CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-071/001

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

MAR 28 2000

NDA #: 21-071 SE1-001

Drug: Avandia (rosiglitazone maleate)

Sponsor: SmithKline Beecham

Indication: Treatment of NIDDM

Date of Submission: July 8, 1999

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Volume Numbers in Statistical Section: Volumes 1-30, 42-45

Medical Input: Robert Misbin (HFD-510)

The sponsor has submitted the results of 3 randomized, double-blind, multicenter controlled clinical trials (Table 1) designed to assess the efficacy and safety of the combined administration of rosiglitazone (RSG) with sulfonylureas (SU).

Table 1. Controlled Clinical Trials

Study (Sites)	Design	Treatment (# randomized)	Duration of Treatment
096 (33 USA)	Add-on to glyburide	Glyburide ≥10mg/day (115) RSG 2 mg daily + GLY (116) RSG 4 mg daily + GLY (116)	~26 weeks
015 (54 European)	Add-on to sulfonylureas	Sulfonylureas (198) RSG 1 mg twice daily + SU (205) RSG 2 mg twice daily + SU (190)	26 weeks
079 (41 USA)	Combination versus components	Glyburide 10 mg twice daily (115) RSG 2 mg twice daily (116) RSG 2 mg twice daily + GLY (116)	26 weeks

Reviewer's Statistical Methods

In all 3 studies, the sponsor's proposed analysis for the primary efficacy variable (HbA1c) is an analysis of covariance of the change from baseline at Week 26 with baseline as a covariate. This reviewer performed analyses using the sponsor's model and also alternate models including center and various covariates to establish the robustness of the results. For all studies, this reviewer's results were in agreement with the sponsor's results. Regarding secondary variables, this reviewer only analyzed the data for fasting plasma glucose, LDL and HDL based on discussions with the medical reviewer. An effort was made to present results in a format similar to the format used in this statistician's review of the original NDA submission for rosiglitazone.

Keywords: Clinical Studies, dropouts, endpoint analysis/LOCF

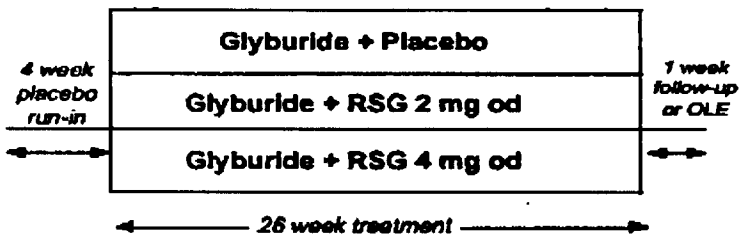
Study 096 (conducted 4/97 to 3/98)

Study 096 was a randomized, double-blind multicenter study to assess the efficacy and safety of rosiglitazone (RSG) as add-on therapy for patients inadequately controlled (140≤FPG≤300) on glyburide (≥10mg/day for a minimum of 2 weeks prior to screening). This study was conducted at 33 centers in the United States.

After screening for inclusion/exclusion criteria, patients were given placebo with glyburide single-blind for 4 weeks (run-in). Patients with 140≤FPG≤300 at screening and after 2 weeks of the run-in and with variation in weight of <10% were randomized to placebo, RSG 2mg daily or RSG 4mg daily (Figure 1) plus glyburide. The glyburide dose was to be kept constant throughout the study. Patients were treated for 26 weeks with visits at Weeks 0, 4, 8,12, 18 and 26.

The primary objective of this trial was to show that each combination therapy arm is superior to the glyburide monotherapy arm; the trial was powered with 65 patients per treatment group to find a treatment effect of 0.75% or greater for HbA1c at endpoint (Week 26 LOCF).

Figure 1. Sponsor's schematic of 096 trial design



Patient Disposition

A total of 549 patients were screened for this study, 456 entered the placebo run-in period. Of 456 patients, 347 (76%) were randomized to treatment (Table 2, 115 to GLY, 116 to RSG 2mg + GLY and 116 to RSG 4mg+ GLY). More than 80% of the patients completed the study with the highest completion rate in the RSG 4mg + GLY group. Very few patients (<2%) withdrew during the last 2 months of the study. All patients but one are included in the intent-to-treat (ITT) population.

Table 2. Study 096 Number (%) of patients on study by treatment group and week.

	GLY	RSG 2 mg daily + GLY	RSG 4 mg daily + GLY
Randomized	115 (100%)	116 (100%)	116 (100%)
Week 4	111 (97%)	114 (98%)	114 (98%)
Week 8	106 (92%)	106 (91%)	111 (96%)
Week 12	102 (89%)	103 (89%)	106 (91%)
Week 18	97 (84%)	96 (83%)	103 (89%)
Week 26	94 (82%)	95 (82%)	102 (88%)
Sponsor's ITT	**115 (100%)**	**115 (99%)**	**116 (100%)**

In the combination therapy groups, dropouts are quite evenly distributed across the reasons for withdrawal (Table 3). In the glyburide group, the primary reason for dropout is lack of efficacy (8%) as would be expected given that patients in this trial were considered inadequately treated with glyburide at the onset of the trial. No pattern between reason for withdrawal and time of withdrawal was seen.

Table 3. Study 096 Reasons for withdrawal from double-blind treatment post-randomization

	GLY	RSG 2 mg daily + GLY	RSG 4 mg daily + GLY
ADE	2 (2%)	5 (4%)	3 (3%)
Lack of Efficacy	9 (8%)	5 (4%)	3 (3%)
Protocol Deviation	7 (6%)	2 (2%)	3 (3%)
Lost-to-Follow-up	0 (0%)	4 (3%)	1 (1%)
Other	3 (3%)	5 (4%)	4 (3%)

Patient Demographics and Baseline Characteristics

The treatment groups were generally well-balanced regarding baseline characteristics (Table 4). The mean age of patients was 60 years (range of 36 to 81); about ⅔ were under 65 years. About ⅔ were male. About 90% were Caucasian.

Table 4. Study 096 Baseline Characteristics

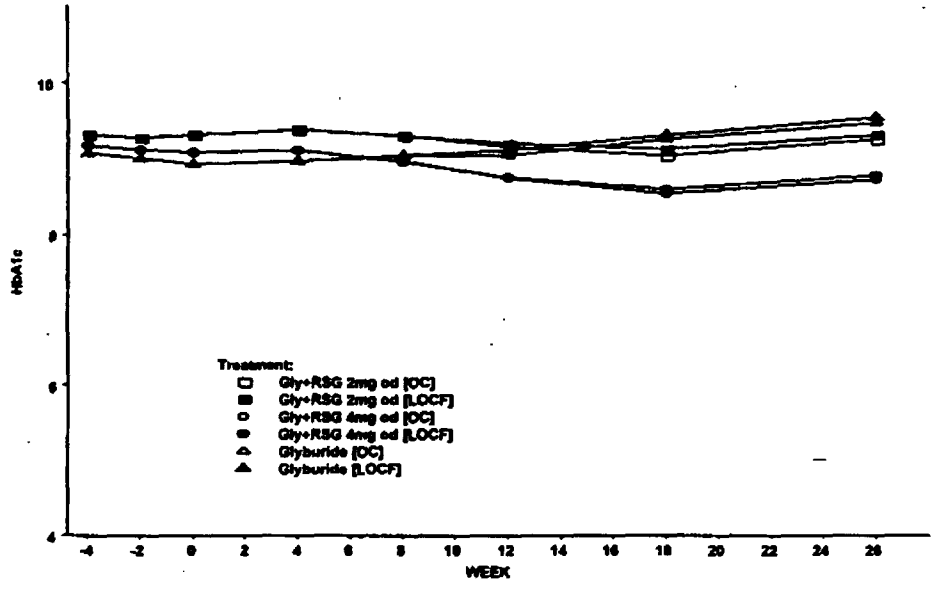
	GLY (n=115)	RSG 2 mg daily + GLY (n=115)	RSG 4 mg daily + GLY (n=116)
Previous Treatment			
Single agent	85 (74%)	75 (65%)	78 (67%)
Combination	30 (26%)	40 (35%)	38 (33%)
# of Years of Diabetes			
Mean (SD)	9.4 (9.1)	8.3 (6.8)	7.9 (6.5)
Median	6.0	6.0	6.5
Range	0 to 52	0 to 38	0 to 40
Prior Antidiabetic meds			
Acarbose	4%	2%	5%
Insulin	1%	0%	2%
Metformin	23%	34%	26%
Sulfonylureas			
Chlorpropamide	2%	1%	1%
Glibenclamide	99%	100%	100%
Glimepiride	2%	2%	1%
Glipizide	16%	16%	16%

Efficacy Results

HbA1c

HbA1c, the primary efficacy variable in Study 096, was measured during the run-in period (Weeks –4 and –2) , at baseline (Week 0) and during double-blind treatment (Weeks 4, 8, 12, 18 and 26). Figure 2 illustrates mean HbA1c overtime for observed cases (OC) and for the last-observation-carried-forward (LOCF) data. A small decrease is seen in all groups during the run-in. A gradual increase in HbA1c is seen in the glyburide group up to Week 26. Essentially no mean change is seen in the GLY+RSG2mg daily group while a decrease is evident in the GLY+RSG4mg daily group.

Figure 2. Study 096 Mean HbA1c by week on study and treatment for last-observation-carried-forward (closed symbols, LOCF) and observed cases (open symbols, OC) data



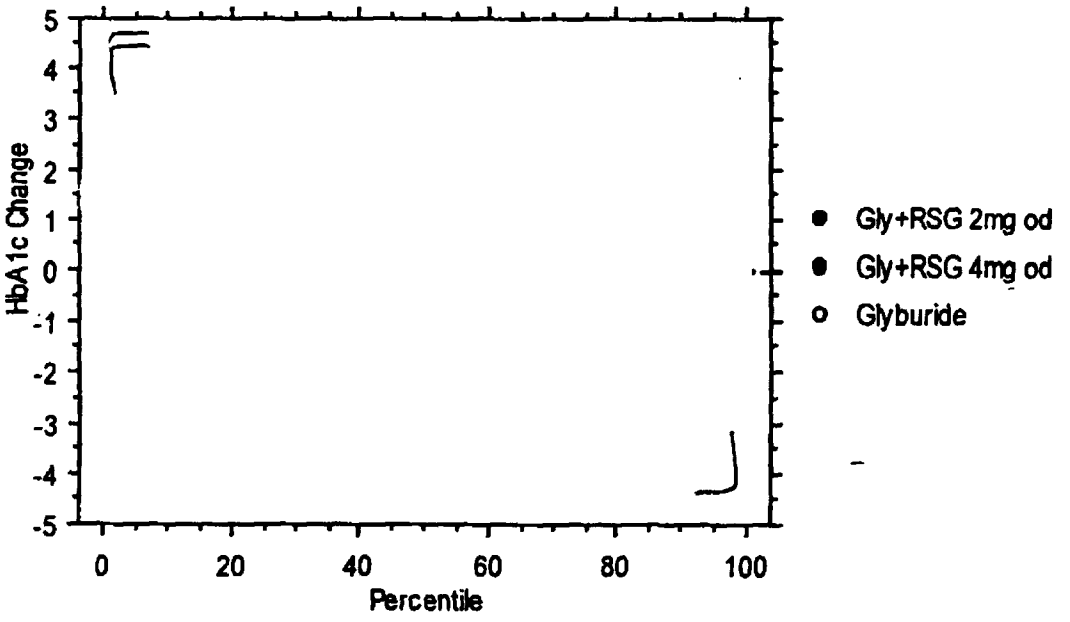
Change from baseline of HbA1c at Week 26 LOCF was pre-specified as the primary endpoint for establishing efficacy. The endpoint results (Table 5) for both combination groups were statistically significantly different from the glyburide group (p<.0001, analysis of covariance (ANCOVA) with baseline as a covariate, alpha level of .027 based on Dunnett's procedure). LOCF and completer results are similar.

Table 5. Study 096 Mean HbA1c (%)

	GLY (n=115) Mean (SD)	RSG 2 mg daily + GLY (n=115) Mean (SD)	RSG 4 mg daily + GLY (n=116) Mean (SD)
Baseline	8.9 (1.4)	9.3 (1.5)	9.1 (1.5)
Change from Baseline Week 26 LOCF	+0.61 (0.98)	+0.003 (1.31)	-0.31 (1.37)
Week 26 Completers	+0.69 (1.04) (n=95)	-0.10 (1.34) (n=95)	-0.38 (1.38) (n=100)

Figure 3 is a cumulative distribution plot which illustrates the data for all patients in the trial; the graph clearly shows that the distributions of the HbA1c change from baseline of the combination groups are similar to each other and different from the glyburide arm. A protocol-defined secondary analysis of responders (patients achieving a 0.7% or greater reduction in HbA1c at endpoint) was performed by the sponsor; 6% of glyburide patients were responders while about 28% of patients in the combination groups were responders.

Figure 3. Study 096 Cumulative Distribution Plot of Change from Baseline of HbA1c Week 26 LOCF (endpoint)



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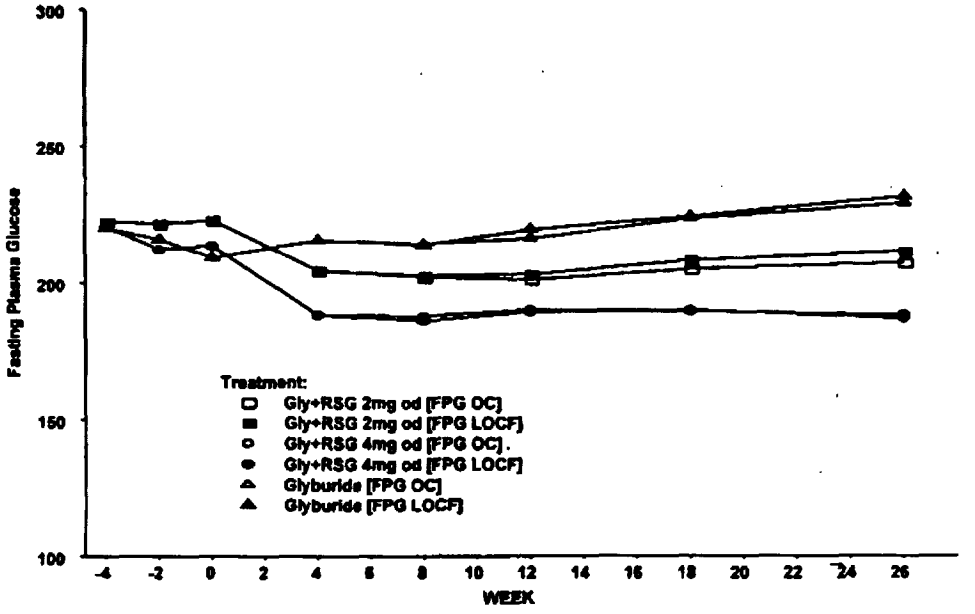
Fasting Plasma Glucose

Means for fasting plasma glucose (FPG), a secondary efficacy variable in Study 096, are shown in Figure 4 below. Decreases in FPG occur during the first 4 weeks of the study in both combination therapy groups; levels remain constant for the remainder of the trial while glyburide levels steadily increase.

Figure 4. Study 096 FPG by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



At Week 26 (LOCF and completers), a statistically significant difference from glyburide is evident for both combination therapy groups ($p<.0001$)

Table 6. Study 096 Fasting Plasma Glucose (mg/dL) Mean (SD)

	GLY (n=115)	RSG 2 mg daily + GLY (n=115)	RSG 4 mg daily + GLY (n=116)
Baseline	209. 1(56.8)	222.8 (53.8)	213.6 (50.4)
Change from Baseline			
Week 26 LOCF	+23.0 (48.1)	-10.5 (51.4)	-25.2 (62.2)
Week 26 Completers	+26.5 (49.6) (n=92)	-14.7 (46.4) (n=95)	-26.3 (62.8) (n=98)

Subgroup Analyses

According to the protocol, descriptive analyses of several subgroups were planned. The following subgroups were defined in the protocol: prior therapy (monotherapy versus combination therapy, age (<65 versus ≥65), BMI (<27 versus ≥27), gender, HbA1c (<9% versus ≥9%) and FPG (<200 versus ≥200). In addition, this reviewer looked at duration of diabetes. The sponsor provided descriptive statistics by subgroup for both HbA1c and FPG; this reviewer only examined subgroups for the primary efficacy variable. To examine subgroups, this reviewer looked at the longitudinal data graphically and assessed interaction (subgroup by treatment) in an analysis model (ANOVA of Week 26 LOCF change from baseline).

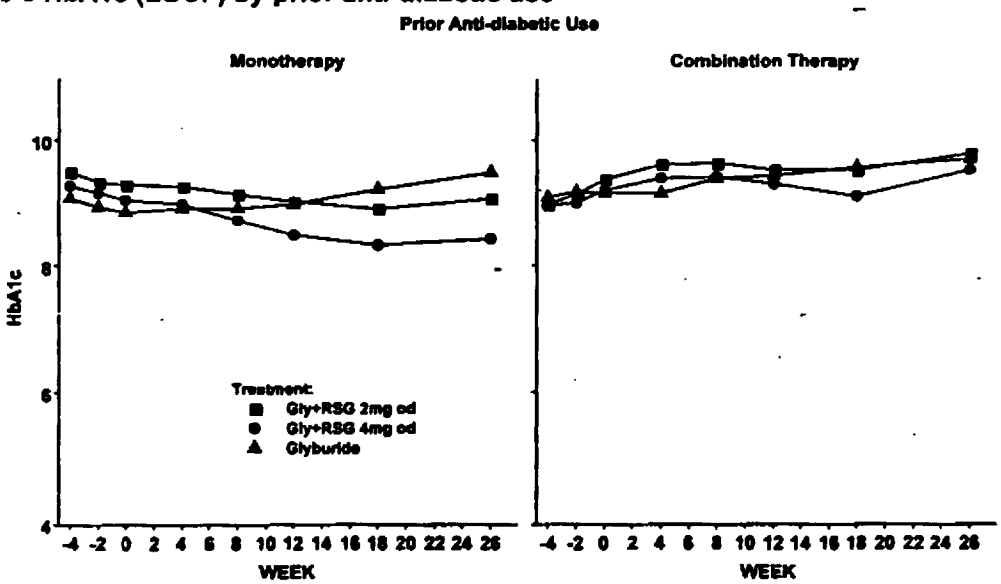
A significant subgroup by treatment interaction was seen for prior therapy (p=.009) and for duration of diabetes (p=.05); for all other subgroups, no significant subgroup differences were seen.

For patients previously on combination therapy, no improvement over glyburide is seen for either combination (p>.50, Table 7 and Figure 6). For patients previously on monotherapy, combination therapy offers significant improvement over glyburide alone (p<.0001)

Table 7. Study 096 Mean HbA1c (%) by Prior Anti-diabetic Therapy

Prior Antidiabetic Therapy	GLY Mean (SD)	RSG 2 mg daily + GLY Mean (SD)	RSG 4 mg daily + GLY Mean (SD)
Monotherapy	(n=85)	(n=75)	(n=78)
Baseline	8.9 (1.4)	9.3 (1.7)	9.1 (1.5)
Change Wk 26 LOCF	+0.6 (0.9)	-0.2 (1.2)	-0.6 (1.2)
Combination Therapy	(n=30)	(n=40)	(n=38)
Baseline	9.2 (1.4)	9.4 (1.3)	9.2 (1.5)
Change Wk 26 LOCF	+0.5 (1.2)	+0.4 (1.4)	+0.3 (1.4)

Figure 6 HbA1c (LOCF) by prior anti-diabetic use

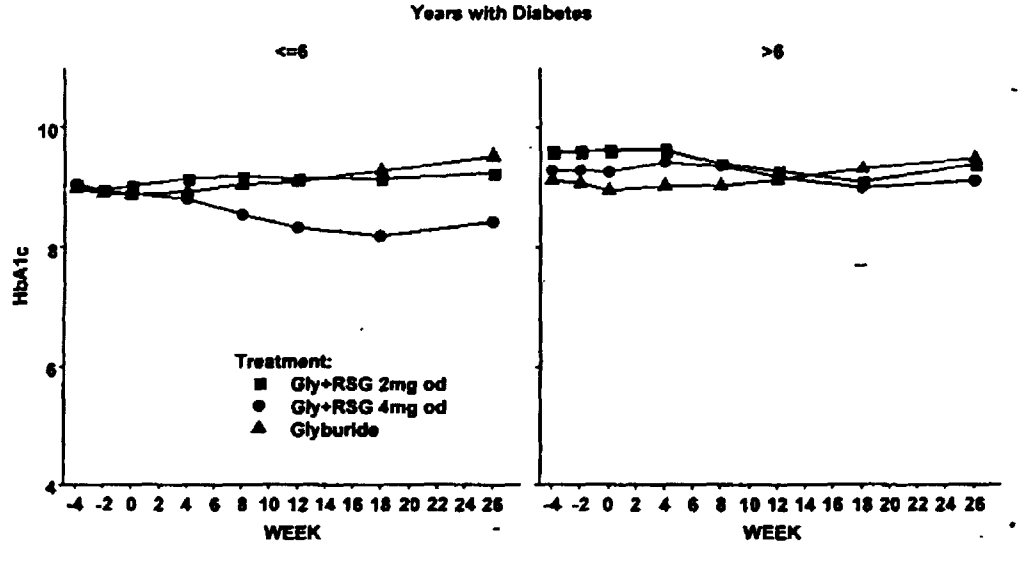


This reviewer examined the effect of duration of diabetes on the treatment response of HbA1c by defining two subgroups based on median years of diabetes (≤6 years versus >6years). A quantitative difference between subgroups was seen with a larger treatment effect seen for patients with six or less years of diabetes (Table 8 and Figure 7).

Table 8. Study 096 Mean HbA1c (%) by Median Years of Diabetes

Years with Diabetes	GLY Mean (SD)	RSG 2 mg daily + GLY Mean (SD)	RSG 4 mg daily + GLY Mean (SD)
≤6 years	(n=59)	(n=60)	(n=58)
Baseline	8.9 (1.5)	9.0 (1.5)	8.9 (1.3)
Change Wk 26 LOCF	+0.6 (0.9)	+0.2 (1.3)	-0.5 (1.3)
>6 years	(n=55)	(n=55)	(n=58)
Baseline	9.0 (1.3)	9.6 (1.5)	9.3 (1.6)
Change Wk 26 LOCF	+0.6 (1.0)	-0.2 (1.3)	-0.1 (1.4)

Figure 7 HbA1c (LOCF) by duration of diabetes with subgroups defined by the median years of diabetes



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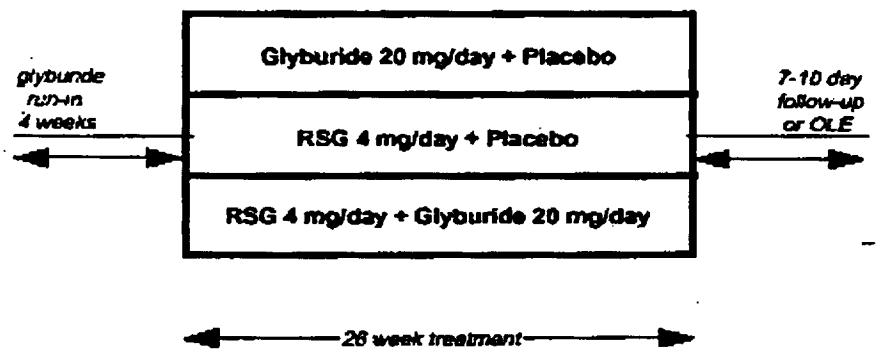
Study 079 (conducted 4/97 to 3/98)

Study 079 was a randomized, double-blind multicenter study to assess the efficacy and safety of rosiglitazone (RSG) in combination with glyburide for patients inadequately controlled (140≤FPG≤300) on glyburide. For this study, patients were on a fixed dose of 20 mg (10 mg twice a day) of glyburide for a minimum of 4 weeks prior to screening. The study was conducted at 41 centers in the United States.

After screening for inclusion/exclusion criteria, patients were given placebo with glyburide single-blind for 4 weeks (run-in). Patients with 140≤FPG≤300 at screening and after 2 weeks of the run-in and with variation in weight of <10% were randomized to placebo plus glyburide, RSG 4mg daily (2 mg twice a day) plus glyburide or RSG 4mg daily (2 mg twice a day) monotherapy (Figure 8). The glyburide dose was to be kept constant throughout the study. Both drugs were administered twice a day. Patients were treated for 26 weeks with visits at Weeks 0, 4, 8,12, 18 and 26.

The primary objective of this trial was to show that combination therapy was superior to the glyburide and rosiglitazone monotherapy arms; the trial was powered with 65 patients per treatment group to find a treatment effect of 0.75% or greater for change in HbA1c at endpoint (Week 26).

Figure 8 Sponsor's schematic of 079 trial design



Patient Disposition

A total of 390 patients passed screening and entered the glyburide run-in period. Of those 390 patients, 309 (79%) were randomized (Table 9, 106 to GLY, 104 to RSG 2mg twice daily and 99 to RSG 2mg twice daily + GLY). The completion rate was significantly higher in the combination therapy group (79%) than either monotherapy group (67% for GLY and 44% for RSG). The intent-to-treat (ITT) population is comprised of about 90% of the randomized patients.

Table 9. Study 079 Number (%) of patients on study by treatment group and week

	GLY	RSG 2mg twice daily	RSG 2mg twice daily + GLY
Randomized	106 (100%)	104 (100%)	99 (100%)
Week 4	99 (93%)	86 (83%)	92 (93%)
Week 8	91 (86%)	73 (70%)	91 (92%)
Week 12	84 (79%)	60 (58%)	87 (88%)
Week 18	75 (71%)	51 (49%)	82 (83%)
Week 26	71 (67%)	46 (44%)	78 (79%)
Sponsor's ITT	99 (93%)	88 (85%)	89 (90%)

An adverse event was the major reason for withdrawal in all treatment groups (Table 10) occurring throughout the trial. In both monotherapy groups, a major reason for withdrawal was lack of efficacy (LOE). In the glyburide group, most of the LOE dropouts occurred after 2 months of therapy while, in the rosiglitazone group, most occurred during the first 3 months of therapy.

Table 10. Study 079 Reasons for withdrawal from double-blind treatment post-randomization

	GLY (n=106)	RSG 2mg twice daily (n=104)	RSG 2mg twice daily + GLY (n=99)
ADE	10 (9%)	21 (20%)	7 (7%)
Lack of Efficacy	7 (7%)	21 (20%)	2 (2%)
Protocol Deviation	4 (4%)	6 (6%)	3 (3%)
Lost-to-Follow-up	5 (5%)	0 (0%)	2 (2%)
Other	9 (9%)	10 (10%)	7 (7%)

Patient Demographics and Baseline Characteristics

The treatment groups were generally well-balanced regarding baseline characteristics. The mean age of patients was 59 years (range of 38 to 80); about 70% were under 65 years. About ⅔ were male. About 70% were Caucasian; 12% were Black and 19% were listed as other races. About 38% were on combination therapy (most metformin plus a sulfonylurea) before randomization (Table 11). The median time of diabetes was 7 years.

Table 11. Study 079 Baseline Characteristics

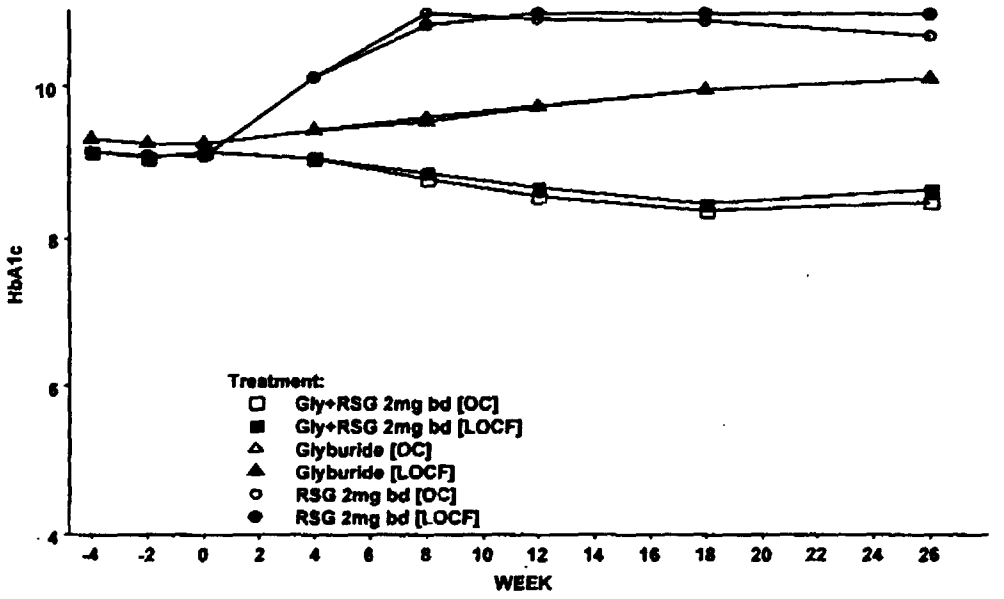
	GLY (n=106)	RSG 2mg twice daily (n=104)	RSG 2mg twice daily + GLY (n=99)
Previous Treatment			
Single agent	59 (60%)	60 (61%)	64 (65%)
Combination	40 (40%)	39 (39%)	34 (35%)
# of Years of Diabetes			
Mean (SD)	8.8 (7.0)	9.4 (8.6)	8.7 (6.0)
Median	7.0	7.0	7.0
Range	1 to 39	0 to 45	1 to 28
Prior Antidiabetic meds			
Acarbose	5%	1%	6%
Insulin	0%	1%	0%
Metformin	38%	38%	4%
Troglitazone	2%	3%	3%
Sulfonylureas			
Chlorpropamide	0%	0%	1%
Glibenclamide	99%	100%	99%
Glimepiride	1%	1%	1%
Glipizide	12%	11%	9%

Efficacy Results

HbA1c, the primary efficacy variable in Study 079, was measured during the run-in period (Weeks –4 and –2), at baseline (Week 0) and during double-blind treatment (Weeks 4, 8, 12, 18 and 26). Figure 9 illustrates mean HbA1c overtime for observed cases (OC) and for

the last-observation-carried-forward (LOCF) data. Essentially no mean changes are seen during the run-in. HbA1c increases over the duration of the trial in both monotherapy arms; a significant decrease is evident in the GLY+RSG 2mg twice daily group.

Figure 9. Study 079 HbA1c by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



Change from baseline of HbA1c at Week 26 LOCF was pre-specified as the primary endpoint for establishing efficacy. An analysis of covariance (ANCOVA) with baseline as a covariate was planned as the primary analysis. Each monotherapy arm was compared to the combination arm; the sponsor adjusted for multiple comparisons using Hochberg's procedure. In this setting where one must show that the combination therapy beats each of its components, no adjustments for multiple comparisons is necessary and therefore no adjustments were made by this reviewer.

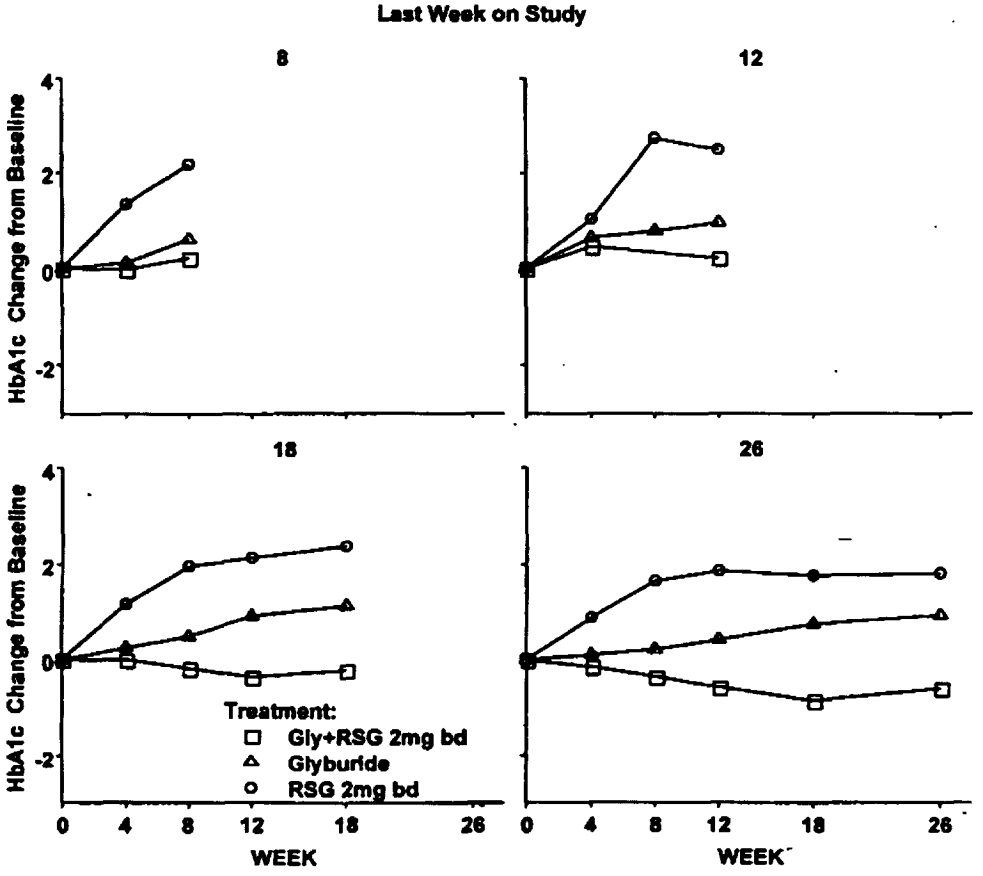
For both the completers analysis and the ITT analysis (LOCF data), the combination is statistically significantly different from each monotherapy arm (Table 12, p<.0001) regardless of the statistical model used.

Table 12. Study 079 Mean HbA1c (%)

	GLY (n=99) Mean (SD)	RSG 2mg twice daily (n=99) Mean (SD)	RSG 2mg twice daily + GLY (n=98) Mean (SD)
Baseline	9.2 (1.4)	9.1 (1.7)	9.2 (1.3)
Change from Baseline Week 26 LOCF	+0.86 (1.2)	+1.9 (1.7)	-0.49 (1.1)
Week 26 Completers	+0.91 (1.2) (n=72)	+1.8 (2.0) (n=49)	-0.59 (1.2) (n=79)

Due to the large number of dropouts in the monotherapy arms, this reviewer examined the influence of these discontinuations on treatment effect. Figure 10 shows the mean change from baseline for 4 cohorts of patients where a cohort is defined by the patients' last week on study. So, for example, patients in the Week 12 cohort includes all patients that only completed 12 weeks on study. Exposure then for each treatment group is the same in each graph of Figure 10. It is evident that the relationship among the treatment groups is similar regardless of week of completion, so the Week 26 LOCF analysis does not appear to be biased by the carrying forward of data from dropouts.

Figure 10. Study 079 HbA1c by week on study and treatment by cohorts of completers

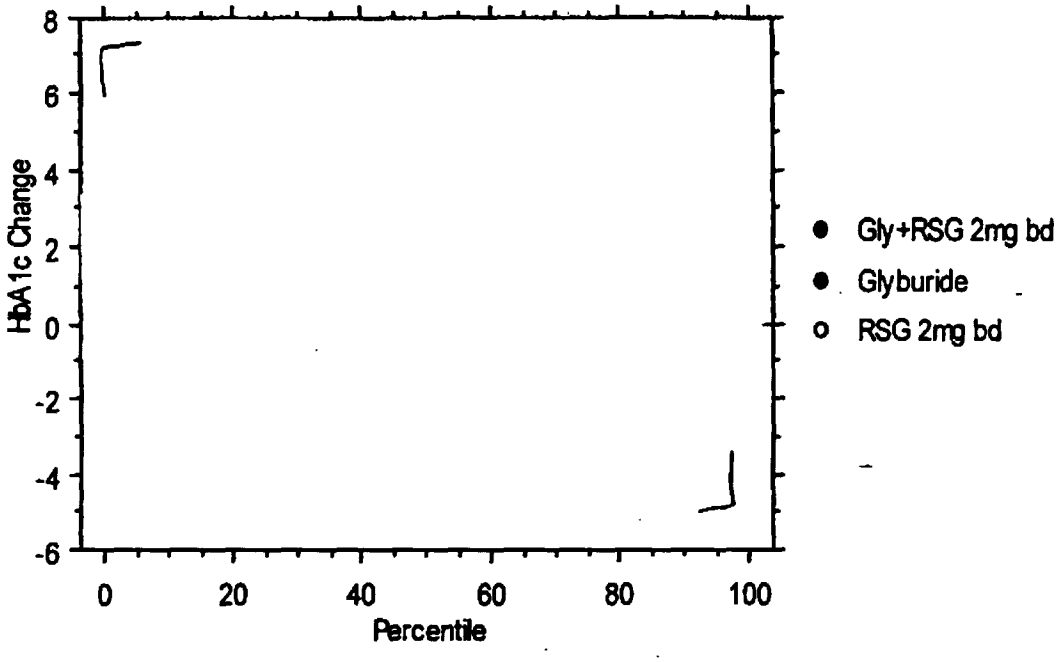


Sample Sizes

Last Week	GLY	RSG 2mg twice daily	RSG 2mg twice daily + GLY
≤8	11	12	4
12	10	13	2
18	6	9	7
26	71	46	78

As a secondary analysis (pre-specified in the protocol), the sponsor computed the percentage of patients achieving a reduction of 0.7% or greater in HbA1c from baseline. In the GLY group, 10% had a reduction of 0.7% or greater, in the RSG monotherapy arm, 5% while in the combination group the percentages was 38%. This reviewer's cumulative distribution plot shows that about 75% of the patients taking SU+RSG 2mg twice daily had a decrease in HbA1c at endpoint while only about 20% of the patients in the monotherapy arms had some decrease (Figure 11).

Figure 11. Study 079 Cumulative Distribution Plot of Change from Baseline of HbA1c Week 26 LOCF (endpoint)



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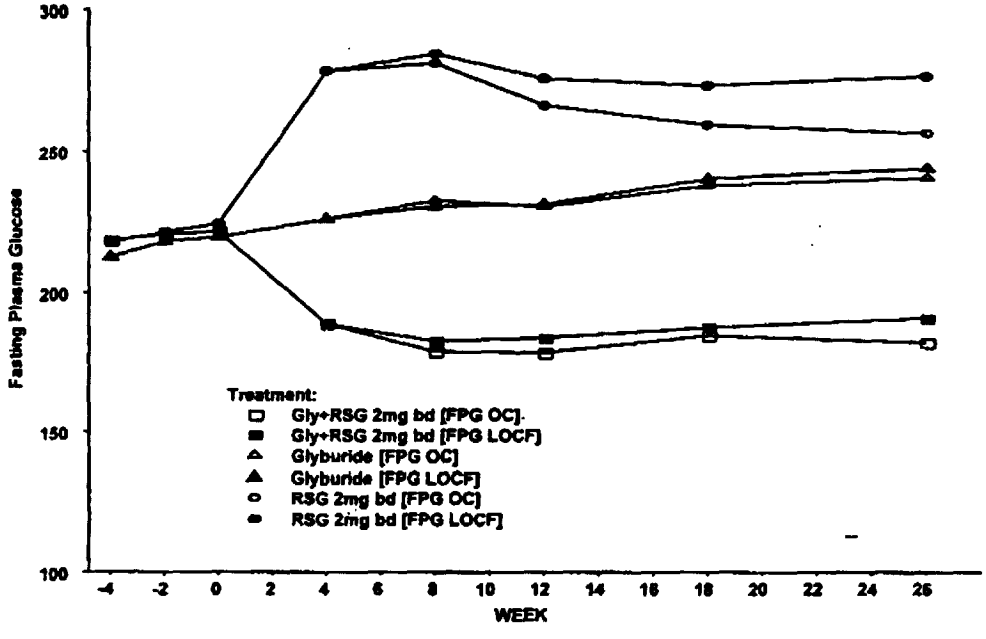
Fasting Plasma Glucose

Means for fasting plasma glucose (FPG), a secondary efficacy variable in Study 079, are shown in Figure 12 below. Decreases in FPG occur during the first 4-5 weeks of the study in the combination therapy group; levels remain constant for the remainder of the trial while glyburide levels steadily increase. In the rosiglitazone arm, FPG increases dramatically during the first month and then steadily decreases for patients who remain on study.

Figure 12. Study 079 FPG by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



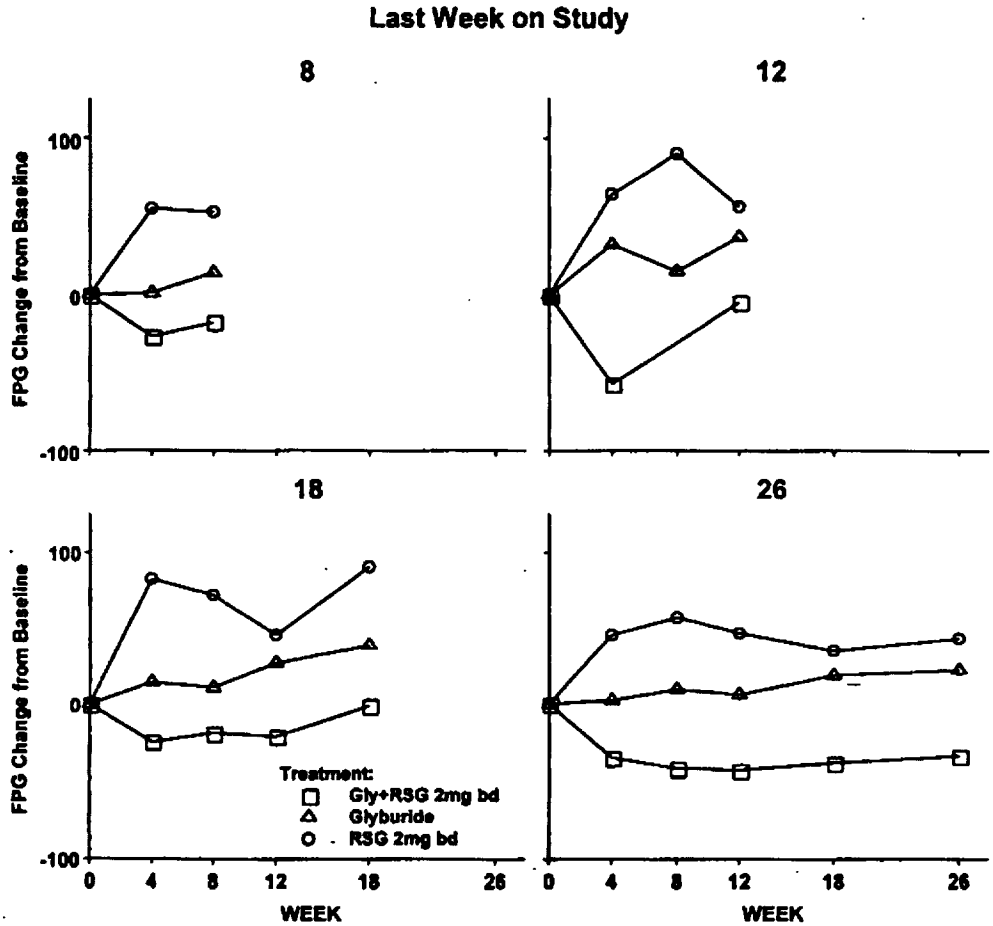
Week 26 LOCF and completer results for the combination therapy show a significant drop in FPG compared to each monotherapy arm ($p<.0001$, ANCOVA, Table 13).

Table 13. Study 079 Fasting Plasma Glucose

	GLY (n=99) Mean (SD)	RSG 2mg twice daily (n=99) Mean (SD)	RSG 2mg twice daily + GLY (n=98) Mean (SD)
Baseline	219.8 (55.9)	224.3 (50.8)	221.7 (55.0)
Change from Baseline			
Week 26 LOCF	+24.0 (50.9)	+52.5 (65.8)	-34.1 (57.5)
Week 26 Completers	+22.0 (51.8) (n=71)	+42.5 (65.8) (n=49)	-31.0 (60.5) (n=98)

As for HbA1c, this reviewer examined the impact of dropout data on the endpoint analysis. Again the relationship among the treatment groups is similar regardless of week of completion so the endpoint analysis does not appear to be unduly biased by the LOCF data.

Figure 13. Study 079 FPG by week on study and treatment by cohorts of completers



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Subgroup Analyses

As for Study 098, this reviewer performed subgroup analyses on pre-defined subgroups: prior therapy (monotherapy versus combination therapy, age (<65 versus ≥65), BMI (<27 versus ≥27), gender, HbA1c (<9% versus ≥9%) and FPG (<200 versus ≥200). No significant treatment by subgroup interactions were found. For comparison to Study 098, graphs for prior therapy (Figure 15) and duration of diabetes (Figure 16) are included here.

Figure 15. HbA1c (LOCF) by prior anti-diabetic use

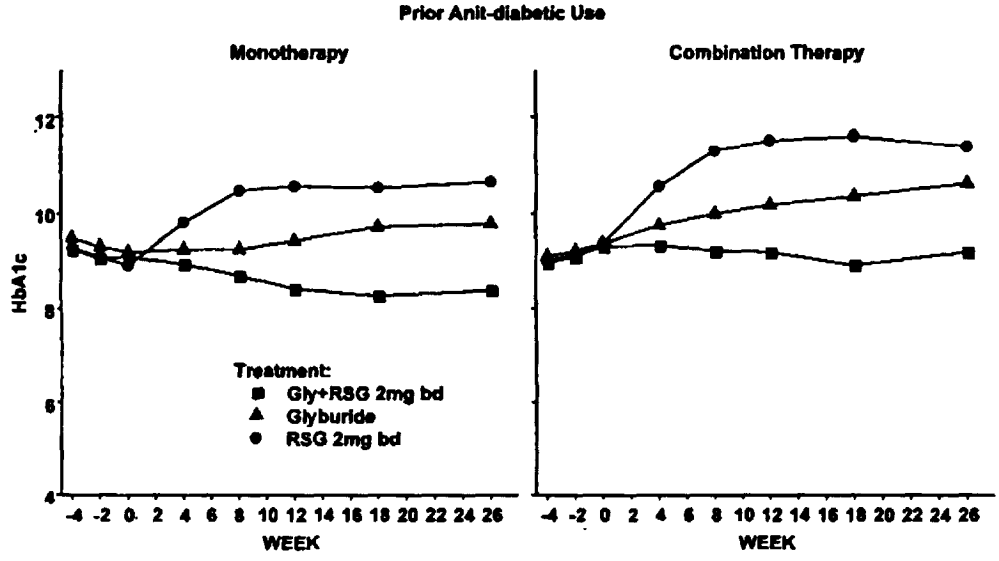
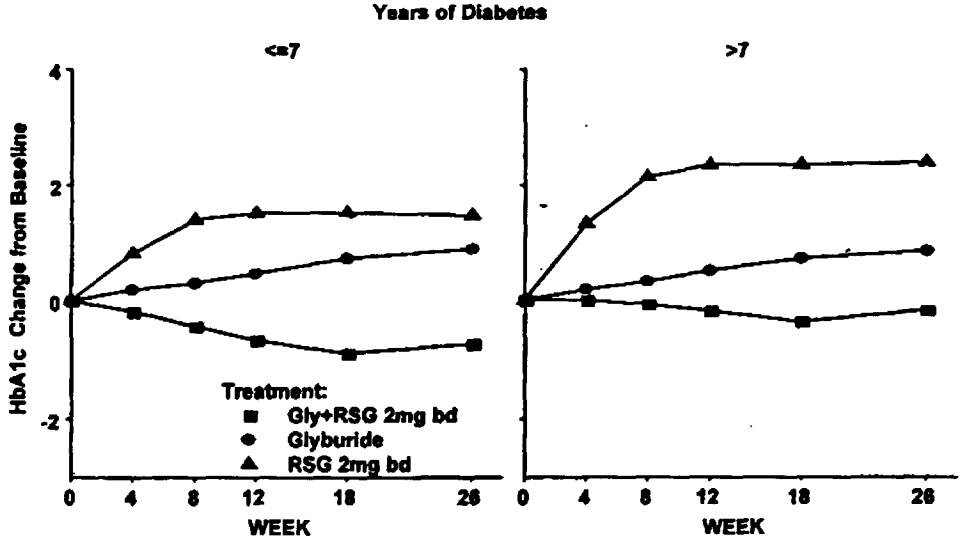


Figure 16. HbA1c (LOCF) by duration of diabetes with subgroups defined by the median years of diabetes



Study 015 (conducted 8/96 to 3/98)

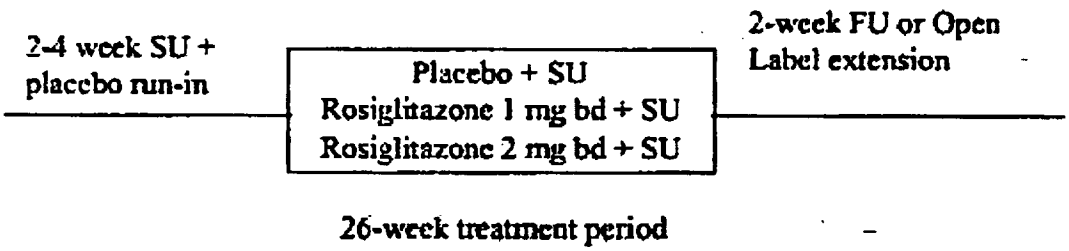
Study 015 was a randomized, double-blind multicenter study designed to assess the efficacy and safety of rosiglitazone (RSG) as add-on therapy to sulphonylurea (SU; glibenclamide, gliclazide or glipizide). Patients were enrolled in 60 centers in 6 European countries (France, Holland, Italy, Spain, Switzerland and United Kingdom). Entry criteria included the following:

- C-peptide≥0.8 ng/ml
- HbA1c≥7.5%
- FPG≤15.0 mmol/l.
- Constant SU dose for 2 months prior to screening

After screening for inclusion/exclusion criteria, patients were given placebo with SU single-blind for 2-4 weeks (run-in). The SU dose was to be kept constant throughout the study. Patients were treated for 26 weeks with visits at Weeks 0, 4, 8,12, 16, 20 and 26.

The primary objective of this trial was to show that each combination therapy arm is superior to the SU plus placebo arm; the trial was powered with 143 patients per treatment group to find a treatment effect of 0.50% or greater for HbA1c at endpoint (Week 26).

Figure 17. Sponsor's schematic of 015 trial design



Patient Disposition

A total of 800 patients entered the placebo run-in period; 593 (74%) were randomized to treatment (Table 2). About ¾ of the patients completed the study with the highest completion rate in the RSG 2 mg twice daily + SU group (76%). The rates of discontinuation were similar for the three groups.

Table 14. Study 015 Number (%) of patients on study by treatment group and week

	SU	RSG 1 mg twice daily + SU	RSG 2 mg twice daily + SU
Randomized	198 (100%)	205 (100%)	190 (100%)
Week 4	186 (94%)	199 (97%)	182 (96%)
Week 8	177 (89%)	190 (93%)	179 (94%)
Week 12	163 (82%)	178 (87%)	168 (88%)
Week 16	154 (78%)	170 (83%)	161 (85%)
Week 20	143 (72%)	159 (78%)	156 (82%)
Week 26	127 (64%)	147 (72%)	144 (76%)
Sponsor's ITT	**192 (97%)**	**199 (97%)**	**183 (96%)**

The primary reason for dropout in all three treatment groups was lack of efficacy; twice as many patients (16%) dropped out in the SU group than in the RSG 2mg twice daily+SU group (8%). A large number of these dropouts occurred during the last 2 months of the study. The major adverse events leading to withdrawal in the SU group were headache (n=4), hyperglycemia (n=4) and hypoglycemia (n=2). In the RSG 1mg twice daily+SU group, 4 patients dropped due to hyperglycemia while none dropped for this reason in the RSG 2mg twice daily+SU group.

Table 15. Study 015 Reasons for withdrawal from double-blind treatment post-randomization

	SU (n=198)	RSG 1mg twice daily+SU (n=205)	RSG 2mg twice daily+SU (n=190)
ADE	23 (12%)	11 (5%)	11 (6%)
Lack of Efficacy	31 (16%)	24 (12%)	16 (8%)
Protocol Deviation	6 (3%)	15 (7%)	10 (5%)
Lost-to-Follow-up	4 (2%)	1 (1%)	3 (2%)
Other	7 (4%)	7 (3%)	6 (3%)

Patient Demographics and Baseline Characteristics

The treatment groups were generally well-balanced regarding baseline characteristics (Table 16). The mean age of patients was 61 years (range of 32 to 80); about 58% were under 65 years. About 58% were male. About 97% were Caucasian. The mean BMI was 28 kg/m^2.

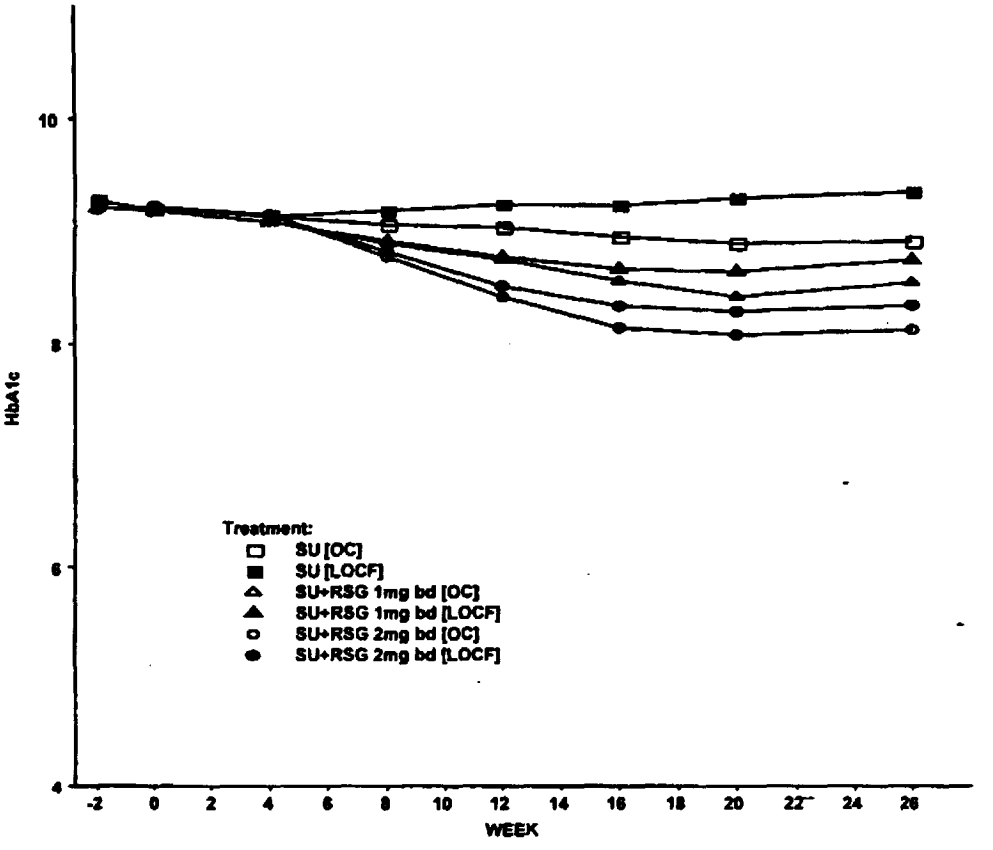
Table 16. Study 015 Baseline Characteristics

	SU (n=192)	RSG 1mg twice daily+SU (n=199)	RSG 2mg twice daily+SU (n=183)
Previous Treatment			
Single agent (SU)	191 (99.5%)	199 (100%)	183 (100%)
Combination	1 (0.5%)	0 (0%)	0 (0%)
# of Years of Diabetes			
Mean (SD)	9.0 (6.5)	8.7 (6.3)	9.1 (7.1)
Median	8.0	7.0	7.0
Range	0 to 30	0 to 34	0 to 33
Sulphonylurea on study			
Glibenclamide	43%	38%	42%
Median dose (range)	15mg (2.5-30)	13mg (5-30)	15mg (2.5-30)
Glicazide	46%	50%	48%
Median dose (range)	160mg (40-480)	160mg (20-480)	160mg (20-480)
Glipizide	11%	9%	9%
Median dose (range)	15 (6-60)	15 (5-60)	15 (5-60)

Efficacy Results

HbA1c, the primary efficacy variable in Study 015, was measured during the run-in period (Week –2), at baseline (Week 0) and during double-blind treatment (Weeks 4, 8, 12, 16, 20 and 26). Figure 18 illustrates mean HbA1c overtime for observed cases (OC) and for the last-observation-carried-forward (LOCF) data. The difference between the LOCF data and the OC data is evident; patients who stay on study in all groups continue to show improvement in HbA1c up until about Week 20. Mean decreases in HbA1c are seen as early as the second month for both combination groups. From Week 20 to Week 26 there appears to be no further lowering of HbA1c.

Figure 18. Study 015 Mean HbA1c by week on study and treatment for last-observation-carried-forward (closed symbols, LOCF) and observed cases (open symbols, OC) data



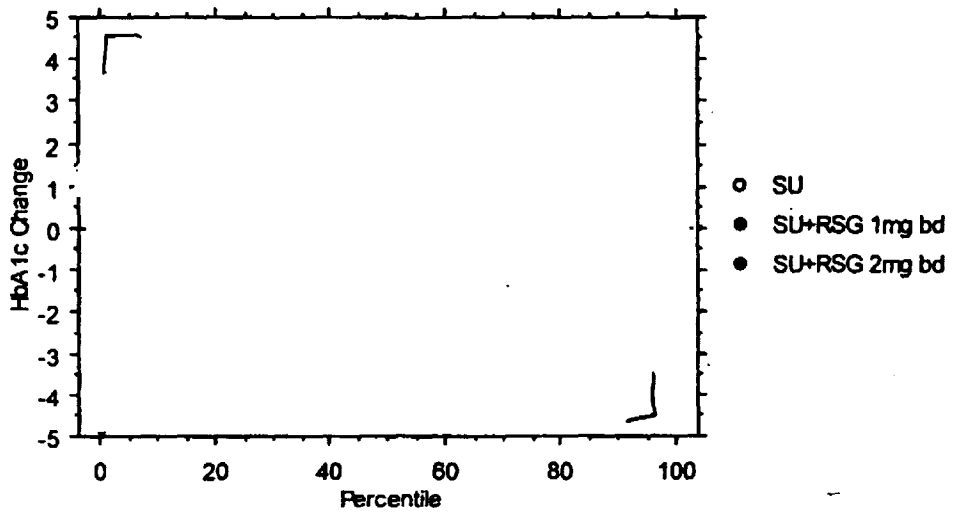
Change from baseline of HbA1c at Week 26 LOCF was pre-specified as the primary endpoint for establishing efficacy. The endpoint results (Table 17) for both combination groups were statistically significantly different from the SU group (p<.0001, analysis of covariance (ANCOVA) with baseline as a covariate, alpha level of .027 based on Dunnett's procedure). LOCF and completer results are similar.

Table 17. Study 015 Mean HbA1c (%)

	SU (n=192) Mean (SD)	RSG 1mg twice daily+SU (n=199) Mean (SD)	RSG 2mg twice daily+SU (n=183) Mean (SD)
Baseline	9.2 (1.3)	9.2 (1.2)	9.2 (1.2)
Change from Baseline Week 26 LOCF	+0.15 (1.11)	-0.44 (1.05)	-0.89 (1.09)
Week 26 Completers	-0.03 (1.05) (n=137)	-0.57 (1.04) (n=155)	-0.99 (1.07) (n=153)

As a secondary analysis, the sponsor computed the percentage of patients achieving a reduction of 0.7% or greater in HbA1c from baseline. In the SU group, 19% had a reduction of 0.7% or greater while in the two combination groups the percentages were 39% (1mg) and 60% (2mg). This reviewer's cumulative distribution plot shows that about 80% of the patients taking SU+RSG 2mg twice daily had a decrease in HbA1c at endpoint while only about 40% of the SU patients had some decrease.

Figure 19. Study 015 Cumulative Distribution Plot of Change from Baseline of HbA1c Week 26 LOCF (endpoint)



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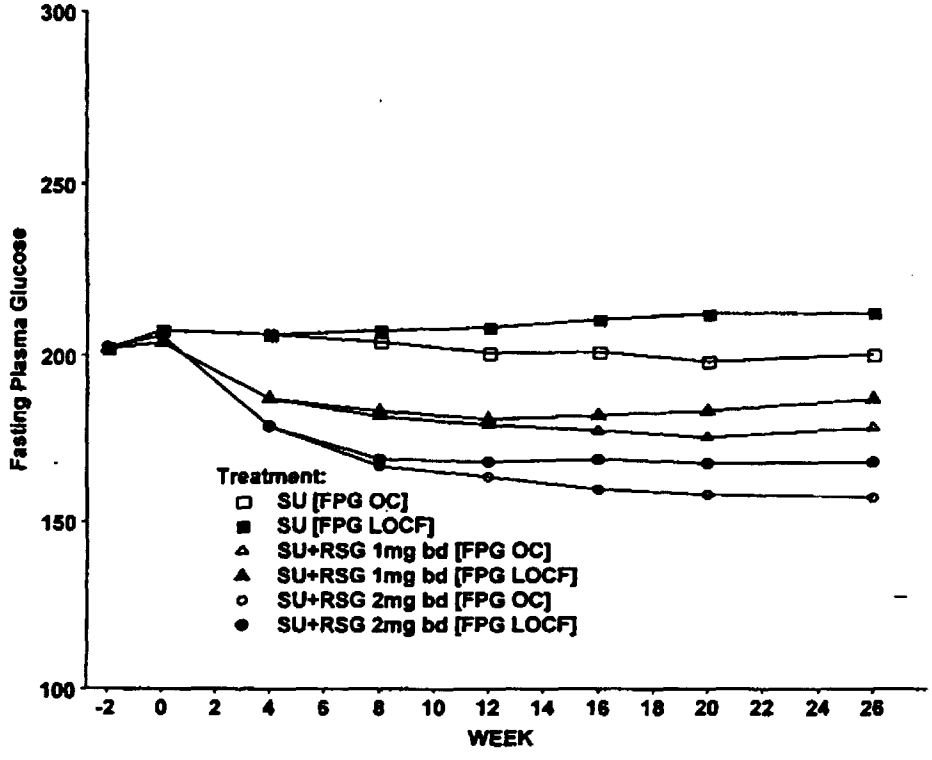
Fasting Plasma Glucose

Means for fasting plasma glucose (FPG), a secondary efficacy variable in Study 015, are shown in Figure 20 below. Decreases in FPG occur during the first 4 weeks of the study in both combination therapy groups; levels remain constant for the remainder of the trial while glyburide levels steadily increase.

Figure 20. Study 015 FPG by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



At Week 26 (LOCF and completers), a statistically significant difference from SU is evident for both combination therapy groups ($p<.0001$, LOCF and completer analyses).

Table 18. Study 096 Fasting Plasma Glucose (mg/dL) Mean (SD)

	SU (n=192) Mean (SD)	RSG 1mg twice daily+SU (n=199) Mean (SD)	RSG 2mg twice daily+SU (n=183) Mean (SD)
Baseline	207.2 (43.3)	203.4 (45.6)	205.5 (49.1)
Change from Baseline Week 26 LOCF	+5.6 (49.0)	-16.5 (49.5)	-37.4 (47.5)
Week 26 Completers	-1.2 (45.4) (n=136)	-19.8 (46.5) (n=154)	-39.7 (47.7) (n=153)

Lipids in Studies 096, 079 and 015

The mean results for LDL and HDL are shown in Table 19 below. Significant increases in LDL and HDL for the combination groups compared to the monotherapy SU groups are evident; increases in total cholesterol, triglycerides and Apo B were also observed. These results are consistent with the lipid results for the combination of metformin plus RSG presented in the original NDA. No correlation between change in HbA1c and change in lipids was found by this reviewer.

Table 19. Summary of mean lipid changes at endpoint LOCF

	Study 096 Once a day dosing			Study 079 Twice a day dosing			Study 015 Twice a day dosing		
	GLY	RSG 2OD +GLY	RSG 4OD +GLY	GLY	RSG 2BID	RSG 2BID +GLY	SU	RSG 1BID +SU	RSG 2BID +SU
LDL									
Base	122	125	120	129	122	121	139	132	142
Ch	+3	+12	+18	+.3	+22	+13	-0.2	+3	+7
%Ch	+4%	+11%	+18%	+1%	+19%	+14%	+1%	+4%	+6%
HDL									
Base	45	45	45	45	44	44	47	44	44
Ch	+0.3	+1	+0.03	+1	+3	+2	+0.7	+2	+5
%Ch	+1%	+4%	+3%	+3%	+9%	+6%	+4%	+6%	+12%

Overall Comments

In all three studies, the combination of sulfonylureas and rosiglitazone showed a statistically significant improvement in glycemic control compared to monotherapy where improvement was measured as a decrease in HbA1c (the primary efficacy variable) and in FPG (a secondary efficacy variable). The results for HbA1c (mean changes and percentage of responders where a responder is a patient with a decrease of 0.7% or greater) are summarized in Table 20 below. There appears to be greater improvement seen for twice a day dosing than once a day however without a head-to-head comparison of the dosing regimens, the significance of this observation is unknown.

Table 20. Summary of HbA1c response at endpoint LOCF

	Study 096 Once a day dosing			Study 079 Twice a day dosing			Study 015 Twice a day dosing		
	GLY	RSG 2OD +GLY	RSG 4OD +GLY	GLY	RSG 2BID	RSG 2BID +GLY	SU	RSG 1BID +SU	RSG 2BID +SU
HbA1c									
Baseline	8.9	9.3	9.1	9.2	9.1	9.2	9.2	9.2	9.2
Change	+0.6	0	-0.3	+0.9	+1.9	-0.5	+0.2	-0.4	-0.9
Responders %	6%	28%	29%	10%	5%	38%	19%	39%	60%

Labeling Comments

This reviewer has the following recommendations regarding the proposed labeling in the Clinical Studies section entitled Combination with Sulfonylurea.:

1. When referring to the first 2 studies in the text, use the study letters (C and D) as in Table 5.

2. Eliminate the [redacted] under HbA1c in Table 5 for both studies. This percentage was not an endpoint in this study.

3. Put a plus sign in front of increases from baseline.

4. Report means not medians for HbA1c for Study D.

5. For Study C, this reviewer obtains a value of [redacted] for baseline FPG of RSG 1mg twice daily +SU, [redacted]

6. For the section describing the third study (Study 079), the following changes in bold and italics are recommended.

Reviewer's Recommendation

Based on the efficacy data in this submission and from a statistical viewpoint, an indication for combination therapy of rosiglitazone and sulfonlyureas for the treatment of Type 2 diabetic patients inadequately treated with sulfonylureas alone is approvable.

/S/

Joy D. Mele, M.S.
Mathematical Statistician

Concur:

/S/ 3/28/00

Todd Sahlroot, Ph.D.
Team Leader

3/28/00

/S/

Ed Nevius, Ph.D.
Director of DOB2