)	4375 (±1614)	9118 (±2494)	3413 (±2092)	12629 (±3373)	
T _{max} (h)	4.84 (±1.26)	4.89 (±1.10)	9.61 (±10.3)	5.65 (±1.29)	
t _{1/2} (h)	19.7 (±5.39)	18.3 (±4.80)	21.0 (±7.03)	19.0 (±5.50)	
K _{el} (1/h)	0.0378 (±0.0101)	0.0402 (±0.00990)	0.0362 (±0.0106)	0.0392 (±0.0105)	
CL _{r/F} (L/h)	1.25 (±0.452)	0.984 (±0.329)	2.27 (±1.25)	0.988 (±0.330)	
Vd _{r/F} (L)	33.7 (±10.1)	24.5 (±5.27)	62.1 (±22.9)	25.4 (±6.37)	

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ON ORIGINAL

NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02059 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		

Ratios (%) of LSM (90% CI) for RP 1824 vs Tricor®

Parameter	B: RP 1824 130 mg (Fed) vs D: Tricor® 200 mg (Fed)	A: RP 1824 130 mg (Fasted) vs C: Tricor® 200 mg (Fasted)	B: RP 1824 130 mg (Fed) vs C: Tricor® 200 mg (Fasted)	A: RP 1824 130 mg (Fasted) vs D: Tricor® 200 mg (Fed)
AUC _{0-t}	64.7 (60.2-69.6)	114.6 (106.5-123.3)	143.1 (133.1-153.6)	51.9 (48.2-55.8)
AUC _{0-inf}	64.9 (60.3-69.8)	113.9 (105.9-122.6)	141.9 (132.0-152.6)	52.1 (48.4-56.0)
C _{max}	69.6 (60.2-80.4)	143.7 (124.4-166.0)	302.0 (261.9-348.3)	33.1 (28.6-38.3)

Fed vs Fasted Ratios (%) of LSM (90% CI) for Individual Formulations

Parameter	B: RP 1824 130 mg (Fed) vs A: RP 1824 130 mg (Fasted)	D: Tricor® 200 mg (Fed) vs C: Tricor® 200 mg (Fasted)
AUC _{0-t}	124.8 (116.0-134.3)	221.1 (205.6-237.6)
AUC _{0-inf}	124.6 (115.7-134.1)	218.8 (203.5-235.2)
C _{max}	210.2 (181.8-242.9)	434.2 (376.5-500.7)

**APPEARS THIS WAY
ON ORIGINAL**

NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02059 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		
<p>Safety Results: Of the 32 subjects dosed with study treatment, 22 (69%) experienced at least 1 treatment-emergent adverse event (AE) during the trial with 5 subjects reporting AEs following RP 1824 in the fasted state, 6 subjects following RP 1824 in the fed state, 9 subjects following Tricor[®] in the fasted state, and 11 subjects following Tricor[®] in the fed state. Headache was the most common AE reported following both RP 1824 and Tricor[®] administration. Of the 49 treatment-emergent AEs reported, 45 were mild in severity and 4 were moderate. The investigator considered 40 of the 49 AEs to be related to RP 1824 or Tricor[®]. No serious adverse events (SAEs) occurred. One subject was dropped from the study by the investigator due to the AE of pregnancy, which was noted at check-in for Period 3 and was considered unrelated to study treatment.</p> <p>There were no treatment-related trends noted with respect to laboratory values, vital sign measurements, electrocardiogram recordings, or physical examination findings regarding subject safety.</p>		
<p>Conclusion:</p> <ul style="list-style-type: none"> • Consumption of a standard high fat meal enhanced the extent (AUC) and rate (C_{max}) of bioavailability of fenofibric acid for both the RP 1824 130 mg and the Tricor[®] 200 mg capsules. • The food effect following a high fat meal observed for the RP 1824 130 mg capsule was approximately 2-fold lower than that observed for the Tricor[®] 200 mg capsule. RP 1824 extent of bioavailability increased by 25% while Tricor[®] increased by approximately 120%. • The extent of bioavailability of fenofibric acid following administration of a RP 1824 130 mg capsule was similar to that of the Tricor[®] 200 mg capsule under fasted conditions; however, the rate of bioavailability was different. • Single oral doses of RP 1824 (130 mg) and Tricor[®] (200 mg) administered under fasted and fed conditions appeared to be safe and well tolerated by the normal healthy subjects in this study. Adverse event incidence was less following both RP 1824 regimens compared to the Tricor[®] regimens. 		
<p>Date of the Report: 22 September 2003</p>		

**APPEARS THIS WAY
ON ORIGINAL**

Synopsis: Bioavailability at Steady State Study

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02060	
RP 1824	Volume: I	
<p>Title of Study: A Randomized, Multiple-Dose, 2-Way Crossover Study to Assess the Relative Bioavailability of RP 1824 130 mg Capsules Versus Tricor[®] 200 mg Capsules at Steady State in Healthy Adult Subjects on a Therapeutic Lifestyle Change Diet</p>		
<p>Investigator:</p>		
<p>Study Center: /</p>		
<p>Publication (Reference): Not applicable</p>		
<p>Studied period: Phase of development: I (Date of first screening) 10 January 2003</p> <p>(Date of last completed) 13 February 2003</p>		
<p>Objectives: The objective of this study was to compare the relative bioavailability of RP 1824 130 mg capsules relative to Tricor[®] 200 mg capsules at steady state after multiple dosing in healthy subjects on a Therapeutic Lifestyle Change (TLC) diet (Appendix A of the protocol [Appendix 16.1.1]).</p>		
<p>Methodology: This was a randomized, multiple-dose, open-label (laboratory-blinded), 2-way crossover study to determine and compare the bioavailability of RP 1824 130-mg oral capsules relative to Tricor[®] 200 mg oral capsules in 28 healthy adult male and female subjects, immediately following consumption of a TLC diet meal.</p>		
<p>Number of Subjects (planned and analyzed): A total of 28 subjects were enrolled in the study, and 26 subjects completed the study. There were 26 subjects included in the safety analysis and 24 subjects included in the pharmacokinetic analysis.</p>		
<p>Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and exclusion criteria.</p>		
<p>Test Product, Dose, Duration, Mode of Administration, and Batch Number: RP 1824 130 mg capsules, manufactured by Ethypharm S.A., Lot No.: D02357, manufactured date: 11 Oct 2002. Subjects randomized to Treatment A received a single oral dose of one RP1824 130 mg capsule taken with 240 mL of room temperature tap water daily for 7 days.</p>		

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ON ORIGINAL

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02060 Volume: I	
RP 1824		
<p>Reference Product, Dose, Duration, Mode of Administration, and Batch Number: Tricor® (fenofibrate) 200 mg micronized capsules, manufactured by Abbott Laboratories, Lot No.: 751172E21, expiration date: 01 Apr 2003. Subjects randomized to Treatment B received a single oral dose of one Tricor® (fenofibrate) 200 mg micronized capsule taken with 240 mL of room temperature tap water daily for 7 days.</p>		
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics: The AUC_{0-24}, $C_{max, 24}$, $T_{max, 24}$, $C_{min, 24}$, $C_{min, 24}$, $T_{min, 24}$, F, $Swing$, and $CL_{m, 24}/F$ pharmacokinetic (PK) parameters were calculated for fenofibric acid from the plasma concentrations from the 24 subjects retained for PK analyses. Descriptive statistics (including arithmetic mean, standard deviation, coefficient of variation, minimum, maximum, median, geometric mean, and sample size) for plasma fenofibric acid concentrations at each time point and for pharmacokinetic parameters were tabulated by treatment.</p> <p>Safety: Physical examination, medical and drug history, clinical laboratory tests, vital signs, electrocardiogram (ECG), and adverse event assessments were evaluated during this study.</p>		
<p>Statistical Methods:</p> <p>Pharmacokinetics: The relative bioavailability of RP 1824 130 mg capsules (test) versus Tricor® 200 mg capsules (reference) after multiple dosing, following consumption of a TLC diet meal, was determined by comparing the respective \log_{10}-transformed steady state (AUC_{0-24} and $C_{max, 24}$) pharmacokinetic parameters. The analysis of variance (ANOVA) model included sequence, formulation, and period as fixed effects and subject nested within sequence as a random effect. The 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the difference between drug formulation least-squares means (LSM) resulting from the analyses on the \ln-transformed parameters AUC_{0-24} and $C_{max, 24}$. The LSM ratios and 90% confidence intervals for the AUC_{0-24} and $C_{max, 24}$ pharmacokinetic parameters were used as an assessment of relative bioavailability.</p> <p>Attainment of steady state was evaluated through linear regression of the \ln-transformed trough levels of fenofibric acid on Days 4, 5, 6, 7, and 8 against time. The slopes of each of the regressions were examined for differences from zero at the $\alpha = 0.05$ level of significance for each analysis. Steady state was concluded if the p-value of the slope between the \ln-transformed trough levels of fenofibric acid and the time were not statistically different ($p > 0.05$).</p>		

APPEARS THIS WAY
ON ORIGINAL

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	Report No.: AA02060 Volume: I
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT		
RP 1824		
<p>Safety: Descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) were calculated for continuous variables (age, height, weight, and body mass index [BMI]) and frequency counts were tabulated for categorical demographic variables (race) by randomized dosing sequence for each gender and overall.</p> <p>Adverse events (AEs) were coded using MedDRA (Version 5.1) and are summarized by preferred term. Number and percentage of subjects experiencing each coded event, total number of each coded event and as a percentage of total adverse events, and by severity and relationship to study drug are displayed for each treatment.</p> <p>Laboratory values were summarized using descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) for continuous serum chemistry and hematology results at each time point (screening and poststudy) and change from screening to poststudy values. The shift from screen to poststudy was provided for each laboratory result for serum chemistry, hematology, and urinalysis. All out-of-range values were listed by subject for each laboratory parameter. Rechecks were used in determination of screen values. Poststudy values were defined as the first observation obtained at that time point.</p> <p>Sitting vital signs measurements (systolic and diastolic blood pressure and heart rate) were summarized using descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) by time point of collection and change from predose for each treatment group. Predose was defined as the last observation obtained prior to dosing for each period on Day 1 (including rechecks). Rechecks were not included as postdose observations.</p> <p>Shifts from screening to poststudy results for physical examinations were tabulated.</p> <p>ECG values were summarized using descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) at screening and poststudy and change from screening to poststudy values. Rechecks were used in determination of screening values. Poststudy values were defined as the first observation obtained at that time point.</p>		
SUMMARY – CONCLUSIONS		
<p>Pharmacokinetic Results: The ratios of LSM (with the 90% confidence intervals) for the AUC_{0-∞}, C_{max,ss}, and Cav,ss pharmacokinetic parameters were 88.4% (84.0–93.0%) and 91.7% (85.1–98.7%), and 88.4% (84.0–93.0%), respectively. The mean T_{max} values at steady state for the RP 1824 130 mg (Fed) and Tricor[®] 200 mg (Fed) treatments were 4.896 and 5.343 hours, respectively.</p> <p>The analysis of trough levels of fenofibric acid established that steady state was attained by Day 6 for both treatments.</p>		

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NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02060 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		
Arithmetic Mean (±SD) Pharmacokinetic Parameters for Fenofibric acid Following Multiple Dosing in Healthy Subjects on a TLC Diet		
Parameter	Treatment A RP 1824 130 mg (Fed)	Treatment B Tricor® 200 mg (Fed)
AUC _{0-∞} (ng·h/mL)	182889 (±53689)	204988 (±50945)
C _{max, ss} (ng/mL)	12664 (±2685)	13810 (±2781)
T _{max, ss} (h)	4.896 (±0.978)	5.343 (±1.281)
C _{av, ss} (ng/mL)	7620 (±2236)	8541 (±2123)
C _{min, ss} (ng/mL)	4859 (±1850)	5878 (±1860)
T _{1/2, ss} (h)	24.0 (±0.0482)	24.0 (±0.0378)
FI (%)	110 (±39.1)	97.6 (±36.1)
Swing (%)	202 (±181)	161 (±120)
CL _{m, ss} /F (L/h)	0.777 (±0.269)	1.04 (±0.293)
<p>Safety Results: A total of 17 of the 28 subjects dosed (61%) experienced at least 1 treatment-emergent AE during the trial. Headache was the most common AE reported following both treatments. All of the AEs were mild in severity and no serious adverse events (SAEs) occurred. One subject was discontinued from the study due to an AE of vomiting, considered unrelated to study drug.</p> <p>There were no treatment-related trends noted with respect to vital signs, ECG, or physical examinations regarding subject safety. Clinical laboratory results, including liver function tests, remained unaffected during the trial.</p>		
<p>Conclusion: The ratios of LSM and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-∞}, ss, C_{max, ss}, and C_{av, ss} for fenofibric acid in plasma were within 80 and 125%. Based on these results, the RP 1824 130 mg capsules and the Tricor® (fenofibrate) 200 mg capsules are exposure equivalent after multiple dosing, immediately following consumption of a TLC diet meal.</p> <p>RP 1824 130 mg capsules were safe and well tolerated at steady state after multiple dosing in healthy subjects on a TLC diet.</p>		
Date of the Report:	18 September 2003	

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Synopsis: Relative Bioavailability after Single Dose Study:

NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02063 Volume: I	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		
Title of Study: A Randomized, Single-Dose, 4-Way Crossover Study to Determine and Compare the Relative Bioavailability of RP 1824 130 mg to Tricor® 200 mg Under Fasted Conditions and Following Consumption of a Therapeutic Lifestyle Change Meal in Healthy Adult Subjects		
Investigator:		
Study Center:		
Publication (Reference):	Not applicable	
Studied period: (Date of first enrollment) 30 December 2002	Phase of development: I	
(Date of last completed) 01 March 2003		
Objectives: The objectives of this study were as follows: <ul style="list-style-type: none"> To determine the relative bioavailability of RP 1824 130 mg oral capsules to Tricor® 200 mg oral capsules under fasting conditions and immediately following consumption of a Therapeutic Lifestyle Change (TLC) diet meal in healthy adults. To determine the relative bioavailability of RP 1824 130 mg oral capsules under fasting conditions and immediately following consumption of a TLC diet meal in healthy adults. To determine the relative bioavailability of Tricor® 200 mg oral capsules under fasting conditions and immediately following consumption of a TLC diet meal in healthy adults. 		
Methodology: This was a randomized, single-dose, open-label (laboratory blinded), 4-way crossover study to determine the relative bioavailability of RP 1824 130 mg oral capsules to Tricor® 200 mg oral capsules under fasted and fed conditions in healthy adult subjects. The relative bioavailability of each formulation under fasted and fed conditions was also assessed.		
Number of Subjects (planned and analyzed): A total of 32 subjects were enrolled in the study and 29 subjects completed the study. There were 30 subjects included in the pharmacokinetic (PK) analyses and 32 subjects included in the safety analysis.		
Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the investigator to be normal, healthy volunteers who met all inclusion and exclusion criteria.		

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NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02063 Volume: I	
RP 1824		
<p>Test Product, Dose, Duration, Mode of Administration, and Batch Number: The test product was RP 1824 130 mg capsules, manufactured by Ethypharm S.A., France, Lot No.: D02357, expiration date: not provided. Subjects randomized to Treatment A received a single oral dose of one RP 1824 130 mg capsule taken with 240 mL tap water under fasted conditions. Subjects randomized to Treatment B received a single oral dose of one RP 1824 130 mg capsule taken with 240 mL of room temperature tap water following a TLC meal.</p>		
<p>Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The reference product was fenofibrate micronized Tricor[®] 200 mg capsules, manufactured by Abbott Laboratories, Lot No.: 751172E21. Subjects randomized to Treatment C received a single oral dose of one Tricor[®] 200 mg capsule taken with 240 mL tap water under fasted conditions. Subjects randomized to Treatment D received a single oral dose of one fenofibrate micronized Tricor[®] 200 mg capsule taken with 240 mL of tap water following a TLC diet meal.</p>		
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics: The AUC_{0-4}, AUC_{0-24}, AUC_{0-4}/AUC_{0-24}, C_{max}, T_{max}, $t_{1/2}$, K_{el}, $CL_{m/F}$, and $Vd_{m/F}$ pharmacokinetic parameters were calculated for fenofibric acid from the plasma concentrations from the 30 subjects retained for PK analyses. Descriptive statistics (including arithmetic mean, standard deviation [SD], coefficient of variation [CV], minimum, maximum, median, geometric mean [GM], and number of observations [N]) for plasma fenofibric acid concentrations at each time point and for pharmacokinetic parameters were tabulated by treatment.</p> <p>Safety: Physical examination, medical and drug history, clinical laboratory tests, vital signs, electrocardiogram (ECG), and adverse event assessments were evaluated during this study.</p>		
<p>Statistical Methods:</p> <p>Pharmacokinetics: Relative bioavailabilities were determined using the parameters AUC_{0-4}, AUC_{0-24}, and C_{max} for the following treatments:</p> <p>Treatment B: RP 1824 130 mg (Fed)/Treatment A: RP 1824 130 mg (Fasted),</p> <p>Treatment D: Tricor[®] 200 mg (Fed)/Treatment C: Tricor[®] 200 mg (Fasted),</p> <p>Treatment B: RP 1824 130 mg (Fed)/Treatment D: Tricor[®] 200 mg (Fed),</p> <p>Treatment A: RP 1824 130 mg (Fasted)/Treatment C: Tricor[®] 200 mg (Fasted),</p> <p>Treatment B: RP 1824 130 mg (Fed) /Treatment C: Tricor[®] 200 mg (Fasted), and</p> <p>Treatment A: RP 1824 130 mg (Fasted)/Treatment D: Tricor[®] 200 mg (Fed).</p>		

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NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02063 Volume: I	
RP 1824		
<p>Pharmacokinetics continued: The analysis of variance (ANOVA) model included sequence, formulation, and period as fixed effects and subject nested within sequence as a random effect. The 90% confidence intervals (CI) for the ratios were derived by exponentiation of the CIs obtained for the difference between drug formulation least-squares means (LSM) resulting from the analyses on the ln-transformed parameters AUC₀₋₈, AUC₀₋₁₂, and C_{max}. If the 90% CI for the ratios of population least-square geometric means (based on ln-transformed parameters) of fed and fasted treatments fell within 80 – 125% for the AUCs and C_{max}, then the presence of a food effect was excluded. If the 90% CI for AUCs and C_{max} fell outside the above limits, then a food effect was assumed.</p>		
<p>Safety: Descriptive statistics (mean, SD, minimum, median, maximum, and N) were calculated for continuous variables (age, height, weight, and body mass index [BMI]) and frequency counts were tabulated for categorical demographic variable (race) by randomized dosing sequence for each gender and overall.</p>		
<p>Adverse events (AEs) were coded using MedDRA (Version 5.1) and are summarized by preferred term. Number and percentage of subjects experiencing each coded event, total number of each coded event and as a percentage of total adverse events, and by severity and relationship to study drug are displayed for each treatment.</p>		
<p>Laboratory values were summarized using descriptive statistics (mean, SD, minimum, median, maximum, and N) for continuous serum chemistry and hematology results at each time point (screening and post study) and change from screening to post study values. The shift from screen to post study was provided for each laboratory result for serum chemistry, hematology, and urinalysis. All out-of-range values were listed by subject for each laboratory parameter. Rechecks were used in determination of screening values. Post study values were defined as the first observation obtained at that time point.</p>		
<p>Sitting vital signs measurements (systolic and diastolic blood pressure and heart rate) were summarized using descriptive statistics (mean, SD, minimum, median, maximum, and N) by time point of collection and change from predose for each treatment group. Predose was defined as the last observation obtained prior to dosing for each period on Day 1 (including rechecks). Rechecks were not included as postdose observations.</p>		
<p>Shifts from screening to post study results for physical examinations were tabulated.</p>		
<p>ECG values were summarized using descriptive statistics (mean, SD, minimum, median, maximum, and N) at screening and post study and change from screening to post study values. Rechecks were used in determination of screening values. Post study values were defined as the first observation obtained at that time point.</p>		

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NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02063 Volume: I	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		

SUMMARY – CONCLUSIONS

Pharmacokinetic Results: The pharmacokinetic results for all parameters and the ratios of LSM (with the 90% CI) derived from the analyses of the ln-transformed AUC₀₋₁₂, AUC₀₋₁₈, and C_{max} pharmacokinetic parameters for all comparisons of interest are tabulated below.

Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Therapeutic Lifestyle Change Meal) Conditions - Arithmetic Mean (±SD)

Parameter	Treatment A: RP 1824 130 mg (Fasted)	Treatment B: RP 1824 130 mg (Fed)	Treatment C: Tricor® 200 mg (Fasted)	Treatment D: Tricor® 200 mg (Fed)
AUC ₀₋₁₂ (ng·h/mL)	126031 (±31875)	130400 (±38928)	123769 (±45252)	159932 (±43760)
AUC ₀₋₁₈ (ng·h/mL)	128020 (±33000)	132987 (±40251)	129798 (±49944)	162332 (±45509)
C _{max} (ng/mL)	4403 (±1303)	7565 (±1583)	2734 (±1312)	7554 (±2934)
T _{max} (h)	4.73 (±1.59)	4.21 (±0.632)	8.37 (±9.68)	4.58 (±0.508)
t _{1/2} (h)	23.1 (±7.32)	23.0 (±6.22)	27.1 (±17.9)	23.3 (±6.81)
K _{el} (1/h)	0.0324 (±0.00913)	0.0324 (±0.00899)	0.0315 (±0.0117)	0.0321 (±0.00870)
CL _{cr} /F (L/h)	1.09 (±0.330)	1.06 (±0.302)	1.89 (±1.28)	1.37 (±0.584)
Vd _{cr} /F (L)	35.6 (±14.4)	34.0 (±11.7)	64.5 (±38.1)	44.5 (±19.4)

Ratios (%) of LSM (90% CI) for RP 1824 vs Tricor®

Parameter	B: RP 1824 130 mg (Fed) vs D: Tricor® 200 mg (Fed)	A: RP 1824 130 mg (Fasted) vs C: Tricor® 200 mg (Fasted)	B: RP 1824 130 mg (Fed) vs C: Tricor® 200 mg (Fasted)	A: RP 1824 130 mg (Fasted) vs D: Tricor® 200 mg (Fed)
AUC ₀₋₁₂	83.3 (75.9 – 91.4)	105.2 (95.9 – 115.5)	109.4 (99.7 – 120.1)	80.1 (73.0 – 87.8)
AUC ₀₋₁₈	83.2 (75.9 – 91.3)	102.5 (93.5 – 112.4)	108.5 (97.1 – 116.7)	80.1 (73.1 – 87.8)
C _{max}	105.7 (90.5 – 123.5)	168.9 (144.6 – 197.2)	295.7 (253.2 – 345.3)	60.4 (51.7 – 70.4)

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NAME OF COMPANY Reliant Pharmaceuticals, LLC		INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824			
NAME OF ACTIVE INGREDIENT RP 1824			
Report No.: AA02083 Volume: I			
Fed vs Fasted Ratios (%) of LSM (90% CI) for Individual Formulations			
Parameter	B: RP 1824 130 mg (Fed) vs A: RP 1824 130 mg (Fasted)	D: Tricor [®] 200 mg (Fed) vs C: Tricor [®] 200 mg (Fasted)	
AUC ₀₋₄	104.0 (94.7 – 114.1)	131.4 (119.7 – 144.2)	
AUC ₀₋₂₄	103.9 (94.8 – 113.9)	127.9 (116.7 – 140.9)	
C _{max}	175.1 (149.9 – 204.6)	279.7 (239.5 – 326.7)	
<p>Safety Results: Of the 32 subjects dosed with study treatment, 14 (44%) experienced at least 1 treatment-emergent adverse event (AE) during the trial with 4 subjects following RP 1824 under fasted conditions, 5 subjects following RP 1824 under fed conditions, 6 subjects following Tricor[®] under fasted conditions, and 5 subjects following Tricor[®] under fed conditions. Headache was the most common AE reported during the trial. All of the 43 treatment-emergent AEs were mild or moderate in severity. The Investigator considered 2 of the 43 AEs (loose stools and somnolence) to be "possibly" related to study drug and considered the remaining AEs to be "unlikely" or "unrelated" to study drug. No serious adverse events (SAEs) occurred and no subjects discontinued the trial due to AEs.</p> <p>No clinically relevant trends were noted with regard to the laboratory, vital sign, electrocardiogram, and physical examination findings.</p>			
Conclusion:			
<ul style="list-style-type: none"> • Following consumption of a TLC meal, the maximum plasma concentration (C_{max}) of fenofibric acid from the RP 1824 130 mg capsules was 105.7% to that of the Tricor[®] 200 mg capsules; the relative extent of bioavailability (AUC₀₋₂₄) was 83.2%. • Under fasted conditions, the relative extent of bioavailability (AUC) of fenofibric acid following administration of RP 1824 130 mg and Tricor[®] 200 mg capsules was 102.5%. The C_{max} of fenofibric acid was 68.9% greater for the RP 1824 130 mg capsules. • Consumption of a TLC meal did not affect the extent of bioavailability (AUC₀₋₂₄) of fenofibric acid for the RP 1824 capsules (103.9%); consumption of a TLC meal affected the extent of bioavailability for the Tricor[®] 200 mg capsules (127.9%). • Consumption of a TLC meal affected the rate of bioavailability (C_{max}) for both the RP 1824 (75.1%) and Tricor[®] 200 mg capsules (179.7%); the food effect was more than 2-fold lower for the RP 1824 130 mg capsules as compared to the Tricor[®] 200 mg capsules. 			
Date of the Report:		08 October 2003	

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ON ORIGINAL

Synopsis: Dose Proportionality Study:

NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02061 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		
Title of Study: A Randomized, Open-Label, Single-Dose, 3-Way Crossover Study to Determine the Relative Bioavailability and Dose Proportionality of RP 1824 43 mg, 87 mg, and 130 mg Capsules Under Fasting Conditions in Healthy Adult Subjects		
Investigator: _____		
Study Center: _____		
Publication (Reference): Not applicable		
Studied period: Phase of development: I (Date of first screening) 24 January 2003 (Date of last completed) 08 March 2003		
Objective: The objective of this study was to determine the relative bioavailability and dose proportionality of RP 1824 43 mg, 87 mg, and 130 mg capsules following single-dose administration in healthy adults under fasting conditions.		
Methodology: This was a randomized, single-dose, open-label (laboratory blinded), 3-way crossover study to determine the relative bioavailability and dose proportionality of RP 1824 (dosed as single 43 mg, 87 mg, and 130 mg capsules) orally administered under fasting conditions to 30 healthy adult male and female subjects.		
Number of Subjects (planned and analyzed): A total of 30 subjects, 19 males and 11 females, were enrolled in the study, and 29 subjects, 19 males and 10 females, completed the study. There were 30 subjects included in the safety analysis and 28 subjects included in the pharmacokinetic analysis. The 2 subjects not included in the pharmacokinetic analysis were Subject 14, who withdrew consent due to personal reasons, and Subject 28 who was excluded due to a vomiting episode 8.5 hours after dosing in Period 1.		
Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and exclusion criteria.		

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NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02061 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		
<p>Test Product, Dose, Duration, Mode of Administration, and Batch Number: Subjects randomized to Treatment A received a single oral dose of one 43 mg capsule of RP 1824 (Lot #D02379). Subjects randomized to Treatment B received a single oral dose of one 87 mg capsule of RP 1824 (Lot #D02380). Subjects randomized to Treatment C received a single oral dose of one 130 mg capsule of RP 1824 (Lot # D02357). All treatments were administered after a 10-hour fast with 240 mL of water.</p>		
<p>Reference Product, Dose, Duration, Mode of Administration, and Batch Number: Not applicable.</p>		
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics: The AUC_{0-2}, AUC_{0-12}, $AUC_{0-\infty}$, $AUC_{0-12}/AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, K_{el}, CL_{int}/F and Vd_{int}/F pharmacokinetic (PK) parameters were calculated for fenofibric acid from the plasma concentrations from the 28 subjects retained for PK analyses. Descriptive statistics (including arithmetic mean, standard deviation [SD], coefficient of variation [CV], minimum, maximum, median, geometric mean, and sample size [N]) for plasma fenofibric acid concentrations at each time point and for pharmacokinetic parameters were tabulated by treatment.</p> <p>Safety: Physical examination, medical and drug history, clinical laboratory tests, vital signs, electrocardiogram (ECG), and adverse event (AE) assessments were evaluated during this study.</p>		
<p>Statistical Methods:</p> <p>Pharmacokinetics: The relative bioavailability of the respective RP 1824 capsules administered under fasted conditions were estimated using mixed model analysis of variance (ANOVA), appropriate for a 3-way crossover design, analyzing dose-normalized (to the 43 mg dose) and ln-transformed AUC_{0-2}, AUC_{0-12}, and C_{max} values. Relative bioavailability was expressed as the ratios of test (87 mg or 130 mg capsule) to reference (43 mg capsule), along with the associated 90% confidence intervals (CI) and the appropriate pairwise estimates. The ANOVA model included sequence, formulation, and period as fixed effects and subject within sequence as a random effect. Point estimates and 90% CIs for differences in median T_{max} values were calculated using nonparametric techniques. A power model (regression of ln-transformed data) was used for assessment of dose proportionality.</p>		

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NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02061 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP1824		
NAME OF ACTIVE INGREDIENT RP1824		
<p>Safety: Descriptive statistics (mean, SD, minimum, maximum, and N) were calculated for continuous variables (age, height, weight, and body mass index [BMI]) and frequency counts were tabulated for the categorical demographic variable (race) by randomized dosing sequence for each gender and overall.</p> <p>AEs were coded using MedDRA (Version 5.1) and are summarized by preferred term. Number and percentage of subjects experiencing each coded event, total number of each coded event and as a percentage of total AEs, and by severity and relationship to study drug are displayed for each treatment.</p> <p>Laboratory values were summarized using descriptive statistics (mean, SD, minimum, maximum, and N) for continuous serum chemistry and hematology results at each time point (screening and post study) and change from screening to post study values. The shift from screen to post study was provided for each laboratory result for serum chemistry, hematology, and urinalysis. All out-of-range values were listed by subject for each laboratory parameter. Rechecks were used in determination of screen values. Post study values were defined as the first observation obtained at that time point.</p> <p>Sitting vital signs measurements (systolic and diastolic blood pressure and heart rate) were summarized using descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) by time point of collection and change from predose for each treatment group. Predose was defined as the last observation obtained prior to dosing for each period on Day 1 (including rechecks). Rechecks were not included as postdose observations.</p> <p>Shifts from screening to post study results for physical examinations were tabulated.</p> <p>ECG values were summarized using descriptive statistics (mean, SD, minimum, maximum, and N) at screening and post study and change from screening to post study values. Rechecks were used in determination of screening values. Post study values were defined as the first observation obtained at that time point.</p>		

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ON ORIGINAL

NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02061 Volume: I	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP1824		
NAME OF ACTIVE INGREDIENT RP1824		

SUMMARY - CONCLUSIONS

Pharmacokinetic Results: The results for all pharmacokinetic parameters, the ratios of least squares mean (LSM) (with the 90% CI) derived from the analysis of the ln-transformed AUC₀₋₄, AUC₀₋₁₂, and C_{max} parameters for the comparisons of interest, and the results of the nonparametric analysis of T_{max} are presented in the following tables.

Arithmetic Mean (±SD) Pharmacokinetic Parameters for Fenofibric Acid Following Single 43 mg, 87 mg, and 130 mg Doses Under Fasted Conditions

Parameter	Treatment A: RP 1824 43 mg (Fasted)	Treatment B: RP 1824 87 mg (Fasted)	Treatment C: RP 1824 130 mg (Fasted)
AUC ₀₋₄ (ng·h/mL)	51333 (±23123)	91187 (±42776)	123932 (±55037)
AUC ₀₋₁₂ (ng·h/mL)	52430 (±23868)	92514 (±44677)	125742 (±51901)
C _{max} (ng/mL)	2242 (±147)	4018 (±1674)	5525 (±2034)
T _{max} (h)	4.16 (±1.73)	4.32 (±1.49)	4.56 (±1.49)
t _{1/2} (h)	20.4 (±4.84)	20.6 (±5.08)	21.8 (±5.78)
K _a (1/h)	0.0356 (±0.00721)	0.0352 (±0.00695)	0.0336 (±0.00736)
CL _{int} /F (L/h)	0.944 (±0.333)	1.09 (±0.395)	1.18 (±0.382)
Vd _a /F (L)	25.3 (±7.00)	30.9 (±9.51)	35.1 (±8.69)

Ratios (%) of Dose-Normalized LSM (90% CI)

Parameter	B: RP 1824 87 mg (Fasted) vs A: RP 1824 43 mg (Fasted)	C: RP 1824 130 mg (Fasted) vs A: RP 1824 43 mg (Fasted)
AUC ₀₋₄	87.5 (83.0 – 92.2)	80.0 (75.9 – 84.3)
AUC ₀₋₁₂	86.7 (82.3 – 91.4)	79.3 (75.2 – 83.5)
C _{max}	88.1 (78.5 – 94.4)	80.7 (73.6 – 88.5)

Summary of Results for Nonparametric Analysis of T_{max}

Comparison of Interest	Sequence		Period		Formulation		90% CI
	Median of S1 – S2 Difference	p-value	Median of P1 – P2 Difference	p-value	Median of F1 – F2 Difference	p-value	
87 vs 43 mg	-0.54	0.1731	0.25	0.1450	0.00	0.3581	0.00 to 0.50
130 vs 43 mg	-0.985	0.2483	0.00	≈1.000	0.50	0.0254	0.04 to 1.00

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NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02061 Volume: I	
RP1824		
<p>Dose proportionality was evaluated for the AUC_{0-4} and C_{max} pharmacokinetic parameters using a power model approach. For both AUC_{0-4} and C_{max}, a statistical linearity was demonstrated between the ln-transformed parameter and the ln-transformed dose. The 95% CIs for the slope of the ln-transformed AUC_{0-4} and C_{max} were 0.7995 (0.7437–0.8554) and 0.8040 (0.7065–0.9015), respectively, using the protocol-defined statistical methodology.</p> <p>Safety Results: Of the 30 subjects dosed with RP 1824, 20 (67%) experienced at least 1 treatment-emergent AE during the trial with 11 subjects following the 43 mg dose, 8 subjects following the 87 mg dose, and 13 subjects following the 130 mg dose. Thus AE incidence did not appear to progressively increase with rising RP 1824 dose. Headache was the most common AE reported, following all three RP 1824 doses. All of the 58 treatment-emergent AEs were mild or moderate in severity. The investigator considered 8 of the 58 AEs to be "possibly" related to study drug; these were gastrointestinal (GI) in nature and included abdominal pain, dyspepsia, nausea, and vomiting. No serious adverse events (SAEs) occurred and no subjects discontinued the trial due to AEs.</p> <p>There were no treatment-related trends noted with respect to laboratory values, vital sign measurements, electrocardiogram results, or physical examination findings regarding subject safety.</p>		
<p>Conclusion: Following administration of the RP 1824 43 mg and 87 mg capsules under fasted conditions, the 90% CIs of the ratios of LSM for the dose-normalized ln-transformed parameters AUC_{0-4} and AUC_{0-12} for fenofibric acid were within 80-125%. The ratio of LSM for the dose-normalized ln-transformed parameter C_{max} was within 80-125%, but the 90% CI fell outside the lower limit.</p> <p>For the RP 1824 43 mg and 130 mg doses under fasted conditions, the 90% CIs of the ratios of LSM for the dose-normalized ln-transformed parameters AUC_{0-4}, AUC_{0-12}, and C_{max} were not within 80-125%.</p> <p>AUC_{0-4} and C_{max} values seemed to increase in a statistically linear manner with increasing doses of RP 1824. Although dose proportionality with the three strengths could not be concluded using the protocol-defined statistical methodology, the statistical linear relationship observed (p-value < 0.05 for AUC_{0-4} and C_{max}) between increasing dose and fenofibric acid exposure, supports a conclusion of predicable drug exposure with incremental dosage strengths of RP 1824. Importantly, the slopes of point estimates for AUC_{0-4} and C_{max} are each within 0.80 and 1.25. Therefore, based on a clinical difference of no more than 20%, the PK parameters AUC_{0-4} and C_{max} may be considered dose proportional.</p> <p>RP 1824 administered in single oral doses up to 130 mg appeared to be safe and well tolerated by the healthy male and female subjects in this study.</p>		
Date of the Report:	19 September 2003	

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Synopsis: Dose Equivalence Study:

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT		Report No.: AA02062
RP 1824	Volume: 1	
Title of Study:	A Randomized, Open-Label, Single-Dose, 4-Way Crossover Study to Determine the Dose Equivalence of Multiple RP 1824 43 mg Capsules Relative to RP 1824 87 mg and 130 mg Capsules Under Fasting Conditions in Healthy Adult Subjects	
Investigator:	_____	
Study Center:	_____ _____	
Publication (Reference):	Not applicable	
Studied period:	Phase of development: I	
(Date of first screening)	06 January 2003	
(Date of last completed)	05 March 2003	
Objectives:	The objective of this study was to determine the dose equivalence of RP 1824 at doses of 43 mg x 2 capsules, 43 mg x 3 capsules, 87 mg x 1 capsule, and 130 mg x 1 capsule in healthy adults under fasting conditions.	
Methodology:	This study utilized a randomized, open-label, single-dose, 4-way crossover design with a ≥ 14-day washout between dosing days.	
Number of Subjects (planned and analyzed):	A total of 32 subjects were enrolled in the study and 27 subjects completed the study. There were 32 subjects included in the safety analysis and 29 subjects included in the pharmacokinetic (PK) analysis.	
Diagnosis and Main Criteria for Inclusion:	All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and exclusion criteria.	
Test Product, Dose, Duration, Mode of Administration, and Batch Number:	The test product was RP1824 administered in 43 mg, 87 mg, and 130 mg capsules. RP 1824 capsules were manufactured by Ethypharm S.A., France. Lot numbers were D02379, D02380, and D02357 for the 43 mg, 87 mg, and 130 mg capsules, respectively. Manufacture dates were 11 October for D02357 and 11 December 2002 for D02379 and D02380. Subjects were to receive 4 single oral RP 1824 doses: Treatment A: 2 x 43 mg RP 1824 capsules; Treatment B: 3 x 43 mg RP 1824 capsules; Treatment C: 1 x 87 mg RP 1824 capsule; Treatment D: 1 x 130 mg RP 1824 capsule. Each RP 1824 dose was administered with 240 mL of tap water.	

NAME OF COMPANY	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
Reliant Pharmaceuticals, LLC	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF FINISHED PRODUCT		
RP 1824		
NAME OF ACTIVE INGREDIENT	Report No.: AA02082	
RP 1824	Volume: 1	
Reference Product, Dose, Duration, Mode of Administration, and Batch Number: Not applicable.		
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics: The AUC_{0-1}, AUC_{0-24}, AUC_{0-12}/AUC_{0-24}, C_{max}, T_{max}, $t_{1/2}$, K_{el}, CL_{tr}/F and Vd_{tr}/F pharmacokinetic parameters were calculated for fenofibric acid from the plasma concentrations from the 29 subjects retained for PK analyses. Descriptive statistics (including arithmetic mean, standard deviation [SD], coefficient of variation [CV], minimum, maximum, median, geometric mean [GM], and number [N]) for plasma fenofibric acid concentrations at each time point and for pharmacokinetic parameters were tabulated by treatment.</p> <p>Safety: Physical examination, medical and drug history, clinical laboratory tests, vital signs, electrocardiogram (ECG), and adverse event (AE) assessments were evaluated during this study.</p>		
<p>Statistical Methods:</p> <p>Pharmacokinetics: Dose equivalence after single dosing was determined using the pharmacokinetic parameters AUC_{0-1}, AUC_{0-12}, and C_{max} for the following treatments:</p> <p>Treatment A: RP 1824 2 x 43 mg (Fasted)/Treatment C: RP 1824 1 x 87 mg (Fasted),</p> <p>Treatment B: RP 1824 3 x 43 mg (Fasted)/Treatment D: RP 1824 1 x 130 mg (Fasted).</p> <p>The analysis of variance (ANOVA) model included sequence, formulation, and period as fixed effects and subject nested within sequence as a random effect. The 90% confidence intervals (CI) for the ratios were derived by exponentiation of the CI obtained for the difference between drug formulation least squares means (LSM) resulting from the analyses on the ln-transformed parameters AUC_{0-1}, AUC_{0-12}, and C_{max}. If the 90% CI for the ratios of least-square GM (based on ln-transformed parameters) of test and reference treatments fell within 80 – 125% for the AUCs and C_{max}, then dose equivalence was concluded.</p>		

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NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02062 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824		
NAME OF ACTIVE INGREDIENT RP 1824		
<p>Safety: Descriptive statistics (mean, SD, minimum, maximum, and N) were calculated for continuous variables (age, height, weight, and body mass index [BMI]) and frequency counts were tabulated for the categorical demographic variable (race) by randomized dosing sequence for each gender and overall.</p> <p>Adverse events were coded using MedDRA (Version 5.1) and are summarized by preferred term. Number and percentage of subjects experiencing each coded event, total number of each coded event and as a percentage of total adverse events, and by severity and relationship to study drug are displayed for each treatment.</p> <p>Laboratory values were summarized using descriptive statistics (mean, SD, minimum, median, maximum, and N) for continuous serum chemistry and hematology results at each time point (screening and poststudy) and change from screening to poststudy values. The shift from screening to poststudy was provided for each laboratory result for serum chemistry, hematology, and urinalysis. All out-of-range values were listed by subject for each laboratory parameter. Rechecks were used in determination of screening values. Poststudy values were defined as the first observation obtained at that time point.</p> <p>Sitting vital signs measurements (systolic and diastolic blood pressure and heart rate) were summarized using descriptive statistics (mean, SD, minimum, median, maximum, and N) by time point of collection and change from predose for each treatment group. Predose was defined as the last observation obtained prior to dosing for each period on Day 1 (including rechecks). Rechecks were not included as postdose observations.</p> <p>Shifts from screening to poststudy results for physical examinations were tabulated.</p> <p>ECG values were summarized using descriptive statistics (mean, SD, minimum, median, maximum, and N) at screening and poststudy and change from screening to poststudy values. Rechecks were used in determination of screening values. Poststudy values were defined as the first observation obtained at that time point.</p>		

NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: AA02062 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)																																												
NAME OF FINISHED PRODUCT RP 1824																																														
NAME OF ACTIVE INGREDIENT RP 1824																																														
<p>SUMMARY – CONCLUSIONS</p> <p>Pharmacokinetic Results: The pharmacokinetic results for all parameters and the ratios of LSM (with the 90% CI) derived from the analyses of the ln-transformed AUC_{0-1h}, AUC_{0-12h}, and C_{max} pharmacokinetic parameters for all comparisons of interest are tabulated below.</p> <p style="text-align: center;">Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted Conditions - Arithmetic Mean (±SD)</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Treatment A: RP 1824 2 x 43 mg (Fasted)</th> <th>Treatment B: RP 1824 3 x 43 mg (Fasted)</th> <th>Treatment C: RP 1824 1 x 87 mg (Fasted)</th> <th>Treatment D: RP 1824 1 x 130 mg (Fasted)</th> </tr> </thead> <tbody> <tr> <td>AUC₀₋₁ (ng·h/mL)</td> <td>82917 (±31384)</td> <td>119906 (±52441)</td> <td>83221 (±30091)</td> <td>117368 (±44085)</td> </tr> <tr> <td>AUC_{0-12h} (ng·h/mL)</td> <td>84295 (±32385)</td> <td>122505 (±55095)</td> <td>84939 (±31655)</td> <td>119809 (±46180)</td> </tr> <tr> <td>C_{max} (ng/mL)</td> <td>3699 (±1252)</td> <td>4722 (±1641)</td> <td>3343 (±969)</td> <td>4766 (±1388)</td> </tr> <tr> <td>t_{max} (h)</td> <td>4.65 (±2.04)</td> <td>4.73 (±1.68)</td> <td>4.52 (±1.77)</td> <td>4.66 (±1.08)</td> </tr> <tr> <td>t_{1/2} (h)</td> <td>20.2 (±6.56)</td> <td>21.8 (±13.4)</td> <td>20.4 (±6.82)</td> <td>21.1 (±7.25)</td> </tr> <tr> <td>K_{el} (1/h)</td> <td>0.0376 (±0.0107)</td> <td>0.0366 (±0.0100)</td> <td>0.0371 (±0.0106)</td> <td>0.0360 (±0.0102)</td> </tr> <tr> <td>CL_{0-12h}/F (L/h)</td> <td>1.18 (±0.491)</td> <td>1.23 (±0.465)</td> <td>1.18 (±0.474)</td> <td>1.25 (±0.476)</td> </tr> <tr> <td>Vd_{0-12h}/F (L)</td> <td>31.4 (±7.63)</td> <td>34.7 (±12.0)</td> <td>31.5 (±7.05)</td> <td>34.9 (±9.36)</td> </tr> </tbody> </table>			Parameter	Treatment A: RP 1824 2 x 43 mg (Fasted)	Treatment B: RP 1824 3 x 43 mg (Fasted)	Treatment C: RP 1824 1 x 87 mg (Fasted)	Treatment D: RP 1824 1 x 130 mg (Fasted)	AUC ₀₋₁ (ng·h/mL)	82917 (±31384)	119906 (±52441)	83221 (±30091)	117368 (±44085)	AUC _{0-12h} (ng·h/mL)	84295 (±32385)	122505 (±55095)	84939 (±31655)	119809 (±46180)	C _{max} (ng/mL)	3699 (±1252)	4722 (±1641)	3343 (±969)	4766 (±1388)	t _{max} (h)	4.65 (±2.04)	4.73 (±1.68)	4.52 (±1.77)	4.66 (±1.08)	t _{1/2} (h)	20.2 (±6.56)	21.8 (±13.4)	20.4 (±6.82)	21.1 (±7.25)	K _{el} (1/h)	0.0376 (±0.0107)	0.0366 (±0.0100)	0.0371 (±0.0106)	0.0360 (±0.0102)	CL _{0-12h} /F (L/h)	1.18 (±0.491)	1.23 (±0.465)	1.18 (±0.474)	1.25 (±0.476)	Vd _{0-12h} /F (L)	31.4 (±7.63)	34.7 (±12.0)	31.5 (±7.05)
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NAME OF COMPANY Reliant Pharmaceuticals, LLC	INDIVIDUAL STUDY TABLE SYNOPSIS	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT RP 1824	REFERRING TO PART 1 OF THE DOSSIER	
NAME OF ACTIVE INGREDIENT RP 1824	Report No.: AA02062 Volume: I	
Ratios of LSM (90% CI) for Fenofibric Acid		
Parameter	A: RP 1824 2 x 43 mg (Fasted) vs C: RP 1824 1 x 87 mg (Fasted)	B: RP 1824 3 x 43 mg (Fasted) vs D: RP 1824 1 x 130 mg (Fasted)
AUC ₀₋₂₄	98.4% (93.6% - 103.4%)	101.3% (96.4% - 106.3%)
AUC ₀₋₂₄ / C _{max}	98.1% (93.3% - 103.1%)	101.5% (96.5% - 106.7%)
C _{max}	108.5% (98.5% - 118.6%)	97.3% (88.4% - 107.1%)
<p>Safety Results: A total of 16 of the 32 subjects dosed (50%) experienced at least 1 treatment-emergent AE during the trial. Fewer subjects reported AEs following the single 130 mg capsule compared to the other treatments. Headache was the most common AE reported. All of the AEs were mild in severity, no serious adverse events (SAEs) occurred, and no subjects were discontinued due to AEs.</p> <p>There were 3 subjects (9%) with Alanine aminotransferase (AST) or creatine kinase (CK) elevations following dosing that were documented as AEs. The investigator considered all of these occurrences unrelated to study drug and probably exercise-induced. All clinical laboratory mean parameters remained within reference range.</p> <p>There were no treatment-related trends noted with respect to vital signs, ECG, or physical examinations regarding subject safety.</p> <p>Conclusion: Single RP 1824 doses of 43 mg x 2 capsules are dose equivalent to single RP 1824 doses of 87 mg x 1 capsule under fasting conditions. Similarly, single RP 1824 doses of 43 mg x 3 capsules are dose equivalent to single RP 1824 doses of 130 mg x 1 capsule under fasting conditions.</p> <p>Single RP 1824 doses of 43 mg x 2 capsules, 43 mg x 3 capsules, 87 mg x 1 capsule, and 130 mg x 1 capsule administered under fasting conditions appeared to be safe and well tolerated by the healthy male and female subjects in this trial.</p>		
Date of the Report:	10 September 2003	

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

/s/

Jayabharathi Vaidyanathan
9/8/04 09:20:28 AM
PHARMACOLOGIST

Hae-Young Ahn
9/8/04 11:06:20 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-695	Brand Name	RP 1824
OCPB Division (I, II, III)	II	Generic Name	Fenofibrate <i>Micromedex</i>
Medical Division	510	Drug Class	Lipid lowering
OCPB Reviewer	Wei Qiu, Ph.D.	Indication(s)	Type IIa, IIb, IV, and V hyperlipidemia
OCPB Team Leader	Hae-Young Ahn	Dosage Form	capsules
Related IND(s)	66, 249	Dosing Regimen	43, 87, and 130 mg
Date of Submission	Dec 1, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Reliant Pharmaceuticals
PDUFA Due Date		Priority Classification	505(b)(2) 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				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
Mutual:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Meta Analysis:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	4		
replicate design; single / multi dose:				
Food-drug interaction studies:	x			Two BE studies (FF2 and FF4C evaluated food effect)
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm ?				
QBR questions (key issues to be considered)	1. Relative bioavailability compared with Tricor micronized capsules 2. Dosage form equivalence 3. Food effect 4. Dose proportionality			
Other comments or information not included above	Since no clinical trial was conducted with the subject of this NDA submission, it is desirable to conduct DSI inspection on the pivotal BE study. Protocol FF4C Title of Study: A Randomized, Single-Dose, 4-Way Crossover Study to Determine and Compare the Relative Bioavailability of RP 1824 130 mg to Tricor® 200 mg under Fasted Conditions and Following Consumption of A Therapeutic Lifestyle Change (TLC) Meal in Healthy Adult Subjects Clinical Site: _____ Analysis Site: _____			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

On Dec 1, 2003, Reliant Pharmaceuticals submitted an original NDA 505(b)(2) for RP 1824 fenofibrate capsules, 43, 87, and 130 mg for the treatments of Type IIa, IIb, IV and V hyperlipidemia.

There were 5 PK studies conducted in support of this application

1. FF4C A randomized, single-dose, 4-way crossover study to determine and compare the relative bioavailability of RP 1824 130 mg to Tricor® 200 mg under fasted conditions and following consumption of a Therapeutic Lifestyle Change (TLC) meal in healthy adult subjects
2. FF3 A randomized, multiple-dose, 2-way crossover study to assess the relative bioavailability of RP 1824 130 mg capsules versus Tricor® 200 mg capsules at steady state in healthy adult subjects on a Therapeutic Lifestyle Change (TLC) diet
3. FF2 A randomized, single-dose, 4-way crossover study to determine and compare the relative bioavailability of RP 1824 130 mg to Tricor® 200 mg under fasted conditions and following consumption of a standard high fat FDA test meal in healthy adult subjects
4. FF4B A randomized, open-label, single-dose, 4-way crossover study to determine the dose equivalence of multiple RP 1824 43 mg capsules relative to RP 1824 87 mg and 130 mg capsules under fasting conditions in healthy adult subjects

5. FF4 A randomized, open-label, single-dose, 3-way crossover study to determine the relative bioavailability and dose proportionality of RP 1824 43 mg, 87 mg and 130 mg capsules under fasting conditions in healthy adult subjects

The pharmacokinetic results of RP 1824 are summarized as follows:

1. (FF4C) Under fasting condition, RP 1824 130 mg and Tricor® 200 mg capsules were equivalence in terms of AUCt or AUCinf, however, RP 1824 exhibited 68.9% higher Cmax. Under low-fat fed condition, RP 1824 130 mg had 17% lower AUCt or AUCinf while Cmax was equivalent. Food (low-fat meal) had no effect on AUCt or AUCinf for RP 1824 but increased Cmax by 75%.
2. (FF3) The RP 1824 130 mg capsules and the Tricor® 200 mg capsules were BE at steady state following consumption of a TLC diet meal.
3. (FF2) As in study FF4C, under fasting condition, RP 1824 130 mg and Tricor® 200 mg capsules were equivalent in terms of AUCt or AUCinf, however, RP 1824 exhibited 43.7% higher Cmax. Under high fat fed condition, RP 1824 130 mg had 35% lower AUCt or AUCinf and 30% lower in Cmax. High fat meal increased AUCt or AUCinf by 25% and Cmax by 110% for RP 1824 130 mg capsules.
4. (FF4B) Under fasting condition, two 43 mg RP 1824 capsules were BE to one 87 mg capsule in terms of AUCt, AUCinf and Cmax. In addition, three 43 mg RP 1824 capsules were BE to one 130 mg capsule in terms of AUCt, AUCinf and Cmax
5. (FF4) The dose-normalized AUCt and AUCinf from RP 1824 87 mg capsule were similar to those of the 43 mg capsule under fasting condition, however, the 90% CI of the dose-normalized Cmax was not within 80-125%. Dose proportionality was not established using power model.

The following dissolution method was proposed:

12-2-91

Apparatus: USP Dissolution Apparatus 2 (paddles)

Rotation: 75 rpm

Medium: 25 mM Sodium Dodecyl Sulfate (SDS) *SLS 37°C*

_____ were used to hold the capsules. *Q = —*

*Both AUC & Cmax Fast vs low fat fed ch. v.
AUC alone not adequate*

*Single dose proposed method to establish BE
Steady-state (study 1+3) Cmin v imp (clinical/healthy)*

Co-micronized is a SLS