

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-460

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: 21-460
Name of drug: Glipizide and Metformin HCl Tablets
Applicant: Bristol-Myers Squibb Co.
Indication: Type 2 Diabetes
Documents reviewed: \\CDSESUB1\N21460\N 000\2001-12-21\clinstar
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Keywords: NDA review, clinical studies, combination drug, analysis of covariance, treatment-by-baseline interaction

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS

The efficacy of combination tablet of glipizide and metformin for first line treatment of type 2 diabetes was demonstrated in the first-line study for doses 2.5mg/250mg and 2.5mg/500mg in HbA_{1c} (%) change from baseline. The 1.25mg/250mg combination therapy was not significantly different from the monotherapies. The second line study demonstrated efficacy of the combination treatment group of 5mg/500mg glipizide and metformin compared to the 5mg glipizide monotherapy and 500mg metformin monotherapy in HbA_{1c} change from baseline. The sponsor considered comparison between the 1.25mg/250mg combination and glipizide monotherapy and metformin monotherapy invalid due to "qualitative" treatment-by-baseline interaction in change from baseline HbA_{1c}. However, this reviewer found the interaction between the 1.25mg/250mg and the monotherapy groups to be not significant; therefore, the comparison was valid.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

The submission included 2 studies on the combination of glipizide and metformin. Study 50 was for the first line use in type 2 diabetic patients who had inadequate glycemic control with diet and exercise. Study 60 was for the second line use in type 2 diabetic patients who have inadequate glycemic control on half-maximum to maximum of the labeled doses of sulfonylurea monotherapy. The sponsor's rationale for the combination therapy as first line therapy was that current available monotherapies often fail to provide adequate glycemic control (HbA_{1c} <7.0). The sponsor argues that fixed combination compared to monotherapy might provide greater efficacy at relatively smaller doses of each agent with comparable or better tolerability and safety profiles. A fixed combination tablet also would offer convenience for administration.

2.2 DATA ANALYZED AND SOURCES

The electronic data sets were located at \\CDSESUB1\N 000\2001-12-21\crt\datasets\cv138-050 for the first line use and at \\CDSESUB1\N 000\2001-12-21\crt\datasets\cv138-060 for the second line use. Table 1 is a summary of the 2 fixed combination studies. It is important to note that the treatment arms for Study 50 in Table 1 denote tablet strengths for a single tablet; patients were titrated up to 4 tablets daily to achieve glycemic control. In Study 60, the G/M and M treatment arms were titrated upward; however, the glipizide arm was a fixed dose for all patients equal to 30 mg/day.

Table 1 Design summary of the combination studies of glipizide and metformin

	First line - CV138-050	Second line - CV138-060
Study design	multicenter, randomized, double blind, parallel group, active controlled	
Treatment arms	1. G 5mg 2. M 500mg, 3. G/M 1.25/250mg 4. G/M 2.5/250mg 5. G/M 2.5/500mg	1. G 30mg (15mg bid) 2. M 500mg 3. G/M 5/500 mg
# of centers	95 (US 55, Israel 15, Russia 25)	108 in the U.S.
Study period	2 week diet and placebo lead in 24 month double-blind treatment with upward titration from 1 up to 4 tablets 6 month open-label treatment	2 week glipizide lead-in 18 week double-blind with upward titration of groups G/M and M
# randomized	815	247
Primary comparison	analysis of mean change from baseline HbA _{1c} was performed using analysis of covariance model with treatment term and baseline as covariate	
Study date	9/6/2000 to 9/14/ 2001	9/15/2000 to 9/18/2001

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

First line study

The primary efficacy variable was the change from baseline in HbA_{1c} at Week 24. The primary efficacy analysis population was the intent-to-treat population with last observation carried forward for the missing values. Each combination group was compared to both monotherapy groups according to the "Min" test. The Min test identifies whether the combination is superior to both of the monotherapies. The sponsor presented the analysis of covariance (ANCOVA) results for the combination groups of glipizide/metformin 2.5mg/250mg and 2.5mg/500mg but not the 1.25mg/250mg group. The sponsor considered the latter comparison to be invalid when a statistically significant treatment-by-baseline interaction effect was detected (Table 2). However, this reviewer's analysis showed that the treatment-by-baseline interaction was not significant (p>0.1) between the low dose combination and the monotherapies. The interaction issue is addressed in section 2.3.3.

Table 2 Sponsor's results for HbA_{1c} change from baseline (%) at Week 24 – 1st line study

	Glip/Met 1.25/250 mg (n = 173)	Glip/Met 2.5/250 mg (n = 166)	Glip/Met 2.5/500 mg (n = 163)	Metformin 500 mg (n = 171)	Glipizide 5 mg (n = 168)
Mean Final Dose (n)	815.3/4.1 mg (176)	790.7/7.9 mg (172)	1476.9/7.4 mg (173)	1748.6 mg (177)	16.7 mg (170)
Baseline Mean (SD)	8.97 (1.21)	9.06 (1.26)	9.10 (1.14)	9.15 (1.10)	9.17 (1.13)
Week 24 Mean (SD)	7.14 (1.22)	6.93(1.02)	6.95 (1.02)	7.67 (1.25)	7.36 (1.11)
LSM Change* (SE)	NA	2.15 (0.08)	2.14 (0.08)	1.46 (0.07)	1.77 (0.08)
Difference vs. Metformin (SE) 1-sided p-value	NA	-0.70 (0.11) < 0.001	-0.69 (0.11) < 0.001		
Difference vs. Glipizide (SE) 1-sided p-value	NA	-0.38 (0.11) < 0.001	-0.37 (0.11) < 0.001		
p-value *	NA	< 0.001	< 0.001		

* Least squared mean change from baseline using ANCOVA model with treatment effect and baseline covariate

* Largest of the 2 one-sided p-values resulting from comparing a combination group versus both monotherapy groups. This p-value is to be evaluated at the one-sided 0.009 significance level (Min Test & Dunnett's Test).

For the first line treatment, the 2.5/250 mg and 2.5/500 mg treatment groups were both statistically significantly different in mean HbA_{1c} change from baseline compared to metformin monotherapy and glipizide monotherapy. The differences in mean HbA_{1c} change from baseline between the combination groups, 2.5/250 mg and 2.5/500 mg, and the metformin group were -0.70% and -0.69%, respectively. The differences between the combination groups and the glipizide group were -0.38% and -0.37%, respectively.

For the second line treatment, the glipizide/metformin combination group was statistically significantly different in HbA_{1c} mean change from baseline compared to the metformin group, -0.98% and to the glipizide group, -1.06% (Table 3).

Table 3 Sponsor's results for HbA_{1c} change from baseline (%) at Week 18 – 2nd line study

	Glip/Met 5/500 mg (n = 80)	Metformin 500 mg (n = 71)	Glipizide 15 mg bid (n = 79)
Mean Final Dose (n)	1747.1/17.5 mg (87)	1926.7 mg (75)	30.0 mg (84)
Baseline Mean (SD)	8.66 (1.20)	8.61 (1.15)	8.87 (1.07)
Week 18 Mean (SD)	7.36 (1.03)	8.30 (1.33)	8.54 (1.22)
LSM Week 18 (SE)	7.39 (0.11)	8.36 (0.11)	8.45 (0.11)
Difference vs. Metformin (SE) 1-sided p-value	-0.98 (0.15) <0.001		
Difference vs. Glipizide (SE) 1-sided p-value	-1.06 (0.15) <0.001		
p-value *	< 0.001		

* Least squared mean change from baseline using ANCOVA model with treatment effect and baseline covariate

2.3.2 STATISTICAL METHODOLOGIES

The primary efficacy variable, HbA_{1c} change from baseline at Week 24 or the last prior measurement was analyzed using analysis of covariance method with treatment as fixed effect and baseline HbA_{1c} as covariate.

The Min test (Laska and Meisner) was used to test whether the combination is superior to both monotherapies. The significant test is based on the greater of the 2 p-values from the comparisons of combination and the 2 monotherapies. The multiplicity of the 3 fixed dose combinations compared to the monotherapies was adjusted using Dunnett procedure.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.3.3.1 First Line Study CV138-050

Patient Disposition

A total of 1631 patients were screened. Of this number, 919 patients were enrolled in the placebo lead-in phase. A total of 868 patients were randomized and 737 (85%) completed the study. Table 4 is the sponsor's table which displays reasons for discontinuation.

Table 4 Reasons for Discontinuation during Double-Blind Phase – 1st line study

Reason for Discontinuation	Number (%) of Subjects					
	Met/Glip 250/1.25 N = 176	Met/Glip 250/2.5 N = 172	Met/Glip 500/2.5 N = 173	Metformin 500 mg N = 177	Glipizide 5 mg N = 170	Total N = 868
Number of subjects discontinued	22 (12.5)	22 (12.8)	22 (12.7)	38 (21.5)	27 (15.9)	131 (15.1)
Adverse event (including hypoglycemia)	6 (3.4)	7 (4.1)	11 (6.4)	11 (6.2)	6 (3.5)	41 (4.7)
Lack of glycemic control	10 (5.7)	7 (4.1)	5 (2.9)	20 (11.3)	14 (8.2)	56 (6.5)
Subject's request	3 (1.7)	3 (1.7)	2 (1.2)	6 (3.4)	5 (2.9)	19 (2.2)
Lost to follow-up	1 (0.6)	3 (1.7)	3 (1.7)	0	1 (0.6)	8 (0.9)
Other	2 (1.1)	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.6)	7 (0.8)
Number of subjects completing DB phase	154 (87.5)	150 (87.2)	151 (87.3)	139 (78.5)	143 (84.1)	737 (84.9)

The two major reasons for discontinuation were lack of glycemic control and adverse events.

Primary Efficacy Analysis –HbA_{1c} change from baseline at Week 24

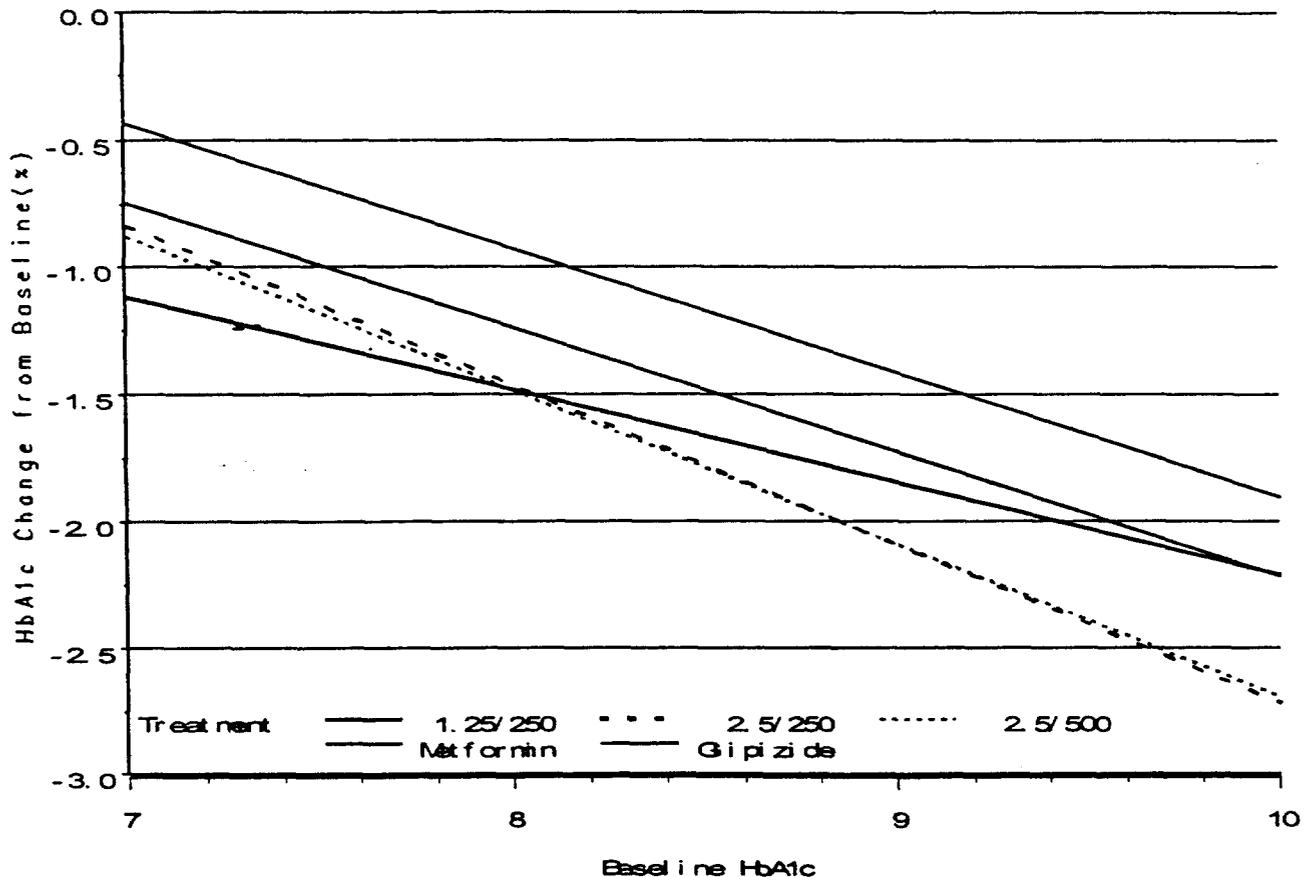
This reviewer examined the treatment-by-baseline interaction between the 1.25mg/250mg combination group and the 2 monotherapies groups. The sponsor considered the interaction “qualitative”, therefore, the comparison invalid.

The sponsor’s rationale was “As the regression lines for the metformin/glipizide 250/1.25 mg combination group crossed with the monotherapies regression lines within the distribution of baseline values, the interaction was regarded as qualitative.” The sponsor indicated that, in an analysis involving all 5 treatment groups, the overall treatment-by-baseline interaction was significant (p=0.0196). However, after further assessment of the slopes of the regression lines (Table 5, Fig 1), this reviewer concluded that the significant treatment-by-baseline interaction occurred only between the low dose combination 250/1.25mg group and the 2 higher dose combination groups 2.5/500mg (p=0.0021) and 250/1.25mg (p=0.0079). The slopes were not significantly different between the 250/1.25mg group and the monotherapy groups, metformin (p=0.166) and glipizide (p=0.160). As the primary study objective was to compare the glipizide/metformin combination to the monotherapies, the significant treatment-by-baseline interaction among the combination groups is irrelevant to the efficacy analysis.

Table 5 Comparisons of slopes of the regression lines

	1.25/250	2.5/250	2.5/500	Metformin	Glipizide
slope	-0.36	-0.63	-0.61	-0.49	-0.49
vs. 1.25/250	-	p=0.002	p=0.008	p=0.166	p=0.160

Figure 1 Regression of HbA_{1c} change from baseline (%) by baseline HbA_{1c} - 1st line study



According to criteria in the sponsor's protocol (below), this reviewer considers the interaction to be not statistically significant ($p > 0.1$) between the 250/1.25mg combination and the monotherapy groups. Table 6 displays the results from all 3 combination groups vs. the monotherapy groups.

If the interaction effect is statistically significant at the 0.10 level, the interaction will be assessed as qualitative or quantitative. This assessment will be based on regression lines for each treatment group, obtained from the ANCOVA model with a treatment-by-baseline interaction term included. If the regression lines for two groups do not cross within the distribution of baseline values or if the crossing is judged to not be severe, the interactions will be regarded as quantitative. In this case, the two groups will be compared using the contrast estimating the difference between groups at the overall mean baseline value. Otherwise, the interaction will be regarded as qualitative, and the two treatment groups will not be compared.

Table 6 Reviewer's analysis of HbA_{1c} change from baseline to Week 24 – 1st line study

	Glip/Met 1.25/250 mg (n = 173)	Glip/Met 2.5/250 mg (n = 166)	Glip/Met 2.5/500 mg (n = 163)	Metformin 500 mg (n = 171)	Glipizide 5 mg (n = 168)
Baseline Mean (SD)	8.97 (1.21)	9.06 (1.26)	9.10 (1.14)	9.15 (1.10)	9.17 (1.13)
LSM Change* (SE)	-1.89 (0.07)	-2.15 (0.08)	-2.14 (0.08)	-1.45 (0.07)	-1.77 (0.08)
Difference vs. Metformin (SE) 1-sided p-value	-0.44 (0.11) <0.001	-0.70 (0.11) < 0.001	-0.69 (0.11) < 0.001		
Difference vs. Glipizide (SE) 1-sided p-value	-0.13 (0.11) p=0.23	-0.38 (0.11) p< 0.001	-0.37 (0.11) p< 0.001		
p-value *	0.23	< 0.001	< 0.001		

* Least squared mean change from baseline using ANCOVA model with treatment effect and baseline covariate

* Largest of the 2 one-sided p-values resulting from comparing a combination group versus both monotherapy groups. This p-value is to be evaluated at the one-sided 0.009 significance level (MinTest and Dunnett's Test).

The larger p-value was 0.23 for the comparison between 1.25/250mg combination and the monotherapies. According to the Min test the 1.25/250mg combination was not statistically different from the monotherapies.

Secondary efficacy variables

The “min” test approach was not used for secondary efficacy analyses for the superiority of the combination group versus the monotherapy groups. Accounting for the 2 families (2 monotherapies) and adjusting within each family for the 3 combination groups versus one control using the Dunnett’s procedure, the 2-sided 0.018 significant level was used.

Fasting Plasma Glucose (FPG)

The sponsor’s result for change from baseline in FPG is summarized in Table 7.

TABLE 7 Mean Change from Baseline in FPG at Week 24 – ITT/LOCF

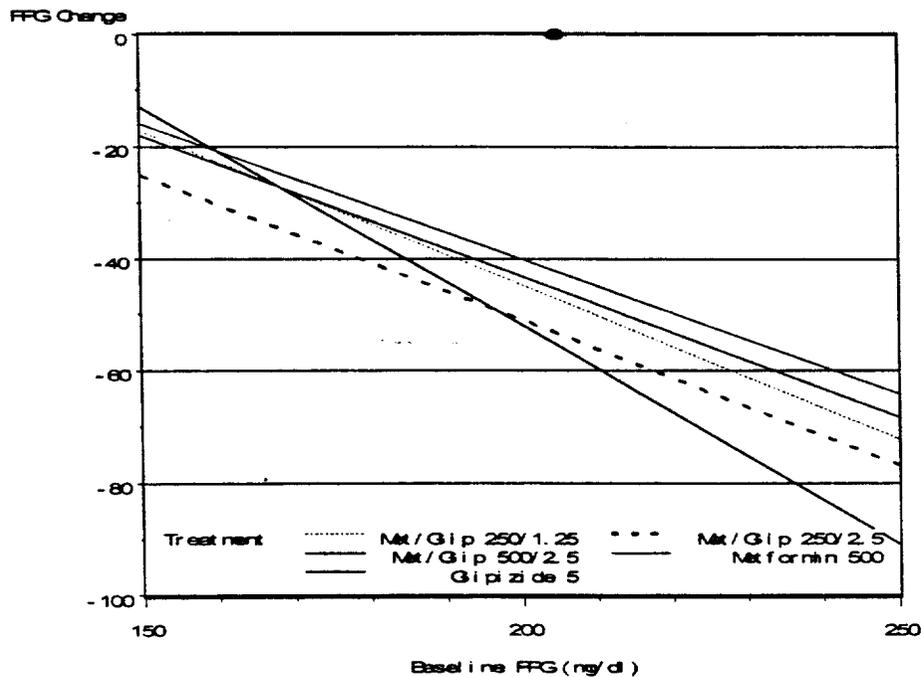
Unit: mg/dL	Met/Glip 250/1.25 mg n = 176	Met/Glip 250/2.5 mg n = 170	Met/Glip 500/2.5 mg n = 169	Metformin 500 mg n = 176	Glipizide 5 mg n = 169
Baseline Mean (SD)	201.6 (49.6)	206.8 (51.9)	203.1 (56.8)	207.4 (53.2)	210.7 (51.6)
Week 24/LPM Mean (SD)	156.0 (35.8)	152.1 (40.5)	148.7 (31.8)	163.8 (46.9)	162.1 (44.1)
Unadjusted Mean Change	-45.6	-54.6	-54.3	-43.6	-48.6
Adjusted Mean Change from Baseline (SE) ^a	-47.9 (2.5)	-54.2 (2.5)	Comparisons are not valid	-42.9 (2.5)	-46.2 (2.5)
Difference vs. Metformin Group ^b (SE) ^a					
(95% CI) ^c	-5.0 (3.5)	-11.3 (3.5)	Comparisons are not valid		
P-value ^d	0.153	0.001	Comparisons are not valid		
Difference vs. Glipizide Group ^b (SE) ^a					
(95% CI) ^c	-1.8 (3.6)	-8.0 (3.6)	Comparisons are not valid		
P-value ^d	0.620	0.025	Comparisons are not valid		

- ^a Standard errors are obtained from the ANCOVA model with terms for treatment and treatment-by-baseline interaction
- ^b Difference = (adjusted mean change for combination group) - (adjusted mean change for monotherapy group)
- ^c Ninety five percent confidence intervals are adjusted for multiple comparisons using critical values from Dunnett test (three experimental agents, one monotherapy control)
- ^d p-value resulting from comparing a combination group versus the specified monotherapy group. This p-value is to be evaluated at the two-sided 0.018 significance level.

The table showed that the comparisons involving 2.5/500mg were not valid and the mean difference of -11.3 mg/dL between 25/250mg and metformin is the only comparison with a significant p-value ≤ 0.018.

The sponsor considered the comparison between the 2.5/250mg combination group and the monotherapies to be invalid, as the treatment-by-baseline was significant and 'qualitative' in nature (Fig. 2). The 3 solid regression lines represent Glip/Met 2.5/500 (black line) and the 2 monotherapies intersected at low FPG baseline (25th percentile). This reviewer does not regard the cross over at low baseline level as "severe" between the 2.5/500mg combination and the monotherapies. Therefore, the overall results should be presented in the label.

Figure 2 Regression lines of Change from baseline in FPG (mg/dL) by baseline FPG



The test of effectiveness on the average is not invalidated by the apparent treatment-by-baseline interaction but needs careful interpretation of different effects in patients with different baselines. Table 8 displays this reviewer's treatment comparisons on average and the estimates of treatment differences between the 2.5/250mg combination and the monotherapies at baseline fasting plasma glucose of 165mg/dl (25th percentile), 198mg/dl (median) and 242mg/dl (75th percentile).

Table 8 LSM difference (SE) between the 2.5/500 mg combination and monotherapies at 3 levels of baseline FPG (X)

LSM difference (SE)	Overall	Baseline FPG 25 th percentile X=165	Baseline FPG 50 th percentile X=198	Baseline FPG 75 th percentile X=242
2.5/500-metformin	-13.6 (3.5) ¹	-2.8 (4.1)	-11.6 (3.6)	-23.3 (4.0)
2.5/500-glipizide	-10.4 (3.6) ²	+0.4 (4.1)	-8.3 (3.6)	-20.0 (4.1)

¹p=0.0001, ²p=0.0039

The analysis showed that the 2.5/500mg combination was more effective than the monotherapies ($p < 0.018$). The absolute difference between 2.5/500mg and the monotherapies increased as the baseline FPG increased.

This reviewer performed exploratory analysis on interaction by excluding patients with baseline FPG greater than 280mg/dl (Fig 3) (the sponsor presented in the proposed label). The interaction was not significant ($n=466$, $p=0.35$) when excluding patients with high baseline FPG.

Figure 3 Change from baseline FPG by baseline FPG ≤ 280

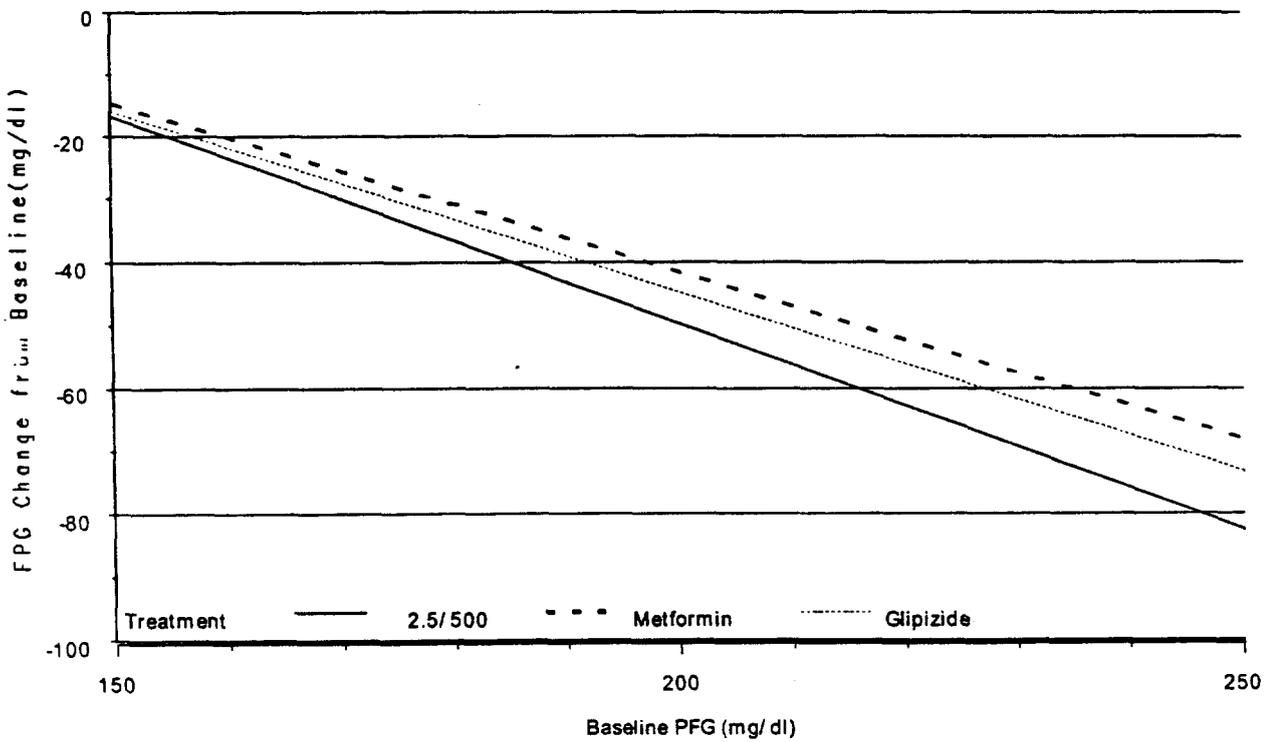


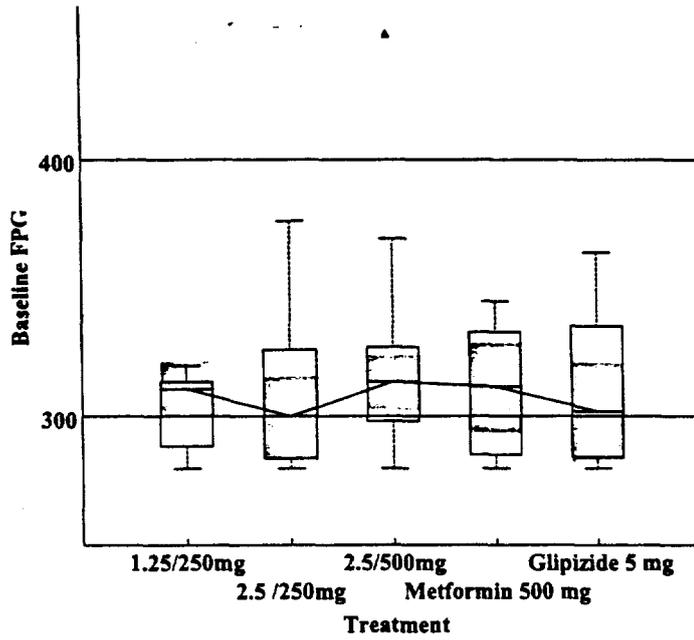
Table 9 displays sponsor's descriptive statistics on mean change from baseline by treatment group and baseline FPG categories.

Table 9 Mean Change from Baseline in FPG at Week 24 by Baseline FPG Category

Baseline FPG Category	Met/Glip 250/1.25 mg N = 176	Met/Glip 250/2.5 mg N = 170	Met/Glip 500/2.5 mg N = 169	Metformin 500mg N = 176	Glipizide 5mg N = 169
< 160 mg/dL, n	41	33	39	33	27
Baseline mean (SD)	143.6 (14.4)	144.4 (10.5)	141.9 (14.0)	137.4 (18.2)	142.5 (13.8)
Mean change (SE)	-12.3 (3.2)	-16.2 (4.3)	-9.7 (3.5)	-10.0 (3.7)	-13.3 (5.1)
160 - < 200 mg/dL, n	57	53	55	45	56
Baseline mean (SD)	180.0 (11.4)	176.8 (11.3)	178.9 (11.6)	177.8 (11.1)	181.4 (11.6)
Mean change (SE)	-31.7 (2.8)	-37.5 (3.7)	-36.4 (3.7)	-31.2 (3.9)	-31.5 (3.5)
200 - < 240 mg/dL, n	35	39	33	51	40
Baseline mean (SD)	218.3 (10.3)	219.8 (11.5)	213.5 (11.0)	215.4 (12.2)	221.3 (11.1)
Mean change (SE)	-63.9 (3.5)	-66.0 (4.5)	-60.0 (6.1)	-48.1 (6.7)	-59.1 (5.3)
240 - < 280 mg/dL, n	30	28	24	29	29
Baseline mean (SD)	258.6 (11.6)	258.7 (12.1)	255.8 (11.9)	255.3 (11.4)	257.3 (11.3)
Mean change (SE)	-78.5 (8.3)	-96.1 (6.4)	-84.6 (7.1)	-72.2 (7.4)	-77.4 (8.5)
≥ 280 mg/dL, n	13	17	18	18	17
Baseline mean (SD)	302.7 (14.0)	305.8 (26.0)	319.7 (39.7)	309.9 (22.5)	311.4 (28.3)
Mean change (SE)	-86.1 (13.6)	-88.4 (11.7)	-155.2 (12.1)	-77.6 (15.9)	-87.3 (15.7)

The sponsor stated that "Subgroup analysis by baseline FPG category showed that in general, within each treatment group the mean reduction from baseline in FPG became greater as the baseline FPG increased. For subjects with a baseline FPG ≥280 mg/dL, the largest mean reduction from baseline was observed in the metformin/glipizide 2.5/500 mg combination group (155.2 mg/dL), while in the other treatment groups, the mean reduction ranged from 77.6 to 88.4 mg/dL in this baseline FPG category." However, the mean baseline FPG and standard deviation (319.7, 39.7) of the 2.5/500mg combination was the greatest among the treatment groups. One patient's baseline FPG was 449 mg/dL (Fig 4). The treatment-by-baseline interaction was not significant (p=0.34) if patients with baseline FPG≥280 mg/dL were not in the analysis.

Figure 4 Box plot of patients with baseline FPG ≥ 280 mg/dL



Weight change from baseline – 1st line study

All 3 combination groups were significantly different from the metformin group but not significantly different from glipizide in weight change from baseline.

Table 10 Mean Change from baseline weight – 1st line study

Unit: kg	Met/Glip 250/1.25 (n = 176)	Met/Glip 250/2.5 (n = 170)	Met/Glip 500/2.5 (n = 169)	Metformin 500 mg (n = 176)	Glipizide 5 mg (n = 169)
Baseline mean (SD)	85.8 (14.8)	86.2 (13.3)	85.8 (16.8)	84.8 (15.7)	86.4 (14.5)
Week 24/LPM mean (SD)	85.1 (15.4)	85.8 (13.8)	85.3 (16.9)	82.9 (15.8)	86.2 (14.5)
Adjusted mean change from baseline (SE) ^a	-0.7 (0.3)	-0.4 (0.3)	-0.5 (0.3)	-1.9 (0.3)	-0.2 (0.3)
Difference vs. Metformin Group ^b (SE) ^a					
(95% CI) ^c	1.2 (0.4)	1.5 (0.4)	1.4 (0.4)		
P-value ^d	(0.3, 2.0)	(0.6, 2.4)	(0.5, 2.2)		
	0.001	< 0.001	< 0.001		
Difference vs. Glipizide Group ^b (SE) ^a					
(95% CI) ^c	-0.5 (0.4)	-0.1 (0.4)	-0.3 (0.4)		
P-value ^d	(-1.4, 0.4)	(-1.0, 0.7)	(-1.2, 0.6)		
	0.198	0.704	0.453		

^a Standard errors are obtained from the ANCOVA model with a term for treatment and covariate for baseline

^b Difference = (adjusted mean change for combination group) - (adjusted mean change for monotherapy group)

^c Ninety five percent confidence intervals are adjusted for multiple comparisons using critical values from Dunnett test (three experimental agents, one monotherapy control)

^d P-value resulting from comparing a combination group versus the specified monotherapy group. This p-value is to be evaluated at the two-sided 0.018 significance level.

2.3.3.2 Second Line Study CV138-060

A total of 521 patients were screened. Of the 521 patients screened, 298 entered into the glipizide lead-in phase with 247 randomized: 87 to the metformin/glipizide group, 76 to the metformin group, and 84 to the glipizide group. Sixty-nine (39%) patients did not complete the double-blind treatment phase. Table 11 displays patient disposition during the double-blind phase.

Table 11 Patient Disposition – 2nd line study

Reason for Discontinuation	Number (%) of Subjects			
	Met/Glip	Metformin	Glipizide	Total
No. of subjects randomized ^a	87	76	84	247
No. of subjects discontinued	20 (23.0)	26 (34.2)	23 (27.4)	69 (27.9)
Adverse Event (including Symptoms of Hypoglycemia)	11 (12.6)	5 (6.6) ^a	3 (3.6)	19 (7.7)
Lack of glycemic control	1 (1.1)	16 (21.1)	15 (17.9)	32 (13.0)
Subject request	2 (2.3)	4 (5.3)	1 (1.2)	7 (2.8)
Lost to follow up	4 (4.6)	1 (1.3)	2 (2.4)	7 (2.8)
Other	2 (2.3)	0 (0.0)	2 (2.4)	4 (1.6)
No. of subjects completing DB phase	67 (77.0)	50 (65.8)	61 (72.6)	178 (72.1)

^a Included patient 0044/009 who never received the randomized medication, metformin

Table 12 displays the incidence of discontinuation due to adverse events.

Table 12 Adverse events discontinuation during the double blind phase

Adverse event	Glip/Met	Metformin	Glipizide
GI (diarrhea, nausea/vomiting and GI reflux)	4 (4.6%)	2 (2.7%)	2 (2.5%)
Cardiovascular	2 (2.3%)	1 (1.3%)	0
Serum creatinine increase	2 (2.3%)	0	0
musculoskeletal pain/wound, hypoglycemia, multiple malignancies	3 (3.4%)	0	0
Dizziness, fatigue	0	1 (1.3%)	0
Serum glucose increase	0	0	1 (1.3%)

Primary Efficacy Analysis – HbA_{1c} Change from baseline (%) at Week 18 or the Last Prior Measurement

The glipizide/metformin was statistically superior to both the monotherapies using the 1-sided min test p-value of 0.025. The treatment difference between the combination and monotherapies was -0.98% for the metformin group and -1.06% for the glipizide group.

Table 13 Mean change from baseline HbA_{1c} at Week 18 – 2nd line study

Unit: %	Met/Glip (n = 80)	Metformin (n = 71)	Glipizide (n = 79)
Baseline Mean (SD)	8.66 (1.20)	8.61 (1.15)	8.87 (1.07)
Week 18/LPM Mean (SD)	7.36 (1.03)	8.30 (1.33)	8.54 (1.22)
Adjusted Week 18/LPM Mean (SE) ^a	7.39 (0.11)	8.36 (0.11)	8.45 (0.11)
Difference vs. Metformin Group ^b (SE) ^a	-0.98 (0.15)		
One-sided P-value	<0.001		
Difference vs. Glipizide Group ^b (SE) ^a	-1.06 (0.15)		
One-sided P-value	<0.001		
Test for Superiority of Met/Glip over monotherapies: P-value ^c	<0.001		
Mean final dose, mg (number of subjects)	1747.1/17.5 mg (87)	1926.7 mg (75)	30.0 mg (84)

^a Standard errors obtained from ANCOVA model with a term for treatment and covariate for baseline

^b Difference = (adjusted mean for combination group) - (adjusted mean for monotherapy group)

^c Largest of the 2 one-sided p-values resulting from comparing the combination group versus both monotherapy groups. This p-value is to be evaluated at the one-sided 0.025 significance level (Min Test).

Secondary efficacy variable

FPG Change from baseline

The glipizide/metformin combination group was superior to the metformin and glipizide monotherapy groups in FPG reduction from baseline. The LSMs for the treatment differences were -37mg/dl for both comparisons.

Table 14 Mean change from baseline FPG – 2nd line study

Unit: mg/dL	Met/Glip (n = 81)	Metformin (n = 75)	Glipizide (n = 82)
Baseline Mean (SD)	194.3 (43.0)	191.3 (48.0)	203.6 (43.8)
Week 18/LPM Mean (SD)	164.6 (50.0)	199.7 (64.1)	208.3 (48.5)
Unadjusted Mean Change from Baseline	-29.7	8.4	4.7
Adjusted Mean Change from Baseline (SE) ^a	-30.4 (5.0)	6.7 (5.2)	7.0 (5.0)
Difference vs. Metformin Group ^b (SE) ^a	-37.2 (7.2)		
(95% CI)	(-51.4, -22.9)		
P-value ^c	< 0.001		
Difference vs. Glipizide Group ^b (SE) ^a	-37.4 (7.1)		
(95% CI)	(-51.4, -23.5)		
P-value ^c	< 0.001		

- ^a Standard errors obtained from ANCOVA model with a term for treatment and covariate for baseline
- ^b Difference = (adjusted mean change for combination group) - (adjusted mean change for monotherapy group)
- ^c P-value resulting from comparing the combination group versus the specified monotherapy group. This p-value is to be evaluated at the two-sided 0.05 significance level.

Weight change from baseline

Weight change from baseline was significantly different between the glipizide/metformin combination and the metformin group favoring metformin (Table 15).

Table 15 Mean Change from baseline weight – 2nd line study

Unit: kg	Met/Glip (n = 81)	Metformin (n = 75)	Glipizide (n = 83)
Baseline Mean (SD)	95.1 (17.8)	94.2 (16.7)	90.0 (17.4)
Week 18/LPM Mean (SD)	94.7 (18.4)	91.5 (16.2)	89.6 (17.3)
Unadjusted Mean Change from Baseline	-0.4	-2.7	-0.3
Adjusted Mean Change from Baseline (SE) ^a	-0.3 (0.3)	-2.7 (0.3)	-0.4 (0.3)
Difference vs. Metformin Group ^b			
(SE) ^a	2.4 (0.4)		
(95% CI)	(1.6, 3.2)		
P-value ^c	<0.001		
Difference vs. Glipizide Group ^b			
(SE) ^a	0.0 (0.4)		
(95% CI)	(-0.8, 0.8)		
P-value ^c	0.919		

^a Standard errors obtained from ANCOVA model with a term for treatment and covariate for baseline

^b Difference = (adjusted mean change for combination group) - (adjusted mean change for monotherapy group)

^c P-value resulting from comparing the combination group versus the specified monotherapy group. This p-value is to be evaluated at the two-sided 0.05 significance level.

Statistical Reviewer's Findings

In contrast to the sponsor's assessment, this reviewer did not find the treatment-by-baseline interaction for HbA_{1c} change from baseline between the 1.25/250mg treatment combination and the monotherapies in the 1st line study to be significant, therefore, the statistical comparisons (based on the ANCOVA model) are considered valid.

The sponsor also considered the 2.5/500mg combination versus the monotherapies on the FPG endpoint to be invalid. Baseline FPGs in the 2.5/500mg combination group were skewed to the right. The significant treatment-by-baseline interaction was no longer statistically significant after removing from the analysis all patients with baseline FPG ≥ 280 mg/dL.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor did not perform subgroup analyses with respect to geographical regions for the 1st line study. No Subgroup section was found under Efficacy Results. The descriptive statistics for subgroups of age, gender and race were presented in the supplemental tables. This reviewer performed subgroup analyses and found no treatment-by-age (≥ 65 or < 65), treatment-by-gender, or treatment-by-race interactions in the first line study.

The 3 countries participating in the first line study were Israel (15 sites), Russia (25 sites) and the U.S. (55 sites). The treatment-by-country interaction was not significant in HbA_{1c} or FPG change from baseline endpoints. Figure 5 displays box plots and Table 16 the median HbA_{1c} change from baseline for the 3 countries. Figure 6 and Table 17 displays box plots and median FPG change from baseline. It is noted that unlike HbA_{1c} there were virtually no differences in median FPG change between treatment groups for centers in Russia, which had the majority of patients (67%).

Figure 5 Box plots for HbA_{1c} change from baseline by country – 1st line study

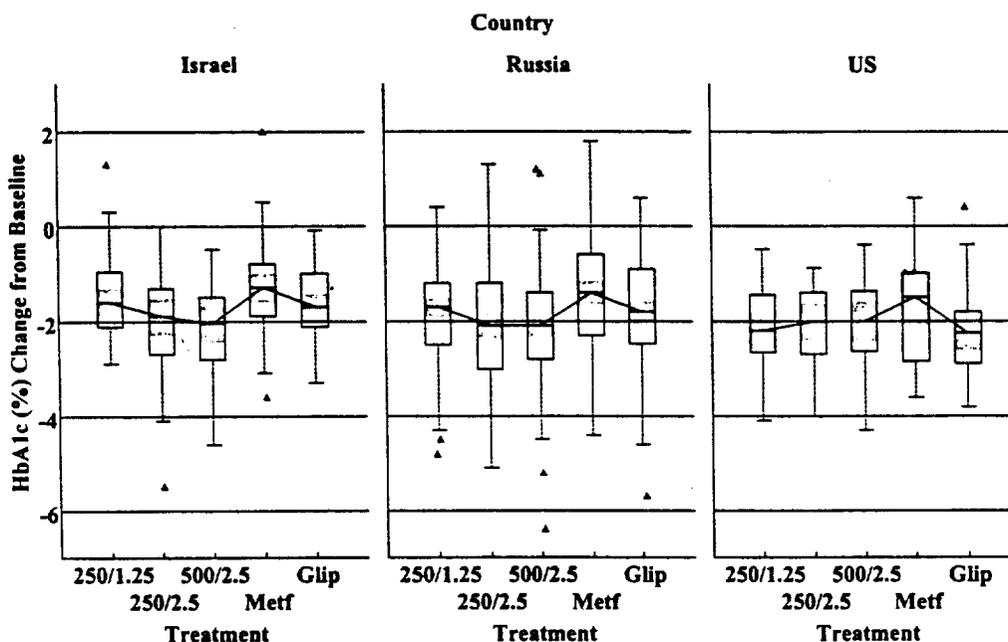


Table 16 Median HbA_{1c} change from baseline by country – 1st line study

Treatment	Israel		Russia		US	
	n	HbA _{1c} Change	n	HbA _{1c} Change	n	HbA _{1c} Change
250/1.25	33	-1.6	116	-1.7	24	-2.2
250/2.5	31	-1.9	109	-2.1	26	-2
2.5/500	28	-2.05	114	-2.1	21	-2
Metformin	34	-1.3	113	-1.4	24	-1.5
Glipizide	33	-1.7	111	-1.8	24	-2.25

Figure 6 Box plots for change from baseline in FPG by country - 1st line study

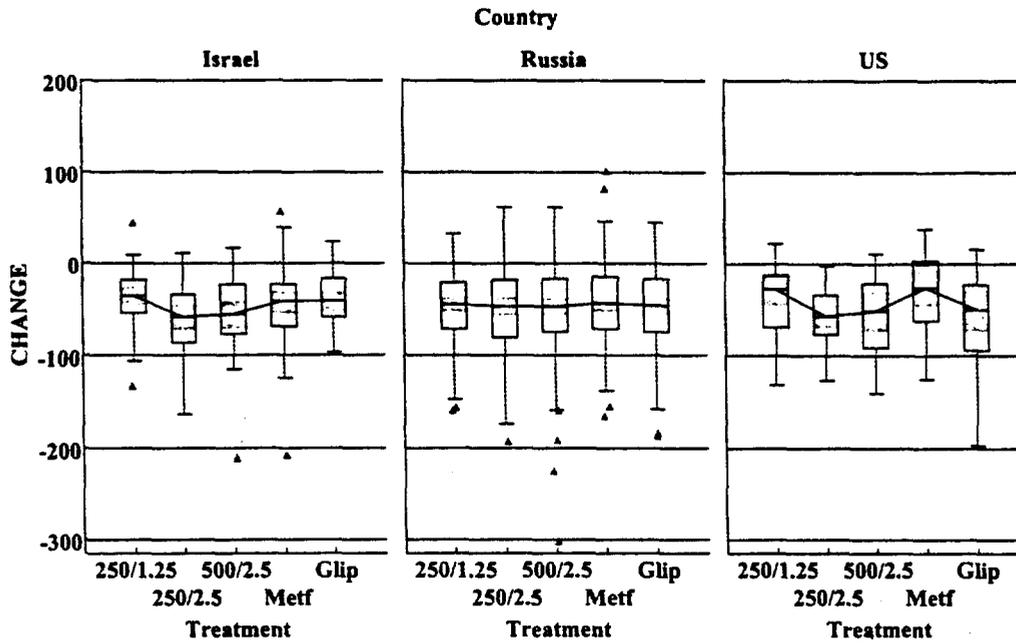


Table 17 Median FPG change from baseline by country - 1st line study

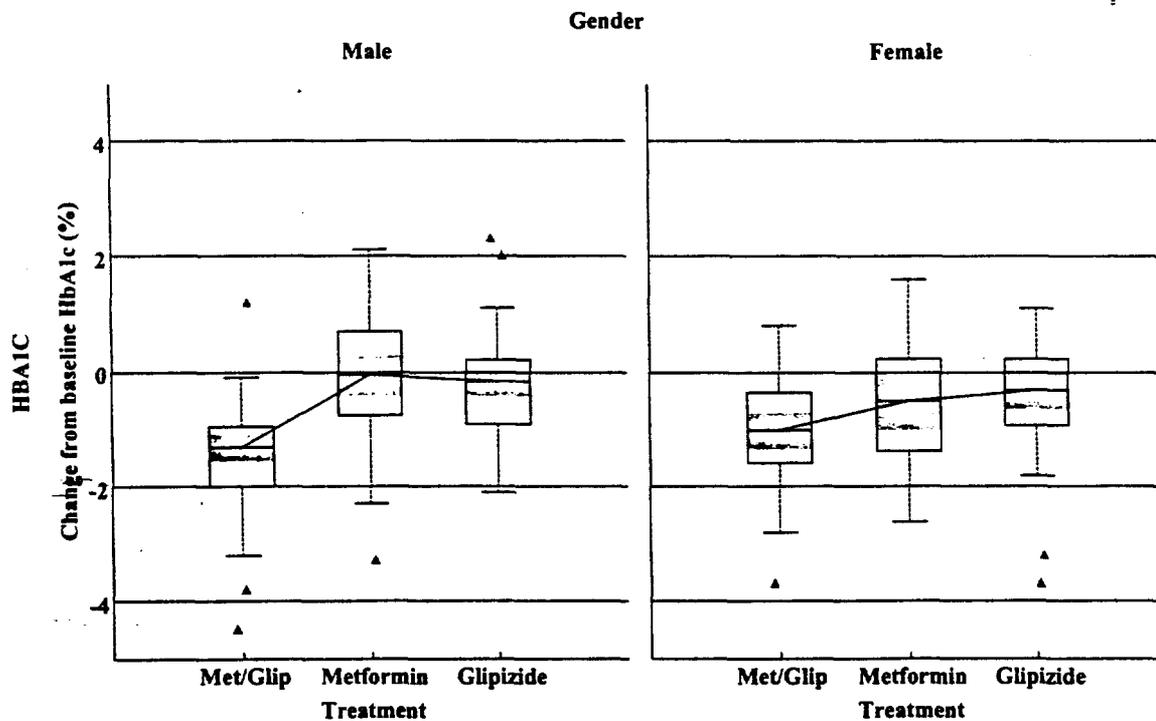
Treatment	Israel		Russia		US	
	n	FPG Change	n	FPG Change	n	FPG Change
250/1.25	34	-35.5	118	-45	24	-27.5
250/2.5	32	-59	111	-47	27	-58
2.5/500	29	-56	115	-47	25	-52
Metformin	35	-42	115	-44	26	-26.5
Glipizide	33	-42	111	-46	25	-51

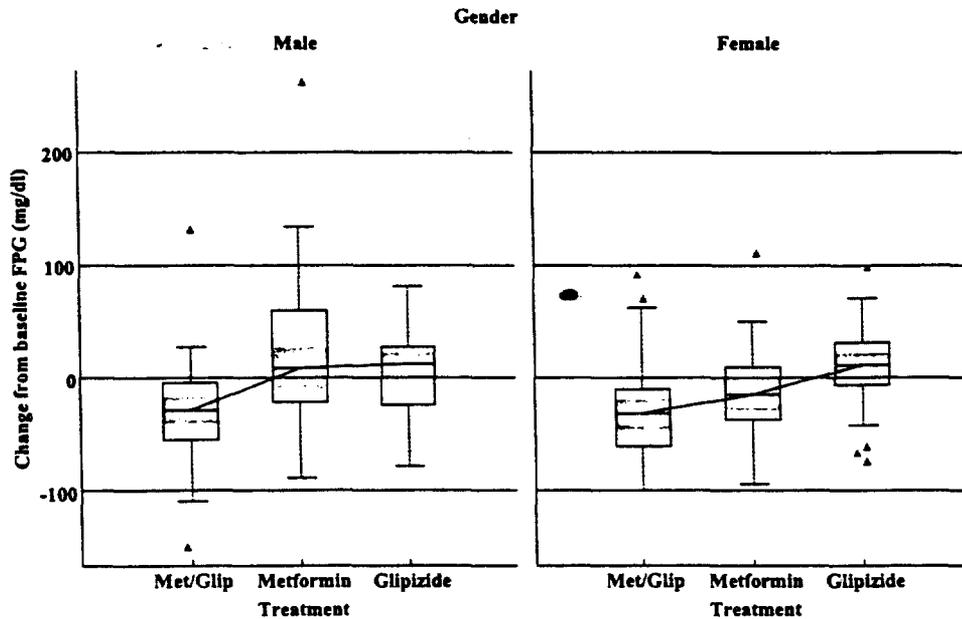
The treatment-by-race interaction was not significant for the second line treatment but it was significant for gender in HbA_{1c} (p=0.07) and FPG (0.03). The median changes from baseline in HbA_{1c} and FPG are displayed in Figure 7 and Table 18. The interaction is between the metformin/glipizide combination and the metformin monotherapy. The magnitude of the median treatment difference in the combination group and the metformin group was greater in the male patients (-1.25%) than in the female patients (-0.5%) in HbA_{1c}. The median treatment differences in FPG were -37.5 mg/dl in male patients and -17.5 mg/dl in female patients.

Table 18 Median HbA_{1c} and FPG change from baseline by gender - 2nd line

Treatment	Male		Female		Male		Female	
	n	HbA _{1c}	n	HbA _{1c}	n	FPG	n	FPG
Met/Glip	45	-1.3	35	-1	46	-28.5	35	-32
Metformin	44	-0.05	27	-0.5	47	9	28	-14.5
Glipizide	50	-0.15	29	-0.3	52	12.5	30	12

Figure 7 Box plot of HbA_{1c} and FPG change from baseline by gender - 2nd line





2.5 STATISTICAL AND TECHNICAL ISSUES

The significant treatment-by-baseline interaction should not invalidate the study results. The analysis should be stratified by center or group the center by geographical areas.

2.6 CONCLUSIONS AND RECOMMENDATIONS

The first line study demonstrated efficacy in HbA_{1c} change from baseline for the glipizide/metformin 2.5mg/250mg combination and 2.5mg/500mg combination versus the metformin and glipizide monotherapies. However, the 1.25mg/250mg combination was not statistically significantly different from the monotherapies. The second line study demonstrated efficacy of the fixed dose combination of glipizide/metformin 5mg/500mg in comparison with the metformin monotherapy and glipizide monotherapy.

2.7 LABELING COMMENTS

1. Table 2 of the Clinical Studies section is a summary of efficacy of the first-line therapy. The _____ mg combination treatment was not reported in the table. As indicated in the review, the comparisons between _____ mg and glipizide and the metformin should not be considered invalid. Therefore, the comparisons of the _____ mg combination to the monotherapies should be presented in the Table.

2. FPG results for 2.5mg/500mg were considered by the sponsor to be not valid due to a "qualitative" interaction. Because the interaction is not "severe", therefore, the results should be presented..
3. The FPG mean change from baseline in _____ should not be presented in Table 2 and in the text following Table 2. This high baseline FPG subgroup consisted only of 10% of the ITT patient population with right-skewed baselines (e.g., 449 mg/dL) in the 2.5mg/500mg group.
4. Table 2 and Table 3 should be consistent in presenting the estimates. For both _____ and FPG the baseline mean and adjusted mean change from baseline are sufficient. The final mean and unadjusted mean change from baseline are not needed.
5. For both the first-line and second-line studies, the sponsor has proposed labeling for postprandial glucose AUC, postprandial insulin response, lipid profile, and weight gain. These less important secondary efficacy variables should not be presented in the label.

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