Table 2
Point Estimates and 90% Confidence Intervals
(Protocol 49653/034)

Parameter	Comparison	Point Estimate[a]	90% CI
AUC(0-24)	B:A	1.05	(1.01, 1.10)
C24	B:A	1.04	(0.98, 1.11)

[a] presented as a ratio of geometric means between regimens
Regimen A – Digoxin + Placebo
Regimen B – Digoxin + Rosiglitazone

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REVIEWER'S COMMENTS FOR STUDY 034:

1. Agree with results.

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Title: A study to assess the effect of rosiglitazone on the anticoagulant effect of warfarin in healthy male volunteers

Investigator: [redacted]

Study Center: [redacted]

PK Objective: 1) Demonstrate the lack of effect of rosiglitazone on the anticoagulant activity of steady-state warfarin; 2) estimate the effect of rosiglitazone on the pharmacokinetics of warfarin enantiomers if an effect was observed.

Study Design: This was a placebo controlled, double-blind (rosiglitazone dosing phase only), parallel group study involving 24 healthy male volunteers (age 20 to 52 years; weight 62.4 to 92.7 kg). During a 14 day open label run-in period, subjects received a single oral 7.5 mg dose of warfarin (Coumadin®) on Days 1 and 2. Dosage adjustments to achieve a steady-state INR within the target range of 1.5 to 3.5 were permitted from Day 3 through Day 5. On Days 6 to 14, subjects were administered the same dose of warfarin once daily. At the end of the open label warfarin run-in, subjects were randomized to either warfarin od plus 4 mg rosiglitazone (batch # M96091) bd, or warfarin od plus placebo bd. On Days 15 to 21, each subject was administered the same dose of warfarin established during the run-in period plus the randomized rosiglitazone or placebo treatment. On Days 14 and 21, blood samples were collected pre-warfarin dose (time 0), and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours postdose.

Three subjects in the rosiglitazone-treated group exhibited an increase in INR from baseline of > 25%. Examination of the individual INR responses by day suggested that these 3 subjects, plus one other subject in the rosiglitazone-treated group, may not have achieved a steady-state INR during the 14 day run-in period. Because of this observation, these 4 subjects and 4 controls who were in the placebo-treated group completed an additional study session (Part 2) where each subject received the opposite regimen to that assigned initially in Part 1.

In Part 1, to assess the lack of effect of rosiglitazone on the anticoagulant activity of warfarin on all subjects who completed all study procedures or were dosed with

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at least 1 dose of double blind study medication (Days 15 through 21) (intent-to-treat-analysis), the INR on Day 21 was subjected to an analysis of covariance (ANCOVA) with terms for treatment (rosiglitazone or placebo), baseline INR (average INR between Days 12, 13, and 14) as the covariate, and the interaction term between treatment and baseline INR included in the model. Approximate point estimates and 90% confidence intervals for the effect of rosiglitazone + warfarin relative to placebo + warfarin were calculated. The ANCOVA modeling allowed examination of the range of responses for baseline between regimens in order to assess whether a relationship existed between regimen and baseline range, and examination of the baseline by regimen interaction term in the general linear model for INR on Day 21 to assess whether the statistical relationship between INR on Day 21 and baseline were different between regimens. The protocol defined acceptance range of (0.75, 1.25) was used for the INR, as this was considered to be the clinically relevant equivalence range. Parts 1 and 2 INR data were descriptively summarized by regimen and day.

Cmax, Tmax and AUC(0-t) of R(+)- and S(-) warfarin were determined using non-compartmental methods. Dose-normalized AUC(0-t) and Cmax were also computed. Following ln-transformation, the Part 1 Day 21 dose normalized AUC(0-t) and Cmax values for R(+) and S(-)-warfarin were separately analyzed by analysis of covariance (ANCOVA) with terms for regimen, the covariate response on Day 14 (baseline), and the interaction between baseline and regimen. Point estimates and 95% confidence intervals for 'warfarin plus rosiglitazone' relative to 'warfarin plus placebo' were calculated based on the pooled residual error term. Pharmacokinetic parameters from Part 2 were descriptively summarized.

Analytical Methodology: Plasma samples were analyzed for R(+)- and S(-)-warfarin using a [redacted] assay with [redacted] [SB Report BF-1007/SB-205312/1]. The lower limit of quantification (LLQ) for each enantiomer was [redacted], using a [redacted] aliquot of plasma. Analyses were performed by [redacted]

Results and Discussion: Summary statistics for each treatment group for INR at baseline and on Day 21 for Parts 1 and 2 are shown in Tables 1 and 2, respectively.

In Part 1, the INR data in the intent-to-treat analysis were influenced by 3 subjects (high baseline and Day 21 values) such that the linear model was skewed in the rosiglitazone + warfarin group compared to the placebo + warfarin group. These data resulted in a statistically significant baseline by regimen interaction ($p<0.05$)

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indicating that a mathematical relationship between last study day INR and baseline INR was dependent upon treatment group (Figure 1). Therefore, calculation of the comparison of interest was not performed in the intent-to-treat analysis. These 3 subjects also had baseline INR values greater than 3.3. Except for these 3 subjects, there were no baseline INR values observed above 2.75 for subjects receiving rosiglitazone + warfarin or above 2.78 for subjects receiving placebo + warfarin. Exclusion of these 3 subjects' data resulted in no significant baseline by regimen effect in the model (Figure 2). The point estimate and approximate 90% confidence interval of 0.97 (0.87, 1.07) were derived for the ratio 'rosiglitazone + warfarin: placebo + warfarin' based on the dataset excluding these 3 subjects0. These results suggested a lack of pharmacodynamic effect of rosiglitazone on warfarin INR at baseline INR values less than 2.75.

None of the 4 subjects receiving rosiglitazone in Part 2 showed greater than 25% increases in INR compared to their baseline; however, one subject showed a 29% reduction in INR. One of the 3 rosiglitazone-treated subjects who had a high baseline INR in Part 1 withdrew prior to entering the double-blind phase. The other 2 subjects had high INR values in Part 2 similar to those seen in Part 1, but did not achieve > 25 % increases in INR after treatment with placebo.

Mean (SD) dose-normalized pharmacokinetic parameters for Parts 1 and 2 are shown in Tables 3 and 4, respectively. The statistical results for Part 1 are shown in Table 5.

Eighteen subjects (10 subjects – rosiglitazone plus warfarin; 8 subjects - placebo plus warfarin) were included in the statistical analysis of pharmacokinetic data from Part 1 of the study; 1 subject had dropped out before completing the study in the rosiglitazone group. Seven subjects (4 subjects – rosiglitazone plus warfarin; 3 subjects - placebo plus warfarin) were included in the pharmacokinetic analysis in Part 2 of the study; one further subject did not complete the placebo arm in Part 2. Coadministration of warfarin and rosiglitazone did not alter the pharmacokinetics of R(+)-warfarin (Cmax or AUC). Furthermore, Cmax values for S(-)-warfarin were also unaffected. However, compared to placebo coadministration, exposure to S(-)-warfarin, as measured by dose normalized AUC(0-t), was, on average, 10% lower when warfarin was coadministered with rosiglitazone. Despite the small number of subjects in Part 2, the observed trends were similar.

Comparison of INR data to R(+)- and S(-)-warfarin from Part 1 showed no apparent differences in the relationship between INR and dose-normalized AUC prior to and following double blind treatment (Figures 3 and 4).

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Conclusions: There was no apparent pharmacodynamic interaction between repeat dose rosiglitazone and warfarin with regard to anticoagulant effect of warfarin (as measured by INR) for baseline INR values of up to 2.75 (range of INRs used to treat deep venous thrombosis and atrial fibrillation with heart valve replacement). There was no pharmacokinetic-based interaction between warfarin and 4 mg rosiglitazone bd, compared to warfarin and placebo. Slight reductions in S(-) AUC(0-t) were noted that did not appear to correlate with alterations in INR. Thus, current recommendations regarding warfarin therapy do not need to be changed when warfarin is coadministered with rosiglitazone.

Table 1
Summary Statistics - INR Data - Part 1
(Protocol 035) BEST POSSIBLE

Regimen	Parameter	Baseline INR	INR on Day 21	Change in INR on Day 21 vs. Baseline	% Change INR on Day 21 vs. Baseline
4 mg Rosiglitazone bd + Warfarin	n	11	11	11	11
	Mean	2.50	2.89	0.39	12.73
	SE	0.20	0.34	0.15	4.71
	SD	0.66	1.12	0.51	15.62
	Min	[redacted]			
	Median	2.56	2.60	0.27	11.80
	Max	[redacted]			
Placebo bd +Warfarin	n	8	8	8	8
	Mean	2.19	2.37	0.17	8.69
	SE	0.16	0.17	0.11	4.80
	SD	0.45	0.47	0.32	13.58
	Min	[redacted]			
	Median	2.16	2.43	0.21	12.05
	Max	[redacted]			

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Table 2
Summary Statistics for INR Data - Part 2
(Protocol 035)

Regimen	Parameter	Baseline INR	INR on Day 21	Change in INR on Day 21 vs. Baseline	% Change INR on Day 21 vs. Baseline
4 mg Rosiglitazone bd + Warfarin	n	4	4	4	4
	Mean	2.22	2.01	-0.21	-8.53
	SE	0.23	0.22	0.21	7.94
	SD	0.47	0.45	0.42	15.87
	Min	[redacted]			
	Median	2.25	1.88	-0.14	-7.10
	Max	[redacted]			
Placebo bd + Warfarin	n	3	3	3	3
	Mean	2.76	2.79	0.03	-2.33
	SE	0.60	0.76	0.16	7.75
	SD	1.04	1.31	0.29	13.43
	Min	[redacted]			
	Median	3.24	3.30	0.06	1.96
	Max	[redacted]			

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Table 3
Mean (SD) Pharmacokinetic Parameter Values for Warfarin – Part I
(Protocol 49653/035)

Parameter		Rosiglitazone Group Warfarin Alone (n=10)	Rosiglitazone Group Warfarin + Rosiglitazone (n=10)	Placebo Group Warfarin Alone (n=8)	Placebo Group Warfarin + Placebo (n=8)
DN-AUC [ug.h/mL]	R(+)	3.09 (0.68)	3.03 (0.66)	2.94 (0.30)	3.01 (0.39)
DN-Cmax [ug/mL]	R(+)	0.183 (0.046)	0.176 (0.037)	0.180 (0.034)	0.179 (0.027)
Tmax* [hours]	R(+)	1.00 (0.50-4.00)	1.00 (0.50-4.00)	1.50 (0.50-4.00)	1.49 (0.50-2.00)
DN-AUC [ug.h/mL]	S(-)	2.29 (0.64)	2.13 (0.56)	2.15 (0.35)	2.27 (0.48)
DN-Cmax [ug/mL]	S(-)	0.149 (0.034)	0.140 (0.026)	0.146 (0.030)	0.150 (0.032)
Tmax* [hours]	S(-)	1.00 (0.50-2.00)	1.00 (0.50-3.00)	1.00 (0.50-2.00)	1.00 (0.50-2.00)

Data for AUC and Cmax are dose-normalized
* Data for Tmax presented as median (range)

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Table 4
Mean (SD) Pharmacokinetic Parameter Values for Warfarin – Part 2
(Protocol 49653/035)

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Parameter		Rosiglitazone Group Warfarin Alone (n=4)	Rosiglitazone Group Warfarin + Rosiglitazone (n=4)	Placebo Group Warfarin Alone (n=3)	Placebo Group Warfarin + Placebo (n=3)
DN-AUC [ug.h/mL]	R(+)	2.82 (0.31)	2.81 (0.24)	3.34 (0.58)	3.28 (0.34)
DN-Cmax [ug/mL]	R(+)	0.182 (0.028)	0.188 (0.021)	0.203 (0.035)	0.192 (0.024)
Tmax * [hours]	R(+)	1.25 (0.50-3.00)	0.50 (0.50-3.00)	1.00 (0.50-1.00)	1.00 (0.50-3.00)
DN-AUC [ug.h/mL]	S(-)	2.04 (0.40)	1.96 (0.41)	2.13 (0.88)	2.04 (0.67)
DN-Cmax [ug/mL]	S(-)	0.148 (0.029)	0.152 (0.031)	0.147 (0.037)	0.135 (0.030)
Tmax * [hours]	S(-)	1.25 (0.50-4.00)	0.50 (0.50-1.00)	0.50 (0.50-1.00)	1.00 (0.50-3.00)

Data for AUC and Cmax are dose-normalized
* Data for Tmax presented as median (range)

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Table 5
Point Estimates and 95% Confidence Intervals – Part 1
(Protocol 49653/035)

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Parameter		Comparison	Point Estimate*	95% CI
DN-AUC	R(+)	Rosiglitazone: Placebo	0.96	(0.91, 1.02)
DN-Cmax	R(+)	Rosiglitazone: Placebo	0.97	(0.90, 1.05)
DN-AUC	S(-)	Rosiglitazone: Placebo	0.90	(0.83, 0.97)
DN-Cmax	S(-)	Rosiglitazone: Placebo	0.93	(0.83, 1.04)

* Ratio of the adjusted geometric means of 'warfarin plus rosiglitazone' relative to 'warfarin plus placebo on day 21

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Figure 1
ANCOVA for Warfarin for All Subjects in Part 1
(Protocol 49653/035)

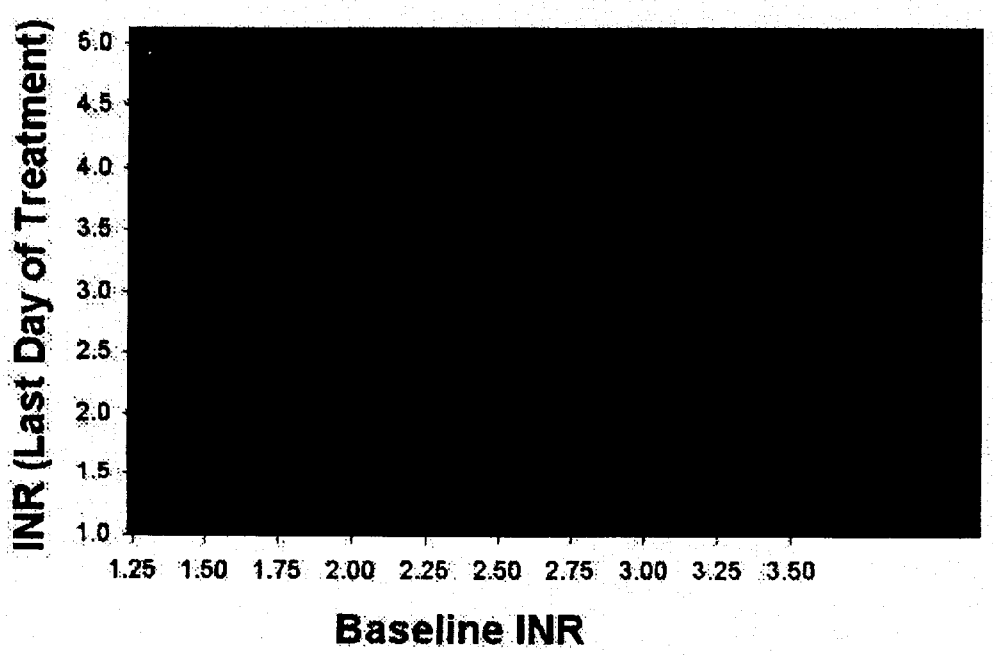

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Figure 2
ANCOVA for Warfarin Excluding Data from 3 Subjects with > 2.75 Baseline INR Values in Part 1 (Protocol 49653/035)

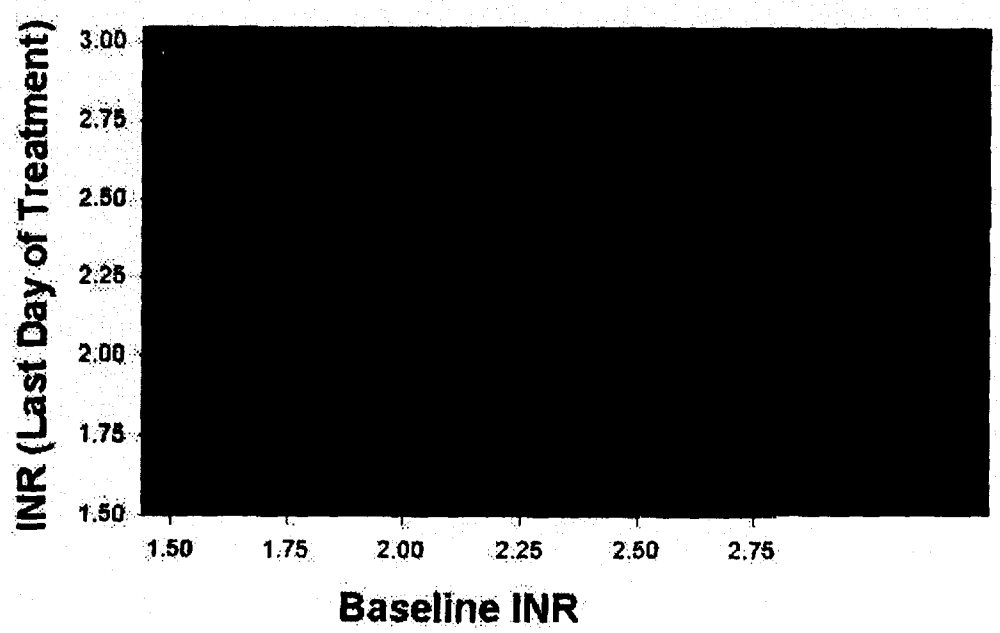

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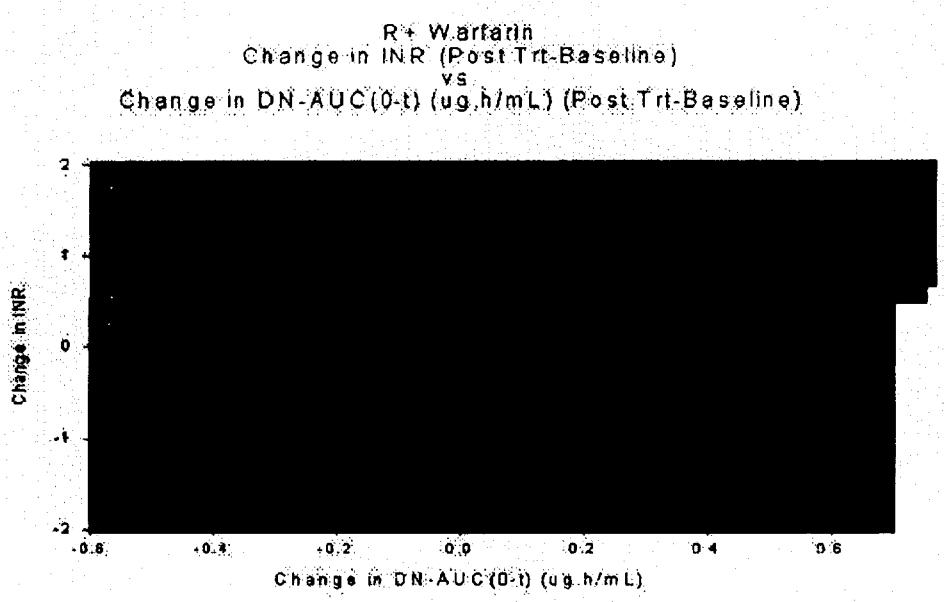
Figure 3

Change in Post Treatment INR versus Change in Post Treatment Dose-Normalized AUC(0-t) (ug.h/mL) for R(+) Warfarin (Part 1) (Protocol 49653/035)



● 4 mg Rosiglitazone bid + Warfarin (N=10)
○ 4 mg Rosiglitazone Matched Placebo bid + Warfarin (N=8)

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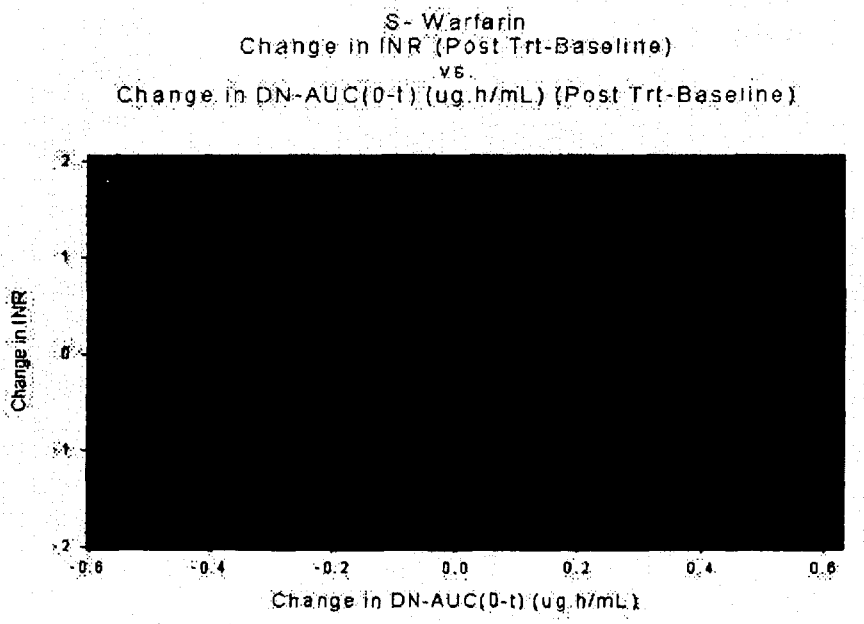
Figure 4

Change in Post Treatment INR versus Change in Post Treatment Dose-Normalized AUC(0-t) (ng.h/mL) for S(-) Warfarin (Part 1) (Protocol 49653/035)



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REVIEWER'S COMMENTS FOR STUDY 035:

1. Due to lack of INR dAPPEARS THIS WAY ON ORIGINAL----------
2. No effect on warfari---------

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DRUG INTERACTION-METFORMIN

Protocol 49653C/036 Issued September 1996

SB Report BRL-049653/RSD-1006FL/1

Title: A study to determine the effects of BRL-49653C on the pharmacokinetics of metformin in healthy male volunteers

Publication: DiCicco R, Allen A, Jerkasky D, Carr A, Preed M. 1998. Lack of pharmacokinetic drug interaction between rosiglitazone (BRL 49653C) and metformin. *Clin Pharmacol Ther*, 63(2), 155.

Investigator: [redacted]

Study Center: [redacted]

PK Objective: 1) To estimate the difference between the steady-state pharmacokinetics of metformin administered alone or in combination with steady-state administration of rosiglitazone; 2) to estimate the difference between the steady-state pharmacokinetics of rosiglitazone administered alone or in combination with steady-state administration of metformin in healthy male volunteers.

Study Design: This was a randomized, open-label, repeat dose, period balanced three-period crossover study involving 16 healthy male volunteers (age 22 to 55 years, weight 71 to 119 kg). Subjects received each of the following three regimens under fed conditions:

Regimen A: Rosiglitazone 2 mg (Capsule formula AB-AA, batch # M94152) every 12 hours x 4 days

Regimen B: Metformin 500 mg (Glucophage®, batch # M5G63A) every 12 hours x 4 days

Regimen C: Rosiglitazone 2 mg every 12 hours plus Metformin 500 mg every 12 hours x 4 days

There was no washout between regimens. Blood samples for pharmacokinetic analysis were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after the morning dose of medication.

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Cmax, Tmax, and AUC(0-12) of metformin and rosiglitazone were calculated using non-compartmental methods. Following ln-transformation, AUC(0-12) and Cmax of both metformin and rosiglitazone were analyzed separately by analysis of variance with terms for sequence, subject within sequence, period and regimen. Additionally, assessments of first-order carryover were performed. Point estimates and the associated 95% confidence intervals for each of these parameters were calculated for the differences 'rosiglitazone plus metformin - metformin alone' and 'rosiglitazone plus metformin - rosiglitazone alone', followed by back transformation. T½ of metformin and rosiglitazone were analyzed in a similar fashion without prior transformation. Tmax values were analyzed non-parametrically.

Analytical Methodology: Plasma samples were analyzed for metformin concentrations using automated solid-phase extraction followed by LC-UV [Pharma-Bio Report PBR-960293]. The lower limit of quantification (LLQ) for metformin was [redacted]. Metformin analyses were performed by [redacted]

The plasma samples were analyzed for rosiglitazone concentrations using [redacted] coupled to [redacted] detection [SB Report RSD-10064P]. The LLQ for rosiglitazone was [redacted]. Rosiglitazone analyses were performed by [redacted]

PK Results and Discussion: Geometric mean (range) pharmacokinetic parameters and statistical results for metformin and rosiglitazone are shown in Tables 1 and 2, respectively.

Repeated oral administration of metformin (500 mg bid) with rosiglitazone (2 mg bid) resulted in very similar exposure, based on AUC(0-12) and Cmax, compared to that obtained when metformin was administered alone. The point estimates for the ratios for AUC(0-12) and Cmax of 'metformin plus rosiglitazone' to 'metformin alone' were 1.01 and 1.02, respectively, and the associated 95% confidence intervals contained the value 1 as a plausible value for the true ratios. There was no evidence of a change in either Tmax or T1/2 for metformin when metformin was co-administered with rosiglitazone, compared to metformin alone. The 95% confidence intervals for the mean difference of T1/2 and the median difference of Tmax contained the value of zero. Median Tmax and mean elimination half-life values ranged from 3.0 to 3.5 hours and from 3.2 to 3.4 hours, respectively.

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Repeated oral administration of rosiglitazone with metformin also resulted in very similar exposure to rosiglitazone, based on AUC(0-12) and Cmax, compared to values obtained when rosiglitazone was administered alone. The point estimates for the ratios for AUC(0-12) and Cmax of rosiglitazone plus metformin to rosiglitazone alone were 1.00 and 0.99, respectively, and the associated 95% confidence intervals contained the value 1 as a plausible value for the true ratios. There was no evidence of a change in either Tmax or T½ for rosiglitazone when rosiglitazone was co-administered with metformin, compared to rosiglitazone alone. The 95% confidence intervals for the mean difference of T½ and the median difference of Tmax contained the value of zero. Median Tmax values ranged from 3.0 to 3.5 hours and mean half-life was to 3.2 hours for both regimens.

Therefore, there was no pharmacokinetic interaction between rosiglitazone and metformin.

PK Conclusion: Co-administration of rosiglitazone and metformin had no significant effect on the steady state pharmacokinetics of either metformin or rosiglitazone, compared to either drug administered alone.

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Table 1
Geometric mean (range) Pharmacokinetic Parameter Values for Metformin with Point Estimates and Corresponding 95% Confidence Intervals
(Protocol 49653/036)

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Parameter	Metformin alone (n=16	Metformin + Rosiglitazone (n=16)	Point Estimate	95% CI
AUC(0-12)[a] [ng.h/mL]	6508 (4694 - 8705)	6575 (4773 - 9230)	1.01[d]	(0.94, 1.08)
Cmax[a] [ng/mL]	901 (620 - 1251)	918 (635 - 1344)	1.02[d]	(0.94, 1.10)
Tmax[b] [hours]	3.0 (1.0 – 6.0)	3.5 (1.5 - 6.0)	0.00[e]	(–1.00, 1.00)
T½[c] [hours]	3.24 (2.56 - 4.19)	3.41 (2.64 - 4.58)	0.17[f]	(–0.05, 0.38)

a Data presented as geometric means
b Data presented as median (range)
c Data presented as arithmetic mean (range)
d Presented as a ratio of geometric means between regimens
e Presented as a median difference between regimens
f Presented as a mean difference between regimens

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Table 2
Geometric Mean (Range) Pharmacokinetic Parameter Values for Rosiglitazone with Point Estimates and Corresponding 95% Confidence Intervals
(Protocol 49653/036)

Parameter	Rosiglitazone alone (n=16	Metformin + Rosiglitazone (n=16)	Point Estimate	95% CI
AUC(0-12)[a] [ng.h/mL]	626 (494 – 866)	629 (418 – 912)	1.00[d]	(0.97, 1.04)
Cmax[a] [ng/mL]	105 (78.9 – 150)	104 (76.5 – 139)	0.99[d]	(0.94, 1.06)
Tmax[b] [hours]	3.0 (2.0 – 4.0)	3.5 (1.5 – 4.0)	0.25[e]	(–0.25, 0.75)
T½[c] [hours]	3.22 (2.45 – 5.01)	3.21 (2.56 – 4.64)	0.00[f]	(–0.15, 0.16)

a Data presented as geometric means
b Data presented as median (range)
c Data presented as arithmetic mean (range)
d Presented as a ratio of geometric means between regimens
e Presented as a median difference between regimens
f Presented as a mean difference between regimens

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REVIEWER'S COMMENTS FOR STUDY 036:

1. Agree with results.

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DRUG INTERACTION-RANITIDINE

Protocol 49653C/037 Issued November 1996

SB Report BRL-049653/RSD-100DG9/1

Title: A study to assess the effect of ranitidine on the bioavailability of BRL-49653C in healthy adult males

Publication: Freed MI, Miller AK, Jorkasky DK, DiCicco RA. 1998. Rosiglitazone pharmacokinetics are not affected by coadministration of ranitidine. *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: 1) To estimate the pharmacokinetics of rosiglitazone following single oral and intravenous doses administered alone and as single doses on the fourth day of repeat dosing with ranitidine 150 mg every 12 hours, and 2) to estimate the absolute bioavailability of rosiglitazone in healthy young adult males.

Study Design: This was an open label, randomized, four period, period balanced, crossover study involving 13 healthy male volunteers (age 23 to 42; weight 65 to 109 kg). Each subject received the following regimens:

A) 2 mg rosiglitazone administered intravenously over 1 hour. [0.1 mg/mL; batch # U95156]

B) 4 mg rosiglitazone administered as a single oral dose. [4 mg oral tablets, batch # M96091]

C) Ranitidine (Zantac®)150 mg orally every 12 hours on Days 1 through 4 + 2 mg rosiglitazone intravenously over 1 hour on the morning of Day 4. [Zantac®; lot # 52PT196]

D) Ranitidine 150 mg orally every 12 hours on Days 1 through 4 + 4 mg rosiglitazone orally on the morning of Day 4.

Rosiglitazone was administered under fasted conditions and, for regimens C and D, rosiglitazone was administered two hours after the ranitidine dose. For Regimens A and C, rosiglitazone was infused in a final volume of 30 mL over the

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1 hour period. During the intravenous dosing arms, blood samples for pharmacokinetic analysis were collected at predose, 0.5 hours after the start of the infusion, immediately post-infusion (1 hour) and at 1.5, 2, 4, 8, 10, 12, 16, and 24 hours after the start of the infusion. During the oral dosing arms, blood samples were collected at predose, 0.5, 1, 1.5, 2, 4, 8, 12, 16, and 24 hours post dose.

Pharmacokinetic parameters (Cmax, AUC(0-inf), Tmax, T1/2, CL, and Vss) were calculated using non-compartmental analysis. Following ln-transformation, the primary parameter, dose-normalized AUC(0-inf), was analyzed by analysis of variance (ANOVA) including terms for sequence, subject within sequence, period and regimen. There was additional assessment of first-order carryover. The point and 95% confidence intervals estimates were determined for the ratios of 'oral:IV rosiglitazone', 'rosiglitazone + ranitidine: rosiglitazone alone'. Following ln-transformation, the secondary endpoints, Cmax from the oral rosiglitazone arms and Vss and CL from the intravenous arms, were analyzed in a similar fashion. T1/2 was analyzed in a similar fashion without prior transformation. Tmax was analyzed non-parametrically using the Wilcoxon matched pairs method. The point estimate and 95% confidence interval were constructed for the median difference 'oral rosiglitazone + ranitidine minus oral rosiglitazone alone'.

Analytical Methodology: Plasma samples were analyzed for concentrations of rosiglitazone using [redacted] detection [SB Report RSD-10064P/1]. The lower limit of quantitation was [redacted]. Analysis was performed by [redacted]

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

There were no apparent differences between dose-normalized AUC(0-inf), Cmax (oral administration only), Vss, and CL (intravenous administration only) of rosiglitazone when administered with or without pretreatment of ranitidine, as the point estimates were close to unity and the 95% confidence intervals included the value 1. Similarly, no apparent differences were observed for rosiglitazone Tmax when rosiglitazone was administered orally alone or with ranitidine. Median Tmax values ranged 0.8 to 1 hour. There were no substantial differences in T½ in the presence or absence of ranitidine after either intravenous or oral administration of rosiglitazone as indicated by the 95% confidence intervals which contained the value of zero. Mean T½ ranged from 3.4 to 3.9 hours across all regimens. These results indicate that pretreatment with ranitidine has no apparent effect on the absorption or elimination of rosiglitazone.

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The mean intravenous plasma clearance of rosiglitazone and steady-state volume of distribution in this study was 2.68 L/h and 12.9 L, respectively. These values suggest that rosiglitazone has a low clearance and is not extensively distributed in man.

The absolute bioavailability (F) for rosiglitazone was on average 99% based on the ratio of the geometric means of dose normalized AUC(0-inf) values (B:A) with a 95% confidence interval (0.84, 1.15). The range of individual values for F was 0.75 to 1.30.

PK Conclusion: The single dose pharmacokinetics of rosiglitazone following oral (4 mg) or intravenous administration (2 mg) of rosiglitazone were similar when administered alone or with pretreatment of ranitidine. Absolute bioavailability of rosiglitazone administered as a 4 mg tablet was, on average, 99%.

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Table 1
Mean (SD) Pharmacokinetic Parameters for Rosiglitazone
(Protocol 49653/037)

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Parameter	IV Rosiglitazone alone (n=13)	Oral Rosiglitazone alone (n=13)	IV Rosiglitazone + Ranitidine (n=13)	Oral Rosiglitazone + Ranitidine (n=13)
AUC(0-inf) [ng.h/mL]	775 (155)	1552 (416)	807 (208)	1540 (418)
Cmax [ng/mL]	153 (29)	319 (97)	156 (31)	302 (60)
Tmax* [hours]	ND	0.78 (0.48 - 2.05)	ND	1.01 (0.50 - 2.00)
T½ [hours]	3.48 (0.94)	3.51 (0.56)	3.92 (1.41)	3.39 (0.74)
CL [L/h]	2.68 (0.57)	2.77+ (0.80)	2.62 (0.84)	2.80+ (0.83)
Vss [L]	12.9 (2.0)	14.7$ (3.9)	13.4 (3.7)	14.9$ (3.7)

* Presented as median (range); ND = not determined
\+ Oral clearance values (CL/F)
$ Oral volume of distribution at steady-state (Vss/F)

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Table 2
Point Estimates and 95% Confidence Intervals
(Protocol 49653/037)

Parameter	Comparison	Point Estimate	95% CI
DN AUC(0-inf)[a]	B:A[d]	0.99	(0.84, 1.15)
	C:A	1.02	(0.88, 1.20)
	D:B	0.99	(0.85, 1.16)
Cmax [a]	D:B	0.97	(0.78, 1.21)
T½ [b]	C-A	0.48 h	(-0.26 h, 1.22 h)
	D-B	-0.12 h	(-0.83 h, 0.60 h)
Tmax [c]	D-B	0.00 h	(-0.47 h, 0.49 h)
CL [a]	C:A	0.94	(0.83, 1.07)
Vss [a]	C:A	0.99	(0.89, 1.11)

[a] presented as the ratio of geometric means, DN = dose normalized
[b] presented as the difference in arithmetic means
[c] presented as the median difference
d Represents absolute bioavailability (F)

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KEY:	Description
Regimen	
A	2 mg rosiglitazone administered intravenously over 1 hour
B	4 mg rosiglitazone administered as a single oral dose
C	Ranitidine 150 mg orally every 12 hours on Days 1 through 4 + 2 mg rosiglitazone intravenously over 1 hour on the morning of Day 4
D	Ranitidine 150 mg orally every 12 hours on Days 1 through 4 + 4 mg rosiglitazone orally on the morning of Day 4

REVIEWER'S COMMENTS FOR STUDY 037:

1. Agree with results.

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PHARMACOKINETICS IN RENAL PATIENTS

Protocol 49653C/038 Issued: June 1998
SB Report BRL-049653/RSD-100J1X/1

Title: An evaluation of the pharmacokinetics of a single oral dose of BRL-49653C in patients with varying degrees of renal insufficiency compared with normal renal function.

[redacted]

PK Objective: To characterize the pharmacokinetics and protein binding of a single oral dose of rosiglitazone in patients with varying degrees of renal insufficiency.

Study Design: This was an open-label, single dose, parallel group study involving subjects who were stratified into four groups based on renal function: normal renal function [n = 12 (8 males), age 25 to 70 years; weight 58 to 93 kg; CLcr > 80 mL/min]; mild chronic renal insufficiency [n = 15 (8 males); age 47 to 75 years; weight 58 to 85 kg; CLcr 60-80 mL/min]; moderate chronic renal insufficiency [n = 18 (9 males); age 49 to 75 years; weight 51 to 104 kg; CLcr 30-59 mL/min]; severe chronic renal insufficiency [n = 12 (7 males), age 25 to 67 years; weight 47 to 104 kg; CLcr ≤ 29 mL/min]. Each subject received a single oral 8 mg (2 x 4 mg) dose of rosiglitazone (batch # M96239) under fasted conditions. Blood samples for pharmacokinetic analysis were collected immediately prior to dosing (0 hours) and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 30 and 48 hours after dosing. An additional sample was obtained 2 hours after dosing for the determination of *ex vivo* plasma protein binding.

Total Cmax, Tmax, AUC(0-inf), T½, CL/F and Vss/F of rosiglitazone were calculated using non-compartmental analysis. Fraction unbound, unbound Cmax, unbound AUC(0-inf), unbound CL/F and unbound Vss/F were also determined. Total and unbound AUC(0-inf) and Cmax values were ln-transformed and analyzed separately by analysis of variance (ANOVA) appropriate to a parallel group study design. Point estimates and associated 95% confidence intervals were calculated for the ratios of these parameters for the mild, moderate and severe groups relative to the normal group. T½ and fraction unbound were similarly analyzed without prior transformation.

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Analytical Methodology: Rosiglitazone was quantitated in plasma samples for pharmacokinetic analysis using [redacted] followed by [redacted] [SB Report BF-1016]. The lower limit of quantification (LLQ) for rosiglitazone in plasma was [redacted] using a 200 uL plasma sample volume. The plasma and ultrafiltrate samples for protein binding determination were assayed using a method based on [redacted] followed by [redacted] analysis employing [redacted] [SB Report No. RSD-100J1X/1, Appendix A]. This method has an [redacted] using a 0.05 mL aliquot of human plasma or ultrafiltrate. 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.

Based on AUC(0-inf) and Cmax values, total (bound and unbound) plasma concentrations of rosiglitazone for the mild and moderate groups were similar to those for the normal group. In contrast, total AUC(0-inf) and Cmax values were, on average, approximately 20-25% lower for the severe group relative to the normal group. The lower total concentrations for the severe group are related to the 38% greater mean fraction unbound value and the consequent 20-30% increases in mean oral clearance (CL/F) and steady-state volume of distribution (Vss/F) observed for this group. Unbound AUC(0-inf) values were slightly higher (on average approximately 10-20%) in patients with varying degrees of renal impairment; however, the changes were small relative to the observed between-subject variability in this parameter (approximately 40%) and were not considered to be clinically relevant. Consequently, considerable overlap of individual values for each parameter were observed between groups. No apparent differences were observed in mean unbound Cmax and T½ values and median Tmax values between groups.

PK Conclusions: Following single oral administration of 8 mg rosiglitazone, there were no clinically relevant changes in the pharmacokinetics of rosiglitazone in patients with mild, moderate or severe renal insufficiency compared to subjects with normal renal function. Thus, no dose adjustment is necessary in individuals with renal insufficiency.

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Table 1
Mean (SD) Pharmacokinetic Parameter Values for Rosiglitazone in Subjects with Normal Renal Function and Renal Impairment
(Protocol 49653/038)

Parameter	Normal (n=12)	Mild (n=15)	Moderate (n=18)	Severe (n=12)
AUC(0-inf) [ng.h/mL]	2838 (781)	3126 (1239)	3236 (1054)	2290 (589)
Cmax [ng/mL]	461 (88)	454 (108)	475 (104)	359 (105)
Unbound AUC(0-inf)* [ng.h/mL]	4.23 (1.56)	5.09 (2.32)	5.04 (2.42)	4.76 (1.66)
Unbound Cmax* [ng/mL]	0.716 (0.191)	0.727 (0.162)	0.739 (0.237)	0.810 (0.282)
Tmax # [hours]	2.0 (1.0-6.0)	2.0 (1.0-4.0)	2.0 (0.5-4.0)	2.0 (1.5-4.0)
%fu*	0.16 (0.03)	0.16 (0.02)	0.15 (0.02)	0.22 (0.06)
T1/2 [hours]	4.1 (1.1)	4.5 (1.9)	4.5 (0.8)	4.1 (1.0)
CL/F [L/h]	3.07 (1.02)	2.87 (0.93)	2.67 (0.69)	3.73 (1.05)
Vss/F [L]	20.0 (3.3)	19.3 (4.1)	18.6 (3.7)	26.0 (7.0)
Unbound CL/F [L/h]	2194 (1036)	1838 (733)	1819 (603)	1903 (742)
Unbound Vss/F (L)	13024 (3310)	12028 (2680)	12304 (3059)	11765 (3693)

* n=10 for normal, n=14 for mild, n=17 for moderate and n=9 for severe
\# Data presented as median (range)

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Table 2
Point Estimates and 95% Confidence Intervals
(Protocol 49653/038)

Parameter	Comparison	Point Estimate	(95% CI)
AUC(0-inf)*	Mild:Normal	1.08	(0.85, 1.37)
	Moderate:Normal	1.14	(0.91, 1.43)
	Severe:Normal	0.81	(0.64, 1.04)
Cmax*	Mild:Normal	0.98	(0.81, 1.17)
	Moderate:Normal	1.02	(0.86, 1.22)
	Severe:Normal	0.76	(0.63, 0.92)
Unbound AUC(0-inf)*	Mild:Normal	1.19	(0.86, 1.64)
	Moderate:Normal	1.18	(0.86, 1.62)
	Severe:Normal	1.13	(0.79, 1.63)
Unbound Cmax*	Mild:Normal	1.02	(0.81, 1.29)
	Moderate:Normal	1.02	(0.81, 1.28)
	Severe:Normal	1.10	(0.85, 1.43)
%fu#	Mild-Normal	0.00	(-0.02, 0.03)
	Moderate-Normal	0.00	(-0.03, 0.02)
	Severe-Normal	0.06	(0.03, 0.09)
T1/2#	Mild-Normal	0.42	(-0.57, 1.42)
	Moderate-Normal	0.38	(-0.58, 1.33)
	Severe-Normal	0.00	(-1.04, 1.05)

* Point estimates represent the ratios of geometric means
# Point estimates represent the differences of arithmetic means

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REVIEWER'S COMMENTS FOR STUDY 038:

1. Changes in protein binding minor.

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DRUG INTERACTION - NIFEDIPINE

Protocol 49653C/039 Issued June 1998
SB Report BRL-049653/RSD-100J1Z/1

Title: An investigation of the effect of BRL-49653C on the safety, tolerability and pharmacokinetics of nifedipine in healthy volunteers.

Publication: Freed MI, Miller AK, Inglis AM, Thompson KA, Ladley D, Jorkasky DK. 1998. Rosiglitazone, a PPAR-gamma agonist, does not alter the pharmacokinetics of nifedipine, a cytochrome P450 3A4-substrate. *Diabetes*, 47 (suppl. 1), 94A.

Investigators and Study Centers: Martin I. Freed, M.D., SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, University of Pennsylvania Health System, Philadelphia, Pennsylvania, USA

PK Objective: To establish the lack of effect of repeat oral doses of rosiglitazone on the pharmacokinetics of a single oral dose of nifedipine compared to the pharmacokinetics of a single oral dose of nifedipine administered alone.

Study Design: This was a randomized, open-label, two-period, period balanced, crossover study conducted in healthy adult volunteers (n = 28; age 20 to 49 years; weight 50.7 to 101.7 kg). Each subject participated in two study sessions separated by a washout period of at least 14 days. Each subject was first administered a single 20 mg oral dose of nifedipine (Procardia®, Pfizer Labs) followed by 14 days of once daily rosiglitazone, 8 mg (2 x 4 mg, batch # M96239). A single 20 mg oral dose of nifedipine was coadministered on the morning of day 14. Blood samples for pharmacokinetic analysis were collected predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 18, and 24 hours following nifedipine dosing.

AUC(0-inf), Cmax, Tmax, and T½ for nifedipine were calculated using non-compartmental methods. The primary endpoint AUC(0-inf) for nifedipine was ln-transformed and analyzed by analysis of variance (ANOVA) appropriate to the study design. Rosiglitazone was considered to have no effect on the AUC(0-inf) of nifedipine if the 90% confidence intervals (nifedipine + rosiglitazone:nifedipine alone) were completely contained with the range (0.70, 1.43. The point estimate and associated 90% confidence interval were calculated for the ratio 'rosiglitazone + nifedipine':'nifedipine alone'. Secondary endpoints Cmax and T½ (without prior transformation) were similarly analyzed by

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ANOVA, and Tmax was analyzed non-parametrically. Point estimates and 95% confidence intervals were constructed for secondary endpoints.

Analytical Methodology: Plasma samples were analyzed for nifedipine using a method based on [redacted] followed by [redacted] with [redacted] detection [SB Report RSD-100R30/1]. The lower limit of quantification (LLQ) for nifedipine was [redacted] using 1.0 mL of sample volume. Analyses were performed by [redacted]

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

Twenty-six subjects completed both study sessions. A lack of rosiglitazone effect on the single dose pharmacokinetics of oral nifedipine was demonstrated. The 90% confidence interval for AUC(0-inf) was completely contained in the protocol-defined 30% equivalence range. However, the confidence interval for AUC(0-inf) did not include unity, implying that after a single dose of nifedipine, small decreases in AUC(0-inf) may occur upon coadministration of rosiglitazone. On average, AUC(0-inf) for nifedipine decreased by 13% during coadministration with rosiglitazone. Coadministration of rosiglitazone with nifedipine, relative to nifedipine alone, resulted in an increase in AUC(0-inf) for 9/26 subjects (range: 11-51%) and a decrease in AUC(0-inf) for 17/26 subjects (range: 1-56%). Six subjects decreased by greater than 30% while one subject increased by more than 30%. All other subjects (19/26) had individual ratios within the 30% range. Cmax and Tmax appeared to be similar between regimens. Coadministration of nifedipine with rosiglitazone, relative to nifedipine alone, resulted in an average 0.77 hour decrease in T½.

PK Conclusions: Repeat dose treatment with rosiglitazone did not alter the pharmacokinetics of a single dose of nifedipine to an extent that would be of any clinical significance.

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Table 1
Mean (SD) Pharmacokinetic Parameter Values for Nifedipine
(Protocol 49653/039)

Parameter	20 mg Nifedipine (Alone) (n=28)	20 mg Nifedipine (+ Rosiglitazone) (n=28)
AUC(0-inf) [ng.h/mL]	338 (135)	298 (110)
Cmax [ng/mL]	137 (86)	136 (88)
T1/2 [hours]	4.95 (2.20)	4.21 (1.74)
Tmax * [hours]	0.95 (0.47-2.98)	0.55 (0.22-3.98)

* Data presented as median (range)

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Table 2
Point Estimates and Confidence Intervals
(Protocol 49653/039)

Parameter	Comparison	Point Estimate	95% CI
AUC(0-inf)	B:A	0.87	(0.79, 0.96)

Parameter	Comparison	Point Estimate	90% CI
Cmax	B:A	0.99	(0.68, 1.43)
Tmax *	B-A	0.01 h	(–0.45, 0.26)
T½ **	B-A	–0.77 h	(–1.40, –0.14)

Regimen A = Nifedipine single dose (20 mg)
Regimen B = Nifedipine single dose (20 mg) at rosiglitazone steady state (8 mg)
* Median difference ** Mean difference

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REVIEWER'S COMMENTS FOR STUDY 039:

1. Agree with results.

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DRUG INTERACTION-ACARBOSE

Protocol 49653C/040 Issued December 1997

SB Report BRL-049653/RSD-100120/1

Title: Effect of acarbose on the pharmacokinetics of BRL-49653C in healthy adult volunteers

Publication: Inglis AL, Miller AK, Thompson KA, Jorkasky DK, Freed MI. 1998. Coadministration of rosiglitazone and acarbose (A): Lack of a clinically relevant pharmacokinetic drug interaction. *Diabetes*, **47 (suppl. 1)**, 94A.

Investigator: Martin I. Freed, M.D.

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

PK Objective: To estimate the effects of repeat oral dosing with acarbose on the pharmacokinetics of a single oral dose of rosiglitazone administered at the start of a standardized meal.

Study Design: This was a two-period, open-label, non-randomized study in sixteen healthy adult volunteers (15 males and 1 female: age 24 to 59 years; weight 72 to 99 kg). Each subject received in Session 1, a single 8 mg (2 x 4 mg, batch #M96239) oral dose of rosiglitazone administered with the first bite of a standardized breakfast, and in Session 2, acarbose (Precose®; batch U97136/6AGN), 100 mg orally, three times daily with the first bite of breakfast, lunch and dinner for seven (7) days + a single 8 mg (2 x 4 mg) oral dose of rosiglitazone administered with the first bite of a standardized breakfast on the morning of the seventh day of acarbose treatment. Blood samples for pharmacokinetic analysis were collected from each subject predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours following dosing with rosiglitazone.

Cmax, Tmax, AUC(0-inf) and T½ of rosiglitazone were calculated using non-compartmental analysis. AUC(0-inf) and Cmax were ln-transformed and analyzed separately by analysis of variance (ANOVA), appropriate to a two-period, non-randomized crossover study. The point estimates and 95% confidence intervals for the difference between the regimens were constructed. The point and interval estimates on the ln-scale were backtransformed to obtain the estimates of the ratio 'rosiglitazone + acarbose: rosiglitazone alone'. T½ was analyzed in a similar

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fashion without prior transformation. Tmax was analyzed non-parametrically. The point estimate and 95% confidence interval for the median difference between the regimens were constructed.

Analytical Methodology: Plasma samples were analyzed for concentrations of rosiglitazone using [redacted] coupled to [redacted] followed by fluorescence detection [SB Report RSD-100NHD/1]. The lower limit of quantification [LLQ] for rosiglitazone was [redacted]. The LLQ for runs containing samples for 5 subjects (both sessions) was raised to [redacted] as a result of instrumental difficulties. Analysis 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.

Co-administration of rosiglitazone with acarbose, relative to rosiglitazone alone, resulted in an average 12% decrease in AUC(0-inf) with the true mean decrease expected to lie between 2% to 21%. Co-administration of rosiglitazone with acarbose, relative to rosiglitazone alone, resulted in an average 1.14 hours decrease in T½. Cmax and Tmax appeared to be similar between regimens. These results suggest that the observed decrease in AUC(0-inf) values when rosiglitazone was co-administered with acarbose were related to an increase in systemic clearance rather than a decrease in absorption. However, the observed decreases in AUC(0-inf) and T½ are considered small and are considered unlikely to be clinically relevant.

PK Conclusion: Healthy subjects after systemic exposure to a single 8 mg dose of rosiglitazone when co-administered with acarbose, 100 mg three times daily for seven days, demonstrated a slight reduction in AUC(0-inf) and shorter T½ compared to that following administration of rosiglitazone alone. These changes were considered unlikely to be clinically relevant.

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Table 1
Mean (SD) Pharmacokinetic Parameter Values for Rosiglitazone
(Protocol 49653/040)

Parameter	Rosiglitazone Alone (n=16)	Rosiglitazone + Acarbose (n=16)
AUC(0-inf) [ng.h/mL]	2793 (581)	2502 (755)
AUC(0-t) [ng.h/mL]	2676 (552)	2394 (705)
Cmax [ng/mL]	428 (86)	451 (141)
Tmax* [hours]	1.48 (0.97 - 5.95)	1.24 (0.95 - 3.98)
T½ [hours]	4.93 (0.78)	3.79 (0.78)

* Data presented as median (range)

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Table 2
Point Estimates and 95% Confidence Intervals
(Protocol 49653/040)

Parameter	Comparison	Point Estimate	95 % CI
AUC(0-inf)* [ng.h/mL]	B:A	0.88	(0.79, 0.98)
Cmax* [ng/mL]	B:A	1.03	(0.85, 1.24)
Tmax** [hours]	B–A	–0.26	(–0.79, 0.48)
T½+ [hours]	B–A	–1.14	(–1.56, –0.72)

* ratio of geometric means between regimens
** median difference
\+ difference in arithmetic mean
Regimen A: Single 8 mg dose of rosiglitazone alone
Regimen B: Single 8 mg dose of rosiglitazone following 7 days of treatment of 100 mg acarbose tid

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REVIEWER'S COMMENTS FOR STUDY 040:

1. Results acceptable.

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Title study 041

A Study to Evaluate the Effect of Ethanol Administration on the Pharmacodynamics of BRL 49653C in Chronically-treated Type 2 Diabetic Patients

Investigator(s) and Center(s)

[redacted]

Publication

None as of August 1998

Study Dates

24 September 1997 to 2 December 1997

Objective(s)

1. To demonstrate a lack of effect of ethanol administration relative to a non-ethanol control on plasma glucose levels the morning after ethanol administration in Type 2 (non-insulin dependent diabetes mellitus) diabetic patients administered 8 mg BRL 49653C once daily for eight weeks;

2. To describe the effect of ethanol administration on post-prandial and fasting plasma glucose and serum insulin levels and the urinary cortisol/creatinine ratio profiles in Type 2 diabetic patients administered 8 mg BRL 49653C once daily for eight weeks;

3. To assess the safety and tolerability of repeat oral doses of BRL 49653C in Type 2 diabetic patients.

Study Design

This was a placebo controlled, repeat dose, randomized, double blind, parallel group study (double blind and parallel group with respect to BRL 49653C or Placebo treatment). Patients were randomized to receive either oral Placebo (Treatment A) or BRL 49653C 8 mg (Treatment B) once daily for 8 weeks (56 days total). During the last week of treatment, on two separate occasions (Day 53 and Day 56), patients participated in a randomized, open-label ethanol/non-ethanol-control crossover challenge session. Patients were randomly assigned to an ethanol challenge session (Challenge E) and crossed over to a non-ethanol control challenge session (Challenge N). Ethanol mixed with orange juice or orange juice alone was administered with a

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standard dinner at each challenge session. Plasma glucose and serum insulin levels were assessed over approximately a 14 hour interval post-challenge period.

Study Population

Male/female patients with diet-treated Type 2 diabetes between the ages of 40 and 70 years and a body mass index of 22 to 38 kg/m^2 were eligible for the study. Twenty-four (24) subjects were enrolled to ensure that at least 8 patients completed each treatment (BRL 49653C or Placebo).

Treatment and Administration

BRL 49653C oral tablets, 4 mg (Lot number M96239, Formula BD-AA); matching Placebo for BRL 49653C (Lot number M96305, Formula EF-AC) and ethanol (grain alcohol) mixed with orange juice.

Evaluation Criteria

Safety Parameters

Clinical monitoring, adverse experiences, ECGs, vital signs and safety laboratory tests were evaluated.

Pharmacodynamic Parameters

The principle endpoint was the fasting plasma glucose level determined the morning after the challenge session. As a secondary endpoint, pre-dinner plasma glucose concentration and 4 hour post-prandial/ethanol challenge plasma glucose concentration were determined. Additional secondary endpoints included 4 hour post-prandial serum insulin levels, fasting serum insulin levels determined the morning after the challenge session, plasma glucose profile over the post-challenge interval and overnight urinary cortisol : creatinine ratio. Tertiary endpoints included fasting serum glucose, body weight, hematocrit, and hemoglobin obtained during the 8 week treatment period.

Statistical Methods

Pharmacodynamic endpoints were plotted and descriptively summarized. Plasma glucose concentrations following ethanol challenge were analyzed by ANOVA appropriate to the study design. Point estimates and approximate 90% confidence intervals were derived for the ratio of ethanol : non-ethanol challenge for Placebo-treated and BRL 49653C-treated patients. Exploratory analyses to examine the effects of BRL 49653C relative to Placebo were conducted.

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Subject Disposition and Key Demographic Data

Twenty-four (24) adult male and female patients with diet-treated Type 2 diabetes were randomized for treatment. There were 12 subjects in the placebo group with an average age of 60 years (range: 45-69), body mass index (BMI) of 23.3 kg/m^2 (range: 22-24) and fasting serum glucose (FSG) of 183 mg/dL (range: 153-215) and there were 12 subjects in the BRL 49653C group with an average age of 51 years (range: 43-60), BMI of 23.3 kg/m^2 (range: 22-25) and FSG of 181 (range: 133-218). One subject withdrew from the BRL 49653C group due to personal reasons. There were no other withdrawals from the study.

Safety Results

A total of 12 adverse experiences (AEs) were reported for 7 subjects following treatment with study medication. Of these, 9 AEs in 5 subjects occurred following administration of BRL 49653C and 3 AEs in 2 subjects occurred following Placebo. All AEs were mild to moderate in nature. All AEs in the BRL 49653C group were considered by the investigator to be not related or unlikely to be related to administration of study medication and 2 AEs in the Placebo group were probably related to the study medication. There were no deaths or withdrawals due to AEs.

Pharmacodynamics

Compared to non-ethanol challenge, mean plasma glucose concentrations were equivalent prior to dinner and 14 hours following dinner/ethanol challenge. There was a mean increase of 12% in plasma glucose concentrations at 4 hours post ethanol challenge which was within the protocol defined 30% equivalence range. Point estimates and approximate 90% confidence intervals for baseline, 4 hours and 14 hours post dinner/challenge plasma glucose are presented below.

Time	Group	N	Comparison[1]	Point Estimate	Apprx. 90% Confidence Interval	CV_w (%)
0 (h)*	BRL 49653C Placebo	11 12	E:N E:N	0.90 0.90	(0.73, 1.08) (0.76, 1.04)	22.4
4 (h)**	BRL 49653C Placebo	11 12	E:N E:N	1.12 1.04	(1.00, 1.24) (0.95, 1.13)	13.4
14 (h)+	BRL 49653C Placebo	11 12	E:N E:N	1.01 0.96	(0.92 , 1.10) (0.89 , 1.03)	10.8

[1] presented as the ratio of adjusted arithmetic means.
* 0 hour is time prior to dinner
** 4 hours post dinner / challenge
\+ Morning following Challenge, Pre-Breakfast. Primary Endpoint

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Mean insulin concentrations and mean cortisol : creatinine ratios appeared similar in both the BRL 49653C and Placebo groups following ethanol : non-ethanol challenge.

During 8 weeks of dosing prior to dinner/challenge session, mean fasting serum glucose (FSG) concentrations, adjusted for a slight difference on Day 1 predose, was 30 mg/dL ($p = 0.055$) to 32 mg/dL ($p = 0.191$) lower at 7 and 8 weeks of dosing, respectively, in the BRL 49653C treated patients relative to the Placebo treated patients. Following 8 weeks of dosing, mean post-prandial plasma glucose (non-ethanol challenge) (AUC(0-14)/14) was lower in patients treated with BRL 49653C relative to Placebo treated patients, although the differences were not statistically significant; post-prandial serum insulin appeared similar between groups. Mean body weight, hematocrit and hemoglobin were also similar between the two treatment groups prior to, during and following 8 weeks of dosing.

Conclusion

Administration of BRL 49653C 8 mg for 8 weeks was safe and well tolerated in Type 2 diabetic patients. 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.

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REVIEWER'S COMMENTS FOR STUDY 041:

1. Ethanol (0.6 g ethanol per kilogram body weight).
2. Agree with results.

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METABOLISM/EXCRETION

Protocol 49653C/049 Issued June 1997

SB Report BRL-049653/RSD-100J27/2

Title: 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.

Investigator: H. Cowley, M.A., FRCA

Study Center: Clinical Pharmacology Unit, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Harlow, Essex, UK

PK Objective: 1) To investigate the disposition and routes of elimination following single oral and single intravenous administrations of [^{14}C]rosiglitazone to human volunteers; 2) to quantify and structurally characterize the major compound-related components in human plasma and excreta (urine and faeces); 3) to obtain estimates of the absolute bioavailability of rosiglitazone from the radiolabelled solution dose and from the non-radioactive tablet dose.

Study Design: Four healthy male volunteers (age 44 to 57; weight 64 to 101 kg) participated in this open, three-part, semi-randomized (radioactive dose forms only) crossover study. Each subject received, under fasted conditions, either an intravenous infusion of approximately 2 mg [^{14}C]rosiglitazone (46.3 to 50.4 uCi; batch # M96265) over 1 hour, an oral dose of approximately 8 mg [^{14}C]rosiglitazone (71.0 to 72.7 uCi, batch # M96265 plus non-radiolabelled rosiglitazone, batch # U95156) in solution, or an oral 8 mg dose (2 x 4 mg tablet formulation; batch # M96091). Sessions 1 and 2 were separated by at least 28 days, and sessions 2 and 3 by at least 21 days.

Blood samples for the measurement of concentrations of rosiglitazone and total radioactivity were collected predose and at 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours, and 2, 3, 4, 7, 14, 21 and 42 days after oral dosing. Following intravenous administration, blood samples were collected predose and at 0.25, 0.5, 1.0 (end of infusion), 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours and 2, 3, 4, 7, 14, 21 and 42 days after commencing the infusion. Additional blood samples were

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taken for metabolite profiling at 1, 4, 8, 24 and 96 hours after oral administration or after commencement of the infusion of [^{14}C]rosiglitazone.

Urine was collected over an approximate 24 hour period prior to dosing and then 0-6, 6-12, 12-24 hours and each subsequent 24 hour period up to 21 days after dosing. Following session 1 only, 24-hour collections were also made on day 28 and day 36.

Faecal samples were collected over an approximate 24 hour period prior to dosing and over approximate 24 hour periods up to 21 days after each dose. Following session 1 only, 24-hour collections were also made on day 28 and day 36.

During the oral non-radiolabelled dosing arm of the study, blood samples for the measurement of rosiglitazone concentrations were collected predose and at 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24 and 48 hours after dosing.

Cmax, Tmax, AUC(0-inf), and elimination T½ for total radioactivity and rosiglitazone were determined following oral and intravenous administration using non-compartmental methods. Systemic plasma clearance (CL) and steady-state volume of distribution (Vss) were calculated for rosiglitazone following intravenous administration of [^{14}C]rosiglitazone. Absolute bioavailability of rosiglitazone was determined by comparing dose-normalized AUC values after oral (tablet formulation and radiolabelled solution) and intravenous administration. The excretion of radioactivity (expressed as percent of dose) recovered in urine were compared following oral and intravenous administration of [^{14}C]rosiglitazone in order to estimate the percent absorbed.

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

Radioactivity was measured in dose solutions, dose residues, plasma, and urine by direct liquid scintillation counting of samples. Feces were homogenized and samples of the homogenate oxidized prior to [redacted] of the [redacted] Analysis was performed in the Department of Biotransformation, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK.

Selected samples of plasma, urine, and extracts of fecal homogenates were subjected to [redacted] with radiochemical detection, to separate and quantify metabolites in the samples. Appropriate physicochemical techniques, such as

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[redacted] were used to identify any metabolites which accounted for greater than 5% of the administered dose. Analysis was performed in the Department of Biotransformation, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK.

PK Results and Discussion: Subject 2 was withdrawn from the study prior to the third arm (oral tablet formulation) as a result of an adverse experience of mild anemia. The exact doses of [^{14}C]rosiglitazone administered to each subject ranged from 7.90 to 7.98 mg following oral administration and 1.83 to 1.99 mg following intravenous administration. The radiochemical purity of the [^{14}C]rosiglitazone in each administered dose was greater than 99.1%.

The excretion of radioactivity in the urine and feces is given in Table 1. Following both oral and intravenous administration of [^{14}C]rosiglitazone, the major route of excretion was via the urine (mean of 69% and 65% of the dose, respectively). Fecal elimination accounted for a mean of 25% of the dose following both routes of administration. Mean total recoveries of radioactivity of approximately 90% and 94% of the dose were achieved after oral and intravenous administration, respectively. These values were estimated to be 93% and 95% when corrected for non-compliance noted in two subjects. The radioactivity in the feces following both routes of administration was probably due to biliary secretion.

Mean (SD) pharmacokinetic parameters of rosiglitazone and total radioactivity are shown in Table 2. Following oral administration of rosiglitazone or [^{14}C]rosiglitazone, maximum plasma rosiglitazone concentrations were observed between 0.5 and 1.0 hours. Rosiglitazone plasma clearance values were low (2.4 to 3.7 L/h), and the volume of distribution at steady-state was small (9.7 to 19.6 L) after intravenous administration. The elimination half-life was 5 to 7 h for all regimens. The mean absolute bioavailability of the rosiglitazone tablet formulation and radiolabelled oral solution was 99% and 95%, respectively.

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 elimination 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 elimination 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.

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