U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 21-178 / (b) (4) -007 (b) (4) |
| **Drug Name:** | Glucovance (glyburide and metformin hydrochloride) Tablets |
| **Indication(s):** | Type 2 Diabetes |
| **Applicant:** | Bristol-Myers Squibb Company |
| **Date(s):** | Submission: July 21, 2003 |
| | PDUFA: January 21, 2004 |
| **Review Priority:** | Priority |
| | |
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**Keywords:** Clinical studies, Pediatric study, NDA review, combination therapy

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## 1. EXECUTIVE SUMMARY

This was a 26-week study which compared combination therapy of metformin/glyburide (glucovance) to monotherapies metformin and glyburide in type 2 diabetes patients 9 to 16 years of age. The combination therapy failed to show superiority to the monotherapies in $HbA_{1c}$ change from baseline (p=0.24, Table 1).

**Table 1 Summary of $HbA_{1c}$ changes from baseline**

| | Metformin/Glyburide N=57 | Metformin N=54 | Glyburide N=49 |
|---|---|---|---|
| Mean dose | 623/3.1 mg | 1500 mg | 6.5 mg |
| Baseline Mean (SD) | 7.85 (1.74) | 7.99 (1.59) | 7.70 (1.69) |
| Week 26/Last Mean (SD) | 7.05 (1.88) | 7.46 (1.98) | 6.80 (1.40) |
| Adjusted Mean change from baseline (SE) | -0.8 (0.19) | -0.48 (0.20) | -0.96 (0.21) |
| Difference of Metformin/Glyburide vs. (95% 2-sided confidence interval) | | -0.32 ( -0.86, 0.23) | +0.16 (0.28) (-0.40, 0.71) |
| Overall p-value: 0.24 | | | |

## 2. INTRODUCTION

### 2.1 Overview

Glucovance (glyburide and metformin hydrochloride tablets) was approved on July 31, 2000 for the treatment of type 2 diabetes in adult patients. The 1.25/250 mg tablets were approved for use as initial or first-line therapy and the 2.5/500 mg and 5/500 mg tablets were indicated for second-line therapy.

Metformin hydrochloride (HCl) is the only oral antihyperglycemic agent labeled for use in the pediatric Type 2 diabetic population.

The purpose of study CV138059 was to gain clinical experience with the use of low-dose Glucovance therapy (1.25/250 mg tablets) compared with metformin HCl (500 mg tablets) and glyburide (2.5 mg tablets) monotherapies in a pediatric/adolescent patient population whose diabetes was not adequately controlled with diet and exercise, with or without oral hypoglycemic agent therapy.

# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

### Study Design and Endpoints

This was a multicenter, randomized, double-blind study to evaluate the safety and efficacy of fixed combination of glyburide/metformin versus metformin monotherapy and glyburide monotherapy in pediatric patients with type 2 diabetes mellitus.

The dietary lead-in phase was different for drug naïve patients and non naïve patients who were receiving single oral antihyperglycemic therapy (Table 2). For drug naïve patients the duration for lead-in was one week. The lead-in for non naïve patients was a 2-4 week washout period.

**Table 2 Glycemic eligibility prior to randomization**

| | Screening | Week -2 or -1 | Week 0 |
|---|---|---|---|
| Naïve | $6.4\% < HbA_{1c} \leq 14\%$ | | MFG<350 mg/dL |
| On one OAD | $6.4\% < HbA_{1c} \leq 9\%$ | 200≤MFG<350 mg/dL | MFG<350 mg/dL |

Eligible patients were randomized to one of 3 double-blind treatment groups of metformin 500 mg, glyburide 2.5 mg or glucovance 1.25/250 mg. Patients were titrated according to glycemic control during the first 14 weeks of double-blind therapy. The maximum allowable total daily doses were metformin 2000 mg, glyburide 10 mg, and glucovance 5/1000 mg (4 tablets). Patients were on a stable dose of medication from Week 14 through Week 26.

The primary efficacy variable was the change in HbA1c from baseline to Week 26 of the double-blind period or the last prior visit. Mean changes for the 3 randomization groups were compared using analysis of covariance (ANCOVA) model with a fixed effect for treatment and the baseline value as the covariate.

At Visit Week 0 patients were randomized to once daily dosing of metformin 500 mg, glyburide 2.5 mg or Glucovance 1.25/250 mg. Study medication was titrated upward as many as 3 times if the MFG was ≥126 mg/dL at any visit during the titration period (Table 3).

Table 3 Dose Adjustments during the Double-Blind Treatment Phase

| | **INITIAL DOSE** | | **FIRST TITRATION (May occur at Week 2 or any subsequent visit)** | | **SECOND TITRATION (May occur at Week 4 or any subsequent visit)** | | **THIRD TITRATION (May occur at Week 6 or any subsequent visit)** | |
|---|---|---|---|---|---|---|---|---|
| **Bottle A** | **Level One 2.5 mg** | | **Level Two 5.0 mg** | | **Level Three 7.5 mg** | | **Level Four 10 mg** | |
| | | | | | | | | |
| | | | | | | | | |
| **Glyburide (2.5 mg) or matching placebo** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** |
| | 1 | 0 | 1 | 1 | 2 | 1 | 2 | 2 |
| | | | | | | | | |
| **Bottle B** | **Level One 500 mg** | | **Level Two 1000 mg** | | **Level Three 1500 mg** | | **Level Four 2000 mg** | |
| | | | | | | | | |
| | | | | | | | | |
| **Metformin (500 mg) or matching placebo** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** |
| | 1 | 0 | 1 | 1 | 2 | 1 | 2 | 2 |
| | | | | | | | | |
| **Bottle C** | **Level One 1.25/250 mg** | | **Level Two 2.5/500 mg** | | **Level Three 3.75/750 mg** | | **Level Four 5/1000 mg** | |
| **GLUCOVANCE® 1.25/250 mg or matching placebo** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** |
| | 1 | 0 | 1 | 1 | 2 | 1 | 2 | 2 |

**Patient Disposition, Demographic and Baseline Characteristics**

A total of 167 patients were randomized with 125 (75%) completing the 26-week, double-blind treatment period. Table 4 presents the disposition of patients.

**Table 4 Disposition of patients**

| | Metformin/Glyburide | Metformin | Glyburide | Total |
|---|---|---|---|---|
| Randomized | 59 | 55 | 53 | 167 |
| Treated | 59 | 55 | 52 | 166 |
| Discontinued | 15 (25%) | 16 (19%) | 11 (21%) | 42 (25%) |
| Adverse Event | 0 | 0 | 1 (2%) | 1 (0.6%) |
| Hyperglycemia | 6 (10%) | 11 (20%) | 6 (11%) | 23 (14%) |
| Patient request | 1 (2%) | 1 (2%) | 4 (8%) | 6 (4%) |
| Lost to follow-up | 2 (3%) | 0 | 0 | 2 (1%) |
| Hypoglycemia | 1 (2%) | 0 | 0 | 1 (0.6%) |
| Other | 5 (9%) | 4 (7%) | 0 | 9 (5%) |
| Completers | 44 (75%) | 39 (71%) | 42 (79%) | 125 (75%) |

Twenty percent of metformin patients and approximately 10% of the glyburide and the metformin/glyburide patients discontinued due to lack of glycemic control.

Table 5 displays baseline demographic and diabetes characteristics for all randomized patients.

**Table 5 Baseline characteristics**

| | Metformin/Glyburide N=59 | Metformin N=55 | Glyburide N=53 | Total N=167 |
|---|---|---|---|---|
| Age (years) | | | | |
| 9-12 | 24 (41%) | 21 (38%) | 23 (43%) | 68 (41%) |
| 14-16 | 35 (59%) | 34 (62%) | 30 (57%) | 99 (59%) |
| Mean (SD) | 13.7 (1.8) | 13.6 (2.0) | 13.7 (2.0%) | 13.7 (1.9) |
| Median | 14.0 | 14.0 | 14.0 | 14.0 |
| Range | 10-16 | 9-16 | 9-16 | 9-16 |
| Gender | | | | |
| Male | 21 (36%) | 16 (29%) | 22 (42%) | 59 (35%) |
| Female | 38 (64%) | 39 (71%) | 31 (59%) | 108 (65%) |
| Race | | | | |
| White | 36 (61%) | 29 (53%) | 38 (72%) | 103 (62%) |
| Black | 14 (24%) | 13 (24%) | 8 (15%) | 35 (21%) |
| Asian/Pacific Islander | 2 (3%) | 3 (6%) | 1 (2%) | 6 (4%) |
| Hispanic/Latino | 7 (12%) | 10 (18%) | 5 (9%) | 22 (13%) |
| Other | 0 | 0 | 1 (2%) | 1 (0.6%) |
| Duration of diabetes | | | | |
| <1 year | 39 (66%) | 35 (64%) | 36 (68%) | 110 (66%) |
| ≥1 year | 20 (34%) | 20 (36%) | 17 (32%) | 57 (34%) |
| Mean (SD) | 1.04 (1.34) | 1.24 (1.80) | 0.95 (1.17) | 1.08 (1.46) |
| Median | 0.33 | 0.66 | 0.50 | 0.41 |
| Range | 0.00, 4.84 | 0.00, 10.21 | 0.00, 5.08 | 0.00, 10.21 |
| $HbA_{1c}$ (%) n | 59 | 54 | 51 | 164 |
| Mean (SD) | 7.82 (1.72) | 7.99 (1.59) | 7.68 (1.66) | 7.83 (1.65) |
| Median | 7.20 | 7.70 | 7.10 | 7.25 |
| Range | 5.0, 13.5 | 5.7, 12.7 | 5.2, 12.7 | 5.0, 13.5 |
| FPG (mg/dL) n | 57 | 53 | 50 | 160 |
| Mean (SD) | 152 (57) | 175 (67) | 153 (53) | 160 (60) |
| Median | 138 | 155 | 141 | 141 |
| Range | 83, 363 | 42, 313, | 61, 320 | 42, 363 |

The majority (66%) of patients were diagnosed with diabetes for less than 1 year. The mean baseline $HbA_{1c}$ was 7.8% and the mean FPG was 160 mg/dL.

Table 6 displays summary of the final dose received during the double-blind phase.

**Table 6 Summary of the final dose by treatment**

| # of tablets | Metformin/Glyburide, 250/1.25 mg N=59 | Metformin, 500mg N=55 | Glyburide, 2.5 mg N=52 |
|---|---|---|---|
| 1 | 16 (27%) | 11 (20%) | 16 (31%) |
| 2 | 14 (24%) | 7 (13%) | 9 (17%) |
| 3 | 13 (22%) | 8 (15%) | 6 (12%) |
| 4 | 16 (27%) | 29 (53%) | 21 (40%) |
| Mean dose | 623/3.1 mg | 1500 mg | 6.5 mg |

**Statistical Methodologies**

The sponsor used a hierarchical testing procedure to control the type 1 error. If the p-value for overall treatment effect was < 0.05 then the primary comparison of the Glucovance therapy group versus metformin monotherapy group was to be performed using a Contrast statement within the ANCOVA model described above. A secondary comparison of the Glucovance group to the glyburide monotherapy group was to be performed similarly.

The sponsor's method is incorrect for assessing efficacy in a combination study. The correct methodology is the Min test (Laska and Meisner). The combination has to be superior to both monotherapies which means the greater of the 2 p-values should be less than 0.05.

**Results and Conclusions**

The primary efficacy variable was $HbA_{1c}$ change from baseline to Week 26 or the last prior value of the double-blind treatment. The least square mean changes from baseline in $HbA_{1c}$ are summarized in Table 7.

**Table 7 Summary of $HbA_{1c}$ changes from baseline**

| | Metformin/Glyburide N=57 | Metformin N=54 | Glyburide N=49 |
|---|---|---|---|
| Mean dose | 623/3.1 mg | 1500 mg | 6.5 mg |
| Baseline Mean (SD) | 7.85 (1.74) | 7.99 (1.59) | 7.70 (1.69) |
| Week 26/Last Mean (SD) | 7.05 (1.88) | 7.46 (1.98) | 6.80 (1.40) |
| Adjusted Mean change from baseline (SE) | -0.8 (0.19) | -0.48 (0.20) | -0.96 (0.21) |
| Difference of Metformin/Glyburide vs. (SE) | | -0.32 (0.27) | +0.16 (0.28) |
| Overall p-value: 0.24 | | | |

The combination failed to show overall statistical significance over the monotherapies in the primary efficacy, change from baseline in $HbA_{1c}$ (p=0.24). It should be noted that the mean doses of

metformin and glyburide in the combination group were less than half the mean doses of the drugs when given as monotherapy.

There were no significant differences in the secondary efficacy variable, change from baseline in fasting plasma glucose (p=0.99). Mean reductions in FPG were 23.4 mg/dL, 24.5 mg/dL, and 22.9 mg/dL for the metformin/glyburide, metformin, and glyburide groups, respectively.

The sponsor concluded that [redacted] (b) (4)

[redacted] " This conclusion is incorrect in that [redacted] (b) (4)

This reviewer performed the Min test. The 2 p values of the comparisons to monotherapies were 0.3 (metformin) and 0.5 (glyburide). The smaller of the 2 p-values, 0.3 was greater than 0.05, therefore the combination is not efficacious in the pediatric population.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Descriptive statistics of $HbA_{1c}$ change from baseline is summarized in Table 8 by gender, race, age, baseline $HbA_{1c}$, and prior medication.

**Table 8 Summary of $HbA_{1c}$ change from baseline in subgroups**

| Subgroup | | Metformin/Glyburide | | Metformin | | Glyburide |
|---|---|---|---|---|---|---|
| | N | Mean change | N | Mean change (SE) | N | Mean change (SE) |
| Gender | | | | | | |
| Male | 21 | -0.88 (0.28) | 16 | -0.85 (0.42) | 21 | -0.68 (0.21) |
| Female | 36 | -0.75 (0.35) | 38 | -0.41(0.18) | 28 | -1.07 (0.35) |
| Race | | | | | | |
| White | 35 | -0.70 (0.18) | 28 | -0.55 (0.17) | 34 | -0.78 (0.19) |
| Black | 13 | -0.26 (0.54) | 13 | -0.53 (0.29) | 8 | -0.85 (1.00) |
| Hispanic/Latino | 7 | -1.79 (1.33) | 10 | -0.84 (0.67) | 5 | -1.58 (0.30) |
| Other | 2 | -2.50 (1.90) | 3 | +0.57 (1.24) | 2 | -1.55 (2.25) |
| Age | | | | | | |
| 9-13 years | 22 | -0.61 (0.50) | 20 | -0.56 (0.20) | 19 | -1.44 (0.37) |
| 14-16 years | 35 | -0.91 (0.24) | 34 | -0.53 (0.26) | 30 | -0.56 (0.25) |
| Baseline $HbA_{1c}$ | | | | | | |
| <7.0% | 20 | -0.09 (0.19) | 17 | -0.44 (0.14) | 22 | -0.40 (0.11) |
| 7.0%-<8.0% | 16 | -0.63 (0.39) | 15 | -0.48 (0.26) | 12 | -0.53 (0.37) |
| ≥ 8.0% | 21 | -1.60 (0.51) | 22 | -0.65 (0.39) | 15 | -1.93 (0.55) |
| Prior antidiabetes medication | | | | | | |
| Naïve | 32 | -1.35 (2.00) | 25 | -0.92 (1.28) | 25 | -1.12 (1.71) |
| Non-naïve | 25 | -0.09 (1.63) | 29 | -0.20 (1.26) | 24 | -0.68 (1.29) |

The treatment-by-subgroup interactions were not significant (p>0.1), however, the interaction test lacks power when the sample size is small. For naïve patients, the between treatment differences with Glucovance were the same as those observed in the adult trial of Glucovance as initial therapy for treatment comparisons with the 1.25/250 mg tablet.

The subgroup of prior antihyperglycemic medication was explored in $HbA_{1c}$ change from baseline for naïve and non-naïve patients (Figures 1 & 2). It showed that in naïve patients the combination performed better than the monotherapies but in the non naïve patients glyburide performed better.

**Figure 1 Boxplot of median $HbA_{1c}$ change from baseline by prior antihyperglycemic medication**

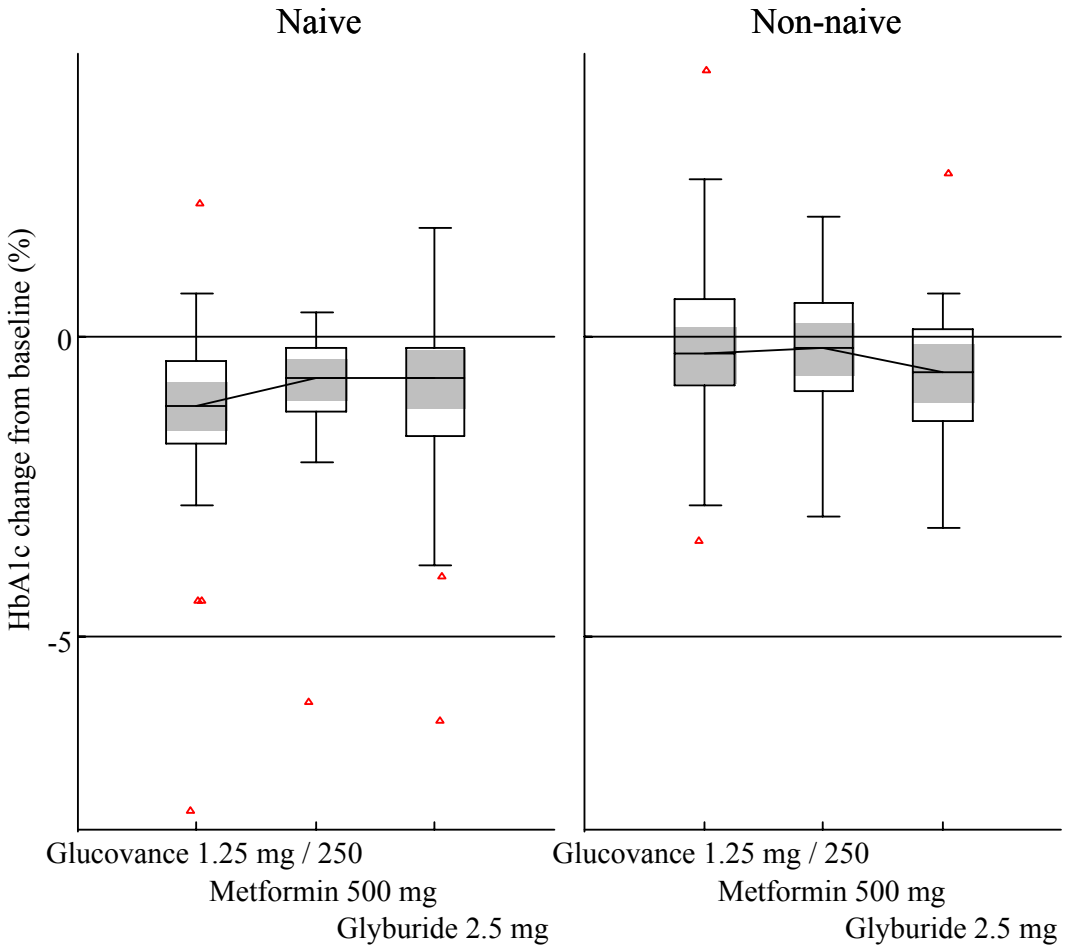
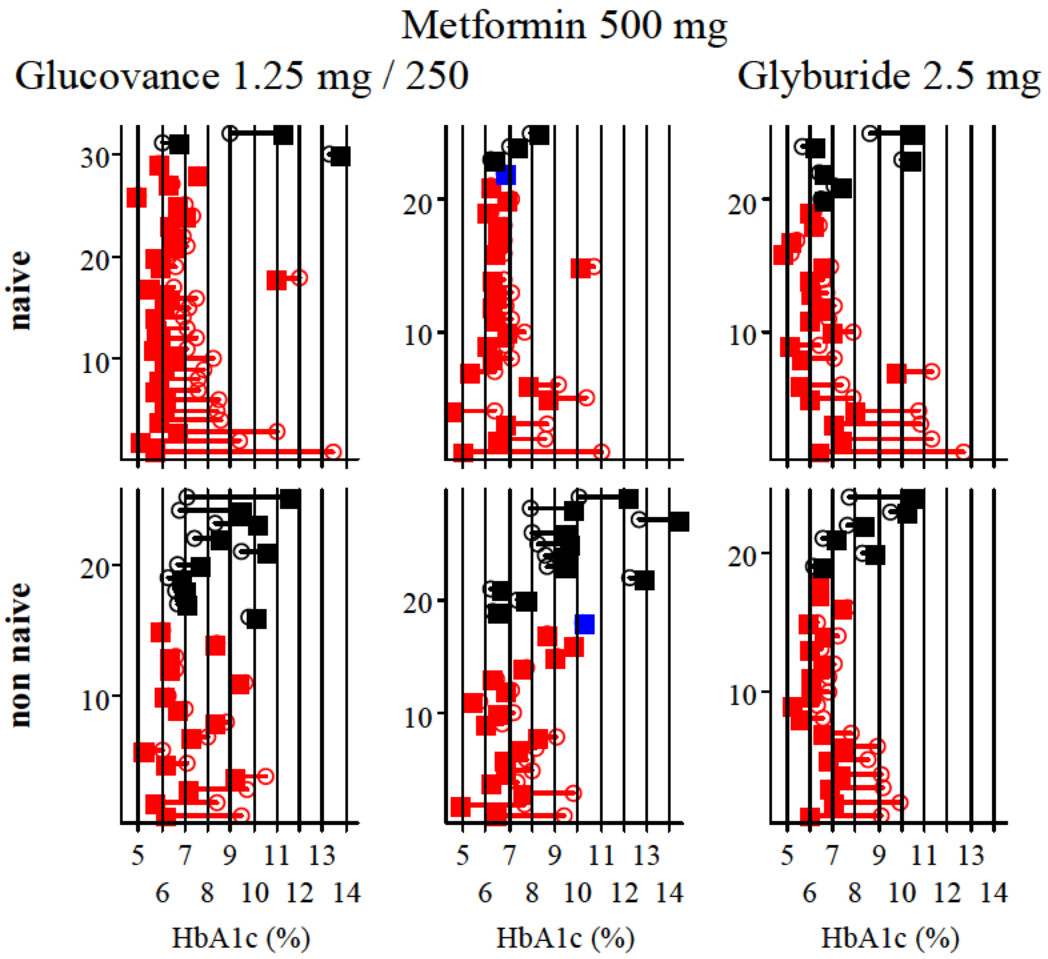


Figure 2 Patient $HbA_{1c}$ from baseline (circle) to endpoint (square) sorted by change from baseline $HbA_{1c}$ (↑, black, ↓, red, no change, blue)



## 5. SUMMARY AND CONCLUSIONS

The combination therapy of metformin/glyburide was not superior to metformin (p=0.3) or glyburide (p=0.5) monotherapies in the pediatric population. The final dose of the fixed combination 1.25/250 mg might not be sufficient for the non naïve patients.

The proposed label indicated that [redacted] (b) (4) The label should instead reflect the actual study results with respect to efficacy that the combination was not shown to be superior to the monotherapies at the doses studied.

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