CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-460

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	NDA 21460.....	APPLICATION TYPE:	NDA.....
SPONSOR:	Bristol-Myers Squibb.....	PROPRIETARY NAME:	MET/GLIP.....
CATEGORY OF DRUG:	Antidiabetic	USAN / Established Name:	Metformin/Glipizide.....
		ROUTE:	Oral.....
MEDICAL REVIEWER:	Robert I Misbin.	REVIEW DATE:	September 20, 2002.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Jan 23, 2002	Jan 24, 2002	Supplement to NDA	
Aug 15, 2001	Aug 16, 2002	Safety Update Information requested	

Met/Glip is a combination product containing metformin plus glipizide. This NDA contains data from two trials. The first trial demonstrated the efficacy/safety of Met/Glip as "first line therapy" in comparison to monotherapy with metformin or glipizide. The second trial demonstrated the efficacy/safety of Met/Glip in comparison to monotherapies with metformin or glipizide in patients who had been taking sulfonylureas. No serious or unexpected safety issues were found

Recommendation – Approval (with revised labeling)

Signed: Medical Reviewer: Robert I Misbin MD Date: September 20, 2002

Medical Team Leader: _____ Date: _____

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Executive Summary:

1. Recommendations:

The use of Metformin/Glipizide resulted in a clinically significant reduction in HbA1c. No new adverse events were observed. The adverse event profile and other physiological changes associated with Met/Glip in this NDA are similar to what has been observed in previous studies of metformin and glipizide

Pending changes in the label, I recommend that this NDA be approved.

2. Summary of Clinical Findings

Background

Metformin and glipizide are mainstays of the treatment of type 2 diabetes. Although it was not available in the United States until 1995, metformin had been widely used in Europe for many years before. The primary glucose lowering activity of metformin is to inhibit glucose production by the liver. Glipizide is one member of the sulfonylurea (SFU) class of compounds. These agents lower glucose levels by stimulating insulin secretion by the pancreatic beta cells. Because they have different mechanisms of action, metformin and glipizide are often used in combination

Met/Glip is a fixed dose combination product containing metformin plus glipizide. This NDA contains data from two trials. The first trial evaluated the efficacy/safety of Met/Glip in comparison to monotherapy with metformin or glipizide in patients who were not using other pharmacological treatment of diabetes when they were screened. This use is referred to as "first line therapy" The second trial compared Met/Glip to monotherapies with metformin or glipizide in patients who had already been taking a SFU at screening.This use is referred to as "second-line therapy".

Efficacy of Met/Glip as first line therapy (study 050):

The NDA contains results of an active-controlled trial designed to compare Met/Glip to monotherapy with metformin and glipizde in patients who were not taking pharmacological agents for treatment of diabetes. The trial was divided into three phases. There was a 2-week lead-in during which time patients were instructed in diet and exercise and home blood glucose monitoring. The double-blind portion consisted of 24 weeks. The patients were randomized into five arms, Met/Glip 250/1.25, Met/Glip 250/2.5, Met/Glip 500/2.5, metformin 500-mg or glipizide 5 mg. Study medication was titrated during the first 12 weeks in order to attempt to achieve a HbA1c of 7%. The

basis of dose titration was mean daily glucose (MDG) > 130 mg/dl with fasting glucose > 100 mg/dl. The maximum dose of study medication was two tablets twice daily. Matching placebo tablets for each of the study medications was provided to maintain blinding. Following the double-blind portion there was an open label extension in which all patients were treated with Met/Glip.

The primary efficacy variable was change in HbA1c after 24 weeks of double-blind treatment As shown in the table. Met/Glip 250/2.5 and Met/Glip 500/2.5 are both superior to each of the monotherapies. Met/Glip 250/1.25 had the same efficacy as Glipizide monotherapy. Dose sparing is also evident. For example, in patients on Met/Glip 250/2.5 a greater reduction in HbA1c was achieved than with metformin or glipizide monotherapies with less than half the dose of each of the components

	Met/Glip ——	Met/Glip 250/2.5	Met/Glip 500/2.5	Metformin 500 mg	Glipizide 5 mg
HbA1c, % baseline	8.97	9.06	9.10	9.15	9.17
HbA1c wk 24 or last	7.14	6.93	6.95	7.67	7.36
HbA1c change	-1.83	-2.3	-2.15	-1.49	-1.81
Weight change, kg	-0.7	-0.4	-0.5	-1.9	-0.2
Mean final Dose, mg	815/4.1	791/7.9	1477/7.4	1749	16.7

The Sponsor performed an analysis of reduction in HbA1c based on quintile of glycemia at baseline. The results of this analysis show that patients with the worst hyperglycemia at baseline got particularly good results with Met/Glip 250/2/5 and Met/Glip 500/2.5. At the lowest quintile of glycemia all five-treatment arms had approximately the same efficacy.

Efficacy of Met/Glip as Second line therapy (study 060):

This was a randomized double-blind active-controlled trial designed to investigate the efficacy of Met/Glip in patients with type 2 diabetes, ages 25-78, who were inadequately controlled on at least half maximal dose of a SFU. Patients were enrolled into a 2-week run-in of Glipizide 15 mg bid. Patients were randomized to one of three treatments for the 18-week double-blind portion. Metformin/Glipizide was started at 500mg/5 mg and increased to 1000 mg/10mg after one week. Metformin was started at 500 mg and increased to 1000 mg after one week. Both these study medications were titrated based for MDG > 130 mg/dl at weeks 3,5, and 8. The maximal dose of Met/Glip was 2000 mg/20 mg (two tablets bid). The maximum dose of metformin was 2000 mg (two 500-mg

tablets bid). Patients randomized to glipizide monotherapy received 30 mg (15 mg bid) throughout the trial. Blinding was accomplished with placebo tablets.

Table 8.1B: Reasons for Discontinuation During Double-Blind Therapy

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)

CV138-060

The primary measure of efficacy, change in HbA1c, is shown in the following table. There was little change with either of the monotherapies, but a mean reduction of about 1% unit with Met/Glip. Dose sparing for each of the components was also demonstrated.

Table 10.1.1.1: Mean HbA_{1c} Level at Week 18 or the Last Prior Measurement

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)

CV138-060

Safety (both trials):

There was one death during the double-blind portion of study 050. This patient received Met/Glip 250/1.25 for 85 days and was diagnosed with acute myelogenous leukemia. The drug was discontinued and she died 21 days later of pulmonary hemorrhage. Three patients died during the open-label extension, two from cerebrovascular accidents and one from an acute myocardial infarction. There were no deaths in Study 060. Serious adverse events were few and appeared unrelated to study medications

Adverse events were largely gastrointestinal (a well-recognized side effect of metformin). Reporting of hypoglycemia as an adverse event was consistent with the reduction in HbA1c. **The one draw back in the use of Met/Glip is that the weight-sparing effect of the metformin component appears to be largely dissipated by the addition of the glipizide component.**

In summary, the use of Met/Glip resulted in clinically significant reduction on HbA1c. No new adverse events were observed. The adverse event profile and other physiological changes associated with Met/Glip in this NDA are similar to what has been observed in previous studies of metformin and glipizide.

Clinical Review

1 Introduction and Background:

Metformin and glipizide are mainstays of the treatment of type 2 diabetes. Although it was not available in the United States until 1995, metformin had been widely used in Europe for many years before. The primary glucose lowering activity of metformin is to inhibit glucose production by the liver. Glipizide is one member of the sulfonylurea (SFU) class of compounds. These agents lower glucose levels by stimulating insulin secretion by the pancreatic beta cells.

Because they have different mechanisms of action, metformin and sulfonylureas are often used in combination. Glipizide and glyburide are the most commonly used sulfonylureas. Bristol-Myers Squibb has previously marketed a fixed dose combination of metformin and glyburide (GLUCOVANCE). Although originally developed to provide the convenience of a single tablet for patients who were taking metformin in combination with a sulfonylurea, Glucovance can be used also as first-line therapy for patients not previously treated with pharmacological agents.

Met/Glip is a fixed dose combination product containing metformin plus glipizide. This NDA contains data from two trials. The first trial (050) evaluated the efficacy/safety of Met/Glip in comparison to monotherapy with metformin or glipizide in patients who had not using other pharmacological treatment of diabetes when they were screened. This use is referred to as "first line therapy" The second trial (060) compared Met/Glip to monotherapies with metformin or glipizide in patients who had already been taking a SFU at screening. This use is referred to as "second-line therapy".

2 **Clinically relevant findings from Chemistry, Toxicology, Biopharmaceuticals, statistics and other consultants:** No additional comments

3 **Human Pharmacokinetics and Pharmacodynamics**: No additional comments

4 **Clinical data and Sources**: The results of two phase 3 trials (138-060 and 138-050) were submitted. This is described in detail in section 6 "Review of Efficacy" and 7 "Review of safety".

5 **Clinical Review Methods**: The review was conducted of the hard copy of the summary of the NDA with reference to other documents that had been submitted electronically No routine inspections of the sites were performed. Although the consent documents were not reviewed, the trials appears to have been conducted in accordance with acceptable ethical standards. The escape criteria for lack of efficacy are praiseworthy. The financial disclosure documentation appears adequate.

Regulatory statements regarding documents reviewed:

The Sponsor, Bristol-Myers Squibb (BMS) submitted debarment and financial disclosure documents. I have examined these documents and found them to be acceptable. The debarment statement indicated that no investigator who had been debarred as of Oct 3, 2002 had data in the submission.

The Sponsor makes reference to FDA form 3455. The following financial disclosure information has been submitted:

1 Form OMB No. 0910-0396. The applicant certifies that BMS has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study – signed by Dr Fred Fiodorek Dec 12, 2001.

2 The applicant furthers certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in BMS.

3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from BMS.

4 List of investigators from whom completed financial disclosure forms were received.

5 Certification pursuant to 21 CFR 54.5(c) that the applicant acted with due diligence to obtain financial disclosure information from a list of investigators from whom completed forms were never received.

6 List of investigators not submitting financial disclosure information and the studies to which they contributed data.

7 The investigators listed as not submitting financial disclosure forms each contributed data from single sites in large, multicenter trials. Analyses of efficacy data in this NDA did not reveal any significant effect of center on outcomes. Furthermore, the data on both safety and effectiveness were consistent across the multiple trials submitted to the NDA. In sum, the absence of financial disclosure information from the investigators listed does not call into question the overall integrity of the data submitted.

6 Review of Efficacy

Study 138 – 50 - Met/Glip as first line therapy

This was an active-control trial to compare Met/Glip to monotherapy with metformin and glipizide in patients who were not taking pharmacological agents for treatment of diabetes. The trial was divided into three phases. There was a 2-week lead-in during which time patients were instructed in diet and exercise and home blood glucose monitoring. They were given placebo tablets to assess compliance. The double-blind portion consisted of 24 weeks. The patients were randomized into five arms, Met/Glip 250/1.25, Met/Glip 250/2.5, Met/Glip 500/2.5, metformin 500-mg or glipizide 5 mg. Study medication was titrated during the first 12 weeks in order to achieve a HbA1c of 7%. The basis of dose titration was MDG > 130 mg/dl and FG > 100 mg/dl based on home glucose monitoring.. The maximum dose of study medication was two tablets twice daily. Matching placebo tablets for each of the study medications was provided to maintain blinding.

Table 5.5.1A: Double-Blind Study Drug Supply

Bottle	Study Drug (or matching placebo)	Level 1 (initial dose)		Level 2		Level 3		Level 4	
		AM	PM	AM	PM	AM	PM	AM	PM
A	Glipizide 5 mg oval-shaped tablet	1	0	1	1	2	1	2	2
B	Metformin HCl 500 mg oval-shaped tablet	1	0	1	1	2	1	2	2
C	Metformin HCl/glipizide 250/1.25 mg or metformin HCl/glipizide 250/2.5 mg oval-shaped tablets	1	0	1	1	2	1	2	2
D	Metformin HCl/glipizide 500/2.5 mg oval-shaped tablet	1	0	1	1	2	1	2	2

CV138-050

Study Drug	Low Dose Met/Glip 250/1.25 mg	Intermediate Dose Met/Glip 250/2.5 mg	High Dose Met/Glip 500/2.5 mg	Metformin 500 mg	Glipizide 5 mg
Level 1	250/1.25 mg	250/2.5 mg	500/2.5 mg	500 mg	5 mg
Level 2	500/2.5 mg	500/5 mg	1000/5 mg	1000 mg	10 mg
Level 3	750/3.75 mg	750/7.5 mg	1500/7.5 mg	1500 mg	15 mg
Level 4	1000/5 mg	1000/10 mg	2000/10 mg	2000 mg	20 mg

. The study outline and entry/withdrawal criteria are shown in the following schematic:

Screening Period

Determination of glycemic control

Subjects were to be either drug naive or have discontinued antihyperglycemic therapy for at least 8 weeks, or thiazolidinedione therapy for at least 12 weeks, prior to screening. On diet and exercise, subjects must have had inadequate glycemic control with HbA_{1c} > 7.5% to ≤ 12.0% but FPG < 300 mg/dL

Period A: Single-Blind Placebo Lead-In Phase (2 weeks)

- Instruction in weight maintenance/ADA recommended diet
- MDG > 140 mg/dL; site fingerstick > 120 mg/dL
- Blood glucose ratio ≥ 0.8 - ≤ 1.2
- Compliance with lead-in study drug ≥ 80% - ≤ 120%
- Subject willing to perform SMBG and continue with the study

Period B: Randomized Double-Blind Treatment Phase (24 weeks)

At Day 15/Week 0, subjects meeting randomization criteria were randomized to one of the following 5 arms:

- metformin/glipizide 250/1.25 mg
- metformin/glipizide 250/2.5 mg
- metformin/glipizide 500/2.5 mg
- glipizide 5 mg
- metformin HCl 500 mg

Scheduled visits at Weeks 2, 4, 6, 9, 12, 18, and 24

Titration Phase (Weeks 0-12):

At Weeks 2, 4, 6, 9, and 12, if MDG > 130 mg/dL and site fingerstick glucose >100mg/dL, subjects were titrated to the next higher dose level until maximum dose was reached.

In addition, subjects not on maximum dose at Week 12 (and not titrated at Week 9) with HbA_{1c} ≥ 7.0% were titrated to the next level.

Dose Stable Phase (Weeks 13-24):

Subjects then continued on a stable dose (unless hypoglycemia criteria for down-titration were met)

Criteria for Discontinuation Due to Inadequate Glycemic Control

- Week 6 MDG > 280 mg/dL
- Week 9 MDG > 240 mg/dL
- Weeks 12 or Week 18 MDG > 200 mg/dL

An open-label phase followed the 24-week double-blind phase. Subjects were given Met/Glip based on their HbA1c level and titrated to achieve glycemic control.

Patient disposition is shown in the following figure and table. The overall level of completion of the double-blind portion was about 85%. The only noteworthy differences

among the five arms is that more patients on metformin monotherapy withdrew than for the other arms.

Figure 8.1: Subject Disposition

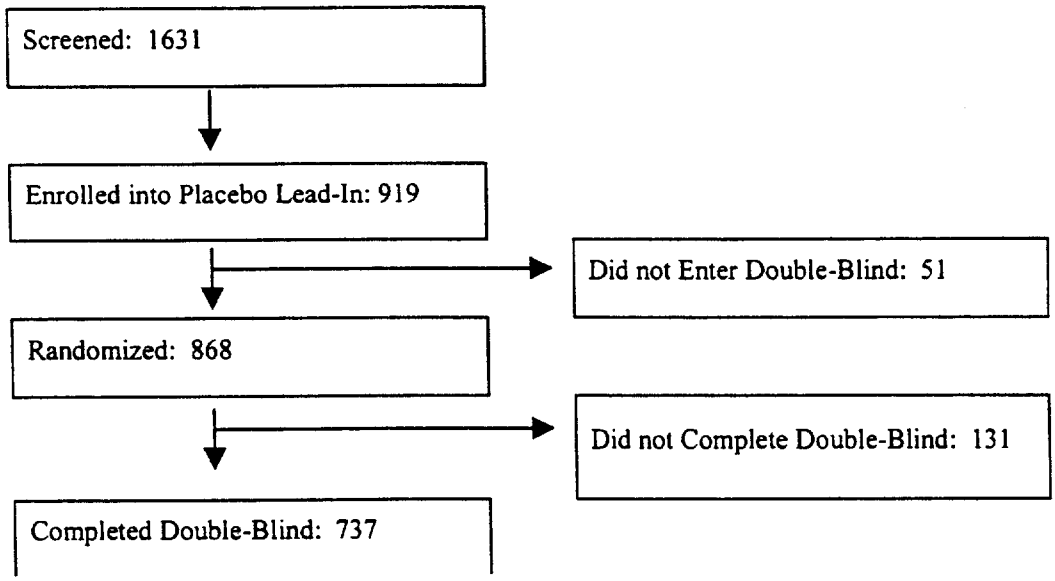


Table 8.1B: Reasons for Discontinuation During Double-Blind Therapy

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)

Table 10.6: Subjects Discontinuing Double-Blind Treatment Due to Lack of Glycemic Control

	Met/Glip 250/1.25 mg N = 176	Met/Glip 250/2.5 mg N = 172	Met/Glip 500/2.5 mg N = 173	Metformin 500 mg N = 177	Glipizide 5 mg N = 170
No. (%) Discontinued due to lack of glycemic control	10 (5.7%)	7 (4.1%)	5 (2.9%)	20 (11.3%)	14 (8.2%)
Difference vs. Metformin Group[a]					
(95% CI)[b]	-5.6% (-16.9, 2.6)	-7.2% (-18.0, 0.8)	-8.4% (-18.9, -0.8)		
P-value[c]	0.084	0.015	0.003		
Difference vs. Glipizide Group[a]					
(95% CI)[b]	-2.5% (-13.7, 5.7)	-4.1% (-14.7, 3.8)	-5.3% (-15.6, 2.2)		
P-value[c]	0.401	0.120	0.035		

At baseline, patients had a mean age of 56 years with 3.3 years duration of diabetes. They were 57% female and 95% white. The mean BMI was 30.8 and body weight 86 kg. 58% were naïve to therapy. Mean HbA1c was 9.1%, FPG 206 mg/dl, fructosamine 330 mM/L and fasting insulin 12 uU/mL. There were no major differences among the treatment arms with respect to baseline characteristics.

Final dose of study medications:

The final doses of study medication for all patients, for patients with FPG 240-280 mg/dl, and for patients with FPG>280 are given in the following three tables.

Table 9.1.1B: Final Dose of Study Medication Received During Double-Blind Therapy

Dose (mg/day)	Met/glip 250/1.25 mg N = 176	Met/glip 250/2.5 mg N = 172	Met/glip 500/2.5 mg N = 173	Metformin 500 mg N = 177	Glipizide 5 mg N = 170
Level 1 n (%)	250/1.25 mg 9 (5.1)	250/2.5 mg 15 (8.7)	500/2.5 mg 23 (13.3)	500 mg 13 (7.3)	5 mg 11 (6.5)
Level 2 n (%)	500/2.5 mg 41 (23.3)	500/5 mg 36 (20.9)	1000/5 mg 43 (24.9)	1000 mg 18 (10.2)	10 mg 28 (16.5)
Level 3 n (%)	750/3.75 mg 21 (11.9)	750/7.5 mg 27 (15.7)	1500/7.5 mg 26 (15.0)	1500 mg 14 (7.9)	15 mg 23 (13.5)
Level 4 n (%)	1000/5 mg 105 (59.7)	1000/10 mg 94 (54.7)	2000/10 mg 81 (46.8)	2000 mg 132 (74.6)	20 mg 108 (63.5)
Mean Final Dose, mg	815.3/4.1 mg	790.7/7.9 mg	1476.9/7.4 mg	1748.6 mg	16.7 mg

Table 9.5A: Final Dose of Study Medication Received During Double-Blind Therapy for Subjects with Baseline FPG Greater Than or Equal to 240 and Less Than 280 mg/dL

Dose (mg/day)	Met/Glip 250/1.25 mg N = 30	Met/Glip 250/2.5 mg N = 28	Met/Glip 500/2.5 mg N = 25	Metformin 500 mg N = 30	Glipizide 5 mg N = 29
Level 1 (500) n (%)	250/1.25 mg 1 (3.3)	250/2.5 mg 0	500/2.5 mg 1 (4.0)	500 mg 1 (3.3)	5 mg 1 (3.4)
Level 2 (1000) n (%)	500/2.5 mg 3 (10.0)	500/5 mg 2 (7.1)	1000/5 mg 2 (8.0)	1000 mg 1 (3.3)	10 mg 1 (3.4)
Level 3 (1500) n (%)	750/3.75 mg 1 (3.3)	750/7.5 mg 5 (17.9)	1500/7.5 mg 2 (8.0)	1500 mg 0	15 mg 3 (10.3)
Level 4 (2000) n (%)	1000/5 mg 25 (83.3)	1000/10 mg 21 (75.0)	2000/10 mg 20 (80.0)	2000 mg 28 (93.3)	20 mg 24 (82.8)
Mean Final Dose	916.7/4.6 mg	919.6/9.2 mg	1820.0/9.1 mg	1916.7 mg	18.6 mg

Table 9.5B: Final Dose of Study Medication Received During Double-Blind Therapy, for Subjects with Baseline FPG Greater Than or Equal to 280 mg/dL

Dose (mg/day)	Met/Glip 250/1.25 mg N = 13	Met/Glip 250/2.5 mg N = 17	Met/Glip 500/2.5 mg N = 18	Metformin 500 mg N = 18	Glipizide 5 mg N = 17
Level 1 (500)	250/1.25 mg	250/2.5 mg	500/2.5 mg	500 mg	5 mg
n (%)	0	0	0	0	0
Level 2 (1000)	500/2.5 mg	500/5 mg	1000/5 mg	1000 mg	10 mg
n (%)	0	1 (5.9)	1 (5.6)	2 (11.1)	0
Level 3 (1500)	750/3.75 mg	750/7.5 mg	1500/7.5 mg	1500 mg	15 mg
n (%)	1 (7.7)	0	4 (22.2)	0	1 (5.9)
Level 4 (2000)	1000/5 mg	1000/10 mg	2000/10 mg	2000 mg	20 mg
n (%)	12 (92.3)	16 (94.1)	13 (72.2)	16 (88.9)	16 (94.1)
Mean Final Dose	980.8/4.9 mg	970.6/9.7 mg	1833.3/9.2 mg	1888.9 mg	19.7 mg

Efficacy results:

The primary efficacy variable was change in HbA1c at 24 weeks or LPM.
The result are shown in the following table.It can be seen that Met/Glip 250/2.5 and Met/Glip 500/2.5 are both superior to each of the monotherapies. Met/Glip —— had the same efficacy as Glipizide monotherapy. Dose sparing is also evident. For example, in patients on Met/Glip 250/2.5 the greater reduction in HbA1c was achieved than with metformin or glipizide monotherapies with less than half the dose of each of the components.

Table 10.1.1.1: Mean Change from Baseline in HbA_{1c} at Week 24 or Last Prior Measurement

Unit: %	Met/Glip 250/1.25 mg (n = 173)	Met/Glip 250/2.5 mg (n = 166)	Met/Glip 500/2.5 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)
Week 24/LPM Mean (SD)	7.14 (1.22)	6.93(1.02)	6.95 (1.02)	7.67 (1.25)	7.36 (1.11)
Unadjusted Mean Change	-1.83	-2.13	-2.15	-1.49	-1.81
Adjusted Mean Change from Baseline (SE)[a]	**Comparisons are not valid**	-2.15 (0.08)	-2.14 (0.08)	-1.46 (0.07)	-1.77 (0.08)
Difference vs. Metformin Group[b] (SE)[a]	**Comparisons are not valid**	-0.70 (0.11)	-0.69 (0.11)		
One-sided p-value		< 0.001	< 0.001		
Difference vs. Glipizide Group[b] (SE)[a]	**Comparisons are not valid**	-0.38 (0.11)	-0.37 (0.11)		
One-sided p-value		< 0.001	< 0.001		
Test for Superiority of Met/Glip over Monotherapies: p-value[c]	**Comparisons are not valid**	< 0.001	< 0.001		
Mean Final Dose, mg (number of subjects)	815.3/4.1 (176)	790.7/7.9 (172)	1476.9/7.4 (173)	1748.6 (177)	16.7 (170)

The distribution of final HbA1c values are shown in the following table:

Table 10.1.1.3: Distribution of Absolute HbA_{1c} and Change from Baseline in HbA_{1c} at Week 24 or LPM

	Number (%) of Subjects				
	Met/Glip 250/1.25 mg n = 173	**Met/Glip 250/2.5 mg n = 166**	**Met/Glip 500/2.5 mg n = 163**	**Metformin 500 mg n = 171**	**Glipizide 5 mg n = 168**
Absolute HbA_{1c}					
< 7.0%	94 (54.3)	99 (59.6)	93 (57.1)	60 (35.1)	73 (43.5)
7.0% - 8.0%	53 (30.6)	48 (28.9)	53 (32.5)	52 (30.4)	57 (33.9)
> 8.0%	26 (15.0)	19 (11.4)	17 (10.4)	59 (34.5)	38 (22.6)
Decrease from Baseline in HbA_{1c}					
< 0.5% or increase	13 (7.5)	9 (5.4)	8 (4.9)	32 (18.7)	23 (13.7)
0.5% - < 1.0%	18 (10.4)	18 (10.8)	16 (9.8)	27 (15.8)	16 (9.5)
1.0% - < 1.5%	30 (17.3)	25 (15.1)	19 (11.7)	31 (18.1)	24 (14.3)
1.5% - 2.0%	38 (22.0)	27 (16.3)	34 (20.9)	25 (14.6)	30 (17.9)
> 2.0%	74 (42.8)	87 (52.4)	86 (52.8)	56 (32.7)	75 (44.6)

Subgroup analysis did not show any differences from the mean values for the whole population. There were no differences based on age, gender or ethnic background, except that males did somewhat better on glipizide monotherapy. There was adequate exposure to patients at least 65 years old as shown in the following table.

Unit: % Subgroup	**Met/Glip 250/1.25 mg N = 173**	**Met/Glip 250/2.5 mg N = 166**	**Met/Glip 500/2.5 mg N = 163**	**Metformin 500 mg N = 171**	**Glipizide 5 mg N = 168**
Age:					
< 65 years, n	143	137	125	133	137
Baseline mean (SD)	8.97 (1.19)	9.15 (1.25)	9.17 (1.11)	9.18 (1.13)	9.15 (1.18)
Mean change (SE)	-1.77 (0.09)	-2.16 (0.10)	-2.16 (0.11)	-1.52 (0.11)	-1.79 (0.10)
≥ 65 Years, n	30	29	38	38	31
Baseline mean (SD)	8.99 (1.34)	8.66 (1.25)	8.87 (1.22)	9.04 (0.97)	9.24 (0.88)
Mean change (SE)	-2.13 (0.19)	-1.99 (0.24)	-2.12 (0.15)	-1.35 (0.21)	-1.88 (0.15)

An interaction with obesity was not analyzed. The only subgroup analysis outcome worth noting is that patients with lower baseline HbA1c did equally well on Met/Glip 250/1.25 as on the two higher dose preparations. Patients with higher HbA1c at baseline did not do as well on Met/Glip 250/1.25 (see below). Although not shown in the table below, it must be born in mind that the maximum dose allowed for any study medication was four tablets per day. Thus the maximal dose of medication that patients randomized to 250/1.25 could achieve was 1000 mg of metformin plus 5 mg of glipizide. Also shown below is that naïve patients did better on all treatments than those who had had a history of previous drug use.

	250/1.25	**250/2.5**	**500/2.5**	**Metformin Glipizide**	
Baseline HbA_{1c} Category:					
< 8%, n	40	33	28	30	23
Baseline mean (SD)	7.62 (0.25)	7.51 (0.36)	7.63 (0.21)	7.68 (0.23)	7.59 (0.33)
Mean change (SE)	-1.23 (0.09)	-1.14 (0.10)	-1.04 (0.12)	-0.85 (0.12)	-0.82 (0.16)
8 - < 9%, n	62	52	50	48	56
Baseline mean (SD)	8.43 (0.28)	8.41 (0.31)	8.44 (0.27)	8.48 (0.28)	8.46 (0.28)
Mean change (SE)	-1.72 (0.08)	-1.58 (0.12)	-1.80 (0.11)	-0.97 (0.16)	-1.47 (0.10)
9 - <10%, n	30	37	49	51	48
Baseline mean (SD)	9.42 (0.28)	9.37 (0.31)	9.42 (0.28)	9.43 (0.29)	9.41 (0.30)
Mean change (SE)	-2.11 (0.17)	-2.56 (0.12)	-2.60 (0.10)	-1.69 (0.16)	-2.11 (0.13)
10 - <11%, n	29	33	25	34	29
Baseline mean (SD)	10.46 (0.28)	10.42 (0.28)	10.40 (0.30)	10.44 (0.28)	10.45 (0.25)
Mean change (SE)	-2.46 (0.24)	-3.03 (0.22)	-2.82 (0.28)	-2.21 (0.22)	-2.36 (0.20)
≥ 11%, n	12	11	11	8	12
Baseline mean (SD)	11.53 (0.36)	11.71 (0.66)	11.53 (0.71)	11.49 (0.48)	11.43 (0.60)
Mean change (SE)	-2.23 (0.57)	-3.64 (0.38)	-3.08 (0.52)	-2.60 (0.46)	-2.70 (0.54)
Prior Use of Anti-hyperglycemics:					
Naive, n	107	98	93	97	94
Baseline mean (SD)	8.86 (1.22)	8.97 (1.26)	9.01 (1.11)	8.97 (1.10)	9.05 (1.08)
Mean change (SE)	-1.98 (0.10)	-2.36 (0.12)	-2.30 (0.12)	-1.76 (0.12)	-1.91 (0.12)
Not naive, n	66	68	70	74	74
Baseline mean (SD)	9.15 (1.19)	9.19 (1.26)	9.23 (1.17)	9.39 (1.05)	9.32 (1.19)
Mean change (SE)	-1.59 (0.12)	-1.81 (0.13)	-1.95 (0.14)	-1.13 (0.14)	-1.67 (0.12)

The Sponsor performed an analysis of reduction in HbA1c based on quintile of glycemia at baseline. The results of this analysis (table follows) show that patients with the worst hyperglycemia at baseline get particularly good results with Met/Glip 250/2/5 and Met/Glip 500/2.5. At the lowest quintile of glycemia all five-treatment arms had approximately the same results.

Table 10.9.3: Mean Change from Baseline in HbA_{1c} at Week 24 or LPM, by Baseline FPG Category

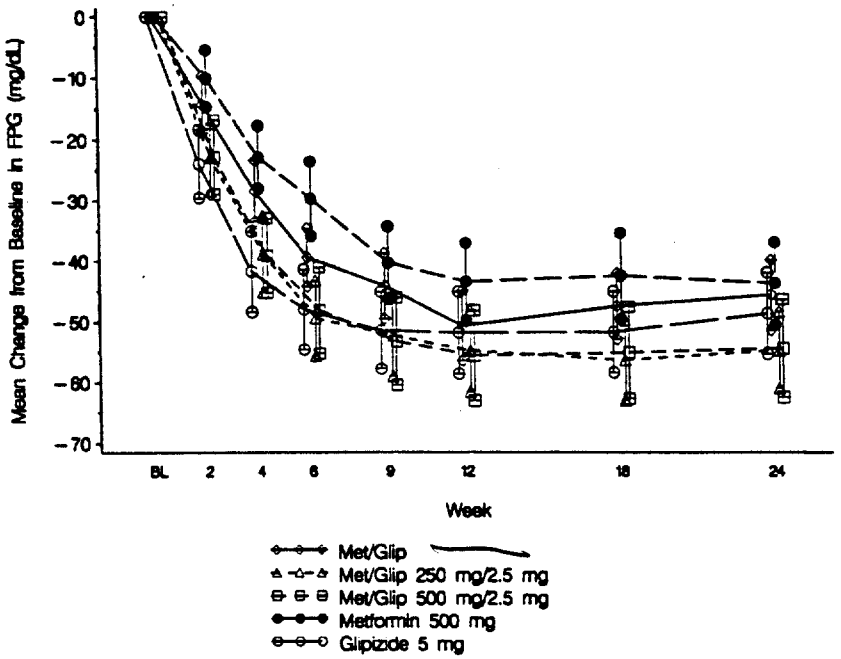
Baseline FPG Category Unit: %	Met/Glip 250/1.25 mg N = 173	Met/Glip 250/2.5 mg N = 166	Met/Glip 500/2.5 mg N = 163	Metformin 500 mg N = 171	Glipizide 5 mg N = 168
< 160 mg/dL, n	40	33	35	33	26
Baseline mean (SD)	8.0 (0.7)	8.0 (0.8)	8.4 (1.2)	8.5 (1.0)	8.2 (0.8)
Mean change (SE)	-1.6 (0.1)	-1.4 (0.1)	-1.8 (0.2)	-1.8 (0.2)	-1.5 (0.2)
160-< 200 mg/dL, n	56	52	53	45	56
Baseline mean (SD)	8.6 (0.8)	8.7 (1.1)	8.8 (0.9)	8.6 (0.8)	8.8 (0.8)
Mean change (SE)	-1.9 (0.1)	-2.1 (0.2)	-2.1 (0.1)	-1.3 (0.1)	-1.7 (0.1)
200- < 240 mg/dL, n	35	38	33	49	40
Baseline mean (SD)	9.1 (1.1)	9.2 (0.8)	9.2 (0.9)	9.2 (0.8)	9.4 (1.0)
Mean change (SE)	-2.0 (0.2)	-2.3 (0.2)	-2.1 (0.2)	-1.5 (0.2)	-2.1 (0.2)
240- < 280 mg/dL, n	29	27	24	27	29
Baseline mean (SD)	10.0 (0.9)	10.0 (1.1)	10.0 (1.1)	10.0 (1.0)	10.1 (0.8)
Mean change (SE)	-1.9 (0.3)	-2.8 (0.2)	-2.5 (0.2)	-1.7 (0.3)	-2.1 (0.2)
≥ 280 mg/dL, n	13	16	18	17	17
Baseline mean (SD)	11.0 (0.5)	10.4 (1.5)	10.1 (0.9)	10.4 (0.9)	9.9 (1.5)
Mean change (SE)	-1.7 (0.4)	-2.1 (0.3)	-2.5 (0.4)	-1.0 (0.4)	-1.4 (0.4)

Changes in fasting glucose are shown in the next table and figure. The results are consistent with the change in HbA1c presented earlier. The two higher dose preparations of Met/Glip are superior to both monotherapies. The maximum effect appears to be evident at 12 weeks

Table 10.2.1.1: Mean Change from Baseline in FPG at Week 24 or LPM

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)

Figure 10.2.1.2A: Mean Change from Baseline (95 Percent CI) in FPG Over Time, (LOCF)



A shown in the table below, Met/Glip 500.2.5 was particularly effective in patients whose FPG was 280 mg/dl or greater at baseline.

Table 10.2.2: Mean Change from Baseline in FPG at Week 24 or LPM, 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)

Changes in fructosamine levels for each quintile of glycemia are shown in the next table. The superiority of Met/Glip 500/2.5 is most evident in patients whose FPG was > 280 mg/dl. These results are consistent with the changes in HbA1c and FPG shown already.

Table 10.9.2: Mean Change from Baseline in Fructosamine at Week 24 or LPM, by Baseline FPG Category

Baseline FPG Category Unit: µmol/L	Met/Glip 250/1.25 mg N = 172	Met/Glip 250/2.5 mg N = 167	Met/Glip 500/2.5 mg N = 165	Metformin 500 mg N = 169	Glipizide 5 mg N = 163
< 160 mg/dL, n	41	33	37	33	24
Baseline mean (SD)	284.2 (43.7)	287.5 (35.8)	288.3 (60.0)	284.2 (42.9)	285.3 (31.3)
Mean change (SE)	-51.2 (6.6)	-47.6 (5.6)	-52.1 (8.4)	-40.5 (5.9)	-49.0 (6.1)
160-< 200 mg/dL, n	56	52	55	42	55
Baseline mean (SD)	316.2 (42.9)	309.1 (44.2)	301.4 (44.1)	307.1 (41.2)	305.3 (32.0)
Mean change (SE)	-75.5 (4.8)	-69.1 (6.0)	-66.3 (5.3)	-49.1 (6.4)	-56.5 (4.4)
200- < 240 mg/dL, n	35	39	32	49	38
Baseline mean (SD)	346.4 (54.7)	356.3 (70.3)	329.6 (43.6)	341.1 (35.2)	347.6 (58.1)
Mean change (SE)	-90.0 (7.7)	-106.3 (10.7)	-85.4 (9.3)	-66.7 (6.5)	-83.6 (7.2)
240- < 280 mg/dL, n	27	28	23	29	29
Baseline mean (SD)	361.9 (57.3)	377.4 (56.4)	370.7 (42.5)	363.2 (40.6)	380.6 (66.9)
Mean change (SE)	-83.5 (10.8)	-110.4 (10.2)	-113.0 (7.3)	-71.6 (8.5)	-98.3 (15.1)
> = 280 mg/dL, n	13	15	18	16	17
Baseline mean (SD)	399.8 (31.6)	402.7 (65.0)	411.6 (60.9)	403.4 (46.2)	382.4 (43.8)
Mean change (SE)	-90.2 (11.8)	-98.3 (13.4)	-138.8 (14.2)	-83.3 (13.3)	-71.1 (16.7)

Table 10.3.1: Mean Change from Baseline in Fructosamine at Week 24 or LPM

Unit: µmol/L	Met/Glip 250/1.25 mg n = 172	Met/Glip 250/2.5 mg n = 167	Met/Glip 500/2.5 mg n = 165	Metformin 500 mg n = 169	Glipizide 5 mg n = 163
Baseline Mean (SD)	328.2 (57.9)	335.7 (65.8)	325.6 (63.4)	331.2 (53.5)	333.7 (59.3)
Week 24/LPM Mean (SD)	253.2 (39.9)	252.7 (38.7)	244.4 (38.5)	271.6 (45.7)	263.0 (48.2)
Unadjusted Mean Change	-75.0	-83.1	-81.2	-59.6	-70.7
Adjusted Mean Change from Baseline (SE)[a]	-76.7 (2.7)	-80.1 (2.7)	-84.4 (2.7)	-59.4 (2.7)	-69.0 (2.8)
Difference vs. Metformin Group[b] (SE)[a]	-17.3 (3.8)	-20.7 (3.8)	-25.0 (3.9)		
(95% CI)[c]	(-26.3, -8.2)	(-29.8, -11.6)	(-34.2, -15.9)		
P-value[d]	< 0.001	< 0.001	< 0.001		
Difference vs. Glipizide Group[b] (SE)[a]	-7.7 (3.9)	-11.1 (3.9)	-15.5 (3.9)		
(95% CI)[c]	(-16.8, 1.5)	(-20.3, -1.9)	(-24.7, -6.2)		
P-value[d]	0.047	0.004	< 0.001		

Changes in postprandial glucose (after a standardized formula meal) are shown below

Table 10.2.1.4: Mean Change from Baseline in Postprandial Plasma Glucose 3-Hour Incremental AUC at Week 24 or LPM

Unit: (mg/dL) x min	Met/Glip 250/1.25 mg n = 156	Met/Glip 250/2.5 mg n = 149	Met/Glip 500/2.5 mg n = 147	Metformin 500 mg n = 153	Glipizide 5 mg n = 153
Baseline Mean (SD)	45982 (12063)	46429 (11413)	46391 (12332)	47340 (12329)	47506 (11048)
Week 24/LPM Mean (SD)	33073 (8136)	32660 (8935)	32517 (7920)	35283 (9042)	35905 (9629)
Unadjusted Mean Change	-12909	-13769	-13874	-12058	-11601
Adjusted Mean Change from Baseline (SE)[a]	-13330 (566)	-13939 (579)	-14065 (583)	-11715 (571)	-11165 (571)
Difference vs. Metformin Group[b] (SE)[a]	-1615 (804)	-2224 (813)	-2350 (816)		
(95% CI)[c]	(-3522, 291)	(-4152, -296)	(-4284, -415)		
P-value[d]	0.045	0.006	0.004		
Difference vs. Glipizide Group[b] (SE)[a]	-2165 (804)	-2774 (813)	-2900 (816)		
(95% CI)[c]	(-4072, -258)	(-4702, -846)	(-4835, -965)		
P-value[d]	0.007	< 0.001	< 0.001		

How this test was performed or how the data were calculated were not reviewed.

Insulin levels:

Changes in fasting and postprandial insulin are shown in the next two tables. In general, patients on metformin monotherapy showed small reductions in insulin levels while patients on Glipizide monotherapy showed small increases. Patients on Met/Glip gave values that were intermediate.

Table 10.4.1: Mean Change from Baseline in Fasting Insulin at Week 24 or Last Prior Measurement

Unit: µU/mL	Met/Glip 250/1.25 mg n = 156	Met/Glip 250/2.5 mg n = 155	Met/Glip 500/2.5 mg n = 152	Metformin 500 mg n = 156	Glipizide 5 mg n = 157
Baseline Mean (SD)	10.7 (6.5)	12.5 (11.8)	12.2 (22.0)	10.6 (7.2)	12.7 (10.9)
Week 24/LPM Mean (SD)	10.3 (8.6)	11.8 (9.5)	10.4 (6.8)	9.3 (7.0)	12.9 (10.6)
Unadjusted Mean Change	-0.4	-0.7	-1.9	-1.3	0.2
Adjusted Mean Change from Baseline (SE)[a]	-1.2 (0.7)	-0.1 (0.7)	-1.5 (0.7)	-2.2 (0.7)	0.9 (0.6)
Difference vs. Metformin Group[b] (SE)[a]					
(95% CI)[c]	1.0 (0.9) (-1.2, 3.1)	2.0 (0.9) (-0.2, 4.2)	0.7 (0.9) (-1.5, 2.9)		
P-value[d]	0.296	0.029	0.477		
Difference vs. Glipizide Group[b] (SE)[a]					
(95% CI)[c]	-2.1 (0.9) (-4.3, 0.1)	-1.1 (0.9) (-3.3, 1.1)	-2.4 (0.9) (-4.6, -0.2)		
P-value[d]	0.021	0.248	0.009		

Table 10.4.3: Mean Change from Baseline in Postprandial Insulin 3-Hour Incremental AUC at Week 24 or LPM

Unit: (μU/mL) x min	Met/Glip 250/1.25 mg n = 148	Met/Glip 250/2.5 mg n = 148	Met/Glip 500/2.5 mg n = 143	Metformin 500 mg n = 146	Glipizide 5 mg n = 149
Baseline Mean (SD)	5550 (3222)	5464 (3355)	5406 (4186)	5276 (2911)	5908 (4363)
Week 24/LPM Mean (SD)	7439 (4621)	7921 (5283)	6688 (4174)	4961 (3024)	8249 (6604)
Unadjusted Mean Change	1888	2457	1282	-315	2340
Adjusted Mean Change from Baseline (SE)[a]	1895 (333)	2443 (333)	1254 (339)	-375 (335)	2434 (332)
Difference vs. Metformin Group[b] (SE)[a]					
(95% CI)[c]	2271 (472) (1150, 3391)	2818 (472) (1698, 3938)	1629 (476) (500, 2759)		
P-value[d]	< 0.001	< 0.001	< 0.001		
Difference vs. Glipizide Group[b] (SE)[a]					
(95% CI)[c]	-539 (470) (-1654, 575)	8 (470) (-1107, 1123)	-1181 (474) (-2305, -56)		
P-value[d]	0.252	0.986	0.013		

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Lipids and body weight

Changes in serum lipids and body weight are shown in the following tables. There were mean reductions in total and LDL cholesterol and increases in HDL cholesterol. The changes from baseline were statistically significant in all treatment arms but little differences among treatments were observed Triglycerides tended to fall but the change was not statistically significant. Mean body weight fell somewhat in all treatment groups, but the mean fall from baseline of 1.9 kg in the metformin arm was statistically greater than that observed in the other arms.

Table 10.7.1: Mean Change from Baseline in Total Cholesterol at Week 24 or LPM

Unit: mg/dL	Met/Glip 250/1.25 mg (n = 169)	Met/Glip 250/2.5 mg (n = 161)	Met/Glip 500/2.5 mg (n = 154)	Metformin 500 mg (n = 163)	Glipizide 5 mg (n = 159)
Baseline mean (SD)	218.4 (43.1)	215.4 (42.5)	214.8 (43.2)	221.1 (51.7)	214.3 (42.0)
Week 24/LPM mean (SD)	215.9 (40.1)	209.6 (42.4)	208.8 (40.4)	210.3 (42.7)	210.2 (39.8)
Mean change from baseline (SE)	-2.6 (2.2)	-5.8 (2.5)	-6.0 (2.3)	-10.8 (3.0)	-4.1 (2.4)
(95% CI)	(-7.0, 1.8)	(-10.7, -0.9)	(-10.4, -1.5)	(-16.8, -4.9)	(-8.8, 0.6)

Table 10.7.2: Mean Change from Baseline in LDL-Cholesterol at Week 24 or LPM

Unit: mg/dL	Met/Glip 250/1.25 mg (n = 159)	Met/Glip 250/2.5 mg (n = 150)	Met/Glip 500/2.5 mg (n = 153)	Metformin 500 mg (n = 153)	Glipizide 5 mg (n = 154)
Baseline mean (SD)	139.0 (37.8)	135.9 (36.4)	134.7 (41.5)	135.9 (39.9)	133.3 (36.3)
Week 24/LPM mean (SD)	129.4 (34.2)	123.9 (35.7)	122.5 (38.3)	123.9 (35.1)	126.7 (35.7)
Mean change from baseline (SE)	-9.6 (1.8)	-12.0 (2.0)	-12.1 (2.0)	-11.9 (2.2)	-6.6 (2.0)
(95% CI)	(-13.2, -5.9)	(-15.9, -8.1)	(-16.1, -8.1)	(-16.2, -7.6)	(-10.6, -2.7)

Table 10.7.3: Mean Change from Baseline in HDL-Cholesterol at Week 24 or LPM

Unit: mg/dL	Met/Glip 250/1.25 mg (n = 169)	Met/Glip 250/2.5 mg (n = 160)	Met/Glip 500/2.5 mg (n = 154)	Metformin 500 mg (n = 163)	Glipizide 5 mg (n = 159)
Baseline mean (SD)	43.9 (9.9)	43.1 (9.2)	43.8 (10.6)	42.3 (9.1)	43.5 (10.9)
Week 24/LPM mean (SD)	51.7 (12.1)	50.1 (11.5)	51.5 (12.4)	49.6 (11.8)	49.6 (12.1)
Mean change from baseline (SE)	7.8 (0.6)	7.0 (0.6)	7.7 (0.6)	7.2 (0.6)	6.1 (0.7)
(95% CI)	(6.7, 8.9)	(5.8, 8.3)	(6.5, 8.9)	(5.9, 8.5)	(4.7, 7.4)

Table 10.7.4: Mean Change from Baseline in Fasting Triglycerides at Week 24 or LPM

Unit: mg/dL	Met/Glip 250/1.25 mg n = 169	Met/Glip 250/2.5 mg n = 162	Met/Glip 500/2.5 mg n = 158	Metformin 500 mg n = 163)	Glipizide 5 mg n = 160
Baseline mean (SD)	191.1 (124.4)	200.5 (162.4)	191.3 (150.5)	226.6 (179.4)	204.0 (144.5)
Week 24/LPM mean (SD)	184.6 (115.1)	196.5 (148.7)	176.1 (98.6)	209.2 (178.6)	189.9 (157.2)
Mean change from baseline (SE)	-6.4 (7.7)	-4.0 (8.7)	-15.2 (10.1)	-17.4 (11.4)	-14.1 (12.0)
(95% CI)	(-21.7, 8.9)	(-21.1, 13.1)	(-35.2, 4.9)	(-40.0, 5.2)	(-37.8, 9.6)

Table 10.8.1: Mean Change From Baseline in Body Weight at Week 24 or LPM

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]	1.2 (0.4)	1.5 (0.4)	1.4 (0.4)		
(95% CI)[c]	(0.3, 2.0)	(0.6, 2.4)	(0.5, 2.2)		
P-value[d]	0.001	< 0.001	< 0.001		
Difference vs. Glipizide					
Group[b] (SE)[a]	-0.5 (0.4)	-0.1 (0.4)	-0.3 (0.4)		
(95% CI)[c]	(-1.4, 0.4)	(-1.0, 0.7)	(-1.2, 0.6)		
P-value[d]	0.198	0.704	0.453		

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Study:138-060

This was a randomized double-blind active-controlled trial designed to investigate the efficacy of Met/Glip in patients with type 2 diabetes, ages 25-78, who were inadequately controlled on at least half maximal dose of a SFU.

Run-in phase: Patients with type 2 diabetes whose HbA1c level was between 7.5 and 12% at screening while taking at least half the maximal dose of a sulfonylurea (SFU) for at least 8 weeks. Patients were enrolled into a 2-week run-in of Glipizide 15 mg bid. Patients were randomized to one of three treatment arms for the 18-week double-blind portion. Metformin/Glipizide was started at 500mg/5 mg and increased to 1000 mg/10mg after one week. Metformin was started at 500 mg and increased to 1000 mg after one week. Both these study medications were titrated based for MDG > 130 mg/dl at weeks 3,5, and 8. The maximal dose of Met/Glip was 2000 mg/20 mg (two tablets bid). The maximum dose of metformin was 2000 mg (two 500-mg tablets bid). Patients randomized to glipizde monotherapy received 30 mg (15 mg bid) throughout the trial. Blinding was accomplished with placebo tablets to maintain a double dummy design. Subjects were discontinued from double blind therapy due to lack of glycemic control according to the criteria listed below.

At Week 5: MDG>280 mg/dl
Beyond Week 5: MDG>240
At Week 12 MDG> 200 mg/dl

Baseline Characteristics: Mean age was about 56 years, with 6.5 years of diabetes. Approximately 61% were male, 70% white, 13% black and 16% Latino. Mean BMI at baseline was about 31 kg/m2, mean body weight 92 kg. 68% of patients had been on a submaximal dose of SFU, and 32% on a maximal dose.

Disposition of patients is shown in the table below. With Met/Glip the major cause of discontinuation was hypoglycemia, while with the monotherapies the major cause of discontinuation was lack of glycemic control

Table 8.1B: Reasons for Discontinuation During Double-Blind Therapy

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)

CV138-060

The primary measure of efficacy, change in HbA1c, is shown in the following table. There was little change with either of the monotherapies, but a mean reduction of about 1% unit with Met/Glip. Dose sparing for each of the components was also demonstrated.

Table 10.1.1.1: Mean HbA_{1c} Level at Week 18 or the Last Prior Measurement

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)

CV138-060

The superiority of Met/Glip to each of the monotherapies was demonstrated in all subsets. There was adequate exposure to patients at least 65 years old as shown in the table.

Subgroups

Subgroup Unit: %	Met/Glip (N = 80)	Metformin (N = 71)	Glipizide (N = 79)
Age			
< 65 Years, n	64	57	63
Baseline Mean (SD)	8.85 (1.24)	8.78 (1.18)	8.99 (1.12)
Week 18/LPM Mean (SE)	7.50 (0.13)	8.40 (0.18)	8.63 (0.16)
≥ 65 Years, n	16	14	16
Baseline Mean (SD)	7.91 (0.62)	7.90 (0.68)	8.39 (0.69)
Week 18/LPM Mean (SE)	6.77 (0.20)	7.88 (0.26)	8.21 (0.26)

It is worthy of note that there is a small difference between patients who had been on maximal SFU previously and those who had been on submaximal SFU patients with respect to response to glipizide monotherapy. As shown in the table below, patients who had previously been on a maximal dose of SFU showed no change with 30-mg glipizide, while those who had been on submaximal SFU demonstrated a small reduction. I take this to mean that the maximal effective dose of glipizide is 30 mg per day. The maximal labeled dose is 40 mg per day.

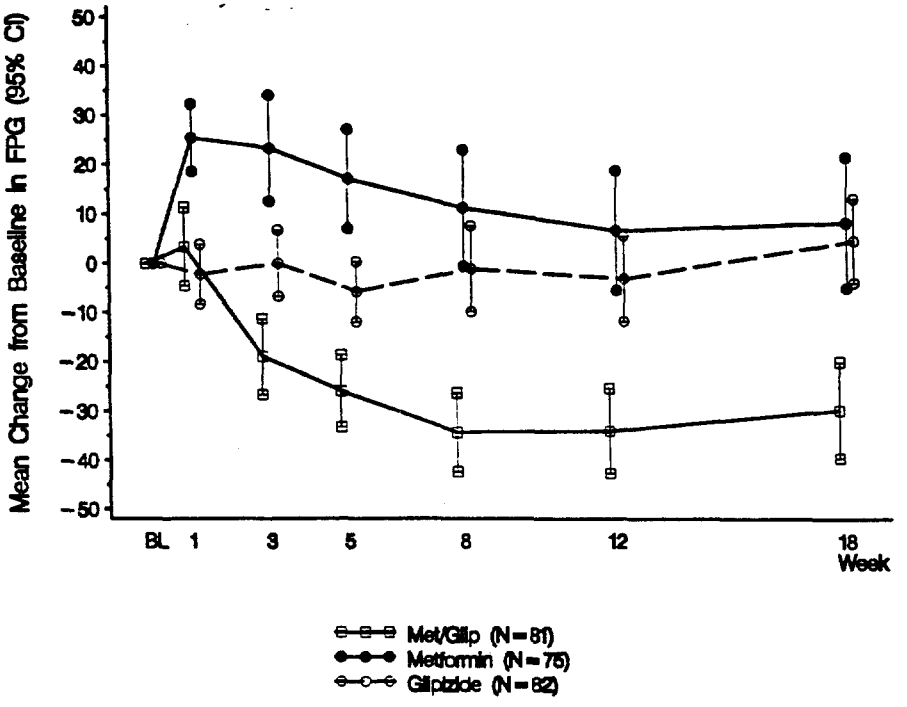
	Met/Glip	Metformin	Glipizide
Level of Sulfonylurea Treatment Prior to Lead-in Therapy:			
Maximal, n	28	18	23
Baseline Mean (SD)	8.78 (1.15)	8.98 (1.23)	8.75 (1.12)
Week 18/LPM Mean (SE)	7.30 (0.21)	8.71 (0.23)	8.73 (0.23)
Submaximal, n	45	51	55
Baseline Mean (SD)	8.61 (1.16)	8.49 (1.12)	8.91 (1.07)
Week 18/LPM Mean (SE)	7.43 (0.15)	8.11 (0.20)	8.44 (0.17)

The changes in FPG in the following table and figure are consistent with the changes in HbA1c. There is initial deterioration of hyperglycemia when patients are switched from SFU to metformin. But it is important to bear in mind that glipizide was given as 30 mg throughout the study while metformin and Met/Glip was titrated until week 8.

Table 10.2.1.1: Mean Change from Baseline in FPG (mg/dL) at Week 18 or the Last Prior Measurement

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		

Figure 10.2.1.2A: Mean Change From Baseline in Fasting Plasma Glucose Over Time (LOCF)



Changes in postprandial glucose levels (after a standardized formulated meal) are shown in the following table.

Table 10.2.1.4: Mean Change from Baseline in PPG 3-Hour Incremental AUC at Week 18 or the Last Prior Measurement

Unit: (mg/dL) x min	Met/Glip (n = 62)	Metformin (n = 59)	Glipizide (n = 63)
Baseline Mean (SD)	42942 (8367)	43269 (8654)	44037 (9153)
Week 18/LPM (SD)	35891 (8806)	40447 (10506)	44612 (8910)
Unadjusted Mean Change from Baseline	-7050	-2823	575
Adjusted Mean Change from Baseline (SE)[a]	-7222 (964)	-2877 (987)	795 (956)
Difference vs. Metformin Group[b]			
(SE)[a]	-4345 (1379)		
(95% CI)	(-7067, -1623)		
P-value[c]	0.002		
Difference vs. Glipizide Group[b]			
(SE)[a]	-8017 (1358)		
(95% CI)	(-10698, -5336)		
P-value[c]	< 0.001		

Although the primary measure of efficacy was change in HbA1c, an alternative way of analyzing the efficacy results is to examine the proportion of patients who demonstrate satisfactory glycemic control. As shown in the table below, significantly more patients withdrew because of inadequate efficacy in the two monotherapy arms than in the Met/Glip arm. (P<0.001).

Table 10.5: Subjects Discontinuing Double-Blind Treatment Due to Lack of Glycemic Control Up to Week 18

	Met/Glip (n = 87)	Metformin (n = 76)	Glipizide (n = 84)
Number (%) of Subjects who Discontinued due to lack of glycemic control	1 (1.1%)	16 (21.1%)	15 (17.9%)
Difference vs. Metformin Group[a]	-20.0%		
(95% CI)[b]	(-34.3, -8.7)		
P-value[c]	< 0.001		
Difference vs. Glipizide Group[a]	-16.8%		
(95% CI)[b]	(-30.3, -5.9)		
P-value[c]	< 0.001		

Insulin levels:

Mean changes for fasting and postprandial insulin levels are shown in the following tables. The only significant change is a fall in insulin level with metformin.

Table 10.4.1: Mean Change from Baseline in Fasting Insulin at Week 18 or Last Prior Measurement

Unit: µU/mL	Met/Glip (n = 60)	Metformin (n = 59)	Glipizide (n = 63)
Baseline mean (SD)	15.4 (12.2)	16.8 (21.5)	14.1 (8.9)
Week 18/LPM mean (SD)	14.3 (10.8)	12.2 (6.6)	15.7 (14.4)
Unadjusted mean change from baseline	-1.1	-4.6	1.6
Adjusted mean change from baseline (SE)[a]	-1.1 (1.2)	-3.8 (1.2)	0.8 (1.2)
Difference vs. Metformin Group[b]			
(SE)	2.7 (1.7)		
(95% CI)	(-0.8, 6.1)		
P-value[c]	0.131		
Difference vs. Glipizide Group[b]			
(SE)	-1.9 (1.7)		
(95% CI)	(-5.3, 1.5)		
P-value[c]	0.270		

Table 10.4.3: Mean Change from Baseline in Postprandial Insulin 3-Hour AUC at Week 18 or the Last Prior Measurement

Unit: (µU/mL) x min	Met/Glip (n = 56)	Metformin (n = 52)	Glipizide (n = 56)
Baseline mean (SD)	6436 (3412)	8110 (5670)	7638 (6414)
Week 18/LPM mean (SD)	6956 (3134)	5841 (3068)	7280 (5057)
Unadjusted mean change from baseline	520	-2268	-358
Adjusted mean change from baseline (SE)[a]	56 (377)	-1907 (390)	-229 (375)
Difference vs. Metformin Group[b]			
(SE)[a]	1963 (545)		
(95% CI)	(887, 3039)		
P-value[c]	<0.001		
Difference vs. Glipizide Group[b]			
(SE)[a]	285 (533)		
(95% CI)	(-766, 1337)		
P-value[c]	0.593		

Changes in lipids and body weight:

As shown in the tables below, there was a tendency for metformin monotherapy to lower total cholesterol, LDL cholesterol, and triglycerides, but the confidence intervals were large. With respect to body weight, however, metformin monotherapy was associated with a net reduction of about 2.4 kg ($p<0.001$) vs the other treatments.

Table 10.6.1: Mean Change from Baseline in Total Cholesterol at Week 18 or the Last Prior Measurement

Unit: mg/dL	Met/Glip (n = 77)	Metformin (n = 67)	Glipizide (n = 76)
Baseline mean (SD)	205.7 (33.2)	195.1 (40.2)	194.9 (37.2)
Week 18/LPM mean (SD)	209.1 (39.5)	188.0 (35.5)	203.6 (36.3)
Mean change from baseline (SE)	3.4 (3.9)	-7.2 (3.6)	8.7 (3.3)
(95% CI)	(-4.3, 11.1)	(-14.4, 0.1)	(2.2, 15.3)

Table 10.6.2: Mean Change from Baseline in LDL-Cholesterol at Week 18 or the Last Prior Measurement

Unit: mg/dL	Met/Glip (n = 74)	Metformin (n = 67)	Glipizide (n = 75)
Baseline Mean (SD)	119.7 (29.5)	109.7 (35.2)	111.2 (34.6)
Week 18/LPM Mean (SD)	119.5 (37.1)	102.5 (30.6)	110.8 (33.4)
Mean Change from Baseline (SE)	-0.2 (3.3)	-7.2 (3.9)	-0.4 (3.1)
(95% CI)	(-6.7, 6.3)	(-15.0, 0.6)	(-6.7, 5.8)

Table 10.6.3: Mean Change from Baseline in HDL-Cholesterol at Week 18 or the Last Prior Measurement

Unit: mg/dL	Met/Glip (n = 77)	Metformin (n = 67)	Glipizide (n = 77)
Baseline Mean (SD)	43.2 (10.0)	42.3 (9.7)	43.5 (9.8)
Week 18/LPM Mean (SD)	44.2 (10.4)	42.7 (9.1)	43.9 (10.6)
Mean Change from Baseline (SE)	0.9 (0.7)	0.4 (0.7)	0.4 (0.6)
(95% CI)	(-0.4, 2.3)	(-1.0, 1.9)	(-0.7, 1.6)

Table 10.6.4: Mean Change from Baseline in Fasting Triglycerides at Week 18 or the Last Prior Measurement

Unit: mg/dL	Met/Glip (n = 77)	Metformin (n = 67)	Glipizide (n = 76)
Baseline Mean (SD)	237.5 (192.2)	218.7 (120.2)	213.8 (127.2)
Week 18/LPM Mean (SD)	256.0 (212.2)	217.0 (108.9)	273.6 (245.9)
Mean Change from Baseline (SE)	18.5 (17.7)	-1.6 (11.8)	59.8 (18.7)
(95% CI)	(-16.8, 53.7)	(-25.3, 22.0)	(22.5, 97.1)

Table 10.7.1: Mean Change from Baseline in Body Weight at Week 18 or the Last Prior Measurement

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)

Summary of efficacy: The use of Met/Glip is better than either metformin or glipizide alone with respect to reduction in HbA1c. Metformin monotherapy and glipizide monotherapy give approximately the same results with respect to HbA1c. However, metformin monotherapy caused a significant weight loss. The use of glipizide in combination with metformin appeared to mitigate the beneficial effects of metformin on weight.

7 Review of safety:

There was one death during the double-blind portion of study 050. This patient received Met/Glip 250/1.25 for 85 days and was diagnosed with acute myelogenous leukemia. The drug was discontinued and she died 21 days later of pulmonary hemorrhage. Three patients died during the open-label extension, two from cerebrovascular accidents and one from an acute myocardial infarction. There were no deaths in Study 060. Serious adverse events were few and appeared unrelated to study medications

Adverse events when Met/Glip is used as first line therapy are shown in the table below

Table 12.1.1.1: Frequencies of Subjects with Treatment-Emergent Clinical Adverse Events, By Body System, During and Up to 14 Days Post Double-Blind Therapy

Body System	Number (%) of Subjects					
	Met/Glip 250/1.25 N = 176	Met/Glip 250/2.5 N = 172	Met/Glip 500/2.5 N = 173	Any Met/Glip N = 521	Met 500 mg N = 177	Glip 5 mg N = 170
Cardiovascular	21 (11.9)	16 (9.3)	23 (13.3)	60 (11.5)	19 (10.7)	26 (15.3)
Dermatologic	4 (2.3)	8 (4.7)	5 (2.9)	17 (3.3)	7 (4.0)	10 (5.9)
Drug Interaction	1 (0.6)	0	0	1 (0.2)	0	1 (0.6)
Endocrine/Metabolic/ Electrolyte Imbalance	4 (2.3)	1 (0.6)	1 (0.6)	6 (1.2)	3 (1.7)	1 (0.6)
Gastrointestinal	28 (15.9)	21 (12.2)	20 (11.6)	69 (13.2)	36 (20.3)	22 (12.9)
General	17 (9.7)	12 (7.0)	14 (8.1)	43 (8.3)	11 (6.2)	13 (7.6)
Hematopoietic	0	2 (1.2)	0	2 (0.4)	1 (0.6)	2 (1.2)
Hepatic/Biliary	1 (0.6)	0	2 (1.2)	3 (0.6)	2 (1.1)	1 (0.6)
Immunology Sensitivity Disorder	3 (1.7)	0	0	3 (0.6)	2 (1.1)	1 (0.6)
Musculoskeletal/ Connective Tissue	13 (7.4)	12 (7.0)	12 (6.9)	37 (7.1)	9 (5.1)	13 (7.6)
Nervous System	17 (9.7)	15 (8.7)	28 (16.2)	60 (11.5)	15 (8.5)	22 (12.9)
Renal/Genitourinary	5 (2.8)	5 (2.9)	7 (4.0)	17 (3.3)	10 (5.6)	6 (3.5)
Respiratory	22 (12.5)	27 (15.7)	24 (13.9)	73 (14.0)	25 (14.1)	23 (13.5)
Special Senses	3 (1.7)	14 (8.1)	4 (2.3)	21 (4.0)	4 (2.3)	9 (5.3)

The gastrointestinal complaints were greater with metformin monotherapy. As shown above, gastrointestinal complaints were reported in 20.3% of patients on metformin monotherapy, 12.9% of patients on glipizide monotherapy and 13.2 % of patients on Met/Glip.Discontinuation of therapy due to gastrointestinal AE's was reported in 4% of patients on metformin monotherapy and none on glipizide monotherapy. Discontinuation

of therapy due to gastrointestinal AE's with Met/Glip was reported in 0.6%, 0.6%, and 1.7% respectively for the 250/1.25, [redacted] and 500/2.5mg formulations.

When used as second-line therapy, gastrointestinal AE's were reported in 23.8% of patients on Glipizide monotherapy, 25.3% on metformin monotherapy and 25.3% on Met/Glip. Discontinuation of therapy occurred in 2.4%, 1.3% and 4.6% of patients on Glipizide monotherapy, metformin monotherapy or Met/Glip.

Hypoglycemia was the major concern in the use of this product. When used as first-line therapy (study 138-050), symptomatic hypoglycemia (confirmed by fingerstick glucose < 50 mg/dl) was reported in 3% of patients on glipizide monotherapy and zero patients on metformin monotherapy. Symptomatic hypoglycemia (confirmed by fingerstick glucose < 50 mg/dl) with Met/Glip was reported in 5%, 8%, and 9% respectively for the 250/1.25, [redacted] and 500/2.5mg formulations. In one patient (on 500/2.5) this hypoglycemia was reported as SAE. During the open-label phase, hypoglycemia (BS< 50 mg/dl) was reported in 38 (5%) patients. In five subjects there were episodes that required assistance, but these patients remained in the study. In three patients (0.4%) hypoglycemia was the cause of discontinuation of study medications. The last HbA1c in these three patients were 6.1, 5.8, and 6.4%.

When used as second-line therapy (study 138-060), symptomatic hypoglycemia (fingerstick glucose< 50 mg/dl) was reported in 1% of patients on metformin monotherapy and zero patients on glipizide monotherapy and 13% of patients on Met/Glip. None was reported as a SAE. One patient on Met/Glip discontinued treatment because of hypoglycemia but none of his finger-stick values were < 50 mg/dl.

Safety in elderly patients

Special attention was paid to potential differences in the adverse event profile of elderly patients. More gastrointestinal AE's would be expected in elderly patients regardless of therapy. As shown in the tables below, there was little difference in adverse events between patients under 65 and those 65 years or older. More gastrointestinal AE's in both age groups were noted when Met/Glip was used as second –line therapy.

First line treatment – study 050

Table 12.1.1.2A: Most Common Treatment-Emergent Clinical AEs, by Age and Primary Term, During and Up to 14 Days Post Double-Blind Therapy for Subjects Treated with Metformin/Glipizide

Primary Term	Number (%) of Subjects	
	< 65 Years N = 423	≥ 65 Years N = 98
Upper Respiratory Infection	37 (8.7)	9 (9.2)
Diarrhea	20 (4.7)	5 (5.1)
Musculoskeletal Pain	18 (4.3)	3 (3.1)
Epigastric Pain	1 (0.2)	4 (4.1)
Dizziness	10 (2.4)	4 (4.1)
Total Subjects with AEs	182 (43.0)	54 (55.1)

CV138-050

Second-line treatment

Table 12.1.1.2A: Most Common Treatment-Emergent Clinical Adverse Events, by Age and Primary Term, During and Up to 14 Days Post Double-Blind Therapy for Subjects Treated with Metformin/Glipizide

	Number (%) of Subjects	
Primary Term	**< 65 Years N = 70**	**≥ 65 Years N = 17**
Diarrhea	11 (15.7)	5 (29.4)
Upper Respiratory Infection	6 (8.6)	3 (17.6)
Nausea/Vomiting	4 (5.7)	3 (17.6)
Decreased Appetite	0	2 (11.8)
Epigastric Pain	0	2 (11.8)
Headache	10 (14.3)	1 (5.9)
Total Subjects with AEs	42 (60.0)	13 (76.5)

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8 Dosing

In the proposed label, the Sponsor has recommended the following dosing schedules:

For patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of TRADENAME is 2.5 mg/250 mg once a day with a meal.

Dosage increases to achieve adequate glycemic control should be made in increments of one tablet per day every two weeks up to maximum of 10 mg/1000 mg or 10 mg/2000 mg TRADENAME per day given in divided doses. In clinical trials of TRADENAME as first-line therapy, there was no experience with total daily doses greater than 10 mg/2000 mg per day.

For patients not adequately controlled on either glipizide (or another sulfonylurea) or metformin alone, the recommended starting dose of TRADENAME is 2.5 mg/500 mg or 5mg/500mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of TRADENAME should not exceed the daily doses of glipizide or metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.

Patients previously treated with combination therapy of glipizide (or another sulfonylurea) plus metformin may be switched to TRADENAME 2.5 mg/500 mg or 5 mg/500 mg; the starting dose should not exceed the daily dose of glipizide (or equivalent dose of another sulfonylurea) and metformin already being taken. The decision to switch to the nearest equivalent dose or to titrate should be based on clinical judgment. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of TRADENAME should be titrated as described above to achieve adequate control of blood glucose.

These recommendations are generally appropriate. But one issue that needs to be addressed relates to initiation of naïve patients with FPG>280. Starting with 2.5/500 once daily is too low for these patients. None of the patients in the trial could be controlled with this low a dose and most required very much more. Since all patients ultimately required twice daily dosing, I do not see why twice daily dosing cannot be the initial recommendation. The risk of inadequate treatment is greater than the risk of hypoglycemia. Also, metformin monotherapy is started at 500-mg twice daily. Few patients do not tolerate this dose because of gastrointestinal complaints. I recommend the following wording or something similar:

For patents whose FPG is 280 – 320 mg/dl a starting dose of Met/Glip 500/2.5 twice daily should be considered. The efficacy of Met/Glip in patients whose FPG exceeds 320 mg/dl has not been established.

9 Special Populations:

Demonstration of safety and efficacy in elderly patients is adequate.

The NDA contains a request for deferral of submission of data in pediatric patients, citing a [redacted] sent to FDA on November 15, 2001. A written request for pediatric studies was issued by FDA on June 18, 2002. Pending finalization of the [redacted] I recommend that the request for deferral be granted.

10 Recommendations :

The use of Met/Glip resulted in clinically significant reduction on HbA1c. No unexpected adverse events were observed. The adverse event profile and other physiological changes associated with metformin/glipizde in this NDA are similar to what has been observed in previous studies of metformin and glipizide.

Labeling changes (for transmission to BMS):

The pharmacological properties and clinical utility of Met/Glip are virtually the same as Glucovance. The labels should therefore be very similar. Differences in the labeling of Met/Glip should be justified by differences in trial design.

Specific comments:

Table 2 – [redacted] the table should give the means at baseline not just the mean change. The final doses should also be included. The explanatory text should indicate that the weight loss was greater with metformin than with Met/Glip

The statement about postprandial glucose and insulin values needs to be revised. A brief description of the methodology should be included. Alternatively, these data might be omitted altogether. It is not generally recognized that reduction in postprandial glucose is desirable except to the extent that it contributes to lowering HbA1c levels.

Second-line Therapy –

The text should be revised to say one-half the maximum *labeled* dose of SFU.

The language regarding [redacted] in unclear.

The section on lipids and weight is misleading. There was [redacted] weight loss on metformin [redacted] This should be stated. Although differences in

lipid levels between metformin and Met/Glip did not achieve statistically significance, I do not think it is appropriate to say the changes in lipid profiles were

Dosing

The recommendations are generally appropriate. But one issue that needs to be addressed relates to initiation of naïve patients with FPG>280. Starting with 2.5/500 once daily is too low for these patients. None of the patients in the trial could be controlled with this low a dose and most required very much more. Since all patients ultimately required twice daily dosing, I do not see why twice daily dosing cannot be the initial recommendation. The risk of inadequate treatment is greater than the risk of hypoglycemia. Also, metformin monotherapy is started at 500-mg twice daily. Few patients do not tolerate this dose because of gastrointestinal complaints. I recommend that following wording or something similar:

For patents whose FPG is 280 – 320 mg/dl a starting dose of Met/Glip 500/2.5 twice daily should be considered. The efficacy of Met/Glip in patients whose FPG exceeds 320 mg/dl has not been established.

Recommendation: Pending changes in the label (see above) I recommend that this NDA be approved.

Robert I Misbin MD
September 20, 2002

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
10/18/02 10:08:56 AM
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