

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-202

STATISTICAL REVIEW(S)

Statistical Review and Evaluation¹

NDA #: 21-202

Applicant: Bristol-Myers Squibb Company

Name of the Drug: Metformin Hydrochloride Extended Release Tablets

Indication: Treatment of type 2 diabetes

Documents Reviewed: Volumes 1.1 to 1.3, 1.18, 1.23 to 1.43 (dated 11-12-99), amendments dated 11-24-99, 6-29-00, 7-10-00, 7-19-00, 7-24-00, 7-25-00 facsimile transmission of codes, and 8-10-00.

Clinical Reviewer: Robert Misbin, M.D. (HFD-510)

Statistical Reviewer: Japobrata Choudhury, Ph.D. (HFD-715)

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The issues in this review have been discussed with the reviewing medical officer, Robert Misbin, M.D. (HFD-510).

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Various Sections of this review are:

I. Background/Introduction

II. Clinical Studies

1. Study CV138-010 (International, placebo-controlled)
2. Study CV138-036 (International, including U.S.A., placebo-controlled)
3. Study CV138-012 (U.S., Active-Controlled)

III. Overall Reviewer's Comments

IV. Overall Conclusion

Attachments

¹ Key words: clinical studies, NDA review, placebo-controlled, active control

I. Background/Introduction

The sponsor states, "Three double-blind, controlled, randomized trials were conducted to demonstrate the safety and efficacy of the extended release product, administered once daily. Two placebo-controlled trials were conducted in type 2 diabetic subjects who had inadequate glycemic control with diet and exercise; one of these examined the effects of a range of doses of the extended release product. The third study was conducted in subjects with good to moderate glycemic control on a regimen of Glucophage®, 500mg BID, who were then randomized to either continue on Glucophage® or receive one of two doses of the extended release, given once daily."

Summary information of these studies is attached as Tables 0.1.1² to 0.1.3.

The CV138-010 study examined subjects with type 2 diabetes, inadequately controlled on diet and exercise, with HbA_{1c} ≥ 7% and ≤ 10% at screening. Following a 2-week single-blind placebo lead-in period, subjects were randomized to Met-MR 1000 mg QD or to placebo, in a 2:1 randomization ratio. At Week 12, subjects with HbA_{1c} ≥ 8% were discontinued, subjects with HbA_{1c} ≥ 7% and < 8% were up-titrated so that those on active drug received 1500 mg QD, and subjects with HbA_{1c} < 7% were continued on the same dose to which they had been randomized. The double-blind phase of the study was 24 weeks in duration. The primary efficacy outcome was the change in HbA_{1c} from baseline at Week 12 or the last available measurement prior to Week 12. Throughout the double-blind period, subjects were to be discontinued if pre-specified criteria for inadequate glycemic control were met.

The CV138-036 study also examined subjects with type 2 diabetes inadequately controlled on diet and exercise, with HbA_{1c} ≥ 7% and ≤ 11% at screening. Following a 2-week single-blind placebo lead-in period, subjects were randomized (in a 1 : 1 : 1 : 1 : 1 : 1 ratio) to one of six treatment groups: placebo, Met-MR 500 mg QD, Met-MR 1000 mg QD, Met-MR 1500 mg QD, Met-MR 2000 mg QD, and Met-MR 1000 mg BID. The double-blind phase of the study was of 16 weeks duration. The primary outcome measure was the change in HbA_{1c} from baseline at Week 16 or the last available measurement prior to Week 16. Throughout the double-blind period, subjects were to be discontinued if pre-specified criteria for inadequate glycemic control were met.

One active-controlled study was performed in the Met-MR clinical program, CV138-012.

² In the Table (Attachment or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

Subjects who were on treatment with Glucophage® 500 mg BID for at least 8 weeks prior to screening, and who had good or moderate glycemic control with $HbA_{1c} \leq 8.5\%$ at screening, were randomized (in a 1 : 1 : 1 ratio) to either Met-MR 1000 mg QD, Met-MR 1500 mg QD, or Glucophage® 500 mg BID. The double-blind phase duration was 24 weeks, and the primary outcome measure was mean change in HbA_{1c} from baseline at Week 12. At Week 12, subjects whose HbA_{1c} was $\geq 8\%$ were up-titrated by 500 mg of the formulation they were originally assigned, hence, received 1500 mg per day of study drug if randomized to 1000 mg, or received 2000 mg per day if randomized to 1500 mg. A total of 217 subjects were randomized in this study. Throughout the double-blind period subjects were to be discontinued if pre-specified criteria for inadequate glycemic control were met.

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer.

1. Study CV138-010 (International, placebo-controlled)

Summary information of this study is attached as Table 0.1.1.

The sponsor's Final Study Report Synopsis (Statistical Section Vol. 1.23, pages 2 to 16) provides all results and additional information.

TITLE OF STUDY: A Double-Blind, Placebo-Controlled, Randomized Trial to Determine the Effects of a Metformin Novel Oral Dose Form (NODF) ——— Tablet) in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

INVESTIGATORS: 54

STUDY CENTERS: Total 52: Belgium (1 site), Finland (6 sites), Israel (8 sites), The Netherlands (20 sites), South Africa (9 sites), and United Kingdom (8 sites)

STUDY PERIOD: Date first subject screened: 27-May-1998
Date last subject completed: 14-May-1999

1A. Objectives

The primary objective of this trial was to compare the change from baseline of HbA_{1c} between

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Met-NODF (or Met-MR) and placebo at 12 weeks of treatment or at the last measurement prior to Week 12.

1B. Disposition of Patients

A total of 240 subjects were randomized to double-blind treatment. Following randomization, 95 (40%) discontinued double-blind treatment for the following reasons:

Reasons for Discontinuation	Number of Subjects		
	Placebo N=79	Met-MR N=161	Total N=240
Inadequate glycemic control	36	41	77
Adverse Event	2	8 ^a	10
Subject request	3	2	5
Other	0	2	2
Required prohibited medication	0	1	1
No. of subjects discontinued	41	54	95
No. of subjects completing double-blind therapy	38	107	145

CV138-010

Source: Appendix 8.1C
Reference: Supplemental Table S.8.1C
Note: N = Number of Randomized
 Subjects

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^a One subject of the Met-MR treatment group was discontinued due to AE without having taken any dose of double-blind study medication.

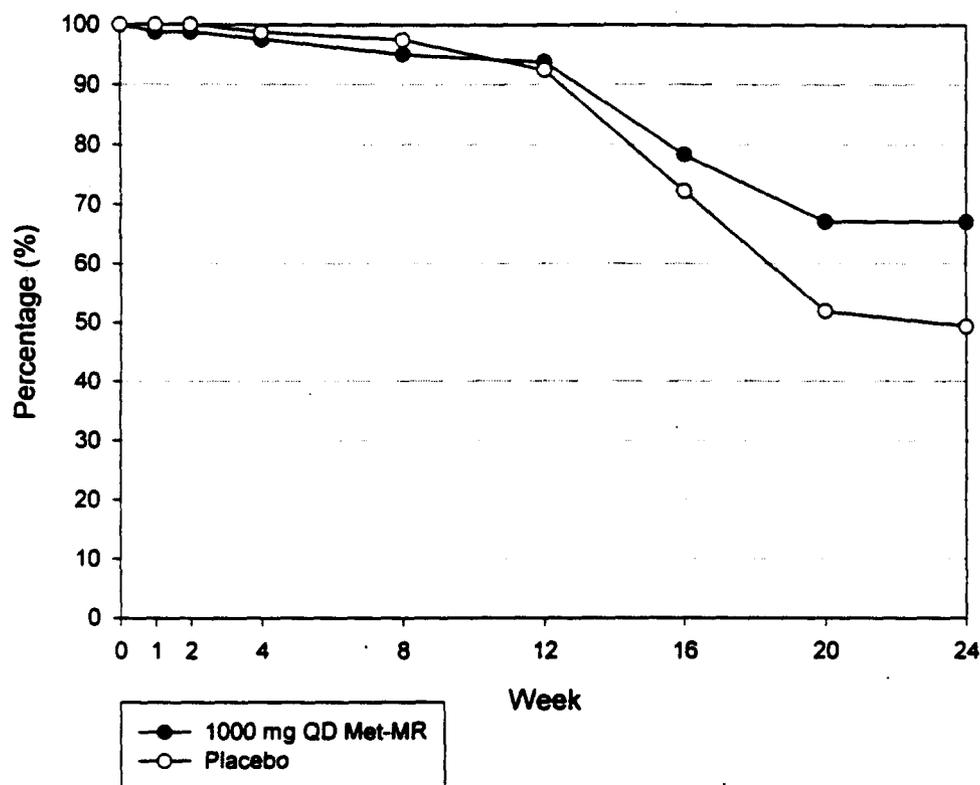
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The most frequently reported reason for withdrawal from double-blind therapy was inadequate glycemic control; this led to study discontinuation in 77 (32%) of subjects. However, at Week 12, only one patient from the Met-MR and four patients from placebo discontinued due to this reason (p-value for treatment comparisons = .042; page 136 of Vol. 1.23).

Following is the graph for the Percentage of Subjects Continuing Over Time:

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Percentage of Subjects Continuing Over Time (Weeks) - Protocol CV138-010



1C. Baseline Comparability of Treatment Groups

At baseline, the two treatment groups differed statistically significantly with respect to Total Cholesterol and LDL-Cholesterol. Detailed results are:

Between Treatment Group Comparisons on Baseline Total Cholesterol and LDL-Cholesterol – One-way ANOVA – Protocol CV138-010

	Placebo	Met-MR
Total Cholesterol (mg/dL)	N=77	N=153
Baseline Mean	216.0	199.3
Difference between Met-MR and Placebo (SE)		-16.8 (5.2)
p-value		0.001
LDL-Cholesterol (mg/dL)	N=77	N=152
Baseline Mean	140.1	130.6
Difference between Met-MR and Placebo (SE)		-9.5 (4.5)
p-value		0.037

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Source: Appendices 5.1B-12 and 5.1B-13

Analyses adjusting for these imbalances did alter neither the estimates nor the conclusion about the primary efficacy (detailed results are on pages 90-91 of the July 19, 2000 submission).

1D. Efficacy Results (Sponsor's Analyses)

The protocol stated: that the primary data-set would include all randomized subjects with a baseline measurement and at least one post-baseline measurement, that no adjustment for multiple testing would be performed, and that the primary measure of efficacy would be the change in HbA_{1c} level from baseline to Week 12 of period B or the last measurement prior to Week 12, if no Week 12 measurement available. There were some details about including baseline value as a covariate.

The sponsor stated, "Prior to unblinding, the following departures from and additions to the "Statistical Considerations" section of the protocol were made:" and listed fourteen items (pages 81 to 83 of vol. 1.23).

The sponsor also stated (p.53 of vol. 1.23), "Administrative letters addressed changes to the protocol that did not significantly affect the safety of the subjects, study scope, or scientific quality of the study and, therefore, could be implemented immediately. ... Four administrative letters were issued for this protocol and are summarized below."

Letter #1 contained many items of changes.

Judging the negligibility of such things is prohibitive with respect to the resources for statistical review. Also, most of them are not quite of statistical nature.

Following are the results for the primary efficacy variable (Met-MR dose is 1000mg QD):

Changes from Baseline in HbA_{1c} to Week 12 and to Week 24 or Last Available Measurement Prior to These Time Points, All Randomized Subjects

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HbA_{1c} (%)

	Week 12 or last available measurement prior to Week 12		Week 24 or last available measurement prior to Week 24	
	Placebo N=79	Met-MR N=155	Placebo N=79	Met-MR N=156
Baseline Mean (SD)	7.88 (0.85)	8.04 (0.85)	7.88 (0.85)	8.04 (0.86)
Week 12 / 24 Mean (as applicable)	8.00	7.47	8.09	7.42
Unadjusted Mean Change	0.12	-0.57	0.21	-0.62
Adjusted Mean Change (SE) ^a	0.09 (0.07)	-0.56 (0.05)	0.19 (0.08)	-0.60 (0.06)
Difference between Met-MR and Placebo ^b (SE), (95% CI)		-0.65 (0.09) (-0.83, -0.47)		-0.79 (0.10) (-0.98, -0.60)
^c P-value		< 0.001		< 0.001

CV138-010

Source:

Appendix 10.0A

Reference:

Supplemental Tables S.10.1.1A-1, S.10.1.1A-2, S.10.1.1B-1 and S.10.1.1B-2.

Note:

N = number of randomized subjects with available baseline and post-randomization data at Week 12 or Week 24 or a last available measurement prior to these timepoints.

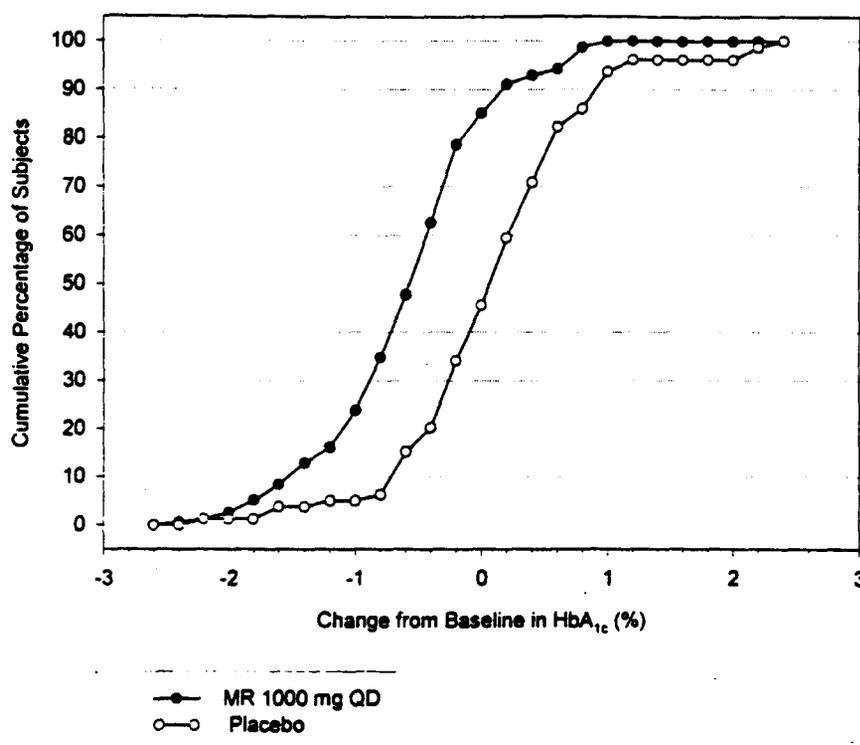
- ^a Standard errors are obtained from the ANCOVA model with a term for treatment and a covariate for baseline.
- ^b Difference = (adjusted mean change for Met-MR group) - (adjusted mean change for Placebo group).
- ^c Ninety-five percent (95%) CI for difference between the Met-MR group and Placebo.

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The mean changes from baseline to Week 12 in HbA_{1c} showed a highly statistically significant difference between Met-MR and placebo of -.65% in favor of Met-MR.

The Cumulative Distribution Function of Change in HbA_{1c} at Week 12 (LOCF) is following. From this, percent of patients (y-axis value) with a value of Change in HbA_{1c} from baseline at Week 12, smaller than or equal to a value on the x-axis can be read.

Cumulative Distribution Function of Change in HbA_{1c} at Week 12 (LOCF)



The following Table summarizes the decision regarding daily dose based on the Week 12 HbA_{1c} evaluation, by treatment group and overall.

Decision Regarding Daily Dose Based on Week 12 Evaluation, All Treated Subjects with a Week 12 HbA_{1c} Evaluation

Decision	Number (%) of Subjects		
	Placebo N = 70 ^b	Met-MR ^a N = 149 ^c	Total N = 219
Continue on two tablets	10 (14.3%)	46 (30.9%)	56 (25.6%)
Titrate to three tablets	29 (41.4%)	63 (42.3%)	92 (42.0%)
Discontinue study medication	31 (44.3%)	40 (26.8%)	71 (32.4%)

CV138-010

Source: Appendix 9.1

Reference: Supplemental Table S.9.1B

^a 1 tablet of Met-MR = 500 mg

^b Of the 79 treated subjects in the placebo group, 8 discontinued prior to having a Week 12 HbA_{1c} evaluation. Additionally, one subject (005/005) did not have an HbA_{1c} evaluation at Week 12 as this subject was lost to follow-up after Visit 6; the subject returned 4 months after Visit 6 to perform an early termination visit.

^c Of the 159 treated subjects in the Met-MR group, 9 discontinued prior to having a Week 12 HbA_{1c} evaluation. Additionally, one subject (017/003), although completing the 24 weeks double-blind phase, did not have an HbA_{1c} evaluation at Week 12 and remained on 1000 mg Met-MR QD throughout the double-blind phase.

The mean changes from baseline to Week 24 in HbA_{1c} showed a highly statistically significant difference between Met-MR and placebo of -.79% in favor of Met-MR. A larger mean decrease from baseline in HbA_{1c} in the Met-MR treatment group and a larger mean increase from baseline in HbA_{1c} in the placebo group both contributed to this larger difference at the Week 24 time-point.

The OC results are on pages 091 and 092 of the 6-29-00 submission, which are highly significant as are the LOCF results.

1E. Reviewer's Comments and Conclusions on Study CV138-010

The sponsor's analyses provided statistical evidence in favor of the efficacy of Metformin-MR treatment.

This reviewer's analyses, performed with the data supplied by the sponsor electronically, did not reveal any concern with respect to the conclusion about the primary efficacy.

At baseline, the two treatment groups differed statistically significantly with respect to Total Cholesterol and LDL-Cholesterol. Analyses adjusting for these imbalances did alter neither the estimates nor the conclusion about the primary efficacy.

In the subgroup results on pages 53 to 60 of the 7-19-00 submission, no serious qualitative concerns were seen. The unusual thing seen is that in the "Baseline HbA_{1c} Category" of "≥9.0%", the 10 placebo patients had a mean decrease of .38% (instead of increase in general) from baseline at the primary time point (page 53).

In the above subgroup analysis, the treatment difference from placebo is the largest in the subgroup of subjects with HbA_{1c} between 8 and 9%.

The treatment difference from placebo is numerically the largest for the subgroup of female subjects.

The treatment difference from placebo is numerically smaller in the drug naive subjects than in the non-drug naive subgroup.

2. Study CV138-036 (International, including U.S.A., placebo-controlled)

Some Design and Enrolled Patients Aspects and accounts of sites are in the attached Table 0.1.2.

The sponsor's Final Study Report Synopsis (Statistical Section Vol. 1.32, pages 2 to 16) provides all results and additional information.

TITLE OF STUDY: A Double-Blind, Placebo-Controlled, Randomized Trial To Determine The Effects Of A Range Of Doses Of Metformin Novel Oral Dose Form (Tablet) Administered Either Once Or Twice A Day In Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control With Diet And Exercise

INVESTIGATORS: 187

STUDY CENTERS: U.S. (116 sites), Poland (7 sites), Israel (4 sites), South Africa (12 sites), Russia (9 sites), United Kingdom (18 sites), Germany (9 sites), Norway (7 sites), Austria (1 site)

STUDY PERIOD: Date first subject screened: 14 July 1998
Date last subject completed: 19 May 1999

2A. Objectives

The primary objective was to compare the change from baseline of HbA_{1c} between several doses of Metformin-MR (Met-MR) and placebo at 16 weeks of treatment (or at the last available measurement prior to Week 16) in subjects with type 2 diabetes mellitus who have inadequate glycemic control with diet and exercise.

2B. Disposition of Patients

A total of 442 subjects were randomized to double-blind treatment. Following randomization, 119 (16%) discontinued double-blind treatment for the following reasons:

Reasons for Discontinuation During Double-Blind Therapy

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Reasons for Discontinuation	Number of Subjects						Total N= 742
	PBO N= 117	Metformin-Modified Release					
		500 mg QD N= 128	1000 mg QD N= 120	1500 mg QD N= 120	2000 mg QD N= 134	1000 mg BID N= 123	
Inadequate glycemic control	19a	13	6b	7	7	4	56
Subject request	4	8	3	6	1	6	28
Adverse event	1	4	3b	5c	4	1	18
Lost to follow- up	2	1	1	2	1	2	9
Other	1	1	1	1	1	0	5
Prohibited medication	0	0	0	0	1	0	1
Death	0	0	0	1	0	0	1
Poor or non-compliance	1	0	0	0	0	0	1
No. (%) ^d of Subjects Discontinued	28 (24%)	27 (21%)	14 (12%)	22 (18%)	15 (11%)	13 (11%)	119 (16%)
No. of Subjects Completing Double-Blind Therapy	89	101	106	98	119	110	623

CV138-036

Source: Appendix 8.1C

Reference: Supplemental Table S.8.1C

Note: N = Number of randomized subjects.

- a One subject (040/020) was discontinued due to inadequate glycemic control as documented on the study status page, but was originally also classified on the CRF AE page as discontinued due to AE hyperglycemia. This subject appears in this table under "inadequate glycemic control." The AE for hyperglycemia was deleted by the Investigator post-database lock. (see Section 18 Errata)
- b One subject (205/0012 in the 1000 mg QD group) who was initially reported as discontinuing due to inadequate glycemic control, was re-classified by the investigator as discontinuing due to an AE. This new information was not available at the time of study data base lock, and hence this table does not reflect the change in status. For more information, see Section 18 Errata.
- c One subject (123/011 in the 1500 mg QD group) had onset of SAE prior to placebo lead in, and was discontinued from the double-blind period.
- d These %'s were computed by this reviewer

The most frequently reported reason for withdrawal from double-blind therapy was inadequate glycemic control; this led to study discontinuation in 55 (7.4%) of subjects. Individual percentages and treatment groups comparisons vs placebo are following:

Proportion of Subjects Discontinuing Due to Inadequate Glycemic Control Up to Week 16 - All Randomized Subjects:

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	PBO N=117	Met-MR 500 mg QD N=128	Met-MR 1000 mg QD N=120	Met-MR 1500 mg QD N=120	Met-MR 2000 mg QD N=134	Met-MR 1000 mg BID N=123
Number (%) discontinuing	19 (16.2)	13 (10.2)	6 (5.0) ^d	7 (5.8)	7 (5.2)	4 (3.3)
Difference (%) between Met-MR and PBO ^a		-6.1	-11.2	-10.4	-11.0	-13.0
[95% C.I.] ^b		(-18.5, 6.5)	(-23.7, 1.7)	(-22.9, 2.6)	(-23.2, 1.4)	(-25.4, -0.2)
P-value ^c		0.186	0.006	0.012	0.006	<0.001

a Difference = (proportion of Met-MR group) - (proportion of placebo group)

b 95% CI for difference in proportion between Met-MR group and Placebo are not adjusted for multiple comparisons

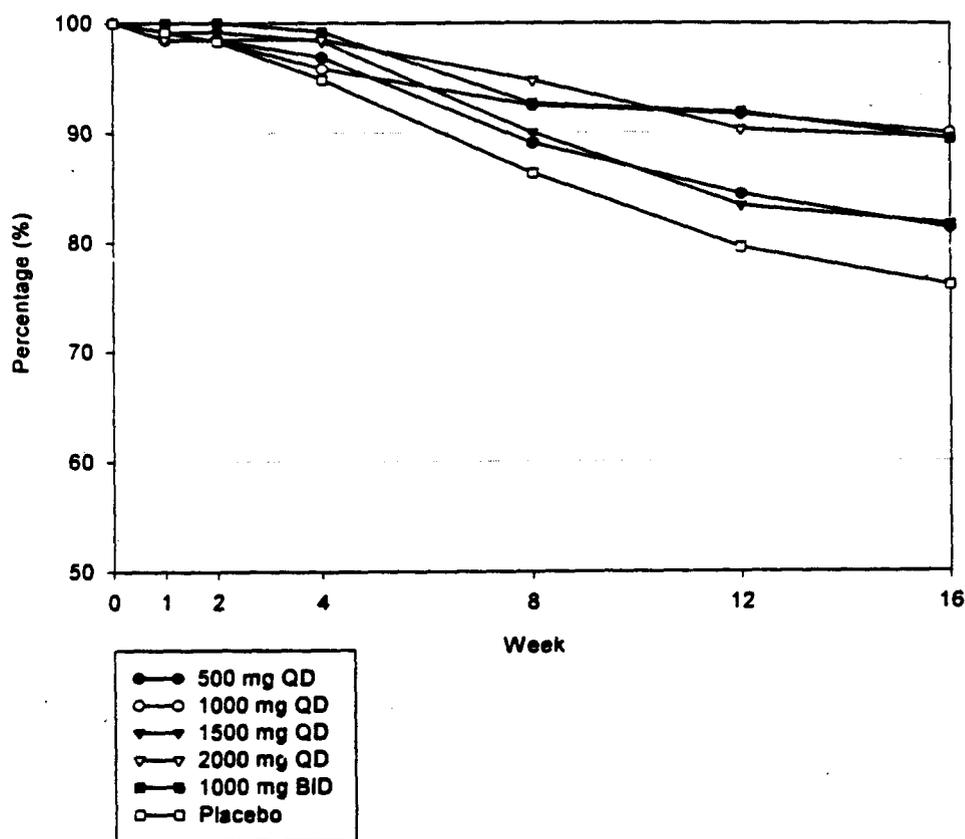
c p-value is for each Met-MR group vs. placebo (comparison-wise significance level =0.05)

d One subject (205/0012 in the 1000 mg QD group) who was initially reported as discontinuing due to inadequate glycemic control, was re-classified by the investigator as discontinuing due to an AE. This new information was not available at the time of study data base lock, and hence this table does not reflect the change in status. For more information, see Section 18 Errata.

CV138-036

Following is the graph for the Percentage of Subjects Continuing Over Time:

Percentage of Subjects Continuing Over Time (Weeks) - Protocol CV138-036



The 1000mg QD continuation rate of 88% was about the same as for 2000mg QD and 1000mg

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BID (both 89%, see also Table above).

2C. Baseline Comparability of Treatment Groups

Although the analyses adjusting for baseline imbalances did not change the efficacy conclusion (pages 83-87 of the 7-19-00 submission), some discussion about the baseline imbalances is made in this Section. Pages 76 to 80 of the 7-19-00 submission (also, original study report) may be looked at for further details and descriptive statistics. Please note that some significant p-values are expected when 240 pair-wise comparisons were made.

The sponsor stated that regardless of the fact that overall F-tests for equality of means performed on continuous variables did not highlight any baseline imbalance (at the 5% significance level), 2-sided p-values for all pair-wise comparisons between treatment groups were computed.

There were slightly more male than female subjects in all of the treatment groups except in the 1000 mg QD group (58.3%). In this group the proportion of female subjects was 10.5% larger than overall which led to significant differences with the Met-MR 500 mg QD (44.5%) and 2000 mg QD (41.0%, $p=.008$) groups in which that proportion was the lowest.

Although mean BMI values were rather similar among treatment groups, mean BMI in the Met-MR 1500 mg QD group (29.7) was statistically significantly lower than in the Met-MR 2000 mg QD group (30.9) (and non-significantly lower than in the Placebo (30.7) also), which is mainly due to a smaller proportion of obese patients ($BMI \geq 30 \text{ kg/m}^2$) in the 1500 mg QD group.

The baseline lipid levels were generally balanced across all treatment groups. Mean total cholesterol levels however were significantly lower in the Met-MR 2000 mg QD group (203.9) versus the Met-MR 1000 mg (217.9) and 1500 QD groups (215.0). Mean LDL-cholesterol levels were significantly lower in the Met-MR 2000 mg QD group (125.9) than in the Met-MR 1000 mg group (134.8). The mean HDL-cholesterol level was significantly lower in the placebo group (39.3) than in the Met-MR 1000 mg BID (42.8).

Although the proportions of subjects not previously treated with anti-hyperglycemic medications were rather similar across treatment groups, a statistically significant larger proportion was detected in the Met-MR 500 mg QD group (75.0%) when compared to the Met-MR 2000 mg QD group (63.4%).

2D. Efficacy Results (Sponsor's Analyses)

The protocol stated that the primary data-set would include all randomized subjects with a baseline measurement and at least one post-baseline measurement and that the primary measure of efficacy would be the change in HbA_{1c} level from baseline to Week 16 or the last measurement

prior to Week 16, if no Week 16 measurement were available.

This variable was analyzed within the framework of an ANCOVA model with treatment group as a main effect and baseline as a covariate. Since there are five Met-MR dose groups to be compared to placebo, Dunnett's procedure was used to adjust for multiple comparisons (i.e., a 2-sided significance level of 0.012, corresponding to a critical t-value of 2.51). Simultaneous ninety-five percent (95%) confidence intervals (CI) for the differences between each Met-MR group and placebo were constructed using the same critical value ($t = 2.51$).

The sponsor stated, "Prior to unblinding, the following departures from and additions to the "Statistical Considerations" section of the protocol were made:" and listed seventeen items (pages 83 to 84 of vol. 1.32).

The sponsor also stated (p.53 of vol. 1.32), "Administrative letters addressed changes to the protocol that did not significantly affect the safety of the subjects, study scope, or scientific quality of the study and, therefore, could be implemented immediately. ... Five administrative letters were issued for this study and are summarized below."

A few of the letters contained several items of changes.

Judging the negligibility of such things is prohibitive with respect to the resources for statistical review. Also, most of them are not quite of statistical nature.

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Following are the results for the primary efficacy variable:

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Change From Baseline in HbA_{1c} at Week 16 or Last Available Measurement Prior to Week 16 - All Randomized Subjects

	HbA _{1c} (%)					
	PBO (N= 111)	Met-MR 500 mg QD (N= 115)	Met-MR 1000 mg QD (N= 115)	Met-MR 1500 mg QD (N= 111)	Met-MR 2000 mg QD (N= 125)	Met-MR 1000 mg BID (N= 112)
Baseline Mean (SD)	8.36 (1.10)	8.20 (0.88)	8.40 (1.10)	8.33 (0.97)	8.38 (1.10)	8.43 (1.09)
Week 16 Mean (SD)	8.47 (1.38)	7.81 (1.00)	7.78 (1.01)	7.47 (1.00)	7.54 (1.23)	7.34 (1.09)
Unadjusted Mean Change	0.11	-0.39	-0.61	-0.86	-0.84	-1.10
Adjusted Mean Change (SE) ^a	0.11 (0.08)	-0.44 (0.08)	-0.60 (0.08)	-0.87 (0.08)	-0.83 (0.08)	-1.06 (0.08)
Difference between each Met-MR group and Placebo ^b (SE) ^a (95% CI) ^c p-value ^d		-0.55 (0.11) (-0.84, -0.27)	-0.71 (0.11) (-0.99, -0.42)	-0.98 (0.11) (-1.27, -0.69)	-0.95 (0.11) (-1.22, -0.67)	-1.17 (0.11) (-1.46, -0.89)
		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

CV138-036

Source: Appendix 10.0A

Reference: Supplemental Tables S.10.1.1A and S.10.1.1B

Note: N = number of randomized subjects with available baseline and post-randomization data

- a Standard errors are obtained from the ANCOVA model with terms for treatment and treatment-by-baseline interaction.
- b Difference = (adjusted mean change for Met-MR group) - (adjusted mean change for placebo group).
- c Simultaneous 95 % CI for difference between a Met-MR group and the placebo group are adjusted for multiple comparisons using critical values from Dunnett's test (Five experimental agents, one control).
- d The p-value is for each Met-MR group vs. placebo group (comparison-wise significance level $\alpha=0.012$)

Mean HbA_{1c} decreased from baseline to Week 16, or last available measurement prior to Week 16, in all of the active treatment groups, while mean levels in the placebo group rose by 0.11%. The differences between each Met-MR treated group and the placebo-treated group in adjusted mean change from baseline HbA_{1c} were highly statistically significant, and became numerically greater with increasing QD dose levels through 1500 mg a day. While the differences from placebo in adjusted mean change in HbA_{1c} were, essentially, the same in both the 1500 mg and the 2000 mg QD treatment groups, a modestly greater decrease was seen in the 1000 mg BID group. The differences versus placebo in adjusted mean changes in HbA_{1c} were -0.55% in favor of the 500 mg QD group, -0.71% in favor of the 1000 mg QD group, -0.98% in favor of the 1500 mg QD group, -0.95% in favor of the 2000 mg QD group, and reached -1.17% in favor of the 1000 mg BID group.

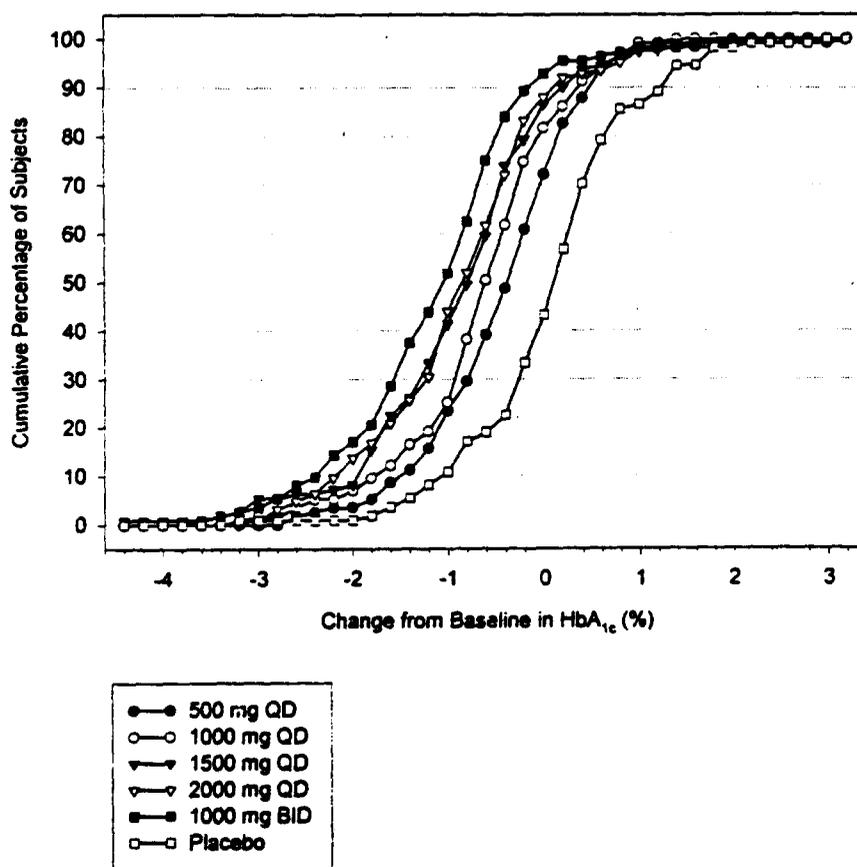
This reviewer does not see any concern in the following conclusion (analyses are on pages 25 to 32 of the 7-19-00 submission) of the sponsor on the dose response:

Strong evidence for a monotone dose-response relationship is seen in all analyses performed. Pair-wise comparisons between the different Met-MR dose groups reveal significant differences in favor of the Met-MR 1000 mg BID group over the 500 mg QD and 1000 mg QD groups, and of the Met-MR 1500 mg QD and 2000 mg QD groups over the 500 mg QD group.

The above statement should not be interpreted as meaning that every dose was statistically superior to the lower dose. In fact, the 2000 mg QD group mean result was even numerically inferior to the corresponding result for the 1500 mg QD group. It should also be noted that the CV138-036 study was designed for detecting differences from the placebo group, and not for detecting differences between Met-MR dose groups.

The Cumulative Distribution Function of Change in HbA_{1c} at Week 16 (LOCF) is following. From this, percent of patients (y-axis value) with a value of Change in HbA_{1c} from baseline at Week 16, smaller than or equal to a value on the x-axis can be read.

Cumulative Distribution Function of Change in HbA_{1c} at Week 16 (LOCF)



The OC results are on page 089 of the 6-29-00 submission, which are highly significant as are the LOCF results.

2E. Reviewer's Comments and Conclusions on Study CV138-036

The sponsor's analyses of this study provided statistical evidence in favor of the efficacy of all Metformin-MR doses studied.

This reviewer's analyses, performed with the data supplied by the sponsor electronically, did not reveal any concern with respect to the conclusion about the primary efficacy.

Strong evidence for a monotone dose-response relationship is seen in all analyses performed. Pair-wise comparisons between the different Met-MR dose groups reveal significant differences in favor of the Met-MR 1000 mg BID group over the 500 mg QD and 1000 mg QD groups, and of the Met-MR 1500 mg QD and 2000 mg QD groups over the 500 mg QD group.

Analyses adjusting for the baseline imbalances did not alter the conclusion about the primary efficacy.

The subgroup results on pages 40 to 47 of the 7-19-00 submission, no serious qualitative concerns were seen. In the subgroup analysis by baseline HbA_{1c} category, treatment differences from placebo were increasing with the (increasing) baseline HbA_{1c} category in each Met-MR treatment group, except for the Met-MR 1500 mg QD group where the smallest difference from placebo is observed in the subgroup with HbA_{1c} of 8 to < 9.0%.

The unusual thing seen is that the placebo patients had a mean decrease (instead of increase in general) from baseline at the primary time point of .19% (page 279) in the category "Duration of Diabetes (years) <1",. This occurred also in the following categories: the males, the subgroup with HbA_{1c} of 8 to < 9.0%, the subgroup with BMI 25 to <30kg/m², the subgroup with baseline insulin 10 to <20μU/mL, and the drug-naïve patients.

Treatment differences from placebo are higher for the female than for the male subgroup in each Met-MR treatment group, largely due to different mean changes from baseline in the male and the female placebo group.

Treatment differences from placebo tend to be larger in the subgroup of non-white subjects than in the other subgroup in each Met-MR treatment group. However, this observation, which is partially due to different mean changes from baseline in the white and non-white placebo groups, has to be interpreted with caution given the small number of non-white subjects in each treatment arm.

In each Met-MR group, treatment differences from placebo were smaller in subjects with diabetes for less than a year than in the other subgroups, but this was largely due to different mean changes from baseline in the placebo subgroups.

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3. Study CV138-012 (U.S., Active Controlled)

Summary information of this study is attached as Tables 0.1.3.

The sponsor's Final Study Report Synopsis (Statistical Section Vol. 1.28, pages 2 to 19) provides all results and additional information.

TITLE OF STUDY: **A Double-Blind, Randomized Study Of The Effects Of A Metformin Novel Oral Dosage Form In Patients With Type 2 Diabetes Who Are Currently Treated With Immediate Release Metformin**

INVESTIGATORS: 44

STUDY CENTERS: 44 sites in the U.S.

STUDY PERIOD: Date first subject screened: 20 July 1998
Date last subject completed: 18 June 1999

3A. Objectives

The primary objective was to assess glycemic control as determined by the change in HbA_{1c} from baseline to 12 weeks after switching from 1000 mg/day Met-IR to each of two dose levels (1000 mg QD or 1500 mg QD) of Met-MR.

3B. Disposition of Patients

The majority of the subjects assigned to randomized study drug completed the required 24 weeks of double-blind therapy: 191 of the 217 randomized subjects (88%) successfully completed the double-blind treatment period, while 26 (12%) subjects discontinued double-blind treatment for the reasons:

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Reasons for Discontinuation During Double-Blind Therapy

Reason for Discontinuation	Number of Subjects			
	Met-IR 500 mg BID N = 71	Met-MR 1000 mg QD N = 75	Met-MR 1500 mg QD N = 71	Total N = 217
Subject request	6	3 ^a	4	13
Adverse event	1	4 ^{a,b}	1	6
Lost to follow-up	1	0	2	3
Inadequate glycemic control	1	0	0	1
Required prohibited medication	0	1 ^b	0	1
Death	0	0	1	1
Other	1	0	0	1
Number of Subjects Discontinued	10	8	8	26
Number of Subjects Completing Double-Blind Therapy	61	67	63	191

CV138-012

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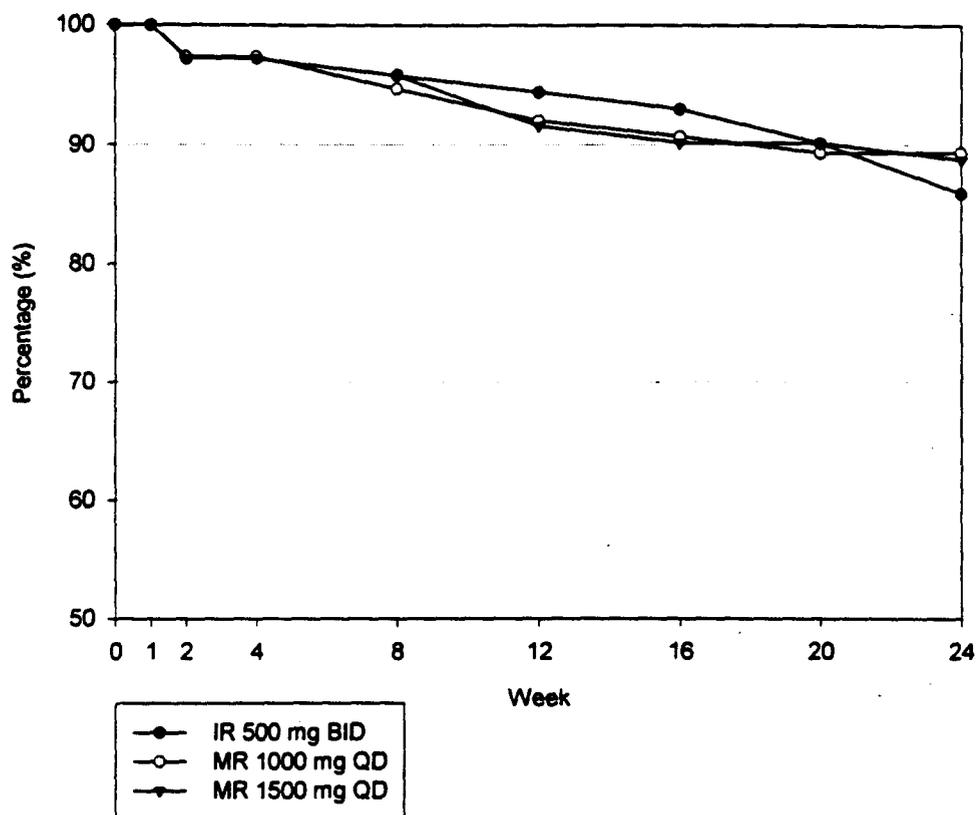
Subject request was the most frequently reported reason for withdrawal from double-blind therapy, leading to study discontinuation in 12 (5.5%) subjects. Adverse events led to discontinuation in 8 (3.7%) subjects. The subjects who discontinued due to adverse events or died are discussed in detail in Section 12.4 and Section 12.2 (of the NDA), respectively. Inadequate glycemic control led to study discontinuation in 1 subject.

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Following is the graph for the Percentage of Subjects Continuing Over Time:

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Percentage of Subjects Continuing Over Time (Weeks) - Protocol CV138-012



Of the 217 randomized subjects, 12 (5.5%) were excluded from the analysis of change in HbA_{1c} from baseline to Week 12, or last available measurement prior to Week 12: 5 subjects did not have a post-randomization measurement, 6 subjects had a measurement taken more than 8 days after discontinuation, and 1 subject did not have a measurement available before the end of the Week 12 window. For the analysis of change in HbA_{1c} from baseline to Week 24, or last available measurement prior to Week 24, 11 (5.1%) of the 217 randomized subjects were excluded: 5 subjects did not have a post-randomization measurement and 6 subjects had a measurement taken too late after discontinuation.

3C. Baseline Comparability of Treatment Groups

Regardless of the fact that overall F-tests for equality of means performed on continuous variables did not highlight any baseline imbalance (at a significance level $\alpha=0.05$), 2-sided p-values for all pair-wise comparisons between treatment groups were computed.

The analyses of baseline variables revealed differences between 500 mg BID Met-IR and 1500

mg QD of Met-MR (p-value < 0.05) for BMI and body weight.

Pairwise Comparisons Between Treatment Groups on Body Mass Index (Kg/m²) – One-way ANOVA* – Protocol CV138-012

	Met-IR 500 mg BID (N=71)	Met-MR	
		1000 mg QD (N=75)	1500 mg QD (N=71)
Baseline Mean	33.2	32.4	31.0
Difference between each Met-MR group and Met-IR (SE) p-value	N/A	-0.8 (1.1) 0.443	-2.2 (1.1) 0.042
Difference between Met-MR 1000 QD and 1500 QD (SE) p-value	N/A	N/A	-1.4 (1.1) 0.192

Source: Appendix 5.1C-4

Note: Pairwise comparisons showing a p-value < 0.08 are presented in bold

N/A = Not applicable

* The p-value of the overall *F-test* for equality across treatment groups of baseline means is 0.119

Pairwise Comparisons Between Treatment Groups on Body Weight (Kg) – One-way ANOVA* – Protocol CV138-012

	Met-IR 500 mg BID (N=71)	Met-MR	
		1000 mg QD (N=75)	1500 mg QD (N=71)
Baseline Mean	95.6	92.2	87.6
Difference between each Met-MR group and Met-IR (SE) p-value	N/A	-3.4 (3.42) 0.326	-8.0 (3.48) 0.023
Difference between Met-MR 1000 QD and 1500 QD (SE) p-value	N/A	N/A	-4.6 (3.43) 0.180

Source: Appendix 5.1C-5

Note: Pairwise comparisons showing a p-value < 0.08 are presented in bold

N/A = Not applicable

* The p-value of the overall *F-test* for equality across treatment groups of baseline means is 0.072

At baseline, mean BMI and mean body weight were significantly lower in the Met-MR 1500 mg QD group as compared to the Met-IR group.

3D. Efficacy Results (Sponsor's Analyses)

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The protocol stated, "The primary efficacy dataset will include all randomized subjects with a baseline measurement and a post-baseline measurement. In practice, subjects without a baseline or on-study measurement of the variable being analyzed at a particular time point will not be included in that summary." It also stated, "The mean change from baseline will be summarized

for each treatment group, along with the 95% confidence interval. No statistical testing will be performed.”

Therefore, any comparison between treatment groups will only be post-hoc. The sample size calculation was not done for any comparison or detecting non-inferiority or inferiority of Metformin-MR to metformin-IR. Any judgement on the results of this study does not involve statistical expertise except for the calculation of the above mentioned confidence interval (for each treatment without any comparison). The protocol stated that the sample size calculation would permit estimation with 95% confidence to within 0.4% of the true value. The study was not designed to provide any statistical evidence other than this.

It should be clearly understood that numerical results are just random outcomes and not the true effects. Statistical tests or confidence intervals enable us to make certain statements with some confidence (and some probability of errors), when studies are designed properly.

An alternative analysis with the last observation carried forward (LOCF) was to be done, if the percent of missing observations at Week 12 turns out to be > 10%.

The sponsor stated, “Prior to unblinding, the following changes and additions were made to the “Statistical Considerations” section of the protocol:” and listed nine items (pages 88 and 89 of vol. 1.28).

The sponsor also stated (p.57 of vol. 1.28), “Administrative letters addressed changes to the protocol that did not significantly affect the safety of the subjects, study scope, or scientific quality of the study and, therefore, could be implemented immediately. ... Six administrative letters were issued for this study and are summarized below.”

Most of the letters contained several items of changes.

Judging the negligibility of such things is prohibitive with respect to the resources for statistical review. Also, most of them are not quite of statistical nature.

Following are the results for the primary efficacy variable:

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Change From Baseline in HbA_{1c} to Week 12 and to Week 24 - All Randomized Subjects

	HbA _{1c} (%)		
	Met-IR 500 mg BID	Met-MR	
		1000 mg QD	1500 mg QD
Week 12	N = 66	N = 70	N = 65
Baseline Mean (SD)	7.03 (0.81)	6.98 (0.79)	7.02 (0.71)
Week 12 Mean	7.18	7.21	7.06
Mean Change (SE)	0.15 (0.08)	0.23 (0.07)	0.04 (0.06)
(95% CI) ^a	(-0.02, 0.31)	(0.10, 0.37)	(-0.08, 0.15)
Week 24	N = 63	N = 67	N = 64
Baseline Mean (SD)	7.02 (0.80)	6.97 (0.77)	7.02 (0.71)
Week 24 Mean	7.08	7.22	7.16
Mean Change (SE)	0.06 (0.07)	0.25 (0.08)	0.14 (0.08)
(95% CI) ^a	(-0.08, 0.20)	(0.09, 0.40)	(-0.02, 0.29)

CV138-012

Source: Appendix 10.0A

Reference: Supplemental Tables S.10.1.1A-1, S.10.1.1B-1, S.10.1.1A-2, S.10.1.1B-2

Note: N = number of randomized subjects with available baseline and post-randomization data at Week 12 or at Week 24

a Ninety-five percent (95%) CI for mean change from baseline within treatment group

Mean HbA_{1c} increased from baseline to Week 12 and to Week 24 in all three treatment groups (statistically significantly only in the Met-MR 1000 mg group, other results are uncertain). At Week 12, for subjects in the Met-IR group, mean increase from baseline HbA_{1c} was 0.15%. Met-MR 1000 mg treated subjects had a mean increase from baseline of 0.23% (statistically significant increase), and in the 1500 mg group, a mean increase of 0.04% (statistically marginally significantly different from the Met-MR 1000mg increase of 0.23%) was seen. Please note that the above statements are applicable only for the patients of this study, who were on Met-IR 500mg BID before switching to Met-MR 1000mg QD or Met-MR 1500mg QD or continuing on Met-IR 500mg BID.

Following 95% confidence intervals for the difference in mean changes from baseline in HbA_{1c} at Week 12 (OC) were provided by the sponsor without multiple comparison adjustments:

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Mean Changes from Baseline in HbA_{1c} at Week 12 - Protocol CV138-012

	HbA _{1c} (%)		
	Met-IR 500 mg BID (N= 66)	Met-MR 1000 mg QD (N= 70)	Met-MR 1500 mg QD (N= 65)
Baseline Mean (SD)	7.03 (0.81)	6.98 (0.79)	7.02 (0.71)
Week 12 Mean (SD)	7.18 (1.06)	7.21 (0.98)	7.06 (0.73)
Unadjusted Mean Change	0.15	0.23	0.04
Adjusted Mean Change (SE) ^a	0.15 (0.07)	0.23 (0.07)	0.04 (0.07)
Difference between each Met-MR group and Met-IR ^b (SE) ^a (95% CI) ^c	N/A	0.08 (0.10) (-0.11, 0.28)	-0.11 (0.10) (-0.31, 0.09)

Source: Appendix 11.1.1A

Note N = number of randomized subjects with available baseline and post-randomization data; N/A = Not applicable

^a Standard errors are obtained from the ANCOVA model with terms for treatment and baseline HbA_{1c}.

^b Difference = (adjusted mean change for Met-MR group) - (adjusted mean change for Met-IR group).

^c 95% confidence intervals for differences between groups are not adjusted for multiple comparisons.

As a cross-check, the corresponding 95% confidence intervals with multiple comparison adjustments (with $\alpha=0.025$ for two comparisons) were calculated by this reviewer for the LOCF dataset:

Met-MR 1000mg QD - Met-IR 500mg BID	Met-MR 1500mg QD - Met-IR 500mg BID
-0.149% to 0.329%	- 0.3257% to 0.125

The corresponding 95% confidence intervals without multiple comparison adjustments (with $\alpha=0.05$) calculated by this reviewer for the LOCF dataset are:

Met-MR 1000mg QD - Met-IR 500mg BID	Met-MR 1500mg QD - Met-IR 500mg BID	Met-MR 1000mg QD- Met-MR 1500mg QD
-0.11941% to 0.299941%	- 0.297% to 0.097%	0.008375% to 0.37163%

As an example, a rough interpretation of the first confidence interval of the last Table is: With 95% confidence (without multiple comparison adjustment; so, actually less confidence), the mean increase in HbA_{1c} at Week 12 from baseline may be as much as 0.299941% (absolute difference between two means; this % sign is the measurement unit for HbA_{1c}) more in the Met-MR 1000mg QD group than in the Met-IR 500mg BID group or as much as 0.11941% less in the Met-MR 1000mg QD group than in the Met-IR 500mg BID group (a whole range of possibilities). Considering multiple comparison adjustments, with 95% confidence, this range is bigger, as seen in the previous Table. As stated before, this statement is applicable only for the patients of this study, who were on Met-IR 500mg BID before switching to Met-MR 1000mg QD or continuing on Met-IR 500mg BID.

The corresponding 95% confidence intervals by adjusting for baseline imbalance in weight and Body Mass Index between 500 mg BID Met-IR and 1500 mg QD of Met-MR and with multiple

comparison adjustments with Studentized Maximum Modulus (GT2) test in SAS GLM (calculated by this reviewer) for the QC dataset are:

Met-MR 1000mg QD - Met-IR 500mg BID	Met-MR 1500mg QD - Met-IR 500mg BID	Met-MR 1000mg QD- Met-MR 1500mg QD
-0.154% to 0.326%	- 0.356% to 0.133%	-0.043% to 0.439%

About titration, based upon their Week 12 HbA_{1c} values, a total of 33 subjects (12 in the Met-IR group, 13 in the Met-MR 1000 mg group, and 8 in the Met-MR 1500 mg group) had their dose titrated up by 500 mg.

At Week 24 (see first Table of this Section 3.D), Met-IR treated subjects had a mean increase in HbA_{1c} from baseline of 0.06%, a slight fall from the Week 12 level. The mean change in the Met-MR 1000 mg group was, essentially, stable from Week 12 to 24; the Met-MR 1500 mg treatment group had a mean increase from baseline of 0.14%, which is higher than the Week 12 value of 0.04%. There was no statistically significant difference between any pair of treatment groups (the study was not powered to detect any differences).

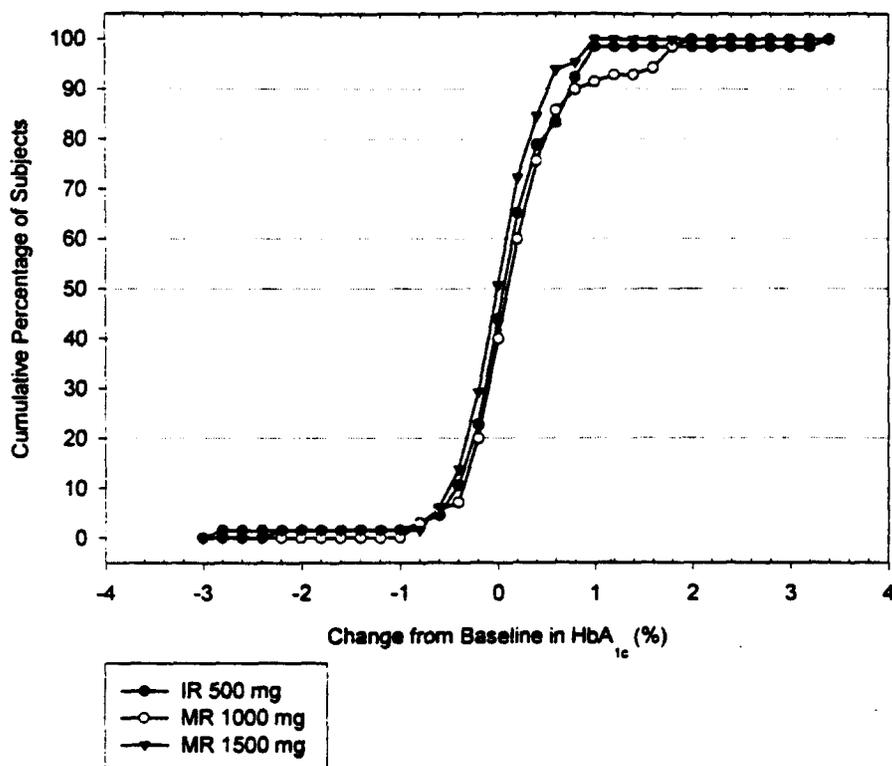
Since few additional HbA_{1c} observations entered the "last observation carried forward" (LOCF) analyses, the results were comparable to the non-LOCF analyses described above, except that in the LOCF analysis, the Met-IR group had a mean increase from baseline of 0.14% at both Week 12 and Week 24 (in the above Table of non-LOCF analysis, these were 0.15% and 0.06%).

Overall, Met-MR 1500mg QD appeared to perform somewhat better than Met-MR 1000mg QD only at Week 12 (not a consistent or dependable statistical evidence) but not at Week 24.

The Cumulative Distribution Function of Change in HbA_{1c} at Week 12 (OC) is following. From this, percent of patients (y-axis value) with a value of Change in HbA_{1c} from baseline at Week 12, smaller than or equal to a value on the x-axis can be read.

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Cumulative Distribution Function of Change in HbA_{1c} at Week 12 (OC)



The cumulative distribution functions of change from baseline in HbA_{1c} to Week 12 were similar for the three treatment groups, except for a modest difference in the right-hand tail. In fact, about 9% of the subjects in the Met-MR 1000 mg QD group showed an increase in HbA_{1c} from baseline larger than 1% versus 1 (1.5%) subject in the Met-IR group and no subject in the Met-MR 1500 mg QD group.

3E. Reviewer's Comments and Conclusions on Study CV138-012

Study 012 was not designed and powered to make any statistical comparisons between pairs of treatment groups. The inability to conclude equivalence, non-inferiority, or superiority from this study does not preclude any of them being true. The Medical Officer should make clinical judgements based on the above efficacy analyses and this reviewer's comments there.

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III. Overall Reviewer's Comments

Both studies 010 and 036 provided statistical evidence in favor of the efficacy of all Metformin-MR doses studied.

This reviewer's analyses, performed with the data supplied by the sponsor electronically, did not reveal any concern with respect to the conclusion about the primary efficacy.

Study 036 with multiple doses showed strong evidence for a monotone dose-response relationship. Pair-wise comparisons between the different Met-MR dose groups revealed significant differences in favor of the Met-MR 1000 mg BID group over the 500 mg QD and 1000 mg QD groups, and of the Met-MR 1500 mg QD and 2000 mg QD groups over the 500 mg QD group.

Analyses adjusting for the baseline imbalances did not alter the conclusion about the primary efficacy in these two studies.

Subgroup and Covariance Analyses

Subgroup and covariance analyses discussed here are those performed after pooling data from the placebo-controlled studies 036 and 010. Individual study results are discussed under each study separately.

The sponsor stated (submission of 7-19-00), "In all three Phase III clinical safety and efficacy studies, baseline variables included demographic and general subject characteristics (i.e., age, sex, race, Body Mass Index (BMI), and body weight), baseline diabetes characteristics (i.e., duration of diabetes, HbA_{1c}, Fasting Plasma Glucose (FPG), Average Daily Glucose, Fructosamine, and Insulin), and baseline serum lipid levels (i.e., Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol, and Triglycerides)".

There were some differences between the two studies, as the sponsor stated, "Baseline HbA_{1c}, gender, body mass index, duration of diabetes, and baseline insulin level showed significant differences (at a comparison-wise $\alpha = 0.10$ level) between the two studies. In fact, mean baseline HbA_{1c} was lower ($p < 0.001$) in CV138-010 (with a mean of 8.0 %) than in CV138-036 (with an average of 8.3%). The proportion of female subjects was larger in the CV138-036 study than in CV138-010 (47.8% versus 40.4%, respectively). Mean BMI was lower ($p < 0.001$) in CV138-010 as compared to CV138-036: 28.8 versus 30.5 kg/m², respectively. The mean duration of diabetes was somewhat higher in CV138-010 (mean = 3.3 years) than in CV138-036 (mean = 2.9 years). In CV138-010, the mean baseline insulin level was lower ($p = 0.056$) than in CV138-036: mean values are 17.8 and 20.3 $\mu\text{U/mL}$, respectively. The differences observed between the studies are rather modest but should be kept in mind when interpreting the results of analyses carried out on the integrated data."

In the pooled data set from the two placebo-controlled studies (the Met-MR 1500 mg QD and 2000 mg QD groups were also pooled to increase power to detect any concern because their results were similar), gender, duration of diabetes, and use of prior anti-hyperglycemic medication were the only variables found to show a significant effect at the $\alpha = 0.10$ level in the Simple Augmented Models (more details on basic and augmented models and other things are on pages 61 to 63 of the 7-19-00 submission).

However, in the subgroup results on pages 66 to 73 of the 7-19-00 submission, no serious qualitative concerns were seen. The unusual thing seen is that in the "Duration of Diabetes (years) Category" of "<1", the 56 placebo patients had a mean decrease (instead of increase in general) from baseline at the primary time point of .19% (page 70).

In the subgroup analysis by baseline HbA_{1c} category, treatment differences from placebo are increasing with increasing baseline levels in all treatment groups.

Treatment differences from placebo are higher for the female than for the male subgroup in each Met-MR group, largely due to different mean changes from baseline in the male and the female placebo groups.

Treatment differences from placebo tend to be somewhat larger in the subgroup of non-white subjects than in the white subjects subgroup in each Met-MR group. However, this observation has to be interpreted with caution given the small number of non-white subjects in each group.

Differences between each Met-MR group and placebo are all statistically significant in favor of Met-MR for both age groups except in subjects of at least 65 years old in the Met-MR 500 mg QD.

In each Met-MR group, treatment differences from placebo are smaller in subjects with diabetes for less than a year than in the other subgroups, but this is largely due to different mean changes from baseline in the placebo subgroups.

IV. Overall Conclusion

Both studies 010 and 036 provided statistical evidence in favor of the efficacy of all Metformin-MR doses studied.

Study 036 with multiple doses showed statistical evidence for a monotone dose-response relationship. Although the study was not designed and powered to make comparisons among Met-MR doses, pairwise comparisons between the different Met-MR dose groups revealed significant differences in favor of the Met-MR 1000 mg BID group over the 500 mg QD and 1000 mg QD groups, and of the Met-MR 1500 mg QD and 2000 mg QD groups over the 500 mg QD group.

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Study 012 was not designed and powered to make any statistical comparisons between pairs of treatment groups. The inability to conclude equivalence, non-inferiority, or superiority from this study does not preclude any of them being true.

[/S/]
Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot [/S/] 8/28/00
 [/S/] 8/28/00
 Dr. Nevius

CC:
Archival NDA 21-202

- HFD-510/Dr. Malozowski
- HFD-510/Dr. Misbin
- HFD-510/Ms. Weber
- HFD-715/Dr. Nevius
- HFD-715/Dr. Sahlroot
- HFD-715/Dr. Choudhury
- HFD-715/Chron
- J.Choudhury:x73110: 08/15/00

This review consists of 29 pages of text and 3 pages of Tables.

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Table 10.0B Summary of Clinical Safety/Efficacy Studies

PLACEBO-CONTROLLED STUDIES										
Protocol Number Completion Status (Start Date) Investigators Centers (Product Code)	Reference (Vol. page): Full Report Data Listings CRF's	Design Treatment(s): Number of Randomized Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/O)	Diagnosis and Criteria for Inclusion	Duration of DB Treatment	Criteria for Evaluation	Results (Efficacy)	Treatment Emergent Adverse Reactions (Number of Subjects)		
								Total AEs/ADEs	SAEs/ Deaths	DCs Du to AEs
CV138-010 Completed (27-May-98) 54 Investigators 52 Centers: Belgium 1 Finland 6 Israel 8 South Africa 9 The Netherlands 20 United Kingdom 8 207150-V500-038-0 (metformin modified release tablets) 207150-A000-039-0 (placebo matching metformin modified release tablets)	(1.23, 001) to (1.27, 192) Electronic: N21202/crf/ datasets CRFs: N21202/crf	Two-week placebo lead-in followed by a 24-week randomized, double-blind placebo- controlled study. Placebo: n=79 Met-MR 1000 mg QD: n= 161 route: po	30-77 years (55.7 years) (60%/40%) (88%/2%/11%)	Men and women aged 21-78 years, with type 2 diabetes inadequately controlled (defined as HbA _{1c} ≥ 7% to ≤ 10%) with diet and exercise, and BMI ≥ 21 to ≤ 38 kg/m ²	24 weeks	Change from baseline in HbA _{1c} at Week 12 or last available measurement prior to Week 12 of double- blind treatment.	Adjusted mean change from baseline to Week 12 or last available measurement prior to Week 12 in HbA _{1c} Placebo: 0.09% Met-MR QD 1000 mg : -0.56* *p < 0.001 compared with placebo	Placebo: 47/12 Met-MR QD 1000 mg: 101/46	1/0 11/0	2 7

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Summary of Clinical Safety/Efficacy Studies (continued)

PLACEBO CONTROLLED STUDIES										
Protocol Number Completion Status (Start Date) Investigators Centers (Product Code)	Reference (Vol. page): Full Report Data Listings CRF's	Design Treatment(s): Number of Randomized Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of DB Treatment	Criteria for Evaluation	Results (Efficacy)	Treatment Emergent Adverse Reactions (Number of Subjects)		
								Total AEs/ADEs	SAEs/ Deaths	DCs Due to AEs
CV138-036 Completed (14-Jul-99) 187 Investigators 183 Centers: Austria 1 Germany 9 Israel 4 Norway 7 Poland 7 Russia 9 South Africa 12 United Kingdom 18 United States 116 207150-V500-038-0 207150-V500-038-1 (metformin modified release tablets) 207150-A000-039-0 207150-A000-039-1 (placebo matching for metformin modified release tablets)	(1.32, 001) to (1.37, 442) Electronic: N21202/crf/ datasets CRFs: N21202/crf	Two week placebo lead-in followed by a 16-week randomized, double-blind placebo- controlled, dose- ranging study Placebo: n=117 Met-MR 500 mg QD: n=128 Met-MR 1000 mg QD: n=120 Met-MR 1500 mg QD: n=120 Met-MR 2000 mg QD: n=134 Met-MR 1000 mg BID: n=123 route: po	26-78 years (55.4 years) (52%/48%) (85%/4%/6%)	Men and women aged 21-78 years, with type 2 diabetes inadequately controlled (defined as HbA _{1c} ≥ 7% to ≤ 11%) with diet and exercise, and BMI 21 to ≤ 38 kg/m ²	16 weeks	Change from baseline in HbA _{1c} at Week 16 or last available measurement prior to Week 16 of double-blind treatment.	Adjusted mean change from baseline to Week 16 or last available measurement prior to Week 16 in HbA _{1c} Placebo: 0.11 Met-MR 500 mg QD: -0.44* 1000 mg QD: -0.60* 1500 mg QD: -0.87* 2000 mg QD: -0.83* 1000 mg BID: -1.06* *p < 0.001 compared with placebo	Placebo: 69/27 Met-MR 500 mg QD: 82/42 1000 mg QD: 81/43 1500 mg QD: 82/38 2000 mg QD: 85/45 1000 mg BID: 79/47	2/0 2/0 3/0 2/1 3/0 4/0	1 4 4 5 4 1

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Summary of Clinical Safety/Efficacy Studies (continued)

ACTIVE-CONTROLLED STUDY										
Protocol Number Completion Status (Start Date) Investigators Centers (Product Code)	Reference (Vol. page): Full Report Data Listings CRF's	Design Treatment(s): Number of Randomized Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of DB Treatment	Criteria for Evaluation	Results (Efficacy)	Treatment Emergent Adverse Reactions (Number of Subjects)		
								Total AEs/ADEs	SAEs/ Death	DCs Due to AEs
CV138-012 Completed (20-Jul-98) 44 Investigators 44 Centers in the United States 207150-V500-0381 Metformin modified release 500 mg tablets 9407-K500-005-0 Metformin immediate release 500 mg tablets	(1.28, 001) to (1.31, 195) Electronic: N21202/crf/ datasets CRFs: N21202/crf	Two week Met-IR lead-in followed by a 24-week randomized, double-blind active- controlled study Met-IR 500 mg BID: n=71 Met-MR 1000 mg QD: n=75 Met-MR 1500 mg QD: n=71 route: po	25-77 years (54.4 years) (43%/57%) (75%/8%/13%)	Men and women aged 21-78 years, with type 2 diabetes previously treated with Met-IR for 8 weeks, HbA1c 8.5% and FBG 200 mg/dL	24 weeks	Change from baseline in HbA _{1c} at Week 12 of double- blind treatment.	Change from baseline to Week 12 in HbA _{1c} after switching from Met-IR to each of 2 doses of Met-MR. Met-IR 500 mg BID: 0.15 95% CI (-0.02, 0.31) Met-MR 1000 mg QD: 0.23 95% CI (0.10, 0.37) Met-MR 1500 mg QD: 0.04 95% CI (-0.08, 0.15)	Met-IR 500 mg BID: 58/18 Met-MR 1000 mg QD: 66/22 Met-MR 1500 mg QD: 60/24	2/0 3/0 5/1	1 6 1

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