CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021071

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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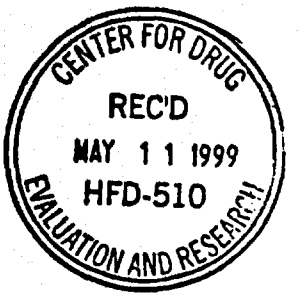
CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-071/N-000	**SUBMISSION DATE:**	**25-NOV-98, 18-FEB-99 (BB), 22-FEB-99(BB), 02-MAR-99(BB), 13-APR-99(BB)**
BRAND NAME:	**Avandia™ 2, 4, 8 mg**	
GENERIC NAME:	**Rosiglitazone maleate tablets; (BRL 49653)**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
CONSULTANT:	**Michael J. Fossler, Pharm.D., Ph.D.**	
SPONSOR:	**SmithKline Beecham, Collegeville, PA**	
TYPE OF SUBMISSION:	**Original NDA (NME)** **Code: 1P**	



TERMS AND ABBREVIATIONS:

AUCa-b ..... area under the plasma-concentration-time curve from time a to time b
DMEDP ..... Division of Metabolic and Endocrine Drug Products
FPG..... ..... Fasting plasma glucose
IV..... ..... Intravenous
NIDDM ..... Non-insulin dependent diabetes mellitus (Type 2)
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
PFB..... ..... Pure free base

SYNOPSIS:

Avandia (rosiglitazone, BRL 49653), a member of the thiazolidinedione class, is a peroxisome proliferator-activated receptor-g (PPARg) agonist developed for the treatment of type 2 diabetes mellitus (NIDDM). The sponsor proposes that Avandia 2, 4, and 8 mg oral immediate-release tablets be indicated as: 1) monotherapy for the treatment of hyperglycemia in patients with type 2 diabetes who are inadequately controlled by diet and exercise and 2) in combination with metformin in patients with type 2 diabetes who are inadequately controlled by metformin monotherapy.

Proposed labeling indicates that: 1) the recommended starting dose of Avandia, when used as monotherapy or with Metformin, is 4 mg/day in single or two divided doses, increasing to 8 mg/day depending on response; 2) Avandia may be taken with or without food; 3) no dosage adjustments are required for the elderly, or patients with renal impairment; 4) in patients with moderate to severe hepatic impairment (Child-Pugh Class B/C) therapy should start at 2 mg daily, and be cautiously titrate upward and Avandia should be used in patients with liver disease only if the benefits of drug therapy clearly outweigh the risks.

Absorption of rosiglitazone in healthy volunteers is rapid, with maximum plasma concentrations occurring about 1 hour after dosing at all dose levels in the fasted state. The absolute bioavailability is 99%. After attaining Cmax, rosiglitazone concentrations decline over time in a mono-exponential manner. The mean terminal elimination half-life is independent of dose and is 3 to 4 hours. Both maximum observed plasma concentrations (Cmax) and area under the plasma concentration versus time curve (AUC) increase

approximately proportionately with the increase in dose over the range 0.2 to 20 mg. Following oral administration of rosiglitazone, the pharmacokinetics exhibit an intra- and inter-subject CV of 35% and 23-31%, respectively, based on a population pharmacokinetic analysis. The extent of absorption (AUC) of rosiglitazone is unaffected by administration following a high fat breakfast although changes in the rate of absorption (20-30% decrease in Cmax and delay in Tmax by 1.75 h) occur when administered with a high fat meal.

Plasma protein binding of rosiglitazone is 99.8% and is independent of concentration up to at least 100-fold higher than concentrations seen clinically. The blood to plasma concentration ratio is 0.57. Following intravenous administration, steady-state volume of distribution is about 14 L.

Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism of rosiglitazone are N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. Rosiglitazone is predominantly metabolized by the cytochrome P450 enzyme CYP2C8, with CYP2C9 representing only a minor pathway. About 64% and 23% of a C14-labeled rosiglitazone dose is excreted in the urine and feces, respectively. In contrast to parent, the elimination half-life of total radioactivity is prolonged (>100 h). The metabolites are not thought to contribute to pharmacological activity of rosiglitazone.

Following intravenous administration, plasma clearance of rosiglitazone is about 3 L/h. Based on a blood:plasma ratio of 0.57, the estimated blood clearance of rosiglitazone is approximately 5.3 L/h which is considerably less than liver blood flow (approximately 90 L/h). Therefore, rosiglitazone is a low hepatic extraction drug (i.e., minimal first-pass metabolism), which is consistent with the high absolute bioavailability observed following oral administration.

Following once daily administration of 1, 2 and 5mg doses for 10 days in obese volunteers, Cmax and AUC values increased in an approximately dose-proportional manner. No accumulation was observed. Decreases (14-28%) in AUC were observed following repeat dosing with the larger decreases seen at the lower two doses. These decreases appeared to be related to a change in clearance as half-life was decreased after multiple dosing.

Rosiglitazone is administered as a racemate; however, following oral dosing in vivo enantiomeric interconversion occurs favoring the (+)-enantiomer, in agreement with in vitro data. Exposure to the (+)-enantiomer, based on AUC and Cmax, is approximately 2- to 3-fold greater than that of the (-)-enantiomer. Both enantiomers are equipotent to the racemate.

The population pharmacokinetics of rosiglitazone were characterized in a total of 1309 Type 2 diabetes mellitus (DM) patients following once and twice daily administration. A one-compartment, first-order oral absorption model with elimination from the central compartment adequately described the data. Both oral clearance (CL/F) and steady-state volume of distribution (Vss/F) were shown to be linear functions of weight with both parameters increasing with increase in weight. Additionally, rosiglitazone CL/F was shown to be lower in female patients compared to males. Race, smoking and alcohol consumption status were not shown to significantly influence the pharmacokinetics of rosiglitazone.

Patients with mild (Clcr 60-80 mL/min) and moderate (Clcr 30-59 mL/min) renal insufficiency showed similar total and unbound Cmax and total AUC values for rosiglitazone compared to subjects with normal renal function (Clcr > 80 mL/min). In contrast, total AUC and Cmax values were approximately 20-25% lower in patients with severe renal insufficiency not on dialysis (Clcr ≤ 29 mL/min) compared to those in the normal group, with a 38% increase in mean fraction unbound value observed in this group. Unbound AUC values were slightly higher (10-20%) in all the renally impaired groups. Similarly, a small decrease (about 10%) in Cmax and AUC(0-inf) was observed in hemodialysis-dependent patients with end stage renal disease on a non-dialysis day compared to healthy volunteers. The dialysis clearance was low with less than 2% of the dose recovered in the dialysate. No dose adjustments seems necessary in patients with mild to severe renal impairment (including hemodialysis-dependent patients).

In patients with moderate to severe (Child-Pugh Class B/C) hepatic disease, the unbound oral clearance

of rosiglitazone was significantly lower compared to healthy subjects. As a result, unbound Cmax and AUC(0-inf) were increased approximately 2- and 3-fold, respectively. The elimination half-life of rosiglitazone was about 2 hours longer in patients with hepatic disease compared to that in healthy subjects. It is recommended that patients with moderate to severe hepatic disease be started on a 50% lower dose and dose escalation in these patients should be undertaken with caution to achieve desired glycemic control.

The 2mg clinical trials tablet formulation used in Phase III was shown to be bioequivalent to the 2mg capsule formulation administered during early clinical development (Phase 1/2). The commercial tablet formulations of rosiglitazone include tablet strengths of 1, 2, 4 and 8mg although the sponsor is not proposing to market the 1mg tablet. The 1, 2 and 4mg tablets have core weights of 150mg while the 8mg tablet has a core weight of 300mg. The active and inactive ingredients for 4 and 8mg dose strengths are proportional, whereas the 1 and 2mg dose strengths are slightly different in proportion. Bioequivalence was demonstrated between the 1 and 8mg commercial tablets compared to the 1 and 4 mg (administered as 2 x 4 mg) clinical trials tablet formulations used in Phase 3 studies.

In vitro rosiglitazone caused a moderate inhibition of CYP2C8 (IC50 18 μM) and a minor inhibition of CYP2C9 (IC50 50 μM), but no inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A enzymes at concentrations up to 250 μM. The IC 50 values are at least 10-fold higher than total Cmax and 1000-fold higher than unbound Cmax for rosiglitazone following a single dose of 8 mg. Rosiglitazone is primarily metabolized by CYP2C8.

Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24 hour plasma glucose concentrations in 13 diabetic patients stabilized on glyburide therapy. These data imply that rosiglitazone does not acutely accentuate the hypoglycemic effects of sulfonylureas. Plasma concentrations of glyburide were not determined.

Concurrent administration of rosiglitazone (2 mg twice daily) and metformin (500 mg twice daily) in 16 healthy male volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone. Additionally, there was no alteration of serum lactate concentrations when rosiglitazone and metformin were coadministered.

Coadministration of acarbose (100 mg three times daily) with meals for 7 days in 16 healthy volunteers resulted in no change in the rate of absorption of a single oral 8 mg dose of rosiglitazone, as assessed by Cmax and Tmax. A slight reduction (12%) in AUC(0-inf) and an approximate 1 hour shorter half-life of rosiglitazone were observed during coadministration with acarbose compared to administration of rosiglitazone alone.

Repeat oral dosing of rosiglitazone (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in 15 healthy volunteers.

The effect of rosiglitazone (4 mg twice daily) for 7 days on the anticoagulant response of steady-state warfarin was investigated in a double-blind, placebo-controlled, parallel group study in healthy male volunteers. Following a 14 day run-in period during which each subject's warfarin dose was titrated to achieve a target baseline prothrombin time ratio of 1.5 to 3.5 [international normalized ratio (INR)], subjects were randomized to receive warfarin plus rosiglitazone (n=11) or warfarin plus placebo (n=8) orally for 7 days. Based on data from all subjects, rosiglitazone did not alter the pharmacokinetics of R(+)-warfarin and decreased by 10% the AUC of S(-)-warfarin.

The effect of multiple oral doses of rosiglitazone (8 mg once daily) for 14 days on the single dose pharmacokinetics of nifedipine was investigated in a randomized, crossover study in 26 healthy male volunteers. Repeat dosing with rosiglitazone did not alter the AUC(0-inf) of nifedipine.

The effect of repeat dose rosiglitazone (8 mg once daily) for 14 days on the steady-state pharmacokinetics of the oral contraceptive Ortho-Novum 1/35 (containing ethinylestradiol and norethindrone) was investigated in a randomized, placebo-controlled, crossover study in 32 healthy female subjects. Repeat

dosing with rosiglitazone did not result in a clinically relevant alteration in the steady-state pharmacokinetics of either ethinylestradiol or norethindrone.

A single administration of a moderate amount of ethanol did not increase the risk of acute hypoglycemia in BRL 49653C-treated Type 2 diabetic patients.

Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone in 12 healthy male volunteers.

No pediatric studies have been conducted.

For all dissolution methods, the dissolution medium remained constant as 900 mL of 0.01M acetate buffer pH 4.0 at 37°C. In all cases USP Apparatus 2 (paddles at [redacted] was used. The dissolution specification has been set as not less than [redacted] of the label claim should be released within [redacted] minutes.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-071/N-000 submitted 25-NOV-98, 18-FEB-99, 22-FEB-99, 02-MAR-99, and 13-APR-99. The overall Human Pharmacokinetic Section is acceptable to OCPB. This recommendation, comments (p. 25), and labeling comments (p. 26) should be sent to the sponsor as appropriate.

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BACKGROUND:

Rosiglitazone (BRL 49653C) is an orally active antihyperglycemic compound of the thiazolidindione class developed for the treatment of non-insulin dependent diabetes mellitus (NIDDM). The thiazolidindiones represent a class of compounds that are thought to act as "insulin sensitizers" in target tissues. Rosiglitazone does not increase pancreatic insulin secretion.

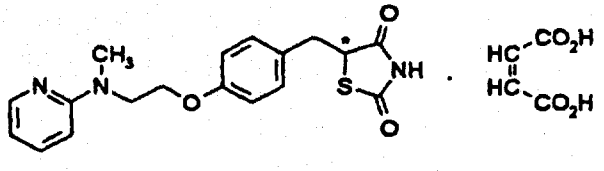
STUDY SUMMARY INDEX

Protocol Number	Title	Page
028	Bioequivalence study of the final market formulation of BRL-49653C compared to the clinical trials formulation.	p. 47
001	Evaluation of the Safety, Tolerability and Preliminary Pharmacokinetics of Single Rising Doses of BRL 49653C in Normal Volunteers	p. 52
002	An evaluation of the safety, tolerability, pharmacokinetics and pharmacodynamics of BRL-49653 after 10 days repeat dosing to obese subjects	p. 55

049	A study to determine the balance/excretion, pharmacokinetics and biotransformation of BRL-49653 given as a single oral (8 mg pfb) and single intravenous (2 mg pfb) doses of [14 C]-BRL 49653C to healthy male adult volunteers and determine the pharmacokinetics of a single oral dose (2 x 4 mg tablets) of BRL-49653C given on a third occasion.	p. 162
D92240 BF-1002	Investigation into the binding of [redacted]C-BRL-49653 to rat, dog and human plasma proteins in vitro	p. 175
D92242 BF-1001	Blood cell partitioning of [redacted]C-rosiglitazone in male rat, dog and human blood.	p. 177
D92226 BF-1030	An in vitro investigation of the potential for drug interactions involving BRL-49653 and the human cytochrome P450s 1A2, 2A6, 2C9/8, 2C19, 2D6, 2E1, 3A and 4A	p. 179
D96044 RSD-100CPZ	A further in vitro investigation of the human cytochrome P450 enzymes involved in the metabolism of BRL-49653	p.182

DRUG FORMULATION:

Avandia™ is the maleate salt of rosiglitazone, (S(-),R(+)) [5-(4-(2-(N-methyl-N-(2-pyridyl) amino)ethoxy)benzyl)-thiazolidine-2,4- dione] (Figure 1). It has the molecular formula $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$, a molecular weight of 473.52 as the maleate salt (1:1) and 357.44 as the free base. Rosiglitazone maleate is isolated as a racemate.



*chiral center

Figure 1.

[redacted]

For phase 1 and 2 clinical studies, rosiglitazone maleate capsules made by a [redacted] process were used, with doses ranging from 0.05 to 5.0mg. For phase 3 studies, capsules and tablets were required. Two different capsule sizes were required for blinding of comparator products; this capsule formulation was exactly the same as the phase 1 and 2 capsule formulation. The phase 3 tablets had the same qualitative composition as the capsules, although the amount of [redacted] was reduced to produce a tablet weight of [redacted] and the amount of [redacted] was [redacted]. The tablets were film coated with [redacted]

Three further variations were introduced on progressing from clinical tablets to commercial tablets; the wet granulation manufacturing process used for the clinical tablet was changed to a [redacted] process, the amount of [redacted] was [redacted] and the film coats were changed to introduce the colors used to differentiate between the tablet strengths. The commercial tablet formulation was not used in phase 3 trials. The commercial formulation includes tablet strengths of 1, 2, 4 and 8mg. The 1, 2

and 4mg tablets have [redacted] weights of [redacted] while the 8mg tablet has a [redacted] weight of [redacted] Thus, the active and inactive ingredients for 4 and 8mg dose strengths are proportional, whereas the 1 and 2mg dose strengths are slightly different in proportion.

Commercial batches of Avandia tablets will be manufactured in [redacted] Development batches were manufactured at three sites: [redacted] Formulations are listed in Appendix 5.

DISSOLUTION:

The dissolution method proposed by the sponsor is:

Medium: 900mL of 0.01M acetate buffer, pH 4.0, 37°C
Apparatus 2: [redacted] rpm
Time: [redacted] minutes
Tolerance: Not less than [redacted] of the labeled amount dissolved.

The solubility of rosiglitazone maleate in aqueous buffer is strongly pH dependent, as shown in Figure 2. Solubility increases as the pH of the buffer decreases from pH 7 to pH 2.

The mean [redacted] dissolution profiles obtained for batches used in the bioequivalence study are provided in Figures 3. These profiles demonstrate the rapid dissolution of rosiglitazone maleate from the clinical and commercial formulations

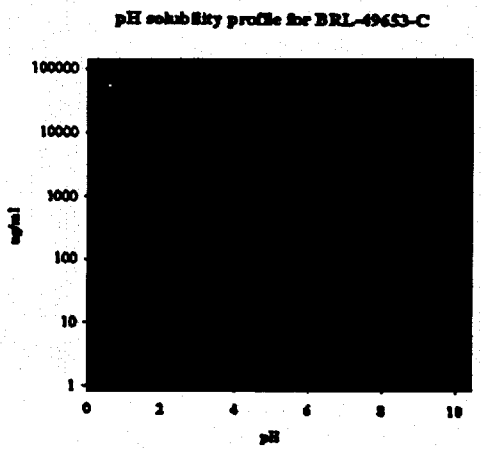


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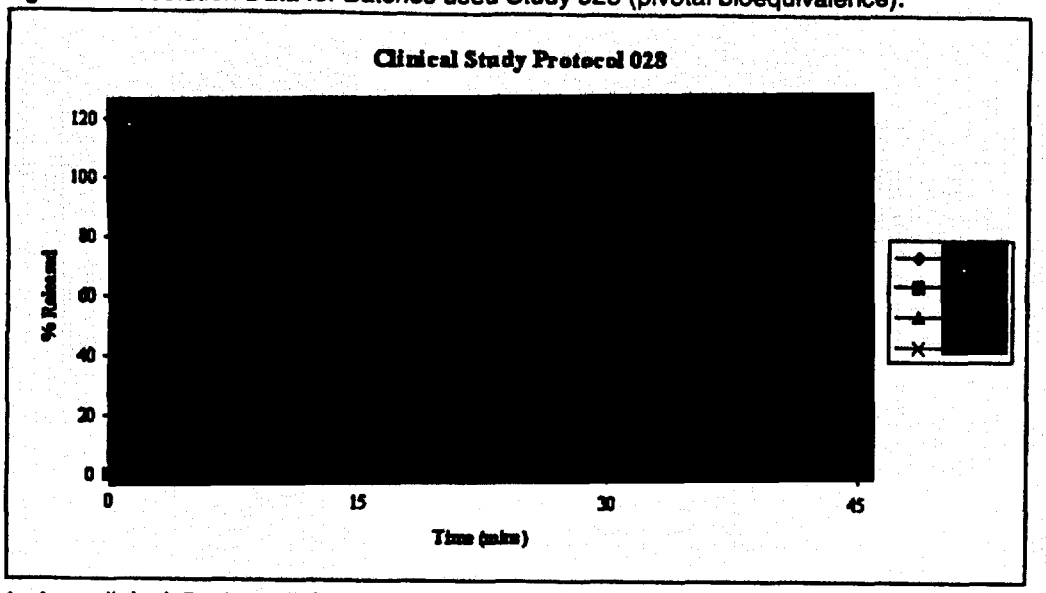
Figure 2.

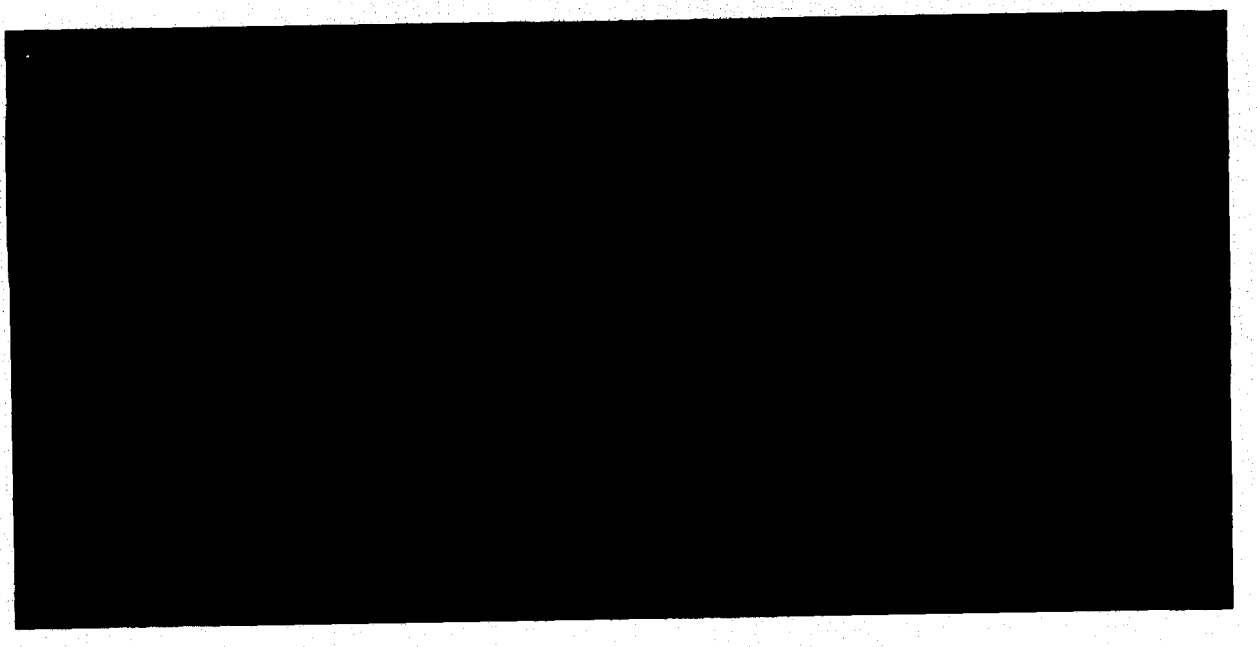
Figure 3. Dissolution Data for Batches used Study 028 (pivotal bioequivalence).



◆=1mg clinical; ■=4mg clinical; ▲=1mg commercial; X=8mg commercial.

ANALYTICAL METHODOLOGY:

[redacted]



HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

The absolute bioavailability of rosiglitazone has been determined following a single 4 mg oral dose (phase 3 tablet formulation) and a single intravenous 2 mg dose (as a one hour infusion) of rosiglitazone to 13 healthy male volunteers (Study 037). The absolute bioavailability of this clinical trials tablet was 99% (95%CI: 84%,115%). Similar results were obtained in the radiolabel study (n=4) where the mean absolute bioavailability of the solution and the clinical trials tablet were 95% and 99%, respectively (Study 049)

B. Bioequivalence

Study 030 investigated the bioequivalence between the 2mg phase 1\2 capsule (formulation AB) and the clinical tablet formulation used in phase 3 trials (formulation AG). The 90%CI for the ratio (tablet/capsule) for Cmax and AUC were (0.97-1.07) and (0.99-1.07), respectively.

Bioequivalence between the clinical tablet and commercial tablet formulations was tested in study 028. The commercial and clinical formulations of the 1mg and 8 mg tablets were tested and found to be bioequivalent. The commercial batches of 1mg and 8mg tablets used in this pivotal bioequivalence study were manufactured at the commercial manufacturing site at approximately 11% of production scale, and are identical in formulation to the proposed commercial formula including debossing, colors and tablet shape. Table 2 indicates the point estimates and 90%CI for AUC and Cmax; Figure 4 shows the mean plasma concentrations of rosiglitazone in this study. (Note: The sponsor is not planning on marketing the 1mg tablet)

Table 2. Point estimates and 90% CI intervals from bioequivalence study 028.

Parameter	Comparison	Point 90% Estimate	C.I.
AUC(0-inf)	B:A	1.00	(0.95, 1.07)
	D:C	0.96	(0.91, 1.02)
Cmax	B:A	0.97	(0.89, 1.05)
	D:C	0.97	(0.89, 1.05)

Key : A - 1 mg clinical trials formulation; B - 1 mg commercial formulation;
C - 2 x 4 mg clinical trials formulation; D - 8 mg commercial formulation

[redacted]

Table 3 indicates the percent (w/w) of excipients in each commercial tablet formulation. The 4 and 8mg tablets are qualitatively and quantitatively proportional. The sponsor has requested a biowaiver for the 2mg tablet based on its similarity to the 1mg tablet, as per SUPAC, and dose proportionality between 1 and 8mg.

[redacted]

Table 3. Ratio of Excipients in Avandia tablets.

[redacted]

C. Inter- and Intra-individual Variability

From the POP PK modeling, the estimates of the inter-individual variability in CL/F and Vss/F were 31% and 23%, respectively. The intra-individual variability (i.e., residual error) was well-estimated at 35%.

II. Pharmacokinetics

A. Single vs. Multiple Dose Administration

Study 001 was an oral dose-rising study, with doses of rosiglitazone ranging from 0.5 to 5mg in capsule formulation. Figure 5 indicates the mean plasma concentrations obtained from 13 healthy male volunteers. Pharmacokinetics are summarized in Table 4 and are proportional between doses.

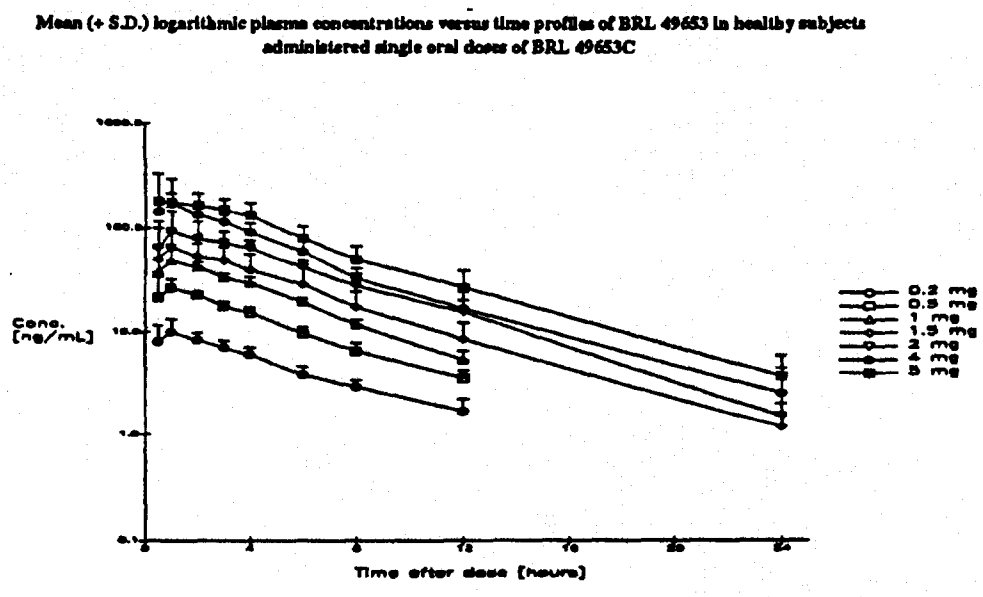


Figure 5.

Table 4. Pharmacokinetics for rosiglitazone (mean±SD and range)

Dose	Cmax [ng/mL]	Tmax * [hours]	AUC(0-inf) [ng.h/mL]	T1/2 [hours]
0.2 mg [n=6]	11.07 ± 2.39	1.0	64.5 ± 10.9	4.0 ± 0.4
0.5 mg [n=6]	28.64 ± 7.04	1.0	157.9 ± 25.7	3.7 ± 0.2
1.0 mg [n=6]	60.30 ± 12.50	1.0	287.8 ± 23.1	3.3 ± 0.4
1.5 mg [n=6]	78.61 ± 33.42	1.0	413.0 ± 174.2	3.6 ± 0.6
2.0 mg [n=6]	111.58 ± 27.90	1.0	630.5 ± 142.7	3.7 ± 0.7
4.0 mg [n=6]	181.84 ± 48.30	1.0	938.4 ± 239.3	3.6 ± 0.7
5.0 mg [n=6]	250.40 ± 92.90	0.8	1269.8 ± 382.4	3.7 ± 0.4

* Tmax - median and range

In vitro work has demonstrated that there is interconversion between enantiomers, with formation of the (+)SB 210232 enantiomer favored. Data from study 001 is in agreement with this *in vitro* data as the AUC and Cmax of (+)SB 210232 appear to be 2-3 times greater than that of the (-)SB 206846 enantiomer. Animal studies indicate that either individual enantiomer and racemic rosiglitazone are equipotent as stimulants of 2-deoxyglucose uptake.

Study 003 examined SD and MD pharmacokinetics of rosiglitazone in healthy obese volunteers. The T1/2 appears to decrease, and CL/F increase, with 10 days of chronic dosing (Table 5). The observed AUC accumulation ratio, Ro, was lower than that predicted from SD data, Rp (Table 5).

Table 5.

Dose [mg]	Ro [Cmax]	Ro [AUC]	Rp [AUC]	Rp [λ]
1	0.94	0.74	1.12	1.04
2	1.01	0.72	1.05	1.02
5	0.97	0.86	1.04	1.02

Ro = Observed accumulation ratio

Rp = Predicted accumulation ratio

where λ is apparent terminal elimination rate constant, τ is dosing interval and

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$$Ro\,[Cmax] = \frac{Cmax\ day\ 10}{Cmax\ day\ 1}$$

$$Ro\,[AUC] = \frac{AUC(0-inf)\ day\ 10}{AUC(0-inf)\ day\ 1} \qquad Rp\,[\lambda] = \frac{1}{(1-e^{-\lambda\tau})}$$

$$Rp\,[AUC] = \frac{AUC(0-inf)\ day\ 1}{AUC(0-\tau)\ day\ 1}$$

In general, the CL/F and Vdss/F are in good agreement with the POP PK analysis.

Table 6.

Parameters	1 mg [n=12]		2 mg [n=11]		5 mg [n=12]	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
AUC[a] (ng.h/mL)	402	278	733	489	1839	1541
Cmax (ng/mL)	64.2	58.4	136.5	127.5	360.7	327.2
Tmax[b] (hours)	1.0	0.5	1.0	1.0	1.0	1.3
T1/2 (hours)	4.68	3.33	3.86	3.04	4.13	3.38
Vdss/F (L)	18.7	18.4	16.8	18.4	17.7	17.1
CL/F (L/h)	2.85	4.15	2.92	4.03	2.82	3.37

Source Data: 11.14, 11.15, 11.17, 11.18, 11.19, 11.20

a = AUC(0-inf) on Day 1 and AUC(0-t) on Day 10 b = Data presented as median (range)

After intravenous administration of rosiglitazone in healthy male volunteers the mean plasma clearance and volume of distribution were approximately 3L/h and 14L, respectively (Studies 029, 037, 049). This is in good agreement with the POP PK analysis (CL/F 2.4L/h and Vss/F 17.6L) indicating bioavailability close to 100%.

B. Healthy volunteers vs. patients

Clearance and volume estimates from healthy volunteers are similar to those parameter estimates from the POP PK analysis.

C. Food Effects

Study 004 examined the effect of a high fat meal on the pharmacokinetics of rosiglitazone. A 2mg

capsule dose was administered in this 2 period crossover study. Results (Table 7) indicate that the AUC is not affected by a high fat meal but that Cmax is decreased and Tmax is delayed. Figure 6 shows the mean plasma concentration curves for the fed and fasted state. Study 005 examined dose proportionality as well as food effect using the to-be-marketed 2, 4, and 8mg tablet formulations. The food effect results are shown in Tables 8 and Figure 7.

Table 7.

Point Estimates and 95% Confidence Intervals for Rosiglitazone
(Protocol 49653/004)

Parameters	Comparison	Point Estimate	95% CI
AUC(0-inf)	Fed:fasted	0.94	(0.82, 1.06)
Cmax	Fed:fasted	0.80	(0.65, 0.97)
Tmax	Fed–fasted	1.75 h	(1.25 h, 2.25 h)
T½	Fed–fasted	0.15 h	(–0.13 h, 0.42 h)

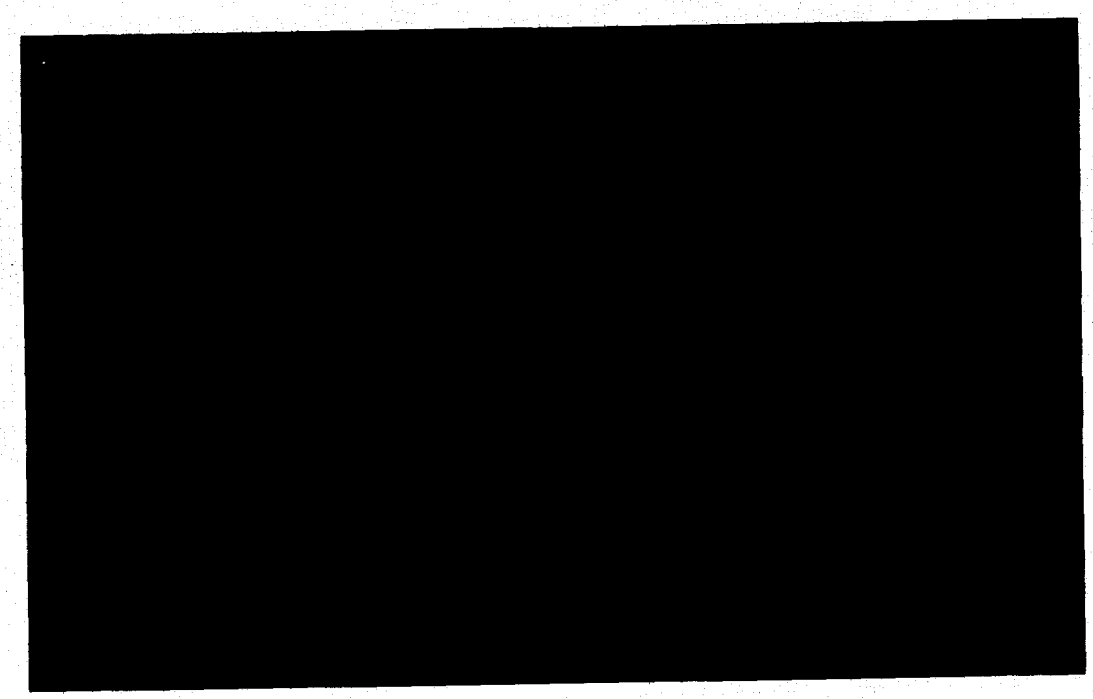


Table 8. Point Estimates and Confidence Intervals for Dose Normalized AUC(0-inf) (ng.h/mL) and Cmax (ng/mL), T1/2 (h)and Tmax (h).

Parameter	Comparison	Point Estimate	95% Confidence Interval
DN-AUC(0-inf)	D:C[1]	0.97	(0.91, 1.02)
DN-Cmax	D:C[1]	0.72	(0.66, 0.79)
T1/2	D-C[2]	0.23	(0.00, 0.45)
Tmax	D-C[3]	1.75	(1.02, 2.24)[4]

1: presented as the ratio of geometric means. (90% confidence intervals)
2: presented as the difference in arithmetic means. (95% confidence intervals)
3: presented as the median difference in median (95% confidence intervals)
4: See text regarding possible period effects

Regimen C: BRL 49653C 8 mg single oral dose, fasting
Regimen D: BRL 49653C 8 mg single oral dose, administered after a high fat breakfast

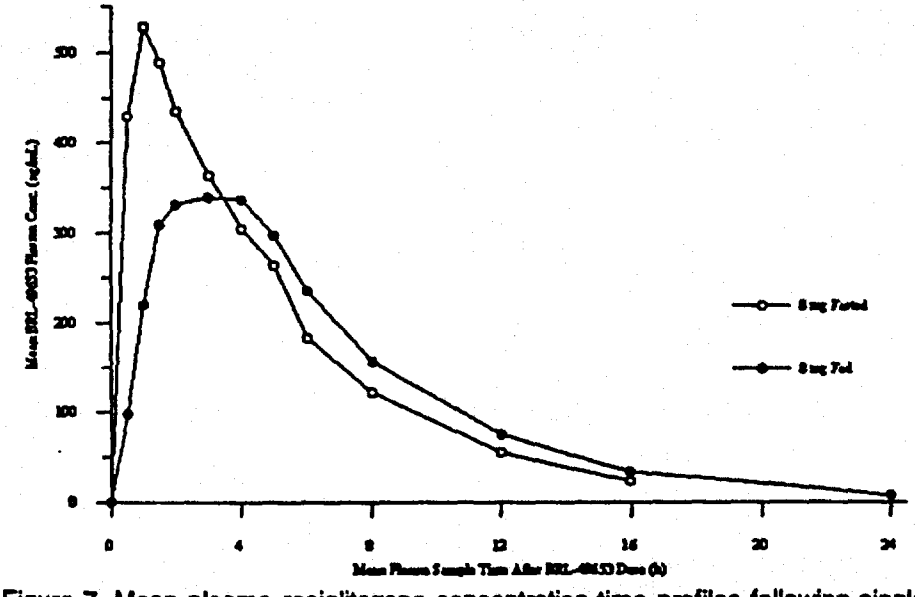


Figure 7. Mean plasma rosiglitazone concentration-time profiles following single oral administration of 8 mg rosiglitazone administered fasted and after a high fat breakfast in healthy subjects.

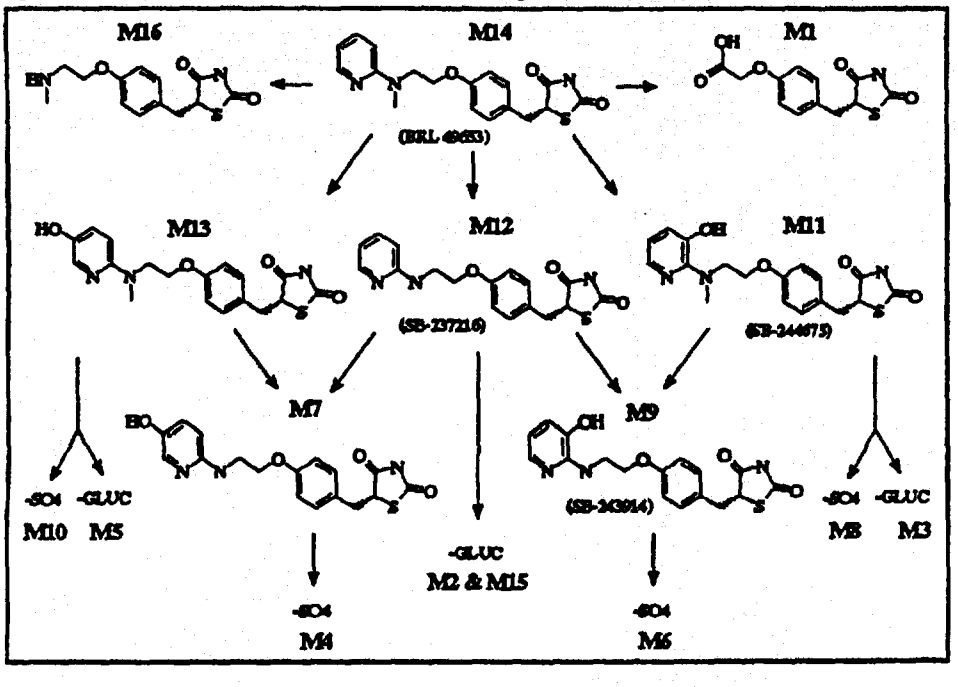
III. Metabolism

Study 049 investigated the metabolism as well as absolute bioavailability of rosiglitazone. Figure 8 shows a proposed metabolic scheme in man, based on information produced in this study. The major routes of metabolism in man seem to be N-demethylation, hydroxylation and subsequent conjugation, and were unaffected by the route of dose administration. Excretion of radioactivity occurred primarily via the urine, with a mean of about 64% and 23% of the administered dose being found in the urine and feces, respectively, following intravenous or oral administration. The mean total recovery of radioactivity was about 92% of the administered dose following oral or intravenous administration. Biliary secretion may account for the radioactivity in the feces following the IV route of administration. The higher proportion of radioactivity in the urine indicates that renal elimination is the major route of excretion of rosiglitazone

metabolites in man.

The absolute bioavailability of rosiglitazone (clinical tablet formulation) observed in this study was estimated to be, on average, 99% [redacted] The absolute bioavailability of rosiglitazone (solution formulation) observed in this study was estimated to be, on average, 95% [redacted]

Figure 8. Proposed metabolic scheme for rosiglitazone (M14) in man.



BEST POSSIBLE

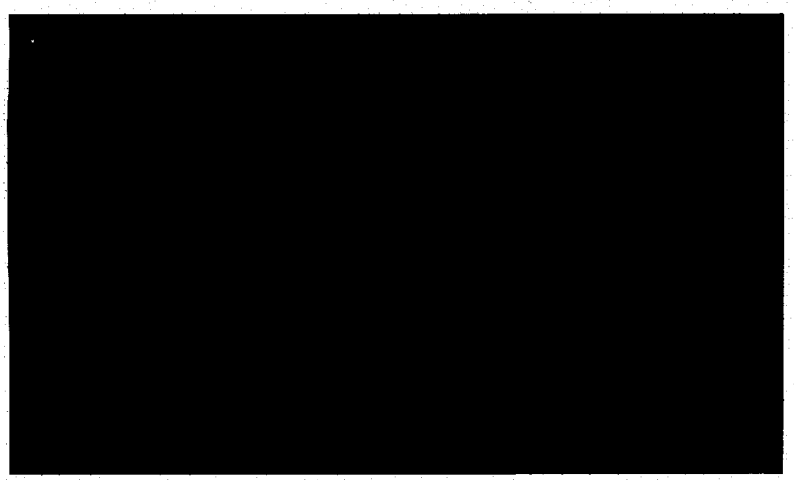
-SO4 = sulphate conjugate, -GLUC = glucuronide conjugate

The concentration time profiles of radioactivity in plasma were quite different from the profiles of rosiglitazone in plasma. The maximum concentration of radioactivity in plasma was approximately 1.4 to 1.9-fold higher than the maximum concentration of rosiglitazone in plasma. Furthermore, the AUC(0-inf) values for radioactivity were 21 to 38-fold higher than the AUC(0-inf) values for rosiglitazone. The Tmax and half-life for radioactivity in plasma were longer than those for rosiglitazone in plasma, with Tmax values ranging from 4 to 6 hours and estimates of half-life ranging from 103 to 158 hours. These data suggest the presence of circulating metabolites, one or more of which may be eliminated much more slowly than rosiglitazone.

M4 and M10 accounted for most of the urinary radioactivity after IV dosing while M7 and M13 accounted for the majority of fecal radioactivity. In plasma, M10 and M12 account for most of the radioactivity.

IV. Dose and Dosage Form Proportionality

Study 001 demonstrated dose proportionality of a capsule formulation up to 5mg. Study 029 evaluated IV doses from 0.2 to 2mg and demonstrated dose proportionality. Study 016 examined the pharmacokinetics of single oral doses up to 20mg using a 5mg phase 1\2 capsule formulation. Figure 9 shows the dose normalized AUC data; there appears to be a decrease in AUC with increasing doses.



Study 005 investigated the dose proportionality of single doses of the 1, 2, and 8mg commercial tablet formulations in healthy volunteers. The results (Table 9 and Figure 10) indicate that the AUC and Cmax are proportional in this range with the commercial formulation.

Table 9. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses of 1, 2 and 8 mg to Healthy Volunteers (Study 005).

Parameter	1 mg	2 mg	8 mg	Point Estimate (Confidence Interval) (2 mg:1mg)	Point Estimate (Confidence Interval) (8 mg:1mg)
AUC(0-inf) (ng.h/mL)	358 (112)	733 (184)	2971 (730)	1.04* (0.99,1.09)	1.05* (1.00,1.10)
Cmax (ng/mL)	76.1 (13.3)	156 (42.6)	598 (117)	1.00* (0.93,1.08)	0.98* (0.91,1.05)
Tmax ** (h)	0.5 [redacted]	1.0 [redacted]	1.0 [redacted]	0.23h^ (-0.01h,0.48h)	0.21h^ (0.00h,0.28h)
T1/2 (h)	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	-0.01h^^ (-0.23h,0.22h)	0.21h^^ (-0.02h,0.44h)

* Ratio of geometric mean of dose-normalized AUC or Cmax (90% confidence interval)
**Median (range)
^Difference in median values (95% CI)
^^Difference in mean values (95% CI)

[redacted] APPEARS THIS WAY ON ORIGINAL

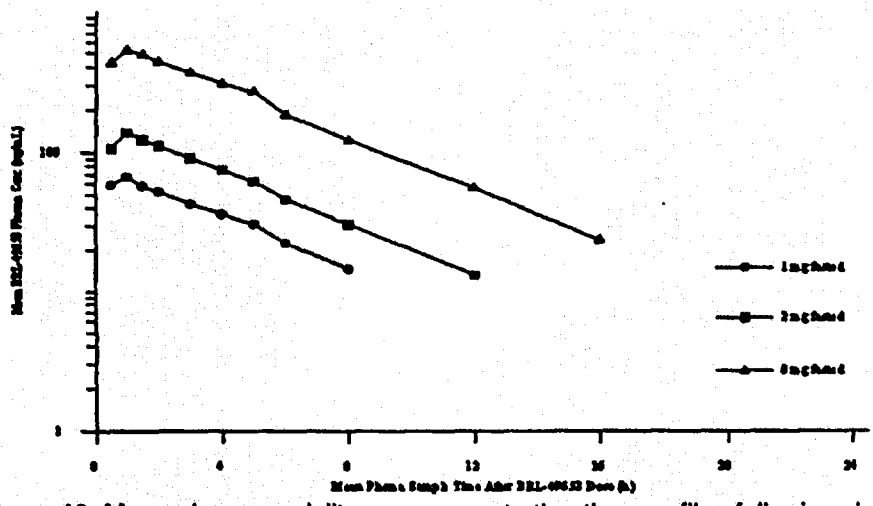


Figure 10. Mean plasma rosiglitazone concentration-time profiles following single oral administration of 1 mg, 2 mg and 8 mg rosiglitazone fasted in healthy subjects.

V. Special Populations

Renal

Study 007 investigated the effect of dialysis on the pharmacokinetics of rosiglitazone. Hemodialysis-dependent patients received a single dose of rosiglitazone on two occasions: a day without dialysis and on a day with dialysis. Healthy volunteers received a single dose once. As seen in Figure 11, hemodialysis did not significantly change the disposition of rosiglitazone.

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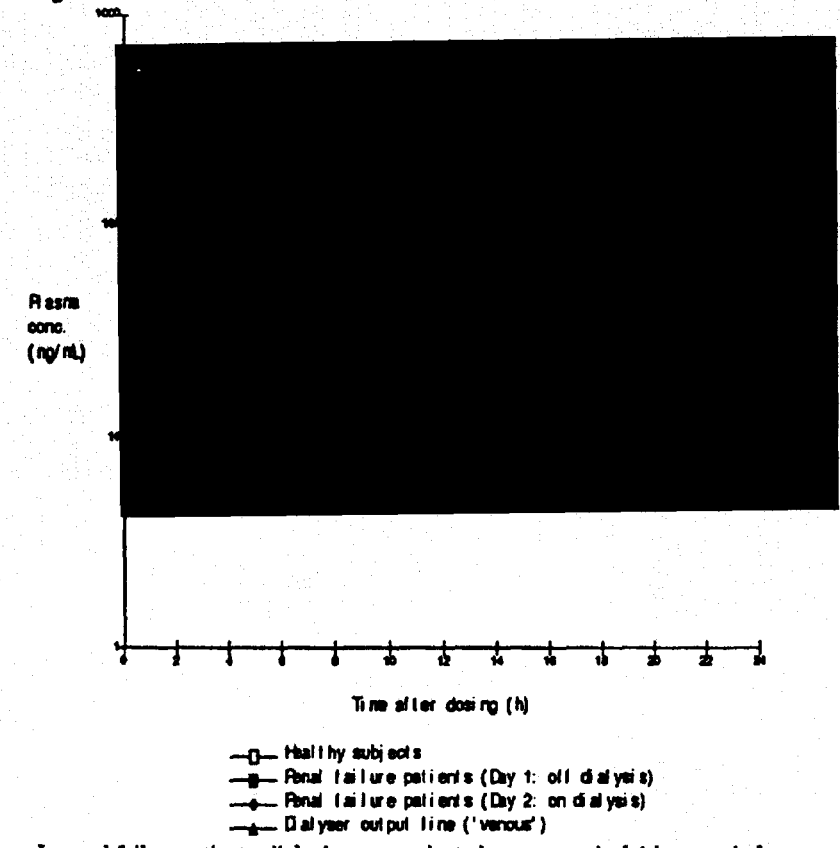
Figure 11. Mean plasma concentrations of rosiglitazone (ng/mL) in Ten Healthy Subjects and Ten Patients with End-Stage Renal Disease (on and between dialysis days) Following a Single 8 mg Oral Dose of rosiglitazone.



In renal failure patients, dialysis was conducted over a nominal 4-hour period from approximately 3 to 7 hours post-dose on Day 2. Mean profile for renal failure patients (Day 2: on dialysis) is a combination of the systemic plasma values prior to and following dialysis and the arterial values from the input line to dialyzer during dialysis

In Study 038, subjects were stratified by Cockroft-Gault estimation of creatinine clearance (Clcr) at screening into the following groups, including normal (n = 12; Clcr > 80 mL/min), mild (n = 15; Clcr 60-80 mL/min), moderate (n = 18; Clcr 30-59 mL/min), and severe, but not on dialysis (n = 12; Clcr ≤ 29 mL/min). Results of this study showed that patients with mild and moderate renal insufficiency had similar total and unbound Cmax and total AUC values for rosiglitazone compared to subjects with normal renal function (Tables 10 and 11). In the severe group, total AUC and Cmax values were approximately 20-25% lower than those in the normal group. The lower total concentrations for the severe group were associated with a 38% increase in the mean fraction unbound (fu) observed in this group. Unbound AUC values were slightly higher (10-20%) in all the renally impaired groups. No differences were observed in mean T1/2 and median Tmax between groups.

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Table 10. Mean (SD) Pharmacokinetic Parameters
for Rosiglitazone Following a Single 8 mg Oral Dose Administered to
Healthy Volunteers and Patients with Chronic Renal Insufficiency (Study 038).

Group	Cmax (ng/mL)	AUC(0-inf) (ng.h/mL)	Tmax (h)	T1/2 (h)	fu (%)	Unbound Cmax* (ng/mL)	Unbound AUC* (ng.h/mL)
Normal (n=12)	461 (88)	2838 (781)	2.0 [redacted]	4.1 (1.1)	0.16 (0.03)	0.716 (0.191)	4.23 (1.56)
Mild (n=15)	454 (108)	3126 (1239)	2.0 [redacted]	4.5 (1.9)	0.16 (0.02)	0.727 (0.162)	5.09 (2.32)
Moderate (n=18)	475 (104)	3236 (1054)	2.0 [redacted]	4.5 (0.8)	0.15 (0.02)	0.739 (0.237)	5.04 (2.42)
Severe (n=12)	359 (105)	2290 (589)	2.0 [redacted]	4.1 (1.0)	0.22 (0.06)	0.810 (0.282)	4.76 (1.66)

* n=10 normal, n=14 mild, n=17 moderate, n=9 severe

Table 11. Point Estimates (PE) and 95% Confidence Intervals for
Rosiglitazone Pharmacokinetics in Patients with Chronic
Renal Insufficiency Compared to Healthy Volunteers (Study 038)

	Cmax*	AUC(0-inf)*	T1/2#	fu#	Unbound Cmax*	Unbound AUC*
Mild:Normal						
PE (95% CI)	0.98 (0.81, 1.17)	1.08 (0.85, 1.37)	0.42h (-0.57h, 1.42h)	0.00% (-0.02%, 0.03%)	1.02 (0.81, 1.29)	1.19 (0.86, 1.64)
Moderate: Normal						
PE (95% CI)	1.02 (0.86, 1.22)	1.14 (0.91, 1.43)	0.38h (-0.58h, 1.33h)	0.00 (-0.03%, 0.02%)	1.02 (0.81, 1.28)	1.18 (0.86, 1.62)
Severe: Normal						
PE (95% CI)	0.76 (0.63, 0.92)	0.81 (0.64, 1.04)	0.00 (-1.04h, 1.05h)	0.06% (0.03%, 0.09%)	1.10 (0.85, 1.43)	1.10 (0.79, 1.63)

* presented as the ratio of geometric means
# presented as the mean difference

Hepatic

Study 008 examined the effect of hepatic impairment on the pharmacokinetics and plasma protein binding of rosiglitazone following administration of a single 8 mg (2x4mg clinical tablet formulation) dose of rosiglitazone to 18 patients with hepatic impairment (Child-Pugh Scores 6-11) and 17 healthy male volunteers (matched to the range of ages and weights of patients with hepatic impairment). A 2-fold higher mean unbound fraction (fu) was observed in patients with hepatic impairment compared to normal subjects (Tables 12 and 13).

Table 12. Mean (SD) Pharmacokinetic
Parameters for Rosiglitazone Following a Single 8 mg Oral Dose
Administered to Healthy Volunteers and Patients with Hepatic Impairment (Study 008).

Group	Cmax (ng/mL)	AUC (0-inf) (ng.h/mL)	Tmax (h)	T1/2 (h)	fu (%)	Unbound Cmax* (ng/mL)	Unbound AUC* (ng.h/mL)
Healthy (n=17)	506 (104)	2645 (677)	1.0 [redacted]	3.79 (1.03)	0.12 (0.03)	0.61 (0.20)	3.20 (1.38)
Hepatic (n=18)	407 (119)	3576 (1083)	1.0 [redacted]	6.03 (2.10)	0.27 (0.12)	1.09 (0.52)	9.88 (5.31)

Table 13. Point Estimates (PE) and 95%
Confidence Intervals for Rosiglitazone Pharmacokinetics
In Patients with Hepatic Disease Compared to Healthy Volunteers (Study 008)

	Cmax*	AUC(0-inf)*	T1/2#	fu#	Unbound Cmax*	Unbound AUC*
PE (95% CI)	0.79 (0.68, 0.93)	1.34 (1.11, 1.62)	2.24h (1.09h, 3.39h)	0.15% (0.09%, 0.21%)	1.70 (1.30, 2.22)	2.88 (2.08, 3.99)

* presented as the ratio of geometric means
\# presented as the difference in arithmetic means

Compared to healthy subjects, unbound AUC(0-inf) and Cmax were about 3- and 2-fold higher, respectively, in patients with hepatic impairment. Total Cmax decrease 21% and total AUC increased 34% in patients with hepatic dysfunction compared to healthy subjects Rosiglitazone elimination half-life was approximately 2 hours longer in subjects with hepatic dysfunction compared to that in healthy subjects. Based on these pharmacokinetic data, the sponsor is recommending that patients with moderate to severe hepatic disease be started on a 50% lower dose and dose escalation in these patients should be undertaken with caution to achieve desired glycemic control.

Age

The Population PK analysis has demonstrated that there is no effect of age on the pharmacokinetics of rosiglitazone with multiple dosing.

Gender

The effect of gender has been investigated in the Population PK analysis.

Pediatric

No studies were done in pediatric subjects.

VI. Drug Interactions / Protein Binding

A. In vitro

Rosiglitazone is highly bound to plasma proteins, primarily to the albumin fraction. The in vitro plasma protein binding of rosiglitazone was, on average, 99.8% (Study D92242). Similarly, after single oral doses, the ex vivo plasma protein binding of rosiglitazone in healthy volunteers ranged from 99.8% to 99.9%

(Studies 008, 038).

In vitro data demonstrated that rosiglitazone is predominantly metabolized via cytochrome P450 CYP2C8 with only minor contribution from CYP2C9.

In vitro rosiglitazone caused inhibition of CYP2C8 (IC50 18 uM) and CYP2C9 (IC50 50 uM), but no inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A enzymes at concentrations up to 250 uM.

B. In vivo

After receiving a stable dose of glyburide (3.75-10 mg/day) for a minimum of 30 days, 12 male and female patients with Type 2 diabetes mellitus were randomized in a double-blind fashion to receive either rosiglitazone 2 mg or placebo orally, every 12 hours for seven days. After a washout period of at least 14 days, the patients were crossed-over to the other treatment arm.

The point estimate and 90% confidence interval for the treatment difference (glyburide + rosiglitazone versus glyburide + placebo) of serum glucose AUC(0-24) were 0.93 and (0.84, 1.02). Plasma concentrations of glyburide were not determined.

Concurrent administration of rosiglitazone (2 mg capsule twice daily) and metformin (500 mg twice daily) in 16 healthy male volunteers for 4 days had no effect on the pharmacokinetics of either metformin or rosiglitazone. Table 14 indicates the point estimate and 95%CI for the AUC and Cmax of each monotherapy vs combination therapy. Additionally, serum lactic acid concentrations remained in the reference range (9-16 mg/dL) throughout the study (one patient had a level of 17 mg/dL once during the study but remained within the reference range at all other sampling times).

Table 14.Mean (SD) Pharmacokinetic Parameters
and Statistical Results for Rosiglitazone and Metformin (Study 036).**

Regimen	Rosiglitazone + Metformin	Rosiglitazone Alone	Point Estimates (95% Confidence Intervals)
Rosiglitazone (n=16)			
AUC(0-12) (ng.h/mL)	629	626	1.00 (0.97, 1.04)
Cmax (ng/mL)	104	105	0.99 (0.94, 1.06)
Metformin (n=16)			
AUC(0-12) (ng.h/mL)	6575	6508	1.01 (0.94, 1.08)
Cmax (ng/mL)	918	901	1.02 (0.94, 1.10)

** 'Rosiglitazone alone' column is actually either drug alone.

Coadministration of acarbose (100 mg three times daily) with meals for 7 days in 16 healthy volunteers resulted in no change in the rate of absorption of a single oral 8 mg (2x4mg clinical tablet formulation) dose of rosiglitazone, as assessed by Cmax and Tmax. A 12% (95%CI: 2-21%) reduction in AUC(0-inf) and an approximate 1 h shorter half-life of rosiglitazone were observed during coadministration with acarbose compared to administration of rosiglitazone alone.

Repeat oral dosing of rosiglitazone (2x4mg clinical tablet formulation once daily) for 14 days did not alter the steady-state trough plasma levels or AUC0-24 of digoxin (0.375 mg once daily) in 15 healthy volunteers.

The effect of rosiglitazone (4 mg clinical tablet formulation twice daily) for 7 days on the anticoagulant response of warfarin was investigated in a double-blind, placebo-controlled, parallel group study in healthy male volunteers. Following a 14 day run-in period during which each subject's warfarin dose was titrated to achieve a target baseline prothrombin time ratio of 1.5 to 3.5 [international normalized ratio (INR)], subjects were randomized to receive warfarin plus rosiglitazone (n=11) or warfarin plus placebo (n=8) orally for 7 days. Based on data from all subjects, rosiglitazone did not alter the pharmacokinetics of R(+)-

warfarin and decreased the AUC of S(-)-warfarin by 10%. No formal analysis of INR values in each group was undertaken by the sponsor because some subjects were not at a steady-state INR; however, median % changes in INR from baseline to Day 21 were similar (rosi+warf: 11.8%; warf: 12.1%).

The effect of multiple oral doses of rosiglitazone (2x4mg clinical tablet formulation once daily) for 14 days on the single dose pharmacokinetics of nifedipine (a 3A4 substrate) capsules was investigated in a randomized, crossover study in 26 healthy male volunteers. Table 15 shows the data analysis for this study.

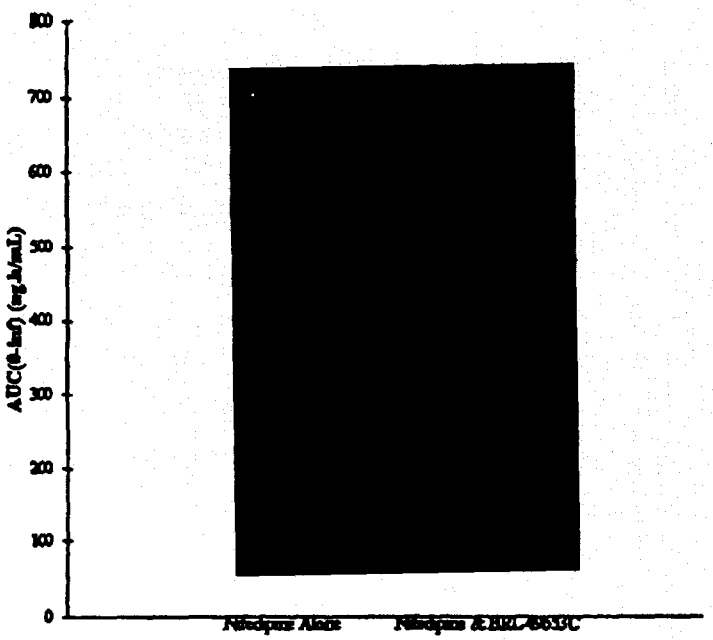
Table 15. Mean (SD) Pharmacokinetic Parameters and Statistical Results for Nifedipine (Study 039).

Parameter	Nifedipine Alone (n=26)	Nifedipine + Rosiglitazone (n=26)	Point Estimate* (Confidence Interval)**
AUC(0-inf) (ng.h/mL)	338 (135)	298 (110)	0.87 (0.79, 0.96)
Cmax (ng/mL)	137 (86)	136 (88)	0.99 (0.68, 1.43)
Tmax (h)#	0.95 [redacted]	0.55 [redacted]	0.01h [redacted]
T1/2 (h)	4.95 (2.20)	4.21 (1.74)	-0.77h (-1.40h,-0.14h)

* Ratio of geometric means of 'nifedipine + rosiglitazone: nifedipine alone'
** For AUC(0-inf), 90% confidence interval; for Cmax, Tmax T1/2, 95% confidence intervals
# Tmax presented as median (range)

The Cmax point estimate of 0.99 indicates no effect; the 95%CI is wide as might be expected with the variability in Cmax The mean 90%CI for AUC ratio indicates that there is a 13% decrease in nifedipine exposure with concurrent rosiglitazone administration. However, when individual responses are examined (Figure 12) it is apparent that the effect is neither consistent nor substantial.

Figure 12. AUC(0-inf) (ng . h/mL) following Single Dose Administration of 20 mg Nifedipine Alone or in Combination with Repeat Dose Administration of 8 mg rosiglitazone.



The effect of repeat dose rosiglitazone (2x4mg clinical tablet formulation once daily) for 14 days on the steady-state pharmacokinetics of the oral contraceptive Ortho- Novum 1/35 (containing ethinylestradiol and norethindrone) was investigated in a randomized, placebo-controlled, crossover study in 32 healthy

female subjects. The results are shown in Table 16 and indicate no effect on oral contraceptives from concomitant rosiglitazone administration.

Table 16. Mean (SD) Pharmacokinetic Parameters and Statistical Results for Ethinylestradiol and Norethindrone (Study 031).

Regimen	Rosiglitazone + Ortho-Novum 1/35 (n=32)	Ortho-Novum 1/35 Alone (n=32)	Point Estimates* (90% CI)
Ethinylestradiol			
AUC(0-24) (ng.h/mL)	1126 (386)	1208 (404)	0.92 (0.88, 0.97)
Cmax (ng/mL)	123 (42)	130 (47)	0.95 (0.88, 1.02)
Norethindrone			
AUC(0-24) (ng.h/mL)	178 (67)	171 (62)	1.04 (1.00, 1.07)
Cmax (ng/mL	21.5 (6.7)	22.1 (6.8)	0.97 (0.91, 1.03)

* Ratio of geometric means of 'rosiglitazone + OC: OC alone'

The results of these two drug interaction studies with nifedipine and oral contraceptives suggest that rosiglitazone is unlikely to cause interactions with other drugs metabolized via CYP3A4.

A single administration of a moderate amount of ethanol did not increase the risk of acute hypoglycemia in BRL 49653C-treated Type 2 diabetic patients.

Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral (4mg clinical tablet formulation) or intravenous doses of rosiglitazone in 12 healthy male volunteers.

VII. Population Pharmacokinetics

A POP PK analysis consult was obtained from Michael Fossler, Pharm.D., Ph.D. (see Appendix 3). Overall, weight and gender were found to affect rosiglitazone clearance and volume in a linear fashion, although the effects are quite modest. At a given weight, clearance for women is about 6% lower than for men. Since weight also affects clearance, the net mean gender difference in clearance between men and women is about 15%, with women having lower values than men on average. The sponsor also proposed labeling based on drug-drug interaction analysis from the POP PK results; however, this analysis was deemed inadequate for labeling by Dr. Fossler.

VIII. Pharmacokinetic / Pharmacodynamic Relationships

A PK/PD analysis consult was obtained from Michael Fossler, Pharm.D., Ph.D. (see Appendix 4). Overall, there is a weak relationship between exposure (AUC or Cmax) and clinical response (hemoglobin A1c or FPG).

COMMENTS TO BE SENT TO SPONSOR:

1) The sponsor should provide dissolution data for the 2 and 4mg (or 8mg) commercial tablets in the media specified by SUPAC for a level 2 change/case C (This was discussed in a T/con).

2). The sponsor is encouraged to conduct drug-drug interaction studies between rosiglitazone and approved compounds that may be expected to effect the metabolism of rosiglitazone through the CYP 2C family (e.g., fluvastatin).

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

1) **Population Pharmacokinetics in Patients with Type 2 Diabetes**
Population pharmacokinetic analyses from three Phase III trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and 2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about [redacted]-15%) in female patients [redacted] The population mean CL/F of rosiglitazone for a typical male weighing 84 kg was 2.48 L/h. The Vss/F in an 84 kg patient was 17.9 L. The inter-patient variability in CL/F and Vss/F were 31% and 23%, respectively.

Gender: Results of the population pharmacokinetic analysis showed that the mean oral clearance of rosiglitazone in female patients (n=405) was [redacted]% lower compared to male patients of the same body weight (n=642) [redacted] Since safety profiles were similar between male and female patients in clinical studies and, as therapy should be individualized, no dose adjustments are necessary based on gender.

☞ When both weight and gender are taken into account, the overall clearance difference is about 15%. The 'pure' gender effect is 6%.

2) [redacted]

☞ 1. The compounds are grouped by therapeutic class, rather than by a more meaningful classification such as metabolizing isozyme. Thus, the results do not generalize to individual drugs, nor could these results be used to predict the likelihood of an interaction with compounds not on this list.
2. Such statements referring to classes of drugs may be construed by health professionals in the future as applying to compounds which were not even approved at the time the studies were performed.

3) **Absorption**
[redacted] The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed ~~by~~ about 1 hour after dosing.

☞ First sentence is unnecessary since actual data are presented .

4) Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), with a an [redacted] approximately 28% decrease in Cmax [redacted] and a delay in Tmax (1.75 hours). These changes are not clinically significant, therefore; Avandia, may be administered with or without food.

☞ Actual data preclude the need for 'small'.

5) **Distribution**

The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately [redacted]17.6 (30%) Liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

☞ As per POP PK Analysis.

6) **Excretion**

Following oral or intravenous administration of [14 C]rosiglitazone maleate, approximately [redacted]64% and [redacted]23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [14C]related material ranged from 103 to 158 hours.

☞ As per data.

7) **Drugs Metabolized by Cytochrome P450**

Avandia has been shown in vitro not to inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8 and, to a lesser extent, 2C9.[redacted]

☞ As per data.

8) Warfarin: [redacted]

values of INR of <2.75. Repeat dosing with Avandia had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

☞ INR data not formally analyzed.

[redacted]APPEARS THIS WAY ON ORIGINAL

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/ [redacted] 07-MAY-99

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 04-MAY-99

CPB Briefing: 07-MAY-99
Attendees: ChenML, AhnH, FosslerM, HuangSM, HaidarS, MadaniS, DoddapaneniS, ChatterjeeD, SelenA, Al-FayoumiS, Shorer.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ [redacted]

CC: NDA 21-071/N-000 (orig.,1 copy), HFD-510(Weber, Misbin, Ysern, RheeH), HFD-340 (Viswanathan), HFD-870(Fossler, Ahn, ChenME), HFD-850(Lesko, Huang) CDR (Barbara Murphy).

Code: AE

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Appendix 1. Proposed Draft Labeling

15 Pages
DRAFT
LABELING

Appendix 2. Study summaries

PHARMACOKINETICS IN HEALTHY VOLUNTEERS
BIOEQUIVALENCE

Protocol 49653C/028 Issued February 1998
SB Report BRL-49653/RSD-100HNG/1

Title: Bioequivalence study of the final market formulation of BRL-49653C compared to the clinical trials formulation.

Investigator: Martin I. Freed, M.D.

Study Center: SmithKline Beecham Clinical Research Unit, Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania, USA

PK Objective: Compare the bioequivalence of single oral doses of the final commercial tablet formulations of rosiglitazone with the clinical trials tablet formulations.

Study Design: This investigation was an open-label, randomized, four period, period-balanced, crossover pharmacokinetic study. The pharmacokinetic profile of rosiglitazone was determined in 28 healthy male volunteers (age 20 to 45 years; weight 65 to 93 kg). At each study session, subjects randomly received one of the following regimens:

Regimen A	Rosiglitazone 1 mg clinical trials formulation [formula AN-AC, batch # N97279]
Regimen B	Rosiglitazone 1 mg commercial formulation [formula BF-AA, batch # M97130]
Regimen C	Rosiglitazone 2 x 4 mg clinical trials formulation [formula BD-AB, batch # M97042]
Regimen D	Rosiglitazone 8 mg commercial formulation [formula BJ-AA, batch # M97141]

Each subject participated in four study sessions separated by a minimum washout period of at least one week. On each occasion, rosiglitazone was administered under fasted conditions. Blood samples (5 mL) were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours from the time of dose administration.

Cmax, Tmax, AUC(0-inf) and T1/2 were determined using non-compartmental methods. The primary parameters, AUC(0-inf) and Cmax, were ln-transformed and separately analyzed by analysis of variance with terms for sequence, subject within sequence, period, dose, and formulation within dose. Point estimates and

associated 90% confidence intervals (CI) were computed separately for the ratio of commercial formulation : clinical trials formulation for each of the 1 and 8 mg doses. At each dose, equivalence was demonstrated if the 90% CI was completely contained within the range 0.80 to 1.25 for both Cmax and AUC. Point estimates and 95% confidence intervals were calculated for the difference between formulations at each dose for secondary end points, Tmax and T1/2.

Analytical Methodology: Plasma samples were analyzed for rosiglitazone using [redacted] coupled to [redacted] [SB Report No. RSD-100K5D]. The lower limit of quantification was [redacted] Analysis was performed at [redacted]

PK Results: Mean (SD) pharmacokinetic parameter estimates for rosiglitazone are presented in Table 1 and the statistical results are shown in Table 2. The maximum observed plasma concentrations of rosiglitazone occurred at approximately 1 hour after dosing. In general, plasma concentrations declined from the maximum concentration in a mono-exponential manner and were typically measurable for up to 12 hours for the 1 mg doses and for the entire 24 hour period following the 8 mg doses.

The 90% confidence intervals for the 1 mg and the 8 mg commercial formulations versus the 1 mg and the 8 mg (administered as 2 x 4 mg) clinical trials formulations, respectively, for AUC(0-inf) and Cmax were completely contained within the acceptance range of 0.80 to 1.25. Therefore, the commercial and clinical trials formulations of rosiglitazone are bioequivalent at doses of 1 mg and 8 mg in terms of the primary parameters in this study. T½ values were similar between regimens.

Significant period effects were observed for AUC(0-inf), Cmax, and T½ in this study. Given these effects, it is possible that the analysis for Tmax confounded systematic differences due to period with differences between formulations. However, based on descriptive statistics, the median Tmax values appeared to be similar between formulations at the 1 and 8 mg doses.

Sample size calculations were based on average within-subject coefficients of variation (CV) of 17.9% and 23.7% for AUC and Cmax of rosiglitazone observed in Protocols 001, 002, 004, 016, and 030. In this study, within-subject variability for AUC(0-inf) and Cmax was 13.4% and 18.5%, respectively, indicating no inadequacy in terms of sample size.

PK Conclusion: The final commercial formulation and clinical trials formulation of rosiglitazone were bioequivalent at both 1 mg and 8 mg.

Table 1
Mean (SD) Pharmacokinetic Parameter Values for Rosiglitazone
(Protocol 49653/028)

Parameter	Clinical trials formulation (1 mg)	Commercial formulation (1 mg)	Clinical trials formulation (2 x 4 mg)	Commercial formulation (8 mg)
AUC(0-inf) [ng.h/mL]	379 (91)	386 (131)	3040 (589)	2957 (678)
Cmax [ng/mL]	75.9 (19.9)	73.8 (20.9)	647 (129)	634 (143)
Tmax* [h]	0.98	0.55	0.96	0.98
T1/2 [h]	3.49 (0.72)	3.72 (0.88)	3.70 (0.75)	3.81 (0.81)

* - Data presented as median (range)

[redacted]

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Table 2
Point Estimate and 90% Confidence Intervals
(Protocol 49653/028)

Parameter	Comparison	Point Estimate	90% CI
AUC(0-inf)*	B:A	1.00	(0.95, 1.07)
	D:C	0.96	(0.91, 1.02)
Cmax*	B:A	0.97	(0.89, 1.05)
	D:C	0.97	(0.89, 1.05)
Tmax**	B–A	-0.03 h	(–0.27, 0.23)##
	D–C	0.02 h	(–0.02, 0.25) ##
T1/2#	B–A	0.23 h	(–0.05, 0.51)##
	D–C	0.11 h	(–0.17, 0.39) ##

* data presented as the ratio of the geometric means
** data presented as the median difference
# data presented as the mean difference
95% C.I.

A - Rosiglitazone 1 mg clinical trials formulation
B - Rosiglitazone 1 mg commercial formulation
C - Rosiglitazone 2 x 4 mg clinical trials formulation
D - Rosiglitazone 8 mg commercial formulation

REVIEWER'S COMMENTS FOR STUDY 028:

1. T1/2 values for B-A comparison are incorrectly reported in this summary: The point estimate is 0.21 h

2. Assay acceptable.

3. There were period and sequence effects in the ANOVA. However, statistician deemed this acceptable.

APPEARS THIS WAY
ON ORIGINAL

Name of Company: SmithKline Beecham Pharmaceuticals

Name of Active Ingredient: BRL 49653C

Title: Evaluation of the Safety, Tolerability and Preliminary Pharmacokinetics of Single Rising Doses of BRL 49653C in Normal Volunteers

Study Number: BRL 49653C/001

Investigator: Martin I. Freed, MD

Study Center: SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, Philadelphia, PA, USA.

Study Period: October 25, 1993 to March 18, 1994

Objectives: 1) To demonstrate the safety and tolerability of BRL 49653C in healthy adult subjects. 2) To evaluate preliminary pharmacokinetics of BRL 49653 and if possible its enantiomers, after single dose administration.

Publications: None as of 1 January 1995

Methodology: Single blind, randomized (with respect to order of placebo), placebo controlled, oral dose rising study. Each subject was to participate in four study sessions separated by at least one week. Each subject was to receive placebo during one of the four treatment sessions based on a randomization schedule provided in advance by Clinical Pharmacology, Statistics. At each of the other three sessions, subjects received progressively increasing single oral doses of BRL 49653C. The protocol was subsequently amended to allow for a two period, double-blind rechallenge study of subject 666 who was withdrawn early (after session 2), by the investigator due to an adverse experience.

Number of Subjects: Sixteen (16) healthy male subjects with an average age of 24 years (range 19 to 33 years) and average weight of 76 kg (range 63 to 95 kg) were enrolled in this study. Thirteen subjects completed this study and 3 subjects were withdrawn.

Diagnosis and Criteria for Inclusion: Healthy non-smoking adult male volunteers who were 18 to 40 years of age.

Test Products, Dose and Mode of Administration: BRL 49653C oral capsules, BRL 49653C 0.1 mg (Lot # G93016); BRL 49653C 1.0 mg (Lot # G93043); BRL 49653C 5.0mg (Lot # G93034); Matching placebo capsule (Lot # G93019) The planned doses for this study were placebo, 0.2, 0.5, 1.0, 2.0, 4.0 and 5.0 mg
BRL 49653C to be administered orally with approximately 240 mL of water.

Criteria for Evaluation: Supine blood pressure and pulse rate were measured immediately prior to dosing and at 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hours following the administration of study medication. Standing blood pressure and heart rate were to be measured at 4 and 8 hours after dosing. Continuous single lead ECG monitoring was performed from prior to dosing until 8 hours after dosing (SpaceLabs, Redmond, Washington, USA). A 12 lead-ECG will be performed prior to dosing and at 2, 4 and 24 hours after dosing. Hematology, clinical chemistry and urinalysis studies were performed at screening, prior to dosing and at 24 hours after dosing during each study session. Blood glucose was determined by glucometer at 4, 8 and 12 hours after dosing during each study session.

Name of Company: SmithKline Beecham Pharmaceuticals

Name of Active Ingredient: BRL 49653C

On every study day, approximately 10 mL blood was obtained form an arm vein or intravenous cannula at 0 hour (predose) and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hours after dosing for the determination of pharmacokinetics of BRL 49653 and its enantiomers.

Summary of Results: Thirteen adverse experiences were reported for 9 subjects. Headache was the most common adverse experience occurring in 3 subjects. An asymptomatic accelerated ventricular rhythm of less than 10 seconds duration was reported in 2 volunteers who received 2 mg BRL 49653C. These events were considered possibly related, serious adverse experiences and both subjects were withdrawn from study. One of these subjects was rechallenged with 2 mg BRL 49653C and placebo in a double-blind fashion with no further ventricular ectopy noted at either dosing session. There were no other serious adverse experiences.

Plasma concentrations of BRL 49653 increased with increasing dose and declined mono-exponentially. Both Cmax and AUC(0-inf) increased approximately proportionately with the increase in dose over the range 0.2 to 5.0 mg. Dose-normalized AUC(0-inf) values for each subject were generally similar for the doses administered. Absorption was rapid, with median Tmax values in the range of 0.8 to 1.0 hours at all dose levels. Terminal phase of elimination half-lives were similar at all doses, with mean values ranging from 3.3 to 4.0 hours.

After administration of racemic BRL 49653C interconversion occurred and favored SB 210232(+). The final equilibrium ratio was independent of dose and was similar in all subjects, with ratios at 6 hours in individual subjects ranging from 70.4 % to 78.8% SB 210232(+) and from 29.6% to 21.2% SB 206846(-).

In general, Cmax and AUC(0-t) values for SB 210232(+) were approximately 1.5 to 2-fold higher than the corresponding Cmax values for SB 206846(-). Terminal phase half-lives for both enantiomers were independent of dose. Elimination of SB 210232(+) was slightly slower than for SB 206846(-), with terminal phase half-lives ranging from 2.11 to 7.99 hours compared to 1.47 to 3.79 hours, respectively. Interconversion was rapid with equilibrium half-lives for the formation of SB 210232(+) from SB 206846(-) ranging from 0.64 to 2.13 hours. In each case the equilibrium half-life was shorter than the corresponding elimination phase half-lives of the enantiomers for each subject.

Conclusions:
BRL 49653C in single doses of up to 5 mg orally was generally safe and well tolerated by healthy male subjects. There were isolated observations of accelerated ventricular rhythms in two subjects following dosing with 2 mg BRL 49653C. This arrhythmia was not reproducible in the one subject who agreed to be rechallenged with 2 mg BRL 49653C and placebo. These rhythm disturbances were reported as serious adverse experiences and were regarded as mild in nature due to their short duration and lack of associated symptoms or hemodynamic changes.

Cmax and AUC(0-inf) of BRL 49653 increased approximately proportionately with increasing dose over the range 0.2 to 5.0 mg and inter-subject variability was generally low.

Absorption of BRL 49653 was generally rapid and elimination half-lives were on average 3 - 4 hours at all doses.
Equilibrium half-lives for attaining a constant ratio for the enantiomers were independent of dose, and in all cases less than the corresponding elimination phase half-lives. Exposure to SB 210232(+) based on AUC and Cmax, was approximately 2-fold greater than that for SB 206846(-).

REVIEWER'S COMMENTS FOR STUDY 001:

1. Agree with results on PKs of rosiglitazone.

APPEARS THIS WAY
ON ORIGINAL

PHARMACOKINETICS IN HEALTHY VOLUNTEERS

Protocol 49653C/002 Issued May 1995
SB Report HP-1004/BRL049653/1

Title: An evaluation of the safety, tolerability, pharmacokinetics and pharmacodynamics of BRL-49653 after 10 days repeat dosing to obese subjects

Investigator: Martin I. Freed, M.D.

Study Center: SmithKline Beecham Clinical Research Unit, Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania, USA

PK Objective: Obtain pharmacokinetic data on single and repeated dose administration of rosiglitazone in obese male and female volunteers.

Study Design: This was a randomized, double-blind, placebo controlled, repeat dose, period balanced, two-period crossover study in which the pharmacokinetic profile of rosiglitazone was determined in 18 obese male volunteers (age 20 to 63 years; weight 77 to 116 kg; body mass index 27 to 35 kg/m^2) and 18 obese female volunteers (age 25 to 59 years; weight 73 to 109 kg; body mass index 28 to 36 kg/m^2). Three treatment regimens of rosiglitazone as a capsule formulation were investigated: 1 mg (1 x 1 mg, lot # G93043) od, 2 mg (2 x 1 mg, lot # G93043) od, and 5 mg (1 x 5 mg; lot # G93034) od. During each of two study periods, patients received 10 days of treatment with placebo or one of the treatment regimens of rosiglitazone with at least a one week washout period between treatment regimens. Rosiglitazone was administered under fasting conditions on Days 1 and 10 where pharmacokinetic assessment was undertaken. On study Days 1 and 10, blood specimens were obtained for pharmacokinetic analysis at predose (0 time), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours following dosing. Trough blood samples were obtained on study Days 7, 8, and 9.

Pharmacokinetic parameters (Cmax, Tmax, AUC(0-t), AUC(0-inf), and T1/2) were calculated using non-compartmental analysis. The linearity accumulation ratio [R_A(AUC)] for AUC was calculated as AUC(0-τ) on Day 10 divided by AUC(0-inf) on Day 1, where AUC(0-τ) is the area under the plasma concentration-time curve from time zero to the end of the dosing interval (τ). Assuming concentration- and time-independent pharmacokinetics, this ratio should equal unity. Additionally, the observed accumulation ratio (Ro) for Cmax and AUC(0-inf) were determined (Cmax day 10/Cmax day 1 and AUC(0-inf)day 10/AUC(0-inf) day 1, respectively). The predicted accumulation ratios from

single dose data (Rp (λ) =1/(1-exp(λT); Rp(AUC) = AUC(0-inf)day 1/AUC(0-τ)day 1) were also determined. Descriptive statistics were used to summarize the pharmacokinetic data. AUC and Cmax values were ln-transformed and analyzed by analysis of variance fitting a model with terms for gender, dose, gender*dose interaction, subject (within gender*dose), day and dose*day interaction. Point estimate and 95% confidence intervals for the difference between day 10 and day 1 were constructed. Linearity accumulation ratio (R_c) values were analyzed following ln-transformation fitting a model with terms for gender, dose and gender*dose interaction. The p-values of a two-tailed t-test and 95% confidence intervals were computed at each dose level to examine whether R_c deviated significantly from unity.

Analytical Methodology: Plasma samples were analyzed for concentrations of rosiglitazone using [redacted] coupled to [redacted] detection [SB Report No. BF-1016]. Analysis was performed in the Department of Drug Metabolism, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania, USA. The lower limit of quantification (LLQ) for rosiglitazone was [redacted]

PK Results and Discussion: The mean (SD) pharmacokinetic parameter values for rosiglitazone for all subjects by dose group and by gender and dose group are shown in Tables 1 and 2, respectively. Statistical results comparing single and multiple dose data are shown in Table 3. Mean (range) observed (Ro) and predicted (Rp) accumulation ratios for Cmax and AUC are shown in Table 4. The study design permitted comparison of mean pharmacokinetic parameters across dose levels in order to examine approximate dose proportionality of rosiglitazone following single and multiple dose administration. Additionally, the data from this study allowed a preliminary assessment of the effect of gender on the pharmacokinetics of rosiglitazone, although the study was not formally powered to investigate gender differences.

Rosiglitazone was rapidly absorbed with maximum observed plasma concentrations occurring within 0.5 to 2 hours in all subjects after single or repeated rosiglitazone administration at all dose levels. Plasma concentrations of rosiglitazone typically declined from the maximum concentration in a monoexponential manner. Mean Cmax and AUC values increased with an increase in dose after single and multiple dose administration of rosiglitazone. Cmax and AUC values were approximately dose proportional over the dose range 1 to 5 mg.

Cmax and Tmax values were similar on Days 1 and 10. As predicted from single dose data (Rp), there was no evidence for accumulation of rosiglitazone (Ro) after once daily dosing of rosiglitazone for 10 days at all dose levels (Table 4). There was, however, an overall decrease in AUC on Day 10 with an associated decrease in T1/2. These results suggest that there may be an increase in systemic clearance after multiple dose administration. These differences were less pronounced at the highest dose of 5 mg as compared to the lower doses.

Dose differences were observed in comparisons of Day 10 to Day 1 AUC(0-inf), Cmax and T1/2. Cmax and AUC(0-inf) geometric mean ratios (Day 10:Day 1) were slightly lower for the 1 and 2 mg dose groups compared to that of the 5 mg dose group. For T1/2, differences were greater at 1 mg than at 2 and 5 mg doses.

In these small groups of subjects, statistical evidence for higher AUC(0-inf) values and longer T1/2 values were observed in female compared to male subjects on both Days 1 and 10. These differences were more evident at the 1 mg dose than at the 2 and 5 mg doses. However, the ranges of values between genders for both AUC and T1/2 were shown to overlap. Cmax was higher for females than for males at 1 mg, similar at 2 mg, and lower at 5 mg, as reflected by a significant sex*dose interaction.

PK Conclusions: Mean rosiglitazone Cmax and AUC values were approximately dose proportional over the dose range of 1 to 5 mg after single and multiple dose administration to obese subjects. No evidence of accumulation was observed after once daily dosing of rosiglitazone for 10 days at all dose levels. Female subjects were observed to have somewhat higher Cmax and AUC(0-inf) and prolonged T1/2 values compared to male subjects.

Table 1
Mean (Range) Pharmacokinetic Parameters for Rosiglitazone
(Protocol 49653/002)

	1 mg [n=12]		2 mg [n=11]		5 mg [n=12]	
Parameter	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
AUC[a] (ng.h/mL)	402	278	733	489	1839	1541
Cmax (ng/mL)	64.2	58.4	137	128	361	327
Tmax[b] (hours)	1.0	0.5	1.0	1.0	1.0	1.3
T1/2 (hours)	4.68	3.33	3.86	3.04	4.13	3.38
Vss/F (L)	18.7	18.4	16.8	18.4	17.7	17.1
CL/F (L/h)	2.85	4.15	2.92	4.03	2.82	3.37

a = AUC(0-inf) on Day 1 and AUC(0-t) on Day 10 where t is ≤ tau
b = Data presented as median (range)

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Table 2
Mean (SD) Pharmacokinetic Parameters for Rosiglitazone by Gender
(Protocol 49653/002)

		1 mg (n=6M/6F)		2 mg (n=6M/5F)		5 mg (n=6M/6F)	
Parameter	Sex	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
AUC[a] (ng.h/mL)	M	288 (80)	186 (48)	666 (183)	451 (72)	1816 (268)	1473 (396)
	F	516 (115)	370 (169)	814 (191)	535 (91)	1862 (509)	1608 (454)
Cmax (ng/mL)	M	56.9 (13.5)	53.8 (9.2)	129 (28)	136 (35)	423 (117)	359 (122)
	F	71.5 (16.2)	63.0 (5.6)	145 (58)	117 (31)	299 (86)	295 (52)
Tmax[b] (hours)	M	0.8	0.5	1.3	0.8	0.8	1.3
	F	1.0	0.5	1.0	1.0	1.5	1.3
T½ (hours)	M	3.82 (0.88)	2.56 (0.56)	3.35 (0.86)	2.73 (0.47)	3.80 (0.47)	3.12 (0.35)
	F	5.53 (1.41)	4.11 (1.35)	4.48 (0.65)	3.42 (0.55)	4.46 (1.21)	3.65 (0.81)

a = AUC(0-inf) on Day 1 and AUC(0-t) on Day 10 where t is ≤ tau
b = Data presented as median (range)

[redacted]

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Table 3
Point Estimates (95% Confidence Intervals) Comparing the Pharmacokinetics of Rosiglitazone on Day 10 relative to Day 1
(Protocol 49653/002)

Parameter	1 mg	2 mg	5 mg
Cmax*	0.93 (0.77, 1.12)	0.95 (0.78, 1.15)	0.92 (0.76, 1.11)
AUC(0-inf)*	0.71 (0.61, 0.82)	0.71 (0.61, 0.83)	0.85 (0.73, 0.98)
T1/2**	−1.35 h (−1.70 h, −0.99 h)	−0.82 h (−1.19 h, −0.45 h)	−0.75 h (−1.10 h, −0.39 h)
R_L(AUC)#	0.66 (0.57,0.76) p<0.001	0.68 (0.58,0.79) p<0.001	0.83 (0.71,0.96) p=0.015

* presented as the ratio of geometric means (AUC(0-t) Day 10 : AUC(0-inf) Day 1)

** presented as difference in arithmetic means (Day 10 - Day 1)

presented as geometric mean (95% CI), p-value based on two tailed t-test

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Table 4
Mean (Range) Observed and Predicted Accumulation Ratios
(Protocol 49653/002)

Dose (mg)	Ro [Cmax]	Ro [AUC]	Rp [AUC]	Rp [λ]
1	0.94	0.74	1.12	1.04
[redacted]				
2	1.01	0.72	1.05	1.02
[redacted]				
5	0.97	0.86	1.04	1.02
[redacted]				

Ro = observed accumulation ratio
Rp = predicted accumulation ratio

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REVIEWER'S COMMENTS FOR STUDY 002:

1. Mean PK parameters and gender effect are in agreement with POP PK analysis.
2. Possible self-induction of metabolism.

APPEARS THIS WAY
ON ORIGINAL

PHARMACOKINETICS IN HEALTHY VOLUNTEERS
FOOD EFFECT

Protocol 49653C/004 Issued March 1995
SB Report HP-1003/BRL049653/1

Title: Investigation of the effect of food on the pharmacokinetics of BRL-49653C in healthy male volunteers

Publication: Bullman S, Allen A, Harris AM, Writer DJ, Freed MI, DiCicco, Zariffa N, Jorkasky DK. 1995. The influence of food on the pharmacokinetics of BRL 49653C in healthy male volunteers. *Br. J Clin Pharmacol*, 40, 517P.

Investigator: Martin I. Freed, M.D.

Study Center: SmithKline Beecham Clinical Research Unit, Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania, USA

PK Objective: To describe the effect of a high fat breakfast on the pharmacokinetics of rosiglitazone in healthy volunteers.

Study Design: This was a randomized, single dose, period balanced, two-period crossover study in 13 healthy male volunteers (age: 18-35 years, weight: 58-88 kg). At each study session, subjects received a single oral dose of rosiglitazone 2 mg (2 x 1 mg capsule, lot # G93043) under fasted conditions or following a standard high fat meal. Each session was separated by at least one week.

Blood samples were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours following oral administration. Cmax, Tmax, AUC(0-t), AUC(0-inf), and T1/2 were calculated using non-compartmental analysis. AUC(0-inf) and Cmax for the fasted state and fed state were analyzed separately by analysis of variance following ln-transformation. Point estimates and 95% confidence intervals (CI) for the comparison fed:fasted were computed. T1/2 (untransformed) was similarly analyzed by analysis of variance and the resulting point estimates and 95% CI were expressed in terms of the difference (fed-fasted). Tmax was analyzed non-parametrically and point estimates and 95% CI estimates for the median difference (fed-fasted) were obtained.

Analytical Methodology: Plasma samples were analyzed for rosiglitazone using [redacted] coupled to [redacted] detection [SB Report No. BF-1016]. The lower limit of quantitation wa[redacted](200 uL aliquot). Analysis was performed

by the Department of Drug Analysis, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK.

PK Results and Discussion: Geometric mean (SD) pharmacokinetic parameter values for rosiglitazone are shown in Table 1 and the statistical results in Table 2. Following oral administration of a single 2 mg dose of rosiglitazone, maximum observed plasma concentrations for rosiglitazone occurred between 0.5 and 3.0 hours in the fasted state and between 1.5 and 4.0 hours in the fed state. In general, plasma concentrations declined from the maximum concentration in an apparent monoexponential manner.

No difference was observed for AUC(0-inf) and T1/2 when the dose was given following a high fat breakfast, compared to results obtained under fasting conditions. Compared to the fasted regimen, Cmax was on average 20% lower and Tmax was delayed by 1.75 h on average when rosiglitazone was administered following a standard high fat breakfast. The 95% confidence intervals for Cmax did not include the value of 1.0 and the 95% CI for Tmax did not include the value of zero suggesting that the rate of absorption is slower in the fed state than in the fasted state.

PK Conclusion: Overall systemic exposure of rosiglitazone, as reflected in AUC(0-inf), and elimination, as indicated by T1/2, were unaffected by administration of rosiglitazone following a high fat breakfast compared to results obtained in the fasted state. Absorption of rosiglitazone was slower after administration of rosiglitazone with food as evidenced by an average decrease of 20% in Cmax and a delay in Tmax by approximately 1.75 hours relative to the fasted state.