CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-178

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

JUL 1 1 2000

NDA#: 21-178

Applicant: Bristol-Myers Squibb Company

Name of Drug: Glucovance® (Metformin HCl/Glyburide) Tablets

Indication: Type 2 Diabetes

Document Reviewed: 1.1, 1.25-1.52
Submission dated September 30, 1999

Medical Reviewer: This review has been discussed with the clinical reviewer, Robert Misbin, M.D. (HFD-510)

NDA 21-178

1. Introduction

This NDA presented results of two double-blind, controlled trials to support safety and efficacy of fixed combination metformin/glyburide tablets. Protocol CV 138-019 investigated combination therapy in type 2 diabetics who have inadequate glycemic control with diet and exercise. Protocol CV 138-011 investigated combination therapy in type 2 diabetics who have inadequate glycemic control with sulfonylurea therapy. The 3 strengths of metformin hydrochloride-glyburide combination tablets studied were 250mg/1.25mg, 500mg/2.5mg, and 500mg/5.0mg. The rationale for using combination as a first line therapy in naive patients was that glycemic control may be achieved at lower doses than either monotherapy with comparable or fewer potential side effects of the individual agents and with the same ease of administration.

2. Protocol CV 138-019

Study Design

This was a double-blind, randomized, placebo-controlled, multicenter, 5-arm study of Glucovance for 20 weeks as first line therapy in type 2 diabetics with inadequate glycemic control (HbA_{1c} >7%) on diet and exercise. The primary objective in the protocol was to compare two fixed combination metformin/glyburide tablet dosage strengths, titrated for glycemic control, on the reduction of HbA_{1c} level versus placebo. Eligible subjects entered a 2-week single-blind placebo lead-in phase (Period A) with placebo once daily during Week 1 and twice daily during Week 2. In Period B, eligible subjects were randomized to enter a 4-week, double-blind, once daily stable dosing of either placebo, glyburide 2.5 mg, metformin 500 mg, fixed combination metformin/glyburide 250/1.25 mg, or fixed combination metformin/glyburide 500/2.5 mg. Subjects then entered a 28-week titration/stable-dosing phase (Period C) with an initial 4-week titration segment followed by a 24-week stable dose phase.

Study medication was titrated to the next dose level if subjects had a FPG and a 5-day mean daily glucose level>= 126 mg/dL with no evidence of hypoglycemia; or an FPG>100 mg/dl but ≤126 mg/dl and a 5-day mean daily glucose of >140 mg/dl with no evidence of hypoglycemia. The maximum titrated daily doses of study medication were: glyburide 10 mg, metformin 2000 mg, fixed combination metformin/glyburide 1000/5 mg, or fixed combination metformin/glyburide 2000/10 mg.

In Period D, patients entered a long-term open-label treatment of fixed combination metformin/glyburide therapy. The long-term, open-label data will be the subject of a separate report. Table 1 is a summary of the study scheme.

Table 1. Summary of the First-Line Study Scheme

Trial Period			
A (2 weeks)	B (4 weeks)	C (28 weeks)	
single-blind, placebo lead-in	double-blind, once daily, stable dosing	titration 4 weeks	stable dosing 24 weeks
Randomization		# of tablets 2 → 3 → 4	maximum titrated daily dose
Daily Placebo Once | Twice	glucovance 500/2.5	→1000/5 →1500/7.5	→ 2000/10 mg
	glucovance 250/1.25	→500/2.5 →750/3.75	→1000/5 mg
	metformin 500 mg	→1000 →1500	→ 2000 mg
	glyburide 2.5 mg	→5 → 7.5	→ 10 mg
	placebo	→ → →	

The primary efficacy variable was the change from baseline in HbA_{1c} levels at Week 20 of the double-blind treatment. The secondary efficacy variables were levels of FBG, fructosamine, fasting and 2-hour PPPG, and insulin levels, serum lipid levels (total cholesterol, HDL, LDL and triglycerides), body weight.

Statistical Methods

The analysis population included all randomized subjects with a baseline measurement and at least one post-baseline measurement.

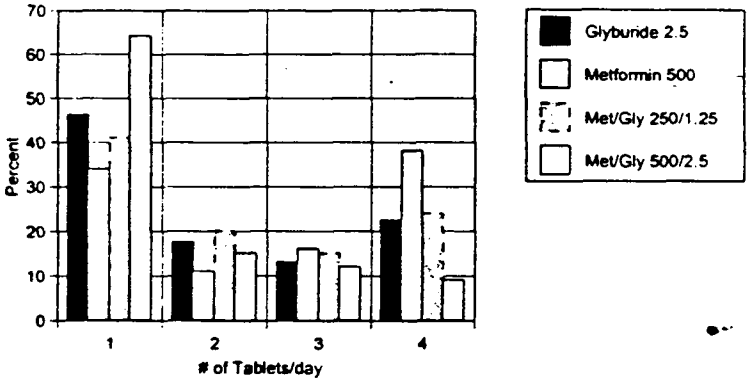
The primary efficacy outcome was the change in HbA_{1c} from baseline to Week 20 after randomization or the last measurement carried forward to Week 20 if no Week 20 measurement was available. The primary comparisons were between each of the 2 combination treatment groups and the placebo group. The 2 comparisons were adjusted by Dunnett's procedure for multiplicity. In order to maintain an overall alpha level of 0.05, each comparison was performed at a nominal two-sided α=0.0271 level. Ninety-five percent confidence intervals for the differences between these treatment groups were constructed using the critical values corresponding to Dunnett's method. For all other efficacy comparisons the tests or confidence intervals were unadjusted. The ANCOVA was performed on the change in HbA_{1c}. The model included treatment effect with baseline HbA_{1c} value as a covariate and the treatment-by-baseline interaction term to assess the parallelism assumption in the ANCOVA model. If a severe qualitative interaction (crossing of the regression lines) occurred, the two treatment groups would not be compared.

Patient Disposition

A total of 847 subjects entered the single-blind, placebo lead-in phase. Of these, 806 subjects were randomized and 533 (66%) subjects completed the double blind therapy. Table 2 displays patient disposition.

Table 2 Patient Disposition – Study 019

	Placebo	Gly 2.5 mg	Met 500mg	Met/Gly 250/1.25mg	Met/Gly 500/2.5 mg	Total
Randomized	161	161	161	158	165	806
Discontinue	88 (55%)	55 (34%)	51 (32%)	34 (22%)	45 (27%)	273 (34%)
Lack of Efficacy	65 (40%)	24 (15%)	26 (16%)	8 (5%)	10 (6%)	133 (17%)
Adverse Event	3 (2%)	11 (7%)	9 (6%)	6 (4%)	18 (11%)	47(6%)
Withdrew Consent	9 (6%)	10 (6%)	4 (3%)	12 (8%)	11 (7%)	46(6%)
Lost to Follow-up	4 (3%)	6 (4%)	7 (4%)	5 (3%)	2 (1%)	24(3%)
Non-Compliance	1 (0.6%)	1(0.6%)	1 (0.6)	2(1%)	1(0.6%)	6(0.7%)
Death	0	0	1 (0.6%)	0	0	1(0.1%)
Other	6 (4%)	3 (2%)	3 (2%)	1(0.6%)	3 (2%)	16(2%)
Completed	73 (45%)	106 (66%)	110 (68%)	124 (79%)	120 (73%)	533(66%)



Efficacy Results - Study 019

HbA_{1c} was measured at baseline, Weeks 20 and 32 post baseline. The primary efficacy variable was HbA_{1c} change from baseline to Week 20 of double blind treatment (4 weeks once daily stable dosing, 4 weeks titration, and 12 weeks stable dosing). The primary comparisons are between the 2 fixed combination treatment groups to the placebo group.

Of the 806 randomized subjects, 75 (9%) were excluded from the primary analysis for reasons of no baseline measurement (n=2) or no post-baseline measurement (n=73). Table 5 displays the results of covariance analysis with baseline HbA_{1c} as covariate plus treatment, and treatment-by-baseline interaction in the model. From Dunnett adjusted LSM result, at the Week 20/endpoint, there were statistically significant greater reductions of HbA_{1c} in Metformin/Glyburide 250/1.25 mg, and 500/2.5 mg-treated patients than placebo-treated patients ($p<0.01$). Both combination groups were also nominally statistically significantly superior ($p<0.05$) to both monotherapy groups on the primary endpoint. This reviewer verified the sponsor's results and furthermore that the treatment-by-baseline interaction in the ANCOVA analysis was statistically significant ($p<0.01$). Figure 1 displays the linear regression of HbA_{1c} change from baseline on baseline HbA_{1c} by the 5 treatment groups. A look at the regression lines indicates that the treatment differences with placebo are greater at a high HbA_{1c} baseline level than at a low baseline level.

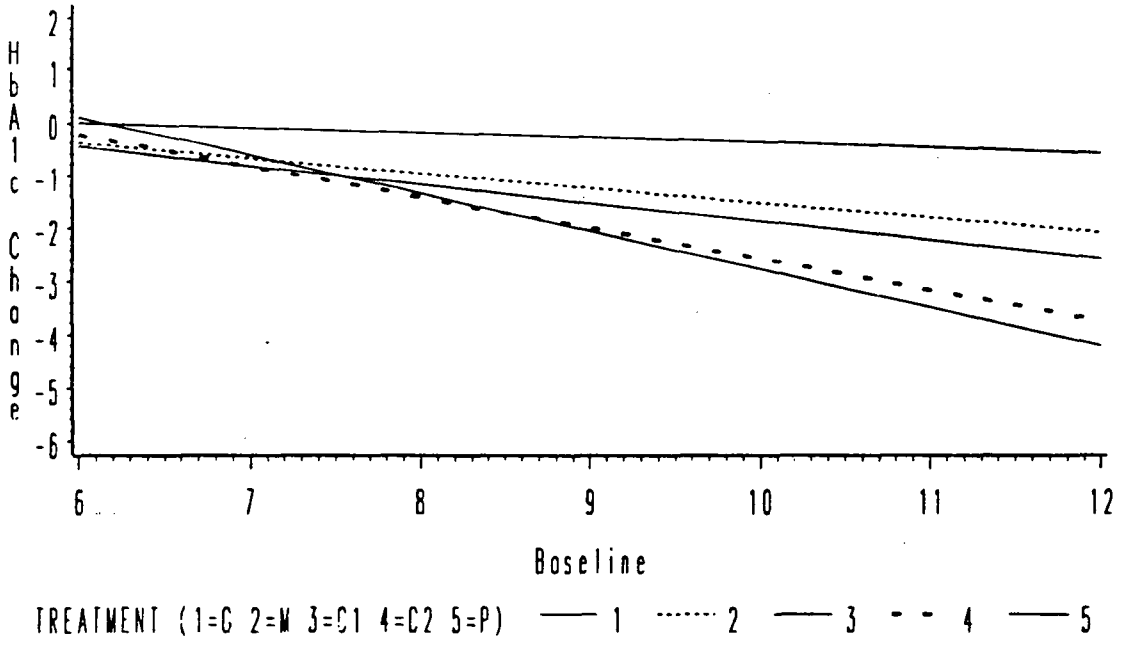
The assumption of parallelism in the ANCOVA model is not satisfied. The heterogeneity or nonparallel regression lines is quantitative, and not qualitative (crossover) in nature. However, the interpretation of the treatment effects becomes ambiguous because the effects are not consistent over the baseline HbA_{1c} levels. This differential treatment effect is further examined across baseline HbA_{1c} quartiles (Table 6 and Figure 3).

Table 5 Adjusted LSM* Change from Baseline in HbA_{1c} (%) to Week 20 (LOCF) – Study 19

	Placebo n=147	Gly 2.5 mg n=142	Met 500mg n=141	Met/Gly* 250/1.25mg n=149	Met/Gly* 500/2.5 mg n=152
Baseline Mean (SD)	8.14 (0.94)	8.23 (1.07)	8.22 (1.09)	8.20 (1.15)	8.14 (1.04)
Change from Baseline (SE)	-0.21 (0.07)	-1.23 (0.07)	-1.03 (0.07)	-1.48 (0.07)	-1.53 (0.07)
Difference from placebo		**-1.02**	**-0.82**	**-1.26**	**-1.31**
(95% C.I.)		(-1.22 -0.82)	(-1.02 -0.61)	(-1.47 -1.05)	(-1.52 -1.10)
p-value				<0.01	<0.01
Diff between Met/Gly and Gly (95% C.I.)				-0.24 (-0.44 -0.05)	-0.29 (-0.49 -0.10)
Diff between Met/Gly and Met 95% C.I.				-0.45 (-0.65 -0.25)	-0.50 (-0.69 -0.30)

* Least Squared Mean and C.I. are Adjusted by Dunnett procedure for the two comparisons between the combinations and the placebo

Figure 1 Regression of HbA_{1c} change from baseline to Week 20 on Baseline HbA_{1c}



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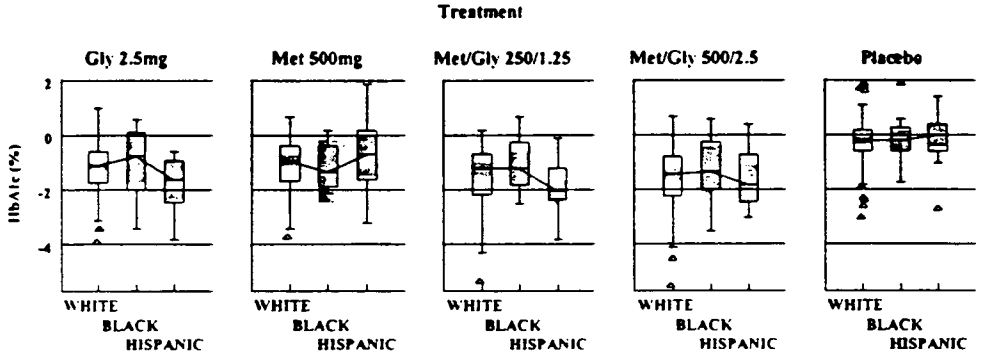
Subpopulations

The treatment-by-gender and the treatment-by-age interactions were not significant. The treatment-by-race interaction was significant when comparing the combination groups to the placebo group (=0.003). Figure 2 displays box plots of HbA_{1c} change from baseline to Week 20 by race. White, Hispanic, and Other subjects had greater mean reduction than Black subjects. However, the numbers of the subjects of the subgroups were too small to make meaningful conclusion.

Figure 2 Box Plots of HbA_{1c} Change from baseline to Week 20 by Race

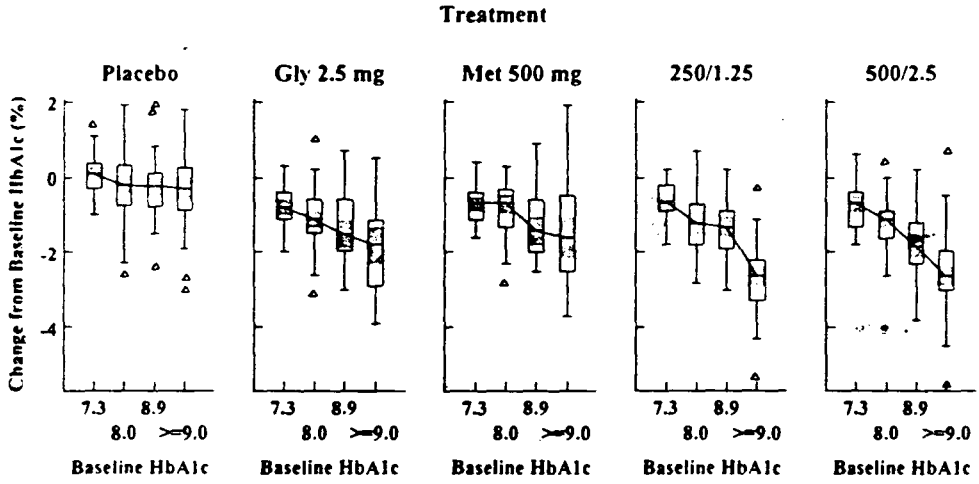


For all treatment groups greater reduction of HbA_{1c} was observed with larger baseline HbA_{1c}. Median changes of HbA_{1c} from baseline to week 20 by treatment groups for the 4 quartiles of baseline HbA_{1c} are displayed in Table 6 and Figure 3. Figure 3 provides another graphical representation of the statistically significant interaction between baseline HbA_{1c} and treatment.

Table 6 Median Change in HbA_{1c} (%) from Baseline to Week 20 by Baseline Quartiles

Baseline HbA_{1c} Quartiles	Placebo	Gly 2.5mg	Met 500mg	Met/Gly 250/1.25mg	Met/Gly 500/2.5 mg
Lower 6.2 – 7.3	n=32 0.1	n=32 -0.8	n=35 -0.7	n=38 -0.65	n=46 -0.7
2nd 7.4 - 8.0	n=51 -0.2	n=47 -1.1	n=39 -0.7	n=35 -1.2	n=29 -1.1
3rd 8.1 - 8.9	n=32 -0.25	n=32 -1.5	n=33 -1.4	n=33 -1.3	n=38 -1.85
Upper 9 – 11.4	n=32 -0.3	n=31 -1.8	n=34 -1.6	n=43 -2.6	n=39 -2.6

Figure 3 Box Plots of HbA_{1c} Change from Baseline to Week 20 by Baseline Quartiles



Mean HbA_{1c} levels from Baseline to Week 32

From Week 20 to Week 32, subjects remained on stable dosing. The purpose of the last 12 weeks of therapy was to assess durability of treatment. Mean HbA_{1c} levels from baseline to Week 32 are displayed in Table 7. and Figure 4.

Table 7 Mean HbA_{1c} Levels from Baseline to Week 32

Week	Placebo			Glyburide 2.5mg			Metformin 500mg			Met/Gly 250/1.25			Met/Gly 500/2.5		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
0	147	8.14	0.94	144	8.13	1.05	146	8.21	1.07	151	8.22	1.09	153	8.19	1.15
20	147	7.93	1.20	142	6.92	1.12	141	7.19	1.18	149	6.72	0.81	152	6.66	0.96
32	147	8.04	1.14	144	7.01	1.10	146	7.29	1.16	151	6.87	0.89	153	6.85	0.91

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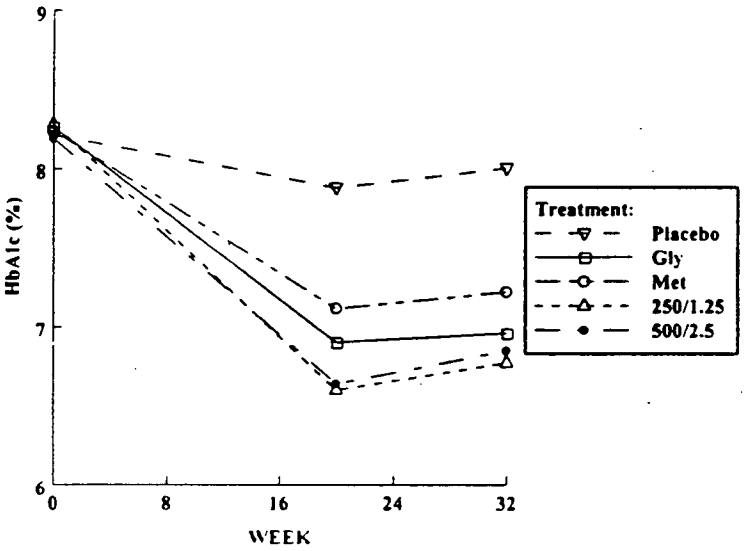
Figure 4 Mean HbA_{1c} Level Over Time (LOCF)



Body Weight

The two combination treatment groups had mean change in weight (from baseline to Week 20) of +1.4 and +1.9 kg compared to a -0.7 kg mean change for the placebo group. The differences from placebo were significant. The mean changes were +1.7 and -0.6 kg in the glyburide monotherapy and metformin monotherapy groups, respectively (Table 8).

Table 8 Mean Change in Body Weight (kg) from Baseline to Week 20

	Placebo n=152	Gly 2.5 mg n=146	Met 500mg n=150	Met/Gly* 250/1.25mg n=148	Met/Gly* 500/2.5 mg n=153
Baseline Mean (SD)	86.7 (16.5)	86.7 (15.3)	89.0 (15.1)	89.2 (15.5)	86.9 (17.2)
Change from Baseline (SE)	-0.7 (0.3)	+.7 (0.3)	-0.6 (0.3)	+1.4 (0.3)	+1.9 (0.3)
Difference from placebo		**2.4**	**0.1**	**2.0**	**2.6**
(95% C.I.)		(1.6, 3.2)	(-0.7, 0.8)	(1.2, 2.9)	(1.7, 3.5)
p-value				<0.01	<0.01
Diff between Met/Gly and Gly (95% C.I.)				-0.4 (-1.1, 0.4)	0.2 (-0.5, 1.0)
Diff between Met/Gly and Met 95% C.I.				2.0 (1.2, 2.7)	2.5 (1.8, 3.3)

Safety Analysis

For the first line treatment, the combination therapy was expected to achieve glycemic control with trends toward decreased adverse events as compared with either agent alone. In the study protocol, the trends in hypoglycemia (compared with slufonylurea alone), gastrointestinal symptoms (compared with metformin alone), and lactate levels were to be assessed without pre-specified analysis planed for safety data. In the study report, the sponsor decided to perform ad-hoc analysis on the hypoglycemic events and the gastrointestinal events comparing to sulfonylurea and metformin, respectively.

In comparison with glyburide monotherapy, the low dose (250/1.25 mg) combination group had statistically significantly fewer reported hypoglycemic events and the medium dose (500/2.5 mg) combination group had a statistically significantly greater hypoglycemic events (Table 9).

Table 9 Number of Subjects with Treatment Emergent Adverse Events of Hypoglycemia or Hypoglycemic Symptoms as Reported by the Investigator

	Placebo	Gly 2.5mg	Met 500mg	Met/Gly 250/1.25mg	Met/Gly 500/2.5 mg
# (%) with event	5 (3.1)	34 (21.3%)	5 (3.1%)	18 (11.4%)	61 (37.7%)
p-value				0.022	0.001

For treatment-emergent gastrointestinal side effects, the low dose (250/1.25 mg) combination had statistically significantly fewer reported side effects when compared to metformin monotherapy. For the medium dose (500/2.5 mg), the incidence of gastrointestinal adverse events was not different from the incidence of the metformin monotherapy (Table 10).

Table 10 Number of Subjects with Treatment Emergent Gastrointestinal Adverse Events

	Placebo	Gly 2.5mg	Met 500mg	Met/Gly 250/1.25mg	Met/Gly 500/2.5 mg
# (%) with event	39 (24.2%)	38(23.8%)	69 (43.4%)	50 (31.6%)	62 (38.3%)
p-value				0.037	n/a

3. Protocol CV 138-011

Study Design

This was a multicenter, randomized, double-blind study of two fixed combination metformin/glyburide tablets (500/2.5 mg and 500/5 mg) in subjects with Type 2 diabetes who failed glycemic control (FPG≥126mg/dL and HbA_{1c}≥7.4%) on at least half maximum doses of sulfonylurea therapy. The objective was to compare, after 16 weeks of two fixed combination metformin/glyburide tablet dosage strengths, titrated for glycemic control, the reduction of HbA_{1c} level to metformin alone and with glyburide alone. Eligible subjects entered a 2-week single-blind glyburide lead-in phase (Period A). Subjects received glyburide 5 mg BID during the first week of Period A and were titrated to glyburide 10 mg BID during the second week. Starting at the 16-week double-blind treatment phase (period B), eligible subjects with HbA_{1c} at screening ≥7.4% and FPG levels at ≥126 mg/dL after one week maximum dose of glyburide were randomized to receive either glyburide 20 mg, metformin 500 mg, fixed combination metformin/glyburide 500 mg/2.5 mg, or fixed combination metformin/glyburide 500 mg/5 mg. The Glyburide monotherapy group received a fixed daily dose of 20 mg. The Metformin monotherapy and both fixed combination metformin/glyburide therapies were titrated throughout the double-blind period until either the maximum dose or a lower effective dose was reached according to the criteria of fasting glucose > 140 mg/dL. The maximum doses were: metformin 2000 mg, fixed combination metformin/glyburide 2000 mg/10 mg, and fixed combination metformin/glyburide 2000 mg/20 mg.

Subjects who completed Period B and those who prematurely discontinued were eligible for long-term, open-label treatment with the fixed combination treatment. The long-term, open-label data will be presented in a separate report.

The primary efficacy variable was the HbA_{1c} levels at Week 16 or the final visit.

The secondary efficacy variables were levels of FBG, fructosamine, fasting and 2-hour PPPG, and insulin levels, serum lipid levels (total cholesterol, HDL, LDL and triglycerides), body weight.

Statistical Methods

The analysis population for the efficacy variables included all randomized subjects with a baseline measurement and at least one post-baseline measurement.

The multiple comparisons of 2 combination groups to each monotherapy were adjusted by Dunnett's test. The comparisons of each combination to its individual components were performed using the Min Test of Laska and Meisner. The protocol statistical plan was altered in the

presentation of the results of the Min Test from 2-sided test to one-sided test. The literature presents Min Test as a one-tailed test. To conform to a 2-tailed test, the plan was to perform 2 one-tailed tests and double the smaller p-value. After unblinding the study, for some secondary variables, one of the monotherapy groups had superior results to the combination groups. The sponsor argues that "presentation of the results as 2-tailed tests would have been misleading and confusing, with small p-values suggesting trends toward superiority of combination therapy when trends actually favor monotherapy." To compensate for the one-tailed nature of the tests, the significance level of the testing was halved from 0.0271 to 0.0136.

In this reviewer's opinion, presenting 2-tailed tests is preferred as long as the few cases when monotherapy is superior are pointed out.

The analysis of variance with treatment as the only effect in the model was performed on the primary efficacy variable HbA_{1c} level at Week 16 or final visit.

Patient Disposition

A total of 717 subjects entered the glyburide lead-in period. Of these, 639 received randomized therapy with 521 (82%) subjects completing the double blind therapy. Table 11 displays patient disposition.

Table 11 Patient Disposition – Study 011

	Glyburide	Metformin	Met/Gly 500/2.5mg	Met/Gly 500/5.0mg	Total
Randomized	164	153	160	162	639
Discontinue	32 (20%)	46 (30%)	21 (13%)	19 (12%)	118 (19%)
Lack of Efficacy	15 (9%)	24 (16%)	2 (1%)	1 (1%)	42 (7%)
Adverse Event	5 (3%)	8 (5%)	5 (3%)	6 (4%)	24(4%)
Withdrew Consent	4 (2%)	9 (6%)	4 (3%)	7 (4%)	24(6%)
Lost to Follow-up	6 (4%)	3 (2%)	4 (3%)	2 (1%)	15(2%)
Prohibited Medication	0	0	0	1(0.6%)	1(0.2%)
Death	0	1 (0.7%)	2 (1.3%)	0	3(0.5%)
Other	2 (1. 2%)	1 (0.7%)	4(2.5%)	2 (1. 2%)	15(2.3%)
Completed	132 (81%)	107 (70%)	139 (87%)	143 (88%)	521(82%)

The most frequent reason for withdrawal was lack of glycemic control or lack of efficacy (~7%). For the metformin, glyburide, 500/2.5, and 500/5.0 treatment groups, the discontinuation rates were 16%, 9%, 1.3%, and 0.6%, respectively. Discontinuations due to adverse events and deaths occurred with the highest frequency in the metformin monotherapy treatment group (~6%), followed by the fixed combination treatment group (4%) and the glyburide monotherapy treatment group (3%).

Baseline Demography

The average age of subjects was 56 years (range 24-78). Subjects were predominately white (68%) and male (60%). The average body weight was 88.4 kg (range 48-138) with an average BMI of 30.4 kg/km^2 (range 18-46).

The mean duration of Type 2 diabetes mellitus was 7.4 years. The range was from 0.1 year to 38 years.

Baseline HbA_{1c} and FPG are displayed in Table 12.

Table 12 Baseline Means for Efficacy Variables – Study 11

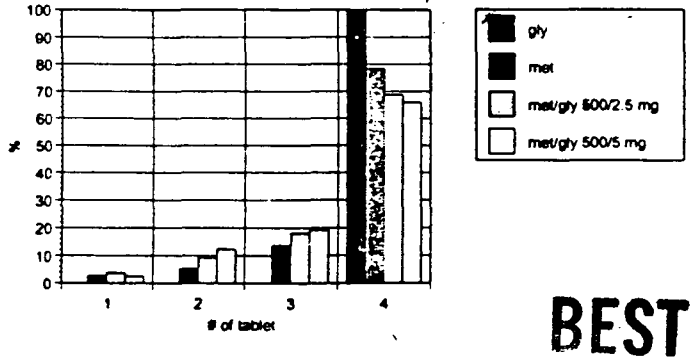
	Glyburide	Metformin	Met/Gly 500/2.5 mg	Met/Gly 500/5 mg	Total
N	164	153	160	162	639
HbA_{1c} (%)					
Mean, SD	**9.64** (1.44)	**9.51** (1.34)	**9.41** (1.47)	**9.42** (1.24)	**9.50** (1.37)
Range	(6.9, 13.4)	(6.3, 13.2)	(6.9, 13.9)	(6.9, 13.1)	(6.3, 13.9)
FPG (mg/dL)					
Mean, SD	**218** (52)	**213** (50)	**212** (51)	**210** (49)	**213** (50)
Range	(115, 386)	(116, 356)	(122, 350)	(101, 417)	(101, 417)

All randomized subjects received previous antihyperglycemic medications. The most frequently reported agents were glyburide (65%), glipizide (39%), and metformin (20%). Approximately 3% (n=17) of subjects received troglitazone and 2% (n=14) of subjects received insulin.

Table 13 and the figure that follows summarize the numbers and percentages of subjects receiving 1, 2, 3, 4 tablets per day during double-blind treatment. All subjects on glyburide monotherapy received maximum dose, ~ ¾ (78%) of metformin monotherpy received maximum dose. Approximately 2/3 of subjects received maximum dose for the combination therapies.

Table 13 Numbers (%) of Subjects by Daily Dose (Tablets)

Dose # of Tablets	Glyburide 5.0 mg n=164	Metformin 500 n=153	Met/Gly 500/2.5 n=160	Met/Gly 500/5.0 n=162
1	0	4 (2.6%)	6 (3.8%)	4 (2.5%)
2	0	8 (5.2%)	15 (9.4%)	20 (12.3%)
3	0	21 (14%)	29 (18%)	31 (19%)
4	164 (100%)	120 (78%)	110 (69%)	107 (66%)



Efficacy Results - Study 011

The primary efficacy variable was HbA_{1c} level at Week 16 or final visit. The primary efficacy variable was not change from baseline HbA_{1c} because the short duration of the glyburide run-in period might not allow the stabilization of HbA_{1c} at the time of the baseline measurement.

Of the 639 randomized subjects, 26 (4%) had no post-baseline measurement in HbA_{1c} level and were excluded from the primary efficacy analysis. Both fixed combination groups achieved statistically significant lower mean HbA_{1c} levels than both monotherapy groups (Table 14). The mean difference between both the combination groups and the glyburide group was -1.7%, whereas the mean difference between both the combination groups and the metformin group was -1.9%.

Table 14 Sample Size and ANOVA Results of Mean HbA_{1c} (%) at Week 16 or Final Visit – Study 11

	Glyburide	Met	Met/Gly 500/2.5 mg	Met/Gly 500/5 mg
N Randomized	164	153	160	162
No postbaseline measurement	6	11	6	3
Included in Analysis	158	142	154	159
Baseline Mean (SD)	9.63 (1.43)	9.51 (1.36)	9.43 (1.48)	9.44 (1.24)
Week 16/Final Mean (SE)	**9.61** (0.12)	**9.82** (0.12)	**7.92** (0.12)	**7.91** (0.12)
Change from baseline	-0.02	0.31	-1.51	-1.53
Diff between Met/Gly and Gly (95% C.I.)[1]			-1.69 (-2.06, -1.32)	-1.70 (-2.06, -1.33)
Diff between Met/Gly and Met (95% C.I.)[1]			-1.90 (-2.28, -1.52)	-1.91 (-2.29, -1.53)
Test for superiority of combination vs. monotherapies[2]			p<0.001	p<0.001

[1] 95% C.I. are Adjusted by Dunnett procedure for the two comparisons between the combinations and one control

[2] Min Test, one-sided significance level α=0.0136

Figure 5 displays box plots and Figure 6 displays HbA_{1c} levels over time.

Figure 5 Box Plots of HbA_{1c} by Weeks

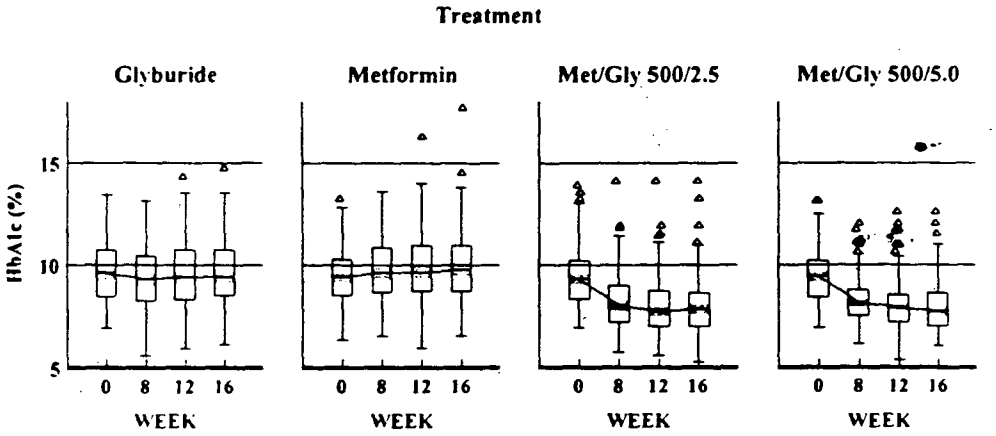
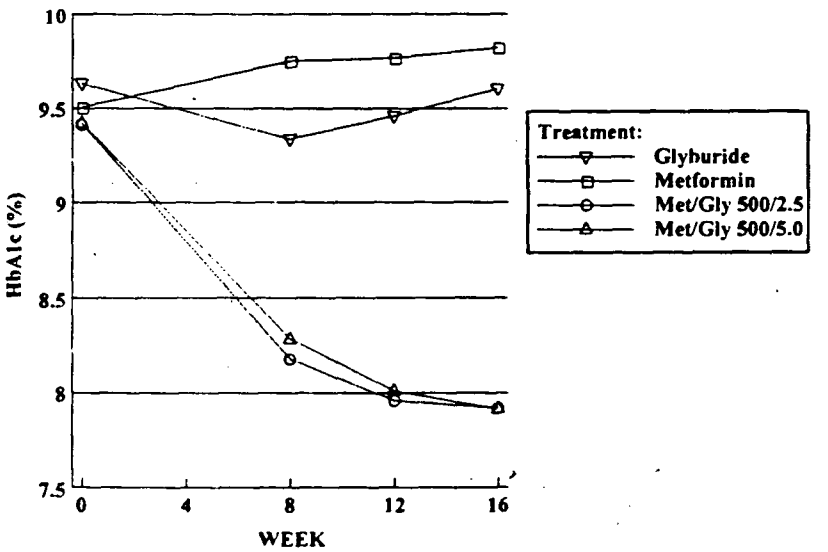


Figure 6 Mean HbA_{1c} Levels by Weeks



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Subgroup Analysis:

The interactions between treatment and gender, race, and age were examined. The treatment-by-race interaction was significant for the combination groups and the metformin group (p=0.01). In figure 7, median HbA_{1c} levels at Week 16 are lower in the Black subjects than in the White or Hispanic subjects for metformin monotherapy group whereas the opposite is true for all the other treatment groups (HbA_{1c} is lower in the White and Hispanic subjects than in the Black subjects). The sample sizes were smaller for Blacks ($n \leq 20$ per group) and Hispanics (n~25 per group) than Whites (n~100 per group). The sample sizes for subgroups were too small to make meaningful conclusion.

Figure 8 displays median HbA_{1c} at Week 16 for subjects ≤65 and >65 years of age.

Figure 7 Box Plots of HbA_{1c} Levels at Week 16 by Race – Study 11

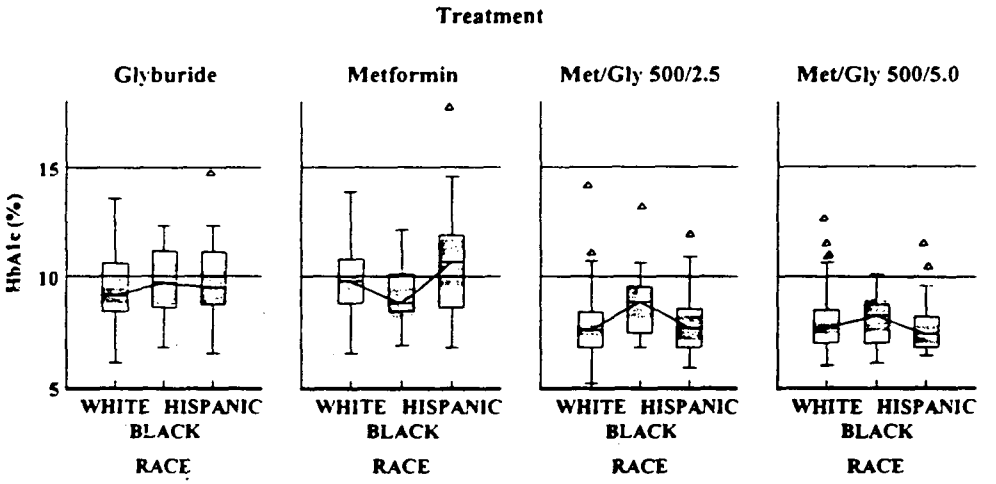
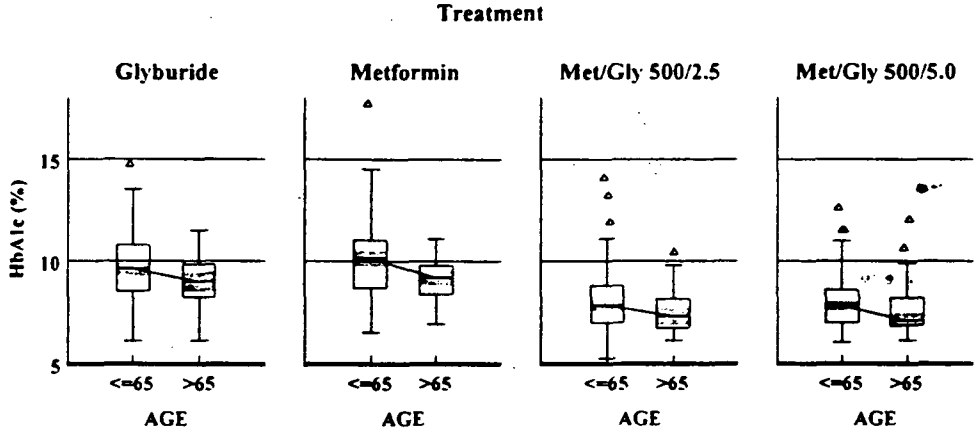


Figure 8 Box Plots of HbA_{1c} Levels by Age Group at Week 16



Body Weight

Subjects in the metformin group had a mean weight loss of 2.8 kg. Subjects in the glyburide and the two combination groups had a mean weight gain of 0.4, 0.8, and 0.5 kg, respectively.

Integrated Efficacy Summary:

As a first line therapy (Study 19) the combination therapies are statistically superior to placebo. As a second line therapy (Study 11), the combination therapies are superior to each of the monotherapies. The HbA_{1c} levels over time for the first line and second line studies are displayed in Figure 9.

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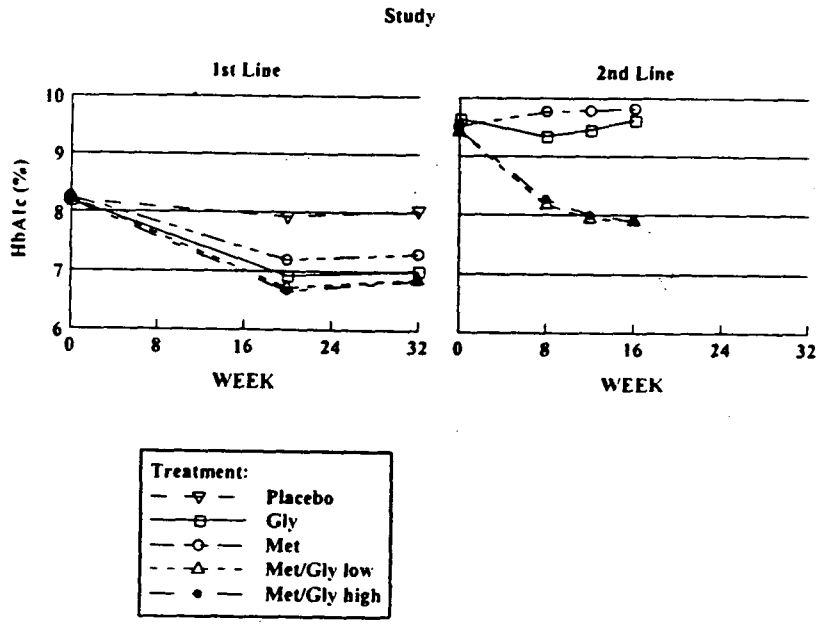
Figure 9 HbA_{1c} Levels over Time by Study



4. Labeling Comments:

1. For Initial Therapy in the Clinical Studies section, the sponsor claimed that [redacted] The study report (p. 116 Vol. 1.33) stated that "Statistical tests of the differences between fixed combination and monotherapy groups at Week 20 were not specified in the protocol statistical plan." The trial was designed to demonstrate superiority of the combinations to placebo. The Dunnett's multiple comparisons procedure applied to the primary comparison only (2 doses of combinations vs. placebo). The statistical tests between the combination and monotherapy groups were post-hoc.

2. The p-values for the comparisons between safety endpoints, gastrointestinal side effects and incidence of hypoglycemic symptoms) should not be displayed because the decision to perform statistical analyses was made after treatment assignments were unblinded. Only the descriptive statistics should be presented for the safety endpoint.

3. The sponsor presented available data for the first 26 weeks (glycemic control) of the open label part of the "Initial Therapy" trial in Table 2. Since the open label portion of the trial is not randomized or controlled, it should not be placed in the label as a stand-alone study with sample size, baseline, and mean change from baseline.

5. Conclusions

In the first line treatment study, mean baseline HbA_{1c} was ~8.2%. Both the combination therapies of metformin/glyburide 250/1.25 mg and 500/2.5 mg were efficacious compared to placebo in change from baseline HbA_{1c} to Week 20 treatment of double-blind medication. The differences from placebo were -1.26% and -1.31% for the low dose and the medium dose combinations. Both combination therapies were also nominally efficacious compared to both monotherapy treatments. When comparing hypoglycemia events with glyburide monotherapy (~21%), subjects treated with medium dose combination, experienced greater events (~38%) whereas subjects treated with low dose combination experienced fewer hypoglycemia events (~11%). The low dose combination treated patients also experienced fewer gastrointestinal events (32%) comparing to metformin monotheray (43%). It is a clinical decision whether metformin/glyburide 2000/10 mg will be the maximum titrated dose for the first line treatment.

In the second line treatment study with subjects mean baseline HbA_{1c} of 9.5%, the two combination treatments of 500/2.5 mg and 500/5 mg were superior to glyburide and metformin in levels of HbA_{1c}. The

Week 16 means of HbA_{1c} were 9.61, 9.82, 7.92, and 7.91 for the treatment groups of glyburide, metformin, combination 500/2.5 mg and 500/5 mg, respectively.

Neither study was designed as a classic combination study in which a combination treatment is compared to its components at a fixed combined dose using the fixed doses of the components. Instead, doses in all treatment groups were titrated to achieve glycemic control. Comparing combination and monotherapy treatment groups having different average doses could lead to biased estimates of treatment effect. However, any such bias in these trials should favor the monotherapy groups (i.e., lead to reduced estimates of the effectiveness of the combinations) since patients receiving combination therapies took lower doses, on average, than patients receiving monotherapy.

[/S/]
Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot [/S/] 7/11/00

Dr. Nevius [/S/] 7/11/00

cc: Arch NDA 21-178
HFD-510
HFD-510/SMalozowski
HFD-510/RMisbin
HFD-510/WKoch
HFD-715/Division file, LPian, TSahlroot
Chron.

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