

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021071

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 21-071

Drug: Avandia (rosiglitazone maleate) tablets

Sponsor: SmithKline Beecham

Indication: 2 indications:

- Monotherapy for the treatment of hyperglycemia in patients with type 2 diabetes who are inadequately controlled by diet and exercise
- As combination therapy with metformin for the treatment of hyperglycemia in patients with type 2 diabetes who are inadequately controlled by metformin monotherapy

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Introduction	3
Dose-Ranging Trials	4
Monotherapy Trials	7
Study 011	7
HbA1c	9
Fasting Plasma Glucose	12
Study 024	14
HbA1c	15
Fasting Plasma Glucose	17
Once-a-day dosing versus twice-a-day dosing	18
Study 020	19
HbA1c	21
Fasting Plasma Glucose	25
Reviewer's general comments on active-controlled Study 020	26
Lipid changes in the monotherapy trials	27
Weight changes in the monotherapy trials	30
Combination Trials	31
Study 093	31
HbA1c	33
Fasting Plasma Glucose	35
Study 094	36
HbA1c	37
Fasting Plasma Glucose	39
Lipid changes in the combination trials	40
Weight changes in the combination trials	43
Reviewer's Overall Comments	44
Summary of HbA1c Results	44
Durability of response	48
Relationship between HbA1c changes and changes in LDL, LDL/HDL and weight	49

Gender effects _____ **50**
ALT _____ **52**
HCT _____ **52**
Conclusions _____ **54**
Appendix 1. Boxplots of fasting plasma glucose _____ **55**
Appendix 2. Boxplots of ALT _____ **58**
Appendix 3 LDL and TG by HbA1c responder status and monotherapy treatment _____ **60**

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Introduction

Rosiglitazone is an oral anti-diabetic drug in the thiazolidinedione class. The sponsor has presented the results of 8 clinical trials (Table 1) to support the efficacy and safety of rosiglitazone as monotherapy and as combination therapy with metformin. In the first section of this review, the dose-ranging studies are briefly described and the results summarized. A greater part of this review is devoted to the review of the monotherapy and combination studies. Rosiglitazone was given priority review status, therefore the review time was abbreviated substantially for this reviewer. All tables and figures in this review were produced by the reviewer.

Table 1. Controlled Clinical Trials

	Doses of rosiglitazone	Duration of treatment (weeks)
Dose-ranging trials		
006	0.05, 0.25, 1 and 2mg BID	12
090	2, 4, and 6 mg BID	8
098	2, 4, and 6 mg BID	8
Monotherapy trials		
011	2 and 4 mg BID	26
020	2 and 4 mg BID	52
024	2 and 4 mg BID 4 and 8 mg OD	26
Combination with metformin		
093	4 mg BID alone and with met.	26
094	4 mg OD with met. 8 mg OD with met.	26

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Dose-Ranging Trials

Studies 006, 090 and 098 were all multicenter, double-blind, randomized, parallel, placebo-controlled studies of NIDDM patients. In all trials, the treatment period was preceded by a dietary run-in period where placebo was administered single-blindly. The length of run-in varied among the studies as can be seen in Table 2. If patients satisfied the entry criteria, they were randomized to a dose of rosiglitazone or placebo. Daily doses of rosiglitazone ranged from 0.1 mg to 12 mg (daily doses of 4 and 8 mg were used in the sponsor's monotherapy trials).

Table 2. Dose- Ranging Trials

	FPG (mg/dl) Entry Criteria	# of Sites	Treatment Arms (# of patients randomized)	Duration of Treatment
006 (3/95 to 2/96)	140 to 240	24 USA	RSG 0.05 mg BID (74) RSG 0.25 mg BID (72) RSG 1 mg BID (79) RSG 2 mg BID (80) Placebo (75)	4 week placebo run-in followed by 12 weeks of therapy
090 (6/97 to 12/97)	140 to 300	35 USA	RSG 2 mg BID (78) RSG 4 mg BID (71) RSG 6 mg BID (79) Placebo (75)	2 week placebo run-in followed by 8 weeks of therapy
098 (5/97 to 11/97)	126 to 269 (7-15 mmol/L)	47 Europe	RSG 4 mg OD (98) RSG 8 mg OD (93) RSG 12 mg OD (93) Placebo (96)	3 week placebo run-in followed by 8 weeks of therapy

More than 75% of the patients in each treatment group for each study were completers (Table 3). The primary reasons for withdrawal were adverse experience and lack of efficacy across all doses. The retention rates were highest among doses of 4 mg or greater.

Table 3. Percentage of patients completing the trial by total daily dose (mg)

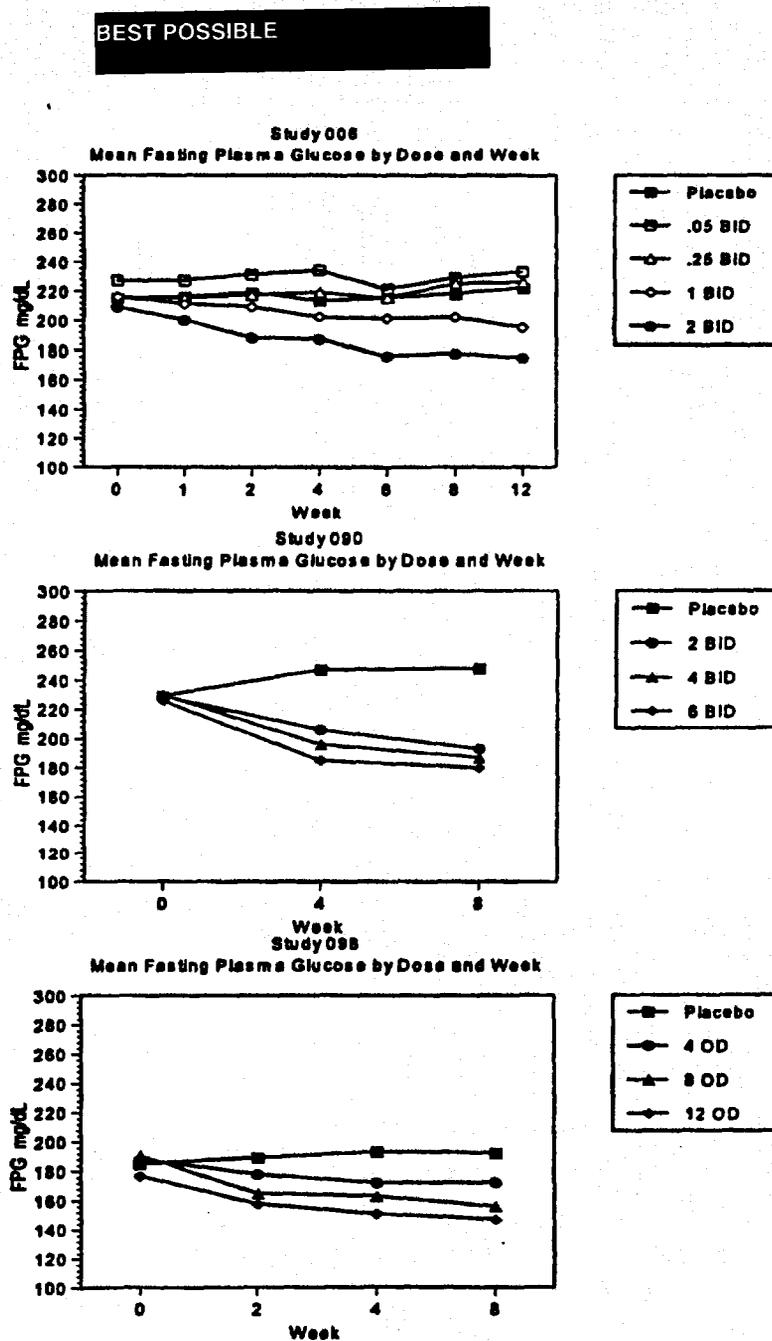
	Placebo	0.1	0.5	2	4	8	12
006	85%	78%	76%	82%	86%	NA	NA
090	76%	NA	NA	NA	89%	80%	92%
098	88%	NA	NA	NA	88%	90%	94%

Patients in these studies ranged in age from 34 to 83; the mean age in Studies 006 and 090 was about 58 years while in Study 098, the mean was higher at about 63 (about 46% of the 098 patients were 65 or older). About 3% of the patients were males. About 75% of the patients in Studies 006 and 090 were white, while in Study 098 about 97% were white. About 70% of the patients in Studies 006, 60% in 098 and 80% 090 were under anti-diabetic therapy within the 30-day period before screening according to the sponsor's tabulations of prior medication use. Sulfonylureas were the most common medication; 71% in 006, 65% in 090 and 43% in 098. Metformin use was only seen in Studies 090 (23%) and 098 (25%).

The primary efficacy measure in all three trials was fasting plasma glucose (FPG) at endpoint (Week 12 or 8). Changes in FPG for total daily doses of 2 mg and above were all statistically significantly different from placebo at endpoint (sponsor's analyses, reviewer's Figure 1). In Study 006, 1 mg BID was identified as the minimally effective dose; however, this

dose was not studied in subsequent trials. The highest dose, 12 mg per day, was studied in 090 and 098 but not in the sponsor's Phase III trials because it was not considered to be more efficacious than an 8 mg daily dose. No formal analyses were performed by the sponsor to establish the relationship between the latter 2 doses.

Figure 1. Mean fasting plasma glucose for dose-response studies



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The results for the secondary endpoints (Table 4) show no significant treatment effects for doses of 2 mg per day and lower compared to placebo. Only the highest dose of 12 mg/day yielded significant treatment effects for all 4 variables.

Table 4. Significant Secondary Endpoint Results by Total Daily Dose (mg)

	0.1	0.5	2	4	8	12
Fructosamine				***	**	**
HbA1c				*	*	*
Plasma Insulin				*		*
C-peptide					*	*

A star indicates comparison to placebo yielded a p-value < .05. Each star represents a positive result in a single trial so multiple stars indicates that positive results were seen in more than one trial.

The results from the dose-ranging studies show that doses above 2 mg/day are effective for significantly reducing FPG. The magnitude of the reduction appears to vary between once-a-day and twice-a-day dosing; however, head-to-head comparisons are needed to establish the differences between the dosing regimens.

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Monotherapy Trials

The sponsor has presented the results of 3 monotherapy trials (Table 5); 2 of these trials (011 and 024) are placebo-controlled and one (020) is active-controlled. In all 3 trials, patients were removed from oral anti-diabetic therapy 2 weeks prior to entering a single-blind placebo with diet run-in. Patients satisfying inclusion/exclusion criteria were randomized to treatment at the end of the run-in. To enter these trials, patients needed to be between 40 to 80 years old, have a fasting c-peptide of 0.8 ng/ml or greater and have an FPG of 140 to 300 mg/dL. The primary efficacy measure in all studies was change from baseline at endpoint of HbA1c and this measure is the primary focus of this review. Also presented here are the results for fasting plasma glucose, a secondary endpoint, because the results of FPG are presented in labeling and for comparison to the dose-ranging studies. Lipids and weight are examined due to concerns expressed by the medical reviewer; both are covered for all 3 trials at the end of this section of the review.

Table 5. Monotherapy Trials

	# of Sites	Treatment Arms (N)	Duration
011 (9/96 to 9/97)	43 USA	RSG 2 mg BID (175) RSG 4 mg BID (182) Placebo (176)	2 week screening 4 week placebo run-in 26 week double-blind treatment
024 (3/97 to 12/98)	65 USA	RSG 2 mg BID (196) RSG 4 mg BID (197) RSG 4 mg OD (194) RSG 8 mg OD (187) Placebo (185)	2 week screening 4 week placebo run-in 26 week double-blind treatment
020 (11/96 to 5/98)	71 Europe	RSG 2 mg BID (200) RSG 4 mg BID (200) Glyberide 5-20 mg/day (titrated) (191)	2 week screening 4 week placebo run-in 52 week double-blind treatment

Study 011

In Study 011, after screening and a 4-week placebo run-in, patients were randomized to treatment (placebo, RSG 2 mg BID or RSG 4 mg BID) and followed for 26 weeks at 43 centers in the USA. Analyses are based on data from 42 centers; data (6 randomized patients) from one center (Fiddes in California) was excluded following an investigation by FDA which found "unethical practices".

Visits on treatment occurred at Weeks 4, 8, 12, 18 and 26. A follow-up visit occurred 1 week after discontinuation of treatment.

Patient Disposition

A total of 876 patients were screened and 623 entered the placebo run-in period. The primary reason for screen failure was FPG not within inclusion levels. Of the 623 patients entering the run-in, 533 completed and were randomized to treatment. Of the 90 patients not randomized, 32 experienced an adverse event (ADE) and 15 did not meet exclusion/inclusion criteria.

Of the 533 patients randomized, 176 were randomized to placebo, 175 to rosiglitazone (RSG) 2mg BID and 182 to RSG 4 mg BID (Table 6). In the rosiglitazone groups, about ¾ of the patients completed the study, while in the placebo group, only 56% completed.

Table 6. Study 011 Number (%) of patients on study by treatment group and week

	Placebo	RSG 2 mg BID	RSG 4 mg BID
Randomized	176 (100%)	175 (100%)	182 (100%)
Week 4	158 (90%)	167 (95%)	175 (96%)
Week 8	134 (76%)	155 (89%)	164 (90%)
Week 12	123 (70%)	140 (80%)	154 (85%)
Week 18	108 (61%)	134 (77%)	143 (79%)
Week 26	99 (56%)	129 (74%)	137 (75%)
Sponsor's ITT	158 (90%)	166 (95%)	169 (93%)

The ITT population is comprised of at least 90% of the randomized patients in each treatment group. Randomized patients with no post-baseline data were excluded; their exclusion should have no appreciable effect on the interpretation of the data.

The major reason for withdrawal (Table 7) in both the placebo group (21%) and the RSG 4 mg (8%) group was lack of efficacy (LOE). Patients could be withdrawn for lack of efficacy due to the following:

- A fasting plasma glucose of 300 mg/dL or more on two consecutive study visits during the placebo-baseline or treatment period(s);
- An increase in fasting plasma glucose to a level deemed by the investigator to represent a safety risk to the patient;
- Requirement of insulin or any additional agent to manage glycemic control;
- Any other metabolic disorder deemed by the investigator to be a safety risk to the patient.

The 2 reasons listed first were the most common reasons for LOE withdrawal.

Table 7. Study 011 Reasons for withdrawal from double-blind treatment

	Placebo (n=176)	RSG 2 mg BID (n=175)	RSG 4 mg BID (n=182)
ADE	14 (8%)	16 (9%)	7 (4%)
Lack of Efficacy	36 (21%)	9 (5%)	15 (8%)
Protocol Deviation	5 (3%)	2 (1%)	12 (7%)
Lost-to-Follow-up	4 (2%)	6 (3%)	2 (1%)
Other	18 (10%)	13 (7%)	9 (5%)

Of the LOE dropouts, all but 3 placebo patients had been administered anti-diabetic medications prior to entering this trial. In the placebo group, half of the LOE withdrawals took place during the first 2 months of therapy; in the RSG groups, LOE withdrawals occurred throughout the treatment period. Interestingly, 6 patients treated with RSG 4mg discontinued due to LOE after 12 weeks on therapy. In the RSG 2 mg group, the major reason for withdrawal was ADE (9%); most occurred during the first 12 weeks of therapy.

Patient Demographics

The treatment groups were well-balanced for baseline characteristics. Patients ranged in age from 36 to 81 years with a mean age of about 60 years; about 35% of the patients were 65 or older. About 3/5 of the patients were male and 3/4 were white. About 73% of the patients had been previously treated with an anti-diabetic agent (66% with a single agent and 7% with combination therapy). The median duration of diabetes was 4 years for placebo and RSG 2 mg and 5 years for RSG 4 mg.

Efficacy Results

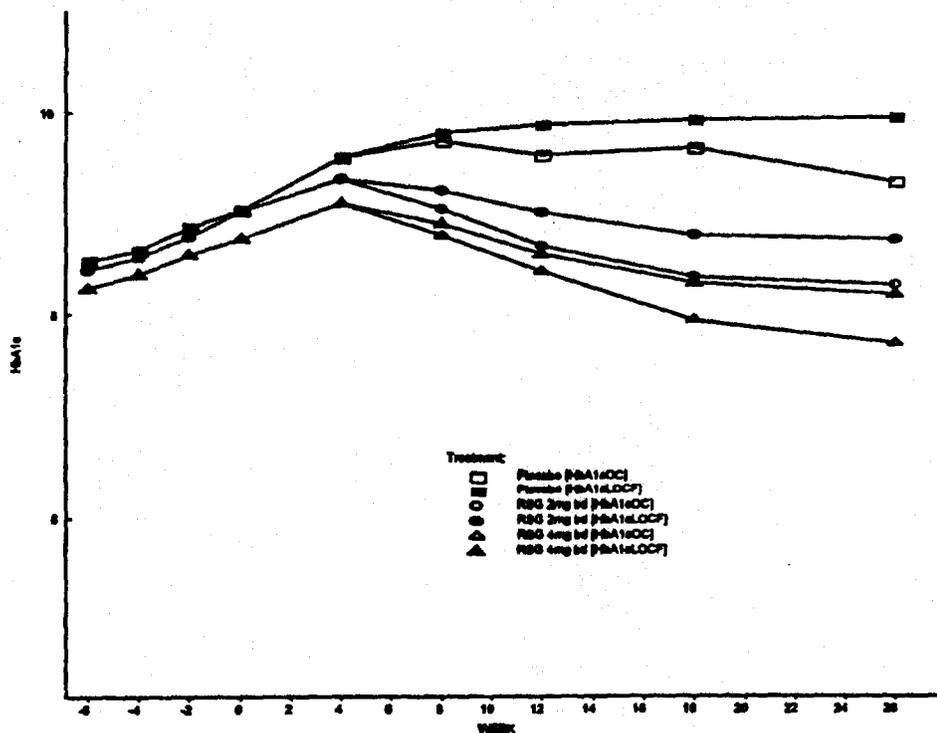
HbA1c

The primary efficacy measure in Study 011 is change from baseline in HbA1c at endpoint (Week 26 LOCF). Each dose group was statistically significantly different from placebo ($p < .0001$, ANCOVA with baseline as covariate) for both Week 26 LOCF (ITT) and for observed cases (OC)¹ (Table 8 and Figure 2).

Table 8. Mean HbA1c for Study 011

	Placebo (n=158)	RSG 2 mg BID (n=166)	RSG 4 mg BID (n=169)
Baseline	9.04 (1.66)	9.02 (1.52)	8.75 (1.56)
Week 26 LOCF	+0.92 (1.21)	-0.28 (1.27)	-0.56 (1.38)
Week 26 OC	+0.61 (1.09) (n=100)	-0.55 (1.23) (n=129)	-0.87 (1.15) (n=141)

Figure 2. Study 011 HbA1c by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



The rise in HbA1c seen from Week -6 (screening) to Week 4 (Figure 2) on treatment is probably due to withdrawal of anti-diabetic medication in a subgroup of patients. Figure 3 illustrates HbA1c levels for naive patients (25% of the sample) and for patients previously

¹ OC refers to those patients who remain on study at a specified week. At the last week of the study patients refers to those patients who completed the study

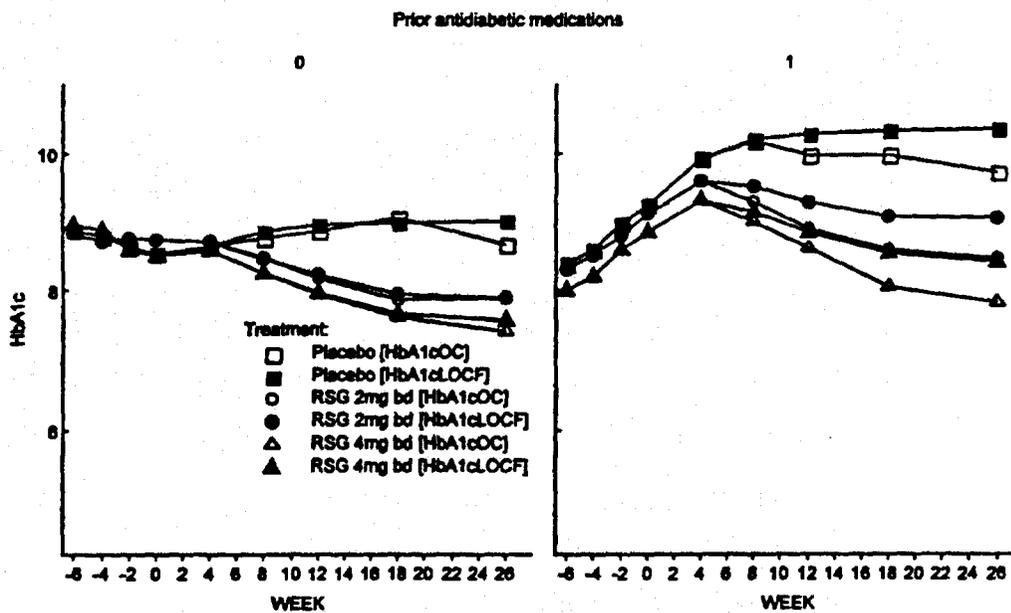
treated with anti-diabetic medications (75% of the sample) and clearly shows that the rise in HbA1c in all treatment groups is due to withdrawal of medication and that a baseline HbA1c is not attained until about 8 weeks off medication.

The treatment effects for naïve (4mg:-1.4) and previously treated patients (4mg:-1.5) are consistent (test for interaction was nonsignificant) with statistically significant differences at endpoint for each treatment group versus placebo ($p < .001$).

Table 9 a. Study 011 Mean HbA1c ITT by previous anti-diabetic medication use

	Placebo	RSG 2 mg BID	RSG 4 mg BID
Naïve	N=45	N=44	N=45
Baseline	8.54 (1.74)	8.74 (1.47)	8.51 (1.50)
Week 26 LOCF	+0.47 (1.14)	-0.83 (0.93)	-0.91 (1.04)
Prev Anti-diab Med	N=113	N=122	N=124
Baseline	9.23 (1.59)	9.12 (1.53)	8.84 (1.58)
Week 26 LOCF	+1.09 (1.20)	-0.09 (1.33)	-0.43 (1.47)

Figure 3. Study 011 HbA1c (LOCF and OC) for naïve patients (0) and patients previously treated with anti-diabetic medications (1)



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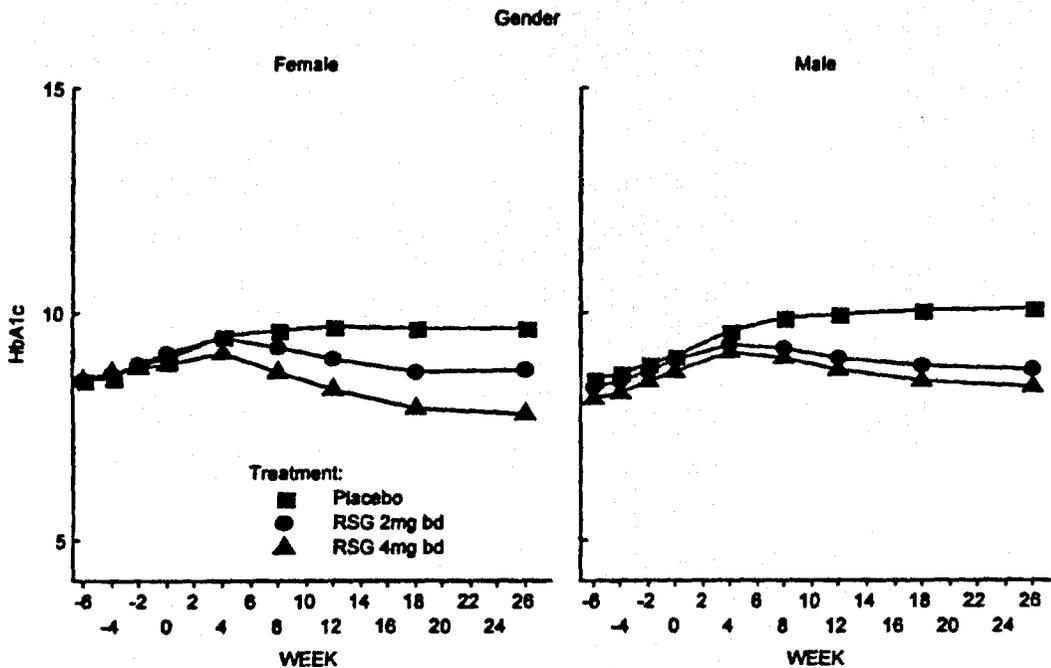
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The sponsor noted a larger effect in females than males. A test for interaction performed by this reviewer revealed a significant treatment by gender interaction ($p=.093$, Table 9 and Figure 4).

Table 9 b. Study 011 Mean HbA1c ITT by gender

	Placebo	RSG 2 mg BID	RSG 4 mg BID
Male	N=104	N=107	N=113
Baseline	9.05 (1.72)	8.97 (1.45)	8.69 (1.56)
Week 26 LOCF	+1.05 (1.24)	-0.24 (1.17)	-0.30 (1.37)
Female	N=54	N=59	N=56
Baseline	9.01 (0.67)	9.12 (1.66)	8.87 (1.56)
Week 26 LOCF	+0.66 (1.14)	-0.37 (1.45)	-1.08 (1.25)

Figure 4. Study 011 HbA1c (LOCF) by gender



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The only significant baseline differences between males and females noted were a difference in weight (this is discussed further on page 50) and in percentage of naïve patients (29%:males and 24%:females). Table 10 gives the results by prior anti-diabetic medication use; the largest difference between the genders is in the 4mg group responses, regardless of anti-diabetic medication use.

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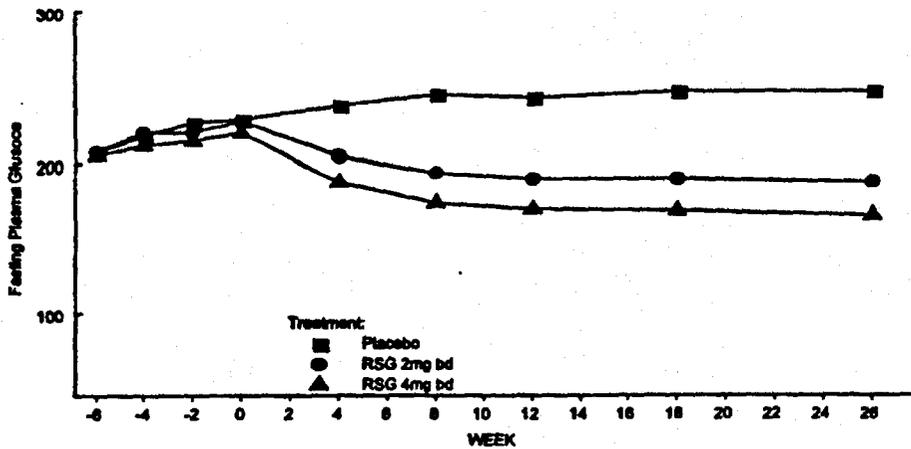
Table 10. Study 011 Mean HbA1c ITT by gender and by previous anti-diabetic medication use

	Placebo	RSG 2 mg BID	RSG 4 mg BID
Naive patients			
Male	N=30	N=33	N=31
Baseline	8.87 (1.90)	8.91 (1.41)	8.33 (1.55)
Week 26 LOCF	+0.49 (1.33)	-0.79 (0.78)	-0.76 (1.09)
Female	N=15	N=11	N=14
Baseline	7.88 (1.14)	8.27 (1.63)	8.90 (1.35)
Week 26 LOCF	+0.45 (0.64)	-0.94 (1.31)	-1.25 (0.87)
Prev. Antidiab. Med			
Male	N=74	N=74	N=82
Baseline	9.12 (1.65)	9.00 (1.48)	8.83 (1.55)
Week 26 LOCF	+1.27 (1.13)	+0.01 (1.23)	-0.13 (1.43)
Female	N=39	N=48	N=42
Baseline	9.44 (1.47)	9.32 (1.62)	8.86 (1.64)
Week 26 LOCF	+0.75 (1.28)	-0.25 (1.47)	-1.02 (1.36)

Fasting Plasma Glucose

Fasting plasma glucose was a secondary endpoint. Statistically significant treatment effects were evident for each dose group after 4 weeks on therapy (Figure 5). At endpoint (LOCF) the mean changes from baseline in each treatment group were; placebo +19, RSG 2 mg BID -38, and RSG 4 mg BID -54.

Figure 5. Study 011 Mean fasting plasma glucose (LOCF) by treatment and week on study

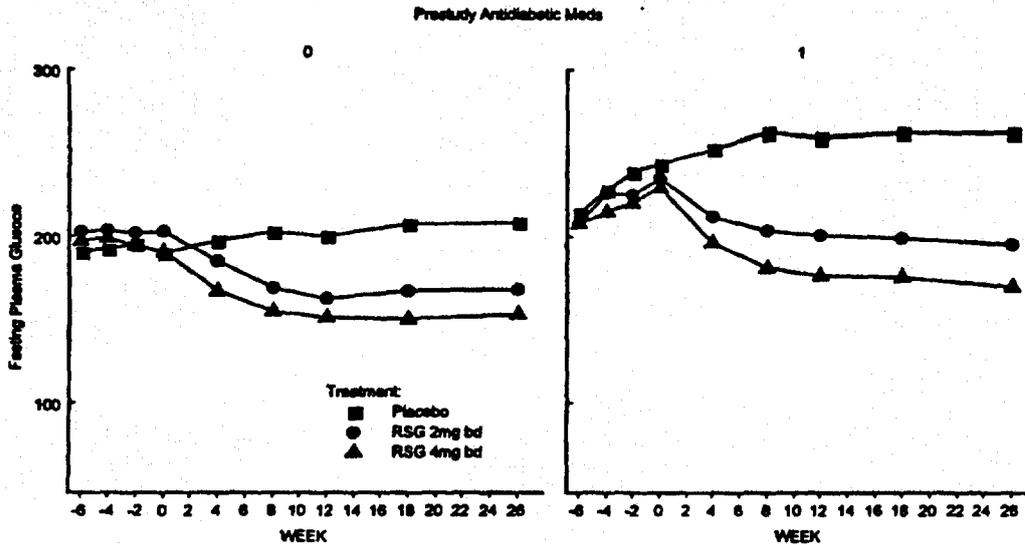


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The pattern of response for FPG by previous anti-diabetic use was similar to what was observed for HbA1c (Figure 6) with the placebo response for previously treated patients continuing to rise after baseline.

Figure 6. Study 011 Mean FPG (LOCF) for naïve patients (0) and patients previously treated with anti-diabetic medications (1)



This reviewer also created boxplots of the FPG (see Appendix 1) to examine outliers (particularly patients with episodes of hyperglycemia defined by levels above 300) and found that generally fewer episodes are evident for treated naïve patients; episodes are evident in all other groups.

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Study 024

The trial duration for Study 024 was the same as Study 011; 4 week placebo run-in followed by 26 weeks of double-blind treatment. Treatment visits on therapy were at Weeks 4, 8, 12, 18 and 26. The trial was conducted at a total of 65 centers; as for Study 011, data (2 randomized patients) from the Fiddes center was excluded so analyses are based on 64 centers. Twelve centers for this study were also used in Study 011. This reviewer found that 2 randomized 024 patients (pt 024.014.02215 and pt 024.001.02900) were screened for Study 011 but not treated under Study 011; one patient was screened for both studies but not treated in either.

The primary objective of this trial was to compare the once-a-day doses (4 mg OD and 8 mg OD) to placebo. A secondary objective was to compare the once-a-day doses to twice-a-day doses.

Patient Disposition

A total of 1,503 patients were screened and 1,488 entered the placebo run-in period. About 77% of the patients who withdrew before randomization did not satisfy the inclusion/exclusion criteria. At the end of the run-in, 959 patients were randomized to treatment; 185 to placebo, 194 to 4 mg OD, 196 to 2 mg BID, 187 to 8 mg OD and 197 to 4 mg BID.

Table 12. Number (%) of patients on study by treatment group and week

	Placebo	RSG 4 mg OD	RSG 2 mg BID	RSG 8 mg OD	RSG 4 mg BID
Randomized	185 (100%)	194 (100%)	196 (100%)	187 (100%)	197 (100%)
Week 4	162 (88%)	172 (89%)	185 (94%)	175 (94%)	184 (93%)
Week 8	141 (76%)	163 (84%)	177 (90%)	164 (88%)	177 (90%)
Week 12	128 (69%)	157 (81%)	168 (86%)	156 (83%)	170 (86%)
Week 18	117 (63%)	152 (78%)	162 (83%)	145 (78%)	162 (82%)
Week 26	114 (62%)	148 (76%)	161 (82%)	145 (78%)	159 (81%)
Sponsor's ITT	173 (94%)	181 (93%)	186 (95%)	181 (97%)	187 (95%)

The completion rates in this study were similar to the rates in Study 011 with 62% of placebo patients and about 80% of rosiglitazone patients completing therapy (Table 12). Overall about 95% of the patients comprise the ITT population.

The 2 major reasons for discontinuation were ADE and LOE (Table 13); about half of these discontinuations took place during the first 2 months of therapy. Of all the LOE dropouts, only 5 patients were naïve to anti-diabetic therapy **BEST POSSIBLE**

Table 13. Reasons for withdrawal from double-blind treatment

	Placebo (n=185)	RSG 4 mg OD (n=185)	RSG 2 mg BID (n=185)	RSG 8 mg OD (n=185)	RSG 4 mg BID (n=185)
ADE	10 (11%)	12 (6%)	11 (6%)	10 (5%)	10 (5%)
Lack of Efficacy	31 (17%)	11 (6%)	13 (7%)	17 (9%)	10 (5%)
Protocol Deviation	2 (1%)	3 (2%)	2 (1%)	2 (1%)	4 (2%)
Lost-to-Follow-up	4 (2%)	8 (4%)	1 (.5%)	5 (3%)	5 (3%)
Other	14 (8%)	12 (6%)	8 (4%)	8 (4%)	9 (5%)

Patient Demographics

The treatment groups were well-balanced regarding baseline characteristics. Patients ranged in age from 35 to 80 years with a mean age of about 58 years; 25% of the patients were 65 or older. About 63% of the patients were male and about 77% were white. Most patients (75%) had been treated previously with anti-diabetic medication; about 60% with monotherapy and 15% with combination therapy. The median duration of diabetes was 4 years (range of 0 to 47 years).

Efficacy Results

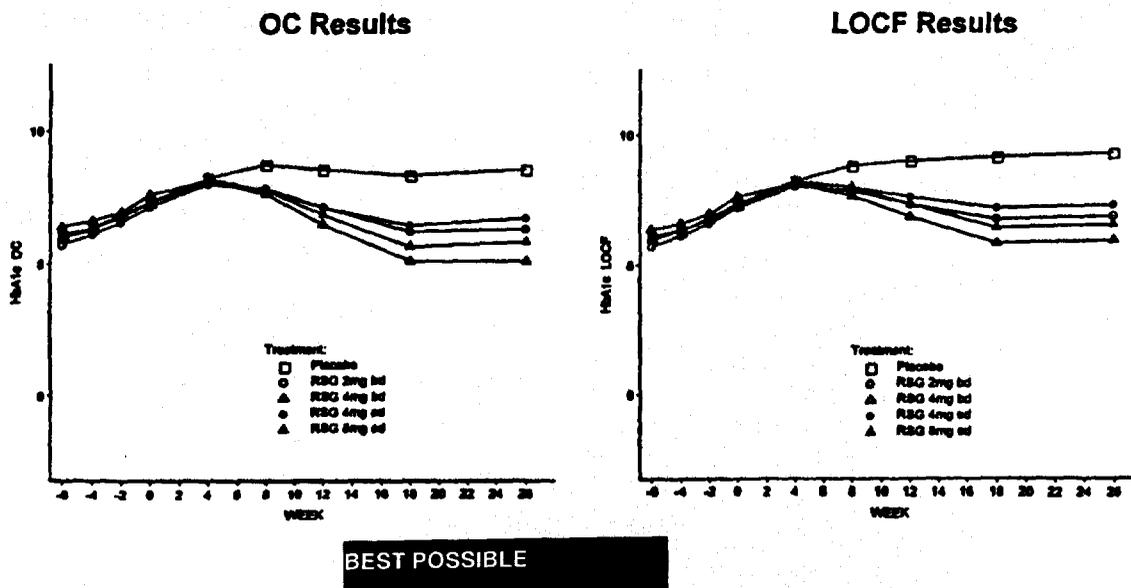
HbA1c

The primary efficacy measure in Study 024 is change from baseline in HbA1c at endpoint (Week 26 LOCF). Each dose group was statistically significantly different from placebo ($p < .0001$, ANCOVA with baseline as covariate) for both Week 26 LOCF (ITT) and for observed cases (OC) (Table 14 and Figure 7).

Table 14. Mean HbA1c for Study 024

	Placebo (n=173)	RSG 4 mg OD (n=180)	RSG 2 mg BID (n=186)	RSG 8 mg OD (n=181)	RSG 4 mg BID (n=187)
Baseline	8.93 (1.52)	8.92 (1.59)	8.87 (1.54)	8.94 (1.52)	9.04 (1.52)
Week 26 LOCF	+0.79 (1.10)	+0.02 (1.40)	-0.13 (1.42)	-0.31 (1.24)	-0.67 (1.37)
Week 26 Completers	+0.71 (1.17) (n=110)	-0.14 (1.39) (n=147)	-0.27 (1.37) (n=158)	-0.49 (1.24) (n=141)	-0.88 (1.19) (n=159)

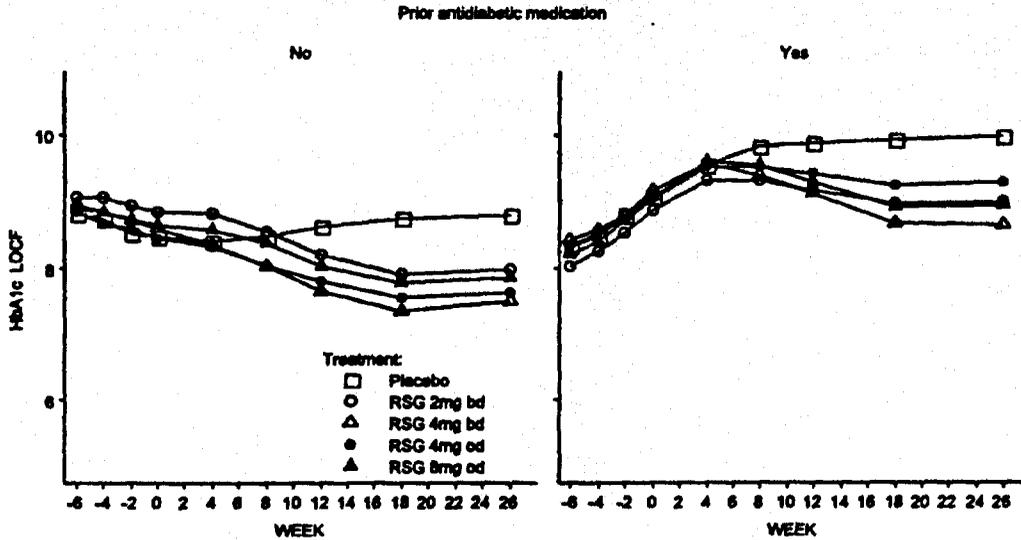
Figure 7. Study 024 Mean HbA1c by week and treatment group



The results for naïve patients (25% of sample) and patients previously treated with anti-

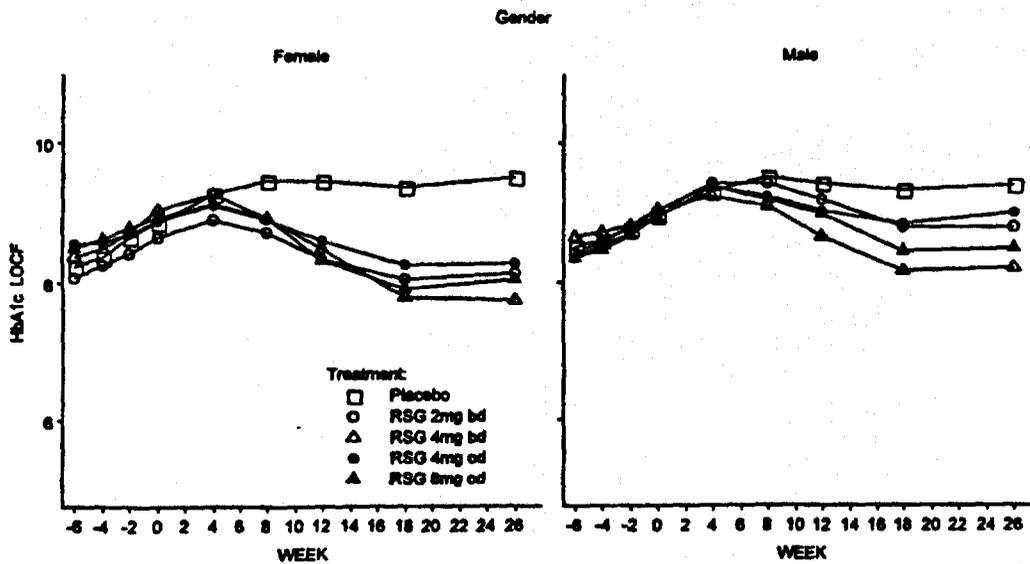
diabetic medications (75% of sample) were similar with significant treatment effects of about -1.45 evident at endpoint for each treatment group compared to placebo (Figure 8).

Figure 8. Study 024 HbA1c (LOCF) for naïve patients and patients previously treated with anti-diabetic medications



The interaction between treatment and gender was highly significant ($p=.003$) and quantitative (Figure 9). For each gender, each dose is significantly different from placebo; $p<.0001$ for females and $p<.05$ for males. This differential gender effect was also seen in Study 011 and is further discussed in the last section of this review (Overall Reviewer Comments).

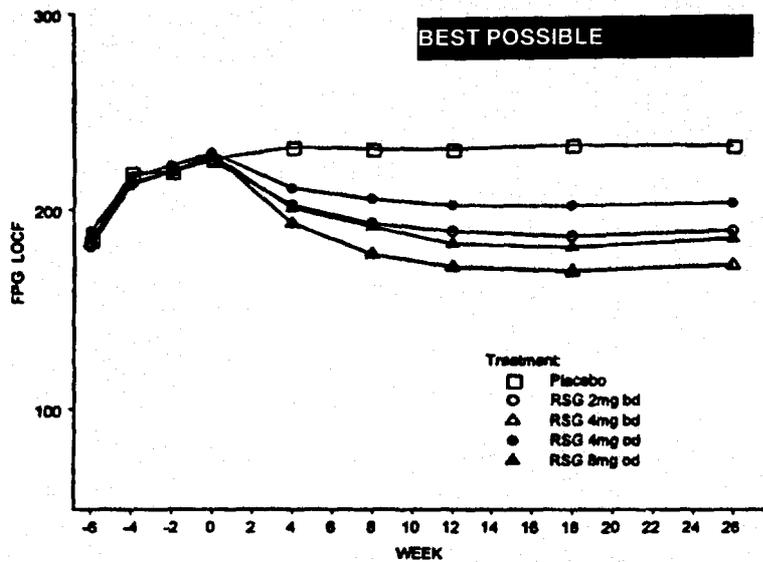
Figure 9. Study 024 HbA1c (LOCF) by gender



Fasting Plasma Glucose

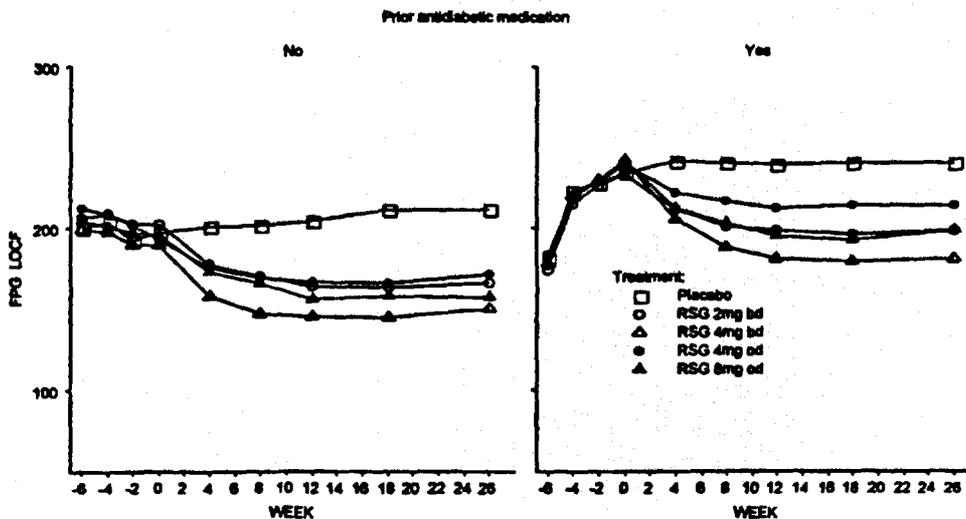
Fasting plasma glucose was a secondary endpoint. Each treatment significantly reduced FPG compared to placebo (Figure 10, $p < .0001$). As for HbA1c, the 4 mg twice-a-day dose (Δ) appears to be the most efficacious dose.

Figure 10 Study 024 Mean fasting plasma glucose (LOCF) by treatment and week on study



FPG results by anti-diabetic use showed a larger treatment effect for naïve patients compared to previously treated patients in the once-a-day dosing group (Figure 11); the effects are the same for the twice-a-day doses.

Figure 11 Study 024 Mean fasting plasma glucose (LOCF) by prior anti-diabetic use



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Once-a-day dosing versus twice-a-day dosing

A secondary objective of Study 024 was to examine the relationship between once-a-day dosing versus twice-a-day dosing. According to the protocol, the doses would be considered comparable if the 95% confidence interval excluded $\pm 0.5\%$ for HbA1c change from baseline; no criteria for FPG was set. The confidence intervals for the LOCF means for HbA1c and FPG (Table 15) indicate that twice-a-day dosing is more efficacious than once-a-day dosing (negative values favor twice-a-day dosing). For FPG, the dosing regimens are statistically significantly different for both daily doses. For HbA1c, the 4 mg twice-a-day dose is significantly superior to the 8 mg once-a-day dose.

Table 15. 95% confidence intervals for twice-a-day minus once-a-day (Week 26 LOCF)

Total Daily Dose	Twice-a-day Mean	Once-a-day Mean	95% CI * (unadjusted)
4 mg HbA1c	-0.12	+0.02	-0.43, 0.14
FPG	-35.4	-24.6	-21.5, -0.2
8 mg HbA1c	-0.68	-0.31	-0.63, -0.10
FPG	-55.4	-42.2	-24.3, -1.2

* Negative values favor twice-a-day dosing

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Study 020

Study 020 is a 52-week European trial designed to compare glyberide to rosiglitazone. The run-in period (2 weeks off prior medication plus 4 weeks of placebo) and the entry criteria were similar to Studies 011 and 024. There were three treatment arms; rosiglitazone 2 mg BID and 4 mg BID and glibenclamide titrated to glycemic control (maximum of 15 mg daily by Week 12).

The trial was powered to show that RSG 4 mg BID is not worse than glibenclamide by 0.5% HbA1c or more based on the upper bound of a 95% confidence interval at Week 52.

Patient Disposition

A total of 851 patients were screened at 71 European sites; 598 were randomized to treatment, about 80% of the patients completed the study and about 98% of those patients comprised the ITT population (Table 17).

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Table 17. Number (%) of patients on study by treatment group and week

	Glibenclamide	RSG 2 mg BID	RSG 4 mg BID
Randomized	207 (100%)	200 (100%)	191 (100%)
Week 2	200 (97%)	195 (98%)	188 (98%)
Week 4	197 (95%)	191 (96%)	186 (93%)
Week 6	195 (94%)	189 (95%)	182 (95%)
Week 8	195 (94%)	187 (94%)	181 (95%)
Week 12	190 (92%)	178 (89%)	179 (94%)
Week 16	189 (91%)	176 (88%)	177 (93%)
Week 26	182 (88%)	168 (84%)	171 (90%)
Week 38	179 (86%)	160 (80%)	164 (86%)
Week 52	173 (84%)	153 (77%)	158 (83%)
Sponsor's ITT	203 (98%)	185 (98%)	189 (99%)

The primary reason for dropout in the rosiglitazone groups was lack of efficacy (LOE) (Table 18). Patients were withdrawn for LOE if FPG_≥270 on 2 consecutive visits during the first 16 weeks of treatment or FPG_≥216 on 2 consecutive visits after Week 16. In the glibenclamide group, the primary withdrawal reason was ADE (6 due to hypoglycemia occurring during Weeks 1, 6, 9, 12, 26 and 36). ADE's in all groups occurred throughout the double-blind treatment period. All but one of the glibenclamide LOE dropouts and about half of the rosiglitazone LOE dropouts occurred at Week 26 or later.

Table 18. Reasons for withdrawal from double-blind treatment

	Glibenclamide (n=203)	RSG 2 mg BID (n=195)	RSG 4 mg BID (n=189)
ADE	13 (6%)	12 (6%)	9 (5%)
Lack of Efficacy	7 (3%)	22 (11%)	15 (8%)
Protocol Deviation	7 (3%)	7 (4%)	12 (7%)
Lost-to-Follow-up	3 (1%)	1 (0.5%)	1 (0.5%)
Other	4 (2%)	5 (3%)	2 (1%)

Patient Demographics

The treatment groups were well-balanced regarding most baseline characteristics; there was a small imbalance for gender (Glib:70% male; RSG2:68% male and RSG4:58% male). The mean age of patients was 61 years; about 36% were 65 or older. Almost all patients (98.3%) were white. About 60% of the patients had been treated previously with anti-diabetic medications (within 30 days prior to enrollment); 51% with monotherapy and 10% with combination therapy. About 18% of the patients were previously treated with glibenclamide. The median duration of diabetes was 4 years (range of 0 to 52).

Glibenclamide Dose Titration

Patients were titrated at the discretion of the investigator; no guidelines regarding titration were provided in the protocol. Titration was blinded with rosiglitazone patients titrated with additional placebo tablets. Titration took place in a step-wise manner up until Week 12; after Week 12, all patients were maintained on the same dose for the remainder of the trial. Seventy percent of the glibenclamide patients were started on a 2.5 mg dose and 30% on 5.0 mg. According to the sponsor, dose changes could be made based on the FPG values at the previous visit. Table 19 shows the mean FPG at the previous visit for each dose level by week on study. These FPG mean values then indicate the level of FPG upon which the decision to maintain or go to the specified dose level was made by the investigator. The standard deviations suggest overlap between dose levels and variability in the investigators' criteria for titration. The adequacy of the titration is left to clinical judgement.

Table 19. Mean FPG at previous visit for each glibenclamide dose level by week on study

	2.5	5.0	7.5	10	12.5	15.0
Week 0	178 (44) (n=147)	227 (49) (n=54)	NA	NA	NA	NA
Week 2	168 (36) (n=101)	203 (48) (n=63)	234 (51) (n=35)	NA	NA	NA
Week 4	157 (32) (n=78)	197 (38) (n=59)	210 (51) (n=37)	248 (48) (n=23)	NA	NA
Week 6	155 (30) (n=66)	191 (40) (n=51)	197 (36) (n=29)	222 (54) (n=30)	242 (54) (n=19)	NA
Week 8	158 (36) (n=58)	175 (39) (n=36)	199 (38) (n=40)	210 (45) (n=16)	217 (54) (n=23)	243 (52) (n=21)
Week 12	159 (33) (n=53)	182 (45) (n=34)	191 (43) (n=29)	194 (35) (n=22)	204 (47) (n=16)	236 (50) (n=33)

The distribution of the final doses (Week 12 doses) is shown below.

2.5 mg	27%
5.0 mg	17%
7.5 mg	17%
10 mg	10%
12.5 mg	11%
15 mg	17%

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It is worth noting that 44% of the patients remained on the starting doses of 2.5 and 5 for the duration of the trial.

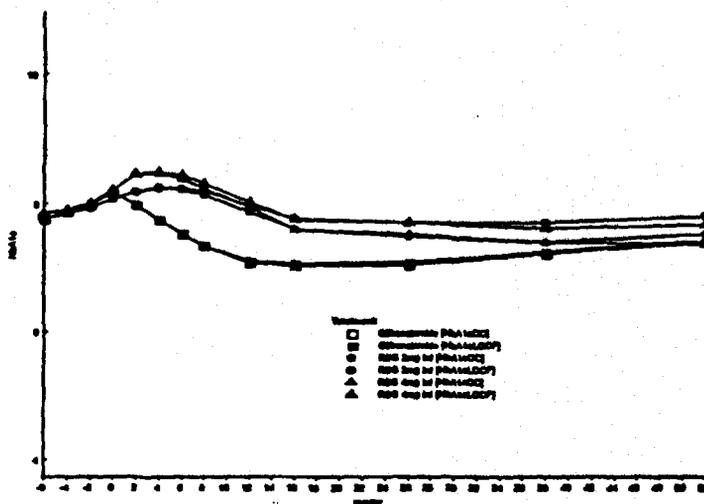
HbA1c

The primary efficacy measure was change from baseline in HbA1c at Week 52 LOCF. Table 20 and Figure present mean changes from baseline and mean HbA1c overtime, respectively, for both completers (OC) and LOCF. For glibenclamide-treated patients, there is essentially no difference between the OC and LOCF results suggesting a minimal impact of dropouts on the LOCF results (also recall that there was only a 16% dropout rate in the glibenclamide group). The medical reviewer expressed concern about the effect of withdrawing glibenclamide patients (5 ITT patients) due to hypoglycemia on the assessment of efficacy; the HbA1c values for those patients at endpoint were 5.8, 5.9, 6.7, 6.7 and 7.9 (mean change of -0.6). Four of the 5 patients are included in the Week 12 completers analysis; all are excluded from the Week 52 completers analysis but judging from the means for LOCF and OC, do not appreciably affect the results.

Table 20. Mean HbA1c for Study 020

	Glibenclamide (ITTn=202)	RSG 2 mg BID (ITTn=195)	RSG 4 mg BID (ITTn=189)
Baseline	8.16 (1.28)	8.07 (1.30)	8.21 (1.45)
Week 12			
LOCF (ITT)	-1.05 (0.80)	-0.10 (0.92)	-0.19 (1.01)
Completers	-1.08 (0.80) (n=191)	-0.15 (0.92) (n=180)	-0.23 (0.99) (n=180)
Week 28			
LOCF (ITT)	-1.06 (0.91)	-0.36 (0.97)	-0.50 (1.25)
Completers	-1.10 (0.92) (n=185)	-0.48 (0.91) (n=172)	-0.62 (1.22) (n=170)
Week 52			
LOCF (ITT)	-0.72 (1.0)	-0.27 (1.04)	-0.53 (1.31)
Completers	-0.73 (1.03) (n=173)	-0.38 (1.02) (n=148)	-0.66 (1.20) (n=150)

Figure 12. Study 020 HbA1c by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data

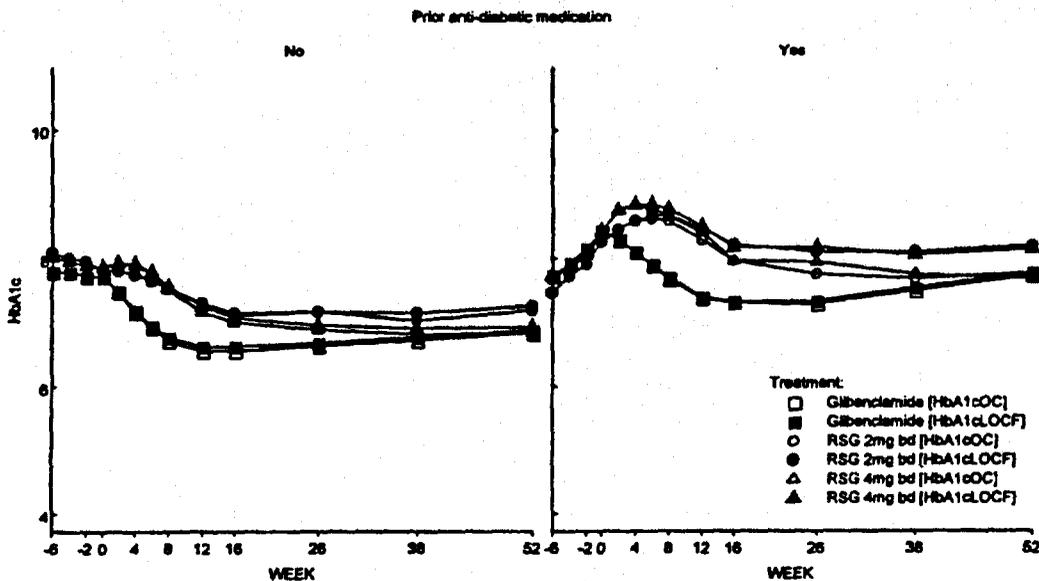


In the rosiglitazone groups, it is evident from Table 20 and Figure 12 that the exclusion of dropouts from a completers (OC) analysis favors rosiglitazone and henceforth makes rosiglitazone appear more comparable to glibenclamide. Since the primary reason for dropout in both rosiglitazone groups is LOE, it does not seem reasonable to exclude those patients from

an ITT analysis; the LOCF analysis then gives a better estimate of the effect.

Subgrouping the results by previous use of anti-diabetic medication (Figure 13) shows that a difference between the LOCF and OC rosiglitazone results occurs for patients previously treated; this is expected since most of the LOE dropouts occurred in this subgroup. The mean HbA1c change for naïve patients treated with RSG 4mg was -0.90 and for previously treated patients -0.26 . For the glibenclamide patients, the change from baseline in both subgroups was about -1.0 .

Figure 13. Study 020 HbA1c (LOCF) for naïve patients (0) and patients previously treated with anti-diabetic medications (1)

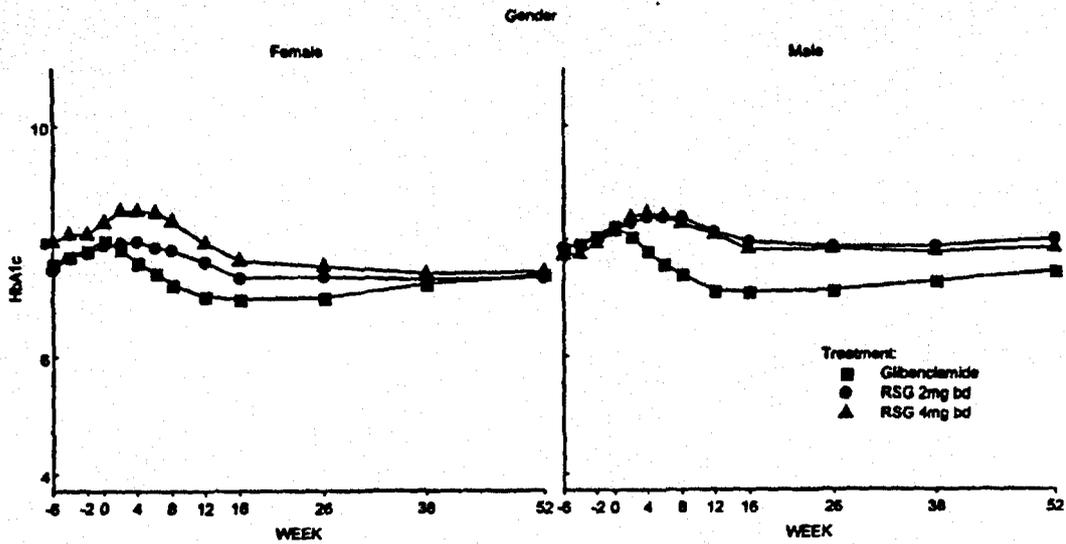


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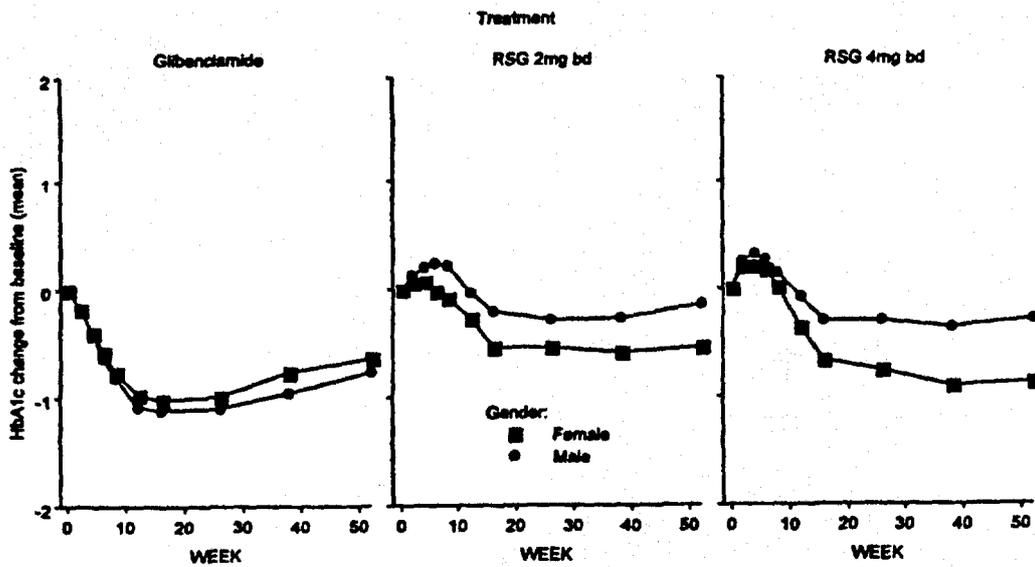
A significant gender by treatment interaction was seen at each week after Week 8 ($p < .10$, Figure 14) with females showing more improvement than males.

Figure 14. Study 020 HbA1c (LOCF) by gender and treatment



The difference between the genders in the rosiglitazone arms is clearly evident in Figure 15 below.

Figure 15. Study 020 HbA1c change from baseline (LOCF) by treatment and gender

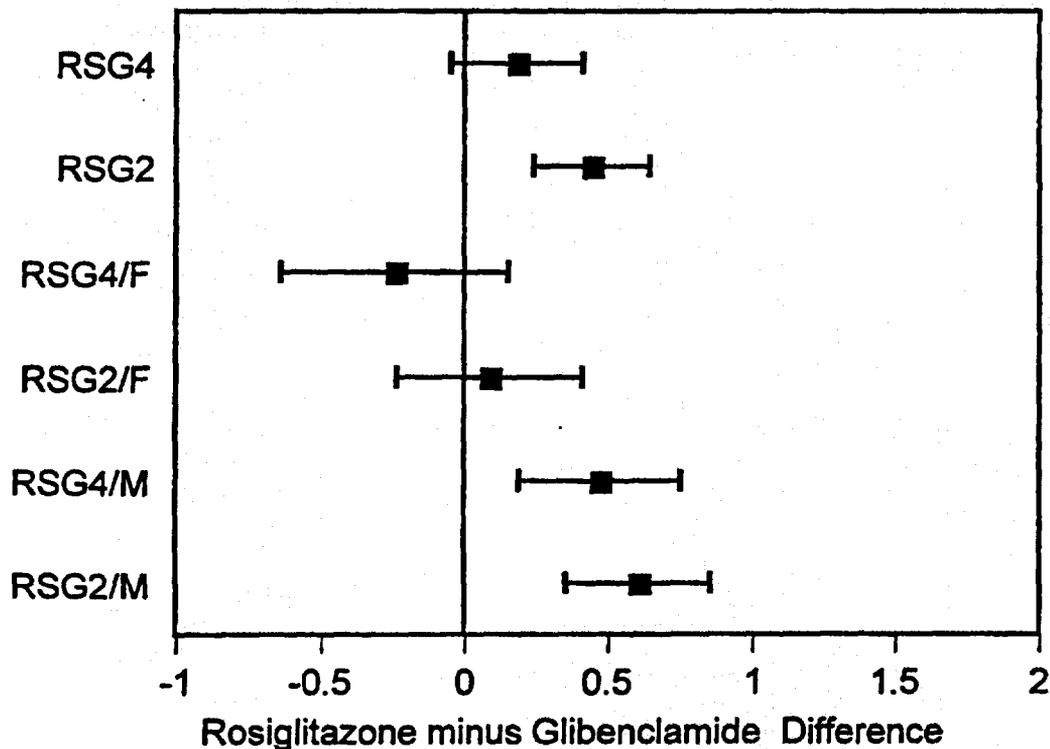


To assess comparability of the rosiglitazone doses to glibenclamide, the protocol stated that the upper boundary of the 95% CI should be less than 0.5. Figure 16 illustrates 95% CI for treatment differences (rosiglitazone change from baseline minus glibenclamide change from baseline) for each dose group overall and by gender. Glibenclamide is statistically significantly superior to rosiglitazone for males and for the 2mg dose; however, it should be noted that the trial was not powered to show comparability in subgroups. Note that most estimates favor glibenclamide (positive values).

Figure 16

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Mean and 95% confidence interval for the difference between HbA1c change from baseline at Week 52 LOCF for glibenclamide compared to rosiglitazone by dose and gender

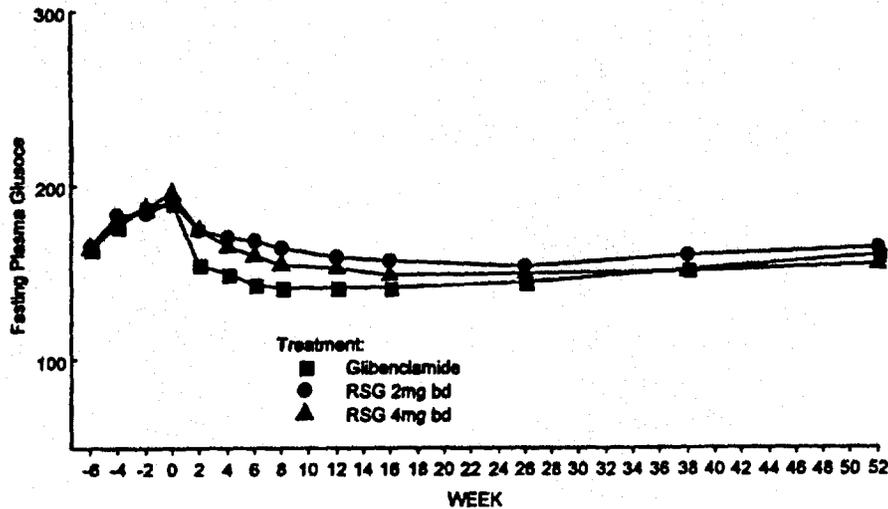


* Positive values favor glibenclamide

Fasting Plasma Glucose

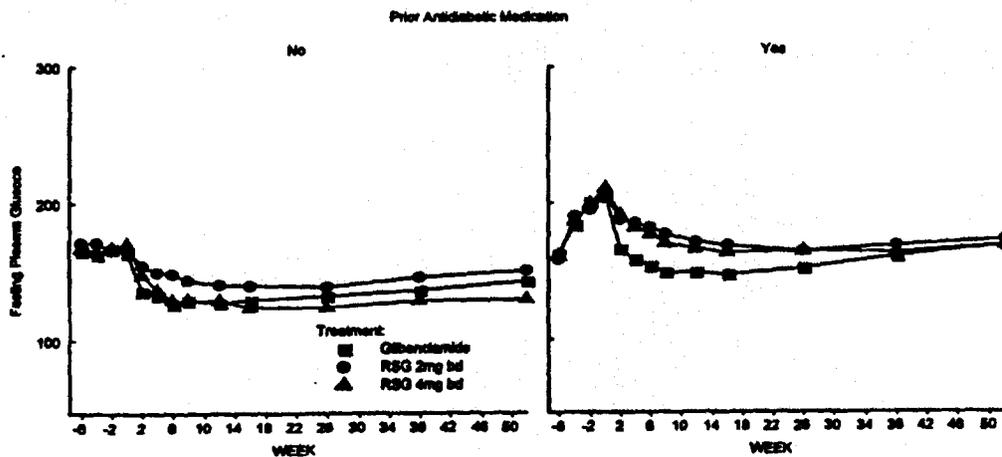
The results for FPG are shown in Figure 17. No criteria was specified in the protocol for establishing comparability between rosiglitazone and glibenclamide. At endpoint, RSG 4mg was significantly different from glibenclamide ($p < .02$, RSG:-41 versus GLIB:-30, Week 52 change from baseline LOCF).

Figure 17. Study 020 Fasting plasma glucose by treatment group and week (LOCF)



The FPG results by prior anti-diabetic medication use are consistent with the overall results.

Figure 18. Study 020 Fasting plasma glucose by prior anti-diabetic use, treatment group and week (LOCF)



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Reviewer's general comments on active-controlled Study 020

Given only the active-controlled trial performed by the sponsor (Study 020) without the results of the placebo-controlled trials, it would be difficult to establish the efficacy of rosiglitazone as monotherapy for the following reasons.

- The results for the 2 mg dose are significantly worse than glibenclamide on the primary efficacy measure.
- The results are borderline for the RSG 4 mg BID dose compared to glibenclamide with an upper bound of 0.42 for the 95% CI based on the criteria (0.50 for the upper bound) pre-specified in the protocol.
- The effect of the active control against placebo from historical data is not given in the NDA making it impossible to assess if the glibenclamide effect observed is consistent with previous data on this drug.
- It is not clear that the active control is being optimally dosed since no dosing adjustments were allowed after Week 12 and if the active control is not optimally dosed then we do not have a fair comparison.
- The criteria for non-inferiority is based on clinical judgement and is therefore somewhat arbitrary. Also note the test drug may satisfy the criteria and still be significantly worse than the active control.
- Differential effects were seen for subgroups based on gender and previous anti-diabetic medication use for rosiglitazone but not for glibenclamide.

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Lipid changes in the monotherapy trials

For LDL and total cholesterol (TC), each treatment group showed a statistically significant increase from baseline compared to placebo and glibenclamide (Figures 19 and 20). Results for subgroups based on gender, previous anti-diabetic use and above/below ideal body weight (IBW) were consistent with the overall results.

Figure 19. Change from baseline of LDL by monotherapy study, treatment and week on therapy

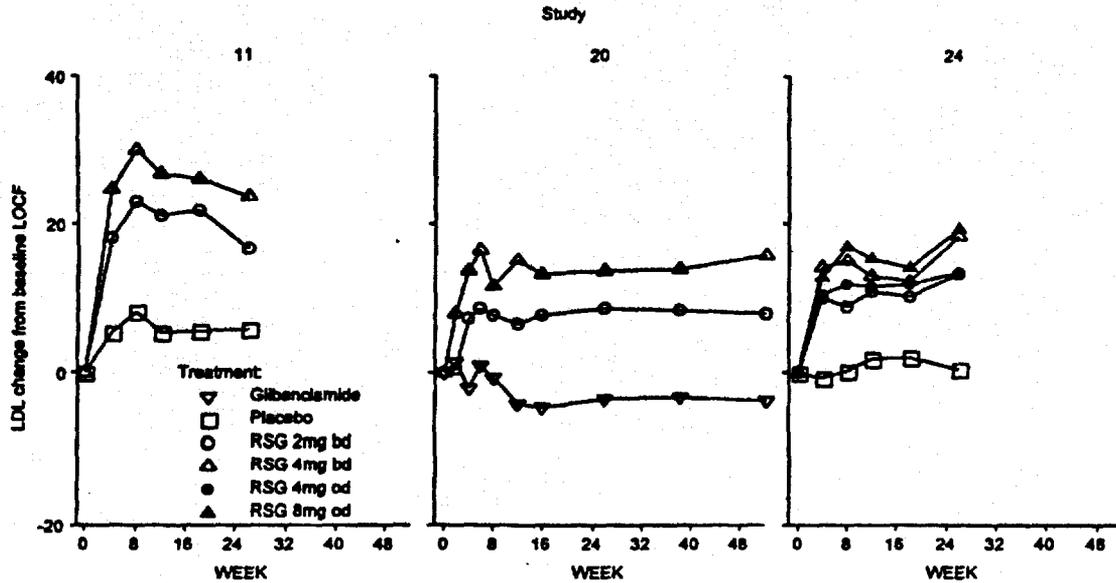
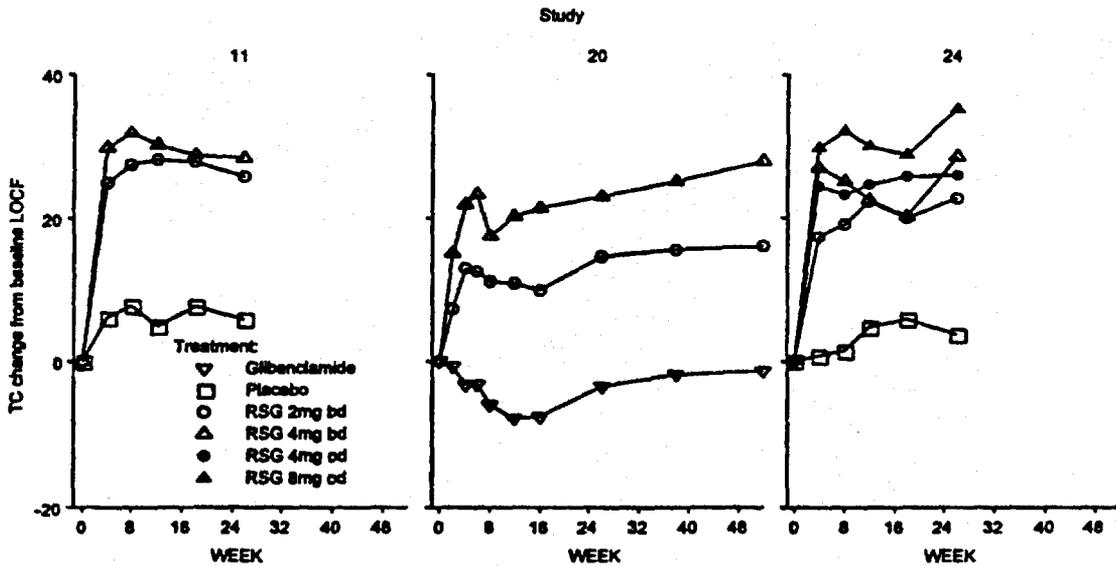


Figure 20. Change from baseline of TC by monotherapy study, treatment and week on therapy



HDL significantly increased for rosiglitazone 8 mg daily groups compared to placebo and glibenclamide (Figure 21). In study 11, the lower dose of 2 mg BID also showed a significant increase over placebo. Likewise, for the ratio of LDL/HDL, statistically significant differences between rosiglitazone and comparator were seen consistently for the duration of the trial (Figure 22).

Figure 21. Change from baseline of HDL by monotherapy study, treatment and week on therapy

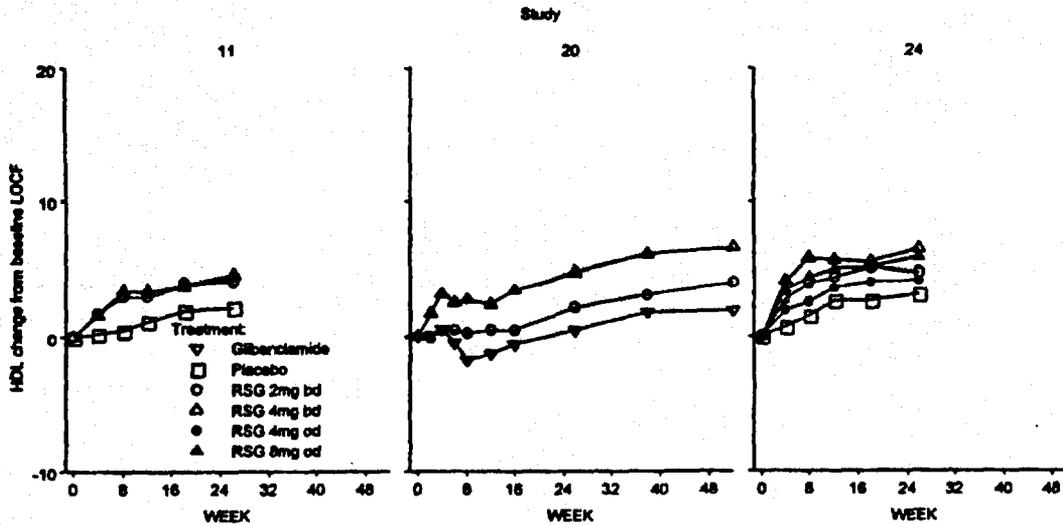
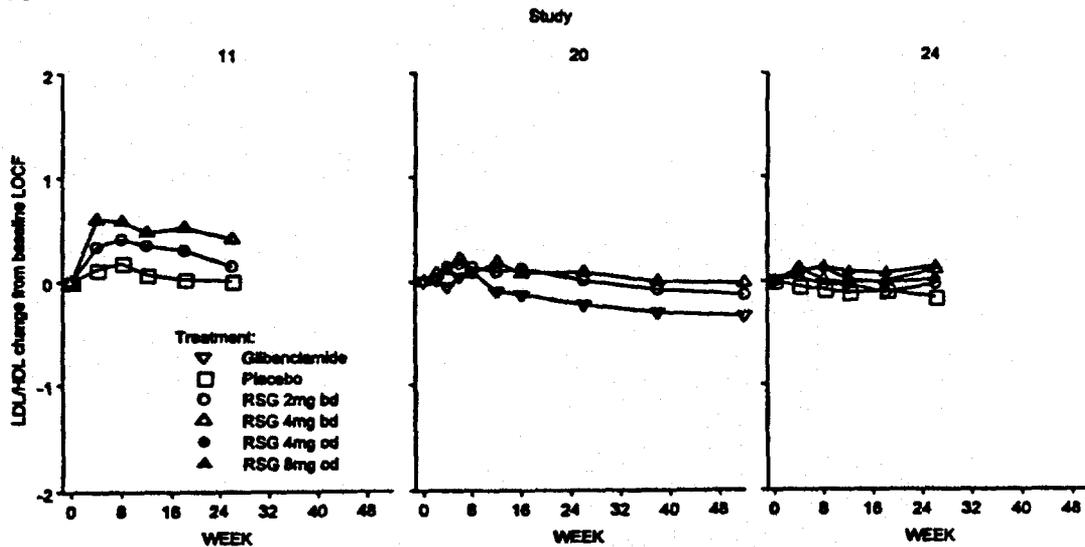
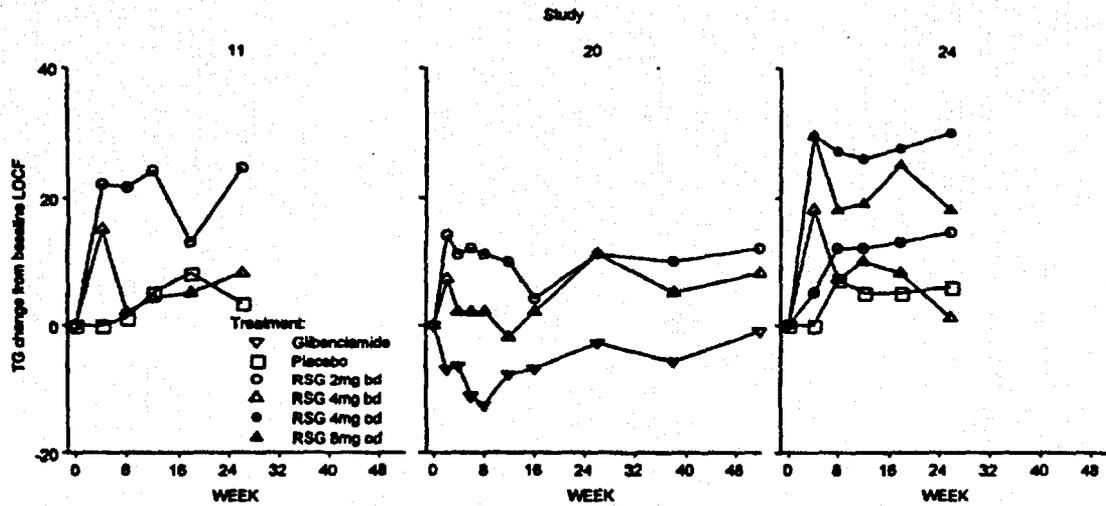


Figure 22. Change from baseline of LDL/HDL by monotherapy study, treatment and week on therapy



The results for TG were less consistent (Figure 23); rosiglitazone 4 mg BID changes were not significantly different from placebo but were statistically significantly different from glibenclamide. Larger increases were observed for lower doses and for once-a-day doses.

Figure 23. Median change from baseline of TG (LOCF) by monotherapy study, treatment and week on therapy



The mean results for lipids are shown below.

Table 21. Summary of mean lipid changes at endpoint LOCF (Week 26 for Studies 11 and 24 and Week 52 for Study 20) for the monotherapy trials

	Study 011			Study 024					Study 020		
	PLA	RSG 2BID	RSG 4BID	PLA	RSG 2BID	RSG 4BID	RSG 4OD	RSG 8OD	GLIB	RSG 2BID	RSG 4BID
LDL											
Base	122	121	124	126	132	124	126	126	142	143	142
Ch	+6	+17	+24	+3	+13	+18	+13	+19	-4	+8	+16
%Ch	+7%	+17%	+24%	+2%	+12%	+17%	+12%	+20%	-1%	+8%	+13%
TC											
Base	214	217	218	210	217	214	210	212	222	224	222
Ch	+6	+25	+28	+4	+23	+28	+26	+35	-2	+16	+28
%Ch	+3%	+13%	+14%	+2%	+11%	+15%	+13%	+18%	+3%	+8%	+13%
HDL											
Base	43	42	42	44	46	44	44	44	47	48	48
Ch	+2	+4	+4	+3	+5	+6	+4	+6	+2	+4	+6
%Ch	+6%	+11%	+12%	+7%	+12%	+17%	+11%	+15%	+8%	+12%	+18%
LD/HD											
Base	3	3	3	3	3	3	3	3	3	3	3
Ch	+.01	+.1	+.4	-.2	-.03	+.1	+.01	+.1	-.3	-.1	-.02
%Ch	+3%	+8%	+17%	-4%	+2%	+4%	+4%	+9%	-3%	-.2%	+4%
TG											
Base	226	252	236	211	209	258	222	241	176	195	170
Ch	+22	+42	+6	+7	+21	+2	+36	+33	-3	-10	+12
%Ch	+14%	+29%	+14%	+8%	+18%	+14%	+26%	+26%	+7%	+17%	+14%

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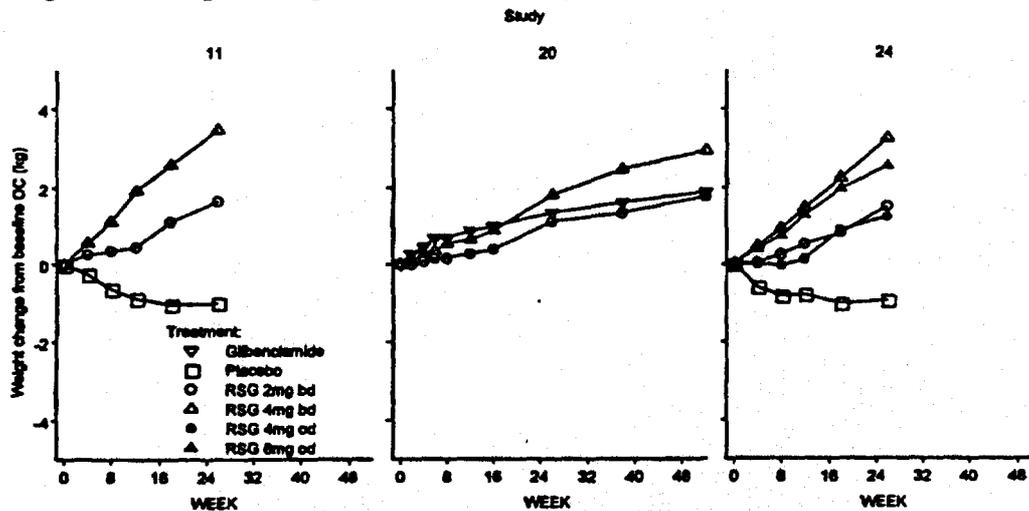
From Table 21 above, it can be seen that for LDL the baseline in Study 20 is higher than in Studies 11 and 24 and that the mean change in LDL in Study 20 is smaller than in the other 2 studies. This reviewer found that mean changes in LDL were baseline related. LDL changes by baseline subgroups are shown below for treatment group RSG 4mg BID.

Baseline LDL	% change from baseline of LDL		
	Study 011	Study 024	Study 020
LDL <130	32%	24%	23%
LDL 130-160	14%	11%	11%
LDL >160	7%	5%	1% (median 3%)

Weight changes in the monotherapy trials

Mean weight gains were seen for the rosiglitazone and glibenclamide patients while small mean losses were seen for placebo patients for the duration of the trial (Figure 24). Changes in weight were consistent for subgroups based on baseline BMI and gender (slightly but not notably higher in women). Results by previous anti-diabetic medication use showed a consistent rise in weight for rosiglitazone regardless of subgroup; the placebo response did vary with naïve patients showing no change in weight and patients previously taking monotherapy or combination therapy showing a significant decrease in weight of about 2-3 kg at endpoint.

Figure 24 Weight change from baseline (OC) by monotherapy study, treatment and week



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Combination Trials

The sponsor has conducted two 26-week trials (Table 22) to assess the efficacy and safety of rosiglitazone in combination with metformin for patients considered inadequately controlled on metformin ($140 \leq \text{FPG} \leq 300$). For Study 093, rosiglitazone 4 mg BID was combined with metformin and for Study 094, rosiglitazone 4 mg OD and rosiglitazone 8 mg OD were each combined with metformin.

Table 22. Combination with Metformin Trials

	# of Sites	Treatment Arms (N)	Duration of Treatment
093 (6/97 to 4/98)	34 (USA)	RSG 4 mg BID+Met (106) RSG 4 mg BID+Plac (107) Metformin+Placebo (109)	3 weeks titration to Met 2.5 mg 4 weeks Metformin 2.5 mg+diet 26 weeks rand. treatment
094 (4/97 to 3/98)	36 (USA)	RSG 4 mg OD+Met (119) RSG 8 mg OD+Met (113) Metformin+Placebo (116)	3 weeks titration to Met 2.5 mg 4 weeks Metformin 2.5 mg+diet 26 weeks rand. treatment

Study 093

Study 093 is a 26-week, double-blind, randomized, parallel study of rosiglitazone 4 mg BID plus metformin 2.5 g/day compared to two monotherapy arms of rosiglitazone 4 mg BID and metformin 2.5 g/day. After screening, all patients were titrated on metformin to a dose of 2.5 g/day and maintained on this dose for 4 weeks. At the end of this maintenance period, patients satisfying the entry criteria and considered inadequately controlled on metformin ($140 \leq \text{FPG} \leq 300$ at the first and second week of the maintenance period) were randomized to treatment. The protocol also states that patients with $\text{FPG} < 140$ anytime during the maintenance period should be withdrawn.

The primary objective of this trial was to show that the combination therapy was superior to each monotherapy arm; the trial was powered to find a treatment effect of 0.75% for HbA1c at endpoint.

Patient Disposition

A total of 458 patients were screened; 454 entered the titration/maintenance phase and 322 of those patients satisfied the entry criteria and were randomized to treatment (109:metformin, 107:RSG 4 mg BID and 106:RSG plus metformin, Table 23). The primary reason (68%) patients were not randomized to treatment was failure to meet the inclusion/exclusion criteria (the specific reason was not given in the NDA). The completion rate in the rosiglitazone alone arm was appreciably less than in the other two arms (62% versus 74% and 85%); likewise, the ITT population for the rosiglitazone arm was comprised of about 10% fewer patients than the other 2 arms.

Table 23. Number (%) of patients on study by treatment group and week

	Metformin	RSG 4 mg BID	RSG+Met
Randomized	109 (100%)	107 (100%)	106 (100%)
Week 4	103 (94%)	88 (82%)	103 (97%)
Week 8	93 (85%)	78 (73%)	100 (94%)
Week 12	92 (84%)	71 (66%)	93 (88%)
Week 18	85 (78%)	67 (63%)	92 (87%)
Week 26	81 (74%)	66 (62%)	90 (85%)
Sponsor's ITT	106 (97%)	95 (89%)	105 (99%)

The primary reason for discontinuation post-randomization in all treatment groups was ADE's (Table 24). LOE was also a major reason for dropout particularly in the rosiglitazone alone arm (12%). Lack of efficacy was defined as in the monotherapy studies with the exception of the FPG level being set higher at 350 mg/dL. Most of the RSG 4 mg dropouts due to ADE and LOE occurred during the first 12 weeks of therapy. Six of the 14 ADE's in the RSG 4 mg group were due to hyperglycemia.

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Table 24. Reasons for withdrawal from double-blind treatment post-randomization

	Metformin	RSG 4 mg BID	RSG+Met
ADE	8 (7%)	14 (13%)	5 (5%)
Lack of Efficacy	5 (5%)	13 (12%)	3 (3%)
Protocol Deviation	6 (6%)	3 (3%)	5 (5%)
Lost-to-Follow-up	2 (2%)	4 (4%)	1 (1%)
Other	7 (6%)	7 (7%)	2 (2%)

Patient Demographics

Patients ranged in age from 38 to 81 years with a mean age of about 59; about 30% were 65 years or older. There were some treatment group imbalances regarding gender and previous treatment as shown below.

	Metformin	RSG 4 mg BID	RSG+Met
Gender			
Males	67%	54%	60%
Females	33%	46%	40%
Previous treatment			
Diet only	4%	6%	4%
Monotherapy	49%	51%	36%
Combination	47%	43%	60%

About 80% of the patients were white. The median duration of diabetes was 6 years.

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HbA1c

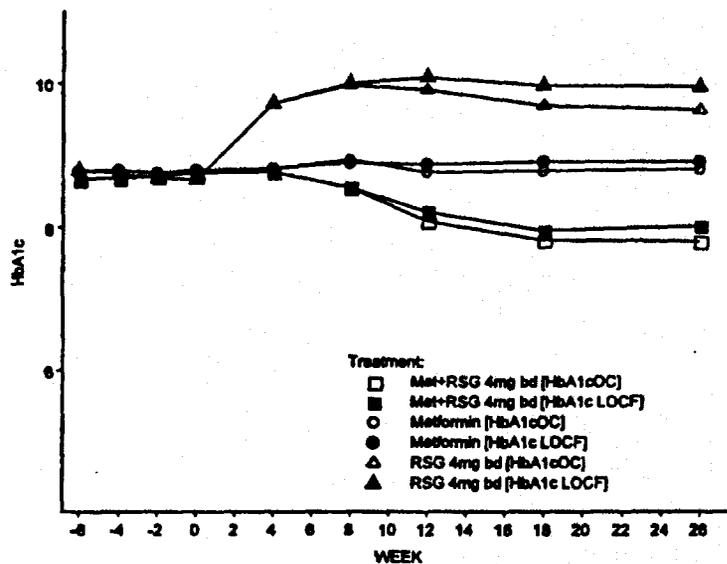
The primary endpoint is the change from baseline in HbA1c at Week 26 with the last-observation-carried-forward for the ITT analysis. Both monotherapy arms showed an increase over baseline in HbA1c (Table 25) while the combination showed a statistically significant decrease compared to each monotherapy arm ($p < .0001$).

Table 25. Mean HbA1c for Study 093

	Metformin (n=106)	RSG 4 mg BID (n=95)	RSG 4 mg BID+Met (n=104)
Baseline	8.77 (1.39)	8.66 (1.30)	8.74 (1.40)
Week 26 LOCF	+0.14 (1.18)	+1.30 (1.80)	-0.67 (1.30)
Week 26 Completers	+0.09 (1.28) (n=83)	+1.11 (1.94) (n=66)	-0.80 (1.30) (n=89)

Figure 25 illustrates the HbA1c levels over the duration of the trial. The difference between the LOCF and OC estimates in the RSG 4mg group is primarily due to the patients who drop because of hyperglycemia. It appears that this population of patients not well-controlled on metformin alone receive benefit when rosiglitazone is added but show a detrimental effect when metformin is removed and rosiglitazone is administered as monotherapy.

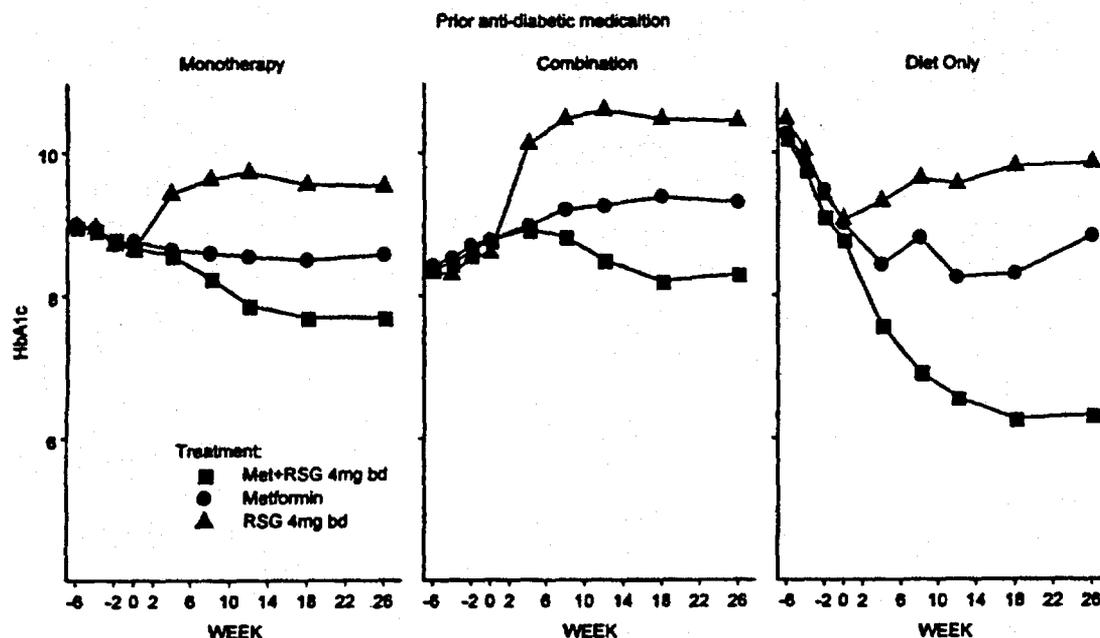
Figure 25. Study 093 HbA1c by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



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The HbA1c results for metformin plus rosiglitazone by subgroups based on prior anti-diabetic medication use (Figure 26) show similar results for patients previously on monotherapy and combination therapy; the results for naïve (diet only) patients is limited to only a total of 14 patients so are difficult to interpret. The detrimental effect (rise in HbA1c) of switching from metformin to rosiglitazone monotherapy is most pronounced for patients previously treated with combination therapy.

Figure 26. Study 093 HbA1c (LOCF) for naïve patients and patients previously treated with anti-diabetic medications



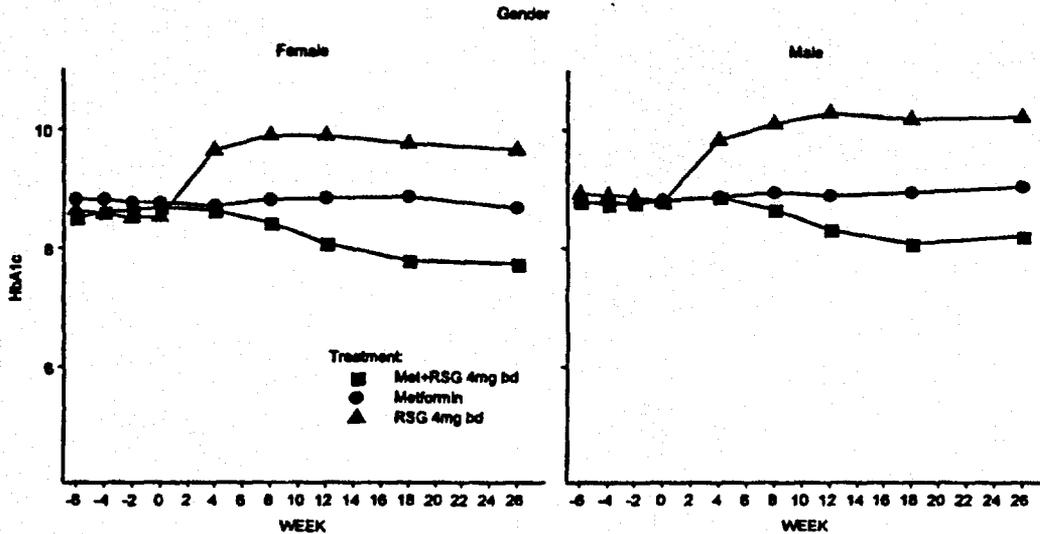
Sample Sizes

	Monotherapy	Combination	Diet Only
Metformin	38	63	4
RSG 4 mg BID	52	50	4
RSG 4 mg + Met	48	41	6

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The results by gender show comparable effects with slightly larger effects seen for females; the treatment by gender interaction is not statistically significant. At Week 26 LOCF the mean change from baseline for females in the combination group is -0.92 while the mean change from baseline for males in the combination group is -0.51 .

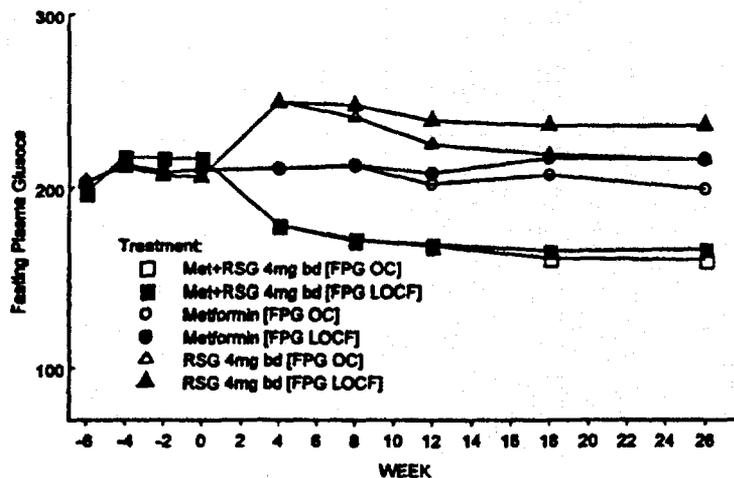
Figure 27. Study 093 HbA1c (LOCF) by gender



Fasting Plasma Glucose

At endpoint, the combination significantly decreased FPG compared to each monotherapy arm ($p < .0001$). The effect of dropouts is evident in the RSG 4mg monotherapy arm with completers showing an endpoint effect similar to the metformin alone arm. Since the RSG 4 mg dropouts are largely due to LOE and hyperglycemia, the LOCF estimates provide the best estimates of effect. The results by subgroups based on previous anti-diabetic medication use and gender give results comparable to what was seen in the analysis of HbA1c.

Figure 28. Study 093 Fasting Plasma Glucose LOCF and OC



Study 094

Study 094 is a 26-week, double-blind, randomized, parallel study of three treatment arms; rosiglitazone 4 mg OD plus metformin 2.5 g/day, rosiglitazone 8 mg OD plus metformin 2.5 g/day and metformin 2.5 g/day. After screening, patients were titrated on metformin to a dose of 2.5 g/day and maintained on this dose for 4 weeks. At the end of this maintenance period, patients satisfying the entry criteria and considered inadequately controlled on metformin ($140 \leq \text{FPG} \leq 300$ at the first and second week of the maintenance period) were randomized to treatment. The protocol also states that patients with $\text{FPG} < 140$ during the maintenance period should be withdrawn.

The primary objective of this trial was to show that each combination therapy arm was superior to the metformin arm; the trial was powered to show a treatment effect of 0.75% for HbA1c at endpoint.

Without the results of Study 093, this trial would be difficult to interpret since the contribution of metformin to the combination cannot be measured in this trial without a rosiglitazone monotherapy arm.

Patient Disposition

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A total of 443 patients were screened at 36 centers in the USA; 437 entered the titration/maintenance phase and 348 of those patients satisfied the entry criteria and were randomized to treatment (116:metformin, 119:RSG 4 mg OD plus metformin and 113:RSG 8 mg OD plus metformin, Table 26). The primary reason patients were not randomized to treatment was failure to meet the inclusion/exclusion criteria (specific reasons were not given in the NDA). The completion rates in all treatment arms were above 80%. Ninety-seven percent of the randomized patients were included in the ITT population of each arm.

Table 26. Number (%) of patients on study by treatment group and week

	Metformin	RSG 4 OD + Met	RSG 8 OD + Met
Randomized	116 (100%)	119 (100%)	113 (100%)
Week 4	109 (94%)	116 (97%)	105 (93%)
Week 8	105 (91%)	114 (96%)	102 (90%)
Week 12	103 (89%)	106 (89%)	99 (88%)
Week 18	101 (87%)	104 (87%)	97 (86%)
Week 26	96 (83%)	101 (85%)	95 (84%)
Sponsor's ITT	113 (97%)	116 (97%)	110 (97%)

The primary reason for discontinuation post-randomization was ADE's in the combination treatment groups and LOE in the metformin alone group (Table 27). Lack of efficacy was defined as in the monotherapy studies with the exception of the FPG level being set higher at 350 mg/dL. Dropouts occurred throughout the treatment period.

Table 27. Reasons for withdrawal from double-blind treatment post-randomization

	Metformin	RSG 4 OD + Met	RSG 8 OD + Met
ADE	5 (4%)	7 (6%)	6 (5%)
Lack of Efficacy	8 (7%)	4 (3%)	4 (4%)
Protocol Deviation	5 (4%)	1 (1%)	3 (3%)
Lost-to-Follow-up	0 (0%)	3 (3%)	4 (4%)
Other	4 (4%)	3 (3%)	1 (1%)

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Patient Demographics

Patients ranged in age from 36 to 82 years with a mean age of about 58; about 27% were 65 years or older. About 80% of the patients were white. The mean duration of diabetes was 7.7 years. As in Study 093, there were some small imbalances regarding gender and previous anti-diabetic medication use.

	Metformin	RSG 4 OD + Met	RSG 8 OD + Met
Gender			
Males	74%	62%	68%
Females	26%	38%	32%
Previous treatment			
Diet only	4%	6%	5%
Monotherapy	49%	40%	44%
Combination	47%	54%	52%

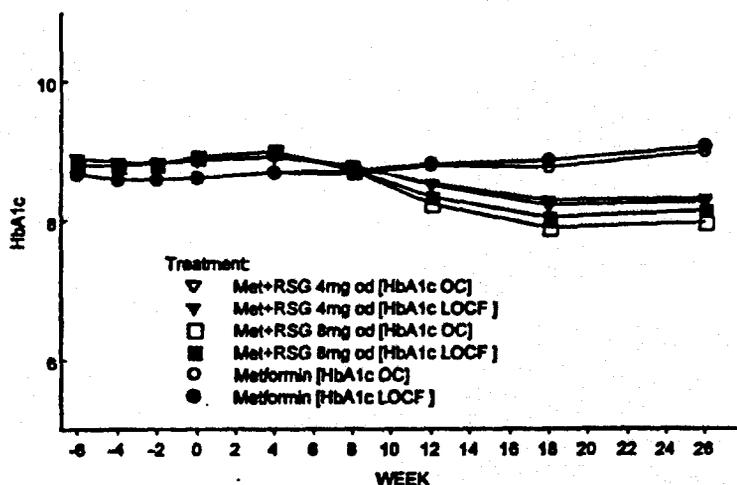
HbA1c

The primary endpoint is the change from baseline in HbA1c at Week 26 with the last-observation-carried-forward for the ITT analysis. Each combination group is significantly different from the metformin arm at Week 26 ($p < .0001$, Table 28 and Figure 29).

Table 28. Mean HbA1c for Study 094

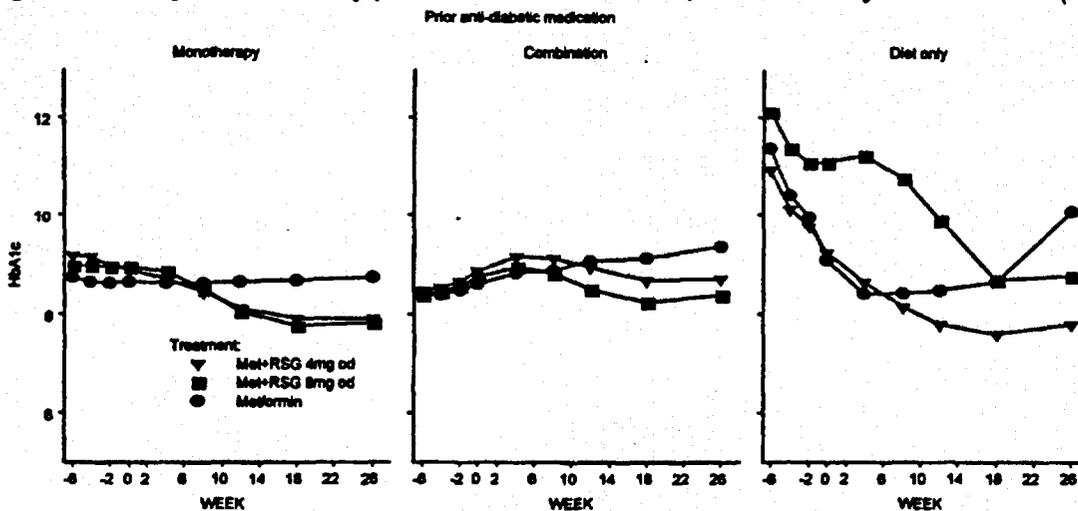
	Metformin (n=113)	RSG 4 mg OD+Met (n=116)	RSG 8 mg OD+Met (n=110)
Baseline	8.64 (1.28)	8.89 (1.30)	8.94 (1.45)
Week 26 LOCF	+0.45 (1.16)	-0.56 (1.29)	-0.78 (1.22)
Week 26 Completers	+0.41 (1.28) (n=94)	-0.61 (1.35) (n=99)	-0.88 (1.18) (n=92)

Figure 29. Study 094 HbA1c by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



The HbA1c results by previous anti-diabetic use show consistent results with the overall results; the sample size for naive patients is too small to draw conclusions.

Figure 30. Study 094 HbA1c by previous anti-diabetic use, week on study and treatment (LOCF)

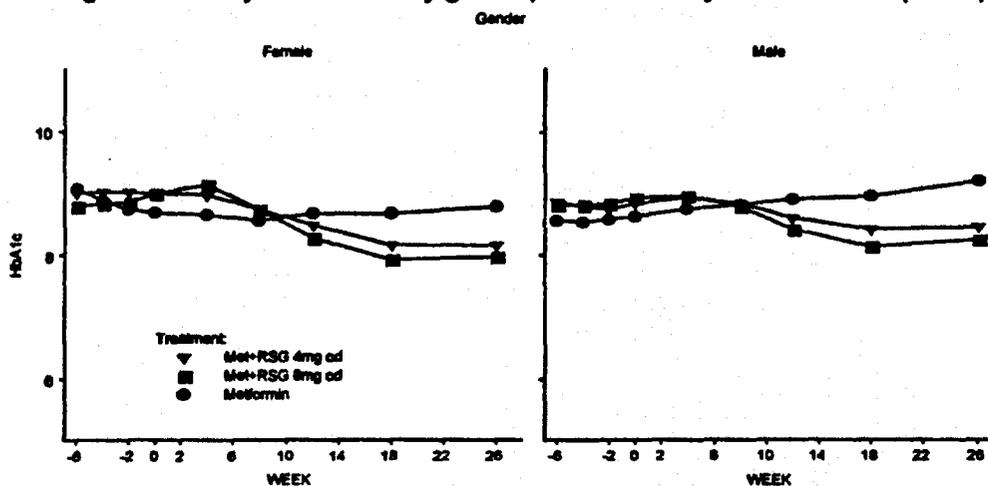


	Sample Sizes		
	Monotherapy	Combination	Diet Only
Metformin	55	53	5
RSG 4 mg + Met	46	63	7
RSG 8 mg + Met	48	57	5

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The HbA1c results by gender revealed comparable treatment effects compared to metformin for females (-1.1, 8mg at wk 26) and males (-1.2, 8mg at wk 26); the gender by treatment interaction was not significant.

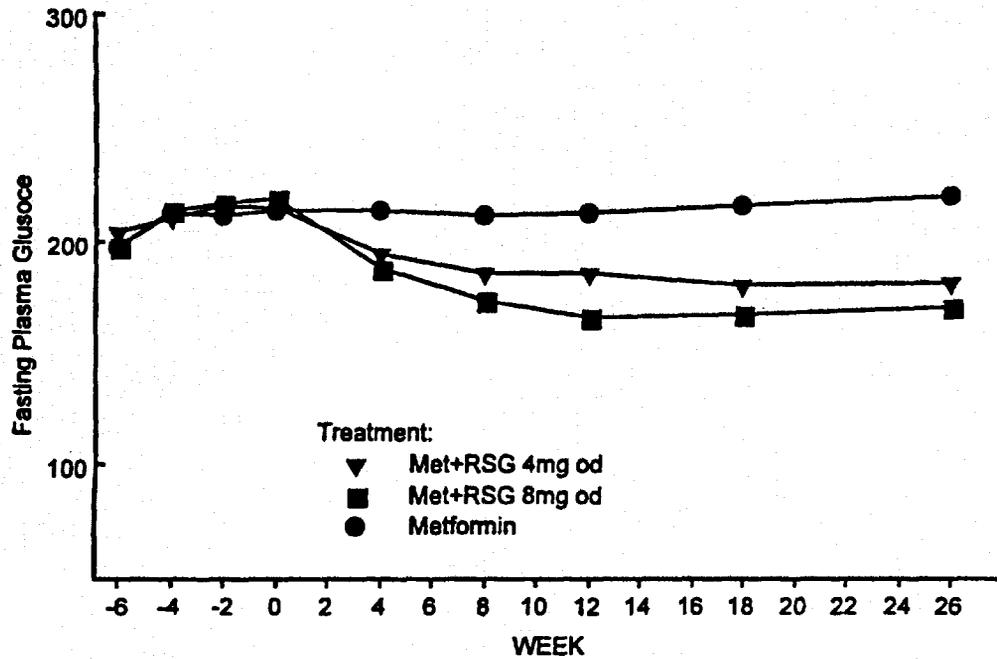
Figure 31. Study 094 HbA1c by gender, week on study and treatment (LOCF)



Fasting Plasma Glucose

The results for FPG showed significant decreases for each combination arm compared to the metformin arm alone (Figure 32).

Figure 32. Study 094 HbA1c by week on study and (LOCF)



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Lipid changes in the combination trials

Figures 33 and 34 clearly show that LDL and TC significantly increase for combination therapy compared to metformin alone. The response appears to level off after about 2 months of therapy (this was also seen from plots of completers).

Figure 33. Change from baseline of LDL by combination study, treatment and week on therapy

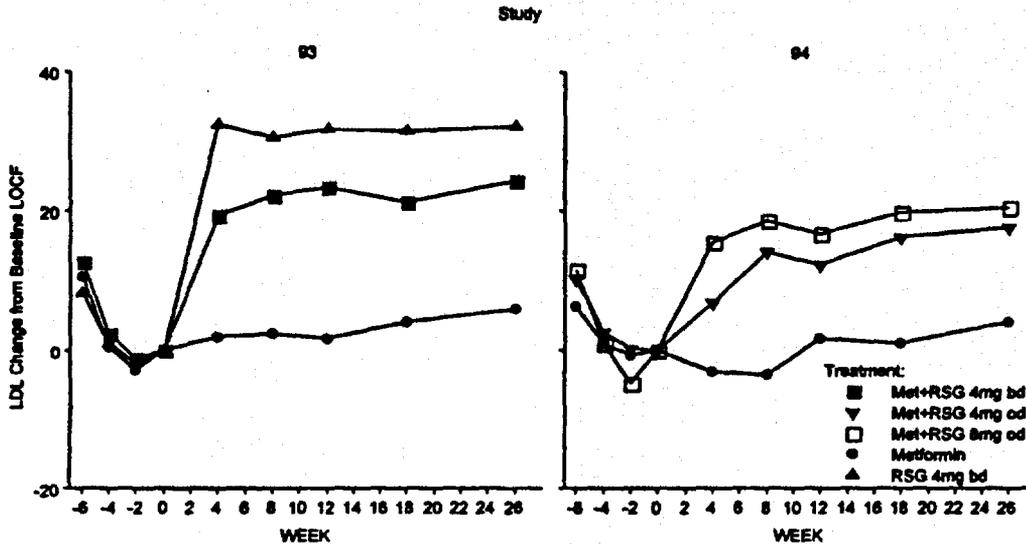
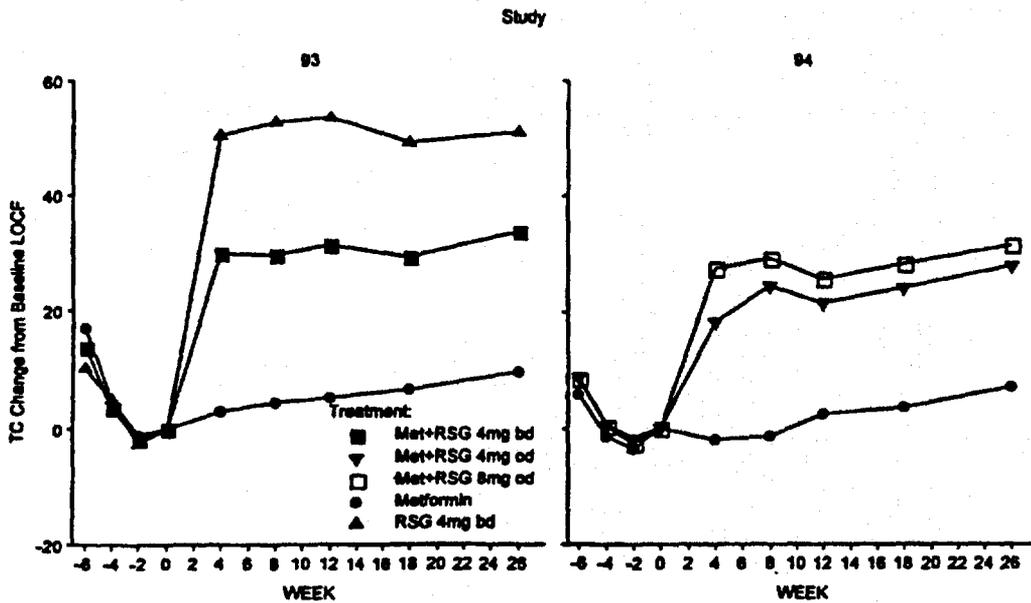
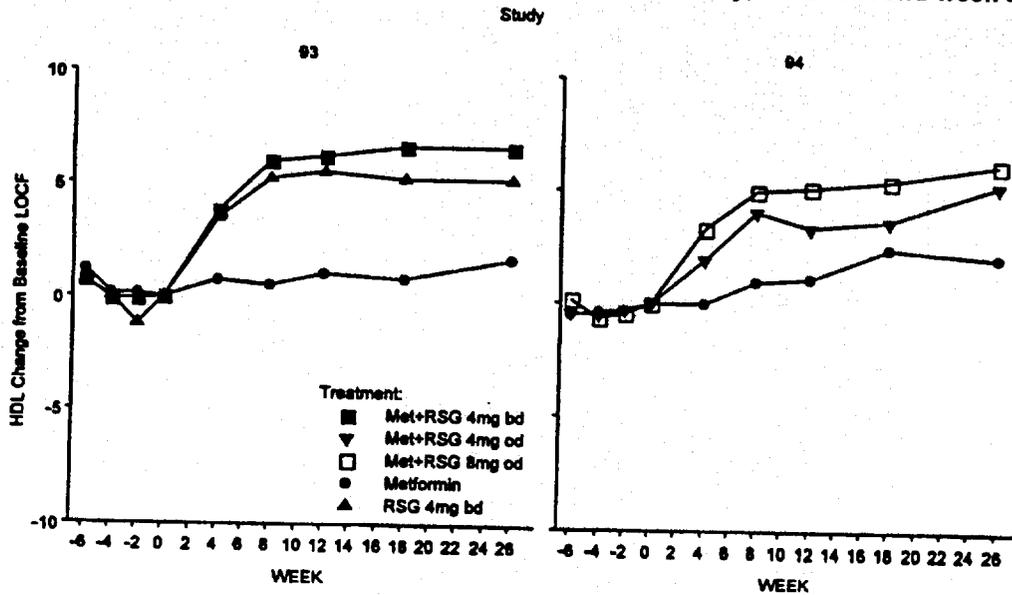


Figure 34. Change from baseline of TC by combination study, treatment and week on therapy



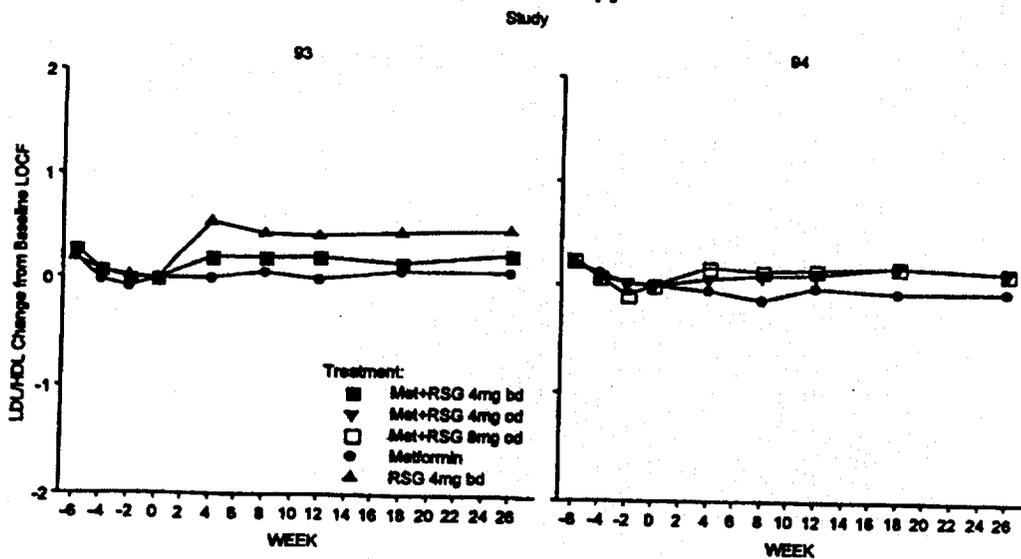
HDL significantly increased in the combination groups compared to metformin with the difference more pronounced in Study 093 (Figure 35).

Figure 35. Change from baseline of HDL by combination study, treatment and week on therapy



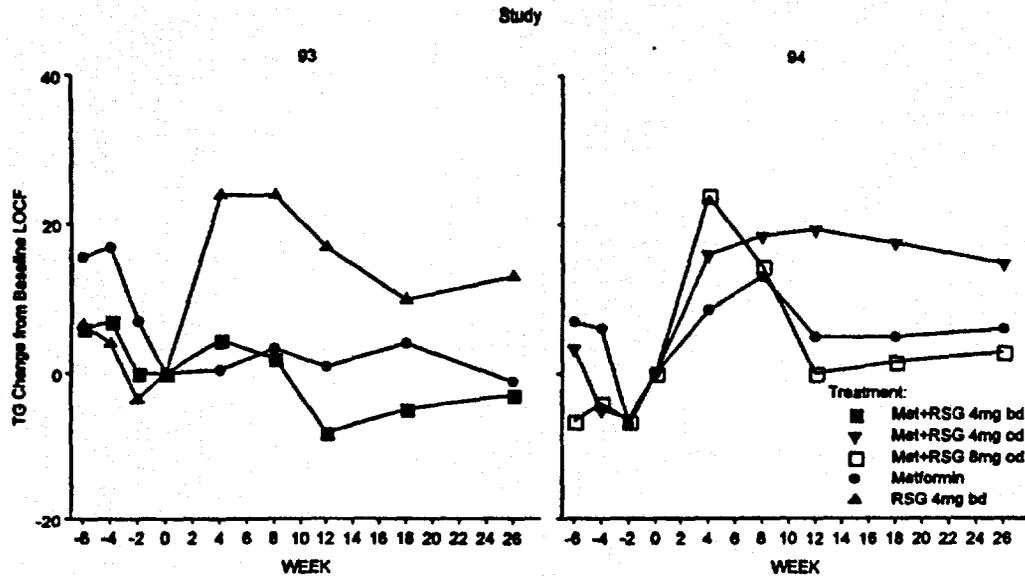
A small difference between the rosiglitazone groups and metformin for the ratio of LDL to HDL was seen.

Figure 36. Change from baseline of LDL/HDL by combination study, treatment and week on therapy



Triglycerides were variable and with the exception of the RSG 4m BID monotherapy do not suggest significant differences from metformin alone.

Figure 37. Median change from baseline of TG by combination study, treatment and week on therapy



The mean lipid changes are summarized in Table 29 below.

Table 29. Summary of mean lipid changes at endpoint LOCF (Week 26) for the combination trials

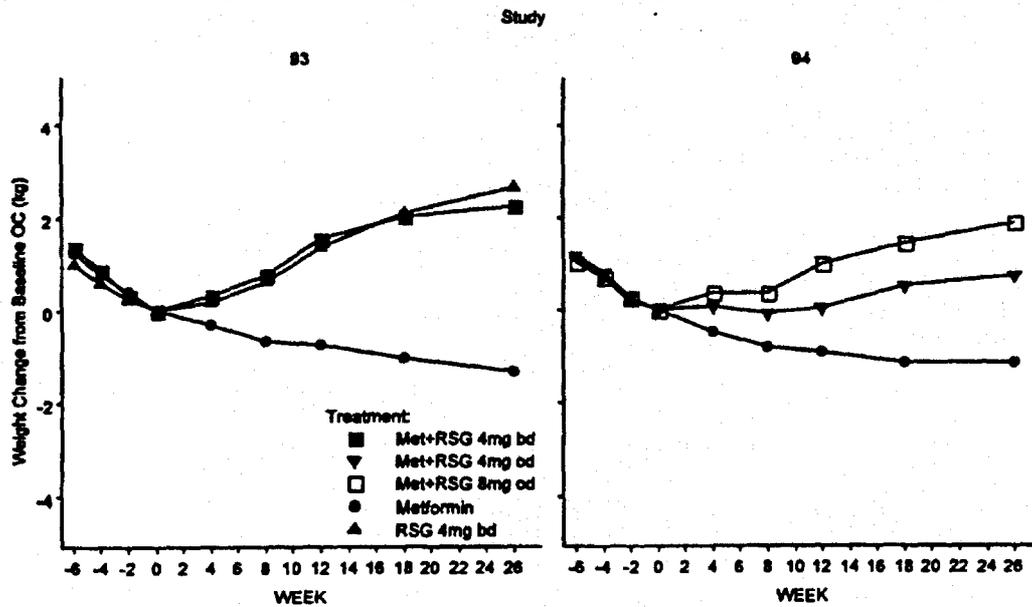
	Study 093			Study 094		
	MET	RSG 4BID	RSG 4BID+MET	MET	RSG 4OD+MET	RSG 8OD+MET
LDL						
Base	111	109	103	116	115	112
Ch	+6	+32	+24	+4	+18	+21
%Ch	+8%	+33%	+26%	+4%	+18%	+21%
TC						
Base	193	201	192	205	203	200
Ch	+10	+51	+34	+7	+28	+32
%Ch	+6%	+25%	+18%	+4%	+15%	+18%
HDL						
Base	46	47	45	44	46	47
Ch	+2	+5	+7	+2	+5	+6
%Ch	+4%	+12%	+16%	+6%	+12%	+15%
LD/HD						
Base	2.5	2.4	2.3	2.7	2.6	2.5
Ch	+0.08	+0.5	+0.3	-0.03	+0.1	+0.1
%Ch	+7%	+23%	+14%	+0.06%	+7%	+9%
TG						
Base	190	249	243	245	225	227
Ch	+11	+38	-11	+7	+7	-3
%Ch	+11%	+21%	+6%	+13%	+11%	+11%

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Weight changes in the combination trials

The weight increase for rosiglitazone in combination with metformin were similar to what was seen in the monotherapy studies with about a 2-3 kg gain.

Figure 38. Weight changes (OC) by treatment and study



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Reviewer's Overall Comments

Summary of HbA1c Results

The primary efficacy measure in the 5 Phase III trials reviewed here was HbA1c change from baseline at endpoint for the ITT population. In this section of the review, means of change from baseline are plotted; to see plots of mean values of HbA1c, see the review of each study. The HbA1c results for 3 monotherapy trials are summarized in Table 30 and for the 2 combination therapy trials in Table 31. **BEST POSSIBLE**

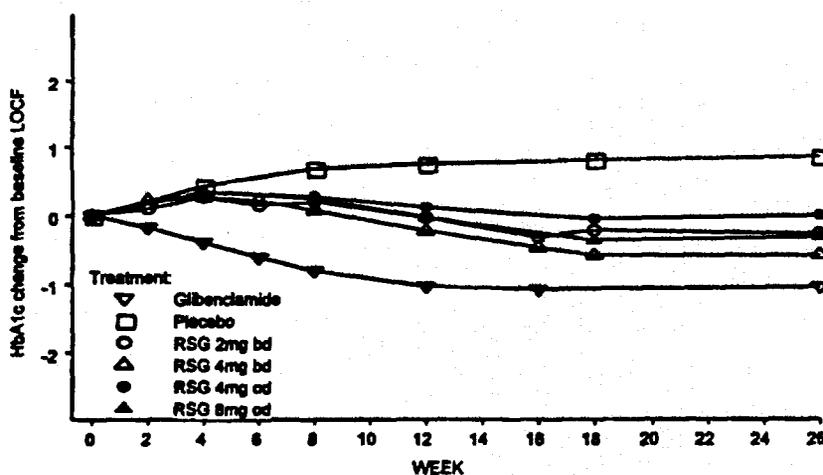
For the monotherapy trials, the mean baseline HbA1c was about 9 in all groups. The completer results for the placebo-controlled trials were consistent with the LOCF results shown here (see body of this report for description of the observed cases data). For the placebo-controlled trials, each rosiglitazone arm was statistically significantly different from placebo ($p < .001$). The active controlled study results for rosiglitazone were not alone convincing for several reasons outlined earlier in this review (see page 26).

Table 30. HbA1c change from baseline results at endpoint (LOCF) for monotherapy trials

	PLA	2BID	4 BID	4 OD	8 OD	Glib
Study 011						
Wk 26	+0.92	-0.28	-0.56	NA	NA	NA
Study 024						
Wk 26	+0.79	-0.13	-0.67	+0.02	-0.31	NA
Study 020						
Wk 26	NA	-0.36	-0.50	NA	NA	-1.06
Wk 52		-0.27	-0.53			-0.72

Results over time (Figure 39) show that patients show an HbA1c response, on the average, after about 3 months on therapy. For this illustration of effect size, the 3 monotherapy trials are combined and data up to Week 26 is shown (for data beyond Week 26 in Study 020, see page 21); this seems reasonable given that the trials were similar regarding design, baseline HbA1c, retention rates and response.

Figure 39. HbA1c change from baseline by week for the monotherapy trials combined



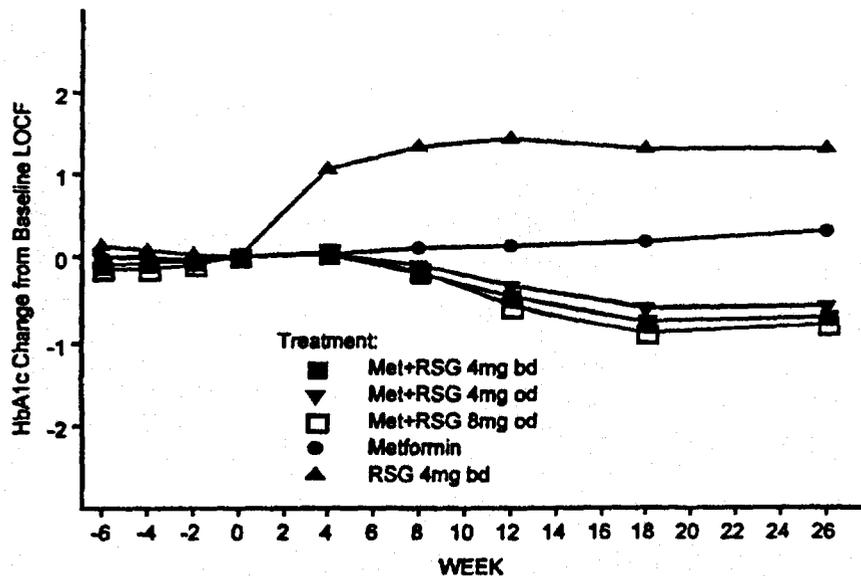
For the combination trials, the mean HbA1c was about 8.7 at baseline in all groups. Each combination of metformin plus rosiglitazone showed a significant decrease in HbA1c compared to monotherapy arms (Figure 40). The changes in the RSG monotherapy arm of Study 093 showed a significant increase in Hba1c which was inconsistent with the results for this treatment group in the monotherapy trials. One possible explanation for the latter is that the patient population is different; patients randomized to treatment in the combination studies were considered inadequately treated on metformin monotherapy and are good candidates for combination therapy not for alternate monotherapy.

Table 31. HbA1c change from baseline endpoint (Week 26 LOCF) results for combination therapy trials

	RSG 4 BID	Met	RSG 4/day+Met	RSG 8/day+Met
Study 093 BID	+1.30	+0.14	NA	-0.67
Study 094 OD	NA	+0.45	-0.56	-0.78

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Figure 40. HbA1c change from baseline by week for the combination trials



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The results for monotherapy and combination therapy by prior anti-diabetic use¹ are shown in Figures 41 and 42. The magnitude of the treatment effect was comparable for naive patients and patients previously treated with monotherapy. The results are less convincing for RSG monotherapy patients previously on combination therapy (a small number of patients in the monotherapy trials, middle graph of Figure 41). In the monotherapy trials, the mean baseline for patients previously on combination therapy was about 9.5, for naive patients and patients previously on monotherapy, mean baselines ranged from about 8 to 8.7. In the combination studies, the mean baseline after metformin treatment was about 9 in all treatment groups regardless of prior anti-diabetic medication use.

Figure 41. HbA1c change from baseline by prior anti-diabetic use for the monotherapy trials

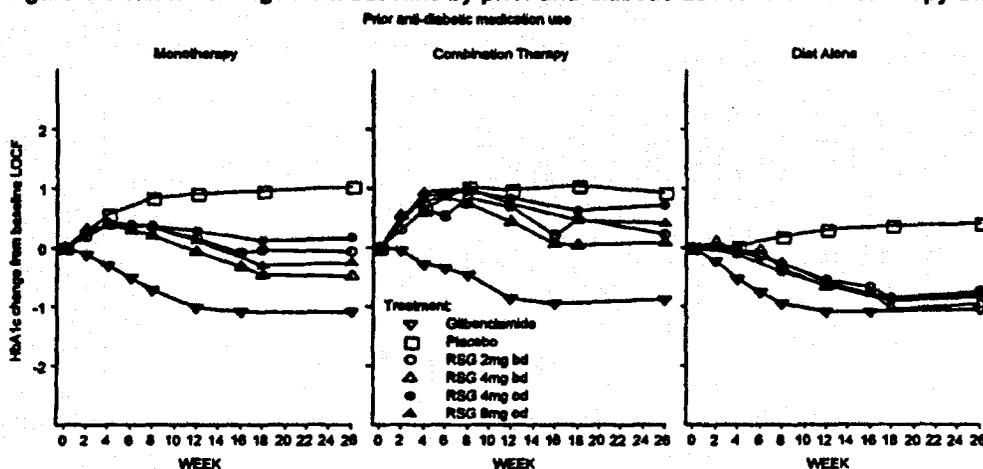
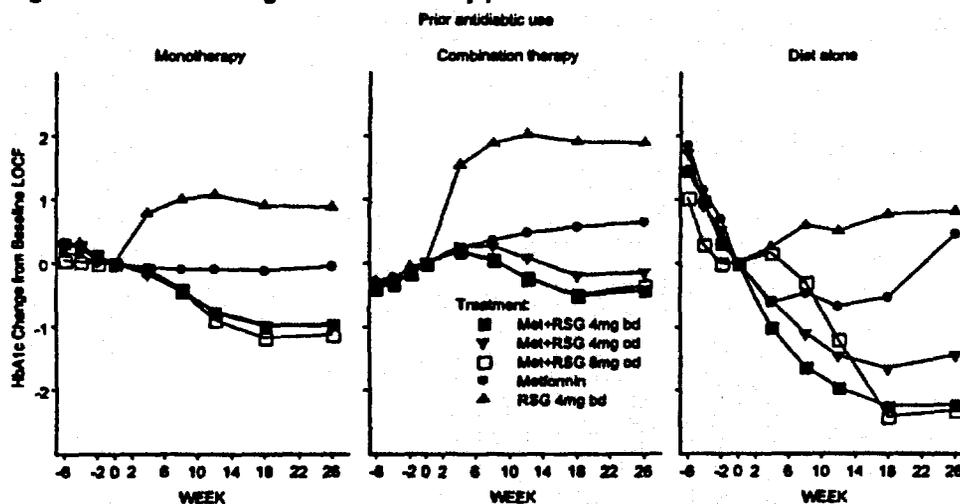


Figure 42. HbA1c change from baseline by prior anti-diabetic use for the combination trials*



*In the combination trials, only about 5% of the patients were naive to anti-diabetic therapy.

1. Patients taking anti-diabetic medication within 30 days prior to randomization were counted as users.

The results by baseline HbA1c (median) generally show a slightly larger treatment effect for patients with baseline HbA1c's above the median.

Figure 43. HbA1c change from baseline by baseline HbA1c for the monotherapy trials

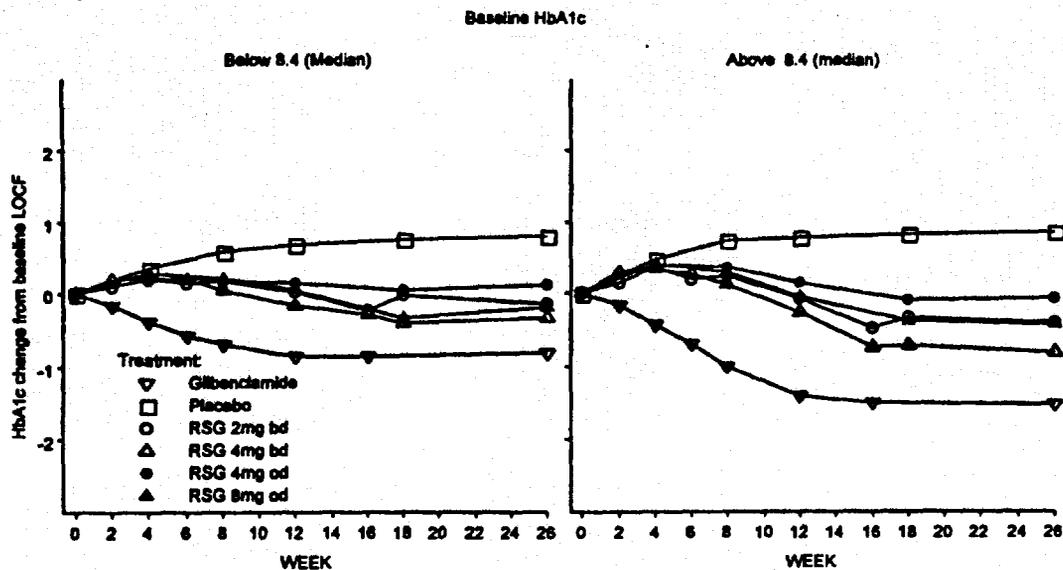
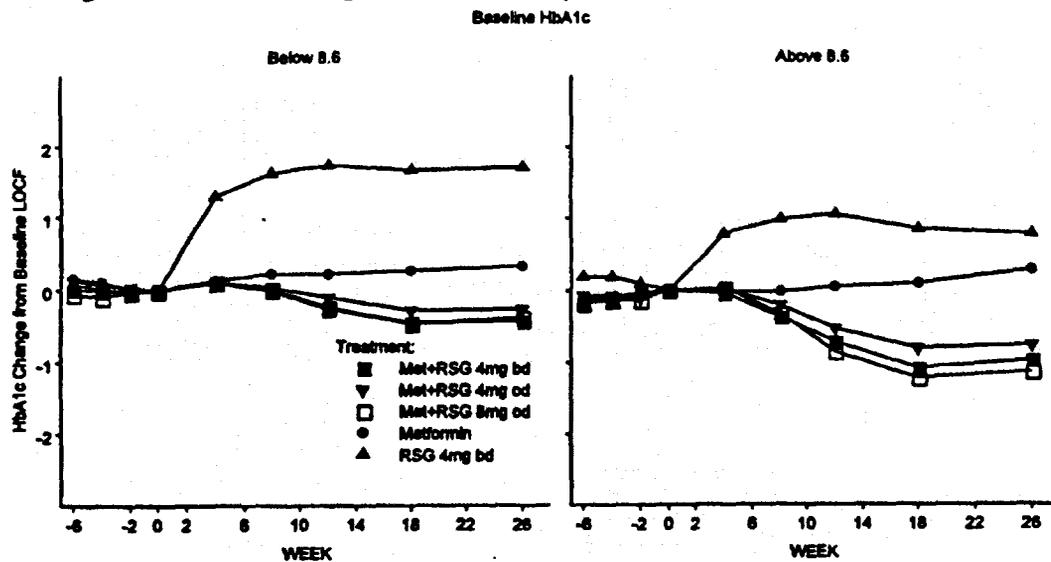


Figure 44. HbA1c change from baseline by baseline HbA1c for the combination trials

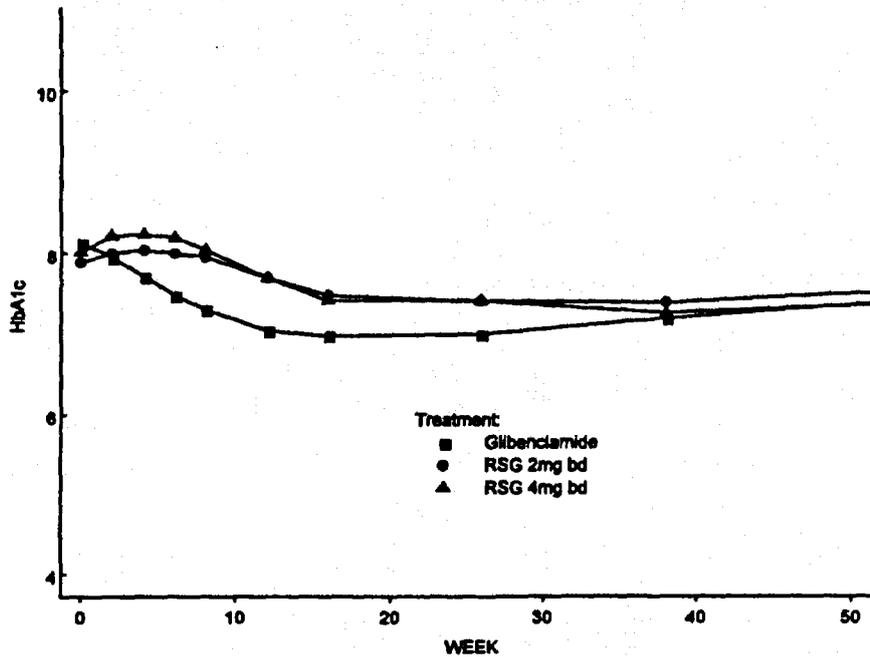


Efficacy results were also examined by age and race. No differential treatment effects were seen.

Durability of response

To examine the durability of the response, the results for completers in the 020 study are shown in Figure 45. Study 020 was the longest controlled study with a treatment period of 52 weeks. It appears for this subgroup of patients (about 80% of the randomized patients) that a peak response is attained after about 3 months of treatment and sustained for the full year.

Figure 45. Study 020 HbA1c by week on study and treatment for patients completing the study (approximately 80% of the patients)



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Relationship between HbA1c changes and changes in LDL, LDL/HDL and weight

Significant increases in LDL, LDL/HDL and weight were noted for rosiglitazone administered as monotherapy and in combination with metformin (see pages 27, 30, 40 and 43 for figures illustrating the changes over time for each individual study). This reviewer looked at the relationship between change in HbA1c and changes in LDL, LDL/HDL and weight (Table 30).

For rosiglitazone administered as monotherapy, larger changes in HbA1c appear to be associated with smaller increases in LDL and LDL/HDL and with larger increases in weight and also the relationship appears to be dose related with larger changes in lipids and weight noted for 8 mg/day doses compared to 4 mg/day doses. Correlation analyses of these measures for each treatment group showed a weak correlation between the lipids and HbA1c with correlation coefficients (R) ranging from .08 to .20. The correlation of weight change to HbA1c change was larger for the once-a-day groups (R=-.40) compared to the twice-a-day groups (R=-.25). In the twice-a-day dosing groups only about 5% of the variation in weight change can be explained by variation in HbA1c suggesting a weak correlation.

Table 30. Changes of LDL, LDL/HDL and weight by change from baseline of HbA1c for the monotherapy trials

LDL % change

	PLA	GLIB	RSG 4OD	RSG 2BID	RSG 8OD	RSG 4BID
HbA1c<-1.5	-23%	-2%	+7%	+8%	+13%	+11%
-1.5< HbA1c<0	+7%	-1%	+11%	+12%	+17%	+17%
HbA1c>0	+4%	+3%	+14%	+14%	+26%	+22%

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LDL/HDL % change

	PLA	GLIB	RSG 4OD	RSG 2BID	RSG 8OD	RSG 4BID
HbA1c<-1.5	-30%	-4%	-8%	-8%	+3%	+3%
-1.5< HbA1c<0	-3%	-2%	+1%	+4%	+4%	+8%
HbA1c>0	+1%	+23%	+7%	+7%	+17%	+15%

Weight change (kg)

	PLA	GLIB	RSG 4OD	RSG 2BID	RSG 8OD	RSG 4BID
HbA1c<-1.5	-2.2	+1.6	+2.6	+2.8	+4.4	+4.0
-1.5< HbA1c<0	-0.6	+1.2	+1.7	+1.4	+2.7	+2.4
HbA1c>0	-1.0	+1.1	+0.1	+0.5	+0.6	+1.3

Number (%) of patients

	PLA	GLIB	RSG 4OD	RSG 2BID	RSG 8OD	RSG 4BID
HbA1c<-1.5	4 (2%)	58 (29%)	19 (11%)	68 (12%)	32 (18%)	121 (22%)
-1.5< HbA1c<0	58 (18%)	125 (62%)	64 (35%)	253 (46%)	72 (40%)	257 (47%)
HbA1c>0	269 (81%)	20 (10%)	98 (54%)	226 (41%)	77 (43%)	167 (31%)

Appendix 3 provides graphs of LDL and TG by responder status. The graphs show that LDL for responders (HbA1c change <- .7%) increases less than for non-responders which is consistent with the results shown above in Table 30.

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In the combination trials (as in the monotherapy trials), the relationship between change in LDL, LDL/HDL and weight with change in HbA1c appears to be dose-related for the RSG+met treatment groups (Table 31). Larger increases in weight appear to be associated with larger decreases in HbA1c for the combination groups. The relationship between lipids and HbA1c is weak with correlation coefficients ranging from -.18 to +.16 for the combination groups.

Table 31. Changes of LDL, LDL/HDL and weight by change from baseline of HbA1c for the combination trials

LDL % change

	RSG 4BID	Met	RSG 4OD+met	RSG 8OD+met	RSG 4BID+met
HbA1c<-1.5	+32%	-6%	+15%	+21%	+32%
-1.5≤ HbA1c<0	+21%	+5%	+17%	+22%	+29%
HbA1c≥0	+35%	+8%	+22%	+19%	+16%

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LDL/HDL % change

	RSG 4BID	Met	RSG 4OD+met	RSG 8OD+met	RSG 4BID+met
HbA1c<-1.5	+13%	-7%	+2%	+15%	+16%
-1.5≤ HbA1c<0	+10%	-.3%	+8%	+6%	+13%
HbA1c≥0	+26%	+5%	+11%	+7%	+15%

Weight change (kg)

	RSG 4BID	Met	RSG 4OD+met	RSG 8OD+met	RSG 4BID+met
HbA1c<-1.5	+3.2	-2.3	+1.8	+4.1	+4.0
-1.5≤ HbA1c<0	+7.3	-1.0	+0.6	+1.3	+1.9
HbA1c≥0	+1.1	-1.1	-0.02	+0.2	+0.4

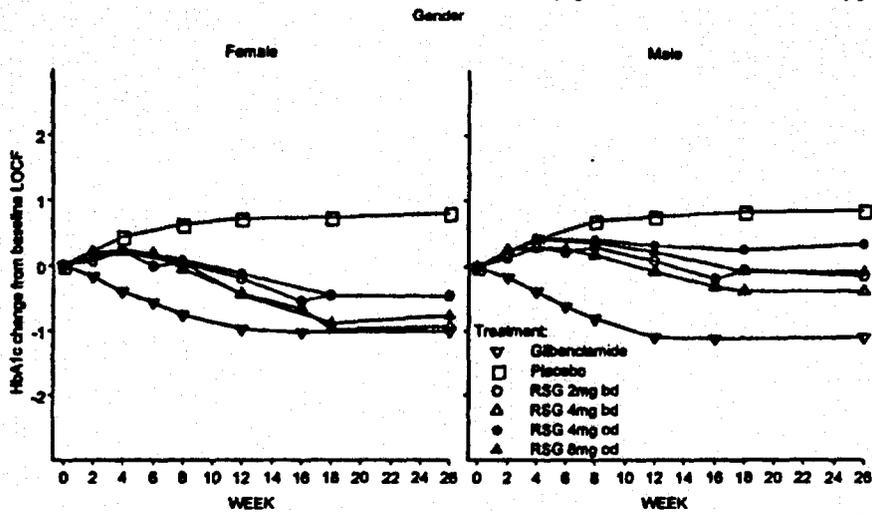
Number (%) of patients

	RSG 4BID	Met	RSG 4OD+met	RSG 8OD+met	RSG 4BID+met
HbA1c<-1.5	7 (7%)	12 (6%)	25 (22%)	28 (25%)	26 (25%)
-1.5≤ HbA1c<0	9 (10%)	75 (34%)	54 (47%)	52 (47%)	49 (47%)
HbA1c≥0	79 (83%)	132 (60%)	37 (32%)	30 (27%)	30 (29%)

Gender effects

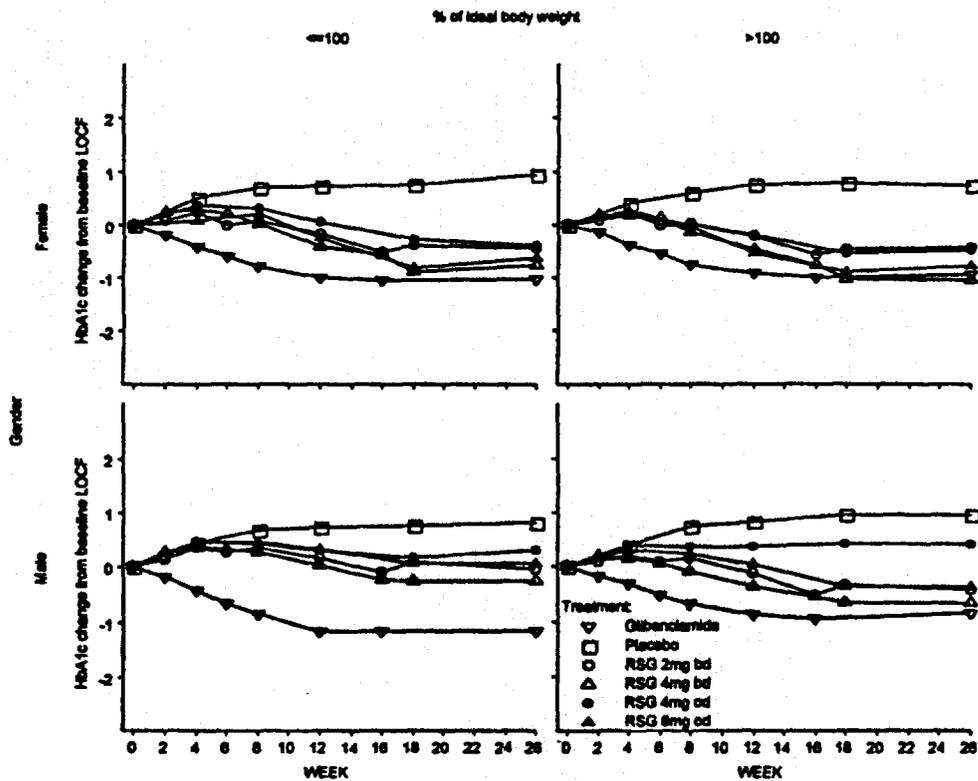
In all 3 monotherapy trials (see pages 11, 16, and 23 for individual study results), a significant treatment by gender effect was observed with a larger treatment effect noted for females (Figure 46 on the following page). A difference in magnitude between males and females was seen in Study 093 but the interaction was not significant; no gender difference was seen in Study 094.

Figure 46. HbA1c change from baseline by gender in the monotherapy trials



This reviewer examined the gender effect by percent of ideal body weight (%IBW) and found that the differential effects are noted among patients with percent of ideal weight of 100% or less. The responses generally are comparable among heavier patients.

Figure 47. HbA1c change from baseline by gender and % IBW in the monotherapy trials



ALT

Boxplots of ALT are presented in Appendix 2 of this review. These plots show the distribution of ALT at each week on study. Outliers are represented by filled in circles beyond the boxes. These figures make it possible to see the number for patients having ALT values above the upper limit of normal (defined as 48 by the sponsor) at each week. Note that ALT rises should not be summed across weeks since a patient may be depicted as a rise at more than one week. The sponsor reported rises in the whole database; the boxplot data is restricted to the controlled studies.

In the monotherapy trials, there was 1 placebo patient and 4 rosiglitazone patients who had rises in ALT 3 times the upper limit of normal. In the combination studies, 13 episodes of ALT 3 times the upper limit of normal in 2 metformin patients (8 and 5 episodes) occurred.

HCT

The hematocrit in both the monotherapy and combination studies significantly decreased in the rosiglitazone groups compared to the comparators. The mean treatment differences were about 2.

Figure 48. HCT (LOCF) by treatment and study for the monotherapy studies

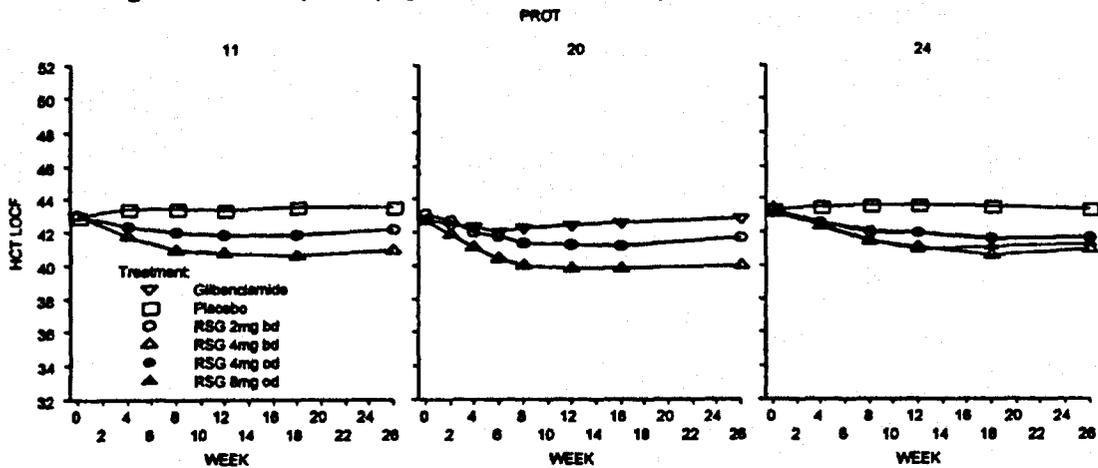
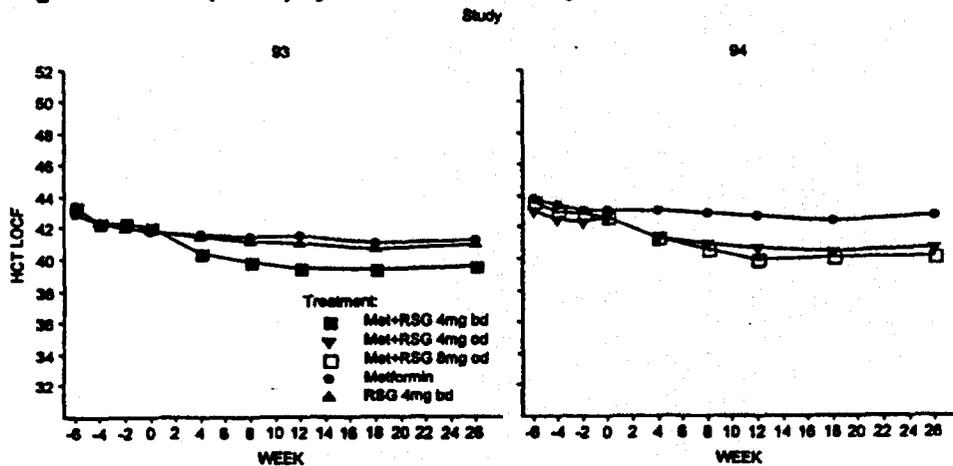
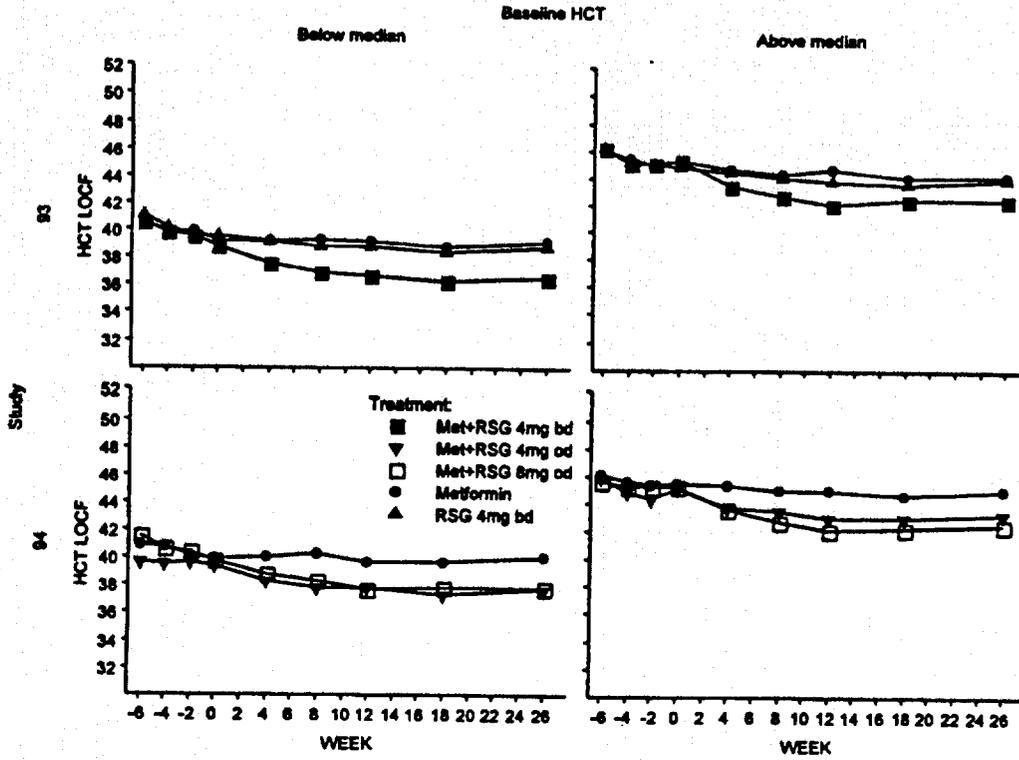


Figure 49. HCT (LOCF) by treatment and study for the combination studies



Results for HCT by baseline HCT (median of 42) show comparable treatment effects.

Figure 50. HCT (LOCF) by treatment and study



HCT results by subgroups based on gender and age showed consistent results with the overall results.

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Conclusions

From a statistical perspective, the sponsor has shown that rosiglitazone is efficacious at lowering HbA1c when administered as monotherapy or when added to metformin at doses of 4 mg daily and 8 mg daily. Twice-a-day dosing was shown to be more efficacious than once-a-day dosing in head-to-head comparisons.

Significant treatment by gender interactions were noted in the three monotherapy trials; larger responses were observed for women than men. Stratification based on ideal body weight showed that overweight men responded similarly to all women.

LDL, TC and HDL were all significantly increased due to rosiglitazone therapy. Increases in LDL were related to baseline and HbA1c response with larger increases seen for lower baselines and for non-responders.

Significant weight increases were observed for rosiglitazone monotherapy and for rosiglitazone in combination with metformin. These increases were dose-related. After 26 weeks on therapy, the mean increase was about 3 kg for RSG 4mg BID; both placebo and metformin showed decreases of about 1 kg.

BEST POSSIBLE

/s/

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Concur:

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cc:

Archival NDA#21-071

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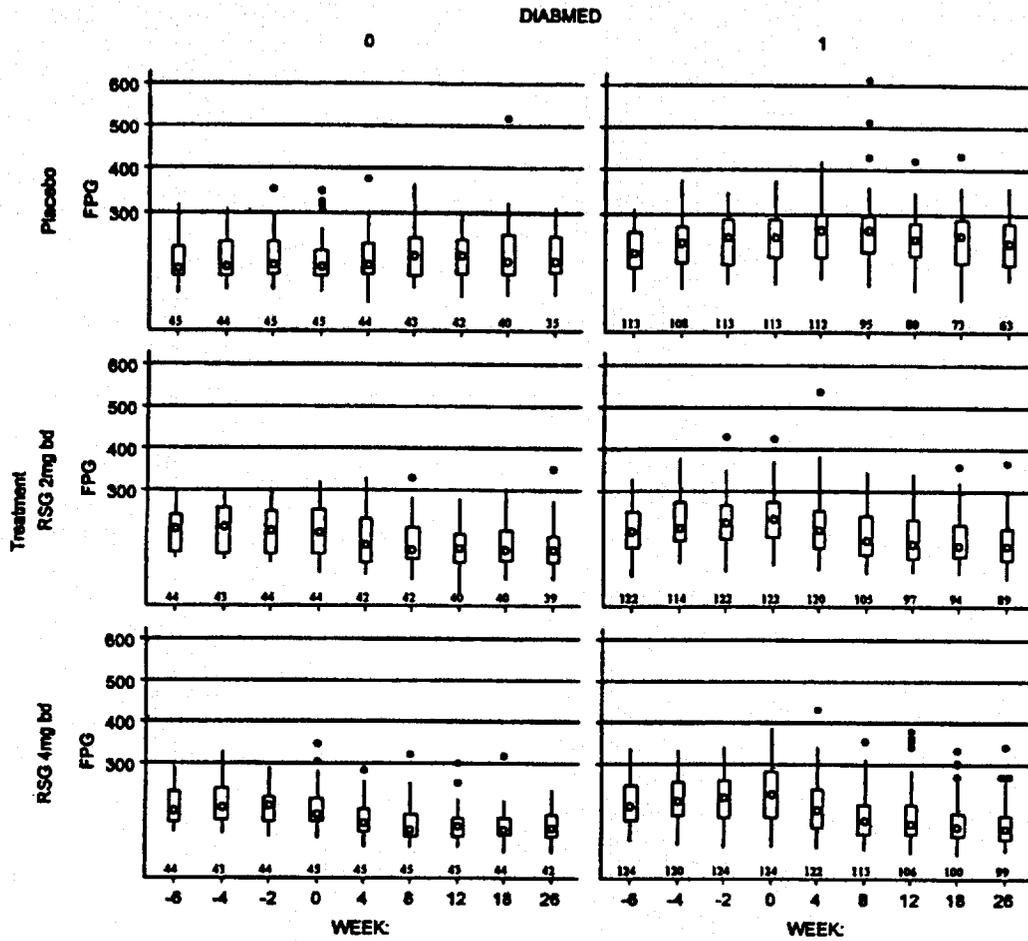
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Appendix 1. Boxplots of fasting plasma glucose

Fasting plasma glucose (OC) in placebo-controlled monotherapy trials for naïve patients (0) and patients previously treated with anti-diabetic medication (1)

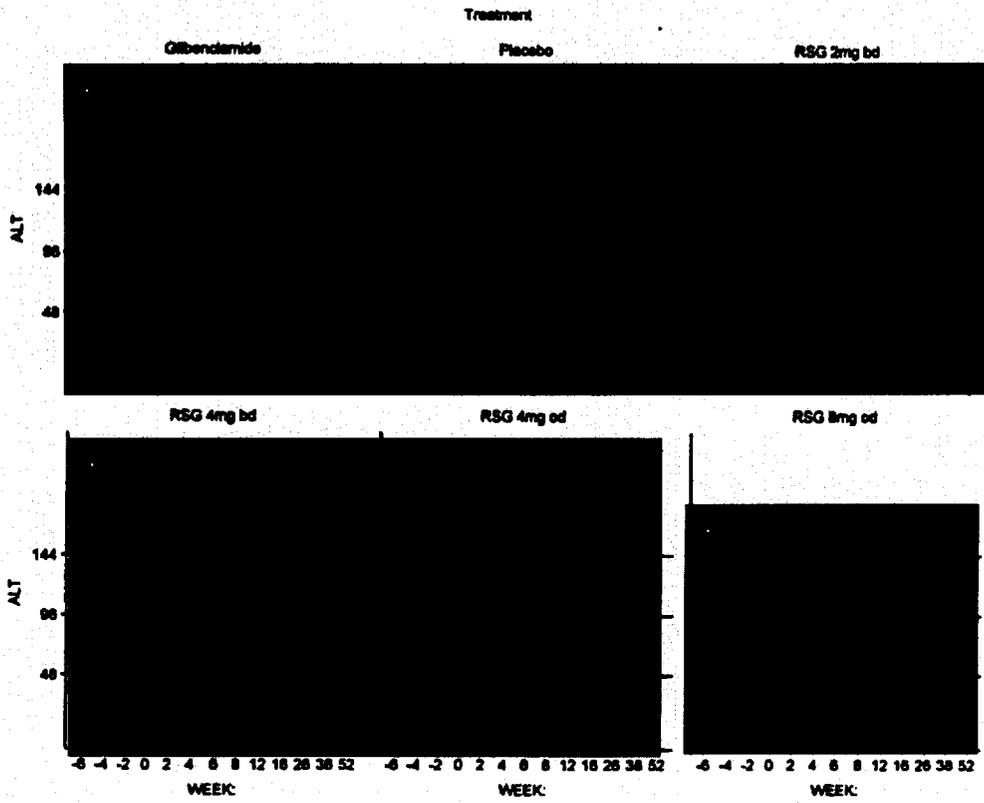
Study 011



BEST POSSIBLE

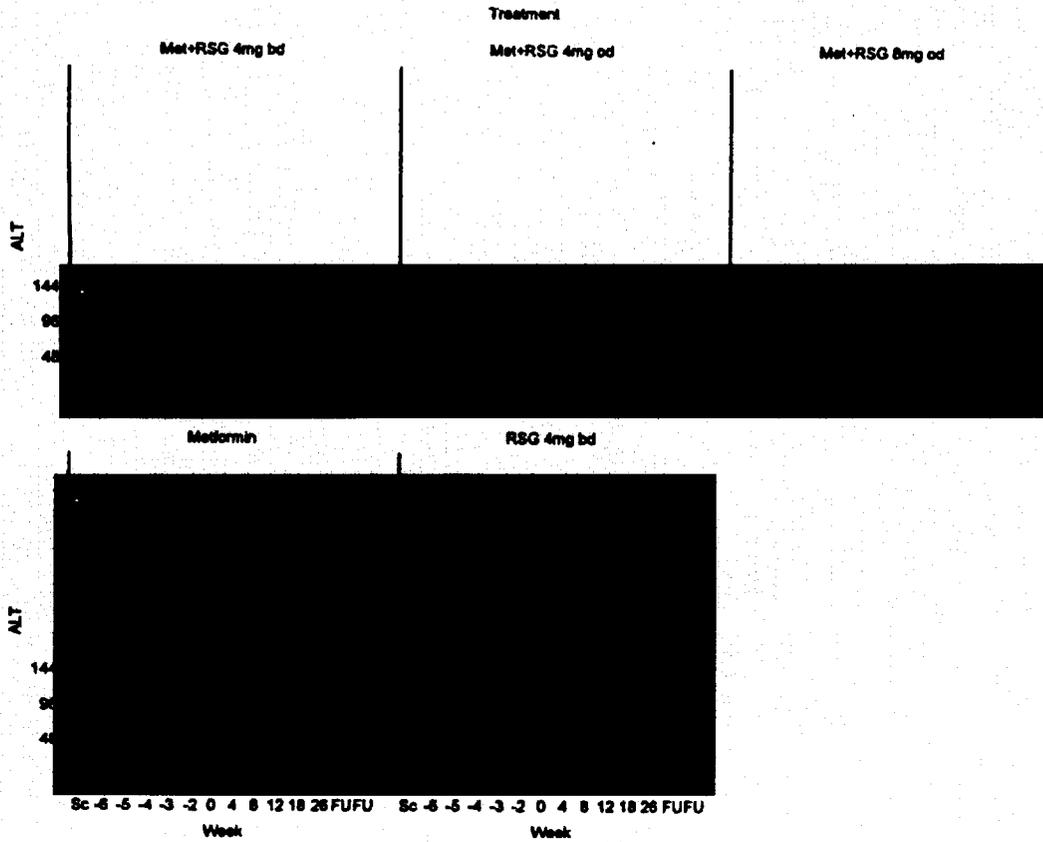
Appendix 2. Boxplots of ALT

ALT Boxplots by treatment for the monotherapy trials combined



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ALT Boxplots by treatment for the combination trials combined

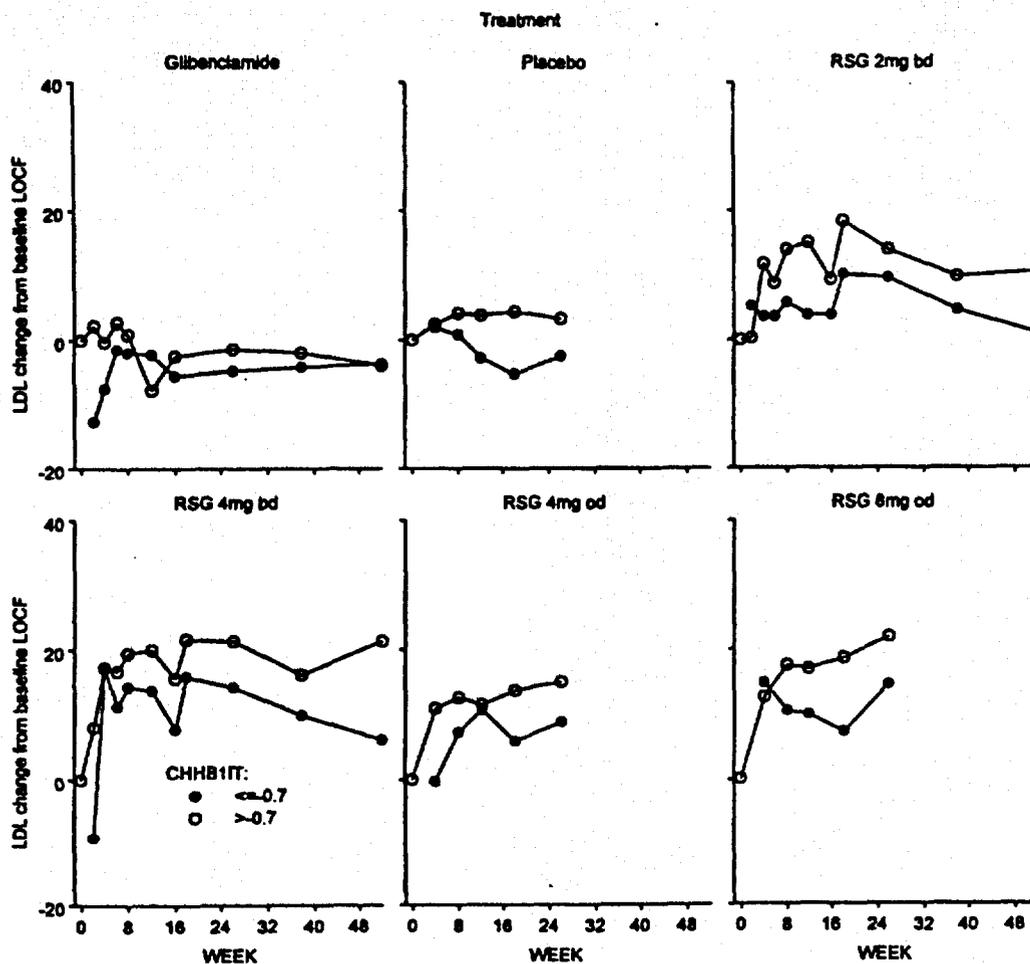


APPEARS THIS WAY ON ORIGINAL

Appendix 3 LDL and TG by HbA1c responder status and monotherapy treatment

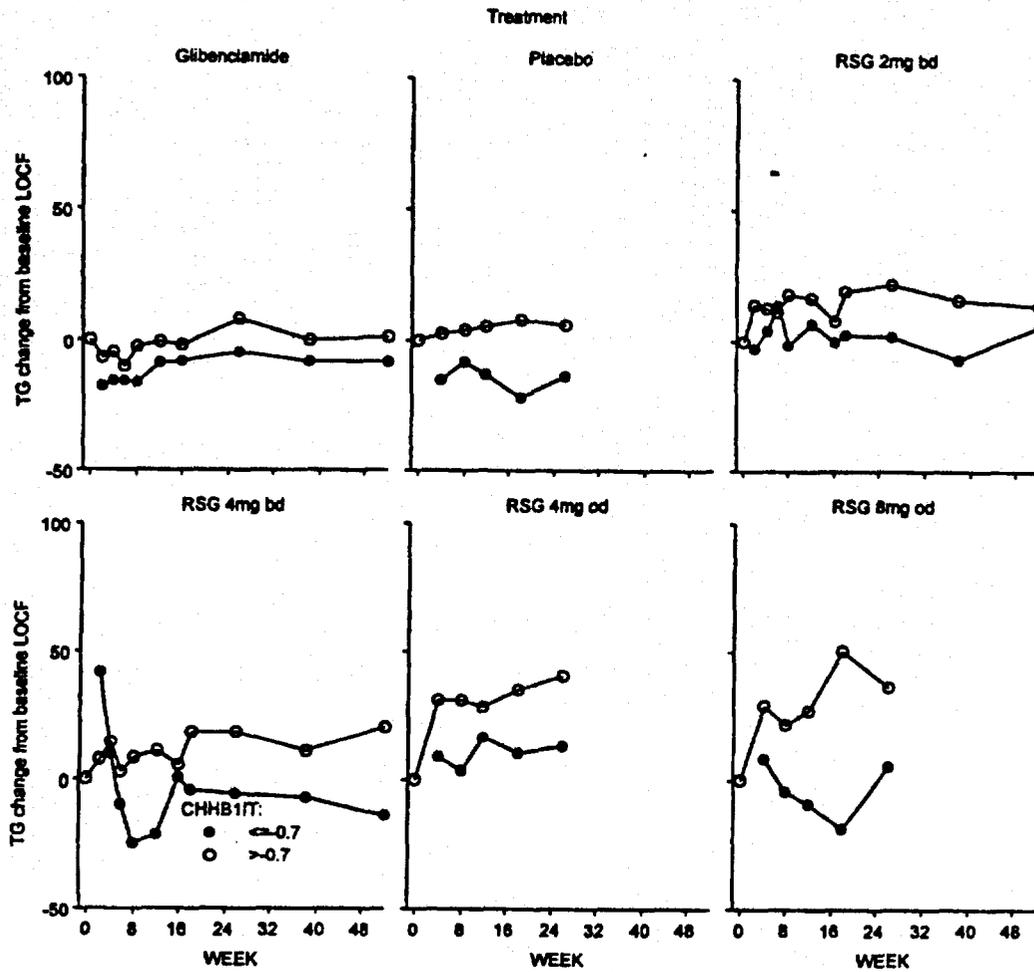
Note that responders are represented by the filled-in circles.

Change LDL (LOCF) by HbA1c responder status and monotherapy treatment



APPEARS THIS WAY ON ORIGINAL

Change in TG (LOCF) by HbA1c responder status and monotherapy treatment



BEST POSSIBLE