CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-178/S-004

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-178/SE1-004
Name of drug:	Glucovance (metformin + glyburide combination)
Applicant:	BMS
Indication:	Type 2 diabetes
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Keywords: NDA review, clinical studies, one study application

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1 Summary and conclusions

This submission consisted of a single randomized, double-blind placebo-controlled 24-week multicenter trial comparing rosiglitazone, a Type 2 oral diabetic agent, to placebo in 365 patients also taking open-label Glucovance (metformin + glyburide antidiabetic therapy) combination therapy.

Rosiglitazone significantly reduced HbA1c values compared to placebo as measured by HbA1c change from baseline, the primary endpoint.(rosiglitazone -0.9% vs placebo +0.1%, p<.001). The mean treatment difference was about 1%. Females had larger treatment differences than males (1.2% vs 0.9%). The observed difference between males and females was nominally statistically significant (treatment-by-sex interaction p=.082).

Rosiglitazone also significantly reduced fasting plasma glucose, a key secondary measure, compared to placebo as measured by change from baseline (-42 mg/dL vs +8 mg/dL, p<.001).

With respect to safety, rosiglitazone was associated with statistically significantly greater increases in weight compared to placebo (+3.0 kg vs 0 kg, p<.001). There were significant between treatment differences in episodes of hypoglycemia as well with rosiglitazone associated with higher rates (p<.001).

This submission is intended to effect changes in the Glucovance prescription label regarding the effectiveness of rosiglitazone in patients who have failed to achieve adequate glycemic control while taking Glucovance. It is the opinion of this reviewer that, consistent with the trial design and the efficacy results from the trial which demonstrate the effectiveness of rosiglitazone compared to placebo and which do not permit inferences about the effectiveness of Glucovance, it would be more appropriate to put the results in the rosiglitazone label rather than the Glucovance label. Additional suggestions for labelling can be found in section 8: "Labelling recommendations".

2 Introduction

The sponsor submitted data for a multicenter randomized, double-blind placebo-controlled clinical trial of rosiglitazone, a Type 2 oral diabetic agent, in patients also receiving open-label Glucovance (gluburide + metformin) combination therapy. This submission is intended to effect changes in the Glucovance prescription label regarding the effectiveness of rosiglitazone in patients who have failed to achieve adequate glycemic control while taking Glucovance.

3 Design

Table 1 shows the major design characteristics of this randomized, double-blind placebo-controlled trial..

Table 1. Study characteristics

Trial # Centers Dates	Patients	# randomized	Design Primary endpt	Duration
CV138-055 65 US centers 8/2000-7/2001	Males and females ages 20-78 with type 2 diabetes HbA1c >7% and ≤10% prior to rand	Rosiglitazone n=181 Placebo n=184	Randomized Placebo-controlled double-blind Glucovance (metformin + glyburide) background therapy HbA1c change from baseline	2 or 12-week lead-in 24 weeks double-blind

The double-blind period was preceded by a Lead-in phase which was either 2 or 12 weeks depending on prior treatment history. At screening, patients with HbA1c between 7% and 10% while taking at least 2000mg of metformin and at least a half-maximum dose of a sulfonylurea were enrolled in a 2-week lead-in group and given a maximum Glucovance dose (metformin 2000mg/ glyburide 10mg). Patients with HbA1c between 7.5% (changed by protocol amendment from 8%) and 11% who were receiving suboptimal doses of combination therapy

or other monotherapies [1] were enrolled in a 12-week lead-in group and titrated to control with Glucovance. Patients were treated with metformin/glyburide using tablet strengths of 500/2.5mg. Patients could be titrated to a maximum of 4 tablets of Glucovance (metformin 2000mg/ glyburide 10mg) as required.

After 1 or 11 weeks (Week –1) of the Lead-in period, patients still not inadequately controlled (HbA1c between 7% and 10%) while taking at least 3 Glucovance tablets (met 1500mg/ gly 7.5mg) were eligible for randomization (Week 0) to rosiglitazone or placebo. The initial randomized therapy was one tablet daily (rosiglitazone 4mg or placebo). At Weeks 8, 12, 16 or 20 of the double-blind period, patients could be titrated to a maximum of two tablets daily of study medication (rosiglitazone 4mg bid or placebo) if the mean daily glucose value was >126 mg/dL or if HbA1c was >7%.

Scheduled Lead-in visits for patients with 12-week lead-ins were Weeks –12, -10, -8, -4 and-1. Scheduled visits for patients with 2-week lead-ins were Weeks –2 and -1. Study visits were every 4 weeks during the double-blind period. HbA1c data were collected at screeening, during Lead-in Weeks –12 (or –2), -1 and 0 and during treatment Weeks 8, 12, 16 20 and 24.

Rosiglitazone/placebo dose reductions were not permitted during the trial. Instead, the Glucovance dose could be reduced by 1 tablet as indicated by symptoms and the investigator's discretion. Dose reduction was required if (1) FBG was <50 mg/dL on multiple occasions or (2) the patient was experiencing symptoms (beyond explainable causes such as skipping meals, exercise, etc.) and fingerstick glucose values were <50 on multiple occasions.

The primary objective of the trial was to compare rosiglitazone and placebo on HbA1c change from baseline at 24 weeks or the last prior visit. The primary endpoint was HbA1c change from baseline. Secondary endpoints included changes from baseline in fructosamine, fasting plasma glucose (FPG), insulin dose, C-peptide and free fatty acids. In addition to the primary endpoint, this reviewer analyzed FPG and weight change since these were addressed in the sponsor's proposed label.

At 150 patients per treatment group, the trial was powered at 90% to detect a 0.35% between-group difference in HbA1c change from baseline assuming a SD of 0.9%, a 2-sided 5% alpha. It was assumed that 5% of patients would not have a post-baseline measurement.

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[1] Includes other anti-diabetic agents. Sponsor's Administrative Letter #1 issued after initiation of the trial expanded the list of other agents patients could be receiving

4 Baseline / demographics

Three hundred sixty-five (365) patients were randomized to study drug in equal numbers, 181 to rosiglitazone and 184 to placebo. Table 2 shows key demographic/ baseline variables for all randomized patients. There were no significant imbalances between groups.

Table 2. Key demographic/ baseline variables

	Rosiglitazone (n=181)	Placebo (n=184)	Total (n=365)
Females	76 (42%)	72 (39%)	148 (41%)
Males	105 (58%)	112 (61%)	217 (59%)
Age (yrs)			
Mean (SD)	57 (9)	57 (10)	57 (9)
Range	31-77	34-78	31-78
Race			
Black	8 (4%)	20 (11%)	28 (8%)
Caucasian	139 (77%)	130 (71%)	269 (74%)
Asian/ PI	2 (1%)	2 (1%)	4 (1%)
Hispanic/ Latino	29 (16%)	30 (16%)	59 (16%)
Other	3 (2%)	2 (1%)	5 (1%)
Body weight (kg)			
Mean (SD)	93 (18)	93 (18)	93 (18)
Range	58-145	56-152	56-152
Lead-in subgroup			
Monotherapy	16 (9%)	15 (8%)	31 (8%)
Sub-maximum therapy	43 (24%)	60 (33%)	103 (28%)
Maximum therapy	122 (67%)	109 (59%)	231 (63%)

5 Disposition

Table 3 shows weeks on double-blind treatment. Two hundred sixty-one (261) patients (72%) completed the study as assessed by the sponsor The discrepancy between totals for completers and Week 24 is due to the roughly 30 patients in each treatment group, called study completers by the sponsor, who completed at least 22 but not 24 weeks of treatment with double-blind medication. The dropout rate in the placebo group was not constant over time, reaching a peak between Weeks 12 and 16.

Table 3. Weeks on double-blind medication [1]

	Rosiglitazone	Placebo	Total
Baseline	181 (100%)	184 (100%)	365 (100%)
Week 4	177 (98%)	179 (97%)	356 (98%)
Week 8	172 (95%)	175 (95%)	347 (95%)
Week 12	167 (92%)	166 (90%)	333 (91%)
Week 16	162 (90%)	144 (78%)	306 (84%)
Week 20	154 (85%)	129 (70%)	283 (78%)
Week 22 [2]	146 (81%)	118 (64%)	264 (72%)
Week 24	113 (62%)	88 (48%)	201 (55%)
Completers [3]	145 (80%)	116 (63%)	261 (72%)
ITT endpoint	177 (98%)	178 (97%)	355 (97%)

[1] Weeks on double-blind medication was computed by taking days on DB medication (electronic data provided by the sponsor) and dividing by 7.
[2] Week 22 was not a scheduled visit during the study but is shown here to provide additional on-study data
[3] Sponsor's designation

Table 4 lists reasons for discontinuation. Patients discontinued early from the study primarily due to lack of glycemic control; ¾ of these patients were in the placebo group. Other reasons for discontinuation were roughly balanced between the groups.

Table 4. Reasons for discontinuation

	Rosiglitazone (n=181)	Placebo (n=184)	Total (n=365)
AE other than hypo/hyperglycemia	9 (5%)	5 (3%)	14 (4%)
Lack of glycemic control	16 (9%)	46 (25%)	62 (17%)
Subject request	5 (3%)	9 (5%)	14 (4%)
Lost/FU	3 (2%)	3 (2%)	6 (2%)
Hypoglycemia	1 (1%)	0	1 (<1%)
Other	2 (1%)	5 (3%)	7 (2%)
Total	36 (20%)	68 (37%)	104 (29%)

6 Efficacy

6.1 HbA1c

The primary endpoint was HbA1c change from baseline. Baseline was defined as the last measurement prior to the start of double-blind study medication but not more than 28 days prior to that.

The protocol-specified statistical model was ANCOVA with terms for treatment and baseline HbA1c (the covariate). Departures from parallelism in the model were to assessed by including a treatment–by baseline interaction term. If the interaction term was significant at the 10% level, the sponsor intended to "examine visually" the interaction using regression lines for each treatment group. Regression lines that crossed would constitute visual evidence of a qualitative treatment-by-baseline interaction.

Table 5 shows results for HbA1c change from baseline and adjusted change from baseline from the ANCOVA model. HbA1c values were significantly reduced for rosiglitazone compared to placebo ($p<.001$). These results agree with the sponsor's results and the numbers in the label. The raw and adjusted results are virtually identical due to the fact that baseline values were so similar between the groups

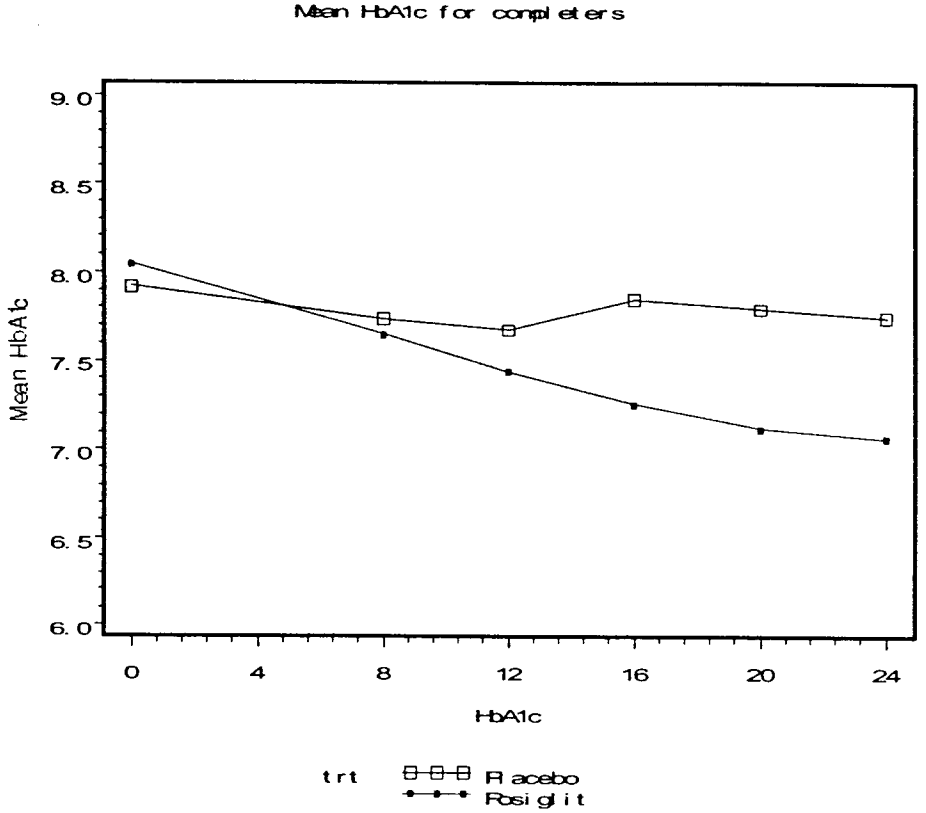
Table 5. HbA1c (%) results
ITT population (LOCF) [1]

	Rosiglitazone (n=177)	Placebo (n=178)
Baseline Mean (SD) Range	 8.14 (0.86) (6.1, 10.8)	 8.09 (0.80) (6.7, 10.5)
Endpoint mean (SD) Completers [1,2] mean (SD)	 7.23 (0.94)	 8.21 (1.18)
Change from baseline Mean (SE) Adjusted mean (SE)	 -0.91 (0.07) -0.91 (0.07)	 +0.12 (0.07) +0.11 (0.07)
Adj. Treatment difference Mean (SE) 95% CI P-value	 -1.02 (0.09) (-1.20, -0.83) <.001	

[1] Except for completers data which is a subset of ITT
[2] Sponsor's designation
note: SD=standard deviation, SE=standard error

Figure 1 shows mean HbA1c over time for completers.

Figure 1



The treatment-by-baseline interaction term in the ANCOVA was statistically significant (p=.005). Figure 2 shows regression plots of change from baseline vs baseline by treatment group. The significant interaction shows up as non-parallel regression lines which, however, do not cross over the range of baseline values seen in the study. This pattern of regression lines has been seen in other trials of anti-diabetic agents. The non-parallelism indicates that the interaction is quantitative in nature, that is, the treatment difference always favors rosiglitazone and the baseline value affects only the magnitude of the treatment difference.

Figure 2

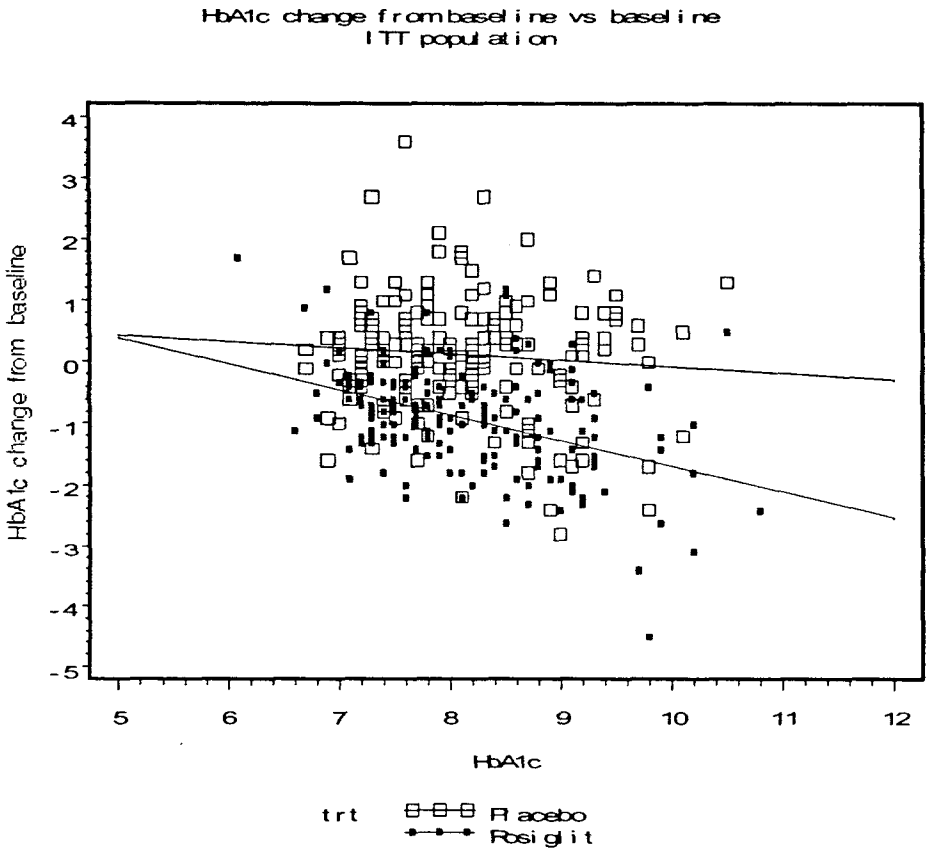


Table 6 shows treatment means by cohorts defined by the last available HbA1c observation on study ("dropout cohorts"). Results for dropouts (cohorts for Weeks 8, 12, 16 and 20) were consistent with the overall results, i.e., the treatment difference in each cohort favored rosiglitazone over placebo. The ITT analysis results for rosiglitazone were somewhat better than results for completers due to the carrying forward of larger mean treatment differences for dropouts.

Figure 3 shows HbA1c values over time for each dropout cohort.

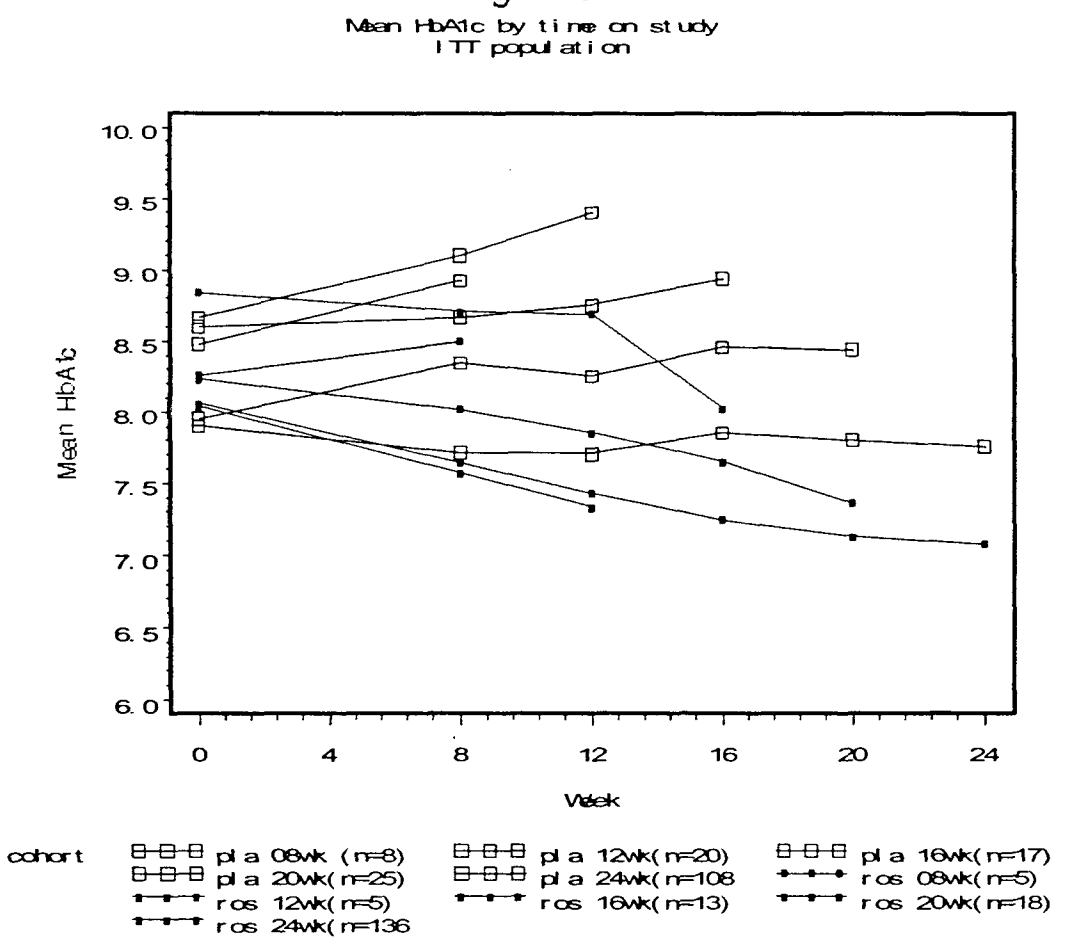
Table 6. HbA1c change from baseline (%) by dropout cohort [1]
ITT population

	Rosiglitazone (n=177)	Placebo (n=178)	Treatment difference
Week 8	+0.24 (n=5)	+0.45 (n=8)	-0.21
Week 12	-0.70 (n=5)	+0.74 (n=20)	-1.44
Week 16	-0.81 (n=13)	+0.34 (n=17)	-1.15
Week 20	-0.87 (n=18)	+0.49 (n=25)	-1.36
Week 24 [2]	-0.98 (n=136)	-0.15 (n=108)	-0.83

[1] A dropout cohort is a group of patients defined by the time of last observation on study

[2] Some patients were categorized as completers by the sponsor but did not have Week 24 data.

Figure 3



Efficacy in subgroups

Interactions between treatment and age, race and sex subgroups were examined in separate statistical models. Effects for the subgroup and the interaction of the subgroup with treatment were added to the protocol-specified model. The categories used for analysis of race were Black, Caucasian, Asian/ Pacific Islander, Hispanic/ Latin and Other. Age was analyzed as 2 categories: <65 years and ≥65 years.

The race-by-treatment and age-by-treatment interactions were not statistically significant (p. ≥38).

The sex-by-treatment interaction was nominally statistically significant at the 10% level (p=.082). The interaction was also statistically significant after adjusting for baseline weight or BMI. As seen in the table below, females had larger mean treatment differences than males:

	Females		Males	
	rosiglitazone	placebo	rosiglitazone	placebo
HbA1c change from baseline	-0.99 (n=74)	+0.23 (n=69)	-0.86 (n=103)	+0.04 (n=109)
Treatment difference	-1.22		-0.90	
Interaction p-value	p=.082			

Glucovance Lead-in subgroups

The sponsor presented HbA1c results by Glucovance (lead-in) dose and lead-in duration (addendum to Final Report; analysis plan submitted in Protocol Amendment #1.) Lead-in (LI) subgroup classifications were (1) maximum Glucovance combination (2 week LI), sub-maximum Glucovance combination (12 week LI) and monotherapy (12 week LI). All rosiglitazone LI subgroups had nominally significant (p<.05) differences in HbA1c change from baseline compared to the corresponding placebo subgroup. There were no differences between subgroups in HbA1c at endpoint. Table 7 shows HbA1c results by LI subgroup which agree with the sponsor's data.

Table 7. HbA1c results by lead-in (LI) subgroup

	Monotherapy (12-week LI)		Sub max comb (12-week LI)		Max comb (2-week LI)	
	Rosi (n=16)	Placebo (n=14)	Rosi (n=42)	Placebo (n=57)	Rosi (n=119)	Placebo (n=107)
Baseline mean (SE)	7.78 (0.19)	7.66 (0.15)	8.22 (0.13)	8.05 (0.10)	8.16 (0.08)	8.16 (0.08)
Endpoint mean (SE)	7.16 (0.25)	7.67 (0.19)	7.19 (0.13)	8.22 (0.14)	7.25 (0.09)	8.27 (0.12)
Adjusted [1] mean change from baseline (SE)	-0.61 (0.17)	0.00 (0.18)	-1.00 (0.13)	+0.14 (0.11)	-0.92 (0.08)	+0.10 (0.09)
Adj [1] trt difference Mean 95% CI	-0.60 (0.09, 1.12)		-1.14 (0.81, 1.47)		-1.02 (0.78, 1.26)	

[1] Estimates adjusted for baseline differences between groups

Figure 4 shows values during Lead-in and double-blind periods by LI subgroup.

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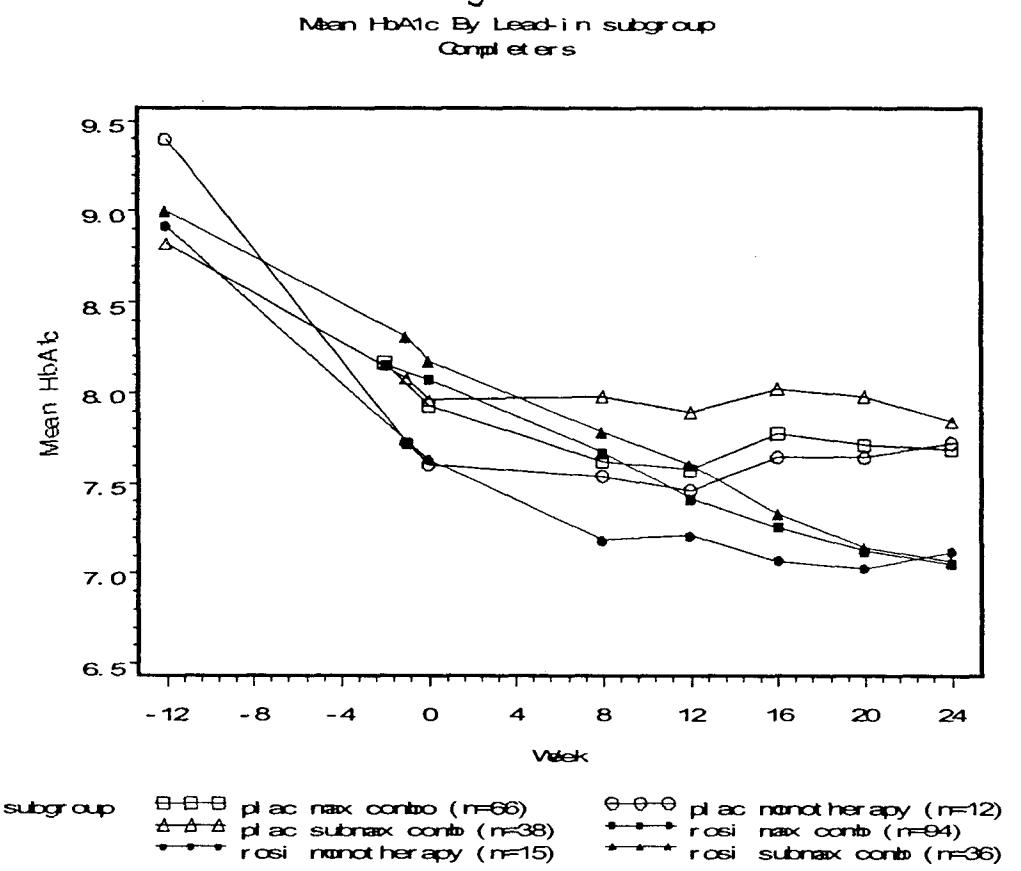
Figure 4



6.2 Fasting plasma glucose

Table 8 shows efficacy results for FPG. FPG values were significantly reduced for rosiglitazone compared to placebo ($p<.001$). These results agreed with the sponsor's results and the numbers in the label. The sponsor used only those samples drawn in the fasting state.

Table 8. Fasting plasma glucose (mg/dL) results
ITT population (LOCF)

	Rosiglitazone (n=176)	Placebo (n=181)
Baseline		
Mean (SD)	178 (45)	173 (46)
Range	(57, 284)	(70, 307)
Endpoint mean (SD)	136 (43)	181 (52)
Change from baseline		
Mean (SE)	-42 (3)	+8 (3)
Adjusted mean (SE)	-41 (3)	+7 (3)
Adj. Treatment difference		
Mean (SE)	-49 (4)	
95% CI	(-57, -41)	
P-value	<.001	

7 Safety

7.1 Weight

Patients receiving rosiglitazone experienced statistically significantly greater weight gains compared to placebo patients (Table 9, p<.001). The mean and median weight gains in the rosiglitazone group were approximately 3kg.

Table 9. Weight change from baseline (kg)
ITT population (LOCF)

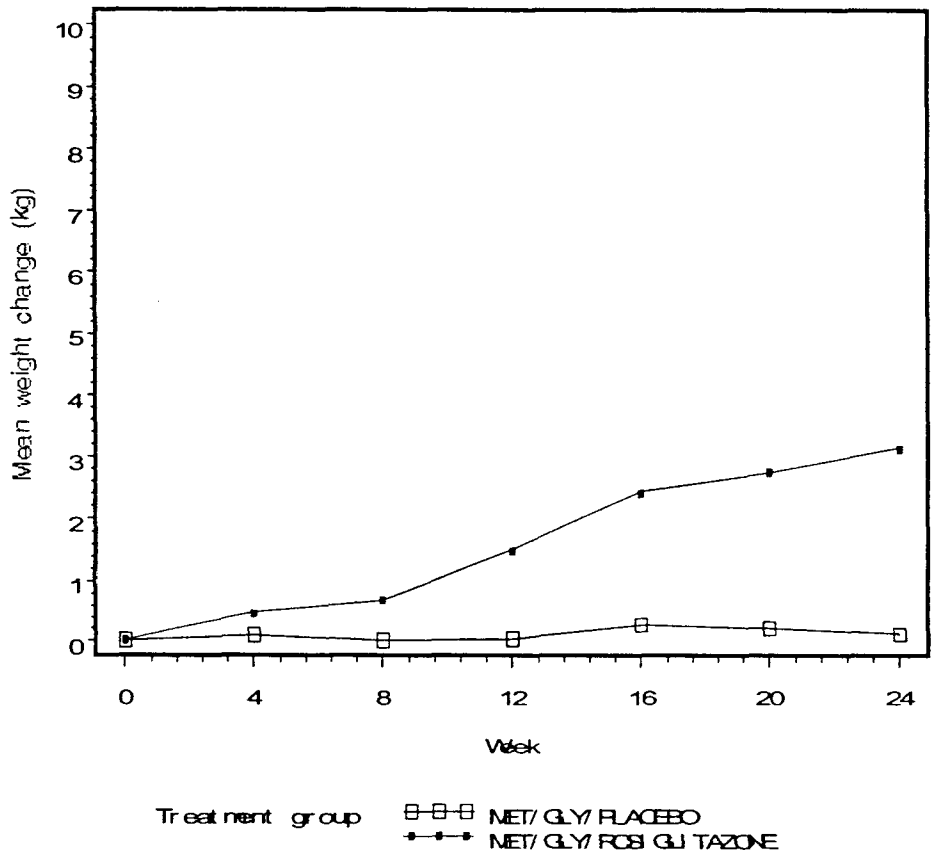
	Rosiglitazone (n=180)	Placebo (n=182)
Baseline Mean (SD)	93.3 (18.2)	92.7 (17.6)
Endpoint mean (SD)	96.3 (19.0)	92.8 (17.9)
Change from baseline		
mean (SD)	+3.0 (3.6)	+0.0 (2.5)
median (25^{th}, 75^{th})	+2.8 (+1.0, +5.1)	-0.2 (-1.4, +1.4)
Treatment difference: change from baseline		
Mean (SE)	-3.0 (0.3)	
95% CI	(-3.7, -2.4)	
P-value	<.001	

Patients receiving rosiglitazone experienced increasing weight gain over the 24 weeks with no evident plateauing of effect by the end of the trial.

Figure 5 shows the time course of baseline changes in weight for completers.

Figure 5

Mean baseline change in weight for completers

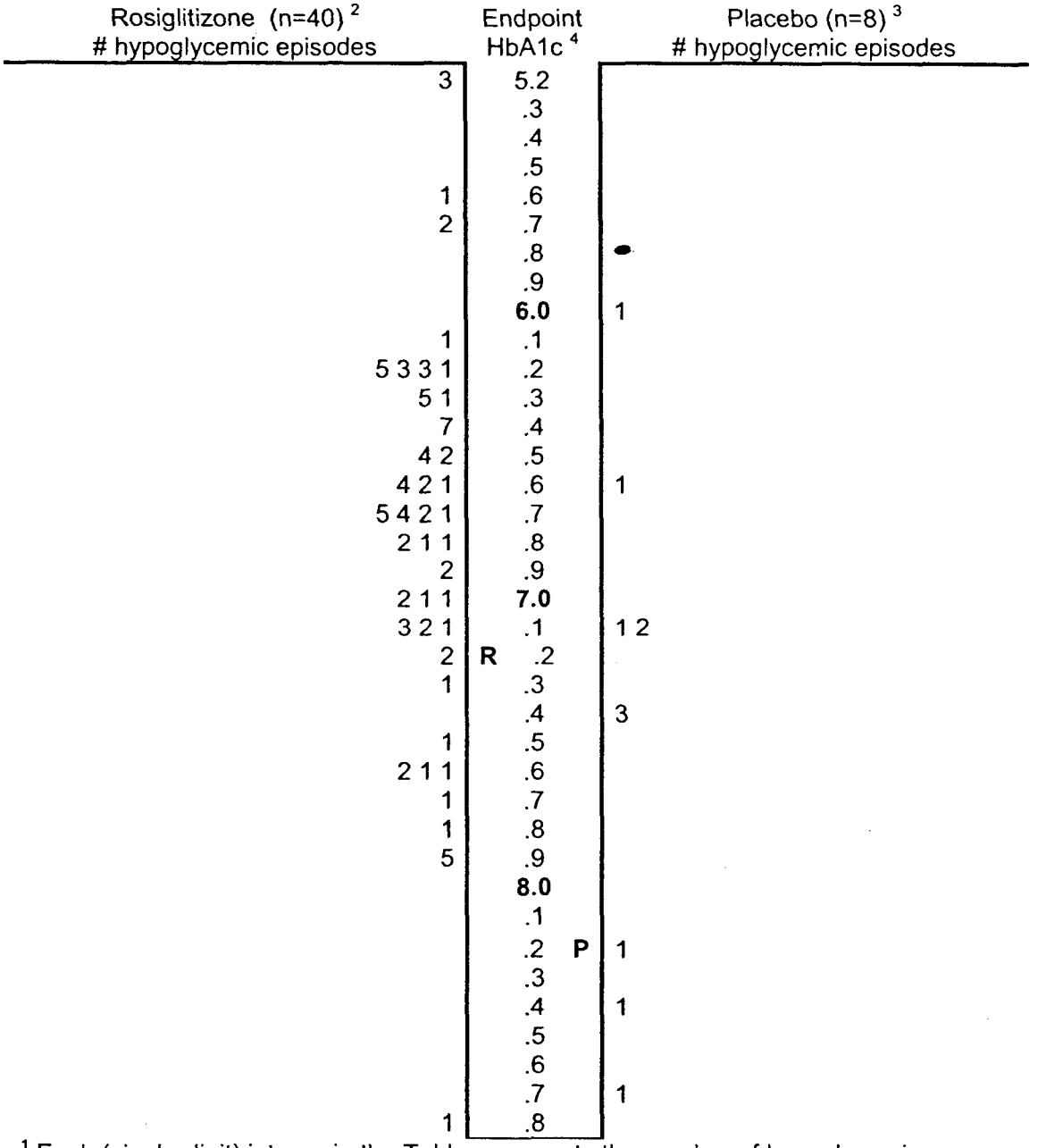


7.2 Hypoglycemia

In consultation with the medical reviewer, this reviewer confined the analysis of hypoglycemic episodes to those episodes also accompanied by fingerstick blood glucose levels < 50 mg/dL Occurences of hypoglycemic events, their severity and fingerstick glucose value at the time of the event were recorded in patient diaries.

Figure 6 is a stem and leaf plot showing the number of hypoglycemic episodes experienced by each patient as a function of the final HbA1c value. *Each single-digit integer in the Figure represents the number of hypoglycemic episodes for one patient.* (No patient experienced more than 7 episodes with fingerstick values ≤ 50 mg/dL.)

Figure 6. Number of hypoglycemic episodes with fingerstick glucose values ≤50 mg/dL for all patients with at least one on-treatment episode ordered by endpoint HbA1c value [1]



[1] Each (single-digit) integer in the Table represents the number of hypoglycemic episodes for one patient.

[2] 141 rosiglitizone patients (78%) did not have any hypoglycemic episodes with fingerstick glucose values ≤ 50 mg/dL

[3] 178 placebo patients (97%) did not have any hypoglycemic episodes with fingerstick glucose values ≤50 mg/dL

[4] **R** = rosiglitizone mean endpoint HbA1c value (7.2%), **P** = placebo mean (8.2%)

It should be borne in mind that Hba1c is itself an outcome variable and therefore one cannot make meaningful treatment group comparisons on rates of hypoglycemia at comparable levels of HbA1c. Nevertheless, the figure illustrates several important points:

- A statistically significantly greater percentage of patients taking rosiglitazone + Glucovance had at least one episode of hypoglycemia (22%) than did patients taking placebo + Glucovance (3%) (chi-square, p<.0001).

- In the subset of patients having at least one hypoglycemic episode during the trial, rosiglitazone patients had more episodes on average (mean 2.4) than placebo patients (mean 1.4). Although Glucovance dose reductions were mandated for patients when FBG was <50 mg/dL on multiple occasions, and many more rosiglitazone patients had Glucovance dose reductions than did placebo patients (18 patients vs 1 patient), these precautions did not prevent rosiglitazone patients from having many more recurrent episodes.

- There was a trade-off between benefit (lower HbA1c with rosiglitazone) and risk (higher overall incidence and rates of hypoglycemia with rosiglitazone). A question related to the trade-off could be posed: Was the trade-off "equal" in the sense that patients in the two groups *with the same benefit* (HbA1c values) experienced comparable incidences of hypoglycemia? Answering this question statistically is difficult -- both HbA1c and hypoglycemia are outcome variables, so comparing treatment groups on one variable within equivalent levels of the other cannot be more than an exploratory (i.e., non-inferential) exercise since treatment groups defined by the subgroup may have quite different characteristics. Nevertheless, Table 9 shows that, in every HbA1c category except one, a higher percentage of rosiglitazone patients had at least one episode of hypoglycemia compared to placebo patients achieving the same approximate endpoint HbA1c value. The only HbA1c category having a higher percentage of placebo patients with hypoglycemia (HbA1c between 8.1 and 8.5) is not associated with a high risk of hypoglycemia.

Table 9. Percentages of patients with at least one episode of hypoglycemia (fingerstick value 50 or below) by endpoint HbA1c[1]

HbA1c:	< 6.1	6.1-6.5	6.6-7.0	7.1-7.5	7.6-8.0	8.1-8.5	8.6-9.0	> 9.0
Rosi	3/13 (23%)	10/26 (38%)	14/44 (32%)	6/40 (15%)	6/21 (29%)	0/15 (0%)	1/12 (8%)	0/6 (0%)
Plac	1/5 (20%)	0/5 (0%)	1/17 (6%)	3/28 (11%)	0/32 (0%)	2/28 (7%)	1/25 (4%)	0/38 (0%)

[1] Sponsor's Table 12.5.2G3 has a similar format to this table but uses different HbA1c endpoint categories (≤6.5, 6.6-7.0, 7.1-8.0 and >8.0).

8 Labelling recommendations

1. The trial demonstrated the efficacy of rosiglitazone compared to placebo when added to Glucovance background therapy; it says nothing about the efficacy of Glucovance. In fact, the trial was conducted in patients who failed to achieve adequate control with Glucovance. It is this reviewer's opinion that the trial results should be put in the rosiglitazone label and not in the Glucovance label. Putting the results in the Glucovance label, even if the efficacy findings were presented fairly, nevertheless could give patients and physicians the mistaken impression that Glucovance was shown to be effective.in this trial.

If the Medical Division determines that it is in the best interests of patients and physicians to put the results in the Glucovance label, at a minimum it should be made absolutely clear that inferences concern rosiglitazone only and that Glucovance was background therapy for all patients. For the Table, in headings of columns for treatment groups, refer only to rosiglitazone and placebo and delete reference to Glucovance.

2. Hypoglycemia data is presented as % of patients having at least one event which obscures the fact that many patients had multiple events. Emphasize the recurrent nature of hypoglycemic events observed in the trial by including a statement "rosiglitazone patients who experienced at least one event of hypoglycemia averaged 2.4 episodes during the trial".

3. In the section describing hypoglycemia, the trial is described as [redacted] This trial was not a controlled trial of Glucovance; it was a controlled trial of rosiglitzone and the wording should be changed to clearly reflect what was test drug and what was background therapy. In addition, the language should emphasize the statistically significant difference (p<.0001) in incidences of hypoglycemia between groups: The first sentence should read [redacted]

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius

Cc:
NDA 21-178/SE1-004
HFD-510/JWeber, RMisbin, DOrloff
HFD-715/ENevius, TSahlroot
HFD-700/CAnello

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