The metabolite profiles in plasma, feces and urine are shown in Tables 3 to 6. The major circulating metabolite found in human plasma was *para*-hydroxy-sulfate metabolite after both routes of administration. Of lesser importance was the N-desmethyl metabolite. Minor circulating metabolites were the N-desmethyl *para*-hydroxy-sulfate and *ortho*-hydroxy-sulfate metabolites. As plasma clearance of the metabolites of rosiglitazone was much slower than anticipated with quantifiable concentrations of radioactivity out to 21 days postdose, these metabolites are likely to accumulate during repeated daily dosing with rosiglitazone.

The predominant urinary metabolites were the *para*-hydroxy-sulfate (16-18% of the dose) and N-desmethyl *para*-hydroxy-sulfate (18%) metabolites. In addition, *para*-hydroxy-glucuronide metabolite was also excreted in significant amounts in the urine (3-4%). The fecal metabolites which were being excreted a week after dosing were the N-desmethyl *para*-hydroxy (9-11% of the dose) and *para*-hydroxy (6-7%) metabolites, both almost certainly secreted in the bile as their sulphate and glucuronide conjugates.

Table 1
Excretion of Radioactivity (Expressed as Percent of Dose) over 21 Days Following Administration of [^{14}C]Rosiglitazone
(Protocol 49653/049)

Sample	Subject 1	Subject 2	Subject 3	Subject 4	Mean**	SD**
Oral dose (8 mg pfb)						
Urine	[redacted]				65.0	6.18
Faeces					24.7	3.04
Total					89.8	8.36
Intravenous dose (2 mg pfb)						
Urine	[redacted]				69.2	3.63
Faeces					24.7	5.60
Total					94.0	2.06

* Known non-compliance in sample collection occurred (Subject 3: Day 9-17), Subject 4: Day 7)

** Excludes Subject 2 (suspected poor compliance of sample collection after both po. and i.v.)

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Table 2

Mean (SD) Plasma Pharmacokinetic Parameters for Rosiglitazone and Radioactivity following Single Oral (8 mg) and Intravenous (2 mg as 1 Hour Infusion) Doses of [^{14}C]Rosiglitazone and Oral (8mg tablet) Doses of Rosiglitazone to Healthy Male Subjects

(Protocol 49653/049)

Parameter	Rosiglitazone (oral solution) 8 mg	Rosiglitazone (oral tablet) 8 mg	Rosiglitazone (i.v.) 2 mg	Radiolabel (oral solution)	Radiolabel (i.v.)
AUC(0-inf)[a] (ng.h/mL)	2902 (548)	2928 (473)	744 (142)	79400 (9787)	20404 (3094)
Cmax [a] (ng/mL)	564 (19)	603 (332)	146 (40)	885 (173)	226 (43)
Tmax[b] (h)	0.50 (0.50 - 1.00)	0.75 (0.75 - 1.00)	1.00 (0.75 - 1.00)	5.00 (4.00 - 6.00)	6.00 (6.00 - 6.07)
T½ (h)	4.65 (1.51)	4.06 (1.23)	4.16 (1.64)	133 (28)	121 (6)
CL (L/h)	ND	ND	2.78 (0.63)	ND	ND
Vss (L)	ND	ND	15.1 (4.1)	ND	ND
F (%)	94.8 (5.7)	99.2 (11.2)	ND	ND	ND

a Units for radioactivity ng-equivalents

b Tmax expressed as median (range)

ND = Not Determined

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Table 3

Nomenclature of Rosiglitazone and its Metabolites (Protocol 49653/049)

Metabolite number	Short form identity	SB number (where applicable)
1	phenoxyacetic acid derivative	SB-271258
2	N-desmethyl-glucuronide (putative)	-
3	*ortho*-hydroxy-glucuronide	-
4	N-desmethyl-*para*-hydroxy-sulphate	-
5	*para*-hydroxy-glucuronide	-
6	N-desmethyl-*ortho*-hydroxy-sulphate	-
7	N-desmethyl-*para*-hydroxy	SB-280789
8	*ortho*-hydroxy-sulphate	-
9	N-desmethyl-*ortho*-hydroxy	SB-243914
10	*para*-hydroxy-sulphate	SB-332650
11	*ortho*-hydroxy	SB-244675
12	N-desmethyl	SB-237216
13	*para*-hydroxy	SB-275286
14	rosiglitazone	BRL-049653
15	N-desmethyl-glucuronide (putative)	-
16	N-despyridinyl (putative)	-

Table 4

Radiometabolite Quantification of Plasma from Human Subjects Following Single oral (A) or I.V. (B) Administration

(Protocol 49653/049)

A. 8 mg free base [^{14}C]rosiglitazone po.

Metabolite No.	% Plasma Radioactivity					ng BRL-49653 equivalents/g				
	1 h	4 h	8 h	24 h	day 4	1 h	4 h	8 h	24 h	day 4
4	0	2	3	10	11	0	19	25	59	26
8	0	2	2	1	2	2	17	13	3	4
10	18	46	60	65	80	143	365	442	394	172
12	11	15	6	17	4	61	119	120	109	9
14	71	34	19	2	0	545	270	138	14	0
Total Identified	100	99	90	95	97	751	790	738	579	211

B. 2 mg free base [^{14}C]BRL 49653C i.v. administration

Metabolite No.	% Plasma Radioactivity					ng BRL-49653 equivalents/g				
	1 h	4 h	8 h	24 h	day 4	1 h	4 h	8 h	24 h	day 4
4	0	3	5	10	12	0	7	13	14	7
8	0	1	2	1	0	1	4	4	1	0
10	9	44	60	65	86	16	107	142	91	47
12	5	16	17	19	2	9	39	39	27	1
14	86	34	15	3	0	151	82	35	4	0
Total Identified	101	98	99	98	100	177	239	233	137	55

Table 5A. Excretion of radioactivity in the urine (expressed as % of administered radioactive dose) from healthy male subjects following an oral dose (8 mg pfb) of [14 C]rosiglitazone.

Collection Period	Subject 1	Subject 2	Subject 3	Subject 4	Mean	SD
Predose	[redacted]				0.01	0.00
0-6 h	[redacted]				5.43	0.62
6-12 h					6.61	1.06
12-24 h					8.28	1.41
Day 1					20.32	1.62
Day 2					10.91	1.51
Day 3					8.33	0.88
Day 4					4.99	2.08
Day 5					3.67	1.32
Day 6					3.02	0.58
Day 7					2.25	0.54
Day 8					1.79	0.49
Day 9					1.49	0.31
Day 10					1.21	0.24
Day 11					0.95	0.41
Day 12					0.93	0.15
Day 13					0.74	0.07
Day 14					0.70	0.12
Day 15					0.57	0.10
Day 16					0.47	0.07
Day 17					0.42	0.07
Day 18					0.41	0.21
Day 19					0.36	0.10
Day 20					0.32	0.08
Day 21					0.27	0.07
Day 28					0.20	
Day 36					0.06	
TOTAL Days 0-21					62.26	7.50

N.C. - Not Collected

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Table 5B. Excretion of radioactivity in the feces (expressed as % of administered radioactive dose) from healthy male subjects following an oral dose (8 mg pfb) of [14 C]rosiglitazone.

Collection Period	Subject 1	Subject 2	Subject 3	Subject 4	Mean	SD
Predose					0.06	0.06
Day 1					2.56	0.70
Day 2					3.15	1.68
Day 3					4.28	3.50
Day 4					3.97	3.56
Day 5					2.18	1.46
Day 6					1.69	0.47
Day 7					1.29	1.16
Day 8					0.80	0.52
Day 9					0.34	0.09
Day 10					0.49	0.52
Day 11					0.41	0.12
Day 12					0.54	0.41
Day 13					0.62	0.03
Day 14					0.32	0.26
Day 15					0.27	0.26
Day 16						
Day 17						
Day 18					0.53	0.31
Day 19					0.39	
Day 20					0.36	
Day 21					0.31	0.31
Day 28					0.16	
Day 36					0.09	
TOTAL Days 0-21					21.58	6.74

N.C. - Not Collected

S.C. - Sample combined with next collection period

N.S. - No Sample

* - No sample on day 18, data for days 16 and 17 combined

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Table 6A. Excretion of radioactivity in the urine (expressed as % of administered radioactive dose) from healthy male subjects following an intravenous dose (2 mg pfb) of [14 C]rosiglitazone.

Collection Period	Subject 1	Subject 2	Subject 3	Subject 4	Mean	SD
Predose	[redacted]				0.01	0.01
0-6 h	[redacted]				5.44	0.67
6-12 h	[redacted]				6.47	0.51
12-24 h	[redacted]				8.76	0.89
Day 1	[redacted]				20.67	0.58
Day 2	[redacted]				12.57	0.72
Day 3	[redacted]				7.91	1.66
Day 4	[redacted]				5.37	0.85
Day 5	[redacted]				3.90	0.43
Day 6	[redacted]				3.20	1.44
Day 7	[redacted]				1.82	1.13
Day 8	[redacted]				1.91	0.55
Day 9	[redacted]				1.52	0.26
Day 10	[redacted]				1.19	0.47
Day 11	[redacted]				1.21	0.19
Day 12	[redacted]				0.98	0.26
Day 13	[redacted]				0.82	0.20
Day 14	[redacted]				0.75	0.15
Day 15	[redacted]				0.61	0.13
Day 16	[redacted]				0.51	0.06
Day 17	[redacted]				0.46	0.14
Day 18	[redacted]				0.43	0.06
Day 19	[redacted]				0.34	0.12
Day 20	[redacted]				0.32	0.04
Day 21	[redacted]				0.24	0.11
Day 28	[redacted]				0.12	
Day 36	[redacted]				0.05	
TOTAL Days 0-21	[redacted]				66.28	6.62

N.C. - Not Collected

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ON ORIGINAL

Table 6B. Excretion of radioactivity in the feces (expressed as % of administered radioactive dose) from healthy male subjects following an intravenous dose (2 mg pfb) of [14 C]rosiglitazone.

Collection Period	Subject 1	Subject 2	Subject 3	Subject 4	Mean	SD
Predose					0.07	0.06
Day 1					1.81	3.04
Day 2					5.64	1.29
Day 3					5.02	0.65
Day 4					3.44	2.26
Day 5					3.42	1.19
Day 6					1.57	1.02
Day 7					0.92	0.58
Day 8					0.98	1.10
Day 9					1.01	0.42
Day 10					0.66	0.41
Day 11					0.40	0.15
Day 12					0.43	0.20
Day 13					0.42	0.38
Day 14					0.43	0.32
Day 15					0.30	0.14
Day 16						
Day 17						
Day 18					0.69	0.17
Day 19						
Day 20						
Day 21					0.46	0.20
Day 28						
Day 36						
TOTAL Days 0-21					25.17	4.66

N.C. - Not Collected

S.C. - Sample combined with next collection period

N.S. - No Sample

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 049:

1. 4mg tablet is clinical tablet formulation.
2. Radioactivity excreted for extended period ; >21 days.
3. CL and Vss estimates after IV are very close to POP PK estimates.

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PROTEIN BINDING (*IN VITRO*)

Protocol D92240/49653 Issued August 1993

SB Report BF-1002/BRL-049653/1

Title: Investigation into the binding of ^{14}C-BRL-49653 to rat, dog and human plasma proteins *in vitro*

Investigator: B. Smith

Study Center: Drug Discovery Department, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK

Objective: To determine the degree of plasma protein binding of rosiglitazone in rat, dog, and man and to determine the extent of binding to human serum albumin and α_1-acid glycoprotein.

Study Design and Methods: *In vitro* plasma protein binding of ^{14}C-rosiglitazone in rat, dog, and human plasma (EDTA as anticoagulant) and binding to human serum albumin and α_1-acid glycoprotein were carried out by equilibrium dialysis in teflon cells at 37°C for 4 hours in separate experiments. Samples were quantitated by determination of radiochemical content using liquid scintillation counting.

In man, plasma protein binding of ^{14}C-rosiglitazone was carried out over a concentration range of 0.3 to 100 ug/mL. Only results in man are summarized. Binding of ^{14}C-rosiglitazone to human serum albumin and α_1-acid glycoprotein were carried out at concentrations of 40 mg/mL and 0.6 mg/mL, respectively.

Results: In human plasma, the protein binding of ^{14}C-rosiglitazone was high with an overall mean of 99.8% ± 0.03%. The protein binding was linear over the concentration range 0.3 - 100 ug/mL in human plasma. Rosiglitazone was highly bound to human serum albumin (99.8%), whereas, there was poor association of ^{14}C-rosiglitazone with human α_1-acid glycoprotein (23.2 - 34.4%).

Conclusion: The plasma protein binding in man was high and linear over a wide concentration range (0.3 to 100 ug/mL). Serum albumin appeared to be the main protein responsible for the high protein binding of rosiglitazone in human plasma.

REVIEWER'S COMMENTS FOR STUDY D92240

1. Acceptable.

BLOOD CELL PARTITIONING (*IN VITRO*)

Protocol D92242/49653 Issued August 1993

SB Report BF-1001/BRL-049653/1

Title: Blood cell partitioning of ^{14}C-rosiglitazone in male rat, dog and human blood.

Investigator: B. Smith and S. E. Yeulet

Study Center: Drug Discovery Department, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK

Objective: To estimate the *in vitro* blood cell partitioning of rosiglitazone in blood from rat, dog and man.

Study Design and Methods: Blood samples taken from rat, dog and man were taken and a hematocrit was determined for each sample. Each blood sample was incubated with ^{14}C-rosiglitazone at 37°C for 60 minutes. The amount of radioactivity in triplicate aliquots of each blood and plasma sample were quantified by liquid scintillation counting.

In man, blood cell partitioning of ^{14}C-rosiglitazone (as free base) was carried out over a concentration range of 0.03 to 30 ug/mL. Only results in man are summarized.

Results: In human blood, the blood:plasma ratio of ^{14}C-rosiglitazone was similar between the four subjects with individual mean ratio of 0.56, 0.52, 0.57, and 0.60, respectively. The overall mean was 0.57 (± 0.04). The majority of the drug was present in the plasma (at least 85%). The blood to plasma ratios in man appeared to be independent of concentration.

Conclusion: The mean blood:plasma concentration ratio of ^{14}C-rosiglitazone was 0.57 in man and was independent of concentration over the concentration range of 0.03 to 30 ug/mL). The majority of the drug was present in the plasma (at least 85%).

REVIEWER'S COMMENTS FOR STUDY D92242:

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P450 INHIBITION (*IN VITRO*)

Protocol D92226/49653 Issued July 1995

SB Report BF-1030/BRL-049653/1

Title: An *in vitro* investigation of the potential for drug interactions involving BRL-49653 and the human cytochrome P450s 1A2, 2A6, 2C9/8, 2C19, 2D6, 2E1, 3A and 4A

Investigator: S.J. Baldwin

Study Center: Department of Biotransformation, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK

Objective: To identify the cytochrome P450 enzyme(s) involved in rosiglitazone metabolism, to determine the potential of rosiglitazone to inhibit the human cytochrome P450 enzymes 1A2, 2A6, 2C9/8, 2C19, 2D6, 2E1, 3A and 4A

Methods: The products of metabolism were investigated by [redacted] of 10 nM rosiglitazone with human liver microsomes followed by [redacted] The effects of the selective P450 inhibitors furafylline, sulphaphenazole, quinidine and ketoconazole on the metabolism of rosiglitazone in human liver microsomes was investigated to indicate the extent of involvement of CYP1A2, 2C9, 2D6, and 3A, respectively. Assays were performed with 10 uM [^{14}C]rosiglitazone in human liver microsome in the presence and absence of each selective P450 inhibitor. Inhibition of cytochrome P450 related activities by rosiglitazone was examined using assays for caffeine N3-demethylase (1A2), coumarin 7-hydroxylase (2A6), tolbutamide hydroxylase (2C9/8), S-mephenytoin 4-hydroxylase (2C19), bufuralol 1'-hydroxylase (2D6), lauric acid ω-1 hydroxylase (2E1), cyclosporine oxidase (3A) and lauric acid ω-hydroxylase (4A) in human liver microsomes in the absence and presence of rosiglitazone (0.1 and 250 uM). For each assay, incubations were performed in duplicate with microsomes from three livers. Additional incubations of [^{14}C]rosiglitazone (10 uM) were performed with expressed microsomes (CYP1A2, 1A2, 2A6, 2B6, 2C9, 2E1, 2D6, and 3A4). Incubates were analyzed by [redacted]

Results: Pyridine ring hydroxylation and N-demethylation were identified as the major products of metabolism in human liver microsomes. Rosiglitazone caused some inhibition of tolbutamide hydroxylase (2C9/8), but no significant inhibition was observed with all other enzymes examined. Results with the selective P450

inhibitors suggested that CYP2C9 and to a small extent CYP3A4 and CYP1A2 contributed to the metabolism of rosiglitazone. Similar results were observed in the P450 expression systems. However, the majority of the activity present in human liver microsomes could not be contributed to these three enzymes or to the P450 enzymes CYP1A1, 2A6, 2B6, 2D6, and 2E1, as shown by the expressed P450 activities.

Although rosiglitazone appears to be a P450 substrate, the specific enzyme(s) responsible for the majority of its metabolism have not been identified. Furthermore, rosiglitazone did not significantly inhibit any of P450 related enzyme activities tested with the exception of a small effect on CYP2C9/8. Taken together, these results suggest that rosiglitazone has little potential to cause clinically significant cytochrome P450 mediated drug-drug interactions.

Conclusions: The major P450 enzyme(s) responsible for the metabolism of rosiglitazone in human liver microsomes could not be identified. Several human P450 enzymes were capable of metabolizing rosiglitazone including CYP2C9, 1A2 and to a small extent CYP3A4. Rosiglitazone caused no significant inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A and 4A.

REVIEWER'S COMMENTS FOR STUDY D92226:

1. Acceptable.

P450 INHIBITION (*IN VITRO*)

Protocol D96044/49653 Issued December 1996

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

Title: A further *in vitro* investigation of the human cytochrome P450 enzymes involved in the metabolism of BRL-49653

Investigator: S.J. Baldwin

Study Center: Department of Biotransformation, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Herts, UK

Objective: To identify the human cytochrome P450 enzyme(s) involved in rosiglitazone metabolism, and to determine the potential of rosiglitazone to inhibit the human cytochrome P450 enzyme CYP2C8.

Methods: [^{14}C]-Rosiglitazone at a final concentration of 10 uM, was incubated with human liver microsomes (n=47) and microsomes from insect cells transfected with human cytochrome P450 cDNA, CYP2C8 and CYP2C9-Arg$_{144}$. The products of [^{14}C]-rosiglitazone metabolism were investigated using [redacted] The effect of retinoic acid on the metabolism of rosiglitazone in human liver microsomes was investigated to indicate the involvement of CYP2C8. Incubations of [^{14}C]-rosiglitazone (10 uM) were performed in the presence and absence of 142 uM retinoic acid (a CYP2C8 inhibitor) in human liver microsomes from three human livers. The inhibitory potential of rosiglitazone on taxol 6α-hydroxylase (CYP2C8) was investigated using an assay in human liver microsomes (n=3) performed in the presence and absence of rosiglitazone over a concentration range of 0.5 to 200 uM. The percentage of inhibition of taxol 6α-hydroxylase by rosiglitazone was determined and IC_{50} values calculated. Tests for statistical significance were performed using SAS/INSIGHT®.

Results: Rates of rosiglitazone 3-hydroxylation and N-demethylation varied over 35-fold in the human livers tested. The formation of 3-hydroxy and N-desmethyl rosiglitazone were inhibited by retinoic acid (greater than 50%). The rate of formation of these two metabolites were found to correlate with taxol 6α-hydroxylation ($p<0.001$) in a bank of human livers and both metabolites were produced by CYP2C9-Arg$_{144}$ and more significantly CYP2C8 supersomes.

Rosiglitazone also had a moderate inhibitory effect on taxol 6α-hydroxylase activity, with a mean IC_{50} of 18 uM.

These data indicate that CYP2C8 is the predominant P450 enzyme responsible for the major metabolic pathways of rosiglitazone, and rosiglitazone has moderate potential to inhibit CYP2C8. The implication of these results with respect to predicting possible drug-drug interactions with rosiglitazone is uncertain, as limited information exists regarding inhibitors or substrates of CYP2C8 in man, *in vivo*.

Conclusions: CYP2C8 is primarily responsible for the hydroxylation and N-demethylation of rosiglitazone in human liver with minor contributions from CYP2C9. Rosiglitazone is a moderate inhibitor of CYP2C8 activity in human liver microsomes.

REVIEWER'S COMMENTS FOR STUDY D96044:

1. Metabolism is 2C family.

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Appendix 3. POP PK Analysis Review

Pharmacometrics Consult

NDA:	21-071
Rosiglitazone Maleate (Avandia®)	
Original Submission Date:	25 November 1999
Sponsor:	SmithKline Beecham
Type of Submission:	New Drug Application (1P) – Population Pharmacokinetics Analysis of Rosiglitazone In Patients with Type 2 Diabetes Mellitus
Primary Reviewer:	Robert Shore
Medical Division:	DMEDP (HFD-510)
Reviewer:	Michael J. Fossler

Submission

The Pharmacometrics group was consulted by Dr. Robert Shore concerning the design and interpretation of a population pharmacokinetics analysis undertaken by the firm in support of their NDA for rosiglitazone, a thiazolidinedione proposed for the treatment of Type 2 diabetes mellitus.

Study Design

Data

The data for this analysis came from three Phase 3 studies in patients with Type 2 diabetes mellitus. Each study is described in Table 1. Plasma concentration data for all subjects deemed to be evaluable for the purposes of this analysis (data exclusion criteria will be described later) were formatted for mixed-effect modeling, along with demographic data such as gender, weight, age, race, and alcohol and tobacco use. For each subject, the study the data were from, as well as the dosing occasion were also recorded.

Data were excluded from the analysis during the data set creation phase under the following criteria:

- Date/time of sample or dose event missing;
- If the time of the dose was recorded to be at the exact same time as the sample, or was recorded to be after the sample time;
- Doses reported after the last observed plasma concentration;

In addition, two patients from Study 024 were removed based on the fact that they used sulfonylurea drugs during the study (a protocol violation).

A total of 69 observations were excluded from the final dataset based on the preceding criteria. In addition, an additional 34 observations in Studies 011 and 015 (where only trough and peak concentrations were drawn) were found to be transposed (pre-dose concentrations were very high, post-dose concentrations were very low or zero). These were left in, but the pre- and post-dose concentrations were switched to conform with what was expected.

Table 1: Description of studies used for the population analysis.

Study	Design and sampling scheme	# patients randomized/included in pop. PK analysis
49653/024	26-week, randomized, double-blind, multi-center (65), placebo-controlled parallel group study comparing 2 doses and 2 regimens (2 mg BID, 4 mg qD, 4 mg BID, 8 mg qD) to placebo. Two samples were taken at week 4, 1 prior to dosing and one between 0.5-2 hours post-dose. At week 12, one sample was taken 3-5 hours post-dose, and one at week 26 between 6 and 10 hours post-dose.	959/603
49653/011	26-week, randomized, double-blind, multi-center (43), placebo-controlled parallel group study comparing rosiglitazone 2 mg BID and rosiglitazone 4 mg BID to placebo. Samples were taken just prior to dosing and 1 hour post-dose at weeks 4, 12, and 26.	533/330
49653/015	26-week, randomized, double-blind, multi-center (60), placebo-controlled parallel group study comparing rosiglitazone 1 and 2 mg BID in patients on background sulfonylurea therapy. Samples were taken just prior to dosing and 1 hour post-dose at weeks 4, 12, and 26.	593/376

The initial dataset was then randomly split, with 80% going to the model-building set, and 20% held as a validation set. Characteristics of the patients in the model-building data set are shown in Table 2.

Table 2: Patient Demographics for the Model-building dataset.

Demographic	Mean (Range) or Distribution
Age	35-80
Weight	48-150 kg
Gender	642 men, 405 women
Race	White: 839, Black:131, Other:77
Tobacco Use	134 smokers, 913 non-smokers
Alcohol Use	698 drinking, 349 non-drinking

An outlier analysis was then performed on the existing data. A baseline PK model was fit (without covariates) and the weighted residuals inspected. Any observation with a weighted residual $\geq |6|$ were excluded from the combined dataset1. A total of 22 observations (0.42% of total) were excluded based on this analysis. It was found that these concentrations were extremely high relative to other data, and so likely represented erroneous measurements. Once the final PK model was developed, the model was re-run with the outliers included to determine the impact their deletion had on any final conclusions.

Pharmacokinetic and Statistical Models

Based on previous Phase 1 data, a one-compartment model with first-order absorption was used for the PK model, parameterized in terms of clearance (CL/f), volume of distribution at steady-state (Vss/f), and absorption rate constant (k_a).

Inter-individual variability for each parameter was modeled as a constant coefficient of variation model. Residual error was modeled as a additive/proportional model. Since, in the studies used for the analysis, data were collected on several occasions, inter-occasional variability was also modeled to account for

1 This is quite conservative; generally, weighted residuals of $\geq |3|$ are considered "large"

within-subject changes in CL/f, Vss/f, or both occurring from one sampling occasion to another. The control streams for both the basic and final models are located in the Appendix.

Covariate Analysis

An examination of the covariates listed in Table 2 was undertaken after the final form of the pharmacostatistical model was established. Plots of post-hoc parameter estimates of Cl/f and Vss/f as a function of each covariate were made in order to determine whether these factors would explain any variability. Those covariates which appeared to explain variability in of Cl/f and/or Vss/f were added to the population model in a linear fashion. A drop in the objective function of > 3.841 of the full model relative to the reduced model was considered significant.

For the final model, the covariates which were shown above to influence the PK of rosiglitazone were added in descending order of magnitude. The parameter was retained if its inclusion resulted in a 10 point change in the objective function, as well as improvement in diagnostic plots (e.g., weighted residuals vs. predicted concentrations).

Results

Base Model

Table 3 shows a summary of the results of the base model (without covariates). It was found that the inter-subject variability for ka was consistently poorly-estimated throughout the building of the basic model. This is most likely due to the fact that there were too few data points in the absorption phase. Therefore, the value for ka was fixed to the mean value (5.37 hr^{-1}) based on the results of a sensitivity analysis which showed that the model fit was not significantly affected by changes in ka above this value (Figure 1). The other PK parameters are estimated with very good precision, as are their estimates of inter-individual variability. Inter-occasion variability ranges between 26 and 38%. Random residual variability is about 35%, and is estimated with reasonable precision. Figure 2 shows a plot of the individual observed vs. predicted values. Some bias is evident at the high end, which hopefully will be accounted for in the final model.

Table 3: Results Summary for the Basic PK model (without covariates)

Parameter	Mean (†precision)	Interindividual CV% (†precision)
ka (hr^{-1})	5.37 (fixed)	Not estimated
CL/f (L/hr)	2.4 (1.6)	33.3 (10.2)
Vss/f (L)	17.6 (1.9)	29.7 (14.0)
††IOV in CL at weeks 4, 12, 26 (†precision)	33.0 (18.4), 25.7 (29.9), 38.1 (18.3)	
††Random Residual Error (†precision)	34.5 (9.5)	

†expressed as %CV
††expressed as % CV

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Figure 1: Sensitivity analysis for ka. The fit of the model is essentially unaffected for values of ka above 5.37 hr^{-1}.

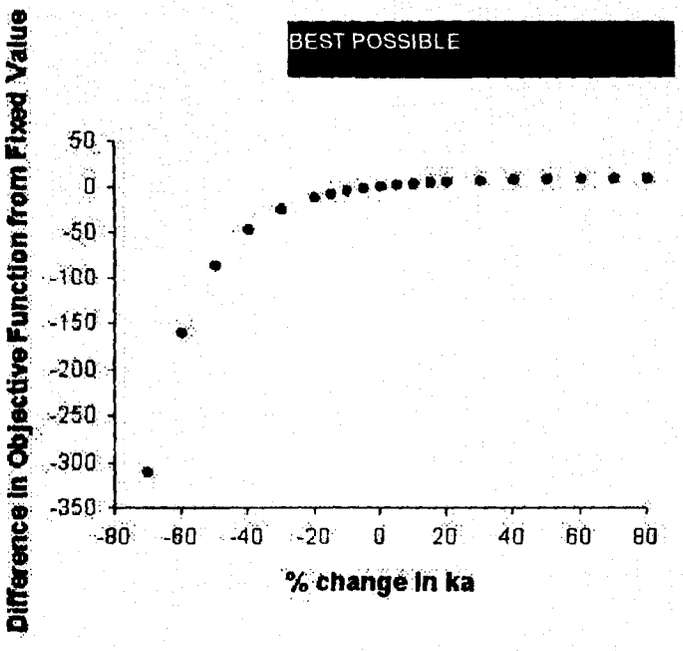

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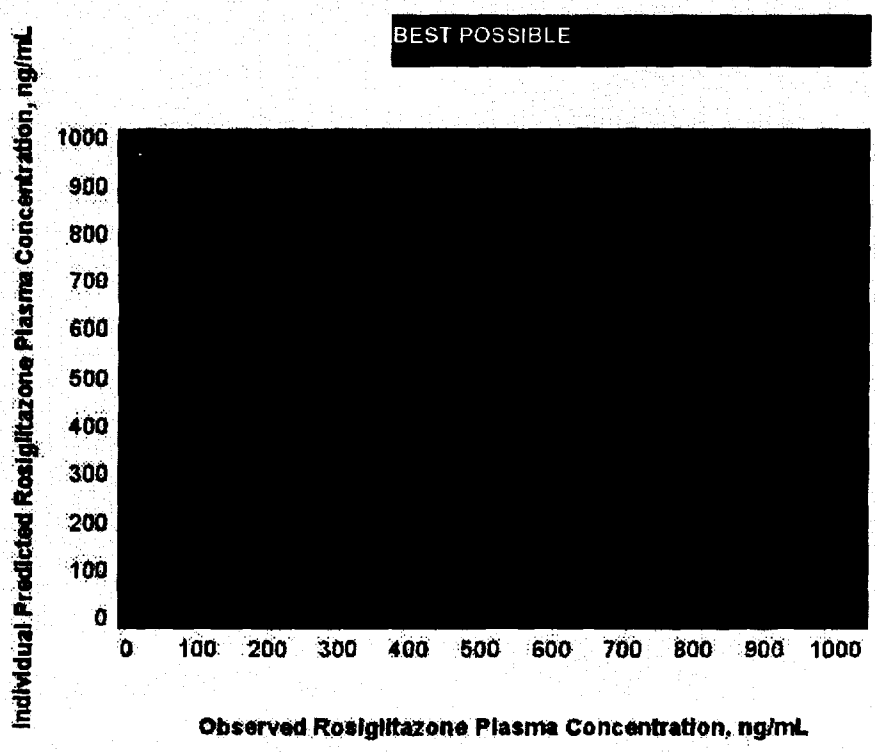
Figure 2: Individual observed vs. predicted rosiglitazone plasma concentrations for the base model. The solid line is the y=x line.



Final Model

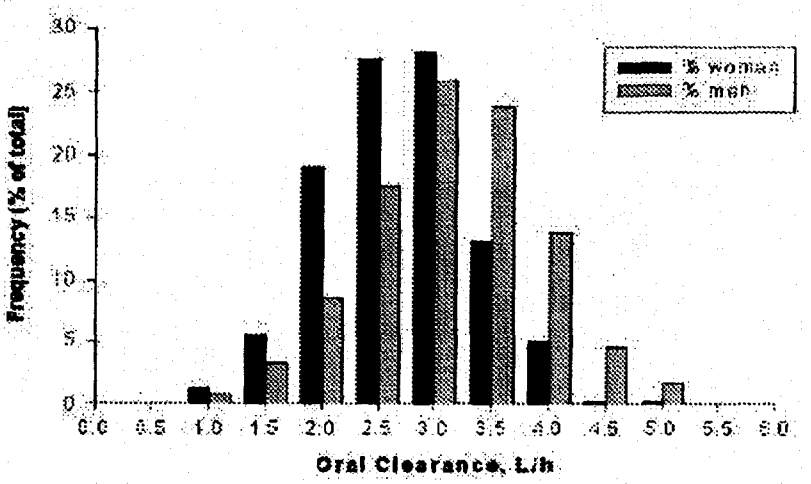
Parameter estimates for the final model are shown in Table 4. Weight and gender were found to affect rosiglitazone clearance and volume in a linear fashion, although the effects are quite modest. At a given weight, clearance for women is about 6% lower than for men. Since weight also affects clearance, the net mean gender difference in clearance between men and women is about 15%, with women having lower values than men on average (Figure 3). However, about 21% of the men studied had clearance values of 4 or greater, whereas virtually none of the women have clearances above 4 L/hr.

Table 4: Results Summary for the Final PK Model

Parameter	Mean (†precision)	Interindividual CV% (†precision)
ka (hr^{-1})	5.37 (fixed)	Not estimated
θ_1	5.23 (30.4)	23.2 (23.0)
θ_2	0.151 (13.1)	
	$Vss = \theta_1 + \theta_2 * weight$	
θ_3	1.41 (19.6)	31.2 (11.7)
θ_4	0.0127 (24.5)	
θ_5	0.942 (4.4)	
	$Cl_{men} = \theta_3 + \theta_4 * weight$ $Cl_{women} = \theta_5 * Cl_{men}$	
††IOV in CL at weeks 4, 12, 26 (†precision)	33.8 (18.0), 26.4 (29.7), 38.5 (17.8)	
††Random Residual Error (†precision)	34.8 (9.2)	

†expressed as %CV
††expressed as % CV

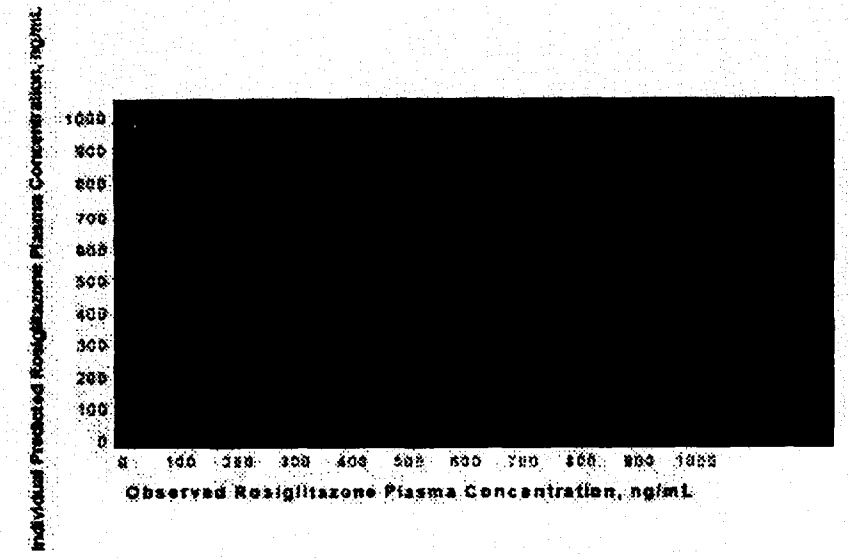
Figure 3: Distribution of individual post-hoc estimates of rosiglitazone clearance in men and women. The mean clearance in men is 2.73 L/hr, in women: 2.31 L/hr; however, more than 20% of the clearance values for males are 4 l/hr or above

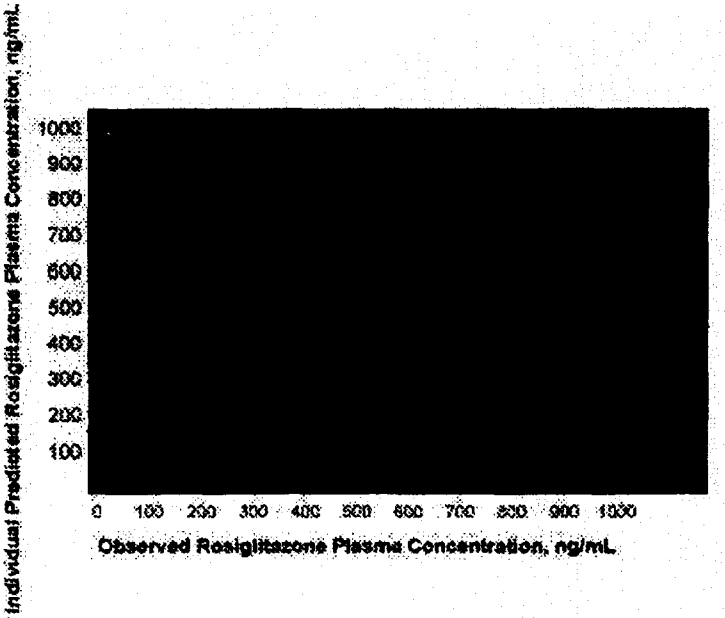


Despite the inclusion of these covariates, the fit of the final model (Figure 4) was not drastically better than the base model (Figure 2), although the drop in objective function between the base and final models (197.95 points) is clearly statistically significant. Based on the magnitude of the effects of the covariates on the pharmacokinetics of rosiglitazone, this is not an unexpected result.

Figure 5 shows the results of using the model results as priors and using Bayesian estimation to predict individual concentrations for patients in the validation data set. Good agreement between observed and predicted was obtained.

Figure 4: Individual observed vs. predicted rosiglitazone plasma concentrations for the final model. The solid line is the y=x line.





Inclusion of the deleted outliers had no discernable effect on the results (data not shown).

Concomitant Medication Analysis

hypoglycemics, analgesics, calcium channel blockers, hypolipidemics, Ace inhibitors, and steroid hormones) was examined graphically using box-whisker plots. No concomitant class of medication was

Reviewer Comments

1) The firm has performed a very thorough and complete population analysis for this compound. Regarding the gender difference in the PK of rosiglitazone, it is interesting to note that in all of the

   example, in Study 011, the mean change in glycohemoglobin in men after 26 weeks of therapy (4 mg BID) was –0.3; that in women at the same dose was –1.1. At first glance, it appears unlikely that the difference in clearance could explain much of this clinical observation, since the mean differences in

   fact that more than 20% of the men studied in this PK analysis had rosiglitazone clearance values in the range of 4-5 L/hr suggests that at least a portion of the men receiving this compound might be under-

   Therefore, the reviewer asked the firm to supply plots from the major PK/PD studies (49653/011 and /20) investigating the effect of clearance and AUC on the clinical efficacy of the compound in men and women. Representative plots are shown below (Figure 6a-b). Neither rosiglitazone clearance nor

   may be more effective in women due to the fact that rosiglitazone binds with high affinity to PPARγ

   a given body weight, this may explain at least part of the gender differences seen in clinical efficacy.

2) The firm has included the following in their drug interaction labeling for rosiglitazone:

Concomitant Medications in Phase III Clinical Trials: Results of the population

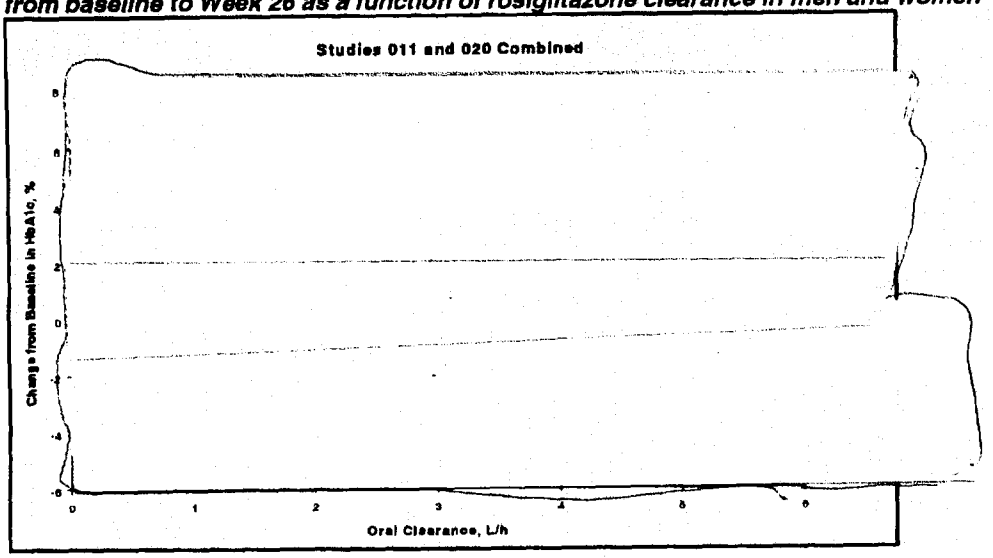
medications (oral hypoglycemics, analgesics, calcium channel blockers, hypolipidemics, ACE inhibitors and steroid hormones) appear to alter the oral
Avandia.

for labeling purposes for the following reasons:

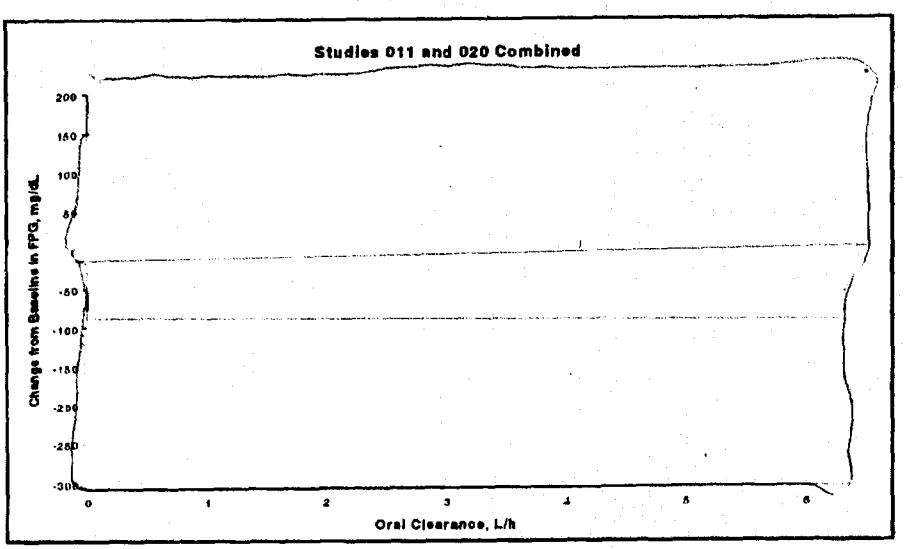
- The compounds are grouped by therapeutic class, rather than by a more meaningful classification such as metabolizing isozyme. Thus, the results do not generalize to individual drugs, nor could
- future as applying to compounds which were not even approved at the time the studies were performed.

Therefore, the reviewer will recommend that this statement be deleted.

Figure 6: Change in (a) hemoglobin A_{1c} or (b) fasting plasma glucose from baseline to Week 26 as a function of rosiglitazone clearance in men and women



(a)



(b)

1) [redacted] 2.

Population Pharmacokinetics in Patients with Type 2 Diabetes

and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the

alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of

weight range observed in these analyses (50 to 150 kg), the range of predicted

rosiglitazone CL/F was shown to be lower (about ——15%) in female patients as compared with males. ————————————————--The population mean CL/F of rosiglitazone for a typical male weighing 84 kg was 2.48 L/h. The Vss/F in an 84 kg patient was 17.9 L. The inter-patient variability in CL/F and Vss/F were 31% and 23%, respectively.

2) The following text on page 12 should be deleted;

[redacted]

Michael J. Fossler, Pharm.D., Ph.D.

Pharmacometrics
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-071(orig., 1 copy), HFD-850(Lesko, Ray Miller, Metz), HFD-870(M.Chen, Ahn, Fossler,)

2 The reason for this change is that , when both weight and gender are taken into account, the overall clearance difference between men and women is about 15% (see Figure 3, above).

Appendix:

Basic Model NONMEM Control Stream

Final Model NONMEM Control Stream

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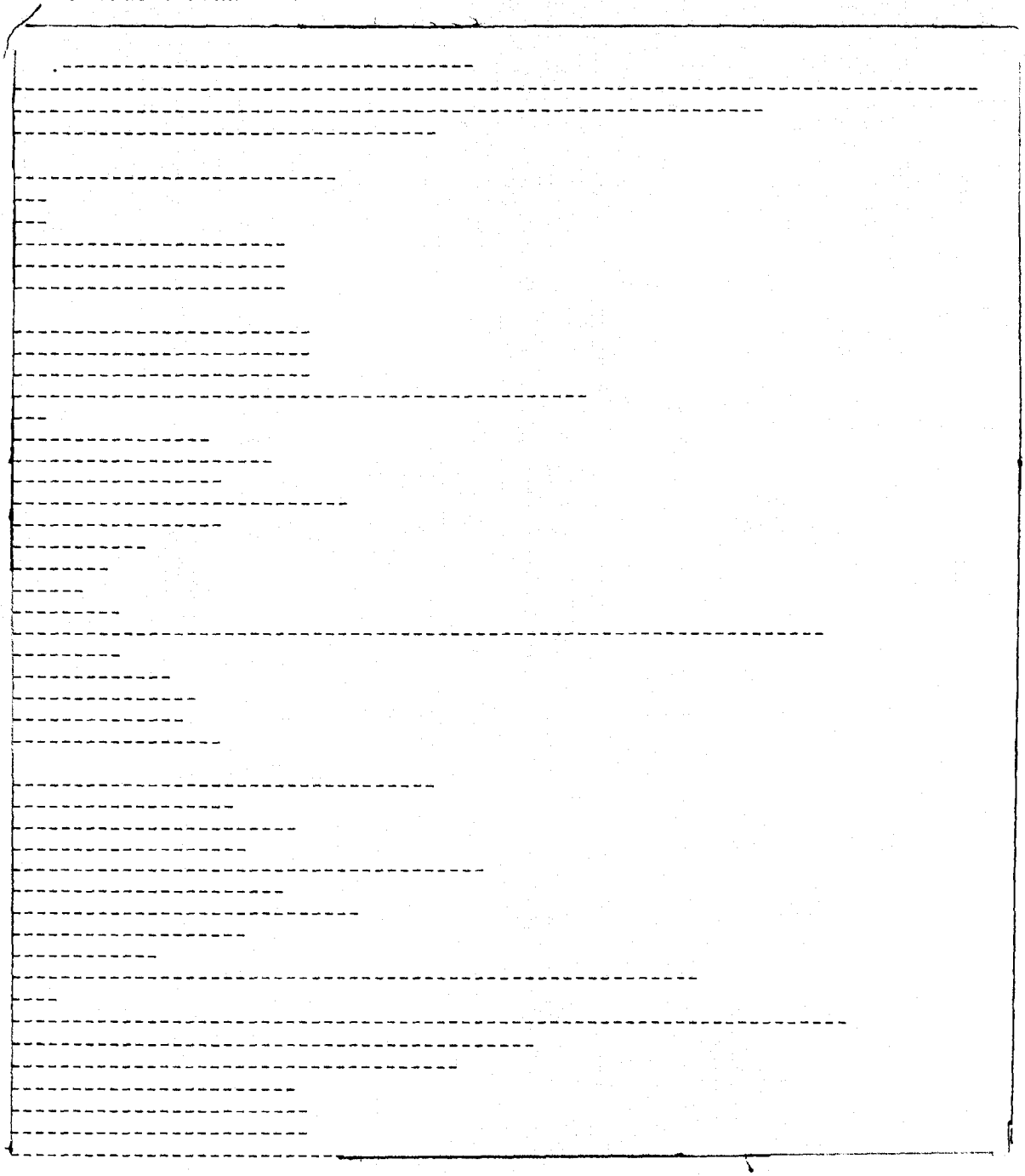
Basic Model NONMEM Control Stream



Final Model NONMEM Control Stream

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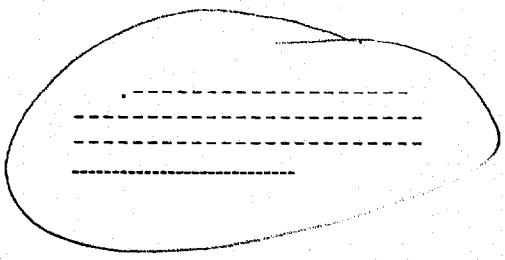

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Appendix 4. PK/PD Analysis

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II (HFD-870)
Pharmacometrics Group

Memorandum

To:	Robert Shore Hae-Young Ahn, Team Leader
From:	Michael J. Fossler Pharmacometrics
Date:	4/1/99
Re:	PK/PD of rosiglitazone

This memo summarizes the relationship between the steady-state exposure of rosiglitazone and its effect on hemoglobin A_{1c} and fasting plasma glucose. The three studies use in the analysis are described in Table 1. The sponsor analyzed these data by plotting the efficacy parameters of interest (Δhemoglobin A_{1c}, Δfasting plasma glucose) as a function of post-dose plasma concentrations of rosiglitazone. At the request of Pharmacometrics, the firm re-analyzed the data by using AUCss in place of individual plasma concentrations, and looking at men and women separately. The AUCss values for each subject were estimated using the population PK model developed by the firm, which was previously reviewed by Pharmacometrics. The individual plots for each study are shown below.

The following points summarize the conclusions that may be drawn from the three studies:

- Overall, there is a significant difference in response when the data are stratified by sex, with women appearing to derive more benefit from the drug than men. As noted in the review of the population PK analysis, the gender differences in PK explain very little of this difference in efficacy.

- There is a weak relationship between exposure and clinical response in women, as may be seen from the smooths[1] plotted on each graph. For men, this relationship also holds, but is much weaker, in general.

- The explanation for the lack of a strong concentration-response relationship is unclear. Some possible explanations are:

    1. The effect compartment is not closely linked to the plasma;
    2. The concentration-response curve is very steep, so that consequently even minimal drug exposure results in maximal effect;
    3. Unknown individual patient characteristics (degree of baseline insulin resistance, compliance to diet and drug therapy, etc) are obscuring the true relationship between drug exposure and efficacy.

[1] second order polynomial

Table 1: Description of studies used for the population and PK/PD analyses.

Study	Design and sampling scheme	# patients included in pop. PK/PD analysis (men/women)
49653/024	26-week, randomized, double-blind, multi-center (65), placebo-controlled parallel group study comparing 2 doses and 2 regimens (2 mg BID, 4 mg qD, 4 mg BID, 8 mg qD) to placebo. Two samples were taken at week 4, 1 prior to dosing and one between 0.5-2 hours post-dose. At week 12, one sample was taken 3-5 hours post-dose, and one at week 26 between 6 and 10 hours post-dose.	298/186
49653/011	26-week, randomized, double-blind, multi-center (43), placebo-controlled parallel group study comparing rosiglitazone 2 mg BID and rosiglitazone 4 mg BID to placebo. Samples were taken just prior to dosing and 1 hour post-dose at weeks 4, 12, and 26.	217/113
49653/020	This was a phase IIIa, multicentre, double blind, parallel group comparative study of two doses of rosiglitazone vs. glibenclamide therapy (titrated to optimal effect over 12 weeks), administered to patients with type 2 diabetes mellitus. After a 6 week run-in (placebo for 4 weeks), patients were randomly allocated to receive 52 weeks treatment with glibenclamide, rosiglitazone 2mg bd or 4mg bd. All patients had blood samples taken for PK analysis after 4, 26 and 52 weeks of treatment. Plasma concentration of rosiglitazone was measured pre-dose and c. 60 minutes post dose.	113/229 (rosiglitazone arms only)

Figure 1: Δ $HgbA_{1c}$ vs. steady state rosiglitazone AUC in Study 011

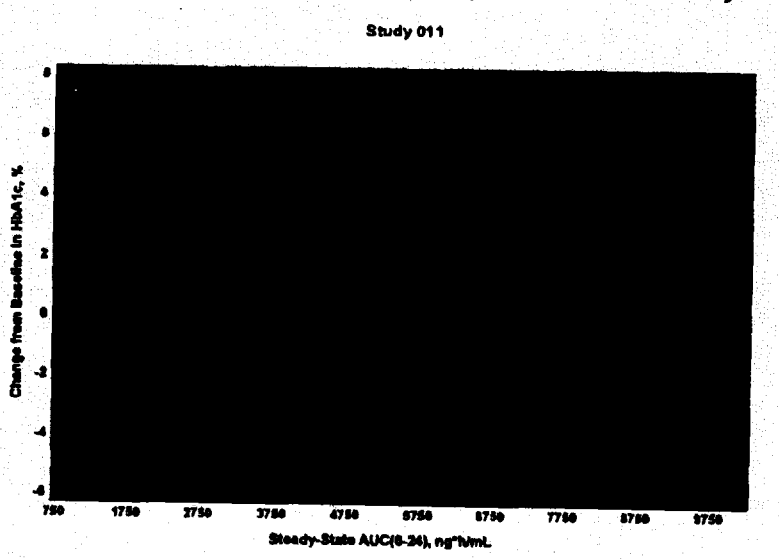


Figure 2: Δ FPG vs. steady state rosiglitazone AUC in Study 011

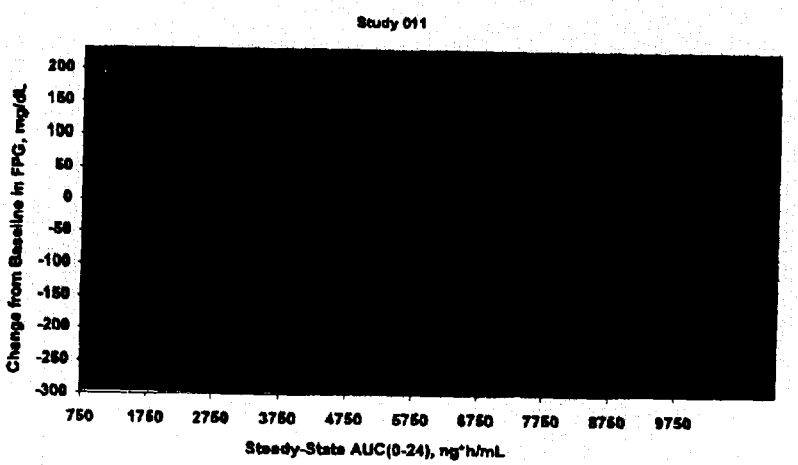


Figure 3: Δ $HgbA_{1c}$ vs. steady state rosiglitazone AUC in Study 020

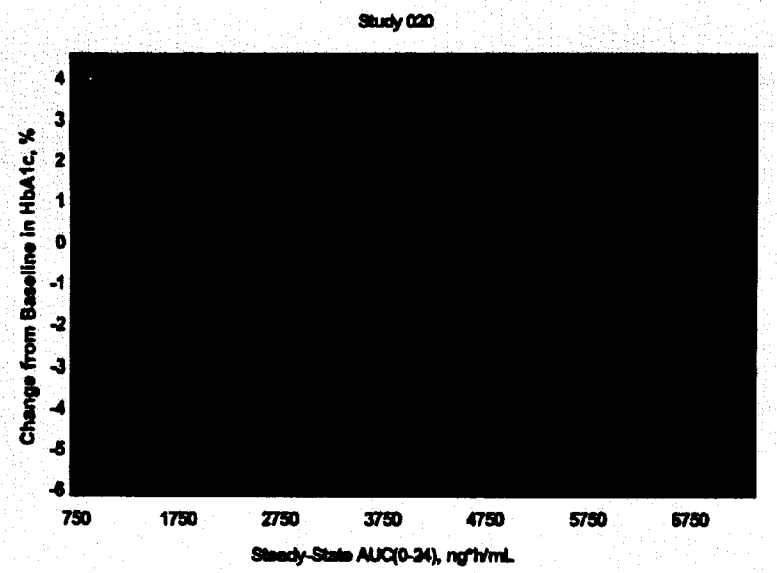


Figure 4: Δ FPG vs. steady state rosiglitazone AUC in Study 020

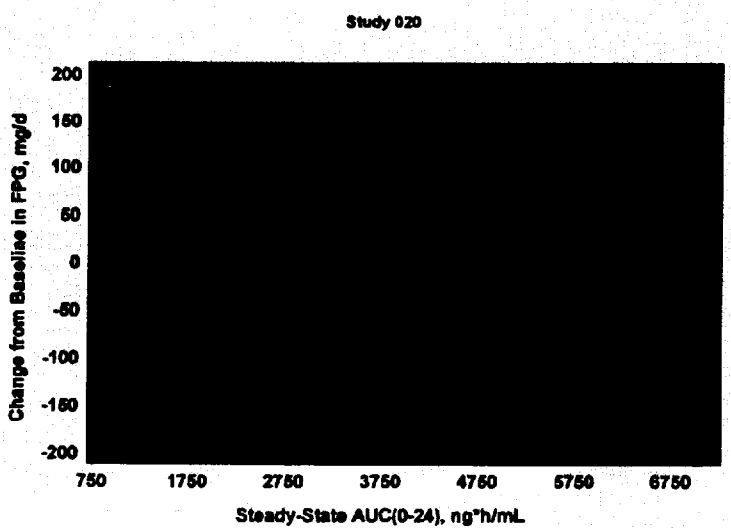
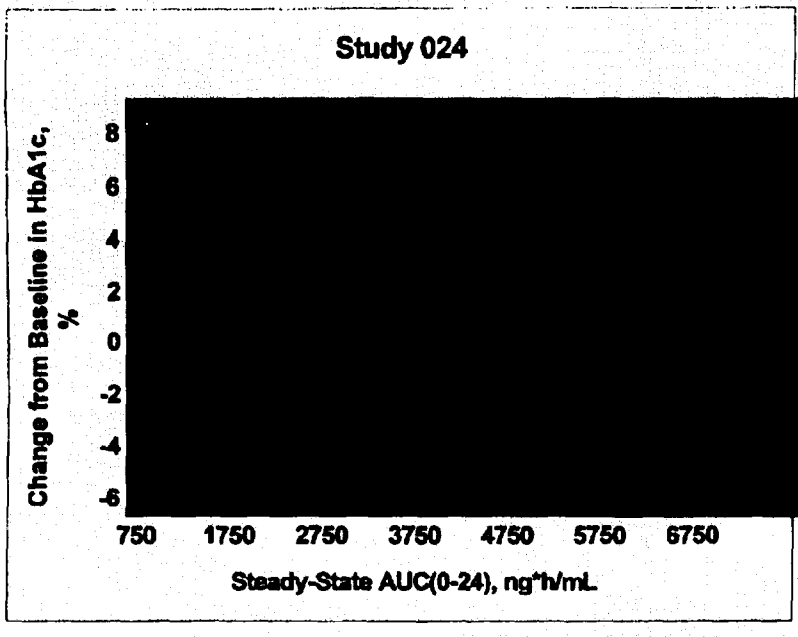


Figure 5 : Δ $HgbA_{1c}$ vs. steady state rosiglitazone AUC in Study 024 Fasting plasma glucose data from this study not available to reviewer



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Appendix 5. Formulation

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14 Pages
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021071

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS