

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-748**

**MEDICAL REVIEW(S)**

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

DATE: February 1, 2005

FROM: David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-748  
Glumetza (metformin hydrochloride extended-release) tablets  
Bioval Labs, Inc.  
Treatment of type 2 diabetes

SUBJECT: NDA review issues and recommended action

**Summary of issues**

The initial action on this NDA was AE pending acceptance of a specified dissolution method and specifications, as cited in the letter of 2-25-05. This product given once or twice daily is clinically similar (non-inferior re: HbA1c lowering) to Glucophage twice daily. This was a 505b1 application with full reports of clinical safety and efficacy. The sponsor has developed a dissolution method and specifications that satisfy OCPB.

**Recommendation**

This application may be approved.

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     § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

     § 552(b)(4) Draft Labeling

# MEDICAL OFFICER REVIEW

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

APPLICATION #:	21748	APPLICATION TYPE:	NDA.....
SPONSOR:	Biovail	PROPRIETARY NAME:	Metformin ER.....
CATEGORY OF DRUG:	Antidiabetic	USAN / Established Name:	Glumetza.....
MEDICAL REVIEWER:	Robert I Misbin..	ROUTE:	Oral.....
		REVIEW DATE:	February 10, 2005....

### SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
April 27, 2004		NDA	
October 14, 2004		Safety update	

Glumetza once daily or twice daily is as effective in lowering HbA1c levels as Glucophage twice daily. The safety profile of Glumetza and Glucophage are similar.

**Pending addition of a table to the PK section of the label, the NDA for Glumetza can be approved.**

Signed: Medical Reviewer: Robert I Misbin MD Date: February 10, 2005

Medical Team Leader: \_\_\_\_\_ Date: \_\_\_\_\_

Executive Summary

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## Executive Summary

### I Recommendations:

The efficacy of Glumetza (Metformin ER) given once daily is approximately the same as of Glucophage (Metformin IR) given twice daily. The safety profiles are similar. Pending addition of a table to the PK section, the NDA for Glumetza can be approved.

### II Summary of Clinical Findings

Metformin ER is a long acting preparation of metformin to be marketed under the trade name, Glumetza. It was designed to be given once daily and achieve the same glucose control as immediate release Metformin given twice daily. The Sponsor performed two phase 3 trials. One of these was a comparison to immediate release Metformin (Glucophage). The second was a placebo-controlled study of Glumetza vs placebo in sulfonylurea-treated patients. A four-week, phase 2 study comparing Glumetza to immediate release Glucophage was also submitted.

#### Efficacy:

Study 003 was a randomized, double blind study that compared three doses of Glumetza (1500 mg in the evening, 500 mg in the morning + 1000 mg in the evening, and 2000 mg in the evening) to a one-dose strength of Metformin IR (1000 mg in the morning +500 mg in the evening). The dose was increased to the final randomized dose after three weeks, and kept constant over the following 21 weeks. As shown in the table below, the efficacy of 1500 mg of Glumetza either as a single or divided dose was virtually the same as 1500 mg of Metformin IR given as a divided dose. Somewhat greater efficacy was observed with 2000 mg of Glumetza.

In-Text Table 7 Analysis of Hemoglobin A<sub>1c</sub>: ITT Population

Hemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) (%)	Treatment Group				Overall Treatment p-value [1]
	Metformin ER 1500 mg QD (N = 178)	Metformin ER 1500 mg (AM/PM) (N = 182)	Metformin ER 2000 mg QD (N = 172)	Metformin ER 1500 mg (AM/PM) (N = 174)	
Baseline					
n	169	175	159	170	
LS Mean (SEM)	8.22 (0.25)	8.50 (0.24)	8.26 (0.24)	8.70 (0.25)	0.483
Change From Baseline To Endpoint					
n	169	175	159	170	
LS Mean (SEM)	-0.73 (0.12)	-0.74 (0.12)	-1.06 (0.12)	-0.70 (0.12)	0.013
95% CI	(-0.97, -0.48)	(-0.98, -0.50)	(-1.30, -0.81)	(-0.94, -0.46)	
Metformin ER versus Metformin IR					
LS Mean Difference (SEM)	-0.03 (0.12)	-0.04 (0.12)	-0.36 (0.12)	NA	
95% CI for Difference	(-0.32, 0.26)	(-0.33, 0.25)	(-0.65, -0.06)		

Source: Post-Test Table 14.1.2-4

LS = least squares; SEM = standard error of LS mean; CI = confidence interval; NA = not applicable

Note: Patients who had both baseline and endpoint data were included in this data analysis.

For the baseline value, the LS mean and SEM were estimated from the ANOVA model that included treatment, center (Site 31 versus all other sites), treatment-by-center interaction factor, and a stratification factor (metformin treatment prior to entry: yes/no).

For the change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center (Site 31 versus all other sites), a stratification factor (metformin treatment prior to entry: yes/no), and baseline value as a covariate.

[1] The p-value (overall) for the overall comparison among all treatment groups was based on the Type III analysis from the models described above.

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Study 14 was a double blind, randomized trial add-on trial of Metformin ER, Sulfonylurea (SU) or the combination of M-ER + SU. The primary efficacy variable was change in HbA1c from baseline to endpoint. As shown in the following table, change in HbA1c was greater for the combined M-ER + SU treatment groups than for the SU only treatment group.

**In-text Table 8 Hemoglobin A<sub>1c</sub> Results: Combined M-ER + SU Treatment Group versus SU Alone Treatment Group: Intent-to-Treat Patients**

Hemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) (%)	Combined M-ER + SU (N = 431)	SU Alone (N = 144)	Overall Treatment p-value [1]
Baseline (n)	416	141	
LS Mean (SEM)	7.79 (0.07)	8.08 (0.13)	0.051
Endpoint (n)	416	141	
LS Mean (SEM)	7.13 (0.05)	7.95 (0.08)	<0.001
95% CI	(7.02, 7.23)	(7.78, 8.12)	
Change from Baseline to Endpoint (n)	416	141	
LS Mean (SEM)	-0.74 (0.05)	0.08 (0.08)	<0.001
95% CI	(-0.85, -0.64)	(-0.08, 0.25)	
M-ER + SU versus SU alone		NA	
LS Mean Difference (SEM)	-0.82 (0.09)		
95% CI for Difference	(-1.00, -0.65)		

Source: Post-text Table 14.1.2-1.

MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylurea; LS = least squares; SEM = standard error of LS mean; CI = confidence interval; NA = not applicable.

Note: Patients who had both baseline and any endpoint were included in this data analysis. For baseline value, the LS mean and SEM were estimated from the ANOVA model that included treatment, center, and treatment by center interaction factor.

For the endpoint and change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and baseline value as a covariate.

[1] The p-value for the treatment effect was based on the Type III analysis from the models described above.

#### Safety:

The adverse event profile of Glumetza and Glucophage (Metformin IR) are similar. The major adverse events are related to the gastrointestinal system.

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## I Introduction and Background

Metformin (Glucophage) has been available in the USA since 1995 and is generally considered the treatment of choice for most patients with type 2 diabetes. It can be used as monotherapy or in combination with other antidiabetic agents including insulin.

Metformin (Glucophage) is given twice or three times per day in doses ranging from 500 mg bid to 850-mg tid. Gastrointestinal discomfort occurs early in treatment and is the major limiting factor in dose escalation. Most patients can tolerate or become tolerant to the gastrointestinal AE's of metformin. A regimen of 1000-mg bid is common. Glucophage is marketed as 500 mg, 850 mg and 1000 mg tablets. Generic metformin is also available. Sustained release formulations are also marketed under the trade names, Glucophage XR and Fortamet.

Metformin ER is a long acting preparation of metformin to be marketed under the trade name, Glumetza. It was designed to be given once daily and achieve the same glucose control as immediate release Metformin given twice daily. The Sponsor performed two phase 3 trials. One of these was a comparison to immediate release Metformin (Glucophage). The second was a placebo-controlled study of Glumetza vs placebo in sulfonylurea-treated patients. A four-week, phase 2 study comparing Glumetza to immediate release Glucophage was also submitted.

II Clinically relevant findings from review from other disciplines: N/A

III Pharmacokinetic and Pharmacodynamics Issues:

The following table comes from section 2.2 of the review by the Biopharmacy Reviewer, Dr Wei.

**Table 3. Summary of PK parameters after one day dosing**

PK Parameter	Glumetza 2X500mg	Glumetza 1X500mg BID	Glucophage 1X500mg BID
AUC <sub>0-36</sub> (ng.hr/mL)	14182±2415	15260±3496	15342±3398
C <sub>max</sub> (ng/mL)	1301.4±285.7	811.9±173.7	959.1±204.0
T <sub>max</sub> (hr)	7.5±1.2	7.1±1.2	4.2±1.6

**Table 4. Summary of statistics comparing Glumetza and Glucophage**

PK parameter	Glumetza 2X500mg Versus Glucophage 500mg BID	
	Ratio of geometric means	90% CI
AUC <sub>0-36</sub>	93.50%	89.45 – 97.72
C <sub>max</sub>	135.31%	128.89 – 142.05
Glumetza 500mg BID Versus Glucophage 500mg BID		
AUC <sub>0-36</sub>	99.00%	94.72 – 103.48
C <sub>max</sub>	84.18%	80.19 – 88.38

As expected the T max for Glumetza is delayed relative to Glucophage. However the metformin exposure for Glumetza 500 bid and Glucophage 500 bid is virtually identical. Metformin exposure with

two 500 mg tablets of Glumetza given as a single dose is 93.5% (90% CI, 89-98%) that of Glucophage 500 mg bid.

IV Description of Clinical Sources  
(See clinical review)

V Clinical Review Methods:

The review was conducted from the NDA submitted electronically. No routine inspections of the sites were performed. Although the consent documents were not reviewed, the trials appear to have been conducted in accordance with acceptable ethical standards. The financial disclosure documentation appears adequate.

Regulatory statements regarding documents reviewed:

The Sponsor, Biovail Labs, submitted debarment and financial disclosure documents.. I have examined these documents and found them to be acceptable. The debarment statement, signed by Eugene Melnyk, President of Biovail Labs on April 05,2004, indicates that the Biovail Labs did not and will use the services of any individual or organization that had been debarred under section 306 of the Federal Food, Drug, and Cosmetic Act.

Financial disclosure information was submitted with Form OMB No. 0910-0396, signed by Greg Szpunar, Vice President of Biovail Labs on April 19,2004,

1 The applicant certifies that Biovail Labs 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.

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

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 Biovail Labs.

4 A list of investigators was attached.

V1 Review of Efficacy

Study 003

This was a randomized, double blind study that compared three doses of Glumetza (1500 mg in the evening, 500 mg in the morning + 1000 mg in the evening, and 2000 mg in the evening) to one dose of (Metformin IR 500 mg in the morning +1000 mg in the evening). Glumetza was given as 500-mg tablets. The study population consisted of patients with type 2 diabetes who were not taking pharmacological treatment, patients on monotherapy, or patients on metformin (up to 1500 mg) plus a SU (up to ½ to maximal dose). In non-naïve, patients there were a six-week washout. The initial dose of study drug was 1000 mg given as 2 x 500 mg tablets with the evening meal. The dose was increased to the final randomized dose after three weeks, and kept constant over the following 21 weeks. Metformin IR was given as 500 mg Glucophage tablets. Glumetza and Glucophage IR placebos were given at appropriate times to maintain blinding.

Characteristics of the ITT population are shown in the following table.

In-Text Table 5 Diabetes History: ITT Population

	Treatment Group				Total (N = 706)	P-value [1]
	Metformin ER 1500 mg QD (N = 178)	Metformin ER 1500 mg (AM/PM) (N = 182)	Metformin ER 2000 mg QD (N = 172)	Metformin IR 1500 mg (AM/PM) (N = 174)		
Duration of Diabetes (years)						
n	178	182	172	174	706	
Mean (SD) (Min, Max)	3.9 (4.5) (0.1, 26.9)	4.5 (4.9) (0.1, 27.2)	3.9 (4.3) (0.1, 24.3)	4.4 (5.4) (0.0, 37.3)	4.2 (4.8) (0.0, 37.3)	0.521
Actual Metformin Treatment 30 Days Prior To Entry-n(%)						
Yes	178 (100%)	182 (100%)	172 (100%)	174 (100%)	706 (100%)	0.570
No	64 (36.0%)	58 (31.9%)	61 (35.5%)	52 (29.9%)	235 (33.3%)	
Diet And Exercise Only Or Newly Diagnosed n(%)						
Yes	114 (64.0%)	124 (68.1%)	111 (64.5%)	122 (70.1%)	471 (66.7%)	0.848
No	178 (100%)	182 (100%)	172 (100%)	174 (100%)	706 (100%)	
Yes	81 (45.5%)	86 (47.3%)	84 (48.8%)	87 (50.0%)	338 (47.9%)	
No	97 (54.5%)	96 (52.7%)	88 (51.2%)	87 (50.0%)	368 (52.1%)	
Diabetes Treatment 30 Days Prior To Entry [2]						
Metformin Only	43 (24.2%)	44 (24.2%)	45 (26.2%)	43 (24.7%)	175 (24.8%)	
Combinations With Metformin Only	0	1 (0.5%)	0	0	1 (0.1%)	
Sulfonylurea Only	29 (16.3%)	30 (16.5%)	22 (12.8%)	30 (17.2%)	111 (15.7%)	
Combinations With Sulfonylurea Only	1 (0.6%)	1 (0.5%)	0	1 (0.6%)	3 (0.4%)	
Combinations With Metformin And Sulfonylurea	20 (11.2%)	12 (6.6%)	17 (9.9%)	10 (5.7%)	59 (8.4%)	
Diet And Exercise Only Or Newly Diagnosed	81 (45.5%)	86 (47.3%)	84 (48.8%)	87 (50.0%)	338 (47.9%)	

Source: Post-Test Table 14.1.1-8

SD = standard deviation

[1] The p-value for the overall comparison among 4 treatment groups was based on the F-test of Type III treatment factor from the ANOVA model including only the treatment factor for numeric data or Chi-square test for categorical data.

[2] Other diabetes treatment category not listed.

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The primary measure of efficacy was change in HbA1c. As shown in the tables below, the efficacy of 1500 mg of Glumetza either as a single or divided dose was virtually the same as 1500 mg of Metformin IR given as a divided dose. Somewhat greater efficacy was observed with 2000 mg of Glumetza.

**In-Text Table 7 Analysis of Hemoglobin A<sub>1c</sub>: ITT Population**

Hemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) (%)	Treatment Group				Overall Treatment p-value [1]
	Metformin ER 1500 mg QD (N = 178)	Metformin ER 1500 mg (AM/PM) (N = 182)	Metformin ER 2000 mg QD (N = 172)	Metformin IR 1500 mg (AM/PM) (N = 174)	
<b>Baseline</b>					
n	169	175	159	170	
LS Mean (SEM)	8.22 (0.25)	8.50 (0.24)	8.36 (0.24)	8.70 (0.25)	0.483
<b>Change From Baseline To Endpoint</b>					
n	169	175	159	170	
LS Mean (SEM)	-0.73 (0.12)	-0.74 (0.12)	-1.06 (0.12)	-0.70 (0.12)	0.013
95% CI	(-0.97, -0.48)	(-0.98, -0.50)	(-1.30, -0.81)	(-0.94, -0.46)	
<b>Metformin ER versus Metformin IR</b>					
LS Mean Difference (SEM)	-0.03 (0.12)	-0.04 (0.12)	-0.36 (0.12)	NA	
98.4% CI for Difference	(-0.32, 0.26)	(-0.33, 0.25)	(-0.65, -0.06)		

Source: Post-Text Table 14.1.2.3

LS = least squares; SEM = standard error of LS mean; CI = confidence interval; NA = not applicable

Note: Patients who had both baseline and endpoint data were included in this data analysis.

For the baseline value, the LS mean and SEM were estimated from the ANOVA model that included treatment, center (Site 31 versus all other sites), treatment-by-center interaction factor, and a stratification factor (metformin treatment prior to entry: yes/no).

For the change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center (Site 31 versus all other sites), a stratification factor (metformin treatment prior to entry: yes/no), and baseline value as a covariate.

[1] The p-value (overall) for the overall comparison among all treatment groups was based on the Type III analysis from the models described above.

**In-Text Table 8 Summary of Hemoglobin A<sub>1c</sub> by Visit: ITT Population**

Hemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) (%)	Treatment Group			
	Metformin ER 1500 mg QD (N = 178)	Metformin ER 1500 mg (AM/PM) (N = 182)	Metformin ER 2000 mg QD (N = 172)	Metformin IR 1500 mg (AM/PM) (N = 174)
<b>Baseline</b>				
n	169	175	159	170
Mean (SD)	8.34 (1.45)	8.50 (1.46)	8.17 (1.37)	8.36 (1.40)
<b>Week 12</b>				
n	153	146	146	149
Mean (SD)	7.49 (1.31)	7.53 (1.27)	7.09 (1.03)	7.24 (1.18)
Mean CFB (SEM)	-0.83 (0.10)	-0.97 (0.10)	-1.11 (0.09)	-0.99 (0.09)
p-value (W) [1]	<0.001	<0.001	<0.001	<0.001
p-value (vs. M-IR) [2]	0.247	0.895	0.342	-
<b>Week 20</b>				
n	128	134	134	125
Mean (SD)	7.08 (1.04)	7.14 (1.10)	6.87 (1.11)	6.96 (0.96)
Mean CFB (SEM)	-1.07 (0.09)	-1.23 (0.11)	-1.29 (0.11)	-1.24 (0.11)
p-value (W) [1]	<0.001	<0.001	<0.001	<0.001
p-value (vs. M-IR) [2]	0.219	0.923	0.774	-
<b>Week 24</b>				
n	132	135	136	123
Mean (SD)	7.06 (1.11)	7.09 (1.08)	6.88 (1.09)	6.90 (0.99)
Mean CFB (SEM)	-1.12 (0.09)	-1.28 (0.11)	-1.32 (0.11)	-1.30 (0.11)
p-value (W) [1]	<0.001	<0.001	<0.001	<0.001
p-value (vs. M-IR) [2]	0.201	0.860	0.911	-
<b>Endpoint</b>				
n	169	175	159	170
Mean (SD)	7.38 (1.51)	7.45 (1.44)	6.96 (1.14)	7.40 (1.50)
Mean CFB (SEM)	-0.96 (0.10)	-1.05 (0.10)	-1.21 (0.10)	-0.96 (0.10)

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As shown in the following table, the same pattern was observed in treatment naïve patients as for the group as a whole. As might have been expected, the efficacy in the treatment naïve subsets was somewhat greater than for the ITT population as a whole.

**In-Text Table 9 Analysis of Hemoglobin A<sub>1c</sub>: Intent-to-treat Patients Who Were on Diet and Exercise Only or Newly Diagnosed Prior to Study Entry**

Hemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) (%)	Treatment Group				Overall Treatment p-value [1]
	Metformin ER 1500 mg QD (N = 81)	Metformin ER1500 mg (AM/PM) (N = 86)	Metformin ER 2000 mg QD (N = 84)	Metformin IR 1500 mg (AM/PM) (N = 87)	
<b>Baseline</b>					
n	76	83	75	84	
LS Mean (SEM)	8.82 (0.19)	8.85 (0.18)	8.60 (0.19)	8.66 (0.18)	0.728
95% CI	(8.45, 9.19)	(8.49, 9.20)	(8.23, 8.97)	(8.31, 9.01)	
<b>Change From Baseline To Endpoint At Mean Of Baseline HbA<sub>1c</sub> (8.73)</b>					
n	76	83	75	84	
LS Mean (SEM)	-1.44 (0.14)	-1.38 (0.13)	-1.79 (0.14)	-1.40 (0.13)	0.049
95% CI	(-1.71, -1.17)	(-1.65, -1.12)	(-2.07, -1.52)	(-1.66, -1.15)	
<b>Metformin ER Versus Metformin IR</b>					
LS Mean Difference (SEM)	-0.03 (0.19)	0.02 (0.19)	-0.39 (0.19)	NA	
95% CI for Difference	(-0.41, 0.34)	(-0.35, 0.39)	(-0.76, -0.01)		

Source: Post-Test Table 14.1.2-2A

NA = not applicable; CI = confidence interval

Note: Patients who had both baseline and endpoint data were included in this data analysis.

For the baseline value, the LS means (least squares mean) and SEM (standard error of LS mean) were estimated from the ANOVA model that included treatment factor.

For the change from baseline to endpoint value, the LS means and SEM were estimated from the ANCOVA model that included treatment factor and treatment by baseline value interaction factor.

[1] The p-value (overall) for the comparison among all treatment groups is based on Type III analysis from the models described above.

As shown in the following table, the change in fasting plasma glucose for the ITT population followed the same pattern as the change in HbA1c.

**In-Text Table 11 Summary of Fasting Plasma Glucose by Visit: ITT Population**

Fasting Plasma Glucose (mg/dL)	Treatment Group			
	Metformin ER 1500 mg QD (N = 178)	Metformin ER 1500 mg (AM/PM) (N = 182)	Metformin ER 2000 mg QD (N = 172)	Metformin IR1500 mg (AM/PM) (N = 174)
p-value (vs. M-IR) [2]	0.579	0.593	0.344	-
<b>Week 24</b>				
n	132	135	136	124
Mean (SD)	145.6 (40.5)	146.3 (36.1)	140.2 (39.3)	142.4 (36.7)
Mean CFB (SEM)	-39.8 (3.7)	-42.2 (4.0)	-44.0 (3.9)	-41.7 (4.2)
p-value (W) [1]	<0.001	<0.001	<0.001	<0.001
p-value (vs. M-IR) [2]	0.727	0.934	0.693	-
<b>Endpoint</b>				
n	175	179	170	172
Mean (SD)	155.0 (33.1)	162.4 (33.5)	144.5 (43.2)	159.8 (37.4)
Mean CFB (SEM)	-41.2 (3.4)	-35.2 (3.7)	-39.3 (3.4)	-33.9 (3.9)
p-value (W) [1]	<0.001	<0.001	<0.001	<0.001
p-value (vs. M-IR) [2]	0.157	0.803	0.291	-

Source: Post-Test Table 14.1.2-19

CFB = change from baseline

Note: Patients who had both baseline and at least one follow-up measurement were included in this data analysis.

Data collected from non-fasting samples were excluded from this data analysis.

[1] The p-value (W) for the test of mean change from baseline within treatment group was based on the paired t-test.

[2] The p-value (vs. M-IR) for the pairwise test of difference of the mean change from baseline between M-ER and M-IR groups was based on the two-sample t-test.

[1] The p-value (overall) for the comparison among all treatment groups is based on Type III analysis from the models described above.

During the treatment phase, patients were withdrawn whose FBG (glucometer readings) were > 250 mg/dl for 7 consecutive days or > 300 mg/dl for three consecutive days. The proportion of patients who withdrew because of lack of efficacy also showed to same pattern as for the mean change in HbA1c. This is shown in the following table:

**In-Text Table 14 Proportion of Patients Who Prematurely Terminated Study Due to Lack of Efficacy: ITT Population**

	Treatment Group				Overall Treatment p-value [1]
	Metformin ER 1500 mg QD (N = 178)	Metformin ER 1500 mg (AM/PM) (N = 182)	Metformin ER 2000 mg QD (N = 172)	Metformin IR 1500 mg (AM/PM) (N = 174)	
Terminated Study Prematurely Due to Lack of Efficacy-n(%)					
Yes	178 (100%)	182 (100%)	172 (100%)	174 (100%)	0.015
No	8 (4.5%)	15 (8.2%)	3 (1.7%)	14 (8.0%)	
Metformin ER Versus Metformin IR Difference in P (Yes)	-3.6%	0.2%	-6.3%	NA	
95% CI of Difference in Proportions	(-8.6%, 1.5%)	(-5.5%, 5.9%)	(-10.8%, -1.8%)	-	
p-value (versus M-ER) [2]	0.169	0.946	0.007	-	

Source: Post-Test Table 14.1.2-17

NA = not applicable; P (Yes) = proportion of patients that terminated study due to lack of efficacy; CI = confidence interval

[1] The p-value (overall) for the overall comparison among all treatment groups was based on two-sided Fisher's Exact test.

[2] The p-value (versus M-ER) for the pairwise test of treatment effect between M-ER and M-IR treatment groups was based on the Z test for the difference in proportions between two groups.

Changes in serum lipids LDL cholesterol are shown in the next two tables. The first table comes from the NDA and the second table comes from the review by FDA statistician, Lee Pian. The reduction in LDL cholesterol favored Glumetza, Although statistically significant, this difference is very small, and is not claimed by the Sponsor is the proposed label.

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Table 14.1.2-3  
Analysis of LDL Cholesterol: Intent-to-treat Patients

LDL Cholesterol (mg/dL)	Treatment Group				Overall Treatment p-value [1]
	Metformin ER 1500 mg QD (N = 178)	Metformin ER 1500 mg (AM/PM) (N = 182)	Metformin ER 2000 mg QD (N = 172)	Metformin IR 1500 mg (AM/PM) (N = 174)	
Baseline					
n	150	150	139	158	
Raw Mean (SD)	123.1 (20.97)	121.7 (21.93)	122.0 (26.29)	125.1 (24.35)	0.999
LS Mean (SEM)	122.3 (6.38)	122.5 (6.92)	126.8 (8.92)	122.4 (6.92)	
95% C.I.	(111.0, 133.7)	(110.9, 134.3)	(112.8, 138.2)	(110.7, 134.0)	
Change from Baseline to Endpoint					
n	150	150	139	158	
Raw Mean (SD)	-20.3 (24.44)	-9.9 (21.73)	-11.8 (24.62)	-2.1 (22.48)	0.015
LS Mean (SEM)	-9.1 (5.20)	-8.2 (5.48)	-10.8 (2.81)	-2.4 (2.47)	
95% C.I.	(-13.0, -5.2)	(-13.3, -2.8)	(-16.9, -5.0)	(-7.3, 2.4)	
Metformin ER Versus Metformin IR				NA	
LS Mean Difference (SEM)	-5.7 (2.45)	-5.8 (2.44)	-7.5 (2.50)	NA	
95% C.I. for Difference	(-10.8, -0.5)	(-10.8, -1.0)	(-12.4, -2.4)		

Note: Patients who had both baseline and endpoint data are included in this data analysis.

Data collected from non-fasting samples are excluded from this data analysis.

NA = Not applicable

For the baseline value, the LS mean (least squares mean) and SEM (standard error of LS mean) are estimated from the ANCOVA model that includes treatment, center (Site 31 versus all other sites), treatment by center interaction factor, and a stratification factor (metformin treatment prior to entry: yes/no).

For the change from baseline to endpoint value, the LS mean (least squares mean) and SEM (standard error of LS mean) are estimated from the ANCOVA model that includes treatment, center (Site 31 versus all other sites), a stratification factor (metformin treatment prior to entry: yes/no), and baseline value as a covariate.

C.I. = confidence interval

[1] The p-value (overall) for the overall comparison among all treatment groups is based on Type III analysis from the models described above.

Source: Listing 14.2.21

Program: SDR1000; (PRD001) (STAT.TABLE) 14610257\_SAS D: 26JAN2003 T: 04582603

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ANCOVA\* on Lipids % change from baseline – Monotherapy Study 03

	MER1500B	MER1500Q	MER2000Q	MIR1500 B
<b>LDL (mg/dL)</b>				
N	150	150	139	155
Baseline LSM (SE)	124.4 (3.8)	126.1 (3.8)	125.1 (3.8)	117.6 (3.8)
LSM % Change <sup>a</sup> (SE)	-6.0(2.7)	-4.8 (2.7)	-5.6 (2.7)	+1.2 (2.7)
MER – MIR (CI)	-7.2 (-12.4, - 2.0)	-6.0 (-11.3, - 0.8)	-6.9 (-12.2, - 1.5)	

\* ANCOVA model included treatment, stratum, and center as fixed effect and baseline as covariate Table displays the least squared mean differences and the 95% simultaneous confidence intervals for the lipid variables The percent change from baseline LDL was statistically different from the immediate release metformin (p=0.02)

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As shown in the table below, there were small changes from baseline triglyceride that were not statistically significant. There is no difference between 1500 mg Glumetza and 1500 mg Metformin IR. Mean weight loss in all groups was approximately 2 kg.

Table 14.1.2-8  
 Analysis of Triglycerides: Intent-to-treat Patients

Triglycerides (TRIG) (mg/dL)	Treatment Group				Overall Treatment p-value [1]
	Metformin IR 1500 mg QD (N = 174)	Metformin IR 1500 mg BID (N = 182)	Metformin IR 2000 mg QD (N = 172)	Metformin IR 1500 mg BID (N = 174)	
Baseline					
N	160	166	151	163	
Raw Mean [SD]	190.5 (148.57)	206.6 (192.29)	201.4 (160.87)	180.6 (133.82)	0.909
LS Mean [SEM]	198.0 (23.24)	195.0 (21.69)	216.2 (29.38)	181.8 (29.27)	
95% C.I.	(141.1, 254.2)	(148.6, 252.1)	(158.8, 275.1)	(118.9, 244.4)	
Change from Baseline to Endpoint at Mean of Baseline TRIG (194.6)					
N	160	166	151	163	
Raw Mean [SD]	13.2 (127.07)	6.2 (115.53)	11.5 (118.45)	-3.4 (77.01)	0.030
LS Mean [SEM]	8.2 (12.19)	6.4 (12.04)	12.0 (12.20)	-13.0 (12.22)	
95% C.I.	(-15.8, 32.1)	(-17.3, 30.1)	(-12.1, 36.2)	(-37.0, 31.0)	
Metformin IR Versus Metformin IR					
LS Mean Difference [SEM]	21.2 (12.03)	19.4 (11.82)	25.1 (12.18)	NS	
95% C.I. for Difference	(-2.4, 44.8)	(-4.6, 42.8)	(1.7, 49.2)		

Note: Patients who had both baseline and endpoint data are included in this data analysis. Data collected from non-fasting samples are excluded from this data analysis.  
 NS = Not applicable  
 For the baseline value, the LS mean (Least Squares mean) and SEM (standard error of LS mean) are estimated from the ANOVA model that includes treatment, center (Site 11 versus all other sites), treatment by center interaction factor, and a stratification factor (metformin treatment prior to entry: yes/no).  
 For the change from baseline to endpoint value, the LS mean (Least Squares mean) and SEM (standard error of LS mean) are estimated from the ANOVA model that includes treatment, center (Site 11 versus all other sites), a stratification factor (metformin treatment prior to entry: yes/no), and treatment by baseline value interaction factor.  
 C.I. = Confidence Interval  
 [1] The p-value (overall) for the overall comparison among all treatment groups is based on Type III analysis from the models described above.

Source: Listing 16.2.20  
 Program: PRB01003: [PRODUCTION].STAT.TABLES\14010208.SAS D: 26JAN2003 T: 04RPR2003

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## Efficacy: Study 4

This was a four-week, phase 2 study to compare the efficacy of Metformin ER given once daily and twice daily to Metformin IR given once daily. Patients had HbA1c of 7 to 12% and had not taken metformin for at least 90 days before screening. The blinded comparison was preceded by a 3-week washout from other antidiabetic medications, if applicable. The initial dose was 1000 mg; the dose was increased by 500 mg per week based on tolerability until the final dose of 2000 mg was achieved.

**Table 6. Summary of Treatment Exposure**

	Treatment Group		
	Metformin ER Once daily N=54	Metformin ER Twice daily N=54	Metformin IR Twice daily N=55
Week 0	54 (100%)	54 (100%)	55 (100%)
Week 1			
1,000 mg	2 (3.7%)	3 (5.6%)	1 (1.8%)
1,500 mg	49 (90.7%)	48 (88.9%)	53 (96.4%)
Week 2			
1,000 mg	2 (3.7%)	2 (3.7%)	1 (1.8%)
1,500 mg	3 (5.6%)	5 (9.3%)	3 (5.5%)
2,000 mg	44 (81.5%)	42 (77.8%)	49 (89.1%)
Week 3			
1,000 mg	2 (3.7%)	3 (5.6%)	1 (1.8%)
1,500 mg	2 (3.7%)	2 (3.7%)	5 (9.1%)
2,000 mg	42 (77.8%)	42 (77.8%)	46 (83.6%)
Week 3 to End of Study			
1,000 mg	2 (3.7%)	3 (5.6%)	1 (1.8%)
1,500 mg	1 (1.9%)	2 (3.7%)	5 (9.1%)
2,000 mg	42 (77.8%)	40 (74.1%)	46 (83.6%)

Percentages are based on the number of randomized patients.

Source: Post-text Table 1.4

**Table 7. Diabetic Characteristics at Baseline for All Randomized Patients**

Characteristic	Treatment Group			P-value
	Metformin ER Once daily N=54	Metformin ER Twice daily N=54	Metformin IR Twice daily N=55	
Current diabetic therapy				
Diet and exercise alone	10 (18.5%)	11 (20.4%)	20 (36.4%)	0.131
Sulfonylurea	18 (33.3%)	23 (42.6%)	16 (29.1%)	
Diet, exercise, sulfonylurea	26 (48.1%)	20 (37.0%)	19 (34.5%)	
Duration of diabetes (yrs)	4.7	4.8	3.4	0.187
Onset age (yrs)	50.8	49.4	50.6	0.764
Weight (lbs)	195.2	194.9	206.9	0.278
Height (in)	66.0	65.5	67.0	0.171
BMI (kg/m <sup>2</sup> )	31.3	31.9	32.2	0.684
Waist-to-hip ratio	0.92	0.94	0.94	0.274

Percentages are based on the number of randomized patients.

Source: Post-text Table 3.1

The primary efficacy variable was change in area under the curve of plasma glucose after a standard meal for Metformin-ER once daily vs Metformin IR given twice daily. As shown below, there was no difference between these two arms.

**Table 8. Analysis of Area Under Curve Based on Fasting Plasma Glucose Measurements: Patients Randomized to Metformin ER Once Daily or Metformin IR Twice Daily**

AUC of Fasting Plasma Glucose (GAUC) (ng <sup>2</sup> h/mL)	Treatment Group		Overall Treatment p-value[1]
	Metformin ER Once daily (N=54)	Metformin IR Twice daily (N=55)	
Change from Baseline to Endpoint			
n	48	53	
LS Mean (SEM)	-103.4 (19.4)	-126.7 (18.9)	0.392
Metformin ER versus Metformin IR			
LS Mean Difference	23.4		
95% CI for Difference	(-30.7, 77.4)		

Note: Patients who had both baseline and endpoint were included in this data analysis. For the change from baseline to endpoint, the least squares (LS) mean and standard error of the mean (SEM) were estimated from the ANCOVA model that includes treatment, center, treatment-by-center interaction factor, and baseline value as a covariate. CI, confidence interval [1] The p-value (overall) for the overall comparison among all treatment groups is based on Type III analysis from the models described above.

As shown in the following table, there was no statistically significant difference among the three arms with respect to change in FPG, although Metformin-ER twice daily tended to be better than Metformin-ER once daily or Metformin IR twice daily.

**Table 10. Analysis of Fasting Plasma Glucose Measurements: Intent-to-Treat Patients**

Fasting Plasma Glucose (FPG) (ng/mL)	Treatment Group			Overall Treatment p-value[1]
	Metformin ER Once daily (N=54)	Metformin ER Twice daily (N=54)	Metformin IR Twice daily (N=55)	
Change from baseline to endpoint				
n	48	53	54	
LS Mean (SEM)	-31.1 (6.5)	-44.6 (6.6)	-36.9 (6.3)	0.342
Metformin ER versus Metformin IR				
LS mean difference	5.9	-7.7		
95% CI for difference	(-12.0, 23.7)	(-25.8, 10.3)		

Note: Patients who had both baseline and endpoint were included in this data analysis. For the change from baseline to endpoint, the least squares (LS) mean and standard error of LS mean (SEM) were estimated from the ANCOVA model that includes treatment, center, treatment by center interaction factor, and baseline value as a covariate. CI, confidence interval [1] The p-value (overall) for the overall comparison among all treatment groups is based on Type III analysis from the models described above.

## Efficacy: Study 14

This was a double blind, randomized trial add-on trial of Metformin ER, Sulfonylurea (SU) or the combination of M-ER + SU. Following a 2 week screening period, patients were stabilized on SU (Glyburide 5 mg in the morning plus 5 mg in the evening for two weeks followed by 10 mg in the morning plus 5 mg in the evening for an additional four weeks) prior to randomization. Patients then underwent a 3-week M-ER titration followed by a 21-week maintenance treatment phase. The starting dose of M-ER was two 500 mg tablets given after the evening meal. This dose was increased over three weeks to final assigned doses. The three M-ER arms received, 1500 mg qd (3 x 500 mg tablets after the evening meal), 1000 mg bid (2 x 500mg tablets after breakfast and 2 x 500 mg tablets after the evening meal) and 2000 mg qd (4 x 500 mg tablets after the evening meal). Placebo tablets were given as appropriate to maintain blinding. Thus the SU only arm received two placebo tablets in the morning and four placebo tablets in the evening.

Inclusion criteria: Eligible patients could be either naïve to treatment or on antidiabetic medications, either as monotherapy or in combination (in doses up to 1000 mg per day of metformin plus 1/2 the maximum dose of SU.) For patients currently on antidiabetic medications, HbA1c were between 6.5 and 12% and FPG between 120 and 250 mg/dl. For patients not currently on antidiabetic medications, HbA1c were between 7.5 and 12% and FPG between 200 and 400 mg/dl. Patients on insulin were excluded.

Discontinuation due to “lack of efficacy” occurred in 11.8% of patients on SU alone compared to 3% of patients on M-ER + SU.

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**In-text Table 5 Demographics and Baseline Characteristics: Intent-to-Treat Patients**

	Treatment Group				Total (N = 575)	p-value [1]
	MER1500Q + SU (N = 144)	MER1000B + SU (N = 141)	MER2000Q + SU (N = 146)	SU Alone (N = 144)		
<b>Age (years)</b>						
Mean (SD)	54 (10.3)	53 (10.5)	53 (10.9)	53 (10.7)	53 (10.6)	0.921
Range	25-80	29-75	26-75	29-74	25-80	
<b>n (%):</b>						0.178
<40	11 (7.6%)	11 (7.8%)	22 (15.1%)	23 (16.0%)	67 (11.7%)	
40-<65	114 (79.2%)	109 (77.3%)	103 (70.5%)	102 (70.8%)	428 (74.4%)	
≥65	19 (13.2%)	21 (14.9%)	21 (14.4%)	19 (13.2%)	80 (13.9%)	
<b>Sex: n (%)</b>						0.631
Male	77 (53.5%)	83 (58.9%)	75 (51.4%)	79 (54.9%)	314 (54.6%)	
Female	67 (46.5%)	58 (41.1%)	71 (48.6%)	65 (45.1%)	261 (45.4%)	
<b>Race: n (%)</b>						0.607
Caucasian	81 (56.3%)	89 (63.1%)	88 (60.3%)	80 (55.6%)	338 (58.8%)	
Black	20 (13.9%)	11 (7.8%)	12 (8.2%)	19 (13.2%)	62 (10.8%)	
Asian	1 (0.7%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	2 (0.3%)	
Hispanic	39 (27.1%)	40 (28.4%)	43 (29.5%)	42 (29.2%)	164 (28.5%)	
Native American	2 (1.4%)	1 (0.7%)	1 (0.7%)	0 (0.0%)	4 (0.7%)	
Other	1 (0.7%)	0 (0.0%)	1 (0.7%)	3 (2.1%)	5 (0.9%)	
<b>Weight (kg)</b>						
Mean (SD)	98 (21.9)	97 (22.5)	97 (23.4)	97 (21.2)	97 (22.2)	0.991
Range	50-158	53-176	52-181	51-161	50-181	
<b>Height (cm)</b>						
Mean (SD)	168 (10.6)	169 (12.2)	169 (12.0)	169 (12.0)	169 (11.7)	0.725
Range	145-188	142-206	135-193	140-196	135-206	
<b>BMI (kg/m<sup>2</sup>)</b>						
Mean (SD)	35 (7.1)	34 (6.3)	34 (7.1)	34 (7.1)	34 (6.9)	0.674
Range	23-54	22-56	22-60	22-65	22-65	
<b>n (%):</b>						0.793
<30	48 (33.3%)	40 (28.4%)	46 (31.5%)	42 (29.2%)	176 (30.6%)	
≥30	96 (66.7%)	101 (71.6%)	100 (68.5%)	102 (70.8%)	399 (69.4%)	

Source: Post-text Table 14.1.1-6.

MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylurea; SD = standard deviation; BMI = body mass index.

[1] The p-value for the overall comparison among four treatment groups was based on the Effect of Type III treatment factor.

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**In-text Table 6 Diabetes History: Intent-to-Treat Patients**

	Treatment Group				Total (N = 575)	P-value [1]
	MER1500Q + SU (N = 144)	MER1000B + SU (N = 141)	MER2000Q + SU (N = 146)	SU Alone (N = 144)		
<b>Duration of Diabetes (years)</b>						
Mean (SD)	5.1 (4.6)	5.0 (5.2)	4.9 (4.9)	5.8 (5.7)	5.2 (5.1)	0.462
Range	(0.2-21.0)	(0.2-31.0)	(0.2-23.3)	(0.2-36.6)	(0.2-36.6)	
<b>Metformin Treatment within 30 days</b>						
Yes	78 (54.2%)	60 (42.6%)	72 (49.3%)	52 (36.1%)	262 (45.6%)	0.013
No	66 (45.8%)	81 (57.4%)	74 (50.7%)	92 (63.9%)	313 (54.4%)	
<b>Diet/exercise Only or Newly Diagnosed</b>						
Yes	27 (18.8%)	42 (29.8%)	42 (28.8%)	33 (22.9%)	144 (25.0%)	0.104
No	117 (81.3%)	99 (70.2%)	104 (71.2%)	111 (77.1%)	431 (75.0%)	
<b>Diabetic Treatment within 30 days[2]</b>						
Metformin only	47 (32.6%)	37 (26.2%)	44 (30.1%)	31 (21.5%)	159 (27.7%)	
Combination with metformin only	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
SU only	33 (22.9%)	29 (20.6%)	26 (17.8%)	48 (33.3%)	136 (23.7%)	
Combination with SU only	1 (0.7%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	
Combination with metformin and SU	31 (21.5%)	23 (16.3%)	28 (19.2%)	21 (14.6%)	103 (17.9%)	
Diet and exercise only or newly diagnosed	27 (18.8%)	42 (29.8%)	42 (28.8%)	33 (22.9%)	144 (25.0%)	
Other	5 (3.5%)	9 (6.4%)	6 (4.1%)	11 (7.6%)	31 (5.4%)	

Source: Post-text Table 14.1.1-10.

MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylurea; SD = standard deviation

[1] The p-value for the overall comparison among four treatment groups was based on the F-test of Type III treatment factor from the ANOVA model including the treatment factor for numeric data or Chi-square test for categorical data.

[2] Patients may have been reported in more than one category.

The primary efficacy variable was change in HbA<sub>1c</sub> from baseline to endpoint. As shown in the following table, change in HbA<sub>1c</sub> was greater for the combined M-ER + SU treatment groups than for the SU only treatment group.

**In-text Table 8 Hemoglobin A<sub>1c</sub> Results: Combined M-ER + SU Treatment Group versus SU Alone Treatment Group: Intent-to-Treat Patients**

Hemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) (%)	Combined M-ER + SU (N = 431)	SU Alone (N = 144)	Overall Treatment p-value [1]
<b>Baseline (n)</b>	416	141	
LS Mean (SEM)	7.79 (0.07)	8.08 (0.13)	0.051
<b>Endpoint (n)</b>	416	141	
LS Mean (SEM)	7.13 (0.05)	7.95 (0.08)	<0.001
95% CI	(7.02, 7.23)	(7.78, 8.12)	
<b>Change from Baseline to Endpoint (n)</b>	416	141	
LS Mean (SEM)	-0.74 (0.05)	0.08 (0.08)	<0.001
95% CI	(-0.85, -0.64)	(-0.08, 0.25)	
<b>M-ER + SU versus SU alone</b>		NA	
LS Mean Difference (SEM)	-0.82 (0.09)		
95% CI for Difference	(-1.00, -0.65)		

Source: Post-text Table 14.1.2-1.

MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylurea; LS = least squares; SEM = standard error of LS mean; CI = confidence interval; NA = not applicable.

Note: Patients who had both baseline and any endpoint were included in this data analysis. For baseline value, the LS mean and SEM were estimated from the ANOVA model that included treatment, center, and treatment by center interaction factor.

For the endpoint and change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and baseline value as a covariate.

[1] The p-value for the treatment effect was based on the Type III analysis from the models described above.

As shown in the table below, all three regimens of M-ER + SU were superior to SU alone. The best results appeared to occur with M-ER 1000 mg bid although the differences among the three M-ER arms were not statistically significant.

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**In-text Table 9 Hemoglobin A<sub>1c</sub> Results: Each M-ER + SU Treatment Group versus SU Alone Treatment Group: Intent-to-Treat Patients**

Hemoglobin A <sub>1c</sub> (HbA <sub>1c</sub> ) (%)	Treatment Group				Overall Treatment p-value [1]
	MER1500Q + SU (N = 144)	MER1000B + SU (N = 141)	MER2000Q + SU (N = 146)	SU alone (N = 144)	
Baseline (n)	136	136	144	141	
LS Mean (SEM)	7.93 (0.13)	7.75 (0.13)	7.68 (0.13)	8.08 (0.13)	0.130
Endpoint (n)	136	136	144	141	
LS Mean (SEM)	7.15 (0.09)	7.05 (0.09)	7.16 (0.08)	7.94 (0.08)	0.931
95% CI	(6.98, 7.32)	(6.88, 7.22)	(7.00, 7.33)	(7.77, 8.10)	
Change from Baseline to Endpoint (n)	136	136	144	141	
LS Mean (SEM)	-0.72 (0.09)	-0.82 (0.09)	-0.71 (0.08)	0.07 (0.08)	0.931
95% CI	(-0.89, -0.55)	(-0.99, -0.65)	(-0.87, -0.54)	(-0.10, 0.23)	
M-ER + SU versus SU Alone					
LS Mean Difference (SEM)	-0.79 (0.11)	-0.89 (0.11)	-0.77 (0.11)	NA	
95% CI for Difference	(-1.01, -0.57)	(-1.11, -0.67)	(-0.99, -0.56)		
p-value (vs. SU) [2]	<0.001	<0.001	<0.001		

Source: Post-text Table 14.1.2-2.

MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylureas; LS = least squares; SEM = standard error of LS mean; CI = confidence interval; NA = not applicable.

Note: Patients who had both baseline and any endpoint were included in this data analysis. For baseline, the LS mean and SEM were estimated from the ANOVA model that included treatment, center, and treatment by center interaction factor. For the endpoint and change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and baseline covariate by treatment interaction factor.

Endpoint and change from baseline to endpoint data are at the mean of baseline HbA<sub>1c</sub> (7.87%).

[1] The p-value (overall) for the overall comparison among all treatment groups was based on the Type III analysis from the models described above.

[2] The p-value (vs. SU) for the pairwise test of difference of the LS mean change from baseline between M-ER + SU and SU alone is based on the t-test of Type III analysis for the models described above.

As shown in the following table, changes in FPG followed the same pattern as change in HbA<sub>1c</sub>.

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**In-text Table 10 Fasting Plasma Glucose Results: Intent-to-Treat Patients**

Fasting Plasma Glucose (mg/dL)	Treatment Group					Overall Treatment p-value [1]
	MER1500Q + SU (N = 144)	MER1000B + SU (N = 141)	MER2000Q + SU (N = 146)	Combined M-ER + SU (N = 431)	SU alone (N = 144)	
Baseline (n)	143	141	145	429	144	
LS mean (SEM)	163.4 (4.64)	163.2 (4.69)	158.8 (4.69)	161.8 (2.70)	164.0 (3.66)	0.851
95% CI	(154.3, 172.5)	(154.0, 172.5)	(149.5, 168.0)	(156.5, 167.1)	(154.8, 173.1)	
Endpoint (n)	143	141	145	429	144	
LS Mean (SEM)	148.0 (3.69)	146.0 (3.71)	152.3 (3.69)	148.7 (2.14)	177.2 (3.70)	0.865
95% CI	(14.7, 155.2)	(139.3, 153.9)	(144.4, 158.9)	(144.5, 152.9)	(169.9, 184.4)	
Change from Baseline to Endpoint (n)	143	141	145	429	144	
LS Mean (SEM)	-13.7 (3.69)	-15.7 (3.71)	-9.4 (3.69)	-12.9 (2.14)	15.5 (3.70)	0.865
95% CI	(-20.9, -6.4)	(-23.0, -8.4)	(-16.7, -2.1)	(-17.1, -8.7)	(8.2, 22.8)	
M-ER + SU versus SU alone						
LS Mean Difference (SEM)	-29.2 (4.88)	-31.2 (40.9)	-24.9 (4.87)	-28.4 (3.98)	NA	
95% CI for Difference	(-38.8, -19.6)	(-40.9, -21.6)	(-34.5, -15.4)	(-36.8, -20.6)		
p-value (vs. SU) [2]	<0.001	<0.001	<0.001	<0.001		

Source: Post-test Tables 14.1.2-5.  
 MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylurea; LS = least squares; SEM = standard error of LS mean; CI = confidence interval; NA = not applicable.  
 Note: Patients who had both baseline and endpoint values were included in this data analysis. For baseline, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and treatment by center interaction factor. For the endpoint and change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and baseline covariate by treatment interaction factor.

Endpoint and change from baseline to endpoint data are at the mean of baseline FPG (161.7 mg/dL).  
 [1] The p-value (overall) for the overall comparison among all treatment groups was based on the Type III analysis from the models described above.  
 [2] The p-value (vs. SU) for the pairwise test of difference of the LS mean change from baseline between M-ER + SU and SU alone is based on the t-test of Type III analysis for the models described above.

As shown in the following table, M-ER +SU was better than SU alone with respect to HDL cholesterol, LDL cholesterol and triglycerides.

**In-text Table 12 Lipid Results: Intent-to-Treat Patients**

Change from Baseline to Endpoint	Treatment Group					Overall Treatment p-value [1]
	MER1500Q + SU (N = 144)	MER1000B + SU (N = 141)	MER2000Q + SU (N = 146)	Combined M-ER + SU (N = 431)	SU Alone (N = 144)	
Total Cholesterol (mg/dL) [3]	n = 134	n = 131	n = 138	n = 403	n = 136	
LS Mean (SEM)	6.98 (3.58)	3.42 (3.65)	4.42 (3.56)	4.94 (2.08)	19.09 (3.60)	0.467
LS Mean Difference (SEM)	-12.11 (4.76)	-15.66 (4.79)	-14.66 (4.72)	-14.15 (3.88)	NA	
95% CI for Difference	(-21.45, -2.77)	(-25.08, -6.24)	(-23.94, -5.39)	(-21.77, -6.52)		
p-value (vs. SU) [2]	0.011	0.001	0.002	<0.001		
HDL Cholesterol (mg/dL) [4]	n = 134	n = 131	n = 138	n = 403	n = 136	
LS Mean (SEM)	3.21 (0.54)	2.44 (0.55)	2.32 (0.54)	2.65 (0.31)	4.15 (0.54)	0.040
LS Mean Difference (SEM)	-0.94 (0.72)	-1.71 (0.72)	-1.83 (0.71)	-1.50 (0.58)	NA	
95% CI for Difference	(-2.33, 0.46)	(-3.13, -0.29)	(-3.23, -0.43)	(-2.64, -0.35)		
p-value (vs. SU) [2]	0.188	0.018	0.010	0.011		
LDL Cholesterol (mg/dL) [4]	n = 117	n = 120	n = 124	n = 361	n = 120	
LS Mean (SEM)	0.26 (2.80)	-4.40 (2.82)	0.28 (2.85)	-1.28 (1.63)	14.31 (2.83)	<0.001
LS Mean Difference (SEM)	-14.05 (3.98)	-18.71 (3.99)	-14.03 (4.02)	-15.59 (3.27)	NA	
95% CI for Difference	(-21.88, -6.22)	(-26.56, -10.85)	(-21.93, -6.12)	(-22.01, -9.17)		
p-value (vs. SU) [2]	<0.001	<0.001	<0.001	<0.001		
Triglycerides (mg/dL) [3]	n = 134	n = 131	n = 138	n = 403	n = 136	
LS Mean (SEM)	25.67 (18.80)	2.96 (19.58)	39.84 (18.89)	22.82 (11.03)	56.94 (18.85)	<0.001
LS Mean Difference (SEM)	-31.28 (26.63)	-53.99 (27.18)	-17.11 (26.69)	-34.12 (21.84)	NA	
95% CI for Difference	(-83.61, 21.06)	(-107.41, -0.56)	(-69.57, 35.36)	(-77.05, 8.80)		
p-value (vs. SU) [2]	0.241	0.048	0.522	0.119		

Source: Post-test Tables 14.1.2-6 through 14.1.2-9.  
 MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylurea; LS = least squares; SEM = standard error of LS mean; HDL = high-density lipoprotein; LDL = low-density lipoprotein.  
 Note: Patients who had both baseline and endpoint values were included in this data analysis. For the total cholesterol and triglycerides change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and baseline covariate by treatment interaction factor. For the HDL and LDL cholesterol change from baseline to endpoint value, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and baseline value as a covariate.  
 [1] The p-value (overall) for the overall comparison among all treatment groups was based on the Type III analysis from the models described above.  
 [2] The p-value (vs. SU) for the pairwise test of difference of the LS mean change from baseline between M-ER + SU and SU alone is based on the t-test of Type III analysis for the models described above.  
 [3] Nonparallel ANCOVA model, estimated at mean of baseline value. [4] Parallel ANCOVA model.

Mean weight gain of 0.53 kg at 24 weeks was somewhat less (p=0.077) with M-ER (combined) +SU than the weight gain of 1.29 kg with SU alone.

V11 Review of Safety:

Study 003

The adverse event profile of Glumetza and Metformin IR were similar. As shown in the following tables, adverse events were related largely to the gastrointestinal system in all treatment arms. There were few adverse events leading to withdrawal and they did not appear related to study medication.

In-Text Table 16 Summary of Adverse Events

	Treatment Group				Total
	Metformin ER 1500 mg QD	Metformin ER 1500 mg (AM/PM)	Metformin ER 2000 mg QD	Metformin IR 1500 mg (AM/PM)	
Number Of Patients Randomized In The Study	191	191	182	186	750
Number Of Patients Who Were Enrolled In Site 61 and Excluded From Safety Population	2	2	4	3	11
Number (%) Of Patients Who Received Treatment	176 (100%)	181 (100%)	171 (100%)	174 (100%)	702 (100%)
Number (%) Of Patients Without Any AE	57 (32.4%)	52 (28.7%)	39 (22.8%)	44 (25.3%)	192 (27.4%)
Number (%) Of Patients With At Least One AE	119 (67.6%)	129 (71.3%)	132 (77.2%)	130 (74.7%)	510 (72.6%)
Number Of Incidences Of AEs	510	561	568	465	2104
Number (%) Of Patients With At Least One SAE	7 (4.0%)	7 (3.9%)	5 (2.9%)	5 (2.9%)	24 (3.4%)
Number (%) Of Patients With At Least One AE Causing The Discontinuation Of Study Drug	12 (6.8%)	8 (4.4%)	9 (5.3%)	11 (6.3%)	40 (5.7%)

Source: Post-Test Table 14.1.3-2 through 14.1.3-7

AE = adverse event; SAE = serious adverse event

Note: Adverse event mapping was based on the MedDRA<sup>®</sup> version 5.1 thesaurus.

A patient may have been reported in more than 1 category.

Adverse events occurring while patients were on study medication during the double-blind treatment period or within 3 days after the discontinuation of study medication were included in this table.

Serious adverse events occurring while patients were on study medication during the double-blind treatment period or within 3 days after the discontinuation of study medication were included in this table.

Incidence is defined as the number of times the event was reported.

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In-Text Table 20 Adverse Events Causing the Discontinuation of Study Drug by Treatment Group and Treatment Period

Treatment Period [1]		Treatment Group				All Metformin ER Groups (N=528)
		Metformin ER 1500 mg QD (N=176)	Metformin ER 1500 mg (AM/PM) (N=181)	Metformin ER 2000 mg QD (N=171)	Metformin IR 1500 mg (AM/PM) (N=174)	
1 - 7 days	Diarrhoea NOS	1 (0.6%)	0	0	2 (1.2%)	1 (0.2%)
	Nausea	0	0	0	3 (1.7%)	0
	Other GI adverse events [2]	1 (0.6%)	1 (0.6%)	0	2 (1.2%)	2 (0.4%)
8 - 14 days	Non-GI adverse events [2]	2 (1.1%)	1 (0.6%)	0	2 (1.2%)	3 (0.6%)
	Diarrhoea NOS	0	0	0	0	0
	Nausea	0	0	0	1 (0.6%)	0
15 - 21 days	Other GI adverse events [2]	0	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
	Diarrhoea NOS	0	0	0	3 (1.7%)	0
	Nausea	1 (0.6%)	0	0	0	1 (0.2%)
22 - 28 days	Other GI adverse events [2]	2 (1.1%)	1 (0.6%)	1 (0.6%)	0	4 (0.8%)
	Diarrhoea NOS	0	0	0	0	0
	Nausea	0	0	2 (1.2%)	0	2 (0.4%)
29 - 168 days	Other GI adverse events [2]	0	1 (0.6%)	1 (0.6%)	2 (1.2%)	2 (0.4%)
	Diarrhoea NOS	0	1 (0.6%)	2 (1.2%)	1 (0.6%)	3 (0.6%)
	Nausea	1 (0.6%)	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
29 - 168 days	Other GI adverse events [2]	1 (0.6%)	0	2 (1.2%)	0	3 (0.6%)
	Diarrhoea NOS	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (0.6%)
	Nausea	4 (2.3%)	2 (1.1%)	3 (1.8%)	1 (0.6%)	9 (1.7%)
	Non-GI adverse events [2]	2 (1.1%)	3 (1.7%)	4 (2.3%)	3 (1.7%)	9 (1.7%)

Source: Post-Test Listing 16.2.2 and 16.2.3.

Note: Adverse event mapping was based on the MedDRA<sup>®</sup> Version 5.1 thesaurus.

A patient may be counted in more than 1 adverse event category.

AE = adverse event.

[1] Treatment period was calculated as (days on medication) + 1 (see Post-Test Listing 16.2.3).

[2] This category was treated the same as "System Organ Class." Patients who had more than 1 adverse event falling under this category were counted only once.

Safety: Study 4

The adverse event profile of Glumetza and Metformin IR were similar. As shown in the following tables, adverse events were related largely to the gastrointestinal system in all treatment arms:

**Table 12. Summary of Treatment-Emergent Adverse Events**

	Treatment Group		
	Metformin ER Once daily N=54	Metformin ER Twice daily N=54	Metformin IR Twice daily N=55
Incidence of AEs	271	265	270
Patients with AEs	43 (79.6%)	47 (87.0%)	43 (78.2%)
Incidence of AEs related to study medication	237	226	230
Incidence of AEs contributing to discontinuation	10	4	3

Percentages are based on the number of exposed patients.

Source: Post-text Tables 15.1, 15.1.2, and 15.5

**Table 17. Frequently Occurring Adverse Events\***

Adverse Event	Treatment Group			P-value
	Metformin ER Once daily N = 54	Metformin ER Twice daily N = 54	Metformin IR Twice daily N = 55	
Diarrhea NOS	24 (44.4%)	30 (55.6%)	35 (63.6%)	0.131
Flatulence	22 (40.7%)	20 (37.0%)	22 (40.0%)	0.939
Nausea	20 (37.0%)	17 (31.5%)	25 (45.5%)	0.344

\*An adverse event that occurred in 5% or more of the total randomized patients. The top three are summarized.

Percentages are based on the number of patients exposed to study medication.

Source: Post-text Table 15.6

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Safety: Study 14

As shown in the following tables, adverse events were more often related to the gastrointestinal system in treatment arms containing M-ER.

**In-text Table 15 Summary of Adverse Events**

	Treatment Group				
	MER1500Q + SU	MER1000B + SU	MER2000Q + SU	Combined M-ER + SU	SU Alone
<b>Number (%) of Patients</b>					
Randomized	153	148	154	455	152
Received Treatment	144 (100%)	141 (100%)	146 (100%)	431 (100%)	144 (100%)
Without Any AE	37 (25.7%)	45 (31.9%)	37 (25.3%)	119 (27.6%)	47 (32.6%)
With at Least One AE	107 (74.3%)	96 (68.1%)	109 (74.7%)	312 (72.4%)	97 (67.4%)
With at Least One SAE	3 (2.1%)	4 (2.8%)	2 (1.4%)	9 (2.1%)	2 (1.4%)
With at Least One AE Causing Discontinuation of Study Drug	7 (4.9%)	18 (12.8%)	15 (10.3%)	40 (9.3%)	3 (2.1%)
With at Least One Severe AE Related to Study Drug	2 (1.4%)	1 (0.7%)	3 (2.1%)	6 (1.4%)	2 (1.4%)
<b>Total Number of AEs</b>	<b>375</b>	<b>350</b>	<b>373</b>	<b>1098</b>	<b>375</b>

Source: Post-text Tables 14.1.3-2, 14.1.3-3, 14.1.3-5, 14.1.3-6, and 14.1.3-10.  
 MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg  
 qd; SU = sulfonylurea; AE = adverse event; SAE = serious adverse event  
 Notes: Adverse event mapping was based on the MedDRA™ Version 5.1 thesaurus. Related = possible, probable, or missing  
 relationship to study drug.  
 A patient may have been reported in more than one category.  
 Adverse events occurring while patients were on study drug during the double-blind treatment period or within 3 days

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**In-text Table 17 Most Frequent Adverse Events**

System Organ Class/ Preferred Term	Treatment Group					Overall Treatment p-value [1]
	MER1500Q + SU (N = 144)	MER1000B + SU (N = 141)	MER2000Q + SU (N = 146)	Combined M-ER + SU (N = 431)	SU Alone (N = 144)	
With at Least One AE	107 (74.3%)	96 (68.1%)	109 (74.7%)	312 (72.4%)	97 (67.4%)	NS
<b>Gastrointestinal Disorders</b>	40 (27.8%)	43 (30.5%)	47 (32.2%)	130 (30.2%)	35 (24.3%)	NS
Diarrhoea NOS	18 (12.5%)	18 (12.8%)	18 (12.3%)	54 (12.5%)	8 (5.6%)	NS
Nausea	10 (6.9%)	8 (5.7%)	11 (7.5%)	29 (6.7%)	6 (4.2%)	NS
Vomiting NOS	7 (4.9%)	3 (2.1%)	10 (6.8%)	20 (4.6%)	4 (2.8%)	NS
Constipation	2 (1.4%)	2 (1.4%)	7 (4.8%)	11 (2.6%)	8 (5.6%)	0.085
<b>Infections and Infestations</b>	40 (27.8%)	29 (20.6%)	36 (24.7%)	105 (24.4%)	39 (27.1%)	NS
Upper Respiratory Tract Infection NOS	10 (6.9%)	5 (3.5%)	10 (6.8%)	25 (5.8%)	11 (7.6%)	NS
<b>Metabolism and Nutrition Disorders</b>	19 (13.2%)	32 (22.7%)	17 (11.6%)	68 (15.8%)	11 (7.6%)	0.003
Hypoglycaemia NOS	15 (10.4%)	30 (21.3%)	14 (9.6%)	59 (13.7%)	7 (4.9%)	<0.001
<b>Musculoskeletal Disorders</b>	30 (20.8%)	25 (17.7%)	29 (19.9%)	84 (19.5%)	30 (20.8%)	NS
Arthralgia	9 (6.3%)	6 (4.3%)	11 (7.5%)	26 (6.0%)	10 (6.9%)	NS
Back Pain	6 (4.2%)	8 (5.7%)	6 (4.1%)	20 (4.6%)	8 (5.6%)	NS
<b>Nervous System Disorders</b>	19 (13.2%)	18 (12.8%)	29 (19.9%)	66 (15.3%)	23 (16.0%)	NS
Headache	8 (5.6%)	9 (6.4%)	11 (7.5%)	28 (6.5%)	14 (9.7%)	NS
<b>Respiratory Disorders</b>	29 (20.1%)	26 (18.4%)	29 (19.9%)	84 (19.5%)	32 (22.2%)	NS
Nasopharyngitis	13 (9.0%)	12 (8.5%)	11 (7.5%)	36 (8.4%)	16 (11.1%)	NS

Source: Post-text Table 14.1.3-4.

Includes adverse events by preferred term that were reported by at least 5% of patients in any treatment group.

MER1500Q = Metformin ER 1500 mg qd; MER1000B = Metformin ER 1000 mg bid; MER2000Q = Metformin ER 2000 mg qd; SU = sulfonylurea; NOS = not otherwise specified.

Notes: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Adverse events occurring while patients were on study drug during the double-blind treatment period or within 3 days after the discontinuation of study drug are included in this table.

[1] The p-value for the overall comparison among four treatment groups are based on a two-sided Fisher's Exact test and presented if <0.10; NS=not statistically significant at 0.10 level.

9 patients (2.1%) of patients in the combined M-ER+SU group reported a serious AE and 2 patients (1.4%) with SFU only. In 4 patients on M-ER + SU the SAE was related to the gastrointestinal system. None of the SAE's was considered by the investigator to be related to study drug and all but one (coronary artery disease with tachycardia) resolved by the end of study. With the exception of one case of abdominal pain after 4 days of M-ER 1000 bid + SU, I agree that the SAE's were not likely related to study drugs.

45 patients (9.3%) of patients in the combined M-ER+SU group discontinued because of an AE compared to 3 patients (2.1%) with SU only. In 20 patients on M-ER + SU and 2 patients on SU only, the reason for discontinuation was hypoglycemia.

## VIII Dosing and Administration Issues

The proposed label for Glumetza borrows much from the Glucophage label. This is acceptable because the clinical studies have demonstrated that Glumetza and Glucophage are therapeutically equivalent. Most patients take 2000 mg of metformin per day. In order to limit gastrointestinal intolerance, the recommended starting dose of Glumetza is 1000 mg per day. This can be increased to 2000 mg per day as a single dose. The label goes on to recommend that consideration be given to dividing the dose of Glumetza if the single dose is not adequately effective. These recommendations are appropriate.

IX Use in Special Populations – No issues pertain

X Conclusions and Recommendations:

The efficacy of Glumetza given once daily or twice daily is close enough to that of Glucophage twice daily that the three treatment regimens can probably be used interchangeably. Splitting the dose of Glumetza provides slightly more metformin exposure and may be slightly more effective, but the difference is so small, that splitting the dose may not be worth the inconvenience. The safety profile of Metformin ER and Glucophage are similar.

The PK data shown in section 2.2 table 3 of the Biopharm review (reproduced in Section 3, page 4 of this review) should be added to the label.

**Final Recommendation:**

**APPROVAL**

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

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Robert Misbin  
2/22/05 02:30:58 PM  
MEDICAL OFFICER

Glumetza review

David Orloff  
2/23/05 05:53:13 PM  
MEDICAL OFFICER  
Concur with recommendation to approve pending final labeling.