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RESEARCH**

APPLICATION NUMBER:

21-700

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

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-700	Submission Date(s): 10/31/03, 1/29/04, 3/8/04, 3/15/04, 3/31/04, 6/24/04
Brand Name	Avandaryl® Tablets
Generic Name	Rosiglitazone Maleate and Glimepiride Tablets
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM Division	Division of Metabolic and Endocrine Drug Products
Sponsor	Glaxo Smithkline
Relevant NDA(s)	21-071 (Avandia®); 20-496 (Amaryl®)
Relevant IND(s)	66,162
Formulation; Strength(s)	4mg/1mg; 4mg/2mg; and 4mg/4mg (rosiglitazone maleate/glimepiride) combination tablets
Indication	Treatment of Type 2 Diabetes Mellitus

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2 Executive Summary

The indication for combination use of two oral anti-diabetic agents, rosiglitazone and a sulfonylurea was previously approved under NDA 21-071/S-001 (Avandia®, rosiglitazone maleate, approved April 2000). The intent of this NDA submission is to support a new formulation, a fixed-dose combination tablet containing rosiglitazone maleate (thiazolidinedione) and glimepiride (sulfonylurea).

To aid in the approval of this application the sponsor has submitted the following pharmacokinetic studies: 1) a dose proportionality study (#797620/001); 2) a bioequivalence study (#797620/002); 3) a food-effect study (#797620/003); and 4) a drug interaction study (# 49653/340). There was also inclusion of an in vitro dissolution method with data and a biowaiver request for the two lower strengths 4 mg/1 mg and 4 mg/ 2 mg Avandaryl® tablets. There were no clinical studies done with the to-be marketed combination product and the pharmacokinetic studies were designed to bridge the proposed combination tablets to the clinical safety and efficacy database supporting the use of rosiglitazone in combination with sulfonylureas existing under the approved NDA 21-071. A clinical study data of rosiglitazone in combination with glimepiride and studies of rosiglitazone in combination with other sulfonylureas conducted since approval was also provided.

2.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the NDA 21-700 and finds the results acceptable. This recommendation and the labeling comments should be sent to the sponsor as appropriate.

CPB briefing was held on 7/12/04. The attendees were Drs. Hank Malinowski, John Hunt, Hae-Young Ahn, Joanna Zawadzki, Jayabharathi Vaidyanathan. It was suggested to the Medical Officer by OCPB to include under the Dosage and Administration section of the package insert, a statement that Avandaryl® is not intended for as a first line therapy in patients with Type 2 diabetes.

2.2 Phase IV Commitments

None

2.3 Summary of CPB Findings

Study 797620/001 examined the dose proportionality of the combination tablet formulation of rosiglitazone and glimepiride (4 mg/1 mg; or 4 mg/ 2 mg; or 4 mg/4 mg)

in healthy subjects. Results of this study showed that glimepiride pharmacokinetics were dose proportional over the dose range of 1 to 4 mg, following single dose administration of the 3 combination tablet formulations.

The bioequivalence study examined the relative rate and extent of exposure of the combination tablet formulation, Avandaryl[®] (4 mg/ 4 mg) to concomitant dosing of Avandia[®] (rosiglitazone 4 mg) and Amaryl[®] (glimepiride 4 mg) tablets in healthy subjects under fasting conditions. Results indicated that the bioequivalence was demonstrated for the rosiglitazone component in terms of AUC and C_{max}. The 90% confidence intervals for the comparisons between the combination tablet and the concomitant tablets fell within the range of 0.8 -1.25 for the AUC of rosiglitazone and glimepiride and C_{max} of rosiglitazone. However, the C_{max} of glimepiride was found to be lower following the administration of the combination tablet compared to the value obtained after concomitant dosing of the commercial tablets.

The food effect study demonstrated that after administration of the combination tablet (4 mg/ 4 mg), the extent of rosiglitazone was not changed in the fed state as compared to the fasted state, but the rate of absorption was reduced (32% decrease). On the other hand, glimepiride AUC_(0-∞) as well as C_{max} increased 19% and 55% respectively following administration of the combination tablets in the fed state as compared in the fasted state. Additionally the rate and extent of absorption of rosiglitazone and glimepiride, in the fed state were equivalent following administration of the combination tablet compared to concomitant administration of rosiglitazone and glimepiride as the currently approved commercial formulations.

Results from the drug interaction study, 49653/340 demonstrate that there was a decrease in both AUC and C_{max} of approximately 22% and 24% respectively for glimepiride following concomitant administration of glimepiride with rosiglitazone. No significant differences were seen in the pharmacokinetics of rosiglitazone between day 7 (alone) or day 8 (with glimepiride) indicating that there was no interaction of glimepiride upon rosiglitazone. Additionally, repeated oral administration of rosiglitazone (8 mg) resulted in a decrease rosiglitazone AUC as compared to single dose AUC.

Multipoint dissolution data from three batches of the to-be-marketed strengths was included for evaluation. Results indicate that the method was appropriate for Avandaryl[®].


Since the individual strength formulations were shown to be proportional, dosage form equivalence was demonstrated between strengths and also dissolution was comparable between strengths and therefore a biowaiver for the lower strengths, 4 mg/1 mg and 4 mg/2 mg not studied in vivo should be granted.

3.1 General Attributes

Q. Are the three respective AVANDARYL® formulations proportional?

The Avandaryl® combination tablets each consist of two _____ excipients _____. The rosiglitazone _____ is identical for each of the three tablet strengths, while the respective glimepiride mixtures are directly proportional to each other being in the ratio _____ for the 3 formulations.

Table 1: Avandaryl[®] tablet composition:

Strength:	4 mg / 1 mg	4 mg / 2 mg	4 mg / 4 mg	Function	Reference to Standard
Product Code:	AA	AB	AC		
Component	Quantity (mg / tablet)				
Rosiglitazone  Ingredients				Active	GlaxoSmithKline
Rosiglitazone Maleate ¹					
Lactose Monohydrate					
Microcrystalline Cellulose					
Sodium Starch Glycolate					
Hypromellose (HPMC) 2910					
Purified Water ²					USP
Rosiglitazone Granular Concentrate					USP

Total Tablet Weight	206.0	206.0	206.0		
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Q. Is the dissolution method appropriate for Avandaryl® tablets?

The solubility of both rosiglitazone and glimepiride is highly pH dependent. Dissolution profiles generated using 0.01M HCl with 0.5% SDS; pH 1.2 and pH 1.5 demonstrated that pH 1.2 and pH 1.5 were not suitable for both active ingredients in the combination tablet. The dissolution media of 0.01 M HCl is therefore acceptable. The sponsor had initially proposed the following dissolution method:

Apparatus: Paddle (type II)

Speed: 75 rpm

Media: 0.01 M Hydrochloric acid with 0.5% SDS

Specification limit: Q = 80% at 15 min for rosiglitazone dissolution

Q = 80% at 45 min for glimepiride dissolution.

However, the concentration of SDS used was high, and the sponsor was requested to provide additional data using lower concentration of SDS as well as using a lower paddle speed. The following figures show the dissolution profiles of glimepiride and rosiglitazone release using 0.1 M HCl with 0.5% SDS and paddle speed 75 rpm and 0.1 M HCl with 0.1% SDS with paddle speed 75 rpm (Figures 1 and 2).

Figure 1: Dissolution profiles- Glimepiride release, 0.01 M HCl with 0.5% SDS and paddle speed of 75 rpm.

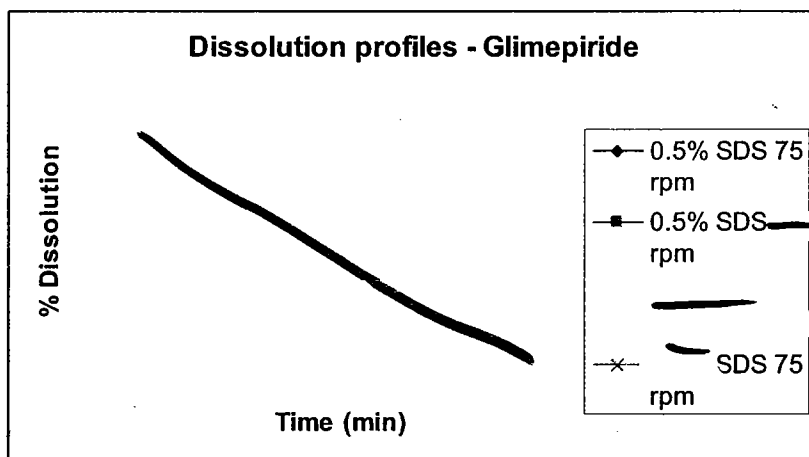
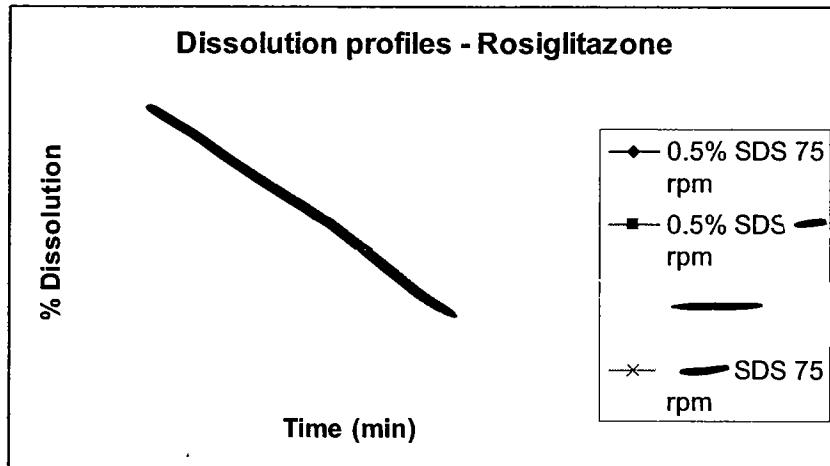


Figure 2: Dissolution profiles- Rosiglitazone release, 0.01 M HCl with 0.5% SDS and paddle speed of 75 rpm.



The above figures indicate that dissolution of Avandaryl tablets in 0.01 M HCl with 0.5% SDS shows complete release of rosiglitazone at 30 min and shows slightly less than 100% release of glimepiride as compared to that using 1.0% SDS (100% release at 45 min). Therefore, the dissolution method conditions of 0.01 M HCl with 0.05% SDS at a paddle speed of 75 rpm appears to be suitable to provide discriminating ability between batches.

Based on this the sponsor has proposed the specifications for dissolution as follows:

Specification limit: Q = 80 at 15 min for rosiglitazone dissolution

Q = 80 at 45 min for glimepiride dissolution.

Comments:

The specification provided for rosiglitazone and glimepiride is acceptable.

3.2 General Clinical Pharmacology

Q. Does this combination drug prolong the QT or QTc interval?

The sponsor has not submitted any study determining the effect of Avandaryl® on cardiac repolarization. However, both Avandia® (rosiglitazone) and Amaryl® (glimepiride) are approved drugs in the US and no reports of any adverse effects of these drugs due to their effect on cardiac repolarization has been reported thus far.

3.3 Extrinsic Factors

Q. Is there any drug-drug interaction between rosiglitazone and glimepiride?

An open-label, non-randomized, two-period, sequential study was conducted in healthy adult subjects (15 enrolled, 14 completed) in order to estimate the effect of repeat oral doses of rosiglitazone (8 mg) on the pharmacokinetics of glimepiride (4 mg) and the effect of a single oral dose of glimepiride (4 mg) on the pharmacokinetics of rosiglitazone (8 mg). Each subject participated in two study sessions. In session 1 (Regimen A), glimepiride 4 mg was administered on day 1 after a light breakfast. After a washout of 7 days, rosiglitazone (8mg) was administered in session 2 (Regimen B) once a day for 8 days after a light breakfast, with the addition of glimepiride 4 mg on day 8. Serial blood samples were collected over 24 h during treatment day (1, 7 or 8) for analysis of rosiglitazone, glimepiride and M1 (cyclohexyl hydroxyl methyl metabolite of glimepiride) concentrations.

The pharmacokinetic parameters of rosiglitazone after administration with and without glimepiride are shown in the following table. Rosiglitazone AUC was very slightly decreased following concomitant administration of rosiglitazone and glimepiride. The C_{max} , T_{max} , $t_{1/2}$ values for rosiglitazone were similar when administered alone or with glimepiride.

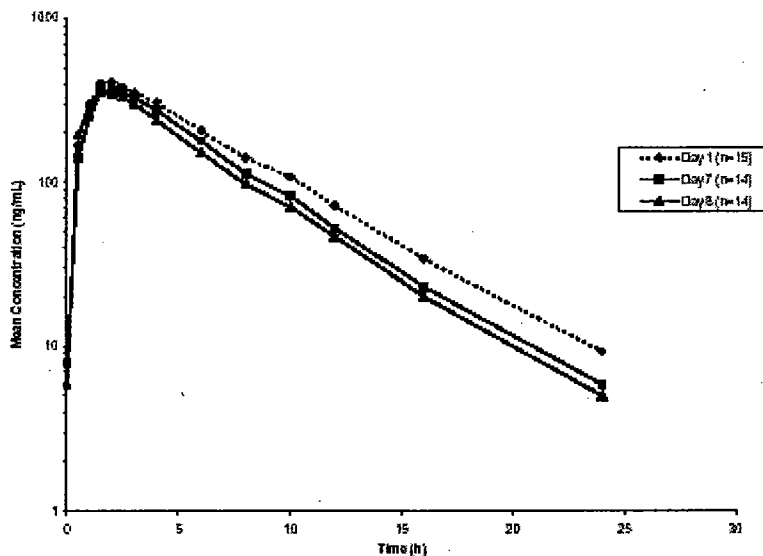
Table 2: Summary of rosiglitazone pharmacokinetic parameters.

Day	AUC _(0-∞) (ng.h/mL) ¹	AUC ₍₀₋₂₄₎ (ng.h/mL) ¹	C _{max} (ng/mL) ¹	t _{max} (h) ²	t _{1/2} (h) ³
1 (n=14)	2854 [2936 (1716-4427)]	2802 [2880 (1710-4311)]	417 [427 (291-658)]	1.75 (1.00-4.00)	3.92 (2.86-4.75)
7 (n=14)	2387 [2441 (1460-3256)]	2360 [2412 (1456-3218)]	397 [415 (262-757)]	2.00 (0.50-3.33)	3.44 (2.58-4.49)
8 (n=14)	2196 [2253 (1417-3022)]	2170 [2225 (1412-2973)]	379 [394 (273-706)]	2.00 (0.50-3.00)	3.46 (2.73-5.14)

1. AUC and C_{max} data presented as geometric mean [arithmetic mean (range)].
2. t_{max} data presented as median (range).
3. t_{1/2} data presented as arithmetic mean (range).

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Figure 3: Mean rosiglitazone concentrations



The statistical summary of rosiglitazone pharmacokinetic parameters is shown in the following table. There was a slight decrease in the AUC of rosiglitazone on repeated administration (Day 7 vs day 1). The 90% confidence interval for AUC and C_{max} for rosiglitazone alone or administered with glimepiride fell within the 80-125% interval.

Table 3: Statistical summary of rosiglitazone pharmacokinetic parameters.

Dose	Comparison	Parameter	P.E.	90% C.I.	C.V.%
rosiglitazone repeat dose: single dose	B(day 7):B(day 1)	AUC ¹	0.83	(0.79, 0.86)	6.96
	B(day 7):B(day 1)	C_{max}	0.95	(0.87, 1.04)	13.24
	B(day 7)-B(day 1)	t_{max}	0.00	(-0.50, 0.50)	
	B(day 7)-B(day 1)	$t_{1/2}$	-0.48	(-0.61, -0.35)	5.61
rosiglitazone + glimepiride: rosiglitazone	B(day 8):B(day 7)	AUC ₍₀₋₂₄₎	0.92	(0.88, 0.96)	6.96
	B(day 8):B(day 7)	C_{max}	0.95	(0.88, 1.04)	13.24
	B(day 8)-B(day 7)	t_{max}	-0.25	(-0.50, 0.25)	
	B(day 8)-B(day 7)	$t_{1/2}$	0.01	(-0.12, 0.14)	5.61

1. Day 1=AUC_(0-∞) and Day 7=AUC₍₀₋₂₄₎.

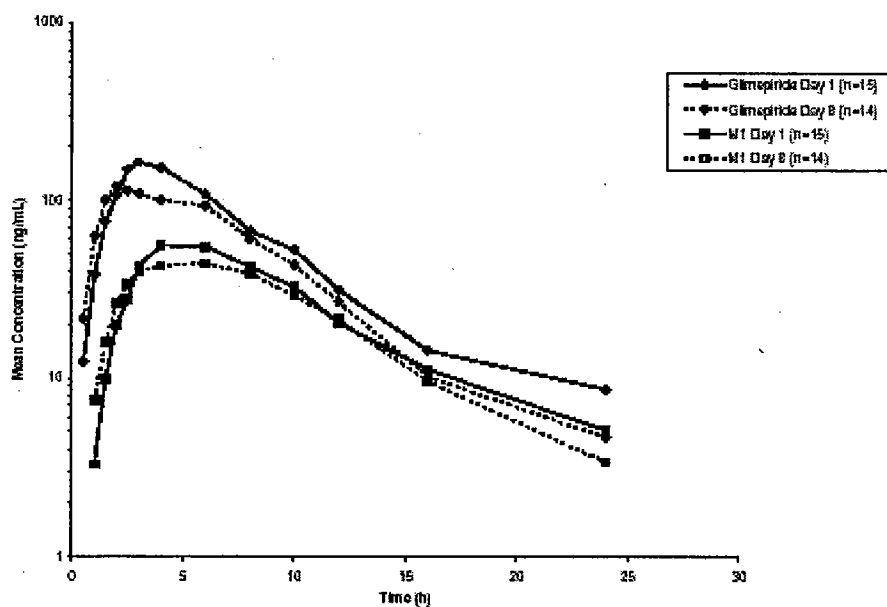
On the other hand, glimepiride AUC_(0-∞) was lower (22%) when glimepiride was given concomitantly with rosiglitazone as compared to when glimepiride was administered alone. The C_{max} of glimepiride was also lower by 24% following concomitant administration of glimepiride and rosiglitazone. Similarly for M1 AUC_(0-∞) and C_{max} also decreased 16% and 11% in presence of rosiglitazone. The summary of glimepiride and M1 pharmacokinetic parameters are shown in the following tables and figure.

Table 4: Summary of glimepiride and M1 pharmacokinetic parameters.

Analyte	Day	AUC _(0-∞) (ng·h/mL) ¹	C _{max} (ng/mL) ¹	t _{max} (h) ²	t _{1/2} (h) ³
Glimepiride	1 (n=14)	1214 [1323 (418-2380)]	205 [221 (107-412)]	3.00 (2.50-10.03)	7.13 (3.33-11.14)
	8 (n=14)	945 [1009 (383-1866)]	157 [172 (83-330)]	4.00 (1.50-10.00)	4.83 (2.61-10.36)
M1 metabolite	1 (n=14)	581 [604 (332-949)]	63.5 [66.6 (41.0-107.0)]	6.00 (3.00-10.03)	6.22 (4.08-7.98)
	8 (n=14)	488 [510 (281-1002)]	56.8 [59.4 (42.7-96.3)]	6.00 (2.00-8.00)	4.47 (2.98-6.59)

1. AUC and C_{max} data presented as geometric mean [arithmetic mean (range)].
2. t_{max} data presented as median (range).
3. t_{1/2} data presented as arithmetic mean (range).

Figure 4: Mean glimepiride and M1 concentrations.



The 90% confidence interval for AUC_(0-∞) and C_{max} for glimepiride when administered alone or concomitantly with rosiglitazone is shown in the following table. The 90% confidence interval for both AUC_(0-∞) and C_{max} fell outside the interval of 80-125%.

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Table 5: Statistical summary of glimepiride and M1 pharmacokinetic parameters

Analyte	Comparison	Parameter	P.E.	90% C.I.	CV _w %
Glimepiride	B(day 8):A(day 1)	AUC _(0-∞)	0.78	(0.72, 0.84)	11.95
	B(day 8):A(day 1)	C _{max}	0.76	(0.68, 0.86)	17.56
	B(day 8):A(day 1)	t _{max}	0.00	(-1.50, 2.00)	
	B(day 8):A(day 1)	t _s	-2.30	(-3.43, -1.16)	28.37
M1 metabolite	B(day 8):A(day 1)	AUC _(0-∞)	0.84	(0.79, 0.89)	8.50
	B(day 8):A(day 1)	C _{max}	0.89	(0.84, 0.96)	10.19
	B(day 8):A(day 1)	t _{max}	-0.02	(-1.50, 0.50)	
	B(day 8):A(day 1)	t _s	-1.75	(-2.52, -0.98)	21.47

3.4 General Biopharmaceutics

Q. Are the different strengths of the combination tablet formulation of rosiglitazone and glimepiride (4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg) proportional with regard to the glimepiride component?

In order to determine dose-proportionality of the combination formulation, an open-label, single dose, randomized, three-period, period-balanced crossover study was conducted in a fed state. Each subject participated in 3 study sessions and dosing in each session was separated by at least 3 days. Blood samples were collected over a 24-hour period following dosing in each session for the pharmacokinetic analysis of plasma glimepiride concentration.

A dose proportionality study with glimepiride was previously conducted by Aventis Pharmaceuticals. This historical data established dose proportionality over the dose range 1 to 8 mg for AUC, but not for C_{max}. This was speculated to be due to low aqueous solubility of glimepiride and dose administration in the fasted state, which would cause dissolution problems at higher doses, i.e., 4 and 8 mg. In the current study, drug was administered in the fed state and the dosing after a light meal thought to improve the dissolution characteristics of glimepiride, through bile salt emulsification and gastric pH changes.

Results indicate that the AUC_(0-t) and C_{max} values were approximately 2-fold greater for the 2 mg as compared to the 1 mg glimepiride dose and approximately 4-fold greater for the 4 mg dose. The geometric mean values of glimepiride PK parameters are shown in Table 6 and the mean glimepiride plasma concentration shown in Figure 3.

Figure 5: Mean glimepiride plasma concentrations (n=20) following single oral dose administration of three combined tablet formulations of rosiglitazone (4 mg) and glimepiride (1, 2 or 4 mg)

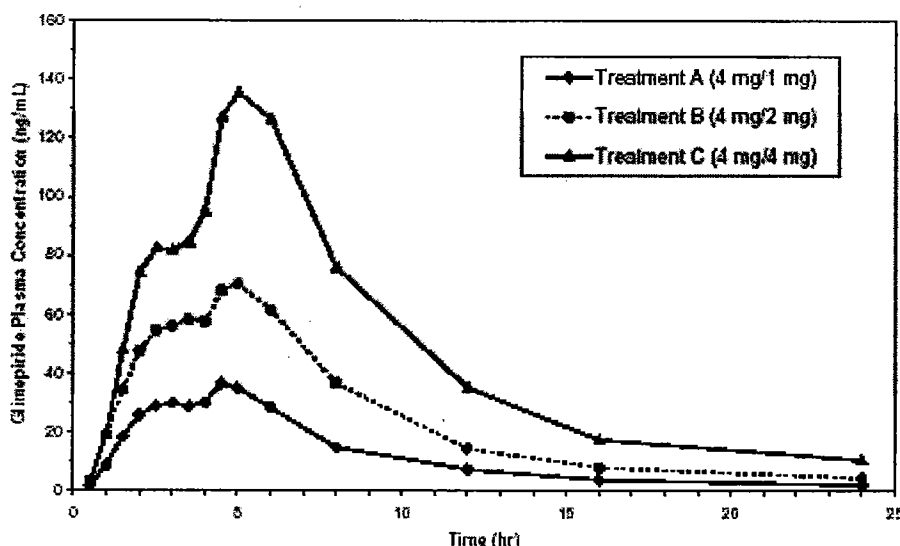


Table 6: Geometric mean (range) values for glimepiride PK parameters (N=20)

Glimepiride PK (n = 20)	AUC(0-t) (ng.hr/mL)	C _{max} (ng/mL)	t _{max} (hr) ¹
A (4 mg/1 mg)	259 (160-448)	45.5 (23.7-98.5)	4.50 (1.50-12.00)
B (4 mg/2 mg)	544 (338-896)	92.1 (56.8-162.8)	4.50 (1.50-8.00)
C (4 mg/4 mg)	1053 (755-1598)	172 (107-368)	5.00 (2.00-12.00)
1. t _{max} presented as median (range)			
Regimen	Regimen Description		
A	rosiglitazone 4 mg/glimepiride 1 mg		
B	rosiglitazone 4 mg/glimepiride 2 mg		
C	rosiglitazone 4 mg/glimepiride 4 mg		

The following Table shows the point estimates and corresponding 90% confidence intervals for the assessment of dose proportionality of glimepiride in the 4 mg/1mg, 4 mg/2 mg, 4 mg/4 mg rosiglitazone/glimepiride combination tablets. The 90% confidence intervals for the comparisons of AUC_(0-t) and C_{max} were completely contained within the range of 0.8- 1.25.

Table 7: Results of statistical analysis for assessment of dose proportionality of glimepiride (N=20)

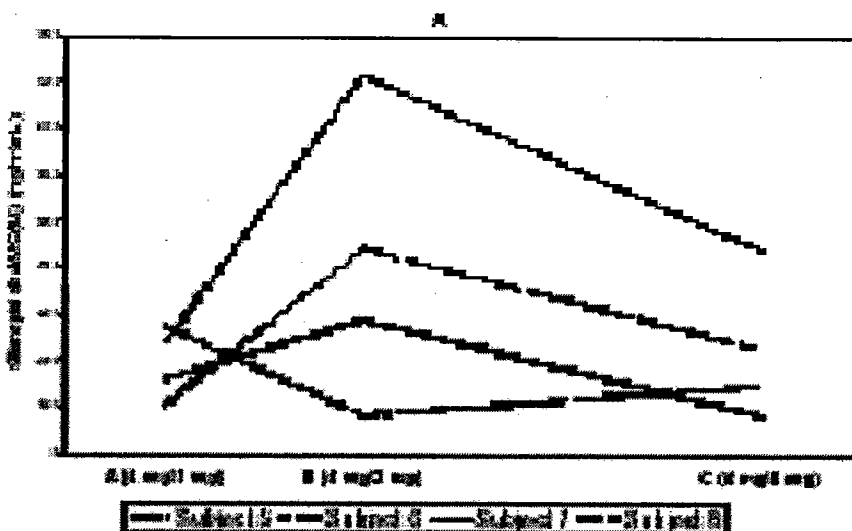
Glimepiride (n= 20)	Comparison ¹	Point Estimate	90% CI	CV%
DN - AUC _(0-t)	A:C	0.99	(0.94, 1.05)	9.7
DN - C _{max}	A:C	1.05	(0.95, 1.15)	17.8
DN - AUC _(0-t)	B:C	1.03	(0.98, 1.09)	
DN - C _{max}	B:C	1.07	(0.97, 1.18)	
1. represents the ratio of adjusted geometric means between regimens.				
DN = dose-normalized				
Regimen	Regimen Description			
A	rosiglitazone 4 mg/glimepiride 1 mg			
B	rosiglitazone 4 mg/glimepiride 2 mg			
C	rosiglitazone 4 mg/glimepiride 4 mg			

Four consecutive subjects exhibited pharmacokinetic data that showed inconsistency between observed PK parameters and assigned dosing sequence. The lowest glimepiride treatments A (1 mg) and B (2 mg) elicited greater glimepiride exposure than the highest glimepiride dose treatment (4 mg). No definitive dosing, subject identification, or sample labelling error could be identified by the sponsor. The analysis that includes these 4 subjects (N=24) indicated that there was a less than dose proportional increase in exposures. Removal of these subjects resulted in changes in the point estimates for both AUC and C_{max} comparisons. Since this data appeared to reflect different treatment sequences than those assigned and were not consistent with the historic glimepiride dose proportionality data (Aventis study), conclusions made by the sponsor were based on statistical analysis obtained after exclusion of these 4 subjects.

Analysis of individual glimepiride AUC_(0-t) for these four subjects (Figure 6), show that the subject receiving low dose of glimepiride had higher plasma concentration. For example Subject 8 got AUC_(0-t) values of 481 (1 mg), 1627 (2 mg) and 879 (4 mg) ng.h/ml. Based on these individual observed values, the reviewer agrees with the conclusions made by the sponsor that there is dose proportional increase in both AUC and C_{max} after removal of the above four subjects.

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Figure 6: Individual glimepiride $AUC_{(0-t)}$ values for subjects 005, 006, 007 and 008 according to treatment sequences provided by the clinical site.



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Q. Is the combination tablet formulation of rosiglitazone and glimepiride (4 mg/4 mg) bioequivalent to concomitant dosing of rosiglitazone 4 mg and glimepiride 4 mg (4 mg + 4 mg) commercial tablets in healthy subjects?

Under fasting conditions:

In order to assess bioequivalence of the combination tablet formulation as compared to the concomitant administration of the commercial tablets, an open-label, single-dose, randomized, two-period, period-balanced crossover study was performed. Subjects (30 enrolled, 27 completed) were randomly assigned to one of the two treatment sequences (AB, BA) under fasting conditions, regimen A being a single tablet formulation of rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg); and regimen B being the concomitant dosing of a single rosiglitazone 4 mg tablet and a single glimepiride 4 mg tablet (4 mg + 4 mg). There was a washout period of at least 3 days between treatments. Blood was collected prior to dose administration and at definite time periods through 24 hours following dosing.

The results indicate that bioequivalence of the combination tablet formulation relative to concomitant dosing of rosiglitazone and glimepiride commercial tablets was demonstrated for the rosiglitazone component in terms of $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ and C_{max} . Bioequivalence was not demonstrated for the glimepiride component as the 90% confidence intervals for the ratio of geometric mean of C_{max} for glimepiride in regimen A:B was not contained within the 80-125% interval. The results are summarized in the following tables and figures.

Table 8: Summary of the pharmacokinetic parameters for rosiglitazone and glimepiride by formulation (N= 28)

Parameter (Units)	Rosiglitazone		Glimepiride	
	Regimen A	Regimen B	Regimen A	Regimen B
AUC _(0-∞) (ng·h/mL)	1259 (833-2060)	1253 (756-2758)	1052 (643-2117)	1101 (648-2555)
AUC ₍₀₋₄₎ (ng·h/mL)	1231 (810-2019)	1224 (744-2654)	944 (511-1898)	1038 (606-2337)
C _{max} (ng/mL)	257 (157-352)	251 (77.3-434)	151 (63.2-345)	173 (70.5-329)
t _{1/2} (h)	3.53 (2.60-4.57)	3.54 (2.10-5.03)	7.63 (4.42-12.4)	5.08 (1.80-11.31)
t _{max} (h)	1.00 (0.48-3.02)	0.98 (0.48-5.97)	3.02 (1.50-8.00)	2.53 (1.00-8.03)

A = Combination Tablet; B = Concomitant dosing of rosiglitazone and glimepiride.

Data presented as geometric mean (range), except t_{1/2} which is presented as arithmetic mean (range) and t_{max}, which is presented as median (range).

Figure 7: Mean rosiglitazone (left) and glimepiride (right) concentrations following single oral administration of the combination tablet or concomitant administration of the rosiglitazone and glimepiride commercial tablets.

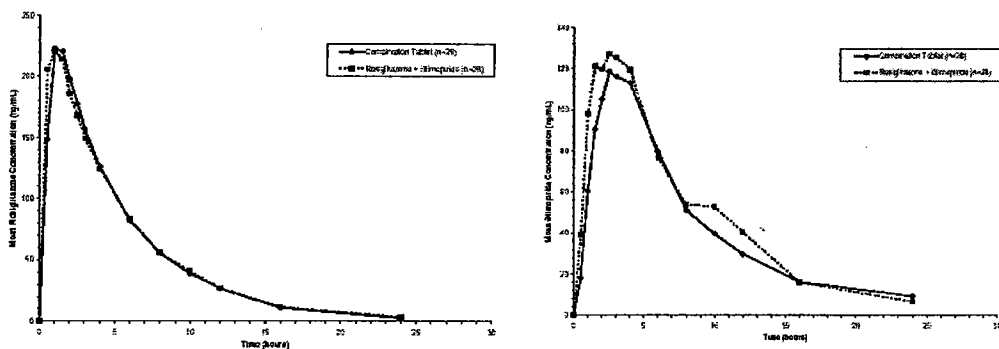


Table 9: Statistical comparisons between formulations for rosiglitazone.

Comparison	Parameter	Point Estimate	90% CI
A:B	AUC _(0-∞) ¹	1.00	(0.96, 1.04)
A:B	AUC ₍₀₋₄₎ ¹	1.00	(0.96, 1.04)
A:B	C _{max} ¹	1.02	(0.92, 1.14)
A-B	t _{max} ²	0.24	(-0.04, 0.48)
A-B	t _{1/2} ³	-0.04	(-0.16, 0.08)

A = Combination Tablet; B = Concomitant dosing of rosiglitazone and glimepiride.

1. Data represent the ratio of the adjusted geometric means between regimens.
2. Data represent the estimated median difference between regimens.
3. Data represent the estimated mean difference between regimens.

Table 10: Statistical comparisons between formulations for glimepiride.

Comparison	Parameter	Point Estimate	90% CI
A:B	AUC _(0-∞) ¹	0.96	(0.91, 1.00)
A:B	AUC ₍₀₋₁₂₎ ¹	0.91	(0.87, 0.96)
A:B	C _{max} ¹	0.88	(0.76, 1.01)
A-B	t _{max} ²	0.26	(-0.47, 1.00)
A-B	t _{1/2} ³	2.50	(1.58, 3.43)

A = Combination Tablet; B = Concomitant dosing of rosiglitazone and glimepiride.

1. Data represent the ratio of the adjusted geometric means between regimens.
2. Data represent the estimated median difference between regimens.
3. Data represent the estimated mean difference between regimens.

The reviewer also performed statistical analysis of rosiglitazone and glimepiride parameters using Winnonlin, and the results were similar to that of the sponsor (shown in the table below).

Table 11: Statistical comparison of pharmacokinetic parameters between formulations.

Rosiglitazone				
Combination tablets	Parameter	GeoLSM	Point Estimate	90% CI
	AUC _{inf}	1136.33	100.03	(96.21, 104.0)
	C _{max}	235.55	104.28	(93.3, 116.55)
Commercial tablets	Parameter	GeoLSM	Point Estimate	90% CI
	AUC _{inf}	1136.01		
	C _{max}	225.88		
Glimepiride				
Combination tablets	Parameter	GeoLSM	Point Estimate	90% CI
	AUC _{inf}	1035.51	95.58	(92.3, 107.7)
	C _{max}	149.97	87.64	(78.82, 121.18)
Commercial tablets	Parameter	GeoLSM	Point Estimate	90% CI
	AUC _{inf}	1083.41		
	C _{max}	171.11		

Under fed conditions:

The food effect study (see below) also assessed simultaneously the relative bioavailability of the combination tablet and concomitant dosing of rosiglitazone and glimepiride marketed tablets in the fed state. The three treatments were:

Regimen A: a single tablet combination formulation of rosiglitazone 4 mg/glimepiride 4 mg (4mg/4mg) in a fed state.

Regimen B: concomitant dosing of a single rosiglitazone 4 mg tablet and a single glimepiride 4 mg tablet (4 mg + 4 mg) in a fed state.

Regimen C: a single tablet combination formulation of rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg) in a fasted state.

Both AUC_(0-∞) and C_{max} for rosiglitazone were similar following administration of the combination tablet compared to concomitant administration of rosiglitazone and glimepiride, both in the fed state (Table 12).

Table 12: Statistical comparisons between formulations for rosiglitazone and glimepiride

Relative Bioavailability			
Rosiglitazone			
A:B	AUC(0-∞)	102.3	98.12 - 106.66
Rosiglitazone			
A:B	Cmax	106.25	98.39 - 114.73
Glimepiride A:B			
A:B	AUC(0-∞)	103.44	98.75 - 108.35
A:B	Cmax	104.39	92.82 - 117.41

A = Combination tablet fed; B = Concomitant dosing rosiglitazone and glimepiride fed;
Data represents the ratio of adjusted geometric least square means between regimens.

Comments:

Under fasting conditions, rosiglitazone component of the combination tablet was bioequivalent as compared to concomitantly administered commercial tablets. However, the C_{max} of glimepiride component was slightly below the 80-125% range. Under fed conditions, both the rosiglitazone and glimepiride component from the combination tablet were bioequivalent to that of concomitantly administered commercial tablets. Since the tablet will be administered chronically to patients the slightly lower C_{max} of glimepiride observed is not clinically significant. Additionally, the package insert of the combination tablet indicates it to be administered with meal.

Q. Does food alter the bioavailability of Avandaryl?

In order to estimate the effect of food on the single dose pharmacokinetics of rosiglitazone and glimepiride in a rosiglitazone/glimepiride (4 mg/4 mg) combination tablet, an open-label, single dose, randomized, three-period, period-balanced crossover study was conducted. Each subject participated in all three study sessions. The study session was as follows:

Regimen A: a single tablet combination formulation of rosiglitazone 4 mg/glimepiride 4 mg (4mg/4mg) in a fed state.

Regimen B: concomitant dosing of a single rosiglitazone 4 mg tablet and a single glimepiride 4 mg tablet (4 mg + 4 mg) in a fed state.

Regimen C: a single tablet combination formulation of rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg) in a fasted state.

There was a washout period of at least 5 days between the study sessions. Blood samples for pharmacokinetic analysis of plasma rosiglitazone and glimepiride concentrations were collected at pre-dose and over a 24-hour period following dosing in each session.

Results indicate that when the combination tablet was administered with a meal, rosiglitazone $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ were unchanged compared to administration in the fasted state. The rosiglitazone C_{max} was decreased to about 32% in presence of food (Figure 8 & Table 13).

Figure 8: Mean rosiglitazone concentrations following dosing with the combination tablet or concomitant administration of the rosiglitazone and glimepiride commercial tablets fed or fasted

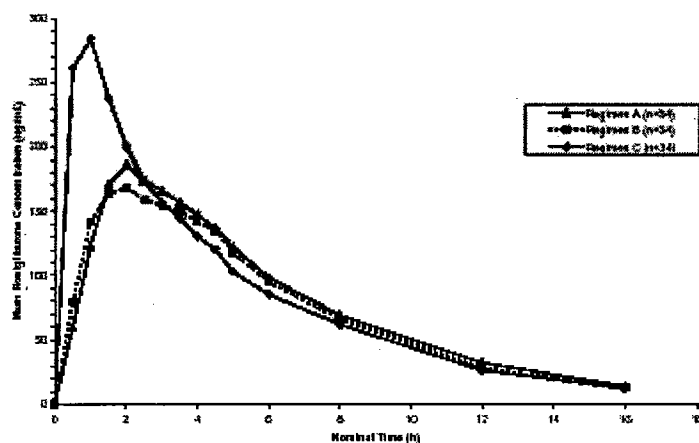


Table 13: Summary of the pharmacokinetic parameters for rosiglitazone by formulation (N=34)

Parameter (Units)	Regimen A	Regimen B	Regimen C
$AUC_{(0-\infty)}$ (ng·h/mL)	1245 ¹ (656-1911)	1222 ¹ (741-1948)	1351 ¹ (788-2134)
$AUC_{(0-t)}$ (ng·h/mL)	1232 (647-2127)	1195 (731-1935)	1331 (770-2108)
C_{max} (ng/mL)	218 (132-565)	204 (130-388)	321 (165-503)
$t_{1/2}$ (h)	3.36 ¹ (2.28-4.37)	3.35 ¹ (2.42-4.53)	3.30 ¹ (2.34-4.28)
t_{lag} (h)	0.00 (0.00-1.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
t_{max} (h)	2.00 (0.50-6.00)	2.00 (0.50-5.00)	0.55 (0.50-4.50)

1. n=33

Data presented as geometric mean (range), except $t_{1/2}$ which is presented as arithmetic mean (range), and t_{lag} and t_{max} which are presented as median (range).

Regimen A = Combination tablet fed; Regimen B = Concomitant administration of the rosiglitazone and glimepiride tablets fed; Regimen C = Combination tablet fasted

When the combination tablet was administered with a meal, both AUC and C_{max} for glimepiride component increased relative to administration in the fasted state. The increase for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} were on average 30%, 19% and 55% respectively. The mean glimepiride concentration time profile after administration of the different regimen is shown in Figure 9 and the pharmacokinetic parameters summarized in Table 14. Both $AUC_{(0-\infty)}$ and C_{max} for glimepiride were similar following

administration of the combination tablet compared to concomitant administration of rosiglitazone and glimepiride, both in the fed state (Table 12). The proposed package insert states that Avandaryl® should be given with a meal.

Figure 9: Mean glimepiride concentrations following dosing with the combination tablet or concomitant administration of the rosiglitazone and glimepiride commercial tablets fed or fasted

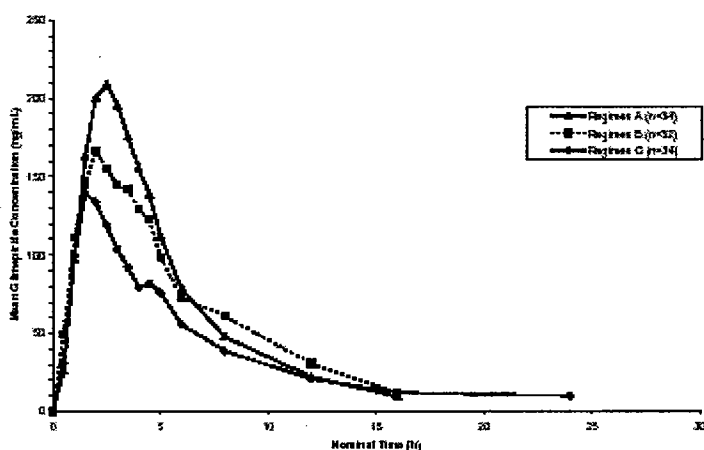


Table 14: Summary of the pharmacokinetic parameters for glimepiride by formulation

Parameter (Units)	Regimen A (n=34)	Regimen B (n=32)	Regimen C (n=34)
AUC _(0-∞) (ng·h/mL)	1136 ¹ (575-2451)	1099 ² (537-2312)	985 ³ (410-1862)
AUC ₍₀₋₈₎ (ng·h/mL)	1056 (546-2374)	1021 (468-2223)	813 (375-1658)
C _{max} (ng/mL)	233 (119-475)	219 (108-399)	150 (63-291)
t _{1/2} (h)	3.60 ¹ (1.93-6.99)	3.34 ² (1.54-6.82)	6.63 ³ (2.92-10.42)
t _{lag} (h)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-0.67)
t _{max} (h)	2.50 (1.00-4.53)	2.26 (0.50-8.00)	2.00 (1.00-8.13)

1. n=29

2. n=27

3. n=16

Data presented as geometric mean (range), except t_{1/2} which is presented as arithmetic mean (range), and t_{lag} and t_{max}, which are presented as median (range).

Regimen A = Combination tablet fed; Regimen B = Concomitant administration of the rosiglitazone and glimepiride tablets fed; Regimen C = Combination tablet fasted

Table 15: Statistical comparisons between formulations for rosiglitazone and glimepiride

Comparison	Parameter	Point Estimate(%)	90%CI
Food Effect			
Rosiglitazone A:C	AUC(0-∞)	90.79	87.08 - 94.66
Rosiglitazone A:C	Cmax	66.44	61.56 - 71.22
Glimepiride A:C	AUC(0-∞)	118.63	112 - 125.65
Glimepiride A:C	Cmax	153.65	136.9 - 172.12

A = Combination tablet fed; B = Concomitant dosing rosiglitazone and glimepiride fed;
C = Combination tablet fasted

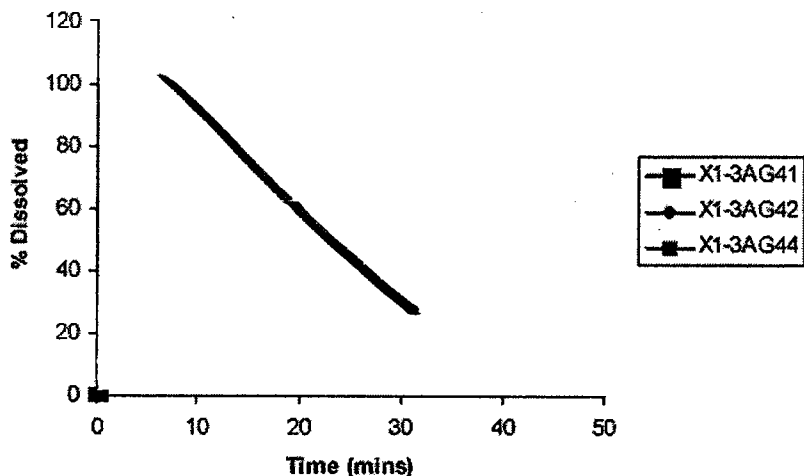
Data represents the ratio of adjusted geometric least square means between regimens.

Q. Can the biowaiver request be granted for the two lower dose strengths of Avandaryl tablets?

In order to grant a biowaiver for lower strengths, formulations should be proportional; in vivo dose-proportionality should be established between the strengths and similar dissolution profiles as determined by f_2 values should be demonstrated. The three strengths are similar in composition and dose-proportional (see above sections). To determine if the 4 mg/ 1 mg, 4 mg/ 2 mg, and 4 mg/ 4 mg Avandaryl tablets are similar, a multipoint dissolution study was conducted using the proposed dissolution method described above. The dissolution was performed for all the 3 strengths of Avandaryl® tablets and were from 3 different lots with a batch size of commercial scale (tablets). Results of this study and the f_2 values are presented in the following figures.

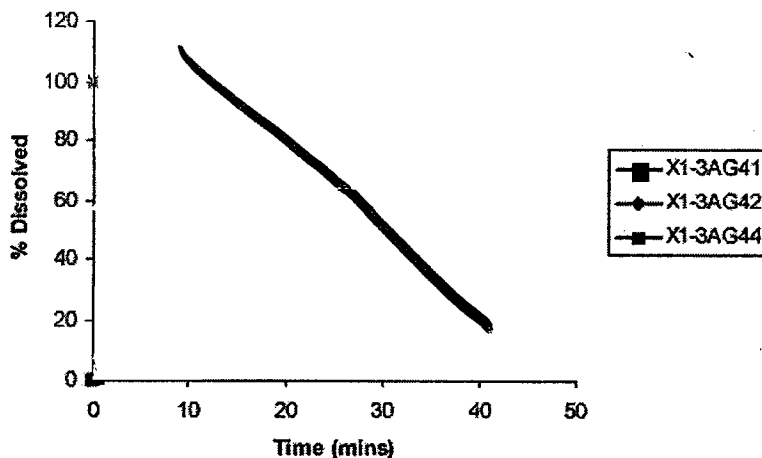
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On Original**

Figure 10: Rosiglitazone dissolution profiles for Avandaryl tablet batches in 0.01 M HCl with 0.5% SDS and paddle speed 75 rpm; 4 mg/ 1mg, 4 mg/ 2 mg and 4 mg/ 4 mg



Over 90% of the drug products are dissolved within 10 minutes and f_2 values can not be calculated. It indicates that dissolution is similar between strengths.

Figure 11: Glimepiride dissolution profiles for Avandaryl tablet batches in 0.01 M HCl with 0.5% SDS and paddle speed 75 rpm; 4 mg/ 1mg, 4 mg/ 2 mg and 4 mg/ 4 mg



Similarity factor for 4 mg / 1 mg and 4 mg / 2 mg doses, $f_2 = 1$
 Similarity factor for 4 mg / 2 mg and 4 mg / 4 mg doses, $f_2 = 1$
 Similarity factor for 4 mg / 1 mg and 4 mg / 4 mg doses, $f_2 = 1$

Since the three tablet strengths have a similarity factor greater than 1 they are considered to have similar dissolution profiles and therefore a biowaiver can be granted.

3.5 Analytical

Q. Have the analytical methods been sufficiently validated?

Plasma samples from the various studies were analyzed for rosiglitazone, glimepiride and its metabolite by _____ GlaxoSmithKline using a validated _____ LC-MS/MS method. The methods for the determination of rosiglitazone, glimepiride and M1 metabolite in human plasma were based on _____ containing stable isotopically labeled internal standards for each _____ followed by LC/MS/MS analysis employing _____

Quality control samples were analyzed with each batch of samples against separately prepared calibration standards. The calibration range for rosiglitazone was _____ For glimepiride the calibration range was _____ for study # 001 and _____ for the other studies. The calibration range for M1 was _____ The precision and bias of quantification during a three-run validation was less than _____ for rosiglitazone and glimepiride (study 001) respectively. For the other studies with glimepiride and M1, the precision and bias of quantification was less than _____ for both _____

4 Labeling Comments

The office of Clinical Pharmacology and Biopharmaceutics has reviewed the package insert labeling for AVANDARYL and finds it acceptable pending the following revision:

Under CLINICAL PHARMACOLOGY section:

17 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Clin Pharm/Bio-

1

Individual Study Synopses for Clinical Studies

Document Number: PM2003/00015/00 Study Number: BRL-049653/340

Title: A Study to Estimate the Effect of Repeat Oral Doses of Rosiglitazone (8 mg) on the Pharmacokinetics of Glimepiride (4 mg) and the Effect of a Single Oral Dose of Glimepiride (4 mg) on the Pharmacokinetics of Rosiglitazone (8 mg) in Healthy Subjects	
Investigator: The co-investigators were _____	
Study center: The study was conducted at the _____ The clinical laboratory facility was _____	
Publication(s): None as of August 2003.	
Study period: 13SEP2002 – 25OCT2002	Phase of Development: I
Objectives: The primary objective was to estimate the effect of repeat oral doses of rosiglitazone on the pharmacokinetics of a single oral dose of glimepiride. Secondary objectives were: <ol style="list-style-type: none">1. To estimate the effect of repeat oral doses of rosiglitazone on the pharmacokinetics of glimepiride metabolite cyclohexyl hydroxy methyl derivative (M1).2. To estimate the effect of a single oral dose of glimepiride on the pharmacokinetics of rosiglitazone.3. To evaluate the pharmacokinetics of rosiglitazone during repeat oral dosing.4. To assess the tolerability of concomitant oral dosing of glimepiride 4 mg and rosiglitazone 8 mg commercial tablets, and when glimepiride 4 mg or rosiglitazone 8 mg are given separately.	
Methodology: This was an open-label, non-randomized, two-period, sequential study conducted in healthy subjects. Each subject participated in two study sessions. In Session 1 (Regimen A), glimepiride (Amaryl®) 4 mg was administered on Day 1 after a light breakfast. After a washout period of at least 7 days, rosiglitazone (AVANDIA®) 8 mg was administered in Session 2 (Regimen B) once a day for 8 days after a light breakfast; with the addition of glimepiride (Amaryl®) 4 mg on Day 8. Each session required subjects to be admitted to the Clinical Research Unit (CRU) for 1 day in Session 1 and 3 days in Session 2. Subjects were asked to return for a follow-up visit at least 10 to 14 days following the last dose of study medication. The duration of each subject's participation in the study from screening to follow-up was approximately 8 weeks.	

Title: A Study to Estimate the Effect of Repeat Oral Doses of Rosiglitazone (8 mg) on the Pharmacokinetics of Glimepiride (4 mg) and the Effect of a Single Oral Dose of Glimepiride (4 mg) on the Pharmacokinetics of Rosiglitazone (8 mg) in Healthy Subjects

The following assessments were performed:

Procedures	Nominal Time(s) Following Dosing
Admission to CRU (fasting)	pre-dose
Baseline signs and symptoms	pre-dose
Update medical and medication history	pre-dose
Limited physical examination	pre-dose
Sitting 12-lead ECGs	pre-dose, 24 h
Sitting blood pressure and pulse rate	pre-dose, 24 h
Meals served	pre-dose (light breakfast) ² , 1.25 h (snack) ¹ , 2 h (snack), 4 h (lunch), 6 h (snack), 10 h (dinner), 13 h (snack), 16 h (snack) ¹ , 24 h (bag breakfast)
Adverse events assessment ²	4 h, 10 h, 24 h
Blood/Urine Specimens	
Safety laboratory studies blood sample and urine specimen	pre-dose, 24 h
Urine drug screen including alcohol ³	pre-dose
Serum β -hCG (female only) ³	pre-dose
Glucometer assessment	pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h
Blood sample for glucose safety levels	pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h
Blood samples for PK analyses	pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h

1. Added as a protocol amendment, in effect for Session 2.

2. Assessed by asking a non-leading question such as "How do you feel?"

3. Results were reported prior to dosing, and must be negative for a subject to proceed with dosing.

Number of subjects: Fifteen subjects were enrolled and 14 subjects completed the study.

Diagnosis and main criteria for inclusion: Subjects were healthy adult male and female subjects between 18 and 55 years of age, inclusive, with a BMI of 20-30 kg/m², inclusive.

Treatment administration: Oral study medication was administered with 240 mL water under the supervision of study personnel. The oral cavity of each subject was examined following dosing to assure that study medication was taken.

Title: A Study to Estimate the Effect of Repeat Oral Doses of Rosiglitazone (8 mg) on the Pharmacokinetics of Glimpiride (4 mg) and the Effect of a Single Oral Dose of Glimpiride (4 mg) on the Pharmacokinetics of Rosiglitazone (8 mg) in Healthy Subjects

Criteria for evaluation:

Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Clinical monitoring and laboratory data were reviewed by the study physician and were not formally analyzed. Adverse events were summarized by formulation. No formal statistical analysis of the safety data was performed.

Pharmacokinetics: Serial whole blood samples were collected over 24 hours during each treatment day (1, 7 or 8) for bioanalysis of plasma for rosiglitazone, glimepiride and M1 (the cyclohexyl hydroxy methyl metabolite of glimepiride) concentrations. PK analysis of the plasma rosiglitazone, glimepiride, and M1 concentration-time data was conducted using non-compartmental methods. $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max} , t_{max} , and $t_{1/2}$ were estimated following single and repeated administration of glimepiride and rosiglitazone separately, or given in combination.

Statistical methods: Following \ln -transformation, AUC and C_{max} of glimepiride, rosiglitazone, and the M1 metabolite of glimepiride were separately analyzed by analysis of variance (ANOVA) fitting a model with terms subject and pharmacokinetic study day (Regimen A, Day 1, and Regimen B, Day 1, 7 or 8). Point estimates and corresponding 90% confidence intervals were constructed for the comparisons of interest using the residual variance. These were back-transformed to provide point estimates and corresponding 90% confidence intervals for the true ratios. $t_{1/2}$ of glimepiride, rosiglitazone, and the M1 metabolite were similarly analyzed without prior transformation to give a point estimate and 90% confidence interval for the true difference for the comparisons of interest. t_{max} of glimepiride, rosiglitazone, and M1 were analyzed using the Wilcoxon Matched Pairs Method to compute point estimates and 90% confidence intervals for the median differences for the comparisons of interest.

Summary:

Safety: Rosiglitazone and glimepiride were well tolerated. Summary details for all treatment-emergent adverse events are as follows:

	Session 1, Regimen A	Session 2, Regimen B	Total
Most Frequent AE (Hypoglycemia)	3	5	8
Total Number of AEs	16	19	35
Number of Subjects with AEs	6	8	9
Number of Subjects Exposed	15	15	15

Title: A Study to Estimate the Effect of Repeat Oral Doses of Rosiglitazone (8 mg) on the Pharmacokinetics of Glimepiride (4 mg) and the Effect of a Single Oral Dose of Glimepiride (4 mg) on the Pharmacokinetics of Rosiglitazone (8 mg) in Healthy Subjects

AUC_(0-∞) and C_{max} of glimepiride were 22% and 24% lower, respectively, when glimepiride was given concomitantly with rosiglitazone, compared to glimepiride administered alone. Similarly, M1 AUC_(0-∞) and C_{max} decreased 16% and 11% respectively, on average, when glimepiride was administered with rosiglitazone compared to the results after administration of glimepiride alone. Glimepiride and M1 t_{max} were similar whether glimepiride was given alone, or concurrently with rosiglitazone. Both glimepiride and M1 t_{1/2} were decreased by approximately 1 to 3 hours when glimepiride was given with rosiglitazone compared to results on administration of glimepiride alone.

Rosiglitazone AUC decreased slightly upon repeated administration, consistent with previous observations, with AUC decreasing approximately 17% on average. Rosiglitazone t_{1/2} was also decreased by approximately 0.5 hours on Day 7 compared to Day 1. C_{max} and t_{max} values were generally similar following single or repeated administration of rosiglitazone. Rosiglitazone AUC was further decreased following concomitant administration of rosiglitazone and glimepiride, although this decrease was only 8% on average. Rosiglitazone C_{max}, t_{max} and t_{1/2} values were similar whether rosiglitazone was administered alone or concurrently with glimepiride.

Conclusions:

Repeated oral administration of rosiglitazone caused modest, clinically insignificant decreases in glimepiride AUC, C_{max}, and t_{1/2}.

Repeated oral administration of rosiglitazone (8 mg) resulted in modest, clinically insignificant decreases in rosiglitazone AUC, consistent with results from previous studies. A single oral dose of glimepiride had no effect on the pharmacokinetics of rosiglitazone.

- Concomitant administration of rosiglitazone and glimepiride was safe and well tolerated by healthy adult men and women.

Date of Report: August 2003

Title: A Dose Proportionality Study with a Combination Tablet Formulation of Rosiglitazone and Glimepiride (4mg/1 mg; or 4 mg/2 mg; or 4 mg/4 mg) in Healthy Subjects	
Investigators: The co-principal investigators were _____ _____	
Study center: The study was conducted at the _____ _____ Clinical laboratory analyses were performed at the _____ _____	
Publications: None as of September 2003	
Study period: 27 May 2003 - 19 July 2003	Phase of Development: I
Objectives: Primary: 1. To assess the dose proportionality of glimepiride in the combination formulations rosiglitazone 4 mg/glimepiride 1 mg (4 mg/1 mg), rosiglitazone 4 mg/glimepiride 2 mg (4 mg/2 mg) and rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg) administered in a fed state. Secondary: 1. To assess the tolerability of dosing with combination formulations of rosiglitazone 4 mg/glimepiride 1 mg (denoted as 4 mg/1 mg), rosiglitazone 4 mg/glimepiride 2 mg (denoted as 4 mg/2 mg) and rosiglitazone 4 mg/glimepiride 4 mg (denoted as 4 mg/4 mg) administered in a fed state. 2. If at any time it appeared there was potential variability in SB 797620 response or handling (e.g., pharmacokinetics, safety, and/or efficacy) in this clinical study or in a series of clinical studies, the following objectives could have been investigated (assuming sample number is adequate and the availability of genotyping assays): <ul style="list-style-type: none">• Relationship between genetic variants and the pharmacokinetics of investigational product• Relationship between genetic variants and safety and/or tolerability of investigational product.	
Methodology: This study was an open-label, single dose, randomized, three-period, period-balanced, crossover study. Each subject participated in 3 study sessions. Dosing in each session was separated by at least 3 days starting from the time of the 24-hour pharmacokinetic (PK) sample. During each session, a subject received one of the following regimens administered after a light breakfast:	

Title: A Dose Proportionality Study with a Combination Tablet Formulation of Rosiglitazone and Glimepiride (4mg/1 mg; or 4 mg/2 mg; or 4 mg/4 mg) in Healthy Subjects	
Regimen	Description
A	A single tablet combination formulation of rosiglitazone 4 mg plus glimepiride 1 mg (denoted as 4 mg/1 mg)
B	A single tablet combination formulation of rosiglitazone 4 mg plus glimepiride 2 mg (denoted as 4 mg/2 mg)
C	A single tablet combination formulation of rosiglitazone 4 mg plus glimepiride 4 mg (denoted as 4 mg/4 mg)
<p>Subjects were assigned to one of six possible treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA) according to a randomization schedule prepared in advance of the study by Clinical Pharmacology Statistics and Programming (CPSP), GlaxoSmithKline, using internal validated software. Blood samples for pharmacokinetic analysis of plasma glimepiride concentrations were collected at pre-dose and over a 24- hour period following dosing in each session. Subjects were discharged from the clinical pharmacology unit (CPU) after a minimum of 24 hours following dosing.</p> <p>A standard light breakfast was provided prior to administration of study medication for subjects in each session for all 3 regimens.</p> <p>To ensure normoglycemia was maintained after study drug administration, subjects were given intravenous Dextrose 10 (10% dextrose solution) at an infusion rate of 20 mL per hour for 1 hour, followed by an increased infusion rate of 40 mL per hour for 1 hour. The infusion rate was then increased to 200 mL per hour for 2 hours, followed by a decreased infusion rate of 100 mL per hour for 2 hours.</p> <p>After 4 hours post-dosing, food and drink were permitted to be consumed to maintain normoglycemia. Study staff ensured that subjects consumed food offered in entirety to maintain normoglycemia during the study. Monitoring of glucose levels included glucometer checks prior to dosing and during inpatient study days. Glucose levels by serum analysis were checked when glucometer reading were less than 60 mg/dL, or if the subjects had symptomatology suggestive of hypoglycemia, or at the discretion of the investigator or designate.</p> <p>Participating subjects were also given the option of participating in pharmacogenetic research. If a subject consented to participate, a blood sample was collected. The DNA could have been extracted and analyzed for variants of genes that could have affected rosiglitazone handling or response.</p> <p>Subjects were asked to return for a follow-up visit at least 10 to 15 days following the last dose of study medication. The duration of each subject's participation in the study from screening to follow-up was approximately 7 weeks.</p> <p>Pharmacokinetics: Blood samples were collected over a 24-hour period following dosing in each</p>	

Title: A Dose Proportionality Study with a Combination Tablet Formulation of Rosiglitazone and Glimepiride (4mg/1 mg; or 4 mg/2 mg; or 4 mg/4 mg) in Healthy Subjects
session for the pharmacokinetic analysis of plasma glimepiride concentrations. Plasma samples were assayed for SB-655209 (glimepiride) using a validated bioanalytical method with LC/MS/MS (lower limit of quantification was 1 ng/mL).
Number of subjects: Twenty-eight subjects were enrolled in the study. Twenty-four subjects completed all 3 sessions and provided evaluable pharmacokinetic data.
Diagnosis and main criteria for inclusion: Subjects were healthy adult male and female volunteers between 18 and 55 years of age, inclusive.
Treatment administration: During each of three study sessions, subjects were randomly assigned to receive, after being fed a light breakfast, a single, oral dose of the rosiglitazone/glimepiride combination formulation (Regimens A, B, or C).
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: The pharmacokinetics of glimepiride were assessed by determining $AUC_{(0-\infty)}$, $AUC_{(0-12)}$, C_{max}, t_{max} and $t_{1/2}$ following single oral dose administration of three combined tablet formulations of rosiglitazone (4 mg) and glimepiride (1, 2 or 4 mg). Dose proportionality was concluded if the 90% confidence intervals for the ratios A:C and B:C were completely contained within the range, 0.70-1.43, for the dose-normalized primary PK endpoint $AUC_{(0-12)}$.</p> <p>Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Adverse events, blood pressure, pulse rate, 12-lead ECG, and clinical laboratory data were reviewed during the study to evaluate the safety of the subjects. Any clinically relevant abnormalities or values of potential clinical concern were described.</p>
<p>Statistical methods: After \log_e-transformation, $AUC_{(0-12)}$ and C_{max} of glimepiride (dose-normalized for Regimens A and B) were separately analyzed by analysis of variance (ANOVA) with terms for sequence, subject (sequence), period, and regimen. Point estimates and associated 90% confidence intervals for the differences A-C and B-C were constructed using the residual variance. These point estimates and confidence intervals were then exponentially backtransformed to obtain point estimates and associated 90% confidence intervals for the ratios A:C and B:C. t_{max} was analyzed nonparametrically using the Wilcoxon's Matched Pairs Method. Point estimates and 90% confidence intervals were calculated for the median differences A-C and B-C. Four subjects were determined to be statistical outliers in the analyses of $AUC_{(0-12)}$ and C_{max}. Consequently, statistical analyses of $AUC_{(0-12)}$ and C_{max} were performed with and without data from these subjects.</p>

Title: A Dose Proportionality Study with a Combination Tablet Formulation of Rosiglitazone and Glimepiride (4mg/1 mg; or 4 mg/2 mg; or 4 mg/4 mg) in Healthy Subjects

Summary:

Pharmacokinetics: Observed pharmacokinetic data for 4 subjects suggested discrepancies between the intended and actual randomization schedules. Statistical analysis determined that Subjects 005, 006, 007 and 008 were statistical outliers for $AUC_{(0-4)}$ and C_{max} . Since removal of these outliers resulted in changes in statistical inference as well as notable changes in the point estimates, statistical and pharmacokinetic results were presented with and without these 4 subjects. Results of the statistical analysis (outliers excluded) are presented in the table below.

Glimepiride (n = 20)	Comparison ¹	Point Estimate	90% CI	CV%
DN - $AUC_{(0-4)}$	A:C	0.99	(0.94, 1.05)	9.7
DN - C_{max}	A:C	1.05	(0.95, 1.15)	17.8
DN - $AUC_{(0-4)}$	B:C	1.03	(0.98, 1.09)	
DN - C_{max}	B:C	1.07	(0.97, 1.18)	

1. represents the ratio of adjusted geometric means between regimens.

DN = dose-normalized

Regimen	Regimen Description
A	rosiglitazone 4 mg/glimepiride 1 mg
B	rosiglitazone 4 mg/glimepiride 2 mg
C	rosiglitazone 4 mg/glimepiride 4 mg

Safety: There were no deaths, serious adverse events or withdrawals due to adverse events reported during the study. Thirty-three AEs were reported in 18 subjects during the study. There were 9 AEs in 7 subjects following administration of rosiglitazone 4 mg/glimepiride 1 mg, 9 AEs in 9 subjects following rosiglitazone 4 mg/glimepiride 2 mg and 15 AEs in 10 subjects following rosiglitazone 4 mg/glimepiride 4 mg. All AEs were mild in severity. The most common AE was headache. Summary details for the non-serious, treatment-emergent AEs reported during this study are listed by regimen in the table below.

Adverse Event (Preferred Term)	Number of Subjects			
	Regimen			
	A	B	C	Total
Most Frequent AE (Headache)	3	2	2	7
Total Number of AEs	9	9	15	33
Number of Subjects with AEs	7	9	10	18 ¹
Number of Subjects Exposed	27	26	25	28

Regimen A: rosiglitazone 4 mg/glimepiride 1 mg

Regimen B: rosiglitazone 4 mg/glimepiride 2 mg

Regimen C: rosiglitazone 4 mg/glimepiride 4 mg

1. Some subjects had an AE following administration of more than one study medication regimen.

Title: A Dose Proportionality Study with a Combination Tablet Formulation of Rosiglitazone and Glimepiride (4mg/1 mg; or 4 mg/2 mg; or 4 mg/4 mg) in Healthy Subjects

Six subjects had post-dose clinical laboratory values of potential clinical concern (as defined by the protocol) during the study, however, these were asymptomatic and not clinically significant as determined by the investigator. These post-dose laboratory values of potential clinical concern were considered unrelated to the study medication by the investigator, except for a decreased glucose in one subject, which was observed at 24 hours following administration of rosiglitazone 4 mg/glimepiride 4 mg. There was one vital signs change (increased diastolic blood pressure following rosiglitazone 4 mg/glimepiride 2 mg) of potential clinical concern reported during the study, which was sporadic, asymptomatic and considered not clinically significant by the investigator. There were no ECG interval values of potential clinical concern reported during the study. Six subjects had ECG morphology findings following their first dose of study medication, which were not present at the pre-dose assessment. These ECG morphology findings were asymptomatic and considered not clinically significant by the investigator.

Conclusions:

- Glimepiride was dose proportional over the dose range 1 to 4 mg, following single dose administration of 3 combined tablet formulations of rosiglitazone (4 mg) and glimepiride (1, 2 or 4 mg). The 90% confidence intervals for the comparisons of AUC_{0-24} and C_{max} were completely contained within the range 0.80-1.25.
- Single, oral doses of rosiglitazone 4 mg/glimepiride 1 mg, rosiglitazone 4 mg/glimepiride 2 mg and rosiglitazone 4 mg/glimepiride 4 mg were generally safe and well tolerated in healthy, adult male and female subjects.

Date of Report: September 2003

Title: A Bioequivalence Study with a Combination Tablet Formulation of Rosiglitazone and Glimepiride (4 mg/4 mg) Compared to Concomitant Dosing of Rosiglitazone 4 mg and Glimepiride 4 mg (4 mg+4 mg) Commercial Tablets in Healthy Subjects	
Investigator: Donald Wallace, MD	
Study center: GlaxoSmithKline Clinical Pharmacology Unit, Presbyterian Hospital, 51 N 39th St, Philadelphia, PA 19104	
Publication(s): None as of September 2003.	
Study period: 13Nov2002 to 10Feb2003	Phase of Development: I
Objectives: The primary objective was to demonstrate the bioequivalence of a combination formulation of rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg) relative to concomitant dosing of rosiglitazone 4 mg AND glimepiride 4 mg (4 mg+4 mg) commercial tablets. The secondary objective was to assess the tolerability of dosing with combination formulation of rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg), and rosiglitazone 4 mg AND glimepiride 4 mg (4 mg+4 mg).	
Methodology: This was an open-label, single dose, randomized, two-period, period-balanced, crossover study. Each subject participated in two study sessions. Each session included one (1) evening pre-treatment in-house stay to collect urine drug screen and pregnancy data (Day-1), followed by one (1) 24-hour inpatient stay at the Clinical Pharmacology Unit (CPU). Study medication was administered orally in each study session in a fasted state. Subjects were assigned to one of two treatment sequences (AB, BA) according to a randomization schedule prepared in advance of the study. There was a washout period of at least 3 days between study sessions. Blood sampling for pharmacokinetic analysis of plasma rosiglitazone and glimepiride concentrations was conducted pre-dose and over a 24-hour period following dosing in each session. Subjects were discharged from the CPU after a minimum of 24 hours following dosing. Subjects were asked to return for a follow-up visit at least 10 to 15 days following the last dose of study medication. The duration of each subject's participation in the study from screening to follow-up was approximately 8 weeks.	
Number of subjects: 63 subjects screened, 30 enrolled, 27 completed	
Diagnosis and main criteria for inclusion: Healthy adult men and women between 18 and 55 years of age with BMI between 20-30 kg/m ² .	
Treatment administration: During each study session subjects received under a fasting condition either a single oral dose of the rosiglitazone/glimepiride combination formulation (Regimen A) or a concomitant dose of a single tablet of rosiglitazone 4 mg AND a single tablet of glimepiride 4 mg (Regimen B). Study medication was administered with 150 mL of water by study personnel. To maintain normoglycemia subjects were given 20% dextrose solution by intravenous infusion.	

Title: A Bioequivalence Study with a Combination Tablet Formulation of Rosiglitazone and Glimpiride (4 mg/4 mg) Compared to Concomitant Dosing of Rosiglitazone 4 mg and Glimpiride 4 mg (4 mg+4 mg) Commercial Tablets in Healthy Subjects

Criteria for evaluation:

Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Clinical monitoring and laboratory data were reviewed by the study physician and were not formally analyzed. Adverse events were summarized by formulation. No formal statistical analysis of the safety data was performed.

Pharmacokinetics: Pharmacokinetic assessments included the collection of serial whole blood samples over 24 hours during each of the two treatment periods for bioanalysis of plasma for rosiglitazone and glimepiride concentrations. PK analysis of the plasma rosiglitazone and glimepiride concentration-time data was conducted using non-compartmental methods. $AUC_{(0-\infty)}$, $AUC_{(0-12)}$, C_{max} , t_{max} , and $t_{1/2}$ were estimated following administration of a single oral dose.

Statistical methods: Following \log_e -transformation, $AUC_{(0-\infty)}$, $AUC_{(0-12)}$ and C_{max} for both rosiglitazone and glimepiride were separately analyzed by analysis of variance (ANOVA) using a model appropriate to the study design, fitting terms for sequence, subject-within-sequence, period and regimen. Point estimates and associated 90% percent confidence intervals for the difference A-B were constructed using the residual variance. These point estimates and confidence intervals were then exponentially back-transformed to provide point estimates and associated 90% confidence intervals for the ratio A:B. A similar analysis, but without \log_e -transformation, was performed for $t_{1/2}$ to provide point estimates and associated 90% confidence intervals for the difference A-B. T_{max} was analyzed nonparametrically using the Hauschke Method to compute point estimates and 90% confidence intervals for the median differences for the comparisons of interest. Bioequivalence was demonstrated if the 90% CIs for both AUC and C_{max} of rosiglitazone and glimepiride were completely contained in the interval (0.80, 1.25).

Summary:

Safety: Rosiglitazone and glimepiride were well tolerated. Summary details for all treatment-emergent adverse events are as follows:

	Combination Tablet, Regimen A	Concomitant Dosing, Regimen B
Most Frequent AE (Hypoglycemia)	7	10
Total Number of AEs	31	43
Number of Subjects with AEs	19	22
Number of Subjects Exposed	29	29

Title: A Bioequivalence Study with a Combination Tablet Formulation of Rosiglitazone and Glimepiride (4 mg/4 mg) Compared to Concomitant Dosing of Rosiglitazone 4 mg and Glimepiride 4 mg (4 mg+4 mg) Commercial Tablets in Healthy Subjects

Hypoglycemia was suspected or considered probably related to study medication, and all subjects with hypoglycemia were treated with protocol prescribed rescue medication (intravenous bolus of 50% dextrose or oral Trulol). All non-hypoglycemic adverse events were mild, except for 1 case of moderate back pain, and all events resolved by the end of the study. Subject 202, who reported baseline nausea, was withdrawn from the study due to headache, vomiting, and dizziness, which were all suspected to be related to study medication. Laboratory values of potential clinical concern were all glucose levels, except for Subject 201 with a one-time elevated WBC count prior to dosing with Regimen B. Two subjects had elevated diastolic blood pressure measurements 24 hours after dosing (Subject 109 after Regimen A, Subject 202 after Regimen B); all other vital signs were within normal limits. 12-lead ECG measurements were within normal limits.

Pharmacokinetics: Bioequivalence of the combination tablet formulation of rosiglitazone and glimepiride (4mg / 4mg) relative to concomitant dosing of rosiglitazone and glimepiride commercial tablets (4mg + 4mg) was demonstrated for the rosiglitazone component (AUC and C_{max}) and for the glimepiride component (AUC). Bioequivalence was not demonstrated for the C_{max} of glimepiride, as the 90% CI for the ratio A:B was not completely contained within the range 0.80 to 1.25 for C_{max} of glimepiride. A summary of the point estimates and the associated confidence intervals is provided below:

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Document Number: PM2003/00099/00 Study Number: SB-797620/003

Title: A Study to Assess the Effect of Food on Pharmacokinetics of a Rosiglitazone 4 mg and Glimepiride 4 mg Combination Tablet Formulation and to Compare the Pharmacokinetics of Rosiglitazone 4 mg and Glimepiride 4 mg Combination Tablet to Concomitant Dosing of Rosiglitazone 4 mg and Glimepiride 4 mg Commercial Tablets in the Fed State in Healthy Subjects	
Investigator: David D Hoelscher, MD	
Study center: _____	
Publications: None as of September 2003	
Study period: 14May2003- 13Jul2003	Phase of Development: I
<p>Objectives: The primary objective of the study was to estimate the effect of food on the single dose pharmacokinetics of rosiglitazone and glimepiride in a rosiglitazone/glimepiride (4/4 mg) combination tablet.</p> <p>Secondary objectives were to compare the pharmacokinetics of rosiglitazone and glimepiride after administration of the combination tablet rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg) to the pharmacokinetics after concomitant dosing of rosiglitazone 4 mg and glimepiride 4 mg in a fed state, and to assess the tolerability of dosing with the rosiglitazone 4 mg/glimepiride 4 mg (4 mg/4 mg) combination tablet and concomitant dosing of rosiglitazone 4 mg and glimepiride 4 mg commercial tablets.</p> <p>Pharmacogenetic objectives were to investigate the relationship between genetic variants and the pharmacokinetics or safety or tolerability of SB 797620, assuming sample number was adequate and genotyping assays were available, if at any time there appeared to be potential variability in SB 797620 response or handling (e.g., pharmacokinetics, safety, and/or efficacy) in this clinical study or in a series of clinical studies.</p>	

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Title: A Study to Assess the Effect of Food on Pharmacokinetics of a Rosiglitazone 4 mg and Glimepiride 4 mg Combination Tablet Formulation and to Compare the Pharmacokinetics of Rosiglitazone 4 mg and Glimepiride 4 mg Combination Tablet to Concomitant Dosing of Rosiglitazone 4 mg and Glimepiride 4 mg Commercial Tablets in the Fed State in Healthy Subjects

Criteria for evaluation:

Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Clinical monitoring and laboratory data were reviewed by the study physician and were not formally analyzed. Adverse events were summarized by formulation. No formal statistical analysis of the safety data was performed.

Pharmacokinetics: Pharmacokinetic assessments included the collection of serial whole blood samples over 24 hours during each of the two treatment periods for bioanalysis of plasma for rosiglitazone and glimepiride concentrations. PK analysis of the plasma rosiglitazone and glimepiride concentration-time data was conducted using non-compartmental methods. $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max} , t_{max} , t_{lag} and $t_{1/2}$ were estimated following administration of a single oral dose in each study session

Statistical methods: After \log_e -transformation, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} of rosiglitazone and glimepiride were separately analyzed by analysis of variance (ANOVA) with terms for sequence, subject(sequence), period, and regimen. Point estimates and associated 90% confidence intervals for the differences A-C and A-B were constructed using the residual variance. These point estimates and confidence intervals were then exponentially backtransformed to obtain point estimates and 90% confidence intervals for the ratios A:C and A:B. A similar analysis, but without \log_e transformation, was performed for $t_{1/2}$ of rosiglitazone and glimepiride to provide point estimates and associated 90% confidence intervals for the differences A-C and A-B. T_{max} was analyzed nonparametrically using the Wilcoxon's Matched Pairs Method. The point estimates and 90% confidence intervals for the median differences were calculated for the differences A-C and A-B.

Summary:

Safety: Rosiglitazone and glimepiride were well tolerated when administered either as the combination tablet or concomitantly. No deaths, serious adverse events, or withdrawals due to adverse events were reported in this study. Summary details for all treatment-emergent adverse events are as follows:

	Regimen A	Regimen B	Regimen C
Most Common AE (Hypoglycemia)	30	19	10
Total Number of AEs	75	51	49
Number of Subjects with AEs	32	26	23
Number of Subjects Exposed	35	35	37

A = Combination tablet fed; B = Concomitant dosing of rosiglitazone and glimepiride fed; C= Combination tablet fasted.

Title: A Study to Assess the Effect of Food on Pharmacokinetics of a Rosiglitazone 4 mg and Glimepiride 4 mg Combination Tablet Formulation and to Compare the Pharmacokinetics of Rosiglitazone 4 mg and Glimepiride 4 mg Combination Tablet to Concomitant Dosing of Rosiglitazone 4 mg and Glimepiride 4 mg Commercial Tablets in the Fed State in Healthy Subjects

Comparison	Parameter	Point Estimate	90% CI
Food Effect Assessment			
rosiglitazone A:C	$AUC_{0-\infty}^1$	0.92	(0.89, 0.96)
rosiglitazone A:C	C_{max}^1	0.68	(0.63, 0.73)
rosiglitazone A:C	t_{max}^2	1.25h	(1.00h, 1.74h)
Relative Bioavailability Assessment			
rosiglitazone A:B	$AUC_{0-\infty}^1$	1.02	(0.98, 1.06)
rosiglitazone A:B	C_{max}^1	1.07	(0.99, 1.15)
rosiglitazone A:B	t_{max}^2	0.00h	(-0.50h, 0.25h)
Food Effect Assessment			
glimepiride A:C	$AUC_{0-\infty}^1$	1.19	(1.12, 1.26)
glimepiride A:C	C_{max}^1	1.55	(1.38, 1.74)
glimepiride A:C	t_{max}^2	0.00h	(-0.75h, 0.50h)
Relative Bioavailability Assessment			
glimepiride A:B	$AUC_{0-\infty}^1$	1.05	(1.00, 1.09)
glimepiride A:B	C_{max}^1	1.06	(0.94, 1.20)
glimepiride A:B	t_{max}^2	0.00h	(-0.50h, 0.20h)
4. Data represent the ratio of the adjusted geometric means between regimens.			
5. Data represent the estimated median difference between regimens.			
A = Combination tablet fed; B = Concomitant dosing of rosiglitazone and glimepiride fed; C = Combination tablet fasted.			
Conclusions:			
<ul style="list-style-type: none"> Following administration of the combination tablet, the extent of absorption of rosiglitazone was unaffected in the fed state compared to the fasted state, but the rate of absorption was reduced. The rate and extent of absorption of glimepiride were modestly increased following administration of the combination tablet in the fed state compared to results obtained in the fasted state. For both rosiglitazone and glimepiride, the rate and extent of absorption were equivalent following administration of the combination tablet compared to results obtained on concomitant administration of rosiglitazone and glimepiride separately as the currently approved commercial formulations, both in the fed state. Rosiglitazone and glimepiride were safe and well tolerated when administered in a combination tablet in either a fed or fasted state, as well as when administered as concomitant single tablets in the fed state. 			

Date of Report: September 2003

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7/13/04 12:50:47 PM
PHARMACOLOGIST

Hae-Young Ahn
7/14/04 10:51:45 AM
BIOPHARMACEUTICS

Addendum to CPB review:

Note: Typing error in CPB review in DFS.

Line 4, pg 6: The concentration of SDS should be 0.5% instead of

The dissolution method and specification is as follows:

Medium: 0.01 M HCl with 0.5% SDS.

Apparatus: Paddle (USP type II)

Speed: 75 rpm

Specification limit: Q = at 15 min for rosiglitazone dissolution.

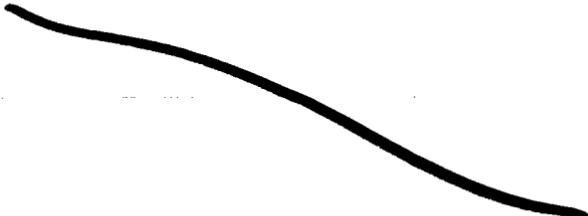
Q = at 45 min for glimepiride dissolution.

Labeling Comments:

It is recommended to move the description of Drug Interactions from PRECAUTION to CLINICAL PHARMACOLOGY section. In addition, the labeling comments sent to sponsor for NDA 21-071/S014 containing drug interaction of rosiglitazone, should also be incorporated into AVANDARYL label.

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

CLINICAL PHARMACOLOGY



8 Page(s) Withheld

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