Table 1

Mean (SD) Pharmacokinetic Parameter Values for Rosiglitazone
(Protocol 49653/004)

Parameter	Fed (n=13)	Fasted (n=13)
AUC(0-inf) (ng.h/mL)	844 (247)	895 (262)
Cmax (ng/mL)	128 (43)	156 (34)
Tmax[a] (hours)	3.5	1.3
T½[b] (hours)	3.78 (0.59)	3.64 (0.63)

a = Data presented as median (range)

b = Data presented as arithmetic mean (range)

Table 2

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)

1. Actual number of subjects used in statistical analysis is 12.
2. Agree with results

APPEARS THIS WAY
ON ORIGINAL

PHARMACOKINETICS IN HEALTHY VOLUNTEERS
DOSE PROPORTIONALITY
FOOD EFFECT

Protocol 49653C/005 Issued February 1998
SB Report BRL-049653/RSD-100J1L/1

Title: A single dose study to assess the safety, tolerability, dose proportionality and food effect of the proposed commercial tablet formulation of BRL-49653C in healthy volunteers

Investigator: Martin I. Freed, M.D.

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

PK Objective: 1) To assess the dose proportionality of single oral doses of 1, 2, and 8 mg using the final commercial tablet formulations of rosiglitazone under fasted conditions; 2) to estimate the difference between the pharmacokinetics of single oral doses of the commercial tablet formulation for rosiglitazone following a standard high fat meal and under fasting conditions in healthy volunteers.

Study Design: This was an open label, randomized, four-period, period balanced, crossover study involving 32 healthy adult male and female volunteers with an average age of 31 years (range 20-47 yr) and average weight of 75 kg (range 53 to 107 kg), 28 of whom completed all 4 study sessions. Subjects were randomly allocated to one of four treatment sequences receiving the following single oral doses: 1 mg (batch # M97130), fasting; 2 mg (batch # M97133), fasting; 8 mg (batch # M97141), fasting; or 8 mg (batch # M97141) under fed conditions (a standard high fat breakfast). During each study session, blood samples (5 mL) for pharmacokinetic analysis were drawn at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours following dosing.

Cmax, Tmax, AUC(0-t), AUC(0-inf) and T1/2 were determined by non-compartmental methods. Dose normalized Cmax and dose-normalized AUC(0-inf) values were obtained by dividing individual estimates by the corresponding dose.

Primary pharmacokinetic endpoints, dose-normalized AUC(0-inf) and Cmax, were ln-transformed and subjected to analysis of variance. For assessment of dose proportionality, point estimates and 90% confidence intervals for these parameters were constructed for the '2 mg:1 mg' and the '8 mg:1 mg' ratios after rosiglitazone

administration under fasting conditions. Strict dose-proportionality for primary endpoints was assessed through an equivalence-type approach using a 30% acceptance range (0.70, 1.43), where 1 mg rosiglitazone served as the reference. To assess the effect of food on the pharmacokinetics of rosiglitazone, point estimates and 95% confidence intervals for the 8 mg rosiglitazone dose fed:fasted were also derived. Secondary endpoint T½ was similarly analyzed without prior transformation, and Tmax was analyzed nonparametrically. Point estimates and 95% confidence intervals were derived for the comparisons of interest for secondary endpoints.

Analytical Methodology: Plasma samples were analyzed for rosiglitazone using automated [redacted] followed by [redacted] detection (lower limit of quantification (LLQ) for rosiglitazone was [redacted] using a 40 uL aliquot) [SB Report No. RSD-100NHD/1]. Analysis was performed at the Department of Drug Analysis, Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, The Frythe, UK.

PK Results and Discussion: Mean (SD) pharmacokinetic parameter values for rosiglitazone for the dose proportionality and food effect portions of this study are shown in Table 1 and statistical results are shown in Table 2. Mean plasma concentration versus time profiles for rosiglitazone are shown in Figure 1. The statistical results for the effect food on rosiglitazone pharmacokinetics are shown in Table 3. Maximum plasma concentrations after single oral doses of 1, 2, and 8 mg dose administration under fasted conditions were observed between 0.5 and 2 hours post-dose. After Tmax was attained, plasma rosiglitazone concentrations generally declined in a monoexponential manner at all dose levels and typically were no longer quantifiable after 12 hours for the 1 and 2 mg doses and after 16 hours following the 8 mg dose, fed and fasted.

For dose-normalized Cmax and AUC(0-inf), the 90% CIs for the ratios of the geometric means for the 2 and 8 mg doses relative to the 1 mg reference dose were contained in the protocol-specified 30% acceptance range for equivalence (0.70, 1.43). Thus, dose proportionality was demonstrated for the commercial formulation of rosiglitazone for single oral doses of 1 to 8 mg administered in the fasted state. Mean T½ (3 to 4 hours) and median Tmax (0.5 to 1 hour) were also similar across this dose range in the fasted state.

Administration of rosiglitazone following a high fat meal resulted in similar extent of absorption, but an apparent decrease in the rate of absorption of rosiglitazone compared to those in the fasted state. Cmax was decreased, on average, by 28% and median Tmax was prolonged by 1.75 hours when

rosiglitazone was administered in the fed state relative to the fasted state. Based on the similar T½ values observed in the fed and fasted states, elimination was considered to be unaffected by administration of rosiglitazone following a high fat breakfast.

PK Conclusion: Dose proportionality was demonstrated for the commercial formulation of rosiglitazone for single oral doses of 1 to 8 mg. The extent of absorption of rosiglitazone in the presence of food was similar compared to that obtained in the fasted state. However, the rate of absorption of rosiglitazone was slower as evidenced by an average decrease of 28% in Cmax and a delay in Tmax by approximately 1.75 hours relative to the fasted state.

Table 1
Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following a Singl
Oral Dose of Rosiglitazone under Fed and Fasted Conditions
(Protocol 49653/005)

Parameter	1 mg fasting (n=32)	2 mg fasting (n=32)	8 mg fasting (n=32)	8 mg fed (n=32)
AUC(0-inf) [ng.h/mL]	358 (112)	733 (184)	2971 (730)	2890 (795)
Cmax [ng/mL]	76.1 (13.3)	156 (43)	598 (117)	432 (92)
Tmax* [h]	0.53	0.98	0.98	1.99
Half-life [h]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)

* Data presented as median (range)

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Table 2
Point Estimates and Confidence Intervals for Dose Proportionality Assessment
(Protocol 49653/005)

Parameter	Comparison	Point Estimate	Confidence Interval
DN-AUC(0-inf)	B:A[1]	1.04	(0.99, 1.09)
DN-AUC(0-inf)	C:A[1]	1.05	(1.00, 1.10)
DN-Cmax	B:A[1]	1.00	(0.93, 1.08)
DN-Cmax	C:A[1]	0.98	(0.91, 1.05)
T½	B–A[2]	–0.01 h	(–0.23 h, 0.22 h)
T½	C–A[2]	0.21 h	(–0.02 h, 0.44 h)
Tmax	B–A[3]	0.23 h	(–0.01 h, 0.48 h)
Tmax	C–A[3]	0.21 h	(0.00 h, 0.28 h)

1: ratio of geometric means (90% confidence intervals)
2: difference in arithmetic means (95% confidence intervals)
3: difference in median values (95% confidence intervals)

Regimen A: Rosiglitazone 1 mg single oral dose, fasting
Regimen B: Rosiglitazone 2 mg single oral dose, fasting
Regimen C: Rosiglitazone 8 mg single oral dose, fasting

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Table 3
Point Estimates and 95% Confidence Intervals For Food Effect Assessment
(Protocol 49653/005)

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)
T½	D–C[2]	0.23	(0.00, 0.45)
Tmax	D–C[3]	1.75	(1.02, 2.24)

1: ratio of geometric means (90% confidence intervals)
2: difference in arithmetic means (95% confidence intervals)
3: difference in median values (95% confidence intervals)

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

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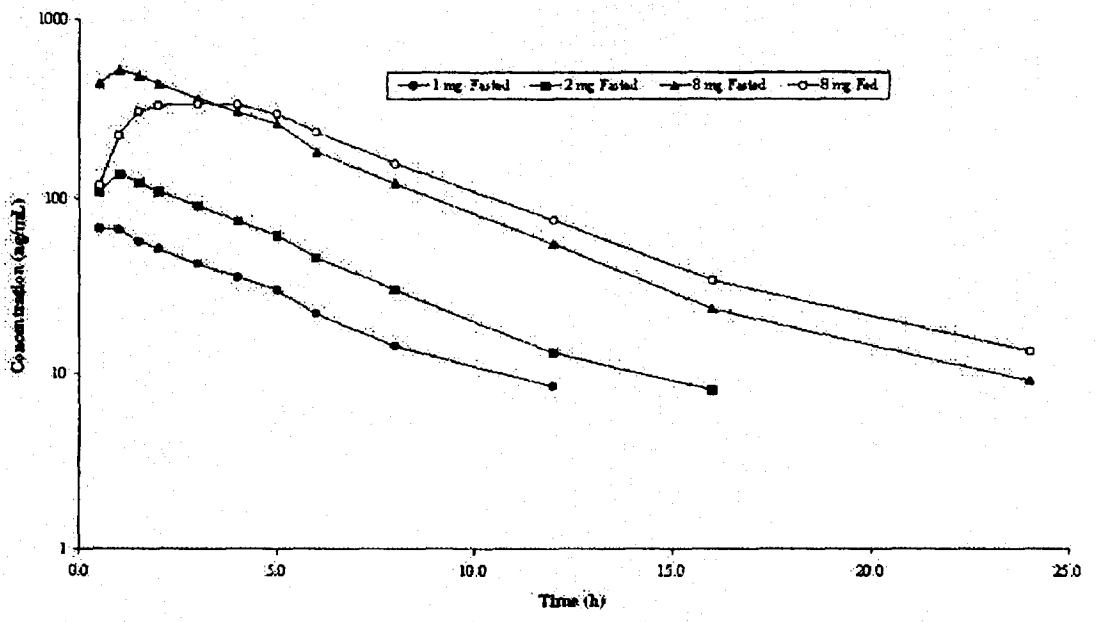
Figure 1
Mean Plasma Concentrations of Rosiglitazone Following Single Oral Administration to Healthy Volunteers



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REVIEWER'S COMMENTS FOR STUDY 005:

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ON ORIGINAL

PHARMACOKINETICS IN PATIENTS WITH RENAL DISEASE

Protocol 49653C/007 Issued June 1998
SB Report BRL-049653/RSD-100HND/1

Title: An evalnation of the pharmacokinetics of a single oral dose of BRL 49653C in hemodialysis-dependent patients with end-stage renal disease compared to volunteers with normal renal function

Investigator: Martin I. Freed, MD

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

PK Objectives: 1) Estimate the pharmacokinetics and the protein binding characteristics of a single oral dose of rosiglitazone in hemodialysis-dependent patients with end stage renal disease on non-dialysis days relative to volunteers with normal renal function; 2) describe the hemodialysis clearance and plasma protein binding characteristics of rosiglitazone during hemodialysis (dialysis day).

Study Design: This was an open-label, parallel group study design in which subjects and patients were administered a single oral dose of 8 mg (2 x 4 mg; batch #M96239) of rosiglitazone. Study participants consisted of 10 healthy volunteers (7 males, 3 females) with normal renal function (age 26 to 52 years; weight 62 to 99 kg) and 10 hemodialysis-dependent patient volunteers with end stage renal disease (age 32 to 65 years; weight 55 to 98 kg). Each healthy subject received a single dose of study medication following a light snack; each hemodialysis-dependent patient received two separate doses of rosiglitazone: the first dose on a non-dialysis day (Day 1) following a light snack, then after a washout period of at least 7 days, a second dose was administered under fasting conditions on a day that the patient had hemodialysis treatment (Day 2). On Day 1, blood samples were obtained predose and at 0.5, 1, 1.5, 2, 4, 8, 10, 12, 16, 24 and 42 hours postdose. A blood sample for *ex vivo* protein binding analysis was collected at approximately 2 hours postdose. On Day 2, blood samples were obtained predose and at 0.5, 1, 1.5, 2, 3, 7, 8, 9, 11, 16, 24 and 46-48 hours postdose (the samples taken at 3 and 7 hours were collected immediately before and after the nominal 4-hour dialysis session, respectively). During dialysis, samples were drawn from the dialyzer input (arterial) and output (venous) lines at the following nominal times: 3.9, 4.9, 5.9 and 6.9 hours. Blood samples for *ex vivo* protein binding analysis were collected at approximately 2 and 7 hours postdose.

Cmax, Tmax, AUC(0-inf), T½, and the dialytic clearance [CLhd] were determined by a non-compartmental method. Technical difficulties with the analytical method prevented the determination of the fraction unbound (fu) for most plasma samples from healthy volunteers and patients. Therefore, unbound Cmax and AUC(0-inf) were not calculated. Following ln-transformation, total Cmax and AUC(0-inf) were analyzed separately by analysis of variance with a single term for group, and point estimates and 95% confidence intervals for the ratio of patients (non-dialysis day) to volunteers were constructed. T½ was similarly analyzed (without prior transformation). Tmax was analyzed non-parametrically, to estimate the median difference and 95% confidence interval.

Analytical Methodology: Plasma was analyzed for rosiglitazone using [redacted] coupled to [redacted] with [redacted] detection [SB Report No. RSD-100LL1/1]. The lower limits of quantification [LLQ] values for rosiglitazone in plasma and dialysate were [redacted] and [redacted] respectively. Drug analysis was performed at [redacted]

The *ex vivo* protein binding of rosiglitazone was attempted using ultrafiltration to separate unbound drug and assayed for rosiglitazone using protein precipitation followed by LC/MS/MS with positive-ion electrospray ionization (LLQ 0.250 ng/mL). However, technical difficulties prevented quantitation in the majority of samples. Protein binding and plasma and ultrafiltrate concentration analyses were performed by the Departments of Biotransformation and Drug Analysis, respectively, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire, UK.

PK Results and Discussion: Mean (SD) pharmacokinetic parameters, based on total plasma concentrations, and statistical results are shown in Tables 1 and 2, respectively.

For both primary endpoints Cmax and AUC(0-inf), mean values were, on average, approximately 10% lower in the patient group (non-dialysis day). Tmax and half-life were similar in the two subject groups. Neither Cmax nor AUC(0-inf) values in the hemodialysis-dependent patients were markedly influenced by the dialysis procedure. Compared to the non-dialysis day, a small reduction (approximately 20%) in mean half-life was suggested, but the resulting reduction in mean AUC(0-inf) was only 10%. With ≤ 2% of the dose recovered in the dialysate during the entire 4-hour treatment session, the dialytic clearance was low, ranging from 0.07 to 0.17 L/h with a mean 0.10 L/h. Only very limited data were obtained on unbound plasma concentrations. Where measurable (n = 10), the percent

unbound was in the range 0.08-0.21% (Table 3). Within this range, the percent unbound tended to be higher in patients, especially on dialysis (Day 2), but the data were too sparse to derive meaningful estimates of unbound AUC(0-inf) and Cmax, or to attempt any formal statistical comparison.

PK Conclusion: In comparison with healthy volunteers, no important pharmacokinetic differences were evident in hemodialysis-dependent patients after administration of a single oral 8 mg dose of rosiglitazone on a non-dialysis day. Moreover, dialysis did not influence the disposition of rosiglitazone in these patients. Based on these data, dose adjustments do not appear to be warranted when administering rosiglitazone to patients who are receiving hemodialysis treatment.

Table 1
Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following a Single Oral 8 mg Dose to Healthy Volunteers and Hemodialysis-Dependent Patients (Protocol 49653/007)

Parameter	Patients Non-Dialysis Day (n=10)	Healthy Volunteers (n=10)	Patients on Dialysis (n=10)
AUC(0-inf) [ng.h/mL]	2192 (598)	2388 (494)	1977 (688)
Cmax [ng/mL]	338 (114)	373 (95)	333 (85)
Tmax * [hours]	2.00	2.98	2.93
Half-life [hours]	3.70 (0.75)	3.81 (0.86)	2.93 (0.77)

* Data presented as median (range)

Table 2
Point Estimates and 95% Confidence Intervals
(Protocol 49653/007)

Parameter	Comparison*	Point Estimate**	95% CI
AUC(0-inf) [ng.h/mL]	Patient:Volunteer	0.90	(0.72, 1.14)
Cmax [ng/mL]	Patient:Volunteer	0.89	(0.66, 1.20)
Tmax [hours]	Patient–Volunteer	–0.03 h	(–2.03 h, 0.47 h)
Half-life [hours]	Patient–Volunteer	–0.11 h	(–0.87 h, 0.65 h)

* All comparisons are 'patient non-dialysis day' versus 'volunteer'

** presented as ratio of geometric means for AUC(0-inf) and Cmax, median difference for Tmax and mean difference for elimination half-life.

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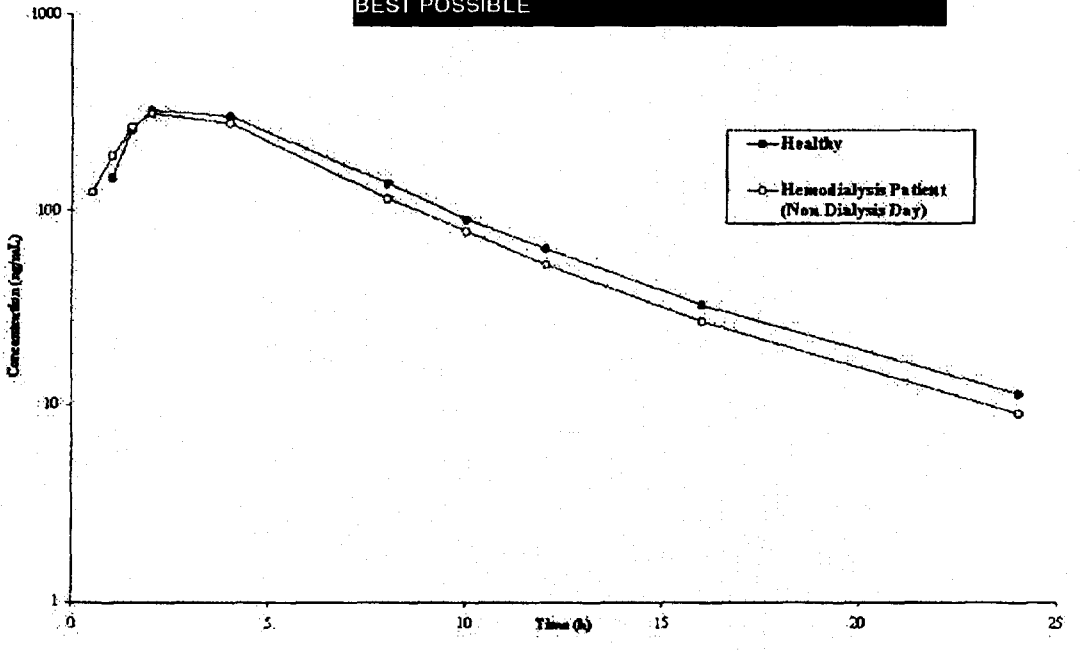
Table 3
Individual Plasma Protein Binding (Free Fraction; %) for Rosiglitazone in Healthy Volunteers and in Hemodialysis-Dependent Patients
(Protocol 49653/007)

	Day 1 2 h Postdose (Non-dialysis Day)	Day 2 2 h Postdose (Dialysis Day)
Healthy Volunteers	0.078, 0.082, 0.114	
Patients	0.109, 0.112, 0.123, 0.147	0.153, 0.204, 0.213

Figure 1
Mean Plasma Concentrations of Rosiglitazone Following Single Oral 8 mg Dose in Healthy Volunteers and End Stage Renal Patients on a Non-Dialysis Day
(Protocol 007)



REVIEWER'S COMMENTS FOR STUDY 007:

1. Dialysis does not seem to effect rosiglitazone clearance.

APPEARS THIS WAY
ON ORIGINAL

PHARMACOKINETICS IN HEPATIC PATIENTS

Protocol 49653C/008 Issued May 1998
SB Report BRL-049653/RSD-100HNF/1

Title: An evaluation of the safety, tolerability, pharmacokinetics and protein binding of BRL 49653C in patients with hepatic impairment

[redacted]

PK Objective: 1) Estimate the influence of hepatic impairment on the single dose pharmacokinetics of rosiglitazone; 2) describe the *ex vivo* plasma protein binding of rosiglitazone in patients with hepatic impairment and in healthy volunteers.

Study Design: This was an open-label, parallel-group, single dose study involving 17 healthy volunteers (16 males, 1 females; age 31 to 59 years; weight 73 to 105 kg) and 18 patients with hepatic disease (17 males, 1 female; age 38 to 48 years; weight 66 to 116 kg). Healthy volunteers were age, weight, and gender balanced with that of the patients with hepatic disease. The inclusion criteria for patients with hepatic disease were as follows:

1) Documented clinical history of chronic hepatic insufficiency diagnosed by liver biopsy, and/or liver/spleen scan, or clinical laboratory tests.

2) Hepatic Disease Score (Child-Pugh Score) ≥ 6.

Each subject and patient received a single oral dose of rosiglitazone 8 mg (2 x 4 mg tablets, batch #M96239) under fasting conditions. Plasma samples for pharmacokinetic analysis were obtained predose and at 0.5, 1, 1.5, 2, 4, 8, 10, 12, 16, 24, 48, 72 and 96 hours after dosing. One blood sample was collected at 2 hours postdose from each subject for *ex vivo* plasma protein binding analysis.

Total Cmax, Tmax, AUC(0-inf), and T½ of rosiglitazone were calculated using non-compartmental methods. Mean fraction unbound (fu) for each individual was calculated by averaging the available *ex vivo* determinations for that individual. Unbound Cmax and unbound AUC(0-inf) for rosiglitazone were determined by multiplying individual Cmax and AUC(0-inf) values by the mean fu for each individual. Unbound CL/F and Vss/F were determined by dividing individual

CL/F and Vss/F values by the mean fu for each individual. Mean serum albumin concentrations collected predose and at 24 and 96 hours postdose were determined for each individual. The relationship between mean serum albumin and fu was examined graphically.

Ln-transformed total and unbound AUC(0-inf) and Cmax, and untransformed fraction unbound and T½, were analyzed using analysis of variance including a single term for group (hepatic or healthy). Point estimates and 95% confidence intervals were calculated for the ratio 'hepatic impairment:healthy' for AUC(0-inf) and Cmax, and for the difference 'hepatic impairment–healthy' for fraction unbound and T½. Tmax was analyzed non-parametrically and the median difference 'hepatic impairment–healthy' was calculated along with a 95% confidence interval.

Analytical Methodology: Plasma concentrations of rosiglitazone were determined using a method based on protein precipitation followed by [redacted] analysis employing [redacted] [SB Report No. RSD-100RFN/1]. This method has a lower limit of quantification (LLQ) of [redacted]. The plasma and ultrafiltrate samples for protein binding determination were assayed using a method based on protein precipitation followed by [redacted] analysis employing positive-ion electrospray ionization [SB Report No. RSD-100HNF/1; Appendix A]. This method has an LLQ of [redacted] Analyses were performed by the Department of Drug Analysis, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire, UK.

PK Results and Discussion: Mean (SD) pharmacokinetic parameter values and statistical results are shown in Tables 1 and 2, respectively.

Subjects with hepatic impairment (Child-Pugh Scores 6-11) tended to have lower serum albumin concentrations (3.0 g/dL) compared to healthy volunteers (4.3 g/dl; Figure 1). The lower serum albumin concentrations were associated with a higher unbound fraction of rosiglitazone. The unbound fraction of rosiglitazone was 2-fold higher, on average, in subjects with hepatic dysfunction, than in healthy subjects.

Mean oral clearance (an estimate of total hepatic clearance for highly metabolized drugs such as rosiglitazone) was reduced indicating a decrease in hepatic enzyme activity. The unbound oral clearance (an estimate of free intrinsic clearance) was decreased by approximately 60% in hepatic disease. The decreases in total and unbound oral clearance were associated with an average 1.3-fold and 2.9-fold

increase in total and unbound AUC(0-inf) in patients with hepatic disease compared to healthy subjects, respectively.

The increase in free fraction would be expected to result in an increase in total oral volume of distribution, with no or a small change in unbound Vss. Patients with hepatic impairment exhibited a less than predicted increase in total Vss, which is suggestive of a decrease in unbound Vss in hepatic disease as was observed in this study. The small increase in total oral Vss observed in hepatic patients was associated with a 21% lower Cmax, whereas the large decrease in unbound Vss in hepatic patients resulted in a 70% increase in unbound Cmax.

Tmax values were similar for both groups. Due to the greater decrease in oral clearance relative to the increase in Vss, T½ in patients with hepatic impairment was, on average, 2 hours longer than values in healthy subjects. The longer T½ is expected to be of minimal clinical consequence since, even with an elimination half-life of 6 hours, only a limited accumulation of rosiglitazone would be expected with once or twice daily dosing.

PK Conclusion: As a result of an observed decrease in oral clearance, mean exposure to rosiglitazone (total and unbound) was higher in patients with hepatic impairment, compared to healthy volunteers. Furthermore, the mean free fraction of rosiglitazone in plasma is higher in patients with hepatic impairment than in healthy volunteers, resulting in an even higher exposure in terms of unbound concentration. This increased exposure was not associated with hypoglycemia. Thus, for Type 2 diabetic patients with hepatic disease, the rosiglitazone starting dose should be reduced by approximately 50% and cautiously titrated.

Table 1
Mean (SD) Pharmacokinetic Parameter Values for Rosiglitazone
(Protocol 49653/008)

Parameter	Healthy Subjects (n = 17)	Patients with Hepatic Impairment (n = 18)
AUC(0-inf) [ng.h/mL]	2645 (677)	3576 (1083)
Cmax [ng/mL]	506 (104)	407 (119)
Tmax* [hours]	1.00 (0.50 - 2.00)	1.00 (0.48 - 4.00)
Half-life [hours]	3.79 (1.03)	6.03 (2.10)
Fraction Unbound (%)	0.12 (0.03)	0.27 (0.12)
Unbound AUC(0-inf) [ng.h/mL]	3.20 (1.38)	9.88 (5.31)
Unbound Cmax [ng/mL]	0.61 (0.20)	1.09 (0.52)
CL/F [L/h]	3.22 (0.85)	2.42 (0.69)
Vdss/F [L]	17.6 (2.7)	20.7 (4.1)

* data presented as median (range)

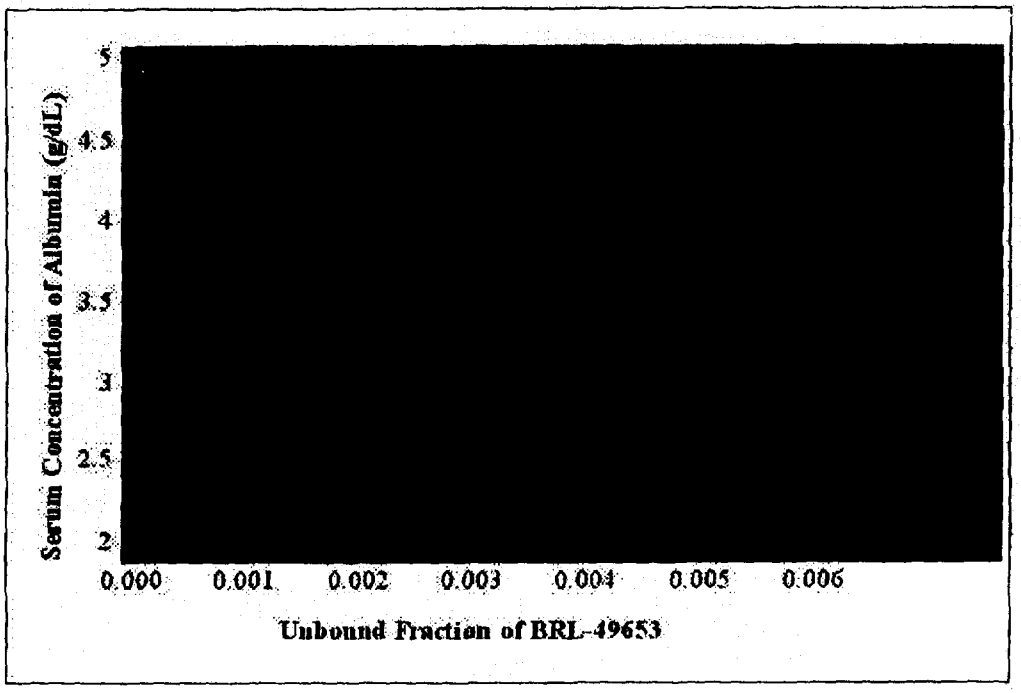
Table 2
Point Estimates and 95% Confidence Intervals
(Protocol 49653/008)

Parameter	Comparison	Point Estimate	95% confidence interval
AUC(0-inf)	Hepatic : Healthy[1]	1.34	(1.11, 1.62)
Cmax	Hepatic : Healthy[1]	0.79	(0.68, 0.93)
Unbound AUC(0-inf)	Hepatic : Healthy[1]	2.88	(2.08, 3.99)
Unbound Cmax	Hepatic : Healthy[1]	1.70	(1.30, 2.22)
Fraction unbound	Hepatic–Healthy[2]	0.15%	(0.09%, 0.21%)
Half-life	Hepatic–Healthy[2]	2.24 h	(1.09 h, 3.39 h)
Tmax	Hepatic–Healthy[3]	0.00 h	(–0.50 h, 0.50 h)

[1] presented as the ratio of geometric means
[2] presented as the difference in arithmetic means
[3] presented as the median difference

Figure 1

Unbound Fraction of Rosiglitazone as a Function of Serum Albumin Concentration (g/dL)* in Healthy Volunteers and Patients with Hepatic Impairment after Single Oral Administration of 8 mg Rosiglitazone (Protocol 49653/008)



* Mean of serum albumin concentrations obtained in serum samples collected predose, 24 and 96 hours postdose

Figure 2
Mean Plasma Concentrations vs. Time Profiles Following Single Oral Doses (8 mg) in Healthy Volunteers and Patients with Hepatic Impairment
(Protocol 008)

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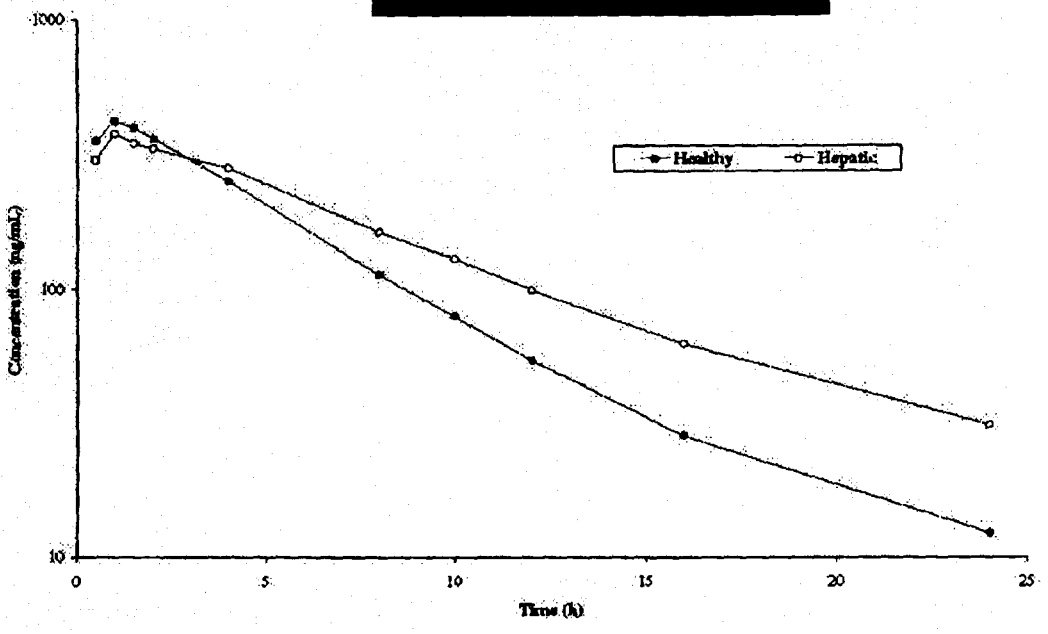

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REVIEWER'S COMMENTS FOR STUDY 008:

1. Agree with results.

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DRUG INTERACTION – GLYBURIDE

Protocol 49653C/014 Issued January 1996

SB Report HP-1006/BRL-049653/1

Title: A Study to Determine the Effect of BRL-49653C on the Steady-State Pharmacodynamics and Pharmacokinetics of Glyburide in Non-Insulin Dependent Diabetic Patients

Investigator: [redacted]

Study Center: [redacted]

Pharmacodynamic and Pharmacokinetic Objectives: 1) To establish that concomitant administration of rosiglitazone and glyburide has no effect on the 24-hour glucose profiles in diabetic patients relative to glyburide plus placebo, 2) if an effect on the 24 hour serum glucose profile is shown, the effect of rosiglitazone on the steady-state pharmacokinetics of oral glyburide would be investigated.

Study Design: This was a randomized, double-blind, placebo-controlled, two-period, period-balanced, crossover study in 13 male and female non-insulin-dependent diabetes mellitus (NIDDM) patients [age 34 to 70 years; weight 60 to 111 kg; BMI 18 to 38 kg/M^2]. Patients on a stable dosing regimen of glyburide [Micronase® tablets 3.75-10 mg/day] for at least 30 days prior to the first dose of study medication were randomized to receive either glyburide plus 2 mg rosiglitazone every 12 hours [oral capsules, lot # M94152] or glyburide plus placebo every 12 hours for seven days. The treatment periods were separated by a minimum washout period of 14 days. Glyburide dosing was continued during the washout period.

On study Days 0 and 7 of each treatment period, blood samples for the measurement of plasma concentrations of glyburide were collected prior to dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20 and 24 hours following administration of glyburide. If an effect of rosiglitazone on the 24 hour serum glucose profile were shown, then the pharmacokinetics of glyburide would be investigated by non-compartmental analysis of the concentration-time data.

On study Days 0 and 7 of each treatment period, blood samples for the measurement of a 24 hour glucose profile in each patient were obtained just prior to dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20 and 24 hours

following administration of glyburide. Individual values of AUC(0-24) for serum glucose in patients was calculated using noncompartmental methods.

To assess the lack of effect of rosiglitazone on the hypoglycemic activity of glyburide, AUC(0-24) for serum glucose on Days 0 and 7 were analyzed separately by analysis of variance (ANOVA) with terms for sequence, patient within sequence, period and treatment (glyburide plus rosiglitazone or glyburide plus placebo). Point estimates and 90% CI for the difference between the two treatments were constructed using the residual variance. Approximations for the point estimates for the ratio between the two regimens and associated 90% confidence interval were calculated by dividing the difference (between the two treatments) and the lower and upper confidence bounds by the least square mean for glyburide + placebo and adding 1. Day 0 data were examined for homogeneity of treatment response at baseline (i.e., a possible treatment effect on the day prior to the start of co-administration of treatment). Equivalence (i.e. no effect) was shown if the 90% confidence interval for the treatment difference (glyburide + rosiglitazone versus glyburide + placebo) was completely contained with the 30% equivalence range (0.70, 1.30) on Day 7.

Results and Discussion: A total of 11 patients were included in the statistical analysis. Summary statistics for the mean glucose AUC(0-24) values are shown in Table 1 and treatment comparisons are shown in Table 2.

At baseline (Day 0), mean AUC(0-24) for serum glucose were shown to be equivalent based as the approximate 90% confidence interval was completely contained in the range (0.70, 1.30). These results indicate that prior to dosing with rosiglitazone, mean AUC(0-24) for serum glucose was similar for the glyburide + rosiglitazone and glyburide + placebo groups.

On day 7, mean AUC(0-24) for serum glucose was 4928 mg.h/dL for glyburide + rosiglitazone and 5326 mg.h/dL for glyburide + placebo. These results supported equivalence as the approximate confidence interval was completely contained in the protocol defined equivalence range of (0.70, 1.30).

Since there was no evidence of a dynamic interaction between rosiglitazone and glyburide, the glyburide assays and pharmacokinetic evaluation were not performed, as defined in the protocol.

Conclusion: Concomitant administration of rosiglitazone and glyburide for 7 days had no effect on the acute 24-hour glucose profiles in diabetic patients stabilized on glyburide therapy.

Table 1

Summary Statistics for Serum Glucose AUC(0-24) (mg.h/dL) By Treatment
(Protocol 49653/014)

Treatment	Day	n	Mean	SD	Minimum	Maximum
Glyburide + Rosiglitazone	0	11	5557	1884	[redacted]	
	7	11	4928	1939		
Glyburide + Placebo	0	11	5416	1985		
	7	11	5326	1973		

Note: Patient 002 (early withdrawal) and patient 005 (a protocol violator) are not included in this table.

Table 2

Comparisons Between Treatments for Mean Serum Glucose AUC(0-24)
(Protocol 49653/014)

Comparison	Day	Point Estimate	90% CI
Glyburide + Rosiglitazone/ Glyburide + Placebo	0	1.02	(0.97, 1.07)
Glyburide + Rosiglitazone/ Glyburide + Placebo	7	0.93	(0.84, 1.02)

REVIEWER'S COMMENTS FOR STUDY 014:

1. Agree with results

APPEARS THIS WAY
ON ORIGINAL

PHARMACOKINETICS IN HEALTHY VOLUNTEERS

Protocol 49653C/016 Issued June 1995
SB Report HP-1005/BRL-49653C/1

Title: Evaluation of the safety, tolerability, and pharmacokinetics of single rising oral doses of 5, 10, 15 and 20 mg BRL-49653C in healthy male volunteers

Investigator: Martin I. Freed, M.D.

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

PK Objective: Provide single dose pharmacokinetic data for rosiglitazone for a capsule formulation of rosiglitazone in healthy male volunteers.

Study Design: This was a randomized, double-blind, placebo controlled, five-period crossover, oral dose rising study involving 10 healthy male volunteers (age 18 to 39 years; weight 63 to 90 kg). At each study session, subjects received either placebo or one of the following single oral doses of rosiglitazone (5 mg capsule formulation, Lot No. G93034): 5 mg, 10 mg, 15 mg, or 20 mg. On each occasion, rosiglitazone was administered under fasting conditions. Blood samples were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours following dosing. Pharmacokinetic parameters (Cmax, Tmax, AUC(0-inf), CL/F, Vss/F and T1/2) were calculated using non-compartmental analysis. Descriptive statistics were calculated to summarize the data for each pharmacokinetic parameter for each regimen.

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

PK Results and Discussion: The mean (SD) pharmacokinetic parameter values for rosiglitazone for each treatment regimen are shown in Table 1. Rosiglitazone was rapidly absorbed with maximum observed plasma concentrations occurring within 0.5 to 3 hours at all dose levels. Plasma concentrations of rosiglitazone typically declined from the maximum concentration in a monoexponential manner.

Elimination half-life values were similar at all doses with mean values ranging from 3.3 to 3.7 hours.

Increases in both Cmax and AUC(0-inf) were approximately dose proportional over the dose range used in this study. Oral clearance (CL/F) was approximately 1.4 to 5.8 L/h. Steady-state volume (Vss/F) values were low and ranged from approximately 8.2 to 24.3 L.

Intersubject variability was generally low, with coefficients of variation less than 30% for Cmax and AUC(0-inf) at the 10, 15, and 20 mg doses, and less than 50% at the 5 mg dose.

PK Conclusion: Following administration of single oral doses of rosiglitazone to healthy volunteers, Cmax and AUC(0-inf) of rosiglitazone increased approximately proportionately with increasing doses over the range of 5 to 20 mg. Mean T½ values were consistent across all dose levels and ranged from 3.3 to 3.7 hours.

Table 1
Mean (SD) Pharmacokinetic Parameters for Rosiglitazone following Single Dose Administration to Healthy Male Volunteers (n=10)
(Protocol 49653/016)

Parameters	5 mg	10 mg	15 mg	20 mg
AUC(0-inf) [ng.h/mL]	1741 (731)	3310 (1085)	4860 (1452)	6147 (1247)
Cmax [ng/mL]	329 (159)	608 (147)	930 (142)	1358 (317)
Tmax* [hours]	1.0 (0.5-3.1)	1.0 (0.5-3.1)	0.8 (0.5-2.1)	1.0 (0.5-2.1)
T½ [hours]	3.74 (0.43)	3.71 (0.73)	3.59 (0.64)	3.29 (0.46)
Vss/F [L]	18.1 (4.6)	18.5 (3.7)	17.2 (2.6)	17.1 (3.6)
CL/F [L/h]	3.22 (0.99)	3.33 (1.13)	3.31 (0.86)	3.37 (0.65)

* Data presented as median (range)

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PHARMACOKINETICS IN HEALTHY VOLUNTEERS

Protocol 49653C/029 Issued July 1996
SB Report BRL049653/RSD-1005TC1

Title: Evaluation of the safety, tolerability, and preliminary pharmacokinetics of single rising intravenous doses of BRL-49653C in normal volunteers.

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 intravenous dose administration of rosiglitazone in healthy male volunteers.

Study Design: This was a single blind, randomized (with respect to placebo), placebo-controlled intravenous dose rising study involving 8 healthy male volunteers (age 19 to 39 years, weight 60 to 92 kg). Subjects received one of the following intravenous doses of rosiglitazone (0.1 mg/mL, batch # U95156): 0.2, 0.5, 1.0 or 2.0 mg or placebo during each of four study periods which were separated by at least 7 days. Rosiglitazone was infused in a final volume of 30 mL saline over a 1 hour period and was administered under fasted conditions. Blood samples for pharmacokinetic analysis were drawn at predose, immediately post infusion (1 hour), and at 1.25, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours after the end of infusion. Pharmacokinetic parameters (Cmax, AUC(0-inf), Tmax, T1/2, CL, and Vss) were calculated using non-compartmental analysis. Cmax and AUC(0-inf) values were normalized to the 0.5 mg dose. Descriptive statistics were calculated by dose to summarize the data for each pharmacokinetic parameter.

Analytical Methodology: Plasma concentrations of rosiglitazone were determined using [redacted] and a [redacted] detection [SB Study no. BF-1012]. The lower limit of quantification of rosiglitazone in this assay was [redacted]. Analysis was performed by the Department of Drug Analysis, Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK.

PK Results and Discussion: Mean (SD) pharmacokinetic parameters for rosiglitazone are shown in Table 1 and mean (SD) dose-normalized AUC(0-inf) and Cmax values are shown in Table 2. At a dose of 0.2 mg, plasma concentrations were typically only quantifiable for up to 8 hours, whereas at the

highest dose (2 mg), values were typically quantifiable for up to 24 hours. Maximum plasma concentrations of rosiglitazone were observed at the end of the one hour intravenous infusion of rosiglitazone followed by an apparent monexponential decline in plasma concentrations. The apparent T1/2 was independent of dose with a mean range of 3.3 to 3.4 hours.

Although this study was not designed to assess dose proportionality, increases in both Cmax and AUC(0-inf) between doses were approximately dose proportional with increasing doses. Both CL and Vss appeared to be independent of dose. Vss ranged from 9 to 26 L and CL ranged from 2.1 to 4.5 L/h.

PK Conclusion: Following a one hour intravenous infusion to healthy male volunteers, mean AUC(0-inf) and Cmax increased approximately proportionately with increasing dose over the 0.2 to 2 mg dose range. Clearance and steady-state volume of distribution were approximately 3 L/h and 15 L, respectively. Apparent terminal elimination half-life was approximately 3.3 hours.

Table 1
Mean (SD) Pharmacokinetic Parameter Values for Rosiglitazone Following a One Hour Intravenous Infusion of Rosiglitazone to Healthy Male Volunteers (Protocol 49653/029)

Dose [mg]	n	AUC(0-inf) [ng.h/mL]	Cmax [ng/mL]	T½ [hours]	CL [L/h]	Vdss [L]
0.2	6	69.8 (15.9)	15.2 (5.1)	3.3 (0.8)	3.01 (0.75)	13.8 (3.5)
0.5	6	182 (23)	37.1 (6.3)	3.3 (0.6)	2.80 (0.40)	13.4 (1.8)
1.0	6	316 (31)	69.8 (11.1)	3.3 (0.5)	3.19 (0.30)	15.0 (2.2)
2.0	6	632 (178)	133 (41.3)	3.4 (0.6)	3.36 (0.84)	16.2 (5.30)

Table 2
Mean (SD) Dose-normalized AUC(0-inf) and Cmax values
(Protocol 49653/029)

Dose [mg]	n	Dose-Normalized AUC(0-inf) [ng.h/mL]	Dose- Normalized Cmax [ng/mL]
0.2	6	175 (40)	38.0 (12.6)
0.5	6	182 (23)	37.1 (6.3)
1.0	6	158 (15)	34.9 (5.6)
2.0	6	158 (45)	33.3 (10.3)

1. Results acceptable.

APPEARS THIS WAY
ON ORIGINAL

PHARMACOKINETICS IN HEALTHY VOLUNTEERS
BIOEQUIVALENCE

Protocol 49653C/030 Issued May 1996
SB Report BRL-49653RSD-1004XV/1

Title: A bioequivalence study of BRL-49653C proposed final market tablet formulation (formula AG-AA) versus BRL-49653C clinical trials capsule formulation (formula AB-AA)

Investigator: Martin I. Freed, M.D.

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

PK Objective: Demonstrate the bioequivalence of single oral doses of the proposed final commercial tablet*formulation of rosiglitazone relative to the clinical trials capsule formulation. (*The tablet formulation used in this study was ultimately not the final commercial formulation, but rather a clinical trials formulation and is referred to s such in this section.)

Study Design: This was an open-label, randomized, period-balanced, two period, crossover study involving 32 healthy male volunteers (age 21 to 47 years, weight 63 to 99 kg). At each of two study sessions, subjects were administered a single oral 2 mg dose of either the tablet formulation (test) of rosiglitazone (Formula AG-AA, Batch # M95066) or the Phase I-II clinical trials reference capsule formulation (Formula AB-AA; Batch # M94152). There was a minimum of a three day washout period between study sessions. Pharmacokinetic parameters Cmax, Tmax, AUC(0-inf) and T1/2 were determined using non-compartmental methods. Blood samples were collected predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours following dosing.

Bioequivalence was assessed using AUC(0-inf) and Cmax as the primary parameters. Following ln-transformation, AUC and Cmax were analyzed separately by analysis of variance with terms for sequence, subject (sequence), period, and formulation. The tablet formulation would be considered bioequivalent to the capsule formulation if the 90% confidence intervals for the ratios (tablet:capsule) for both primary parameters were completely contained within the acceptance range (0.80, 1.25). T½ was similarly analyzed without ln-transformation and 95% confidence intervals were constructed. Tmax was analyzed non-parametrically to obtain a point estimate and 95% confidence

interval for the median difference between the tablet formulation and the capsule formulation.

Analytical Methodology: Plasma concentrations of rosiglitazone were quantified by an [redacted] (SB Report # BF-1016). The lower limit of quantification (LLQ) for rosiglitazone was [redacted]. Analysis was performed at DMPK, Department of Drug Analysis, SmithKline Beecham, The Frythe, Welwyn, Herts, UK.

PK Results: Mean (SD) pharmacokinetic parameter values for rosiglitazone are shown in Table 1 and the statistical results in Table 2. Plasma concentration-time profiles for the tablet and capsule formulation were similar (Figure 1). Peak plasma concentrations of rosiglitazone were typically observed between 0.5 and 2 hours after dosing, and subsequently declined in a monoexponential manner.

The 90% confidence intervals for both Cmax and AUC(0-inf) were completely contained within the protocol specified equivalence range of 0.80 to 1.25. Therefore, the tablet formulation can be considered bioequivalent to the Phase I-II capsule formulation. The 95% confidence interval for Tmax contained the value of zero (-0.26,0.03). These results suggest that both the rate and the extent of absorption of rosiglitazone following administration of the tablet formulation were similar to the capsule formulation.

The mean (SD) terminal elimination half-life for rosiglitazone following oral administration was 3.98 (1.23) and 3.82 (1.07) hours for the tablet and capsule formulations, respectively. The point estimate of the mean difference of tablet relative to the capsule formulation, for T½, was 0.16 hours and the 95% confidence interval was -0.29 to 0.61 hours suggesting T½ was similar for both formulations.

The within-subject residual coefficient of variation for Cmax and AUC(0-inf) were 11.2% and 9.0%, respectively, which were lower that those from previous studies used to determine the sample size for this study. Thus no inadequacies were indicated in terms of sample size.

PK Conclusion: The 2 mg clinical trials tablet formulation of rosiglitazone was bioequivalent to the 2 mg Phase I-III clinical trial capsule formulation.

Table 1
Mean (SD) Pharmacokinetic Parameter Values for Rosiglitazone
(Protocol 49653/030)

Parameter	Test Formulation Tablet (2 mg) (n=32)	Ref. Formulation Capsule (2 mg) (n=32)
AUC(0-inf) (ng.h/mL)	752 (148)	726 (129)
Cmax (ng/mL)	140 (30)	137 (25)
Tmax[a] (hours)	0.98 (0.48 – 1.53)	0.98 (0.50 – 2.02)

a = Data presented as median (range).

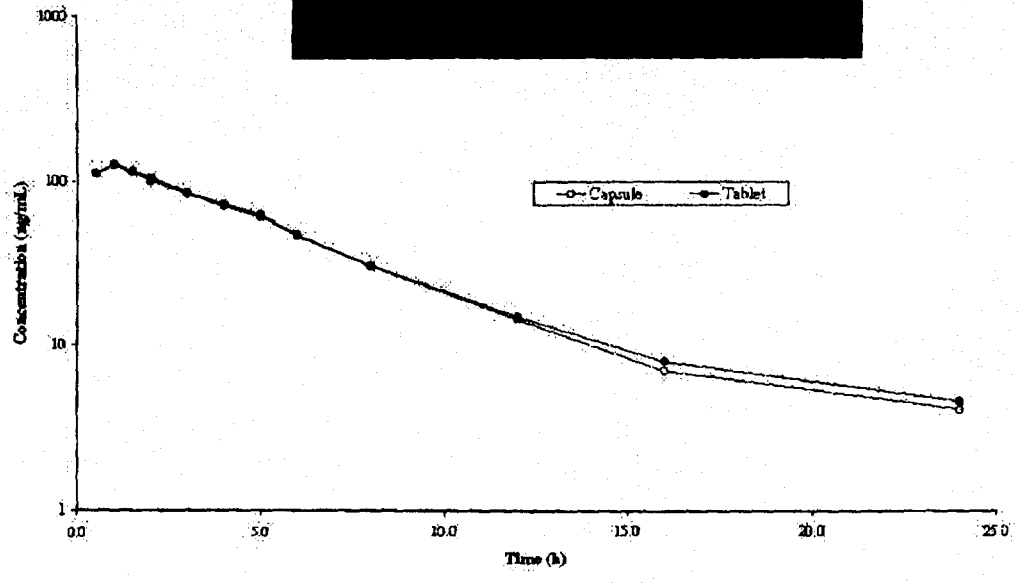
Table 2
Point Estimates and 90% Confidence Intervals
(Protocol 49653/030)

Parameter	Comparison	Point Estimate[a]	90% CI
AUC(0-inf)	(tablet:capsule)	1.03	(0.99, 1.07)
Cmax	(tablet:capsule)	1.02	(0.97, 1.07)

a = Data represent the ratio of the geometric means for the tablet (test) formulation to the capsule (reference) formulation

Figure 1
Mean Concentration-Time Profiles
(Protocol 49653/030)

BEST POSSIBLE



APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 030:

1. Bioequivalence accepted.

APPEARS THIS WAY
ON ORIGINAL

DRUG INTERACTION – ORAL CONTRACEPTIVE

Protocol 49653C/031 Issued October 1998

SB Report BRL-049653/RSD-100HNH/1

Title: An investigation of the effects of BRL-49653C on the safety, tolerability and pharmacokinetics of oral contraceptives in healthy female volunteers

Investigator: Martin I. Freed, M.D.

Study Center: SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, University of Pennsylvania Health System, Philadelphia, Pennsylvania, USA.

PK Objective: Evaluate the effect of repeat dose rosiglitazone on the pharmacokinetics of ethinylestradiol and norethindrone following chronic dosing with oral contraceptives.

Study Design: This was a double-blind, randomized, placebo-controlled, crossover study involving 32 healthy female volunteers (age 20 to 42 years, weight 50 to90 kg) who have been taking the oral contraceptive (OC) Ortho-Novum® 1/35 for at least one cycle prior to receiving the first dose of study medication. All volunteers received either 8 mg rosiglitazone (batch # M96305) plus Ortho-Novum® 1/35 or placebo plus Ortho-Novum® 1/35 once a day on Days 1 through 14 of each cycle. OC administration was continued on Days 15 through 28 of each cycle.

Blood samples for pharmacokinetic analysis were collected on Day 14 of each regimen immediately prior to administration of study medication (0 hour), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing.

Values of ethinylestradiol and norethindrone AUC(0-24), Cmax, and Tmax were calculated using non-compartmental analysis. AUC(0-24) and Cmax of ethinylestradiol and norethindrone, were ln-transformed and analyzed separately by analysis of variance (ANOVA) appropriate to the study design. The point estimates and associated 90% confidence intervals were calculated for the ratio of 'rosiglitazone plus oral contraceptive : placebo plus oral contraceptive'. Statistical equivalence was to be demonstrated if the 90% confidence interval was completely contained within the range 0.80 to 1.25 for the primary endpoints AUC(0-24) and Cmax. Tmax was analyzed non-parametrically, and point

estimate and 95% confidence interval for the median difference between the regimens were constructed.

Analytical Methodology: Plasma concentrations of ethinylestradiol and norethindrone were determined using GC/MS [SB Report RSD-100SDL/1]. The lower limits of quantification (LLQ) for ethinylestradiol and norethindrone in plasma were [redacted] respectively. Sample analysis was conducted at [redacted]

PK Results and Discussion: Mean (SD) pharmacokinetic parameter values and statistical results are shown in Tables 1 to 2, respectively.

Statistical lack of effect of rosiglitazone on the pharmacokinetics of ethinylestradiol and norethindrone was demonstrated as the 90% confidence intervals were contained completely within the specified equivalence range of (0.80; 1.25). It was noted that coadministration of rosiglitazone with oral contraceptive, relative to placebo plus oral contraceptive, resulted in an average 8% and 5% decrease in ethinylestradiol AUC(0-24) and Cmax, respectively. A few volunteers showed substantially greater decreases in ethinylestradiol exposure (up to 41%). The magnitude of these decreases may be partially reflective of intra-individual variability in ethinylestradiol pharmacokinetics since other volunteers showed increases (up to 29%) in ethinylestradiol exposure. On average, there was a 4% increase and a 3% decrease in norethindrone AUC(0-24) and Cmax, respectively, when rosiglitazone was co-administered with the oral contraceptive relative to placebo plus oral contraceptive. Values of Tmax were very similar between the two regimens for both ethinylestradiol and norethindrone.

There were 5 subjects who experienced breakthrough bleeding during the study. All episodes were observed during rosiglitazone administration of the OC dosing cycle. However, there was no apparent relationship of these events to alterations in either the AUC(0-24) or Cmax for either ethinylestradiol or norethindrone (Table 3). Based on the results of this study, repeat dose administration of rosiglitazone (8 mg once daily for 14 days) had no clinically relevant effect on the steady-state pharmacokinetics of either ethinylestradiol or norethindrone.

PK Conclusion: Based on a 20% equivalence range, administration of rosiglitazone 8 mg once daily did not affect the steady-state pharmacokinetics of ethinylestradiol or norethindrone.

Table 1
Mean (SD) Pharmacokinetic Parameters for Ethinylestradiol and Norethindrone
(Protocol 49653/031)

Compound	Parameter	Ortho-Novum 1/35-28 + Rosiglitazone (n=32)	Ortho-Novum 1/35-28 + Placebo (n=32)
Ethinylestradiol			
	AUC(0-24) [pg.h/mL]	1126 (386)	1208 (404)
	Cmax [pg/mL]	123 (42)	130 (47)
	Tmax * [hours]	1.50 (1.00 – 2.00)	1.50 (1.00 – 4.00)
Norethindrone			
	AUC(0-24) [pg.h/mL]	178 (67)	171 (62)
	Cmax [pg/mL]	21.5 (6.7)	22.1 (6.8)
	Tmax * [hours]	1.00 (1.00 – 2.00)	1.00 (1.00 – 2.03)

* Data presented as median (range)

Table 2
Point Estimates and 90% Confidence Intervals
(Protocol 49653/031)

Compound	Parameter	Comparison	Point Estimate	90% CI
Ethinylestradiol	AUC(0-24)	B : A	0.92	(0.88, 0.97)
	Cmax	B : A	0.95	(0.88, 1.02)
	Tmax *	B – A	–0.08 h	(–0.48, 0.23)
Norethindrone	AUC(0-24)	B : A	1.04	(1.00, 1.07)
	Cmax	B : A	0.97	(0.91, 1.03)
	Tmax *	B – A	0.00 h	(–0.24, 0.24)

* median difference (95% confidence interval)

A: Ortho-Novum 1/35-28 + Placebo
B: Ortho-Novum 1/35-28 + Rosiglitazone (8 mg)

Table 3
Individual Ratios for AUC(0-24) and Cmax for Ethinylestradiol and Norethindrone for Subjects who Developed Breakthrough Vaginal Bleeding (Protocol 49653/ 031)

Subject	Regimen/ Study Day**	Ethinylestradiol		Norethindrone	
		AUC(0-24)	Cmax	AUC(0-24)	Cmax
002	RSG/ D11	1.00	1.00	1.32	1.07
003	RSG/D7	0.59	0.62	1.17	1.10
006	RSG/D14	0.92	1.19	1.04	1.27
016	RSG/D5, D27	0.92	0.78	1.08	0.90
017	RSG/D17	1.02	1.36	0.86	0.78

** Regimen RSG= rosiglitazone during which breakthrough bleeding occurred and the study day(s) in which bleeding was observed

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 031:

1. No effect on OC pharmacokinetics.

APPEARS THIS WAY
ON ORIGINAL

DRUG INTERACTION-DIGOXIN

Protocol 49653C/034 Issued April 1997
SB Report BRL-049653/RSD-100HNK/2

Title: A study to assess the effects of BRL-49653C on the pharmacokinetics of digoxin in healthy adult males

Publication: DiCicco RA, Allen A, Jorkasky D, Freed M. 1998 Chronic administration of rosiglitazone (RSG) does not alter the pharmacokinetics of digoxin. *Diabetes*, 47 (suppl. 1), 353A.

Investigator: Martin I. Freed, M.D.

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

PK Objective: To demonstate a lack of effect of rosiglitazone on the steady-state pharmacokinetics of digoxin.

Study Design: This was an open label, 2 period, period balanced, crossover study involving 15 healthy male volunteers (age 21 to 42 years, weight 65 to 93 kg). Each subject received a 0.375 mg oral dose of digoxin (3 x 0.125 mg Lanoxin®) alone (Regimen A) once a day for 14 days and rosiglitazone 8 mg (2 x 4 mg; tablet formula BD, lot no. M960911) with 0.375 mg oral dose of digoxin once a day for 14 days (Regimen B). Each study period was separated by at least 14 days. Subjects were dosed on study days under fed conditions. Blood samples for pharmacokinetic analysis were collected from each subject on Day 14 of each session predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours after dosing. Trough samples were also collected prior to dosing on Days 9-13 of each session. Urine was collected over the approximate time period of 0-12 and 12-24 hours following digoxin administration at the end of each treatment period (Day 14).

Cmax, Tmax, and AUC(0-24) and oral clearance (CLo) of digoxin were calculated using non-compartmental methods. Digoxin trough concentrations (C24) were calculated as the mean of the trough values on days 9 to 14 and 24 hours after the last dose on Day 14 inclusive. Renal clearance (CLr) was calculated as AE(0-24)/AUC(0-24) where AE(0-24) was the amount of digoxin excreted in the urine between 0 and 24 hours. Nonrenal clearance was the difference between CLo and CLr. Summary statistics were calculated for all pharmacokinetic parameters. The primary parameters, AUC(0-24) and C24 were

analyzed separately following ln-transformation using analysis of variance with terms for sequence, subject(sequence), period and regimen. Point estimates and 90% confidence intervals were calculated for the difference (digoxin with rosiglitazone minus digoxin alone) on the ln-scale and subsequently back transformed. Rosiglitazone was considered to have no effect on the pharmacokinetics of digoxin if the 90% confidence intervals for the ratios 'digoxin + rosiglitazone: digoxin alone' for both primary parameters were completely contained within the bioequivalence range (0.80,1.25).

Analytical Methodology: Concentrations of digoxin were determined in plasma and urine using [redacted] [SB Report nos. BP-1002 and BP-1003, respectively]. The lower limit of quantification (LLQ) was [redacted] for the human plasma assay and [redacted] for the human urine assay. Analyses were performed at [redacted]

Results and Discussion: Mean (SD) pharmacokinetic parameter values for digoxin are shown in Table 1 and statistical results are shown in Table 2. Following repeat oral administration of digoxin alone or with steady-state rosiglitazone, maximum plasma concentrations of digoxin were observed between 0.5 and 3 hours. Subsequently, plasma concentrations declined in an apparent biexponential manner.

The 90% confidence intervals of the ratios for AUC(0-24) and C24 of digoxin plus rosiglitazone to digoxin alone were completely contained within the range (0.80, 1.25). Therefore, rosiglitazone can be considered to have no effect on the steady-state pharmacokinetics of digoxin. Cmax, Tmax, Clr and Clnr appeared to be similar, on average, between regimens.

Conclusion: Repeat oral dosing of rosiglitazone (8 mg od) for 14 days had no effect on the steady-state pharmacokinetics of digoxin.

Table 1
Mean (SD) Pharmacokinetic Parameter Values of Digoxin following Repeat Oral Dosing of Digoxin Alone or with Rosiglitazone for 14 Days
(Protocol 49653/034)

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Parameter	Digoxin plus Placebo (n=15)	Digoxin plus Rosiglitazone (n=15)
AUC(0-24) [ng.h/mL]	18.5 (4.2)	19.1 (3.5)
C24 [ng/mL]	0.579 (0.154)	0.594 (0.103)
Cmax [ng/mL]	1.68 (0.34)	1.61 (0.23)
CLr [L/h]	9.37 (2.65)	8.87 (2.48)
CLnr [L/h]	12.0 (6.2)	11.4 (4.6)
Tmax[a] [hours]	1.97 (0.45 – 2.98)	2.50 (1.45 – 3.08)

a = Data presented as median (range)

APPEARS THIS WAY
ON ORIGINAL