CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021071

MEDICAL REVIEW(S)

W9 bey

Medical Officer's Review of New Drug Application

21-071 – Rosiglitazone (AVANDIA)

APR 16 1999

Sponsor: Smithkline Beecham

Concur

/S/ [redacted] 4/16/99

Robert I Misbin MD
HFD 510

April 2, 1999
(updated April 12, 1999)

Introduction

Rosiglitazone (RSG or R) is the second thiozolidinedione to be considered for approval. The first of this class, troglitazone, was approved in early 1997 for patients whose hyperglycemia could not be controlled adequately with insulin. It was approved to be used as monotherapy and in combination with sulfonylureas later that year. The major problem with the use of troglitazone has been hepatitis, sometimes leading to hepatic failure. Based on a preliminary review of the liver-related events in this application, it appeared that RSG was less likely to cause hepatitis than troglitazone. For this reason, RSG was given a priority review. Liver related events are discussed in detail at the end of this application. Other safety issues are also discussed in the "safety" section but are not included in a discussion of the individual trials except where pertinent. The application consists of three placebo-controlled dose finding studies and five pivotal studies. Two of the pivotal studies were 26 week placebo controlled studies of monotherapy, each of which had a 26 week open-label extension. There was one 52 week controlled comparison to glyburide. There are also two 26 week placebo-controlled studies of the use of RSG in combination with metformin.

Pharmacology

The primary action of rosiglitazone is believed to be the nuclear receptor PPAR(peroxisome proliferator activated receptor gamma). Binding activity for this nuclear receptor is higher with rosiglitazone than for either troglitazone or pioglitazone. Cell surface insulin receptors and GLUT 4 glucose transporters are increased in fat cells taken from animals treated with rosiglitazone. However, the drug does not appear to insulin receptor kinase activity. In diabetic rodents a lag time of about three days is needed before any antihyperglyemic action is observed. Following withdrawal of rosiglitazone from these animals, it takes four days before glucose levels return to their previously elevated level. This slow onset and offset are consistent with a mechanism of action that requires gene transcription and de novo protein synthesis. Rosiglitazone is 100 times more potent than troglitazone and 10- 30 times more potent that pioglitazone in rodent models of type 2 diabetes. This concordance in dose-response activity between the binding activity to the PPAR receptor and antidiabetic activity provides strong support for the putative mechanism of action of all thiozolidinediones. Not unexpected for an insulin-sensitizer, treatment of diabetic animals with rosiglitazone causes hyperphagia, weight gain and increased fat deposition. Nevertheless, the glucose-lowering effect of the drugs is maintained. Reduction of plasma triglycerides and free fatty acids are also observed in rodent models of type 2 diabetes. Similar results are seen with pioglitazone but at a higher dose reflecting its lower potency.

The bioavailability of R in man is about 95%. It has a t ½ of about 4 hours and is metabolized by the liver. Based on studies with radiolabeled drug, some metabolites appear in the feces, reflecting biliary excretion, but most of the radioactivity is recovered in urine.

Dose ranging studies:

Dose-response relationships were examined in three studies using both once daily and twice daily dosing regimens. The initial study, 006, compared four dose levels of RSG to placebo. The primary efficacy measure was reduction in FPG (fasting plasma glucose) over 12 weeks. The baseline FPG was about 215 mg/dl which rose about 5 mg/dl in patients given placebo and in patients on 0.05 mg bid and 0.25 mg bid R. The lowest effective dose, 1 mg bid, was associated with a mean reduction in FPG of 23.4 mg/dl from baseline. The placebo-subtracted reduction was 28 mg/dl. The highest dose studied, 2 mg bid, gave a mean reduction from baseline of 35.8 mg/dl. The mean placebo subtracted reduction in FPG was 40.4 mg/dl. Based on a reduction in FPG of 40 mg/dl, the response rate was 27.8% at 1 mg bid and 40.5% at 2 mg bid. The placebo response rate was 13.5% which was indistinguishable from the response rates of 11.3 and 11.1% for the two lower doses of R. Subsequent dosing studies lasted 8 weeks and utilized 2 mg bid and 4 mg od as their lowest doses.

Study 098 was an 8 week study conducted in Europe which examined the effects of 4-12 mg R given as 4 mg tablets once per day on fasting plasma glucose reduction. Patients were treated after a three week washout from previous therapy drug therapy that was present in 63% of patients. 13% of patients were on combination therapy Mean FPG was about 185 mg/dl at baseline. Mean FPG rose 7.4 mg/dl from baseline in placebo patients but fell in patients treated with R. As shown in the table below, three 4 mg tablets was no more effective than two 4 mg tablets. Similar results were seen with changes in fructosamine. The response rate was (reduction of at least 30 mg/dl) was 14, 28.4, 52.2, and 54.9% for placebo and 4, 8, 12, mg R respectively.

	R dose, given once daily		
Placebo subtracted	4 mg	2x 4mg	3x 4mg
Baseline reduction FPG, mg/dl	23.2	43.1	37.6
PK data			
Trough, mean ng/dl	7.3	13.2	17.8
Median	5.5	8.5	11.5
Post-dose, mean	244	461	708

Study 090 was conducted in the United States. It was similar to 098 except that R was given according to a twice daily regimen and there was only a two week washout instead of three weeks. 74 % of patients had been on antidiabetic drugs previously, 16 % in combination therapy. Mean FPG was about 228 mg/dl at baseline. Mean FPR rose 19.2 mg/dl from baseline in placebo patients but fell in patients treated with R. The placebo subtracted change was –55.5, -61.7 and -65.1 for 2 mg bid, 4 mg bid, and 6 mg bid respectively.
A comparison of the two regimens is shown in the table

Total daily dose

Change in FPG mg/dl	Placebo	4 mg	8mg	12mg
Twice daily*	17.2	-39.0	-44.9	-48.5
Once daily **	7.4	-15.8	-37.7	-30.2
Responder rate >30 fall,%				
Twice daily *	10.1%	52.1%	57.6%	65.3%
Once daily **	14%	28.4%	52.2%	54.9%

* study 90 **study 98

At first glance, the data shown above suggest that RSG is more effective given by a twice a day than once per day. However, differences between the two studies preclude a direct comparison. The shorter washout before baseline in study 90 (two weeks) than study 98 (three weeks), and the greater percentage of patients taken off previous antidiabetic medications help to explain the greater rise in FPG which occurred in patients on placebo during the trial of study 90. With the greater percentage of patients previously on antidiabetic medication it is not surprising that the mean baseline FPG was higher in study 90 (228 mg/dl) than in study 98 (185 mg/dl). Since a "response" was defined as an absolute fall in FPG of 30 mg/dl or more, the higher response rate with R in study 90 could simply reflect the higher basline value. While the higher response rate to placebo in study 98 could reflect the greater percentage of patients who had previously been on " diet alone" and did not really require any antidiabetic medication. Despite these shortcomings, the data in the table suggest that twice per day dosing is better than once per day dosing. A direct comparison of these two regimens was performed in study 24 described in detail below.

EFFICACY

Monotherapy:

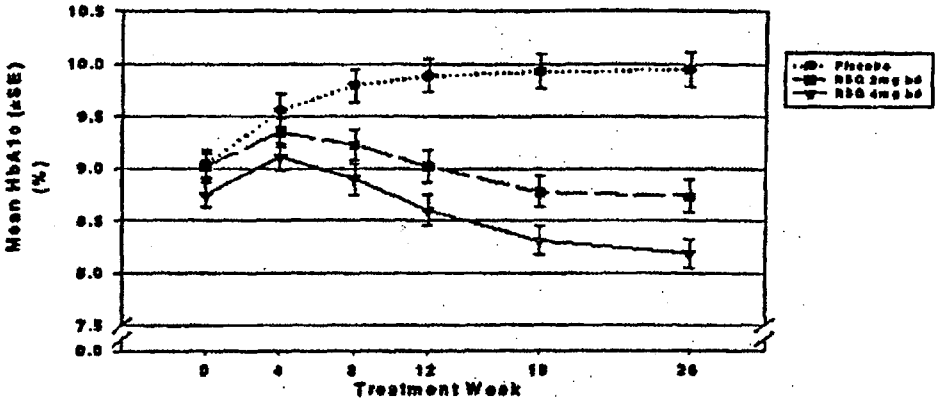
011 – This 26 week placebo-controlled study was performed in the United States.

This study compared placebo to RSG at 2 mg bid and 4 mg bid. Inclusion criteria include a FPG between 140 and 300 mg/dl. There was a minimum of two week withdrawal from previous antidiabetic therapy (66% of patients had been on previous monotherapy) followed by a four week placebo run-in. The major efficacy variable was HbA1c. A responder analysis originally based on reduction of 1.0% units in HbA1c was changed to 0.7% presumably based on a draft of the FDA guidance. A second definition of response was fall of FPG of 30 mg/dl or greater from baseline. Patients had type 2 diabetes with FPG between 140-300 mg/dl at baseline (at least two weeks off previous antidiabetic medication if applicable). Patients had fasting C peptide over 0.8 ng/dl. Patients were excluded for liver chemistry over 2.5 x ULN. Patients were withdrawn for FPG of 300 or greater on two successive clinic visits. Patients studied by DR Fiddes where excluded from analysis because of an FDA probe.

Approximate 75% of patients were white, 65% were under 65 years old, 65% were male and 74% had a BMI of 27 or greater. There were no baseline imbalances among these characteristics. Approximately 27% had previously been on diet alone previously. Previous combination therapy was reported for 7.6% of placebo patients, 4.8% for patients on R 2 mg bid and 7.7% for patients on R 4 mg bid. The remaining patients had been on single agent therapy, about 65% in all groups. Patients had a baseline HbA1c of about 9%, FPG of about 225 mg/dl, and average duration of diabetes of about 5 years. Approximately 75% of patients in each of the two R groups completed the study compared to 56% of patients in the placebo group. Withdrawal due to lack of efficacy occurred in 16/175 (9.1%) on R 2 mg bid, 15/182(8.2%) of patients on R 4 mg bid and 36 (20.5%) of placebo patients. Withdrawal due to AE's occurred in 9.1% and 3.8% in low and high dose R groups and 8.0% in the placebo group.

A time course of the change in HbA1c is shown in the figure. (NOTE: labeling for figures and tables refers to how they appear in the NDA) Patients on placebo showed a mean rise on A1c of 0.9% units compared to falls of 0.5 and 0.6 in patients on 2 mg bid and 4 mg bid of R. The rise in A1c in placebo and the difference between the placebo groups and both R groups were highly significant ($p<0.0001$).

Figure 3 Mean HbA1c Over Time (ITT Population)

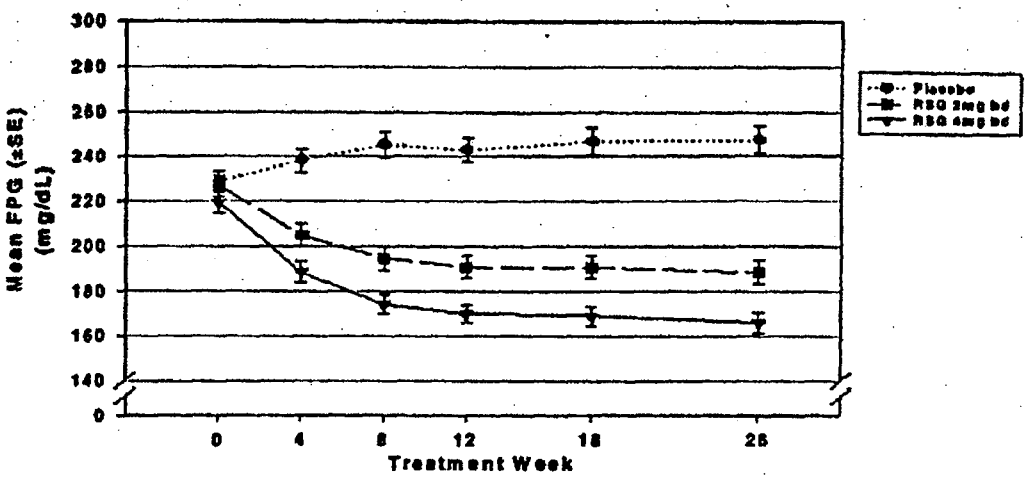


(ROSIGLITAZONE/811 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2A

A time course of the change in FPG is shown in the figure. Placebo patients had a mean rise in FPG of 18.9 mg/dl compared to mean falls of 38.4 and 53.9 mg/dl on 2 mg bid and 4 mg bid. All these changes from baseline and differences between R and placebo are highly significant.

Figure 6 Mean Fasting Glucose Over Time (ITT Population)



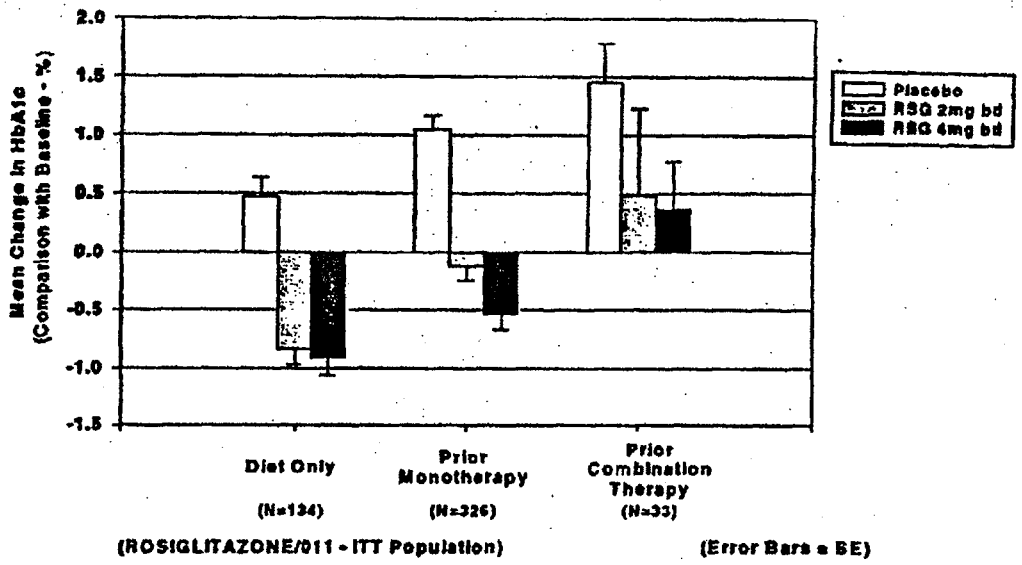
(ROSIGLITAZONE/011 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2A

Based on a reduction in FPG of at least 30 mg/dl at 26 weeks, the responder rate was 15.8% for placebo, 54.2% for 2 mg bid and 63.9% for 4 mg bid. The difference between placebo and both doses of R were significant ($p<0.0001$). For patients achieving a FPG under 140 mg/dl at week 26, there were 2.5% placebo patients, 25.3 and 39.1% for 2 mg bid and 4 mg bid R respectively.

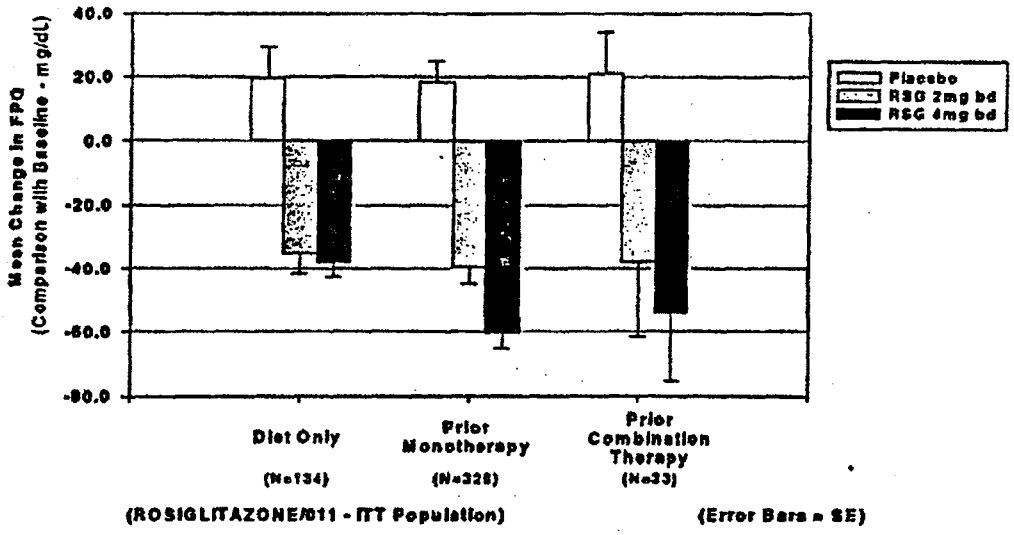
A comparison between the time course in HbA1c and FPG is of interest. Mean FPG rose in the placebo group during the first 8 weeks of treatment but remained constant thereafter. For patients on R, most of the fall in FSG occurred by 12 weeks but there was a continued drift downward even at week 26. By contrast, mean HbA1c levels rose in all groups during the first four weeks. Thereafter, A1c levels continued to rise in placebo patients but fell in R patients. Two point emerge from these figures. The first is that the full effect of R on glucose reduction requires 12 weeks or longer. The second is that the initial rise in HbA1c probably reflects a delayed effect of the rise in FPG that occurred during the six weeks between discontinuation of previous therapy and beginning the trial. Indeed, patients previously on monotherapy showed a mean 27 mg/dl rise in FPG from screening to baseline. Patients previously on diet alone showed no change.

Figure 9 Change from Baseline at Week 26 in HbA1c by Prior Therapy



Data Source: Section 14, Table 14.5.6A

Figure 10 Change from Baseline at Week 26 in FPG by Prior Therapy



Data Source: Section 14, Table 14.5.6A

SKB has provided a subgroup analysis based on prior therapy that shows that R was effective vs placebo in ALL groups. The full table with statistics is shown in TABLE 23..

Table 23 HbA1c at Selected Time Points by Prior Therapy

(Efficacy Evaluable Population)

	Placebo			RSG 2mg bid			RSG 4mg bid		
	Diet*	Mono**	Combo†	Diet*	(Mono**	Combo†	Diet*	Mono**	Combo†
HbA1c (%)									
Reference range: 56.4%									
Week -6, N	43	98	12	42	112	8	41	102	12
Mean ± SD	9.0 ± 1.90	8.3 ± 1.63	8.7 ± 1.12	8.9 ± 1.54	8.3 ± 1.41	8.2 ± 2.33	8.9 ± 1.79	8.1 ± 1.46	8.4 ± 1.18
Baseline, N	43	98	12	42	112	8	42	103	12
Mean ± SD	8.6 ± 1.76	9.1 ± 1.64	9.9 ± 1.15	8.8 ± 1.49	9.1 ± 1.48	9.6 ± 2.34	8.5 ± 1.52	8.9 ± 1.55	9.7 ± 1.31
Week 4, N	42	98	12	41	109	8	41	103	11
Mean ± SD	8.7 ± 1.90	9.8 ± 1.85	10.8 ± 1.64	8.8 ± 1.70	9.5 ± 1.78	10.7 ± 2.68	8.7 ± 1.58	9.3 ± 1.74	10.3 ± 1.42
Week 26, N	35	61	3	39	81	5	39	85	8
Mean ± SD	8.7 ± 1.59	9.7 ± 1.84	10.7 ± 1.56	8.0 ± 1.48	8.4 ± 1.70	9.6 ± 3.37	7.5 ± 1.16	7.8 ± 1.35	9.1 ± 1.96

* Patients previously treated with diet only.

** Patients previously treated with a single oral anti-diabetic agent (i.e., monotherapy).

†

† Patients previously treated with more than one oral anti-diabetic agent (i.e., combination therapy).

Data Source: Section 14, Table 14.2.1; Appendix F, Listing F.L.1

An abbreviated table, shown below, is presented to illustrate several major points. I have displayed the data according to previous therapy (diet only, monotherapy or combined) and have only included the HbA1c value at screening (to reflect the efficacy of previous therapy) and at the end of R treatment. Since the data are efficacy evaluable patients, without last observation carried forward, a strict statistically valid comparison is not intended

Looking first at patients previously on diet alone (see table below), one sees that there was a small fall in HbA1c (9.0 to 8.7) over the course of the study. This probably means that the patients were maintained on a regimen of diet and exercise which was at least as good as what they had been on before entering the study. The reduction in A1c attributable to R represents value added over and above continuation of previous management. This is different from many trials DMEDP has reviewed in which a rise in A1c in placebo patients has been attributed to "disease progression", even though relaxation of diet and exercise during the trial would be equally likely.

HEMOGLOBIN A1c

Previous Rx: DIET ONLY

	Placebo	2mg bid	4 mg bid
Previous Rx, -6 weeks	9.0 n=43	8.9 n=42	8.9 n=41
Study Rx, 26 weeks	8.7 n=35	8.0 n=39	7.5 n=39

For patients previously on monotherapy, a rise in HbA1c from 8.3% to 9.7% for patients put on placebo is not surprising. That mean HbA1c levels changes little for patients put on R (rise of 0.1 an 2 mg bid and fall of 0.3 on 4 mg bid) suggests that monotherapy with R was roughly comparable to what the patients had been taking previously.

Previous Rx : MONOTHERAPY

Previous Rx , –6 weeks	8.3 n=98	8.3 n=112	8.1 n=102
Study Rx, 26 weeks	9.7. n=61	8.4 n=81	7.8 n=85

By contrast, monotherapy with R was not as effective as previous combination therapy although it was more effective than placebo (see table below).

Previous Rx: Combination

Previous Rx, –6 weeks	8.7 n=12	8.2 n=8	8.4 n=12
Study Rx, 26 weeks	10.7 n=2	9.6 n=5	9.1 n=8

derived from TABLE 23 vol009 EE patients

RSG was effective in all subgroups studies. The only potentially important factor that emerged from subgroup analysis was gender. R was more effective in females than in males both in terms of absolute improvement in hyperglycemia and improvement relative to placebo. No important differences were found with respect to age, baseline hyperglycemia or obesity.

In summary, these data support a labeling claim that RSG is effective for monotherapy in general, both as INITIAL monotherapy and for patients already on other forms of monotherapy. At 4 mg bid, the response rate based on FPG reduction from baseline was 67% for patients previously on diet alone and 74% for patients taken off monotherapy with other drugs. To cause hyperglycemia by discontinuation of standard treatment as part of a placebo-controlled trial does raise serious ethical questions. This issue will be dealt with in a later section. Suffice to point out here, however, that this study ran from 12 Sep 1996 through 26 Sep 1997. To withhold active treatment from patients with HbA1c >8% is inconsistent with the standards of medical care recommended by the American Diabetes Association since 1994, let alone to intentionally cause hyperglycemia by discontinuation of standard antidiabetic medications.

Other results of interest were reduction of insulin, proinsulin, split proinsulin and C peptide at 4 mg bid R vs placebo, and increased body weight, particularly in R responders (TABLE 27). LDL/HDL rose barely from 2.98 to 2.99 in placebo patients but rose significantly from 3.03 to 3.43 in patients on RSG 4 mg bid .

Table 27 Change in Weight at Week 26 Compared to Baseline by HbA1c Responder Status

(All Randomized Population)

Change in Weight (kg)	Placebo	RSG 2mg bd	RSG 4mg bd
HbA1c Responders*, N**	9	61	67
Mean ± SD	-1.0 ± 2.97	2.4 ± 3.21	4.2 ± 4.17
Non-responders, N**	91	68	73
Mean ± SD	-1.0 ± 2.89	0.9 ± 2.80	2.7 ± 2.63

* Responders defined as ≥0.7 percentage points reduction in HbA1c from baseline.

** N = number of patients with values at both baseline and week 26.

Data Source: Section 14, Table 14.6.3.2; Appendix E, Listing E.L2A.

024 – This 26 weeks placebo controlled study was conducted in the United States.

The treatment arms were RSG 4 mg d, 2 mg bid, 8 mg od, 4 mg bid or placebo The primary purpose was to investigate the efficacy of R monotherapy. A secondary purpose was to investigate differences between a once daily and twice daily regimen of R administration. The patient population and study design are the same as for protocol 011 except for R dosage. There were five arms. 2mg each morning and placebo tablet in the evening, 2 mg tablets morning and evening, one 4 mg tablet in the morning and placebo tablet in the evening, 4 mg tablets morning and evening and placebo tablets morning and evening. .

Withdrawals due to lack of efficacy occurred in 9.1% of patients on 8 mg od compared to 5.1% of patients on 4mg bid and 5.7% and 6.6% of patients on 4 mg od and 2 mg bid;.withdrawal for patients on placebo was 16.8%. The time course of the changes in HbA1c and FPG are largely the same as observed in study 011. Analysis of the primary efficacy variable, HbA1c is shown in TABLE 14 below

Table 14 Change from Baseline in HbA1c (%) at Week 26 Compared to Placebo

(ITT Population)

	Treatment Group				
	Placebo	RSG 4mg od	RSG 2mg bd	RSG 8mg od	RSG 4mg bd
HbA1c (%)					
Reference Range: <6.5(%)					
n	173	180	186	121	187
Baseline (mean ± SD)	8.93 ± 1.521	8.91 ± 1.589	8.87 ± 1.542	8.94 ± 1.516	9.04 ± 1.521
Median	8.70	9.00	8.75	8.80	8.90
Week 26 (mean ± SD)	9.72 ± 1.882	8.93 ± 2.007	8.74 ± 1.927	8.62 ± 1.806	8.37 ± 1.941
Median	9.50	8.40	8.30	8.20	7.80
Change From Baseline (mean±SD)	0.79 ± 1.102	0.02 ± 1.398	-0.13± 1.417	-0.31± 1.235	-0.67± 1.372
95% CI	0.62, 0.96	-0.19, 0.22	-0.33, 0.08	-0.49, -0.13	-0.87, -0.48
p-value*	<0.0001	0.8815	0.2138	0.0008	<0.0001
Difference From Placebo (adjusted mean)	-	-0.77	-0.93	-1.10	-1.45
95% CI	-	-1.07, -0.46	-1.24, -0.62	-1.41, -0.79	-1.75, -1.14
p-value††	-	<0.0001	<0.0001	<0.0001	<0.0001
Equivalence of od vs bd	-		-		-
Adjusted Mean Difference	-	0.17	-	0.35	-
95% CI‡	-	-0.14, 0.47	-	0.04, 0.65	-

* Note: All values calculated are only for those patients who had a baseline and week 26 (last on-therapy observation carried forward if week 26 is missing)

† p value for statistical significance = 0.05

†† p value for statistical significance = 0.0271

‡ Confidence intervals adjusted by Bonferroni method

Data Source: Section 14, Tables 14.3.A, 14.4A and 14.3C; Appendix C, Listings C.1.1 and C.1.2

Mean HbA1c rose in the placebo group reflecting discontinuation of previous antidiabetic therapy 6 weeks before randomization. Mean HbA1c levels at 26 weeks were little changed from baseline in the 2 mg bid and 4 mg od groups, but fell in the 4 mg bid and 8 mg od groups. The mean placebo subtracted difference in HbA1c was –0.77, -0.93, -1.10 and – 1.75 for 4 mg od, 2 mg bid, 8 mg od, 4 mg bid respectively. The twice a day regimen appeared to be better than the once a day regimen at both dosage levels. But for 4 mg, the analysis of confidence intervals for the mean difference between the two regimens was consistent with the two regimens being equivalent. The confidence interval did not include zero for 8 mg qd compared to 4 mg bid. This shows that the 4 mg twice daily regimen was better. A responder analysis using HbA1c is shown in TABLE 17 and yields largely the same conclusion.

Table 17 Fasting Plasma Glucose Responder Analysis

(Intent-to-Treat Population)

Reduction in Fasting Plasma Glucose at week 24, n(%)	Placebo (n* =173)	RSG 4mg od (n* = 180)	RSG 2mg bd (n* = 186)	RSG 8mg od (n* = 181)	RSG 4mg bd (n* = 187)
Nonresponders					
<30mg/dL	141 (81.5)	99 (55.0)	86 (46.2)	77 (42.5)	56 (29.9)
Responders**					
30 - <40mg/dL	9 (5.2)	16 (8.9)	19 (10.2)	16 (8.8)	21 (11.2)
40 - >50mg/dL	5 (2.9)	15 (8.3)	17 (9.1)	15 (8.3)	18 (9.6)
≥50mg/dL	18 (10.4)	50 (27.8)	64 (34.4)	73 (40.3)	92 (49.2)
Total Responders, n(%)	32 (18.5)	81 (45.0)	100 (53.8)	104 (57.5)	131 (70.1)
Comparison with Placebo					
Diff. in Proportion of Responders	--	26.5	35.3	39.0	51.6
95% CI	--	15.5, 37.5	24.7, 45.9	28.0, 49.9	41.0, 62.1
Odds Ratio	--	3.8	5.7	6.5	11.7
95% CI	--	2.2, 6.6	3.3, 10.1	3.7, 11.5	6.6, 20.9
p-value†	--	0.0001	0.0001	0.0001	0.0001
Patients who achieved FPG <140mg/dL at week 24	9 (5.2)	31 (17.2)	46 (24.7)	52 (28.7)	65 (34.8)

* n = number of patients with values at baseline and week 24 (last observation carried forward if week 24 is missing).

** Responders defined as patients with ≥30mg/dL reduction in FPG from baseline.

† p value for statistical significance = 0.0271

Data Source: Section 14, Table 14.7.1A; Appendix C, Listing C.2.1

However a different conclusion about the equivalence of 4 mg od and 2 mg bid comes from analysis of FPG and fructosamine data, TABLE 16, a summary of which is shown below:

FPG	4 mg RSG od	2 mg RSG bid	8 mg RSG od	4 mg RSG bid
Baseline mg/dl	229	225	228	228
Placebo subtracted change	-31	-43	-49	-62
Fructosamine				
Baseline, uM	367	367	370	375
Placebo subtracted change	-29	-39	-42	-64

Ones sees that 2 mg bid appears better than 4 mg od with respect to reduction in FPG and fructosamine. Indeed, 2 mg bid is almost as effective as 8 mg od.

Table 16 Change in Fasting Plasma Glucose and Fructosamine at Week 26 Compared To Baseline and Placebo

(Intent-to-Treat Population)

Glycemic Parameter	Treatment Group: Placebo	RSG 4mg bid	RSG 2mg bid	RSG 8mg bid	RSG 4mg bid
Plasma Glucose (mg/dL)*					
n**	173	180	186	181	187
Baseline (mean ± SD)	225.4 ± 57.71	228.9 ± 60.85	225.2 ± 56.30	228.4 ± 58.19	228.3 ± 57.68
Median	218.0	229.0	220.0	232.0	232.0
Week 26 (mean ± SD)	233.2 ± 62.96	204.4 ± 68.37	189.8 ± 61.71	186.2 ± 63.92	173.0 ± 60.93
Median	228.0	187.5	175.0	169.0	153.0
Change From Baseline (mean±SD)	7.8 ± 48.13	-24.6 ± 56.67	-35.4 ± 46.95	-42.2 ± 57.32	-55.4 ± 52.00
95% CI	0.5, 15.0	-32.9, -16.2	-42.2, -28.6	-50.6, -33.8	-62.9, -47.9
p-value†	0.0353	<0.0001	<0.0001	<0.0001	<0.0001
Difference From Placebo (adjusted mean)	-	-31.1	-43.3	-49.2	-62.2
95% CI	-	-42.8, -19.5	-54.8, -31.8	-60.8, -37.6	-73.7, -50.7
p-value††	-	<0.0001	<0.0001	<0.0001	<0.0001
Fructosamine (mcmol/L) (Reference range: 200-278 mcmol/L)					
n	173	180	186	181	187
Baseline (mean ± SD)	372.2 ± 77.28	366.7 ± 77.85	367.3 ± 82.68	370.4 ± 83.12	375.1 ± 85.16
Median	374.0	361.0	354.5	366.0	364.0
Week 26 (mean ± SD)	393.2 ± 94.71	359.5 ± 103.69	350.0 ± 90.69	349.0 ± 89.58	332.2 ± 87.57
Median	386.0	331.0	329.5	323.0	305.0
Change From Baseline** (mean±SD)	21.1 ± 63.69	-7.3 ± 64.69	-17.3 ± 69.06	-21.4 ± 62.91	-42.9 ± 62.33
95% CI	11.5, 30.6	-16.8, 2.3	-27.3, -7.3	-30.6, -12.1	-51.8, -33.9
p-value†	<0.0001	0.1342	0.0008	<0.0001	<0.0001
Difference From Placebo (adjusted mean)	-	-28.9	-39.3	-42.8	-63.6
95% CI	-	-44.0, -13.8	-54.2, -24.4	-57.8, -27.7	-78.5, -48.7
p-value††	-	<0.0001	<0.0001	<0.0001	<0.0001

* Reference range: 13 to 49 years, 70 to 115mg/dL; ≥50 years, 70 to 125mg/dL.

** All values and calculations are for those patients who had baseline and week 26 values (last on-therapy observation carried forward if week 26 is missing).

† p value for statistical significance = 0.05

†† p value for statistical significance = 0.0271

NOTE: *All laboratory values are fasting.*

Data Source: Section 14, Tables 14.3A and 14.4A; Appendix C, Listings C.1.1 and C.1.2

The reduction in HbA1was associated with increased body weight and increased LDL/HDL (table)

	HbA1c		Body Weight (kg)	
	Placebo	RSG 4 mg bid	Placebo	RSG 4 mg bid
Baseline	8.93	9.04	88.4	88.5
26 weeks	9.72	8.37	87.4	91.7
Delta	0.79	-0.67	-0.9	+3.3
		-1.45		+4.2

		Placebo	RSG 4 mg bid
LDL/HDL	baseline	3.021	3.024
	26 weeks	2.854	3.119*
	*different from placebo		

Changes in HbA1c based on previous therapy is shown below for EE population (TABLE 21) RSG was effective vs placebo in all groups with respect to changes in the primary measure of efficacy which was reduction from baseline of HbA1c. But I shall focus here on changes in HbA1c from screening (-6 weeks from baseline) in order to provide and approximate comparison of RSG to the therapy patients had been on previously.

Table 21 HbA1c at Selected Time Points by Prior Therapy

(Efficacy Evaluable Population)

	Treatment Group				
	Placebo	RSG 4mg od	RSG 2mg bd	RSG 8mg od	RSG 4mg bd
HbA1c (%)					
Diet Only					
Week -6, N	37	37	45	49	45
Mean ± SD	8.69±1.86	8.94±1.85	9.07±1.90	8.88±1.45	9.06±1.71
Baseline, N	37	37	46	50	45
Mean ± SD	8.40±1.45	8.55±1.47	8.86±1.53	8.64±1.36	8.68±1.36
Week 4, N	36	37	46	50	45
Mean ± SD	8.33±1.33	8.42±1.33	8.83±1.47	8.56±1.28	8.39±1.34
Week 26, N	30	34	44	42	43
Mean ± SD	8.54±1.66	7.54±1.35	7.83±1.35	7.75±1.25	7.53±1.35
Monotherapy					
Week -6, N	106	109	104	98	120
Mean ± SD	8.36±1.51	8.21±1.61	8.04±1.50	8.25±1.64	8.47±1.47
Baseline, N	106	109	104	98	120
Mean ± SD	8.97±1.55	8.80±1.61	8.64±1.46	9.01±1.62	9.18±1.57
Week 4, N	105	109	104	97	118
Mean ± SD	9.43±1.67	9.20±1.73	9.06±1.57	9.43±1.75	9.52±1.78
Week 26, N	65	91	88	76	102
Mean ± SD	9.74±1.78	8.71±1.77	8.52±1.72	8.36±1.56	8.26±1.69

Table 21 HbA1c at Selected Time Points by Prior Therapy (continued)

(Efficacy Evaluable Population)

Combination therapy					
Week -6, N	27	29	36	29	19
Mean ± SD	8.13±1.28	8.66±1.59	7.96±1.29	8.00±1.28	8.07±1.32
Baseline, N	27	29	36	29	19
Mean ± SD	9.40±1.33	9.98±1.17	9.55±1.62	9.28±1.28	9.27±1.45
Week 4, N	27	29	36	28	19
Mean ± SD	9.96±1.38	10.83±1.17	10.12±1.78	10.18±1.34	9.98±1.67
Week 26, N	12	19	26	20	12
Mean ± SD	9.59±1.72	10.70±1.66	9.62±2.15	9.57±1.81	8.08±1.55

Data Source: Section 14, Table 14.2.1; Appendix F, Listing F1.1

For patients previously on "diet alone", R was effective in lowering HbA1c in all groups with little change in patients on placebo. For patients previously on monotherapy, mean A1c rose from 8.36% to 9.74 in patients randomized to placebo. Mean HbA1c levels rose about 0.5% units for patients randomized to 4 mg RSG and were largely unchanged for patients on 8 mg. The effectiveness of R in these patients is manifested by the difference in HbA1c change vs placebo and by the higher withdrawal rate in placebo patients. One can make a tentative conclusion from these results to 8 mg R is approximately as effective as previous monotherapy. 4 mg appears somewhat less effective. The same conclusion can be drawn from FPG. HbA1c generally rose in patients previously on combination therapy. Mean HbA1c was 8.13 initially and was 9.59% after 26 weeks of placebo. Patients on R 2 mg bid, 4 mg od, and 8 mg od did not do very much better. For patients on 4 mg bid, HbA1c was 8.07% initially and rose to 9.98 after 4 week of R. however, the final value was 8.08% for the 12/19 patients who remained in the study. These results lead to the tentative conclusion that 4 mg bid RSG is approximately as effective as the combination therapy some of these patients had been receiving previously. But other regimens, including 8mg od, are inferior. Rigorous comparisons of RSG vs sulfonylureas and vs metformin are provided in trials discussed later.

Safety: The only safety issue noting in this study is that 6 patients on 4 mg bid had cardiac events including two myocardial infarctions. There were 2 patients on 8 mg od who had cardiac events, both"coronary artery disorder". There were 5 placebo patients with cardiac events including 2 myocardial infarctions.

020 – This was a 52 week active controlled study conducted at several centers in Europe

This was a 52 week double dummy controlled comparison of R at 2 mg bid and 4 mg bid with a titrated dose of glyburide (glibenclamide is the European name for glyburide).. Patients were taken off other antidiabetic agents at least 6 weeks before randomization.. There was a two week washout followed by a four week placebo run-in. Patients non-compliant during the placebo run-in were excluded. To insure blinding, all patients took three identical-appearing capsules, two with breakfast and one before dinner. Inclusion criteria were fasting C peptide of > 0.8 ng/dl and a FBG between 126 mg/dl and 270 mg/dl at the end of the 6 week run-in. Patients with liver enzyme above 2.5 x ULN were excluded. Patients were randomized to one of three arms: R 2 mg bid, R 4mg bid or glyburide. The doses of R were constant while the dose of glyburide was titrated to a maximum of 15 mg. All glyburide was given in the morning. The starting dose of glyburide was 2.5 mg , which was increased every 2 weeks for 12 weeks at the discretion of the investigator. For patients randomized to R, the "titration" would consist of increasing the "dose" of glyburide placebo After 12 weeks all doses remained constant. Termination due to lack of efficacy for the first 16 weeks was FPG > 279 mg/dl, beyond 16 weeks was 216 mg/dl The primary efficacy variable was change in HbA1c. Equivalence of R to glyburide was based on the upper limit of 95% confidence. Other measure of metabolic control were listed as secondary variables. PK studies were done in the R patients at weeks 4, 26, and 52. A responder analysis was defined as a reduction of A1c at least 0.7 % units, fall in FPG of at least 30 mg/dl or achievement of targets FPG of under 140 mg/dl.

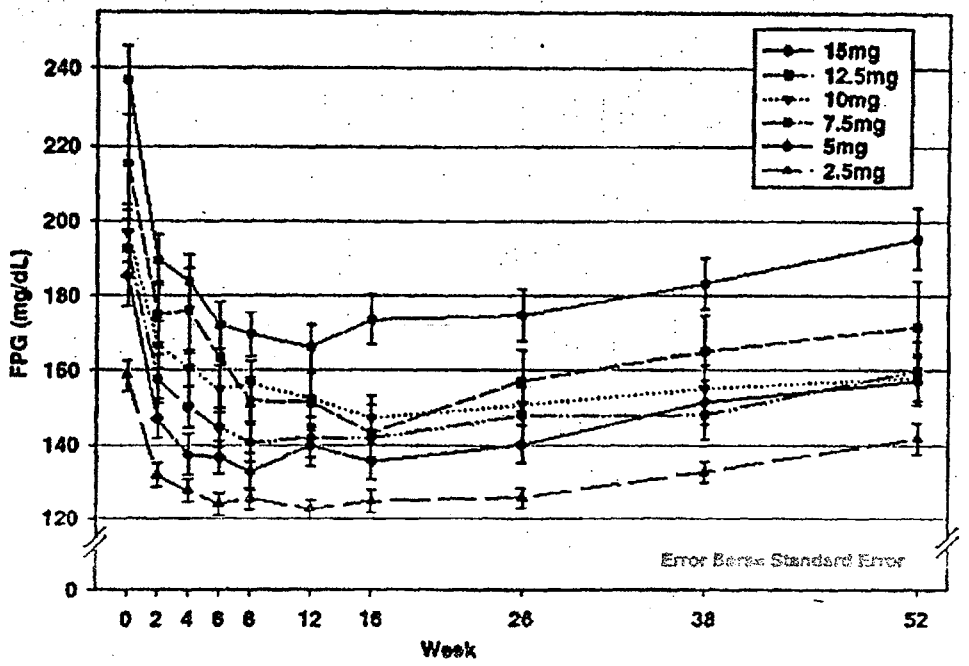
About 2/3 of the patients were men, BMI > 27. The mean age 60.4 year with average duration of diabetes of 6 years. 98% were white. About 50% had been on previous monotherapy, 40% on diet only, and 10% on combination therapy. 23% had been on metformin, 5% on acarbose, and the rest on SFU's. There were no baseline imbalances among these demographic characteristics (see table).

	Glyburide n=203	RSG 2mg bid n=195	RSG 4mg bid n=189
Baseline HbA1c	8.16	8.07	8.21
Baseline FPG	190.4	190.2	195.7 -

Withdrawal due to lack of efficacy occurred in 7/207 (3.4%) of patients on glyburide, 22/200(11%) of patients on 2 mg bid R and 15/191 (7.9%) of patients on R 4 mg bid. All but one of the withdrawals for lack of efficacy in glyburide patients occurred at 26 weeks or after. Withdrawals in the R groups were distributed equally throughtout the study. Of patients who completed the 12 week titration period, 47.1% had a final dose of glyburide of 2.5 – 5 mg. The median final dose was 7.5 mg. As shown in figure 3, FPG fell rapidly in patients on glyburide achieving a nearly complete effect by 6 weeks. Dose escalation was not permitted beyond week 12. Glucose levels remained nearly constant week 12 – 26. Beyond 26 weeks glucose levels began to rise.

BEST POSSIBLE

Figure 3 Mean FPG Over Time by End Titrated Glibenclamide Dose Level (ITT Population)



Data Source: Section 14, Table 14.9A

ITT analysis of the primary variable, HbA1c is shown in TABLE 16

APPEARS THIS WAY ON ORIGINAL

Table 16 Change in HbA1c at Study Endpoint (Week 52) Compared to Baseline and Glibenclamide

Intent-to-Treat Population

	Treatment Group		
	Glibenclamide (N = 202*)	RSG 2mg bd (N = 195)	RSG 4mg bd (N = 189)
HbA1c (%)**			
Baseline (mean ± SD)	8.15 ± 1.256	8.07 ± 1.296	8.21 ± 1.449
Week 52 (mean ± SD)	7.43 ± 1.334	7.80 ± 1.513	7.68 ± 1.613
Change from baseline**			
mean ± SD	-0.72 ± 0.996	-0.27 ± 1.040	-0.53 ± 1.313
95% CI	-0.86, -0.58	-0.42, -0.12	-0.72, -0.34
p-value	<0.0001	0.0003	<0.0001
Difference from glibenclamide			
adjusted mean difference		0.44	0.21
95% CI		0.23, 0.65	-0.01, 0.42

* Excludes one patient who did not have a baseline and an on-therapy value for HbA1c.

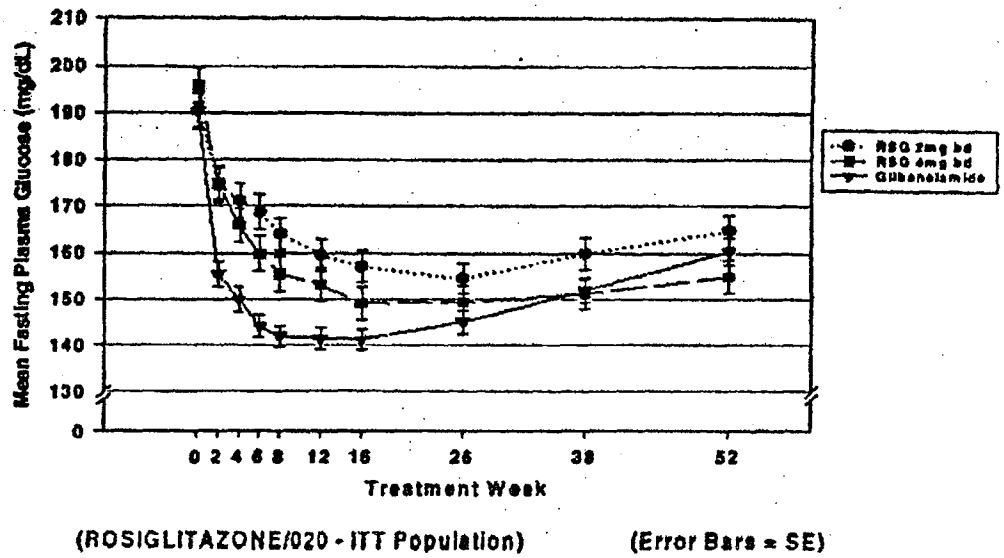
** SBCL reference range: <6.5%

† All values calculated are only for those patients who had a baseline and an on-therapy value (last on-therapy observation carried forward if week 52 is missing).

Data Source: Section 14, Tables 14.3A and 14.8.1A: Appendix C, Listing C.L1

As shown in FIG 5, the fall in glucose appears to be quicker and deeper with glyburide, but RSG may be more durable. The response rate, based on reduction > 30 mg at 52 weeks was 48% with Glyburide, 37% for R 2 mg bid and 42% for R 4 mg bid. For patients reaching a FPG < 140 mg/dl the response rate was 37% for glyburide, 36% and 51% for 2 mg bid and 4 mg bid R respectively. (This response rate SHOULD NOT be equated with the response rate currently in the label for Rezulin because 1) it was measured at 52 weeks instead of 6 weeks, and 2) most patients in this trial were coming off of antidiabetic therapy. The response rate in the Rezulin label reflects only naïve patients.)

Figure 5 Mean Plasma Glucose Over Time (ITT Population)



(ROSIGLITAZONE/020 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2A

Insulin and proinsulin levels rose in glyburide patients but fell in R patients. C peptide and split proinsulin was unchanged in Glyburide patients but fell in R patients. Free fatty acids fell from baseline in all groups but the decline was greater at both doses of R ($p<0.001$) than on Glyburide. Relative to glyburide, total cholesterol, HDL cholesterol, LDL cholesterol, and apo B rose in patients on R. The LDL/HDL ratio fell in patients on Glyburide but was little changed in patients on mg bid R ($p=0.0037$) VLDL rose in patients on both doses of R. Despite the statistical significance, the changes in lipids were of small magnitude. The most troublesome was LDL cholesterol, which was 142 at baseline, fell to 138 in patients on glyburide but rose to 158 in patients on R 4 mg bid ($p<0.0001$). Body weight rose 1.9 kg on glyburide but 2.95 kg on RSG 4 mg bid ($p<0.02$)

Hypoglycemia:

Hypoglycemia was reported in 25/207 patients on glyburide compared to 1/200 on 2 mg bid and 3/191patients on 4 mg bid R. Two patients on glyburide had an event requiring the assistance of a third party compared to 1 event for patients on 4mg bid R. Nearly half of the events in glyburide patients occurred during the first 14 days of treatment. The events in R-treated patients were evenly distributed over the first 6 months. Hypoglycemia led to withdrawal in 6 patients on glyburide and 1 patients on 4 mg bid R. Since hypoglycemia can be viewed as a manifestation of efficacy, unequal withdrawal of patients with hypoglycemia on glyburide could potentially lead to underestimation of its efficacy. An ITT analysis with LOCF of FPG would not take into account a low glucose value that occurred sporadically. Still worse, withdrawal due to hypoglycemia early in the trial (as was often the case with glyburide) would remove low HbA1c values that would have been present had those patients not been withdrawn. The statistician has been alerted to this issue in order to determine if there is reason to doubt the claim of therapeutic equivalence between glyburide and 4 mg bid R based on HbA1c levels.

Body weight increased significantly in all groups. Initial mean body weight was about 81 kg. The weight increase was 1.9 kg on Glyburide, 1.75 kg on R 2 mg bid and 2.95 kg on R 4 mg bid. The 1.05 kg greater increase on high dose R compared to glyburide was itself significant also(p=0.0139). The time course of change in body weight mirrored changes in glycemia. Mean body weight declined in all groups during the 6 week run-in. Body weight tended to increase more rapidly in glyburide patients than in R patients for the first 16 weeks of treatment. Beyond that, weight increased was more rapid in R patients.

A dose related decrease in hemoglobin and hematocrit was observed in patients treated with R. Mean hemoglobin was about 14.5 g/dl in all groups at baseline. This rose 0.01 with glyburide but fell 0.48 and 0.98 with 2 mg bid and 4 mg bid R after 52 weeks respectively. Hematocrit fell somewhat in all groups. Mean starting hematocrit was about 43%. The decrease after 52 weeks was 0.69 for glyburide compared to 1.92 and 3.33% for 2 mg bid and 4 mg bid R. The fall in mean hemoglobin and hematocrit occurred during the first 16 weeks of treatment. A small decrease in wbc count was observed with R. At 4 mg bid, wbc count fell from 6.40 to 6.03 . Granulocytes fell from 56.7% to 55.8% while lymphocytes increased from 32.4 % to 33.7%. I suspect that the fall in granulocyte count from baseline and in comparison to glyburide would be statistically significant, although of no clinical significance.

Mean liver chemistries fell in patients treated with R in a dose-dependent fashion.

Table 52 Summary of Predose Rosiglitazone Plasma Concentrations (ng/mL) Following Oral Administration of 2 mg bd Rosiglitazone

	Week 4[a]	Week 26[b]	Week 52[c]
n	167	154	144
Mean	21.6	20.9	22.2
Median	16.0	16.6	18.1
SD	19.2	18.2	19.4
Min	NQ(<5.00)	NQ(<5.00)	NQ(<5.00)
Max	118	99.2	116
CV%	89	87	88

a Includes 21 concentration values reported as not quantifiable which were set equal to half the LLQ (2.50).
b Includes 16 concentration values reported as not quantifiable which were set equal to half the LLQ (2.50).
c Includes 14 concentration values reported as not quantifiable which were set equal to half the LLQ (2.50).
Data Source: Section 16, Tables 16.1 and 16.2.

PK studies were done at weeks 4, 26, and 52. Results are shown above in table 52 For patients on 2 mg bid, produce plasma concentrations were 21.6, 20.9, and 22.2 mg/ml at 4, 26, and 52 weeks respectively. Post-doe values were 157, 138, and 133 ng/ml. For patients on 4 mg bid, predose values were 169, 148, and 131 ng/ml at 4, 26, and 52 weeks. Post-dose values were 155, 137, and 127 ng/ml.
more of a risk with glyburide than with RSG but RSG causes more weight gain and adversely affects serum lipids than glyburide.

094 – This was a 26 week add–on to metformin study conducted in the United States

This study was and consisted of a 7 week metformin titration to 2.5 g/day followed by a three arm double blinded comparison of R at 4 mg or 8 mg given once daily vs placebo.
In order to be randomized patients had to have FPG between 140 and 300 mg/dl while taking metformin 2.5 g/d. Metformin was given as five 500 mg tablet in two or three divided doses. R was given once daily as two 2mg or 4 mg tablets. Three weeks of metformin titration (except patients who were already on 2.5 g) was followed by a four week run-in of metformin plus placebo. Patients were withdrawn because of lack of efficacy if they had FPG > 350 mg/dl on two consecutive visits during the treatment period.

Approximately 28% were 65 years of age or older; 80% white and 78% had BMI equal to or 27. Two baseline imbalances of potential importance existed. With respect to gender. 25.7% of placebo patients were female compared to 37.9% and 31.8% female patients on low and high dose RSG respectively. Also, 46.9% of placebo patients had previously been on combination therapy compared to 54.3% and 51.8% for low and high dose R respectively. Mean baseline HbA1c was 8.6% for placebo patients and 8.9% for R patients. Mean baseline FPG was 214, for placebo patients and 215 and 220 mg/dl for low and high dose R patients respectively.

During the 7 week metformin/placebo run-in HbA1c rose 0.04% units for patients on placebo, 0.1% for patients on 4 mg R and fell 0.14% units for patients on 8 mg R. During the 26 week treatment period HbA1c rose 0.45% for patients on placebo but fell 0.56 and 0.78% units for patients on low and high dose R. Statistical analysis of changes in HBA1c during the study are shown in TABLE 16. The placebo subtracted treatment effect of – 1.32 and –1.53 for low and high dose R are both highly significant (p<0001). I do not think that the small differences in the change in HBA1c during the 7 week run-in need be considered Based on a fall of 0.7%, the response rate was 10.6 for patients on placebo compared to 44.8% and 51.8% for patients on low and high dose R.

Table 16 Change in HbA1c (%) at Week 26 Compared to Baseline and Metformin Monotherapy

(ITT Population)

	Treatment Group		
	Met + Pbo	Met + RSG 4mg od	Met + RSG 8mg od
HbA1c (Reference Range: <6.5%)			
n	113	116	110
Baseline (mean ± SD)	8.64 ± 1.276	8.89 ± 1.306	8.94 ± 1.450
Median	8.40	8.90	8.70
Week 26 (mean ± SD)	9.09 ± 1.698	8.34 ± 1.536	8.16 ± 1.333
Median	9.00	8.00	8.00
Comparison with Baseline* (mean ± SD)	0.45 ± 1.163	-0.56 ± 1.292	-0.78 ± 1.219
95% CI	(0.23, 0.66)	(-0.79, -0.32)	(-1.01, -0.55)
p-value**	< 0.0001	<0.0001	<0.0001
Difference From Metformin + Placebo (mean)	---	-0.97	-1.18
95% CI	---	(-1.32, -0.63)	(-1.53, -0.83)
p-value†	---	<0.0001	<0.0001

* calculated only for those patients who had both a baseline and a week 26 value.
** From paired t-test.
† Significance level is 0.0270
Data Source: Section 14, Tables 14.3A and 14.4A; Appendix C, Listings C.1.1 and C.1.2; Appendix F, Listing F.1.1.

Efficacy based on changes in FPG and fructosamine give largely the same results as HBA1c. During the pretreatment period, FPG fell 22mg/dl in placebo patients and fell 10.5 and 16.6 mg/dl in patients randomized to low and high dose R. During the 26 week treatment period, FPG rose in placebo patients but fell in patients on RSG. Similar changes were seen with fructosamine. The response rate based on reduction of 30 mg/dl in FPG was 20.4% for patients on placebo compared to 44.8 and 60.9% for patients on low and high dose R.

Table 18 Change in Secondary Glycemic Parameters At Week 26 Compared To Baseline and Metformin

(ITT Population)

Glycemic Parameter	Treatment Group		
	Met + Pbo	Met + RSG 4mg od	Met + RSG 8mg od
Plasma Glucose (mg/dL)			
Reference range: 13-50 yrs, 70-115mg/dL; ≥50 yrs, 70-125mg/dL			
n	113	116	110
Baseline (mean ± SD)	213.9 ± 52.43	214.5 ± 57.09	219.6 ± 54.88
median	212.0	205.5	209.5
Week 26 (mean ± SD)	219.8 ± 61.54	181.5 ± 51.76	171.2 ± 48.24
median	212.0	169.0	165.0
Change From Baseline* (mean ± SD)	5.9 ± 45.98	-33.0 ± 47.68	-48.4 ± 52.82
95% CI	(-2.7, 14.5)	(-41.8, -24.2)	(-58.4, -38.5)
p-value**	0.1757	<0.0001	<0.0001
Difference From Metformin (mean)	—	-39.8	-52.9
95% CI	—	(-52.8, -26.9)	(-66.1, -39.8)
p-value†	—	<0.0001	<0.0001
Fructosamine (micromol/L)			
Reference range: 200-278micromol/L			
n	113	116	110
Baseline (mean ± SD)	341.7 ± 68.17	340.9 ± 64.03	351.8 ± 78.20
median	340.0	339.5	347.5
Week 26 (mean ± SD)	354.1 ± 77.50	312.9 ± 66.66	315.0 ± 73.01
median	338.0	298.5	311.5
Change From Baseline* (mean ± SD)	12.3 ± 56.67	-27.9 ± 48.19	-36.8 ± 68.56
95% CI	(1.8, 22.9)	(-36.8, -19.1)	(-49.7, -23.8)
p-value**	0.0224	<0.0001	<0.0001
Difference From Metformin (mean)	—	-41.3	-47.2
95% CI	—	(-57.5, -25.1)	(-63.7, -30.7)
p-value†	—	<0.0001	<0.0001

* Change from baseline calculated only for those patients who had both a baseline and a week 26 value.

** Significance level is 0.05.

† Significance level is 0.0270.

NOTE: These laboratory values reflect the fasting state.

Data Source: Section 14, Tables 14.3A and 14.4A, Appendix C, Listings C.1.1 and C.1.2; Appendix F, Listing F.1.1.

The reduction in HbA1c due to R was present in all subgroups. Thus the minor baseline imbalances noted above would not affect the results. Reduction in HbA1c appeared to be greater in females than in males, in obese patients than in thin patients, and in younger patients than in older patients. The greatest reduction in HbA1c was observed in patients who had been previously on diet only and the least reduction in patients who been on combination therapy. For patients previously on combination therapy, HbA1c rose 0.76 in placebo patients (metformin only) but fell 0.20 and 0.35% in patients on low and high dose R. These decreases in patients on R were NOT statistically different from zero. But at a minimum one can conclude that the combination of metformin plus R was about as efficacious as the combination that these patients had been taking previously (largely SFU plus metformin).

Insulin and C peptide levels fell somewhat in all groups but the differences were not statistically significant from each other. LDL cholesterol rose 4 mg/dl in placebo patients but 17.8 mg/dl and 20.5 mg/dl in patients on low and high dose R. The differences vs placebo were significant at $p<0.0001$. VLDL was about 20 mg/dl in both groups at baseline. It rose 5.1 on placebo but 9.9 on RSG 8 mg ($p=0.03$) There was a significant reduction in FFA in patients on R. Mean body weight fell 1.2 kg($p<0.0001$) in patients on placebo but rose 0.7kg ($p=0.009$) and 1.9 kg ($p<0.0001$) for patients on low and high dose R.

Safety: Fifteen patients reported on therapy AE's of anemia. 7 patients (6.2%) on 8 mg R, 7 patients (5.9%) on 4 mg R and 1 patients (0.9%) on placebo. None of the reports were severe. Nine patients had anemia as a previous condition . All but one of the cases occurred during the first 182 days of treatment that the Sponsor presents as being consistent with the effect being related to "hemodilution". Hypoglycemia requiring assistance of a third arty occurred in 1(0.8%) of patient on 4 mg R, 2 patients (1.8%) on 8 mg R and zero patients on placebo.

Conclusion: The combination of RSG plus metformin is better than metformin alone (maximum dose) with respect to treatment of hyperglycemia but is associated with weight gain and a rise in LDL and VLDL cholesterol. The problem of anemia appears more prominent when RSG and metformin are used in combination.

093 – United States Study of Metformin monotherapy, RSG monotherapy and the combination

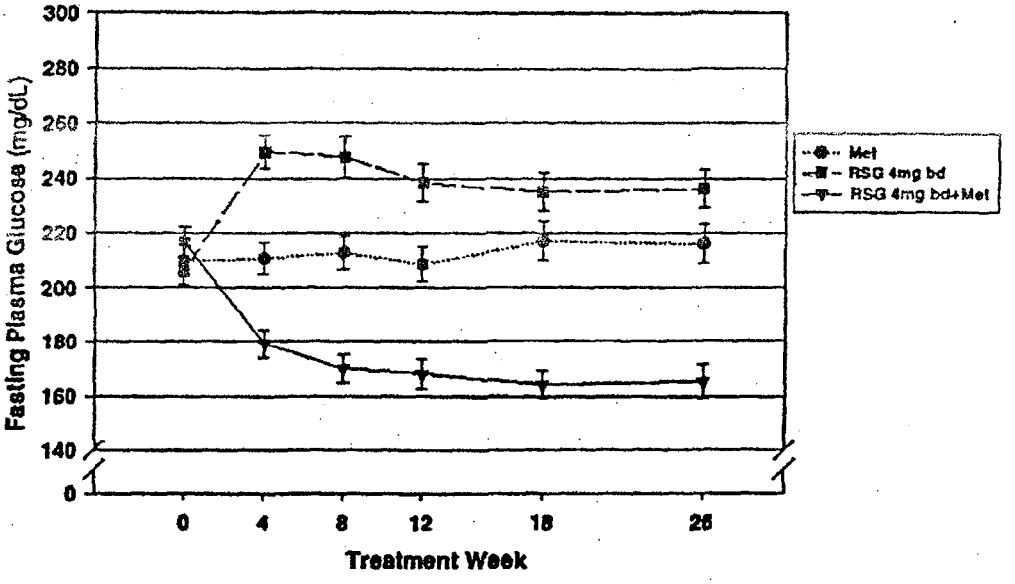
This was a double-blind double dummy placebo-controlled comparison of R monotherapy, metformin monotherapy and the combination of R + Metf . The study began with a six week open label metformin titration to a dose of 2.5 g/d. This was followed by a four week metformin maintenance/placebo run-in period during which time patients took 2.5 g/d of metformin and R placebo. Patients whose FPG was between 140-300 mg/dl were then randomized to one of three treatment arms for the 26 week double-blind trial. One arm continued on metformin 2.5 g/d plus R placebo. A second arm was switched form metformin to metformin placebo and started on R 4 mg bid. The third arm received combination metformin 2.5g/d and R 4 mg bid. Metformin was given 250 mg tablet, four in the morning, two in the afternoon, and four in the evening. R was given as 4 mg tablets in the morning and evening. Patients were withdrawn if the FPG exceeded 350 mg/dl on two occasions.

A potentially important baseline imbalance existed with respect to sex. 67% of metformin patients were male compared to 53.7% of R patients. 60% of patients on combination were male. 60% of patients randomized to R + metformin had previously been on combination therapy compared to 47.2% randomized to metformin and 43.2% randomized to R. . Otherwise there were no serious baseline imbalances. About 69% were under 65 years of age, 21% had BMI under 27 and about 80% were white. Baseline HbA1c was about 8.7% and baseline FPG was about 210 mg/dl. There was little change in HbA1c during the run-in period. Only a small reduction of 0.13% in patients randomized to R monotherapy is worthy of mention. After 26 weeks however, HbA1c rose 1.3% ($p<0.0001$) patients on R and fell 0.7% ($p<0.0001$) in patients on the combination of R plus metformin. The small rise of 0.1% in patients continued on metformin monotherapy was not statistically significant. The same findings were apparent using changes in FPG or fructosamine. A time course of the changes in FPG shows rapid deterioration in patients switched from

metformin to R. This stabilizes by week 18 but shows no sign of returning to baseline. Responder analysis based on reduction in FPG of 30 mg/dl from baseline shows that the combination of R+ metformin (66.7%) was superior to either metformin monotherapy (21.7%) or R monotherapy(14.7%). Since patients began from a background of metformin monotherapy it is reasonable to subtract the metformin "responder rate" and say that 45% improved when R was added to metformin while there was a net 7% loss of responders when patients were switched from metformin to RSG. Of patients achieving a FPG < 140 by week 26, there were 46.7% among the combination therapy patients compared to 8.5% and 8.4% for metformin and R monotherapy respectively. Patients withdrawn due to lack of efficacy were 5/109 (4.6%) on metformin, 13/107 (12.1%) on R and 3/106 (2.8%) on the combination.

Subgroup analysis showed that combination therapy was superior to either monotherapy in all groups and that metformin monotherapy was better than RSG monotherapy..

Figure 6 Mean Fasting Plasma Glucose (FPG) Over Time



(ROSIGLITAZONE/093 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2A

Insulin levels fell in R+ M compared to M alone. Total chol/HDL chol rose from 4.55 to 5.19 ($p<0.0135$) in patients on R monotherapy with little change in the other groups. LDL/HDL rose 0.49 ($p<0.0001$) from 2.39 to 2.88 in patients on R and rose 0.25 (($p=0.003$) for patients on combination but was unchanged in patients on metformin. VLDL rose in all groups but the rise was greatest (11 mg/dl) in patients on R . FFA was unchanged in metformin patients but fell in both R groups. Body weight decreased 1.3 kg from 90.3 to 89.0 kg in patients on metformin monotherapy but increased 2.7 kg and 2.3

kg in patients on R monotherapy and the combination respectively. All weight changes from baseline were statistically significant.($p<0.0001$).

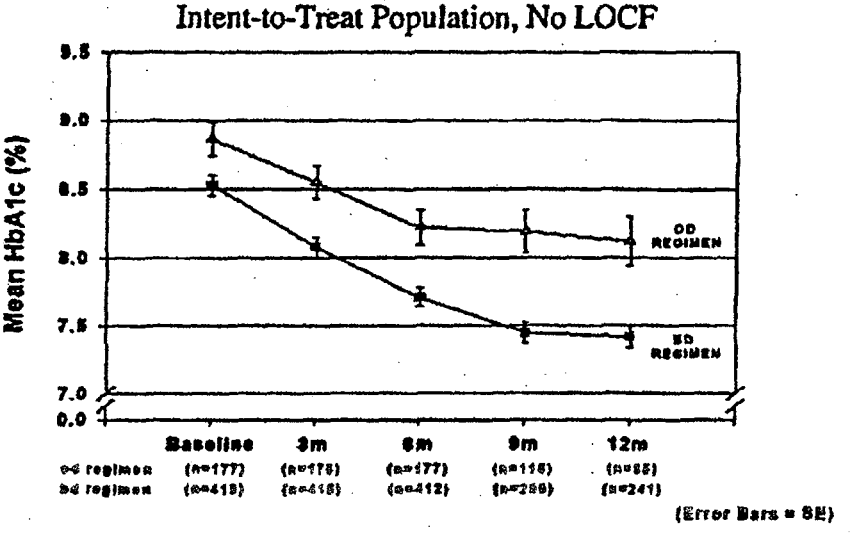
Safety: Anemia was reported as a AE in 4/109 (3.7%) of patients on metformin, 1/107 (0.9%) of patients on R treatment emergent and 10 (9.4%) on the combination of R + metformin. Four of the 15 patients with AE's of anemia were described as "being of potential clinical concern" (hct under 36 for a man and under 30 for a women). All four of these occurred in the combination group. In 8 of 10 patients in the combination arm with anemia, the event occurred within the first 84 days. Mean ALT levels decreased slightly in all groups. From means of about 24 U/L at baseline the decreases were 3.5 , 7.1, and 7.6 for metformin, R and R+metformin respectively. Mean lactic acid levels were about 1.6 mM at baseline which rose 0.2 mM in metformin patients and fell 0.3 and 0.4 mM in patients on R monotherapy and R+ metformin respectively.

Conclusion: RSG plus metformin is better than monotherapy with either agent for control of hyperglycemia, but anemia appears to be a prominent problem when the two agents are used in combination.. Patients switched from metformin monotherapy to RSG monotherapy experience deterioration of glucose control. RSG causes weight gain and adversely affects lipid levels.

Long Term Effectiveness:

A draft guidance for the development of new treatments for diabetes indicated that improvement in HbA1c should be durable for 12 months (Advisory Committee March 1998). The respect to monotherapy, durability of the effect of RSG was demonstrated in Study 20, the 52 week that used glyburide as an active control. Further evidence of durability comes from open-label extensions of the placebo-controlled monotherapy trials (figure 8.G.4.40). At a dose of 8 mg per day HbA1c reduction is durable for 12 months, although the effect appears to be greater when RSG is given as 4 mg bid than as 8 mg od.

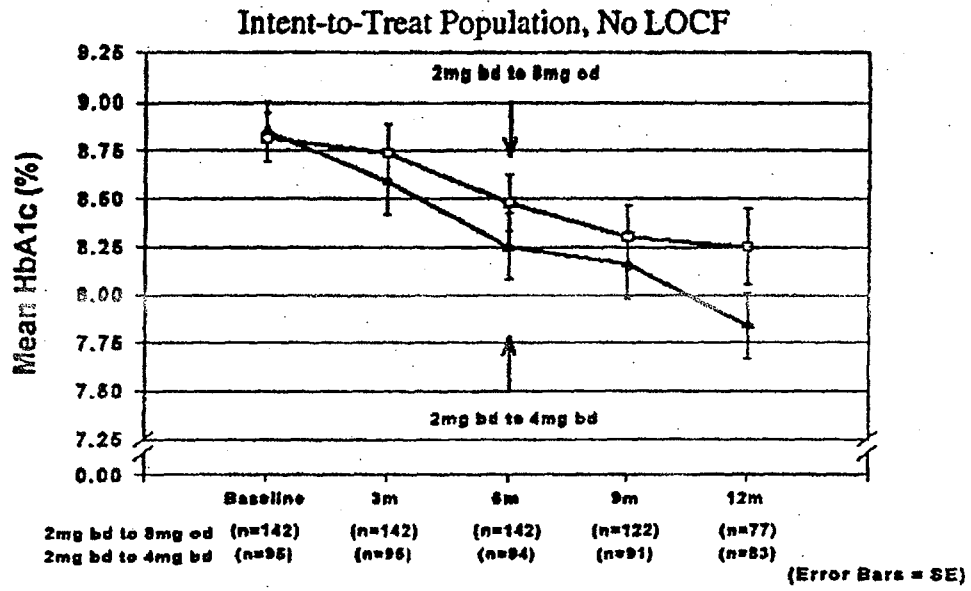
Figure 8.G.4.40: Long-term Effectiveness of Rosiglitazone 8mg/day: Mean HbA1c (%) Over Time



Data Source: ISE, Tables 10.1a and 10.1b, Figures 10.1a and 10.1b, Listing 10.1

Increasing the dose from 4 mg to 8 mg during months 6-12 was associated with additional reduction in HbA1c. Again we see that RSG appears to be more effective as monotherapy when given twice a day than one a day (figure 8.G.4.41) Considering that there is a lag of several weeks for changes in glucose to be reflected in changes in HbA1c, the reduction between months 9 and 12 for 4 mg bid in the following figure is a particularly impressive difference. The greater retention of patients on the bid regimen should also be noted.

Figure 8.G.4.41: Long-term Effectiveness of Rosiglitazone: Mean HbA1c (%) Over Time - Dose Increase after 6 Months of Therapy (2mg bd to 4mg bd or 8mg od)



Data source: ISE Tables 10.1a and 10.1c, Figures 10.1a and 10.1c, Listing 10.1

For the studies where RSG was added to metformin only three months of open label extension was submitted. Results from 6 to 9 months show no loss of efficacy at 8 mg/d and further reduction in HbA1c when the dose is increased form 4 mg od to 8 mg od.

Subgroup Analysis:

Two consistent findings are that RSG is more effective as in women than in men and in patients whose BMI is > 27 kg/m2. That women often have greater body fat than men may be a link between these two observations. Effectiveness as monotherapy tended to be greater in patients over 65 but this was not the case when used in combination with metformin. RSG was effective as in white and non-white patients.

SAFETY

Total exposure to rosiglitazone in phase 2/3 trial is as follows

	TOTAL	6 months or longer	12 months or longer
Rosiglitzone	4327	2664	1005
Metformin	225	176	0
Sulfonylurea (SFU)	626	482	175
Placebo	601	215	0

The data shown above do not include 22 patients in open label cardiac safety studies. 2860 patients were exposed to a twice a day dosing regimen, and 1752 were exposed to a once daily regimen. Among the patients on monotherapy, 2137 were on 8 mg/d and 1119 were on 4 mg/d. 172 patients were exposed to 12 mg/d . The NDA breaks down adverse events adverse events according to bid or od regimen. In this review data from the combined data base will be presented, unless otherwise specified because few, if any, safety differences exist between the OD and bid dosing regimens. 546 patients used R in combination with metformin and 974 in combination with a SFU. These patients are included in the total R data base and are not analyzed separately unless otherwise indicated. Since most of the phase 3 trials lasted only six months, much of the long term safety data therefore come from patients treated with R in open labeled extensions studies. Total cumulative exposure is shown in Table 8.H.2.4

Table 8.H.2.4: Cumulative Exposure by Treatment - Double-blind and Open-label Population

	All RSG N = 4327		Placebo N = 601		MET N = 225		SU N = 626	
Exposure	n	%	n	%	n	%	n	%
Total	4327	100.0	601	100.0	225	100.0	626	100.0
≥ 1 month	4153	96.0	559	93.0	218	96.9	605	96.6
≥ 3 months	3591	83.0	311	51.7	195	86.7	551	88.0
≥ 6 months	2664	61.6	215	35.8	176	78.2	482	77.0
≥ 9 months	1749	40.4	0	0.0	0	0.0	180	28.8
≥ 12 months	1005	23.2	0	0.0	0	0.0	175	28.0
≥ 15 months	292	6.7	0	0.0	0	0.0	0	0.0
≥ 18 months	42	1.0	0	0.0	0	0.0	0	0.0

Data Source: ISS Table 2.2.a.1

Deaths and Serious Adverse Events

Demographic characteristics for the monotherapy trials are shown in TABLE 8.H.3.2

Table 8.H.3.2: Demographic Characteristics - Rosiglitazone Monotherapy, Double-blind and Open-label Population

	RSG Monotherapy - Double-blind and Open-label N = 2902		RSG Monotherapy - Double-blind N = 2526		Placebo N = 601	
	n	%	n	%	n	%
Age (years)						
< 65	1945	67.0	1694	67.1	404	67.2
≥ 65	957	33.0	832	32.9	197	32.8
Mean ± SD	59.2 ± 9.90		59.2 ± 9.96		59.1 ± 10.20	
Range	30-83		30-83		34-83	
Gender						
Male	1832	63.1	1599	63.3	392	65.2
Female	1070	36.9	927	36.7	209	34.8
Race*						
White	2389	82.4	2060	81.6	481	80.0
Black	174	6.0	158	6.3	42	7.0
Other	338	11.7	307	12.2	78	13.0
BMI (kg/m^2)**						
< 27	835	28.8	719	28.5	179	29.8
≥ 27	2065	71.2	1806	71.5	421	70.2
Mean ± SD	29.6 ± 4.13		29.6 ± 4.12		29.6 ± 4.25	
Range	19.2-42.8		19.2-42.8		20.9-40.9	

* Racial designation is missing for 1 patient in the RSG Monotherapy double-blind and open-label population and for 1 patient in the RSG Monotherapy double-blind population

** BMI is missing for 2 patients in the RSG Monotherapy double-blind and open-label population, for 1 patient in the RSG Monotherapy double-blind population and for 1 patient in the placebo population

Data Source: ISS Table 3.2.1.1.a

Although patients tended to be obese white males under 65 years old, all major subgroups were adequately represented. Although there were only 174 black patients in the monotherapy trials, there were 41 black patients in which R was used in combination with metformin and 69 black patients in which R was used in combination with SFU. Therefore the total data base for black patients was 274.

The major issues regarding safety of rosiglitazone relate to hepatitis, edema, anemia and the heart. These are each discussed in detail in the following sections. Hypoglycemia and changes in body weight are also discussed in the following sections, but changes in serum lipids have been discussed under the individual trials Serious Adverse events leading to withdrawal of therapy occurred in 2% on TR monotherapy and 1.8% of patients in placebo. There were 21 deaths which occurred in the 4327 patients on R, 17 on R alone, one on R plus metformin and four on R + SFU. Among the patients who died while on R monotherapy, 7 deaths occurred during the double blind study and 10 occurred during the open-label extension study. There were 2 deaths among the SFU patients and one death among the placebo patients. If one considers the 6 month exposure given in the table above, the death rate for R monotherapy is 7/2664 (0.26%), for SFU is 2/482 (0.41%), and for placebo is 1/215(0.47%).

APPEARS THIS WAY ON ORIGINAL

Serious adverse events are reported in TABLE 8.H.6.1

Table 8.H.6.1: Summary of Serious Non-fatal On-therapy Adverse Experiences (≥ 0.3 %) - Rosiglitazone Monotherapy, Double-blind and Open-label Population

	Treatment							
	RSG Monotherapy N = 2902		Placebo N = 601		MET N = 225		SU N = 626	
Preferred Term*	n	%	n	%	n	%	n	%
Total PTS. w/ SAEs	168	5.8	21	3.5	8	3.6	32	5.1
Injury	14	0.5	1	0.2	0	0.0	4	0.6
Angina Pectoris	11	0.4	1	0.2	1	0.4	1	0.2
Chest Pain	9	0.3	0	0.0	0	0.0	3	0.5
Coronary Artery Disorder	9	0.3	1	0.2	1	0.4	0	0.0
Myocardial Infarction	9	0.3	1	0.2	1	0.4	2	0.3
Pneumonia	6	0.2	1	0.2	0	0.0	2	0.3
Therapeutic Response Increased	5	0.2	0	0.0	0	0.0	2	0.3
Cerebrovascular Disorder	4	0.1	3	0.5	1	0.4	0	0.0
Fibrillation Atrial	4	0.1	0	0.0	1	0.4	1	0.2
Hyperglycemia	2	0.1	3	0.5	1	0.4	2	0.3
Arrhythmia Atrial	1	0.0	0	0.0	1	0.4	0	0.0
Skin Ulceration	1	0.0	0	0.0	1	0.4	0	0.0
Constipation	0	0.0	0	0.0	1	0.4	0	0.0

* Sorted by RSG monotherapy

Data Source: ISS Table 6.2.1.1.a; Appendix 6.0

Cardiac Abnormalities:

Serious cardiac adverse events are shown in TABLE 8.H.6.2.

Table 8.H.6.2: Summary of Serious Non-fatal On-therapy Cardiovascular Adverse Experiences - Rosiglitazone Monotherapy, Double-blind and Open-label Population

	Treatment							
	RSG Monotherapy N = 2902		Placebo N = 601		MET N = 225		SU N = 626	
	n	%	n	%	n	%	n	%
Ischemic Heart Disease[2]	36*	1.2	3	0.5	3	1.3	4	0.6
Cardiac Rhythm and Conduction Abnormalities[3]	11**	0.4	1	0.2	2	0.9	1	0.2
Heart Failure[4]	5	0.2	1	0.2	0	0.0	1	0.2
Cerebrovascular Disorder	4	0.1	3	0.5	1	0.4	0	0.0
Hypertension	0	0.0	1	0.2	0	0.0	0	0.0

* 44 events in 36 patients
** 12 events in 11 patients
One patient (015.612.00872) in the SU group had an adverse experience of endocarditis
Data Source: ISS Table 6.2.1.1.a; Appendix 6.0

New ECG findings suggestive of acute myocardial infarction developed in 9/2902 patients on R monotherapy. Two of these were identified as having an acute MI as an SAE. There were 4/2525(2 inferior wall and 2 posterior wall) in the double blind population compared to 0/601 placebo patients.(8.H.9.19). 1/225 metformin patients had an EKG change of acute MI. and 0/626 patients on SFU.

In the metformin combination study 3/324 R + metformin patients (0.9%) were identified as having ECG finding of old inferior MI that was not present at baseline. There were 6/216 patients (2.8%) on metformin only who had this finding.

In the monotherapy trial (011), chest pain was reported in 3/175 (1.7%) of patients on R 2 mg bid, 6/182(3.3%) of patients on R 4 mg bid and no placebo patients. Of these 9 patients who developed chest pain on R, 3 were considered to be or cardiac origin. Two had abnormal EKG's on entry and one had hypercholesterolemia and hypertension. In this same study, there were 5 patients reported to have had acute MI's on RSG therapy. One placebo patient developed a serious but non-fatal MI 15 days after the last study medication.

A difficulty in reviewing the presentation of cardiac events is that data are presented PER event and not PER patient. It is not always clear how many unique patients were involved. At the reviewer's suggestion, SKB has clarified this point in the briefing document they prepared for the advisory committee A table showing the results is shown below. Acute myocardial infarctions occurred in 22 patients (0.5%) of patients on RSG and was fatal in six. This result would appear somewhat higher than in other treatment arms When adjusted for time on drug, however, the incidence of 8.8/1000 pt years on RSG is about the same as the 7.9/1000 pt years in the comparator arms combined Not shown in the table are 14 (0.3%) or patients on RSG and 1 (0.4%) of patients on metformin who had EKG changes without supporting evidence of acute MI , all of whom continued on therapy.

Treatment (number exposed)	# patients (%)	per 1000 pt years
RSG (4327)	22 (0.5%)	8.8
Placebo (601)	1 (0.2%)	6.0
Metformin (225)	1 (0.4%)	10.0
SFU (626)	3 (0.5%)	8.0

Adapted from SKB briefing document page 192

Two studies were done to determine the effects of R on myocardial size and function as determined by echocardiography. Study 080 compared 4mg R bid to glyburide for 52 weeks. Study 097 compared 8 mg R qd to glyburide for 26 weeks. No differences between R and glyburide were detected.

No significant changes in heart rate or blood pressure were noted during the monotherapy trials. However a small fall in blood pressure relative to glyburide was noted at 52 weeks in study 080. Mean blood pressure rose slightly in patients on glyburide but fell slightly in patients on R. The difference in systolic BP was – 3.5 mm Hg (p=0.022) and in diastolic pressure – 2.7(p=0.005).

Liver Abnormalities:

In view of the cases of liver failure reported with troglitazone, special attention was paid to liver abnormalities in patients taking R. There were 3 patients on R monotherapy who were reported as having hepatic related AE's. Patient 091.214.80203 experienced a rise in liver enzymes following halothane anesthesia after having been on R for 228 days. Patient 105.035.60594 experienced a rise in ALT 29 days following a dose increase of simvaststatin. She had previously been on R for 275 days and had no liver abnormalities. Her peak ALT was 336 which returned to normal by ten days after stopping both medications. Patient 105.022.60245 was reported to have "viral hepatitis" after 293 day of R 8mg/d

Mean ALT levels decreased by 5 U/L in patients on R monotherapy. As shown in TABLE 8.20, there were 4/2553 patients on R monotherapy who had a treatment emergent rise in ALT to greater than 3xULN (high F3) compared to 1/530 patients on placebo and 1/585 patient on SFU. Looking only at the double blind populations there there was 1/1684 patients on R. The were 2 additional patients who had ALT values greater than 3xULN but who started with values which were slightly elevated. Of the total of 6/2902 patients in the monotherapy studies with ALT values over 3x ULN, 2 patients had values 5-8 xULN . There was one addition patient(006.003.00359) who had an ALT value >8xULN(640) on R, 2 mg/d whose repeat value taken 8 days later was 105. R was continued and the ALT value returned to normal.

Table 8.H.8.20: Transitions from Baseline to High F1 or High F3 at Anytime On-therapy for Liver Function Tests - Rosiglitazone Monotherapy, Double-blind and Open-label Population

	RSG Monotherapy			Placebo		
	N→High F1	N→High F3	High F1 →High F3	N→High F1	N→High F3	High F1 →High F3
ALT/SGPT (IU/L)	2552→100	2552→4	175→2	530→18	530→1	31→0
AST/SGOT (IU/L)	2542→95	2542→1	84→2	512→13	512→1	18→0
Alk Phos (IU/L)	2558→45	2558→3	165→0	514→42	514→0	46→0
T. Bilirubin (umol/L)	2649→45	2649→5	75→5	536→12	536→0	22→5
Total Protein (g/L)	2624→185	2624→0	100→1	537→41	537→1	23→0
	MET			SU		
	N→High F1	N→High F3	High F1 →High F3	N→High F1	N→High F3	High F1 →High F3
ALT/SGPT (IU/L)	204→8	204→0	15→2	585→37	585→1	24→1
AST/SGOT (IU/L)	215→3	215→0	4→1	597→23	597→1	12→1
Alk Phos (IU/L)	217→8	217→0	2→0	584→21	584→0	25→0
T. Bilirubin (umol/L)	215→11	215→1	4→1	585→22	585→2	24→4
Total Protein (g/L)	217→10	217→0	1→0	595→13	595→0	13→0

Note: One ALT value of N→High F3 and one AST value of N→High F3 for patient 006.003.00359 in the rosiglitazone monotherapy group (2mg total daily dose, bd regimen) is not captured on this table since this value was not duplicated on the first repeat measure for the visit interval (see 8.H.8.2). The patient's repeat test taken on-therapy 8 days later were High F1 for ALT and N for AST. The levels returned to normal with continued rosiglitazone monotherapy.
Data Source: ISS Table 8.2.1.1.2.b and 8.2.1.1.2.c

A Comparison of R to other treatments is shown in TABLE 8.22. Even including the open label population, the liver abnormalities with R is no higher than in the other groups For completeness, there is one additional patient, 011.002.00544 with past history of alcoholic cardiomyopathy who developed transiently elevated transaminases and bilirubin during a hospitalization for congestive heart failure. R had been stopped four weeks previously at week 26 when the study ended.

BEST POSSIBLE

Table 8.H.8.22: Patients with Clinically Relevant Increases in Liver Function Tests - Rosiglitazone Monotherapy, Double-blind and Open-label Population

	RSG Monotherapy N=2902			Placebo N=601		
LFT**	Pts w/ data*	n	%	Pts w/ data*	n	%
ALT/SGPT (IU/L)						
>3 ≤5 x ULRR	2727	4	0.1	561	1	0.2
>5 ≤8 x ULRR	2727	2	0.1	561	0	0.0
> 8 x ULRR	2727	0	0.0	561	0	0.0
AST/SGOT (IU/L)						
>3 ≤5 x ULRR	2727	3	0.1	561	0	0.0
>5 ≤8 x ULRR	2727	0	0.0	561	1	0.2
> 8 x ULRR	2727	0	0.0	561	0	0.0
Alk Phos (IU/L)						
>3 ≤5 x ULRR	2727	1	0.0	561	0	0.0
>5 ≤8 x ULRR	2727	1	0.0	561	0	0.0
> 8 x ULRR	2727	1	0.0	561	0	0.0
T. Bilirubin (umol/L)						
>1.5 ≤3 x ULRR	2727	9	0.3	561	5	0.9
>3 ≤5 x ULRR	2727	1	0.0	561	0	0.0
> 5 x ULRR	2727	0	0.0	561	0	0.0
	MET N=225			SU N=626		
LFT**	Pts w/ data*	n	%	Pts w/ data*	n	%
ALT/SGPT (IU/L)						
>3 ≤5 x ULRR	219	1	0.5	609	1	0.2
>5 ≤8 x ULRR	219	1	0.5	609	1	0.2
> 8 x ULRR	219	0	0.0	609	0	0.0
AST/SGOT (IU/L)						
>3 ≤5 x ULRR	219	1	0.5	609	2	0.3
>5 ≤8 x ULRR	219	0	0.0	609	0	0.0
> 8 x ULRR	219	0	0.0	609	0	0.0
Alk Phos (IU/L)						
>3 ≤5 x ULRR	219	0	0.0	609	0	0.0
>5 ≤8 x ULRR	219	0	0.0	609	0	0.0
> 8 x ULRR	219	0	0.0	609	0	0.0
T. Bilirubin (umol/L)						
>1.5 ≤3 x ULRR	219	2	0.9	609	6	1.0
>3 ≤5 x ULRR	219	0	0.0	609	0	0.0
> 5 x ULRR	219	0	0.0	609	0	0.0

* Pts. with on-therapy data for a given parameter

** Pt. only counted once for worst case value per parameter

Note: One ALT value of >8 x ULRR (640 IU/L) and one AST value of >5 x ULRR (212 IU/L) for patient 005.003.00359 in the rosiglitazone monotherapy group (2mg total daily dose, bd regimen) is not captured on this table since this value was not duplicated on the first repeat measure for the visit interval (see 8.H.8.2). The patient's repeat test taken on-therapy 8 days later were 105 IU/L for ALT and 34 IU/L for AST. The levels returned to normal with continued rosiglitazone monotherapy.

Data Source: ISS Table 8.3.1.1.4.a

In the metformin combination trial there were no patients who had normal ALT values at baseline and developed ALT values> 3x ULN. Among patients with mild ALT elevations at baseline, there was 1/546 patients (0.2%) on R plus metformin and 2/225 patients (0.9%) on metformin alone who developed values > 3x ULN. One of these metformin patients was 5-8 x ULN.

Patients reported as having ALT values over 3x ULN are listed below. Not included are patients 105-022-60245 (male originally reported with "jaundice" associated with serological findings of hepatitis A after 293 days of RSG 8 mg. Jaundice diagnosis was later altered. ALT of 151 was 2.1 x ULN of 72 U/L) associated with admission for documented sepsis requiring Ancef, vancomycin and bactrim.). 009-465-00078 (male with liver involvement from cancer and patient 011.003.00663 who had pancreatic cancer. In constructing the table shown later, I used an ULN of 34 to be consistent with other databases. Since SKB used a higher ULN (usually 48 U/L) some cases, like 105-022-60245 described above, may have been omitted.

1 – 006.003.00359 – 51M with ALT of 649 on day 50 of 2mgR per day. ALT was 105 on day 58 and 32 on day 91 of drug treatment. ALT value was 121 seven days AFTER R was stopped. No additional information

2- 011.042.00985 - 78M with one abnormal ALT value of 217 (normal to 48) was reported on day 28 of 4 mg bid which was reported to be associated with a "viral infection". ALT value was 20 on day 1 and was also 20 on day 57. The patient completed the study and went on to open-label extension without reoccurrence.

3 – 091.214.80203 – 64M This elevation of ALT to 230 on February 16, 1998 followed an episode of halothane anesthesia. The patient had been on 8 mg per day from Jul 3 1997 through January 13 1998. He was on insulin from January 24 through Feb 9 1998. R was restarted on February 6 following surgical removal of a villous edema of the stomach on January 24 1998. R was discontinued but ALT elevation has persisted at about the same level for 115 days.

4 – 105.035.60594 – 62F with ALT to 336 on day 235 of 8 mg/d following increase in simvastatin. Values return to normal after both drugs are stopped.

5 – 105.042.60126 – 47F with ALT of 164 on day 313 of 4mg/8mg. R discontinue no follow-up values known

6 – 091-206-80319 – 61M with ALT elevated to 52 at baseline- 12 mg/8 mg during extension. 9 months on treatment, May 1998, ALT is 157. ALT progressively declined while on RSG but remained elevated. Last ALT about 80 on day 593.

7 – 098-103.80036 54M with ALT about 60 at screening. Rose to about 120 after 63 days of 8 mg R Value below initial baseline on day 271

8 - 024-028-02261 49F with ALT about 6 x ULN on day 185 of RSG 8 mg. Drug withdrawn on day 152 because of lack of efficacy. ALT was still elevated but under 3x ULN

9 - 024-052-03129 53M with ALT 0f 219 after 56 days of RSG 8 mg. Value normalized despite continuation of RSG and remained normal when RSG was stopped at the end of one year.

10-96-24.7173 63F ALT of 241 after 132 days of RSG 2 mg. + glyburide. ALT normalized despite increasing the dose of RSG to 4 mg . ALT was within normal range at day 462

11 –097-035-15198 54M ALT was 9xULN on day 127 of 8mg RSG associated with abdominal pain. ALT dropped rapidly and was normal of day 226 despite continuation of RSG.

12 – 094.009.04021 – 68M with ALT 8x ULN after 63 days of metformin monotherapy. 8 mg R later added during OLE. ALT was normal on day 404 but rose again later. Both drugs stopped..

13 – 015.316.00433 – 68M with ALT 4x ULN recorded BEFORE first dose of R 2 mg is given. No increment after R is added to SFU.

Comparison to Troglitazone:

Patients 1-11 listed above had treatment emergent ALT values>3xULN after starting RSG. These results are displayed in the table below. I have included patient #1 who the Sponsor did not include in table 8.22, although this patient is described in the footnote. This patient's peak value of 640 returned to normal despite continuation of RSG . Patients 12 and 13 had ALT> 3x ULN before RSG and ALT values did not show a further rise. They are not included in the table.

In the table shown below, I used an ULN of 34 to show a "worst case scenario" for potential liver toxicity of RSG vs troglitazone. SKB used a ULN of 48 U/L.

BEST POSSIBLE

ALT elevation during RSG treatment

	Continued on RSG	Withdrawn	Total
> 3xULN (102 U/L)	6	5	11 (0.25%)
> 5xULN (140)	5	5	10 (0.23%)
> 8xULN (272)	2	0	2 (0.05%)
> 30xULN(1020)	0	0	0

N= 4421(updated total): 3172 (monotherapy) + 550 (with metformin) + 974 (with SFU)

For comparison, results from the troglitazone NDA tabulated in a similar way are shown below.

ALT elevation during Troglitazone treatment

	Continued	Withdrawn	Total
> 3xULN	25	23	48 (1.9%)
>5xULN	22	20	42 (1.7%)
>8xULN	8	14	22 (0.9%)
>30xULN	0	5	5 (0.2%)

N=2510

Both the incidence of ALT elevation and the severity of the elevation was greater with troglitazone than with RSG even when the ULN is taken as 34 U/L instead of 48 U/L used by SKB. One potential source of this difference is differences in criteria for withdrawal. It was not known during the trials that troglitazone could cause liver failure, hence there were no definite criteria for withdrawal. Delay in withdrawing troglitazone from patients with mild elevations could be a potential reason for why some patients developed very high values. However, of the five patients with ALT > 30xULN, only one had had an earlier mild elevation (> 5xULN) which did not lead to troglitazone withdrawal.

It should be noted that there were eight patients in the troglitazone trials with ALT > 8 x ULN in whom the values returned toward normal despite continuation of troglitazone. Patients #1 in the RSG trial followed a similar pattern. His peak ALT was about 19 xULN and returned to normal despite continuation of RSG. His peak ALT value was higher than that seen with any troglitazone patients who returned to normal despite continuation of troglitazone. Other cases of reversible ALT elevation on RSG followed a similar pattern to that seen with troglitazone. Putting everything together, I believe that RSG causes a similar hepatitis to troglitazone, but is less likely to do so because RSG is effective in much smaller doses.

Edema-related SAE's

Edema lead to withdrawal of in 12/3172 (0.4%) patients on R alone, 4/550 (0.7%) of patients on R + metformin and no patients on SFU or placebo. This includes one case of pulmonary edema. There were two other cases of pulmonary edema on RSG which did not cause withdrawal of RSG. One of the placebo patients (011.003.00660) also had CHF reported as an AE with edema. Total reporting (double blind plus open label) of edema was 267/3172 (8.4%) of patients on RSG. Looking just at the double blind population, reporting of edema occurred 4.8% of patients on RSG monotherapy, 4.4% on RSG + metformin and 3.0% on RSG + SFU, compared to1.3% patients on placebo, 2.2% on metformin monotherapy and 1.0% on SFU monotherapy. In summary, edema is reported 2-3 times as frequently in patients on RSG as in other groups. This is consistent with what was found with troglitazone.

Hematological SAE's and Withdrawals

Four patients had hematological SAE's. One of these had biopsy proven myelodysplastic syndrome 42 days after starting treatment. Follow-up obtained 11 days post-treatment showed that her platelet count had fallen from 76,000 to 12,000 but wbc had risen to 3.7 from 2.7. The investigator felt that this event was unrelated to RSG. There were 3 patients who developed anemia. One patient (084.004.70042) was withdrawn from RSG because of a hematocrit of 23.5 which rose to 29.2 17 days later. A second patient(024.030.02226) was withdrawn because of a hct of 28.1, which rose to 30.4 three days later. In a third patient (020.720.01004) hct was 26.7 after 279 days of R 83 days later her hct was 19.6 but RSG was continued.

In monotherapy studies, 8 patients (0.3%) on RSG were withdrawn because of anemia compared to no patients on metformin, SFU or placebo. In the combinations studies, 5 patients(0.9%) on R plus metformin were withdrawn because of anemia compared to no patients on metformin alone.

Development of low hematocrit for RSG monotherapy is shown in TABLE 8.H.8.13 with other hematological measurements shown in table 8.17. 9/2121 (0.4%) patients developed a low hematocrit (F3 means below 31 for men and below 28 for women) on R monotherapy This abnormality generally occurred after 60 days of treatment. For patients on metformin, 16/461(3.5%) developed a low hematocrit (F3) while on R compared to 0.5% on metformin alone. Again, the abnormality generally developed beyond 60 days of treatment. A low wbc count (F3 means under 2.8) developed in 0.6% of patients on R plus metformin compared to 0 on metformin alone.

Table 8.H.8.13: Transitions from Baseline to Low F1 or Low F3 for Hematocrit by Regimen- Rosiglitazone Monotherapy, Double-blind Population

	RSG Monotherapy BD		
Days	N→Low F1	N→Low F3	Low F1→Low F3
Anytime	1596→333	1596→9	100→20
1	0→0	0→0	0→0
2-30	1406→98	1406→0	84→9
31-60	1417→153	1417→0	85→12
61-90	1213→133	1213→4	71→6
91-196	1027→175	1027→6	60→7
197-280	336→46	336→2	19→1
281-378	257→26	257→1	12→2
379-560	26→5	26→0	0→0
	RSG Monotherapy OD		
	N→Low F1	N→Low F3	Low F1→Low F3
Anytime	525→61	525→0	23→7
1	0→0	0→0	0→0
2-30	469→13	469→0	18→1
31-60	464→27	464→0	20→3
61-90	305→25	305→0	17→4
91-196	272→35	272→0	16→6
197-280	19→1	19→0	0→0
281-378	0→0	0→0	0→0
379-560	0→0	0→0	0→0
	Placebo		
	N→Low F1	N→Low F3	Low F1→Low F3
Anytime	485→24	485→0	31→2
1	0→0	0→0	0→0
2-30	423→12	423→0	23→1
31-60	392→4	392→0	28→0
61-90	286→7	286→0	18→1
91-196	216→10	216→0	15→0
197-280	15→0	15→0	0→0
281-378	0→0	0→0	0→0
379-560	0→0	0→0	0→0

Data Source: ISS Table 8.2.1.2.1.b and 8.2.1.2.1.c

Table 8.H.8.17: Transitions from Baseline to Low F1 or Low F3 at Any Time On-therapy for Hematological Parameters - Rosiglitazone Monotherapy, Double-blind Population

Parameter	N→Low F1	N→Low F3	Low F1→Low F3
	RSG Monotherapy BD		
WBC (10^9/L)	1703→170	1703→9	34→7
Neutrophils (%)	1704→133	1704→6	39→3
Lymphocytes (%)	1693→79	1693→1	36→0
Platelets (10^9/L)	1705→95	1705→5	62→2
	RSG Monotherapy OD		
	N→Low F1	N→Low F3	Low F1→Low F3
WBC (10^9/L)	603→23	603→0	14→4
Neutrophils (%)	605→58	605→0	22→0
Lymphocytes (%)	597→30	597→1	21→1
Platelets (10^9/L)	595→41	595→0	32→1
	Placebo		
	N→Low F1	N→Low F3	Low F1→Low F3
WBC (10^9/L)	535→12	535→0	16→1
Neutrophils (%)	548→18	548→0	7→0
Lymphocytes (%)	547→25	547→1	9→0
Platelets (10^9/L)	537→23	537→0	20→1

Data Source: ISS Table 8.2.1.2.1.b and 8.2.1.2.1.c

The development of anemia when patients on metformin are treated with RSG is of concern and cannot be explained simply be expansion of vascular volume. Metformin itself can rarely cause anemia by inhibition of B12 absorption. I would not expect a B12 related anemia to occur so quickly but I have no other explanations.

Hypoglycemia

"Hypoglycemia" was reported in 0.8 of patients on R, 0.2% on placebo, 1.3% on metformin and 5.9% on SFU. However, there was only 1 patient with hypoglycemia who require the assistance of a third party. This patient was on SFU. He was hospitalized, received iv glucose, and was discharged after two days. There was one additional case of a patient on R where hypoglycemia was documented with FPG <50 mg/dl Although not submitted with the NDA, a death was reported on January 29, 1999 of a patient taking insulin plus RSG. The patients had had two hypoglycemic episodes and were later found unresponsive in his car. A finger stick glucose performed by emergency personnel was 20 mg/dl. He was given intravenous dextrose but never regained consciousness and died soon thereafter.

Body Weight

Mean changes in body weight during the monotherapy trials are shown in TABLE 8.H.9.42
At 196 days there is a mean gain of 1.9kg in R compared to a mean loss of 1.3 kg each in patients on metformin or placebo and a mean gain of 0.6 kg in patients on SFU. The weight gain progressed for patients who continued on R monotherapy. By 560 days the mean weight gain was 4.2 kg.

Ethical Issues

Protocol 011 and 024 were comparisons of RSG monotherapy vs placebo. Patients already receiving antidiabetic medication were required to have those medications withdrawn before entering the study. The majority of patients in the study had indeed been previously receiving antidiabetic medication and many had been on combination therapy. To discontinue these medications would predictably lead to hyperglycemia. The American Diabetes has recommended since January 1995 (based in technical review, Diabetes Care 17: 1514, 1994) that treatment be aimed at bringing a patient's HbA1c down toward 7% in order to reduce the risk of retinopathy, nephropathy and neuropathy. Given that most of the patients in these studies already had HbA1c levels that were greater than 7%, to discontinue drug treatment would be exactly the opposite of what would generally be considered good medical practice. How can one ethically justify deliberately causing a condition like hyperglycemia for the sole purpose of determining if a new drug will be effective in treating that condition?

I raised this question in a "letter to the editor" of The Washington Post, August 6, 1998, and in subsequent articles in Annals of Internal Medicine (February 2, 1999) and J Clin Endocrinol Metab (Feb 1 1999). The FDA answer has come from CDER's Associate Director for Policy, Dr Robert Temple. who was reported in Dickinson's FDA Review to have responded:

" ... People come off their drugs all the time. If the treatment is predominantly symptomatic, you may get uncomfortable, but you don't die or you don't get sick, and people can volunteer for that....For most symptomatic conditions, you can do that. Diabetes, I would say is similar. If you wanted to take someone briefly off a sulfonylurea ..., you could do that because a short period of impaired control doesn't do anything....No one has even shown any evidence that sulfonylureas are even good for you* Robert Temple, Dickinson's FDA Review, September 1998.

(*Although this statement about sulfonylureas may have been correct when it was made in response to my letter of August 6, 1998, it was no longer correct when the statement was actually published. The UKPDS study reported in Lancet, September 12, 1998 showed that treatment of hyperglycemia with sulfonylureas did indeed reduce complications of diabetes. These results corroborate the benefits of control of hyperglycemia with insulin reported previously in type 1 and type 2 diabetes.)

Based on Dr Temple's statement, withdrawal of SFU's would be ethical provided that informed consent was obtained. The consent form for study 024 indicates that patients were informed that may develop hyperglycemia while taking RSG or placebo and this can cause polyuria, blurred vision, etc. It also states "You will be asked to stop taking ALL of your current antidiabetic medications for a minimum of 14 days" and later "You will be taken off ALL antidiabetic medication for a period of time during the study. The same risks of hypoglycemia (Although the text says 'hypoglycemia', I believe 'hyperglycemia' was intended here) apply." By contrast similar language is absent from the consent form for study 011. No where does it say that withdrawal of previous medication is part of the study or that symptomatic hyperglycemia is likely to occur. The Procedures section ends with the curious statement "Bring all of you study medication and glibenclamide tablets to the clinic". This statement is undoubtedly an error that resulted from modification of the consent form used for Study 20. Medications used in Study 011 were RSG and placebo, not glibenclamide. Although probably an innocent error, one wonders if some readers might have been confused into thinking that patients were receiving active treatment when in fact they were only taking placebo.

The protocol lists among the inclusion criteria is a FPG between 140 and 300 mg/dl at screening and states: that "patients were required to stop all antidiabetic medications for a minimum of two weeks prior to obtaining screening FPG". This requirement affected the 326 patients who had previously been on single agent therapy and the 33 patients who had been on combination therapy. Data for patients in study 011 taken off combination tharapy and placed on placebo are shown in the table.

	FPG mg/dl	HbA1c	n
- 6 weeks	247	8.7	12
Baseline	282	9.9	12
4 weeks	—	10.8	12
26 weeks	267	10.7	2

Based on the errors in the consent documents noted earlier, I believe that SKB did not take as much care with the consent process as would have been desirable. Patients in study 24 appear to been told that they were required to discontinue other antidiabetic medications and that symptomatic changes in glucose control might ensue. In study 11, however, I have not found evidence that patients were told that they were being taken off their previous medication as part of a drug trial, or that symptomatic hyperglycemia was likely to develop. Patients could easily have been allowed to believe that their previous medication had been discontinued for some valid medical reason while the real reason was to make patients eligible to participate in a trial. For this reason, I believe that only data from naïve patients in study 11 should be used to support approval of RSG. Data from patients taken off antidiabetic medications should not be used unless SKB can provide evidence that these patients agreed to having their medications withdrawn as part of a drug trial in which many would get a placebo instead of active treatment. In support of this recommendation I cite the Code of Federal Regulations 314.125 :

" FDA may refuse to approve an application...(if)... any clinical investigation involving human subjects subject to IRB regulations or informed consent regulations was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected."

Labeling Issues:

PD/Clinical effects:

The paragraphs dealing with changes in body weight and changes in serum lipids are inadequate. It is clear that R causes weight gain and this may one of the major drawbacks to its use as first-line in comparison to other drugs, particularly metformin. A similar problem exists with respect to changes in serum lipids where RSG tends to cause HDL/LDL cholesterol and VLDL to go in the wrong direction with respect to cardiac risk. These issues can be dealt with either in the PD section or in the clinical studies section

Clinical studies:

Illustrations should separate naïve patients from previously treated patients. Data from previously treated patients in study 011 should be omitted entirely because these patients appear to have been studied without having properly obtained informed consent. (see "ethical issues" section). It would be more effective to give these data in a figure as bar graphs of change from baseline at 0, 4 mg od, 2 mg bid, 8 mg od and 4 mg bid. Naïve patients could be shown at the left and previously treated patients at the right. The other figures are not very effective, seem redundant or do not add much to what is already in the text, such as the right portion of figure 3. A figure needs to be added showing the time-course of the effect of R on FPG. I would suggest using the figure from study 20.The point needs to be made somewhere that R takes a long time to act. Patients switched from SFU need to expect a temporary deterioration in glucose control. Rather than state this as a warning in the "Dosage" section, it would be preferable to present the data, from study 24 in the clinical studies section. Also, with respect to study 20, it should be stated that the median dose of glyburide was 7.5 mg. The figure showing reduction in insulin should be omitted unless balanced by a figure showing increased body and lipids with RSG relative to glyburide. The statement that patients switched to RSG from metformin showed increases in FPG and HbA1c needs to be expanded to include undesirable changes in weight and lipids

Precautions/Warning/Adverse Events:

Liver – The problem with troglitazone cannot be totally ignored. Although there were no cases of "fulminent hepatitis" attributed to RSG, there was one patient with a reversible elevation in ALT of 19x ULN. There was also a case of jaundice attributed to hepatitis A, but the documentation. I do not see a reason to require routine monitoring, but any treatment emergent rise in ALT should be taken very seriously. The label should include a reference to troglitazone hepatatotoxicity and the recommendation that RSG should not be used in patients who had developed liver function abnormalities on troglitazone.

Hemogram – A comment is needed about the fall in wbc. The anemia which develops when RSG is used with metformin requires additional discussion. There should be some specific instruction about what to expect and what to do.

Cardiac effects – There needs to be mention of treatment emergent EKG changes, chest pain, etc. even if not statistically different from comparators. Based on animal findings a of cardiomegally, and edema in clinical trials, RSG should be used with caution in patients with heart failure

Weight /Lipids – Patients treated with RSG manifest undesirable changes in weight and lipids. As mentioned above, these issues need to be discussed somewhere in the label.

Dosage and Administration:

The first paragraph should be redone. It seems clear that the twice daily regimen is better than the once daily regimen, at least for monotherapy. For patients started on 2 mg bid, 6-8 weeks is not enough time to observe the full effect on FPG.

Discussion:

The studies in this application show that RSG is safe and effective treatment for hyperglycemia both when used alone and in combination with metformin. Its efficacy persists for at least 12 months without evidence of deterioration. The durability of the thiozolidinediones in controlling hyperglycemia appears to be greater than that of other classes of oral antidiabetic medications. Whether RSG favorably affects the natural history of type 2 diabetes is open to question. Long-term improvement in HbA1c should decrease the risk of retinopathy, nephropathy and neuropathy. However the increase in body weight and undesirable effects on serum lipids is cause for concern. Heart disease due to atherosclerosis is a major cause of morbidity and mortality in patients with type 2 diabetes, and it cannot be assumed that treatment with RSG will decrease the risk. As an "insulin sensitizer", RSG appears to lower glucose levels by converting glucose to fat. The decrease in free fatty acid levels probably reflects deceased fat mobilization from adipose tissue and is another manifestation of insulin action. My concern about deleterious long-term effects on the heart should be addressed by requiring the Sponsor to provide adequate information in the label about changes in weight and lipids. A postmarketing study to address these issues needs to be a condition of approval.

Based on our experience with troglitazone, the major safety concern related to RSG is that it may cause liver failure. The data presented in this application is very reassuring but not completely reassuring. The incidence of ALT elevation greater than 3x ULN was not greater in RSG-treated patients than in patients who did not receive RSG. There was no patient at all whose ALT level reached 20x ULN. This is very different from the situation with troglitazone. With an exposure of 2510 patients in the troglitazone NDA, 39 (1.6%) patients had treatment emergent elevation of ALT of > 3x ULN. In 19 of these 39 patients (0.8% of total) the elevation was greater than 8xULN and in 5 of these (0.2%) it exceeded 30xULN. In the RSG data set there is one patient who had a brief elevation in ALT to 649 (approximately 19xULN) which was 105 eight days later and had returned to normal a month later despite continuation of RSG. That this case is the most troublesome in a data base of over 3000 patients is strong evidence that the risk of

hepatic toxicity from RSG is much less than that from troglitazone. On the other hand, a sharp but transient rise in ALT was also seen in troglitazone patients and is difficult to explain in this case except as a toxic reaction to RSG. Putting everything together, I believe that RSG does have the potential to cause liver damage but is much less likely to do so than troglitazone because it is used in much smaller doses. I am concerned that long-term exposure to RSG may give rise to a similar liver problem as with troglitazone but with a time lag reflecting the lower dose. At a troglitazone dose of 400 mg per day the median time to development of hepatitis was about four months. The possibility that 4-8 mg per day of RSG could cause a similar problem after prolonged use needs to be considered.

A post-marketing study to evaluate the long-term safety of RSG should be required for approval. This trial should run at least three years and should be powered to detect a 0.5% increase (approximate doubling of the underlying rate in diabetic patients) in the incidence of ALT elevation greater than 3x ULN. Th study should also evaluate changes in cardiovascular and hematological events as discussed above in addition to changes in HbA1c, body weight and serum lipids. One possible design would be a three-arm comparison of RSG monotherapy, metformin monotherapy, and the combination of RSG plus metformin. Having two arms receive RSG would provide additional power to detect a rare event like hepatotoxicty. Based on the results of UKPDS, it would appear that metformin monotherapy itself may decrease the risk of cardiovascular events, and the inclusion of a combination arm would answer the question whether improved glycemic control reduces the risk still further. An alternative design would be a two arm comparison of RSG monotherapy vs metformin monotherapy with the combination of RSG plus metformin used for patients who fail on monotherapy alone.

RSG should not be used in patients who had previously developed liver function abnormalities on troglitazone. However, it may be possible to develop a RSG treatment protocol for patients who had had mild transaminase elevations with troglitazone. A protocol for the potential use of RSG in patients with heart failure should also be considered. In both cases, the medical need for RSG would have to be compelling in order to justify the potential risk.

Recommendation:

RSG is approvable for treatment of type 2 diabetes either as monotherapy or in combination with metformin. This approval should be contingent on label changes described previously. Approval should also be contingent on a commitment from the Sponsor to do post-marketing studies along the lines of what is described above.

/S/ [redacted] 4/16/99

Robert I Misbin MD
Medical Officer, DMEPD
HFD 510
April 2, 1999
Updated, April 12, 1999

[redacted] APPEARS THIS WAY ON ORIGINAL

HFD 510 misbin/sobel/malozowski