CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-748

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-748
Name of drug:	Glumetza (metformin hydrochloride) Extended Release Tablets 500 and 1000 mg
Applicant:	Biovail Laboratories Incorporated
Indication:	Type 2 Diabetes
Documents reviewed:	\\Cdsesub1\n21748\N_000\2004-04-27\
Project manager:	Jena Weber (HFD-510)
Clinical reviewer:	Robert Misbin, M.D. (HFD-510)
Dates:	Received 4/27/04; user fee (10 months) 2/27/05
Statistical reviewer:	Lee-Ping Pian, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Biometrics division director:	Edward Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, noninferiority trial

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS

As monotherapy, Glumetza 1500 mg once a day, Glumetza 1500 mg per day in divided dose of 500 mg in the morning and 1000 mg in the evening are noninferior to the 1500 mg immediate release metformin (divided dose). The efficacy of once daily and twice daily dosing was similar with Glumetza. The changes from baseline HbA_{1c} were approximately -0.7% for all 3 treatment groups. In addition, Glumetza 2000 mg once a day is noninferior to the 1500 mg immediate release metformin in divided dose of 500 mg AM and 1000 mg PM. As an add on therapy to sulfonylurea, Glumetza 1500 mg once a day, 2000 mg once a day, and 2000 mg per day in divided dose were all superior to placebo plus sulfonylurea (Table 1).

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

This submission included two 24-week phase 3 studies of Glumetza, an extended release dosage form of metformin (MER) in 500 and 1000 mg tablets. The monotherapy study compared 3 MER groups of 1500 mg per day in the evening, 2000 mg per day in the evening or 1500 mg in divided dose of 500 mg in the morning and 1000 mg in the evening to the 1500 mg immediate released metformin (MIR) in divided dose (500 mg AM and 1000 mg PM). The combination study compared 3 MER groups: 1500 QD, 2000 mg QD and 1000 mg BID in combination with sulfonylurea (SU) to sulfonylurea alone. The statistical objectives were to show noninferiority of MER to MIR in the monotherapy study and superiority of MER+SU to SU alone in the combination study.

Table 1 HbA_{1c} summary of phase 3 trials

Study-ID	# of Centers	ITT Sample Size for HbA_{1c}		Baseline HbA_{1c} (%)	Change	MER minus MIR (CI)
03	85 US	MER 1500Q	169	8.22	-0.73	-0.03 (-0.32, +0.26)
		MER 1500(AM/PM)	175	8.50	-0.74	-0.04 (-0.33, +0.25)
		M ER 2000Q	159	8.26	-1.06	-0.36 (-0.65, -0.06)
		MIR 1500(AM/PM)	170	8.70	-0.70	
		Total	673			
14	68 US	Combined MER+SU	416	7.79	-0.74	-0.82 (-1.00, -0.65)
		MER 1500Q+SU	136	7.93	-0.72	-0.79 (-1.01, -0.57)
		MER 1000B+SU	136	7.75	-0.82	-0.89 (-1.11, -0.67)
		MER 2000Q+SU	144	7.68	-0.71	-0.77 (-0.99, -0.56)
		SU	141	8.08	+0.07	

The rationale for the studies was that the controlled-release formulation of metformin is at least as efficacious as the IR and that a more rapid titration period for MER QD might be well tolerated and more convenient for the patient. In addition, from the phase 2 study, the MER demonstrated comparable efficacy with MIR in FPG and it was observed that the twice-daily dosing of MER might improve safety and efficacy outcomes over MER once-daily dosing.

The primary objective of the monotherapy study was to demonstrate at least one of the once-daily or twice-daily dosing regimens of MER 1500 mg and a higher dose of MER (2000 mg QD) is noninferior to twice daily dosing of 1500 MIR (500 mg AM/1000 mg PM).

To allow for MER use in a broad type 2 diabetes population, patients on metformin therapy were included in the study and were stratified by metformin therapy in expectation of a smaller HbA_{1c} reduction in patients with prior treatment of metformin.

The combination study included both drug naïve and patients who had previously been treated with either drug alone or with a combination of both drugs. The primary objective was to show superiority of MER in combination with SU to SU alone in glycemic control in patients with type 2 diabetes.

2.2 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.2.1 SPONSOR'S RESULTS AND CONCLUSIONS

In both studies, the primary efficacy variable was the change from baseline in HbA_{1c} at Week 24. The primary efficacy analysis population was the intent-to-treat population with last observation carried forward for the missing values.

In the monotherapy study, all 3 MER treatments were noninferior to MIR with the upper limit of the confidence interval for the mean treatment difference within the noninferiority margin (0.4%). For the combination to SU study, the 3 MER treatment groups were all superior to MIR in HbA_{1c} change from baseline.

2.2.2 STATISTICAL METHODOLOGIES

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

The 2-sided 98.4% confidence interval used to assess the difference between the 3 MER groups and the MIR group was a Bonferroni multiple comparison adjustment of the one-sided 0.025 alpha to 0.008 (0.025/3). The pre-specified noninferiority margin was at 0.4%.

2.2.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.2.3.1 Monotherapy Study 03

This double-blind, multicenter, randomized, active-controlled dose-ranging, parallel-group study compared MER 1500Q, 1500B, and 2000Q to MIR 1500B in patients with Type 2 diabetes. The study phases included screening, a 6 week washout (if already on diabetic medication), a 3 week titration, and a 21 week period at the maximum targeted dose level. Male and female patients 18 to 79 years of age who were newly diagnosed, treated only with diet and exercise, or on metformin monotherapy up to 2000 mg/day or up to 1500 mg/day in combination with a sulfonylurea at doses $\leq$ ½ of the maximum dose allowed or already on monotherapy with an antihyperglycemic agent were permitted to participate after a 6-week washout of prior diabetes medication. Eligible patients were randomized and began a 3-week titration treatment period followed by a 21-week period at the maximum targeted dose. Patients in the MER 1500 Q and 2000 mg Q groups were dosed after the evening meal and patients in the MER 1500 mg B and MIR 1500 mg B groups were dosed with 500 mg after breakfast and 1000 mg after the evening meal. Baseline HbA_{1c} was to be between 7.0% and 12.0% for newly diagnosed patients or patients treated with diet and exercise alone. For

patients on monotherapy or combination therapy the baseline level was to be between 6.5% and 10.0%. The first 3 weeks of blinded titration was to allow patients to gradually increase the metformin dose. Doses began at 1000 mg/day during the first week and the total increased to 1500 mg during the 2nd and the 3rd week of titration. To maintain the blind, patients took 2 tablets each morning and 6 tablets each evening using a combination of active and placebo pills according to the treatment assignment.

Patient Disposition

The study randomized 750 patients with 706 patients in the ITT population. Among the 44 patients excluded from the ITT population 33 were not dispensed study medication and 11 were from site 61 which failed to follow GCP. Table 2 displays the disposition of patients and Table 3 reasons for discontinuation.

Table 2 Patient disposition - Monotherapy

	MER1500Q	MER1500B	MER2000Q	MIR1500B	Total
# randomized	191	191	182	186	750
# not receiving treatment	11	7	6	9	33
# excluded from Site 61	2	2	4	3	11
# in ITT	178	182	172	174	706
# did not take study drug	2	1	1	0	4
# (%) Took drug and terminated prematurely	44 (24.7%)	45 (24.7%)	34 (19.8%)	50 (28.7%)	173 (24.5%)
# completed study	132 (74.2%)	136 (74.7%)	137 (79.7%)	124 (71.3%)	529 (74.9%)
# (%) included in the safety analysis	176 (98.9%)	181 (99.5%)	171 (99.4%)	174 (100%)	702 (99.4%)

Table 3 Reasons for Discontinuation - Monotherapy

Reasons for discontinuation	MER1500Q	MER1500B	MER2000Q	MIR1500B	Total
# in ITT	178	182	172	174	706
# completed study	132 (74.2%)	136 (74.7%)	137 (79.7%)	124 (71.3%)	529 (74.9%)
# withdrew	46 (25.8%)	46 (25.3%)	35 (20.3%)	50 (28.7%)	177 (25.1%)
Adverse event	10 (5.6%)	7 (3.9%)	6 (3.5%)	10 (5.8%)	33 (4.7%)
Protocol violation	3 (1.7%)	4 (2.2%)	4 (2.3%)	2 (1.2%)	13 (1.8%)
Lack of efficacy	8 (4.5%)	15 (8.2%)	3 (1.7%)	14 (8.1%)	40 (5.7%)
Withdrawal consent	17 (9.6%)	15 (8.2%)	11 (6.4%)	21 (12.1%)	64 (9.1%)
Lost to follow-up	7 (3.9%)	5 (2.8%)	11 (6.4%)	0	23 (3.3%)
Other	1 (0.56%)	0	0	3 (1.7%)	4 (0.6%)

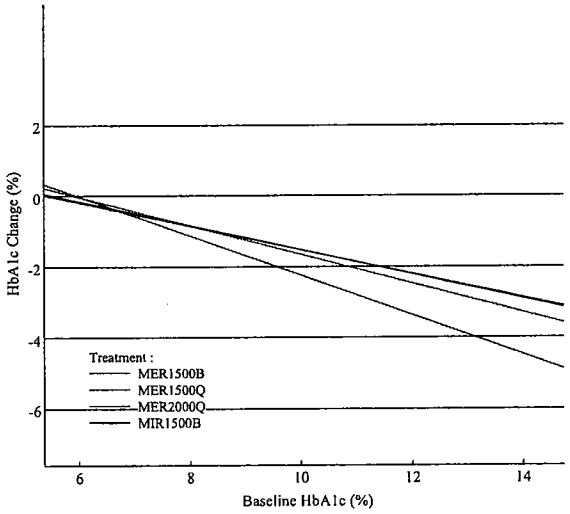
Efficacy Analysis –HbA_{1c} change from baseline

Primary Analysis

The analysis of covariance (ANCOVA) was performed on the ITT population with available data for the HbA_{1c} change from baseline to endpoint (Table 4). Baseline measurements were the last available measurements taken prior to receiving the study medication. The endpoint was defined as the last available measurement up to the end of the 24-week treatment period. The fixed effects in the analysis were treatment, pooled center, and the stratification factor (prior metformin use) and baseline HbA_{1c} as covariate. The treatment-by-baseline

interaction was included in the model due to statistical significant (p=0.05). In Figure 1 the regression lines of MER 1500Q and the MIR 1500B were similar in slope (-0.33, -0.35) but the slopes of MER 1500B (-0.46) and MER 2000Q (-0.62) were greater in absolute value.

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



Baseline HbA_{1c} was comparable among the 4 treatment groups. The 2-sided 98.4% confidence intervals for the differences between the MER groups and the MIR group were adjusted using a Bonferroni multiple comparison procedure based on the 1-sided alpha of 0.025/3=0.008.

The upper limits of the 98.4% confidence interval were all less than the 0.4% margin (Table 5 & Fig 2). As a result, all 3 MER treatment groups were noninferior to MIR 1500B.

Table 4 Number of Patients in HbA_{1c} Primary Analysis - ITT

	MER1500Q	MER1500B	MER2000Q	MIR1500B	Total
# in ITT	178	182	172	174	706
Missing baseline or endpoint	9	7	13	4	33
# (%) in the primary analysis	169 (94.9%)	175 (96.2%)	159 (92.4%)	170 (97.7%)	673 (95.3%)

Table 5 Least Square Means and 98.4% Confidence Intervals – ITT Monotherapy

HbA_{1c}	MER1500Q	MER1500B	MER2000Q	MIR1500B
n	169	175	159	170
LSM baseline*(SE)	8.50 (0.25)	8.22 (0.25)	8.26 (0.24)	8.70 (0.25)
LSM change**SE)	-0.73 (0.12)	-0.74 (0.12)	-1.08 (0.12)	-0.70 (0.12)
MER difference from MIR	-0.03	-0.04	-0.38	
(98.6% CI)	(-0.32, 0.26)	(-0.33, 0.25)	(-0.68, -0.08)	

*estimated from the ANOVA model: treatment, center (Site 31 & all other sites pooled), treatment-by-center interaction, and stratification

** estimated from the ANCOVA model: treatment, center (Site 31 & all other sites pooled), stratification & baseline HbA_{1c} as covariate and treatment-by-covariate interaction.

Figure 2 LSM difference between MER and MIR with 2-sided 98.4% Confidence Interval

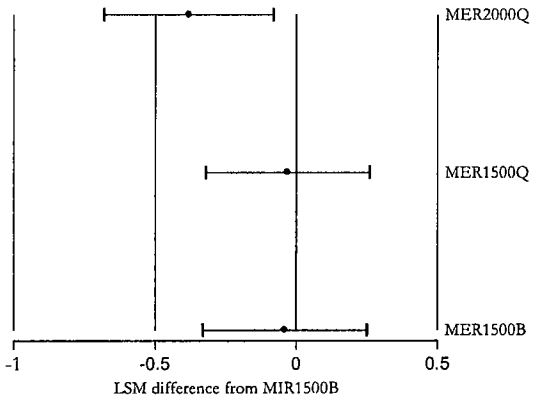


Table 6 displays the completers analysis with 95% confidence intervals as a check on the robustness of the ITT results.

Table 6 Least Square Means and 95% Confidence Intervals – Completers Monotherapy

HbA_{1c}	MER1500Q	MER1500B	MER2000Q	MIR1500B
n	132	136	137	124
LSM baseline (SE)	8.10 (0.11)	8.27 (0.11)	8.13 (0.11)	8.12 (0.12)
LSM change (SE)	-1.12 (0.08)	-1.13 (0.08)	-1.28 (0.08)	-1.25 (0.08)
Difference from MIR	+0.13	-0.12	-0.04	
(95% CI)	(-0.09, 0.34)	(-0.10, 0.33)	(-0.25, +0.18)	

Site 61 was excluded from the ITT analysis. Table 7 displays the descriptive statistics for site 61 and the remaining sites. The efficacy analyses on change from baseline HbA_{1c} including or excluding the 9 patients were similar.

Table 7 Mean (Standard Deviation) of HbA_{1c}

	Site 61				Sites without 61			
	E1500B	E1500Q	E2000Q	I 1500B	E1500B	E1500Q	E2000Q	I 1500B
n	2	2	3	2	175	169	159	170
Baseline Mean	8.90	8.00	8.00	8.25	8.50	8.34	8.17	8.36
(SD)	(0.28)	(2.97)	(0.89)	(1.91)	(1.46)	(1.45)	(1.37)	(1.40)
Mean Change	-1.70	+0.70	-1.37	-1.85	-1.05	-0.96	-1.21	-0.96
(SD)	(0.00)	(0.42)	(0.45)	(1.63)	(1.30)	(1.27)	(1.24)	(1.28)

Table 8 displays the analysis by the randomization stratum for prior metformin use. The baseline HbA_{1c} was greater in the no prior metformin stratum than in the prior metformin stratum and so is the reduction of HbA_{1c} from baseline. Similarly, the difference between MER and MIR favors MER more in the no prior metformin stratum than in the prior metformin stratum. Figure 3 displays the regression lines of the two strata and Figure 4 the LSM differences and 98.4% confidence intervals for the treatment differences between the 3 MER groups and MIR 1500B by stratum.

Table 8 HbA_{1c} change from baseline by stratum

	MER1500B		MER1500Q		MER2000Q		MIR1500B	
Stratum	Not	On	Not	On	Not	On	Not	On
n	118	57	109	60	100	59	118	52
Baseline	8.98 (0.17)	8.11 (0.21)	8.83 (0.17)	8.05 (0.21)	8.57 (0.17)	7.91 (0.21)	8.68 (0.17)	8.17 (0.21)
Change	-0.98 (0.14)	-0.50 (0.17)	-0.93 (0.14)	-0.53 (0.17)	-1.34 (0.14)	-0.72 (0.17)	-0.88 (0.14)	-0.59 (0.18)
MER-MIR	-0.10 (0.15)	+0.07 (0.22)	-0.06 (0.15)	+0.06 (0.21)	-0.47 (0.15)	-0.14 (0.21)		
98.6% CI	(-0.45, 0.25)	(-0.43, 0.60)	(-0.42, 0.30)	(-0.45, 0.56)	(-0.83, -0.10)	(-0.65, 0.37)		

Figure 3 Regression of HbA_{1c} change from baseline over baseline HbA_{1c} by stratum

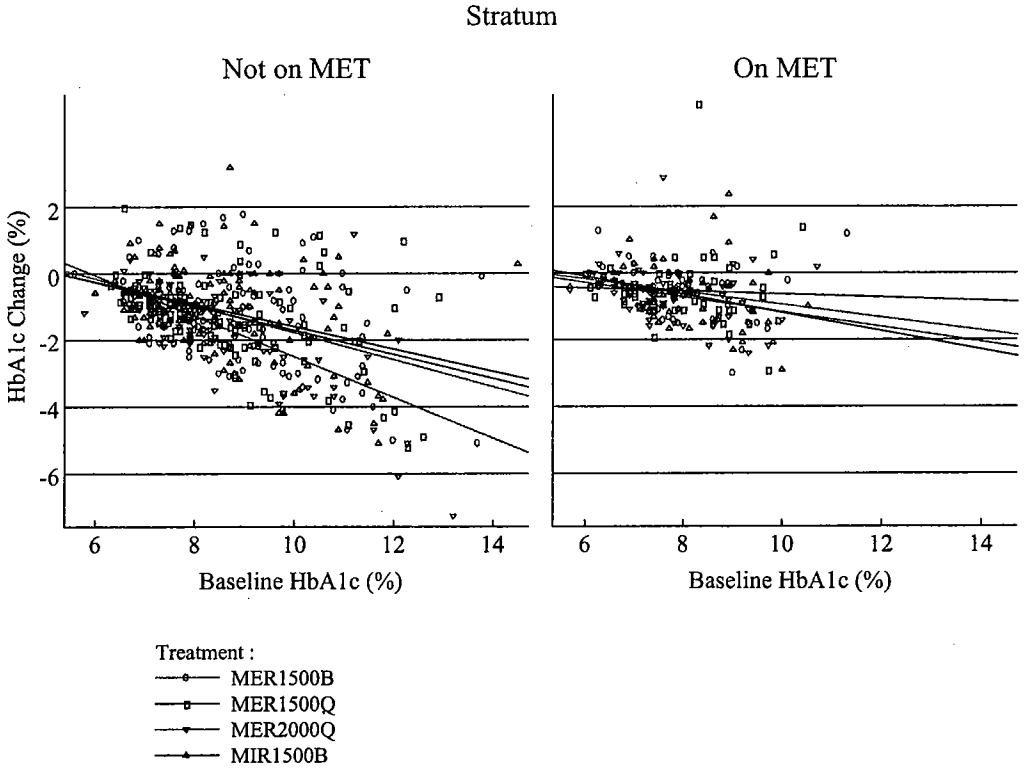
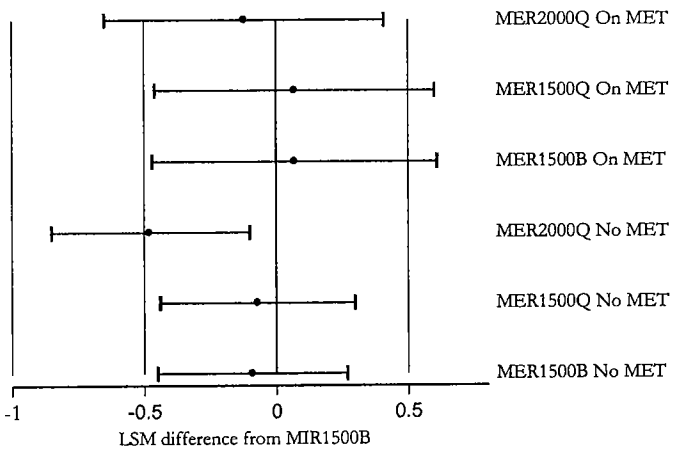


Figure 4 The LSM difference between MER and MIR 1500mg B by treatment and stratum of prior metformin use



2.2.3.2 Glyburide add on study 14

This was a double-blind, randomized, multicenter study in patients with type 2 diabetes who were newly diagnosed, treated with diet and exercise alone, or were receiving monotherapy with metformin, sulfonylureas, alpha-glucosidase inhibitors, ghiazolidinediones, or meglinitides; or treated with combination therapy at doses up to 1000 mg metformin plus 10 mg glyburide per day. Eligible patients were stabilized on a sulfonylurea for a 6-week period, and then randomized to one of 4 treatment groups: MER 1500 mg QD + SU, MER 2000 mg QD + SU, MER 1000 mg bid + SU, and SU alone. A 3-week MER titration phase was followed by a 21-week maintenance treatment.

In the first 2 weeks of the 6-week washout/stabilization period 5 mg SU was taken with the morning and evening meals. At weeks 3 through 6 SU 10 mg (2x5mg) was taken with the morning meal and 5 mg with the evening meal. During the 3 week titration period, the initial dose of MER was 1000 mg QD with dinner for week 1, 1500 mg/day for week 2 and 1500 or 2000 mg/day for week 3 (per randomization).

The primary efficacy comparison was between the combined MER+SU treatment groups and SU alone treatment group in change from baseline HbA_{1c}. The primary analysis used an ANCOVA model which included treatment and center as fixed factors and baseline HbA_{1c} as covariate.

A total of 741 patients were screened and received SU treatment during the stabilization period. Of the 741 screened patients, 607 patients were randomized. 575 patients who received the double-blind study drug were included in the ITT population. A total of 417 ITT patients completed the study and 158 patients withdrew prematurely (Table 9).

Table 9 Patient disposition and reasons for termination – SU add on

	MER1500Q+SU	MER1500B+SU	MER2000Q+SU	SU	Total
Randomized	153	148	154	152	607
Did not receive treatment	9	7	8	8	32
# in ITT	144	141	146	144	575
# completed study	112 (74.7%)	98 (69.5%)	105 (71.9%)	102 (70.8%)	417 (72.5%)
# in primary efficacy analysis	136 (94.4%)	136 (96.5%)	144 (98.6%)	141 (97.9%)	557 (96.9%)
# in safety analysis	144 (100%)	141 (100%)	146 (100%)	144 (100%)	575 (100%)
# withdrew	32 (22.2%)	43 (30.5%)	41 (28.1%)	42 (29.2%)	158 (27.5%)
Adverse event	5 (3.5%)	15(10.6%)	11(7.5%)	3(2.1%)	34 (5.9%)
Protocol violation	2 (1.4%)	2 (1.4%)	3 (2.1%)	1 (0.7%)	8 (1.4%)
Non compliance	1 (0.7%)	1 (0.7%)	0	0	2 (0.3%)
Lack of efficacy	6 (4.2%)	2 (1.4%)	5 (3.4%)	17 (11.8%)	30 (5.2%)
Withdrawal consent	11 (7.6%)	8 (5.7%)	8 (5.5%)	12 (8.3%)	39 (6.8%)
Lost to follow-up	3 (2.1%)	6 (4.3%)	5 (3.4%)	6 (4.2%)	20 (3.5%)
Terminated by sponsor	0	1 (0.7%)	0	0	1 (0.2%)
Low blood glucose	4 (2.8%)	8 (5.7%)	7 (4.8%)	3 (2.1%)	22 (3.8%)
Other	0	0	2 (1.4%)	0	2 (0.3%)

The primary analysis compared the combined MER+SU groups to the SU alone group. The combined MER+SU groups was superior to SU alone in HbA_{1c} change from baseline (Table 10).

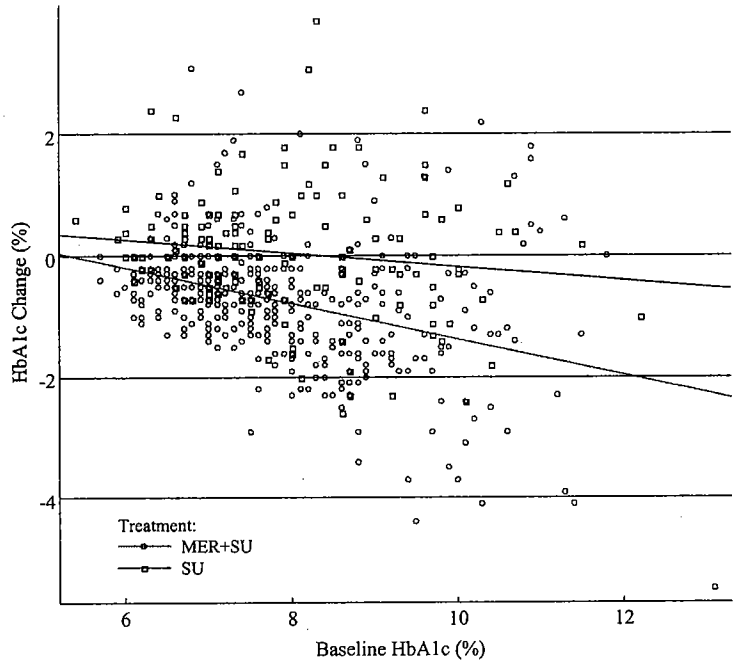
Table 10 Primary analysis on HbA_{1c} (%) change from baseline – ITT, SU add on

	MER + SU	SU alone
n	416	141
HbA_{1c} baseline	7.79 (0.07)	8.08 (0.13)
HbA_{1c} change	-0.74 (0.05)	0.06 (0.08)
Difference from SU alone	-0.81 (-0.99, -0.63)	

[a] Least squared mean change from baseline using ANCOVA model with treatment effect and baseline covariate

The treatment-by-baseline HbA_{1c} interaction was significant (p=0.06). Figure 5 displays the regression of HbA_{1c} change from baseline by baseline HbA_{1c}. This is a quantitative interaction with a greater difference between the treatment groups in HbA_{1c} change at higher HbA_{1c} baselines compared to lower HbA_{1c} baselines.

Figure 5 HbA_{1c} change from by baseline HbA_{1c} – SU add on



LDL analysis – Monotherapy study & Glyburide add-on study

An analysis of covariance was performed on LDL cholesterol as requested by the Medical Officer, Dr. Robert Misbin. The percent change from baseline LDL was statistically different from the immediate release metformin (p=0.02). Table 11 displays the least squared mean differences and the 95% simultaneous confidence intervals for the lipid variables.

Table 11 ANCOVA on Lipids % change from baseline – Monotherapy Study 03*

	MER1500B	MER1500Q	MER2000Q	MIR1500B
LDL (mg/dL)				
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[a] (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

In the glyburide add on study, the mean LDL in the combined MER groups was significantly different from LDL in the Sulfonylurea groups (p=0.0003). Table 12 displays the least squared mean difference and the confidence limits. The LDL percent changes from baseline for the MER groups were 4.3%, 1.5%, and 1.4% for 1000B, 1500Q and 2000Q, respectively.

Table 12 ANCOVA on LDL % change from baseline – Glyburide add on Study 14*

LDL (mg/dL)	MER combined	SU
n	361	120
Baseline LSM (SE)	121.8 (2.1)	122.9 (3.2)
LSM % Change[a] (SE)	2.4% (1.4)	11.0% (2.2)
MER – SU (95% CI)	-8.6% (-13.2, -4.0)	

* ANCOVA model included treatment, stratum, and center as fixed effects and baseline as covariate

2.3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Treatment-by-age or race or gender interactions were not detected for either of the studies.

2.4 CONCLUSIONS

The monotherapy study showed noninferiority of extended released Glumetza in 1500 mg QD, 1500 mg AM/PM, and 2000 mg QD to immediate released metformin 1500 mg AM/PM in change from baseline HbA_{1c}. The glyburide add on study showed superiority of glumetza 1500 mg QD+SU, 1000 mg BID+SU and 2000 mg QD+SU to placebo+SU. The efficacy of once daily and twice daily dosing was similar with Glumetza.

2.5 LABELING COMMENTS

1. should not be presented. should be deleted. In addition, the last 2 sentences describing the monotherapy study in the Clinical Studies section " ..." should be deleted.
2. Similarly for the glyburide add-on study, the d the sentence " should be deleted.

4. oes not provide any valid comparison between randomized treatment groups; therefore, it should not be presented.

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

/s/

Lee-Ping Pian
2/2/05 05:01:26 PM
BIOMETRICS

Todd Sahlroot
2/3/05 08:49:23 AM
BIOMETRICS