

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020357, S010**

**STATISTICAL REVIEW(S)**

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** OCT 16 1998  
**FROM:** Mathematical Statistician (HFD-715)  
**THRU:** Edward Nevius, Ph.D. *ES/ 10-16-98*  
Director, Division of Biometrics II. (HFD-715)

**SUBJECT:** Proposed Labeling Revision for Metformin and Insulin

**APPLICANT:** Bristol-Myers Squibb

**TO:** File Glucophage Tablets (NDA 20-357/SE1-010)

The sponsor has proposed the labeling revisions for Study 16 shown in Table 4. The results use the observed cases of the evaluable population:

	GLUCOPHAGE	Placebo	P-Value
Hemoglobin A <sub>1c</sub> (%)			
Baseline	9.16 ± 1.30	9.40 ± 1.49	NS
Change at FINAL VISIT	-2.60 ± 1.52	-1.63 ± 1.03	0.01
Insulin Dose (μ/day)			
Baseline	94.25 ± 46.70	98.68 ± 44.23	NS
Change at FINAL VISIT	-2.80 ± 27.75	+26.28 ± 32.96	0.01

Reviewer's Comments:

1. The sample size is not mentioned in the proposed revision. The sample sizes at baseline were 20 and 19 and at final visit were 18 and 16, respectively, for the metformin and placebo groups for observed cases of the evaluable patient population.
2. The p-value for change at final visit is from the analysis of covariance.

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We propose to use the sponsor's results from the intent-to-treat population (total n=54) with LOCF data as well as this reviewer's analysis of variance results shown in Table 1.

**Table 1 Sponsor's ITT (LOCF) Population**

Combined GLUCOPHAGE/Insulin vs Insulin			
Summary of Mean Changes from Baseline in HbA <sub>1c</sub> and Daily Insulin Dose			
	GLUCOPHAGE	Placebo	Treatment difference Mean ± SE
N	26	28	
Hemoglobin A <sub>1c</sub> (%)			
Baseline	8.95	9.32	
Change at FINAL VISIT	-2.10	-1.56	-0.54 ± 0.43 <sup>a</sup>
Insulin Dose (μ/day)			
Baseline	93.12	94.64	
Change at FINAL VISIT	-0.15	+15.93	-16.08 ± 7.77 <sup>b</sup>

<sup>a</sup> statistically insignificant for analysis of variance, significant using analysis of covariance with baseline as covariate

<sup>b</sup> statistically significant for insulin

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/S/  
Lee-Ping Pian/Ph.D.  
Mathematical Statistician

Concur: Dr. Todd Sahlroot

/S/ 10/16/98

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cc:  
Arch NDA 20-357/SE1-010  
HFD-510  
HFD-510/SSobel, GTroendle, RMisbin, JWeber  
HFD-715/ENevius, TSahlroot, LPian, Division 2 file  
Chron.

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Statistical Review and Evaluation

OCT 1 1998

NDA#: 20-357/Class 3S

Applicant: Bristol-Myers Squibb Company

Name of Drug: Glucophage Tablets® (metformin hydrochloride)

Indication: Adjunct to diet to improve glycemc control in patients with NIDDM<sup>1</sup> whose hyperglycemia cannot be managed by diet alone

Document Reviewed: Vols. 49.1-49.13  
Submission dated April 23, 1998

Medical Reviewer: John Gueriguian M.D.

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Background:

Glucophage (metformin HCl tablets) is an oral antihyperglycemic agent approved for the management of type 2 diabetes. The current submission included two controlled studies of Glucophage with adjunctive use of insulin in type 2 diabetics. The conduct of the two studies is different. Study 16, which included patients with baseline HbA<sub>1c</sub> ≥ 10% (normal <7.1%) and insulin units ≥ 50 units per day, compared metformin to placebo in improving blood glucose control and controlling body weight in **poorly controlled** insulin treated type 2 patients. Study 20 included patients with **insulin resistance** who are on at least 0.7 units/kg of insulin per day at study entry. Baseline HbA<sub>1c</sub> level was not an inclusion criterion. The aim of study 20 was to compare metformin to placebo in conjunction with a standard insulin regimen with respect to insulin dosage and HbA<sub>1c</sub> in patients with type 2 diabetes.

is the CRO (Contract Research Organization) which is responsible for retrieval and review of CRFs, data entry and quality assurance of CRFs, statistical analyses, and the final clinical study report.

The submission was dated April 23, 1998. The sponsor discovered errors in the calculation of mean changes in daily insulin dose in study 20. The revised documents were submitted on July 16, 1998.

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<sup>1</sup> NIDDM: non-insulin-dependent diabetes mellitus

**Study CV138-016**

Protocol Summary

The protocol consisted of a core protocol, a supplemental protocol and a letter from the investigator to inform the Institutional Review Board of 2 changes in the protocol.

The aim of the study was to investigate the efficacy of metformin, as compared to placebo in improving blood glucose control and controlling body weight in poorly controlled insulin treated type 2 diabetics. The study enrolled patients \_\_\_\_\_ years of age with a total glycated hemoglobin level > 10% (normal <7.1%) who were receiving more than 50 units of insulin per day. The study started on June 25, 1996 and was completed on September 4, 1997.

The study endpoints were 1) glycated hemoglobin level (GHB), 2) total daily insulin dose and 3) body weight. The supplemental protocol studied additional endpoints of 1) insulin sensitivity as determined by a euglycemic clamp, 2) body weight and composition as determined by underwater weighing, 3) plasma lipids and lipoproteins and 4) glucose induced thermogenesis.

The 7 study visits were at weeks -1 (baseline week), 0 (randomization), 2, 4, 8, 16, and 24. The inclusion and exclusion criteria were evaluated at week -1. At week 2, insulin and metformin doses were adjusted. In a letter from the investigator, Dr. Raskin, M.D., to the Institutional Review Board there were 2 changes to the protocol:

- (1). "A glycated hemoglobin will be drawn in Visit 1 (Baseline) instead of Visit 2 (Randomization)"
- (2). "Titration of study drug will be done according to patient tolerance rather than blood sugar level. At week 0 patients will start at one tablet b.i.d. with morning and evening meal until tolerated, then will increase to t.i.d. with morning, noon, and evening meal. When t.i.d. is tolerated, the dose will be increased to five tablets per day; two tablets with morning meal, one tablet with lunch meal, and two tablets with evening meal. Patients will remain on maximum dose tolerated for remainder of study."

The letter also noted that "Because enrollment has closed, a revised consent is not required." The IRB approved the changes on July 29, 1997.

In the Additional Statistical Considerations, it stated that the sample size of 25 patients per group was sufficient to compare insulin sensitivity between baseline and 6 months.

The protocol stated in the Statistical Considerations section that "The main endpoint will be the change in GHB between baseline and the 6 month measurement. This will be analyzed using the paired t-test."

### Primary Efficacy Variable Consideration

In the protocol, total glycated hemoglobin (HbA<sub>1c</sub>) was one of the inclusion criteria and the main endpoint. In the study report, the primary endpoints were the changes in glycated hemoglobin and HbA<sub>1c</sub> between baseline and end of study (Visit 24). After consulting with the Medical Officer, it was determined that HbA<sub>1c</sub> is the primary efficacy variable.

### Patient Disposition

A total of 54 patients were randomized and received treatment, 26 in the metformin group and 28 in the placebo group.

**Table 1 Disposition of Patients – Study 16**

Patient Status	Placebo	Metformin	Total
Randomized	28	26	54
Intent to Treat	28	26	54
Completed	22 (79%)	22 (85%)	44 (81%)
Withdrawn	6 (21%)	4 (15%)	10 (18%)
Adverse events	3 (108, 119, 125)	1 (109)	4
Voluntary withdrawal	2 (102, 144)	0	2
Lost to Follow-Up	1 (110)	3 (117, 128, 139)	4
Efficacy Evaluable	19 (68%)	20 (77%)	39 (72%)
Violation of inclusion criteria	6 (111, 113, 138, 141, 152, 154)	5 (114, 117, 129, 139, 150)	11 (20%)
No Post-Baseline HbA <sub>1c</sub>	3 (102, 108, 119)	1 (109)	4 ( 7%)

One patient (#143) in the metformin group discontinued from treatment in the sixth month due to an adverse event (diarrhea). The investigator considered this patient as having completed the study.

One metformin patient (#114) of the 11 patients with inclusion criteria violations did not meet three of the inclusion criteria, <30 years of age at NIDDM diagnosis, baseline total glycated hemoglobin <10% and baseline daily insulin <50 units. Of the 10 other patients, one from each treatment group were diagnosed with NIDDM prior to 30 years of age, 3 each with total glycated hemoglobin <10% and 2 placebo patients received daily insulin dose less than 50 units. All 11 patients with inclusion criteria violations were excluded from the efficacy evaluable patient population.

One placebo patient (#122) who used an experimental drug (Ultram) within 30 days prior to study entry (exclusion violation) was not excluded from the efficacy evaluable patient population.

### Study Results

Baseline comparison of treatment groups is displayed in Table 2. The baseline was not different between the two treatments in HbA<sub>1c</sub> (p=0.37), insulin (p=0.9) and glucose (p=0.70)

**Table 2 Patient Demographics and Baseline Characteristics – Study 16**

		Placebo n=28	%	Metformin n=26	%
Gender	Male	11	39%	8	31%
	Female	17	61%	18	69%
Race	Caucasian	13	46%	9	35%
	Black	6	21%	5	19%
	Hispanic	5	18%	5	19%
	Native Amer	1	4%	2	8%
	Other	3	11%	5	19%
Age (yrs)	Mean SD	53.68	8.01	53.12	8.33
	Min - Max				
Weight (lbs)	Mean SD	232.61	50.84	227.85	53.25
	Min - Max				
Glucose (mg/dl)	Mean SD	209.36	65.18	202.31	67.33
	Min - Max				
HbA <sub>1c</sub> (%)	Mean SD	9.32	1.59	8.95	1.39
	Min - Max				
HbA <sub>1</sub>	Mean SD	12.58	2.31	12.05	2.03
	Min - Max				
Daily Insulin Dose (unit)	Mean SD	94.64	43.85	93.12	42.61
	Min - Max				

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### Sponsor's Efficacy Evaluation

The evaluable efficacy analysis included patients who met all inclusion criteria and had a baseline HbA<sub>1c</sub> and at least one post-baseline HbA<sub>1c</sub> measurement. A total of 39 patients (19 placebo, 20 metformin) were in efficacy evaluable population (Table 3). Treatment comparison in change from baseline was based on a one-way analysis of covariance. The following table displays the mean change from baseline of HbA<sub>1c</sub> level over time for the Last Observation Carried Forward (LOCF) data of the evaluable patients.

**Table 3 Mean & Mean Change from Baseline of HbA<sub>1c</sub> (%) –Study 16, Sponsor’s Evaluable Patients (LOCF)**

	Placebo n=19		Metformin n=20		P-value <sup>†</sup>
	Mean	(SD)	Mean	(SD)	
Baseline	9.40	(1.49)	9.16	(1.30)	0.59
Week 8	7.92	(1.08)	7.75	(1.52)	
Week 8 Change	-1.48	(1.81)	-1.41	(1.37)	0.81
Week 16	7.59	(1.02)	6.80	(1.07)	
Week 16 Change	-1.82	(1.87)	-2.36	(1.56)	0.03
Week 24	7.58	(1.05)	6.73	(1.14)	
Week 24 Change	-1.82	(1.71)	-2.43	(1.59)	0.03

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<sup>†</sup> Student’s two-sample t-test (baseline) or ANCOVA (change from baseline) with baseline as covariate

The sponsor’s intent-to-treat population with LOCF analysis included all treated patients with only baseline HbA<sub>1c</sub> but no follow-up HbA<sub>1c</sub> measurements. The baseline HbA<sub>1c</sub> value was carried forward for imputation. The results of covariance analysis are displayed in Table 4.

**Table 4 Mean & Mean Change from Baseline of HbA<sub>1c</sub> (%) –Study 16, Sponsor’s ITT (LOCF)**

	Placebo n=28		Metformin n=26		P-value <sup>†</sup>
	Mean	(SD)	Mean	(SD)	
Baseline	9.32	1.59	8.95	1.39	0.37
Week 8	8.00	1.32	7.76	1.56	
Week 8 Change	-1.33	1.68	-1.19	1.29	0.85
Week 16	7.77	1.29	6.93	1.42	
Week 16 Change	-1.55	1.73	-2.02	1.57	0.04
Week 24	7.76	1.34	6.85	1.49	
Week 24 Change	-1.56	1.60	-2.10	1.60	0.04

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<sup>†</sup> Student’s two-sample t-test (baseline) or ANCOVA (change from baseline) with baseline as covariate

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### Reviewer's Analysis

The Week 8 mean HbA<sub>1c</sub> and mean change from baseline HbA<sub>1c</sub> generated from the dataset provided by the sponsor is not consistent with the sponsor's week 8 evaluable patients analysis (Table 3) as displayed in the following table. Three evaluable patients (metformin 116, 118 & placebo 103) had no data at week 8.

**Table 5 Week 8 HbA<sub>1c</sub> Mean Change from Baseline – Study 16**

Visit Week	Placebo n=18 Mean (SD)	Metformin n=18 Mean (SD)	P-value ANCOVA
8	7.81 (1.07)	7.33 (0.95)	
Change	-1.61 (1.80)	-1.61 (1.32)	1.0

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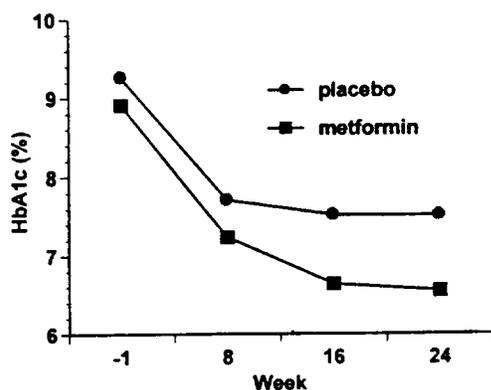
For the reviewer's analysis, an intent-to-treat population is used which includes patients with a baseline and at least one post baseline HbA<sub>1c</sub> measurement. A total of 48 patients were in this group with 25 placebo patients and 23 metformin patients. Three patients from each treatment group were not in the ITT population (102, 108, & 119 placebo, 109, 117 & 139, metformin). At week 8 the sample size is different from other weeks with 24 placebo and 20 metformin patients in the analysis. Table 6 displays the results for analysis of variance (no baseline covariate.)

**Table 6 Mean & Mean Change from Baseline of HbA<sub>1c</sub> (%) Over Time – Reviewer's ITT, LOCF**

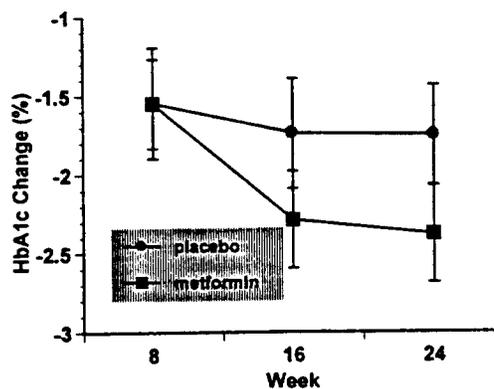
Week	Placebo n=25		Metformin n=23		Difference Metformin-Placebo A <sub>1c</sub> Change (C.I.)	P-value t-test
	A <sub>1c</sub>	A <sub>1c</sub> Change	A <sub>1c</sub>	A <sub>1c</sub> Change		
Baseline	9.26 (1.65)	-	8.92 (1.37)	-	-	0.45
8 <sup>a</sup>	7.71 (1.16)	-1.55 (1.72)	7.24 (0.95)	-1.55 (1.26)	-0.004 (-0.94, 0.93)	0.99
16	7.52 (1.08)	-1.74 (1.74)	6.63 (1.10)	-2.29 (1.47)	-0.55 (-1.49, 0.39)	0.25
24	7.51 (1.15)	-1.75 (1.59)	6.54 (1.17)	-2.37 (1.49)	-0.63 (-1.52, 0.27)	0.17

<sup>a</sup> n=24 placebo, n=20 metformin

**Study 16 - HbA<sub>1c</sub> over Time**



**Study 16 - HbA<sub>1c</sub> Change from Baseline**

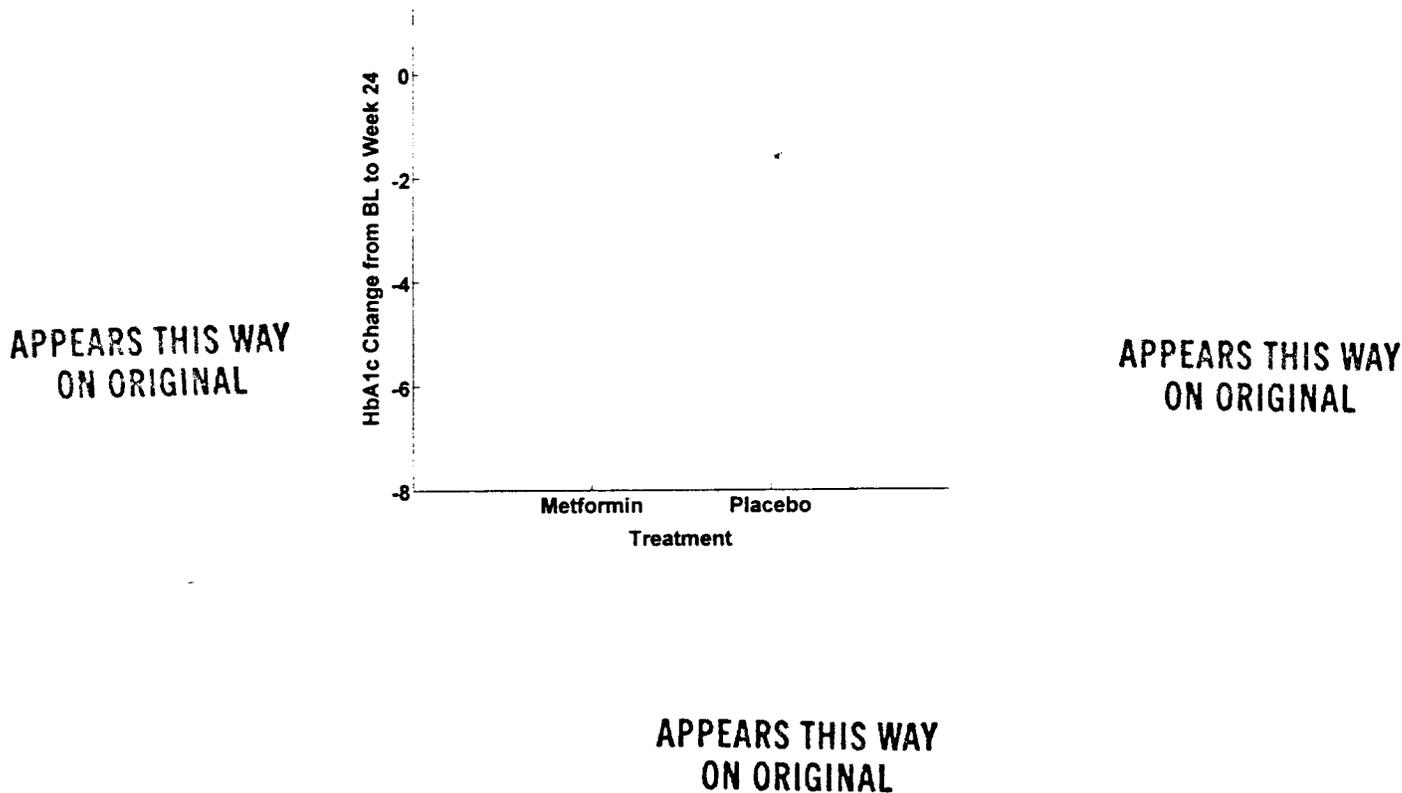


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The p-values from the two-sample t-test for the evaluable patients population at week 16 and week 24 were 0.32 and 0.26, respectively.

The trial outcome is very sensitive to change of analysis which indicates that the result is not robust. In exploring the HbA<sub>1c</sub> dataset as displayed in the following box plot, one placebo patient (#110) with a baseline HbA<sub>1c</sub> of ... experienced a reduction of 7.5% to a HbA<sub>1c</sub> measurement of ... at week 8 and ... at week 16. The HbA<sub>1c</sub> measurement for patient #110 was missing at week 24. The t-test on HbA<sub>1c</sub> change from baseline to week 24 if excluding patient #110 was statistically significant for the evaluable LOCF population (p=0.04) and for the ITT LOCF population (p=0.05).

**Figure Box Plot for HbA<sub>1c</sub> Change from Baseline to Week 24 by Treatment**



### Other Efficacy Variables

The two-sample t-test results from HbA<sub>1c</sub> were similar to HbA<sub>1c</sub> as displayed in the following table:

**Table 7 Mean & Mean Change from Baseline of HbA<sub>1c</sub> (%) Over Time – Study 16**

Week	Placebo n=25		Metformin n=23		Difference Metformin-Placebo A <sub>1</sub> Change (C.I.)	P-value
	A <sub>1</sub>	A <sub>1</sub> Change	A <sub>1</sub>	A <sub>1</sub> Change		
Baseline <sup>a</sup>	12.58(2.31)	-	12.05(2.03)	-	-	0.37
8	10.34(1.72)	-2.15(2.48)	9.48(1.40)	-2.52(1.98)	-0.37 (-1.69, 0.94)	0.57
16	9.97(1.57)	-2.52(2.52)	8.64(1.56)	-3.36(2.16)	-0.84 (-2.21, 0.53)	0.22
24	9.93(1.67)	-2.55(2.30)	8.59(1.66)	-3.41(2.21)	-0.86 (-2.17, 0.46)	0.20

<sup>a</sup> n=28 placebo, n=26 metformin

Total insulin dose which included regular, isophane insulin (neutral protein Hagedorn), lente, 70/30, and other was expressed as units. The treatment comparison is displayed in Tables 8-10.

**Table 8 Total Daily Insulin Dose, ITT (LOCF) – Study 16**

Week (n)	Placebo n=27		Metformin n=23		Difference of Insulin Change (CI) Metformin-Placebo	P-value
	Insulin (SD)	Change (SD)	Insulin (SD)	Change (SD)		
Baseline	94.64 (43.85)	-	93.12 (42.61)	-	-	
2	100.92 (46.14)	2.92 (15.02)	96.43 (41.17)	4.52 (14.58)	-1.60 (-10.22, 7.01)	0.71
(25,23)						
4	101.00 (42.47)	4.70 (24.73)	95.63 (40.63)	3.72 (15.11)	-0.99 (-12.90, 10.92)	0.87
(27,23)						
8	106.50 (47.25)	10.20 (30.90)	95.41 (44.01)	3.50 (14.81)	-6.70 (-20.88, 7.48)	0.35
16	109.78 (48.77)	13.48 (31.67)	95.89 (44.65)	3.98 (18.42)	-9.50 (-24.59, 5.58)	0.21
24	112.81 (49.15)	16.52 (32.60)	91.74 (47.39)	-0.17 (25.62)	-16.69 (-33.59, 0.20)	0.05

**Table 9 Total Daily Insulin Dose, Evaluable (LOCF) – Study 16**

Week	Placebo n=19				Metformin n=20				p-value	
	Insulin	SD	Change	SD	Median Insulin	SD	Change	SD		Median
-1	98.68	44.23	-	-	-	94.25	46.70	-	-	-
2*	102.89	50.10	4.56	13.75	4.00	99.13	42.40	4.88	15.64	4.00
4	104.74	45.79	6.05	26.82	5.00	98.28	41.79	4.03	16.24	5.50
8	111.45	52.18	12.76	34.14	7.50	98.23	45.33	3.98	15.87	5.50
16	115.68	53.89	17.00	34.55	9.00	98.73	46.08	4.48	19.77	8.50
24	117.76	54.78	19.08	34.73	15.00	94.18	49.35	-0.08	27.57	-2.25

\* Placebo n=18

**Table 10 Total Daily Insulin Dose Evaluable (OC) – Study 16**

Week	Placebo						Metformin						p-value
	n	Insulin	SD	Change	SD	Median	n	Insulin	SD	Change	SD	Median	
-1	19	98.68	44.23	-	-	-	20	94.25	46.70	-	-	-	0.76
2	18	102.89	50.10	4.56	13.75	4.00	20	99.13	42.40	4.88	15.64	4.00	0.95
4	18	101.03	44.08	6.47	27.53	7.00	19	98.82	42.86	2.76	15.64	5.00	0.62
8	18	110.36	53.47	12.31	35.07	6.00	20	98.23	45.33	3.98	15.87	5.50	0.34
16	17	119.88	55.33	20.76	34.60	11.50	17	96.50	49.74	3.50	21.33	4.00	0.09
24	16	127.84	52.74	26.28	32.96	20.25	18	96.92	51.16	-2.81	27.75	-7.75	0.01

The statistical significance from the two-sample t-test on insulin dose is dependent on the different sample populations. It can be either significant in the observed cases for the evaluable patients (p=0.01) or marginally significant with the LOCF of the evaluable patients (p=0.064) and the intent-to-treat population (p=0.0527).

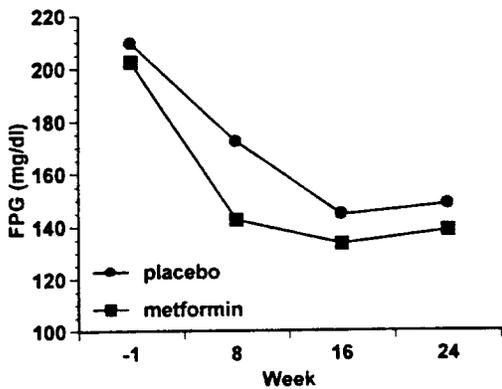
For fasting glucose the difference was not statistically significant between metformin and placebo as displayed in Table 11.

**Table 11 Fasting Blood Glucose (mg/dl) and Change from baseline of FBG – Study 16**

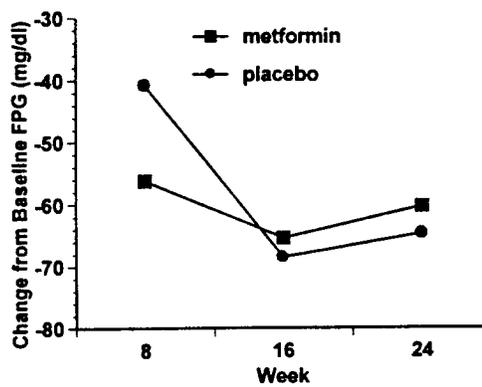
Week	Placebo n=26		Metformin n=23*		Difference Metformin-Placebo FPG Change (C.I.)	P-value
	FPG	FPG Change	FPG	FPG Change		
Baseline	209.36 (65.18)	-	202.31 (67.33)	-	-	0.70
8	172.12 (60.56)	-40.85 (93.24)	142.52 (32.29)	-56.22 (62.14)	-15.37 (-61.56, 30.81)	0.51
16	144.46 (52.61)	-68.50 (83.74)	133.35 (40.73)	-65.39 (66.05)	3.11 (-40.64, 46.86)	0.89
24	148.35 (37.23)	-64.62 (71.30)	138.52 (30.65)	-60.22 (63.88)	4.40 (-34.71, 43.52)	0.82

\*n=28 at baseline

**Study 16 - Mean Fasting Plasma Glucose over Time**



**Study 16 - Mean Change from Baseline FPG over Time**



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The baseline, Week 24, and Week 24 change from baseline of mean plasma lipid and lipoprotein levels are displayed in Table 12 for ITT patients.

**Table 12 Change from baseline in Plasma Lipid and Lipoprotein Levels – Study 16**

LABTEST	Treatment	n	Baseline	SD	Week 24	SD	Change	SD	P
C-PEPTIDE	Metformin	21	2.15	1.15	3.11	2.65	0.96	2.34	0.21
C-PEPTIDE	Placebo	22	2.24	1.46	2.32	2.08	0.08	2.23	
Total Cholesterol	Metformin	22	210.82	39.30	207.64	45.57	-3.18	27.65	0.20
Total Cholesterol	Placebo	21	225.48	60.36	211.76	57.87	-13.71	25.60	
VLDL CH	Metformin	14	29.57	19.15	30.71	17.19	1.14	12.64	0.37
VLDL CH	Placebo	19	46.63	57.68	40.16	39.43	-6.47	29.03	
HDL	Metformin	14	34.29	10.67	35.50	28.26	1.21	29.75	0.49
HDL	Placebo	19	33.74	10.08	29.63	13.30	-4.11	12.64	
LDL	Metformin	14	129.07	30.73	97.43	40.98	-31.64	46.53	0.36
LDL	Placebo	19	136.74	41.09	116.53	44.65	-20.21	23.36	
LDL Triglyceride	Metformin	14	215.07	129.80	207.07	95.30	-8.00	99.29	0.95
LDL Triglyceride	Placebo	19	244.32	198.79	234.11	184.05	-10.21	108.77	
TOTAL Triglycerides	Metformin	22	210.27	120.98	196.64	93.69	-13.64	81.30	0.42
TOTAL Triglycerides	Placebo	22	228.41	191.15	183.45	93.04	-44.95	162.32	
VLDL Triglyceride	Metformin	14	139.43	115.29	142.36	89.19	2.93	66.65	0.54
VLDL Triglyceride	Placebo	19	182.58	180.89	168.00	149.77	-14.58	88.12	

No statistically significant differences between metformin and placebo were observed for the mean plasma protein and lipoprotein levels at baseline and change from baseline at Week 24.

Mean body weight changes in pounds from baseline are displayed in Table 13. The baseline and mean change from baseline were not statistically significantly different between treatment groups.

**Table 13 Mean Body Weight – Study 16**

Week	Treatment	n	Baseline	SD	Weight	SD	Change	SD	p-value
2	Metformin	22	217.64	39.21	220.09	39.64	2.45	5.54	0.69
2	Placebo	24	232.79	46.50	234.69	46.72	1.90	3.80	
4	Metformin	22	227.43	53.89	228.98	54.92	1.80	6.58	0.71
4	Placebo	25	228.60	45.66	230.19	44.34	1.59	5.33	
8	Metformin	23	225.65	54.27	227.78	55.23	2.13	8.08	0.63
8	Placebo	24	227.13	46.03	228.29	44.55	1.17	5.37	
16	Metformin	20	227.35	57.88	228.85	59.34	1.50	9.65	0.41
16	Placebo	22	226.50	47.95	230.23	45.89	3.73	7.70	
24	Metformin	21	226.62	56.45	227.33	57.93	0.71	11.55	0.15
24	Placebo	22	234.55	53.12	239.55	51.91	5.00	7.09	

No statistically significant differences were detected in sponsor's analyses on the secondary efficacy variables for the evaluable patients.

Reviewer's Comment on the Weight Data

In the sponsor's weight dataset, patient # 124 had 2 records for visit week 4. The first weight 145 lb was deleted which left the second weight 148 lb as the patient recorded weight.

**APPEARS THIS WAY  
ON ORIGINAL**

Safety

Most common drug-related adverse events were associated with the digestive system (54% metformin and 46% placebo.) Diarrhea occurred in 46% and 21% (p=0.083) and nausea occurred in 35% and 18% (p=0.218) of the metformin and placebo patients, respectively. 8% of the metformin patients and 4% of the placebo patients reported hypoglycemia (blood glucose  $\leq$ 50 mg/dl) during the study.

**APPEARS THIS WAY  
ON ORIGINAL**

Conclusion on Study 16

The analysis of variance result, or two-sample t-test in this case, with treatment in the model on the primary efficacy variable, change from baseline to Week 24 HbA<sub>1c</sub>, was not statistically significant (p=0.17) for the intent-to-treat population with LOCF data. In the sponsor's analysis baseline HbA<sub>1c</sub> was added as the covariate in the model and the result was statistically significant (0.03). Moreover, the covariate analysis was not specified in the protocol and without the pre-specification, we have no way of determining if the covariance analysis was performed ad hoc. Thus the data are not robust and are very sensitive to the method of statistical analysis. In addition, if the outlier placebo patient who had a reduction of 5.6% HbA<sub>1c</sub> is excluded from the t-test, the p-value becomes significant. The study was powered just enough to detect a treatment difference of 1.5% (SD 1.75%) in HbA<sub>1c</sub> but the difference from the study was 0.61% in HbA<sub>1c</sub> for the evaluable patients (0.54%, ITT). In conclusion, based on the primary efficacy variable, this study does not provide robust evidence, only marginal evidence, of efficacy because the sensitivity analyses were not consistent in terms of statistical significance.

Study CV138-020

**APPEARS THIS WAY  
ON ORIGINAL**

From the protocol, the primary objectives of the study were

1. To determine the effect of metformin vs. placebo in conjunction with a standard insulin regimen on insulin dosage and HbA<sub>1c</sub> in patients with Type 2 diabetes and
2. To determine the effect of metformin vs. placebo in conjunction with a standard insulin regimen on weight and blood pressure.

In the Statistical Methodology section of the study report, the primary efficacy parameters were a) insulin dosage, b) HbA<sub>1c</sub>, c) change in body weight and d) change in blood pressure. The secondary efficacy parameters were a) change in lipids, b) C-peptide, and c) quality of life

This was a randomized, double-blind, parallel group, placebo-controlled trial to evaluate adding metformin or placebo to a standard insulin regimen in a total of 40 insulin-resistant Type 2 diabetes patients. The study included a 8-week baseline period to reach optimal glycemic control by adjustment of insulin dose to standardized insulin regimen<sup>1</sup>. After randomization at week 8 visit, there was a 3-week treatment titration phase with weekly increases of 1 tablet of metformin (500 mg) or placebo to 3 tablets at week 11. In the 13 weeks treatment stable phase, patients were taking 4 tablets of metformin (2000 mg) or placebo. The insulin dosage was adjusted during the adjunct therapy phase according to standard clinical insulin adjustment guidelines to maintain glucose control<sup>2</sup>.

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ON ORIGINAL

#### Patient Disposition

The first patient was enrolled on November 5, 1996 and the last patient completed on October 23, 1997. A total of 51 patients were randomized, 25 to the placebo group and 26 to the metformin group. One of the metformin treated patients (#58) had an adverse event (worsening diarrhea) and was withdrawn from treatment. However, this patient was noted on the CRF as having completed all 24 weeks of study and was included in the efficacy analyses. Nine patients (metformin, 6 & placebo, 3) were excluded from the evaluable patient population because they were diagnosed with type 2 diabetes at age <35 years (inclusion criteria violation.)

**Table 14 Patient Disposition – Study 20**

Patient Status	Placebo	Metformin	Total
Randomized	25	26	51
Intent to Treat	25	26	51
Withdrawn from treatment	0	1	1 (2%)
Efficacy Evaluable	22 (88%)	20 (77%)	42 (82%)
Violation of inclusion criteria	3 (#10, 18, 49)	6 (# 31, 37, 45, 52, 55, 62)	9 (18%)

APPEARS THIS WAY  
ON ORIGINAL

1 At visit 1 all patients were standardized to \_\_\_\_\_ units of insulin/kg. Those patients on  $\geq 0.7$ U/kg but  $< 1.0$  U/kg started on 0.7 U/kg. Those patients on  $\geq 1.0$  U/kg started at 1.0U/kg. 2/3 of the total insulin dose was given pre-breakfast (1/3 Regular+2/3 NPH), 1/6 Regular pre-supper and 1/6 NPH pre-bedtime/evening snack

2 Insulin was adjusted for optimal control of fasting and premeal home blood glucoses \_\_\_\_\_ mg/dl and/or HbA<sub>1c</sub>  $\leq 7.5\%$

Patient Demographics and Baseline Characteristics are displayed in Table 15. Baseline glucose ( $p=0.04$ ) was different but not baseline HbA<sub>1c</sub> ( $p=0.21$ ) between placebo and metformin.

**Table 15 Patient Demographics and Baseline Characteristics – Study 20**

		Placebo n=25	%	Metformin n=26	%
Gender	Male	11	44%	12	46%
	Female	14	56%	14	54%
Race	Caucasian	25	100%	25	96%
	Black	0		1	4%
Age (yrs)	Mean SD	62.12	9.33	57.58	9.86
	Min - Max				
Weight (lbs)	Mean SD	233.87	43.14	224.50	46.07
	Min - Max				
HbA <sub>1c</sub> (%)	Mean SD	7.41	0.98	7.76	0.98
	Min - Max				
Glucose (mg/dl)		n=24		n=25	
	Mean SD	142.04	45.49	170.40	49.54
Daily Insulin Dose (unit)	Mean SD	129.96	59.89	122.12	43.34
	Min - Max				

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ON ORIGINAL

The primary statistical hypothesis test was the comparison of insulin units between metformin and placebo four months after baseline. The sponsor proposed to examine two variables, insulin units at 4 months and change of insulin units from baseline to month 4. "If, at baseline, there was a significant difference between groups on insulin units used then the change would be a better method. If the two groups are the same at baseline (which is expected) then a direct look at the 4 month data makes sense." In the protocol, it specified **two sample student's t-test** comparing treatment and control as the analysis for both the 4 month data on insulin units and change from baseline to month 4. Between group comparisons using the two sample student's t-test were performed as well for weight, BMI, HbA<sub>1c</sub>, blood pressure, lipid levels, and QOL.

APPEARS THIS WAY  
ON ORIGINAL

Sponsor's Analysis on Total Daily Insulin Dose

The analysis results on the evaluable patients population is displayed in Table 16.

**Table 16 Total Daily Insulin Dose, Evaluable Patients – Study 20**

Week	Placebo n=22			Metformin n=20			p-value		
	Insulin	SD	Change	SD	Insulin	SD		Change	
8	118.59	52.34	0.00	0.00	124.40	47.03	0.00	0.00	0.7082
9	116.64	53.37	-1.95	5.57	124.48	48.09	0.08	8.20	0.3708
10	112.36	53.39	-6.23	12.46	119.43	52.66	-4.98	16.77	0.8076
11	113.82	54.92	-4.77	14.83	113.68	52.85	-10.73	21.65	0.2998
12	113.09	54.91	-5.50	18.60	109.38	52.80	-15.03	27.63	0.2066
16	117.55	57.50	-1.05	23.25	102.20	49.44	-22.20	27.65	0.0121
20	120.89	57.60	2.30	24.52	100.93	52.17	-23.48	30.30	0.0050
24	119.02	57.64	0.43	25.20	100.73	53.19	-23.68	30.22	0.0088

APPEARS THIS WAY  
ON ORIGINAL

Reviewer's Analysis

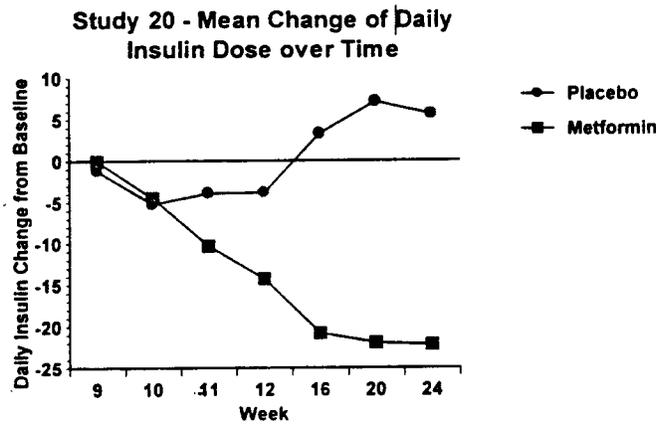
APPEARS THIS WAY  
ON ORIGINAL

The analysis on the intent-to-treat population in insulin dose change from baseline is displayed in Table 17.

**Table 17 Total Daily Insulin Dose – Study 20**

Week	Placebo n=25				Metformin n=26				p-value		
	Insulin	SD	Change	SD	Median Insulin	SD	Change	SD		Median	
8	129.96	59.89	0.00	0.00	0.00	122.12	43.34	0.00	0.00	0.00	0.5934
9	128.76	61.94	-1.20	5.87	0.00	122.10	44.63	-0.02	7.31	0.00	0.5288
10	124.72	62.48	-5.24	12.15	-3.00	117.63	48.85	-4.48	15.22	-5.50	0.8451
11	126.04	63.47	-3.92	14.20	-1.00	111.79	48.82	-10.33	19.65	-9.50	0.1897
12	126.12	64.10	-3.84	18.21	0.00	107.83	48.56	-14.29	24.57	-9.00	0.0918
16	133.24	70.57	3.28	25.48	1.00	101.35	46.08	-20.77	24.89	-19.50	0.0013
20	137.10	72.54	7.14	27.76	6.00	100.17	48.40	-21.94	27.25	-19.25	0.0004
24	135.58	73.05	5.62	28.87	2.00	99.94	49.29	-22.17	27.20	-18.00	0.0009

APPEARS THIS WAY  
ON ORIGINAL



APPEARS THIS WAY  
ON ORIGINAL

Sponsor's Analysis of HbA<sub>1c</sub>

Table 18 displays the analysis of covariance results with HbA<sub>1c</sub> at week 8 (baseline) as covariate on the evaluable patients.

APPEARS THIS WAY  
ON ORIGINAL

**Table 18 HbA<sub>1c</sub>, evaluable Patients – Study 20**

Week	Placebo					Metformin					p-value
	n	HbA <sub>1c</sub>	SD	Change HbA <sub>1c</sub>	SD	n	HbA <sub>1c</sub>	SD	Change HbA <sub>1c</sub>	SD	
8	22	7.23	0.88	-	-	20	7.72	1.02	-	-	0.1029
16	21	7.09	0.74	-0.03	0.42	18	7.12	0.87	-0.66	0.44	0.0010
24	21	6.97	0.62	-0.25	0.64	20	7.15	0.61	-0.57	0.76	0.7994

APPEARS THIS WAY  
ON ORIGINAL

Reviewer's Analysis

The t-test results on the evaluable patient population for change of HbA<sub>1c</sub> is as follows:

**Table 19 HbA<sub>1c</sub> Change from Baseline, Evaluable Patients – Study 20**

Week	Placebo				Metformin				Difference (95% C.I.)	p-value
	n	HbA <sub>1c</sub>	Change	SD	n	HbA <sub>1c</sub>	Change	SD		
16	21	-0.03	0.094	0.094	18	-0.66	0.64	0.64	-0.62 (-0.90, -0.34)	0.0010
24	21	-0.25	0.153	0.153	20	-0.57	0.76	0.76	-0.32 (-0.76, 0.13)	0.1559

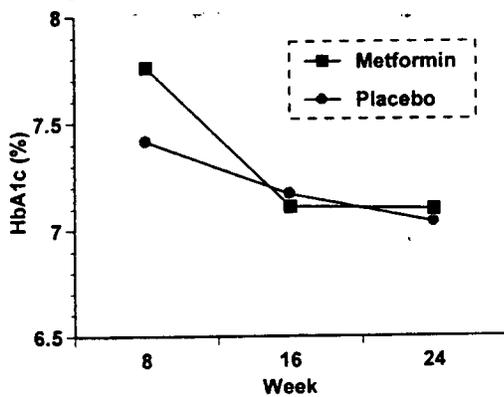
APPEARS THIS WAY  
ON ORIGINAL

The t-test results on the intent-to-treat population are displayed in Table 20.

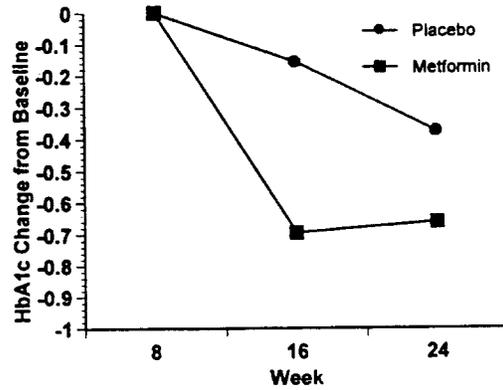
**Table 20 HbA<sub>1c</sub> Change from Baseline, ITT – Study 20**

Week	Placebo					Metformin					p-value
	n	HbA <sub>1c</sub>	SD	Change HbA <sub>1c</sub>	SD	n	HbA <sub>1c</sub>	SD	Change HbA <sub>1c</sub>	SD	
8	25	7.41	0.98	-	-	26	7.76	0.98	-	-	0.2125
16	24	7.17	0.73	-0.16	0.52	24	7.11	0.85	-0.70	0.44	0.0003
24	25	7.04	0.60	-0.38	0.77	26	7.10	0.65	-0.66	0.72	0.1772

**Study 20 - HbA<sub>1c</sub> by Week, ITT**

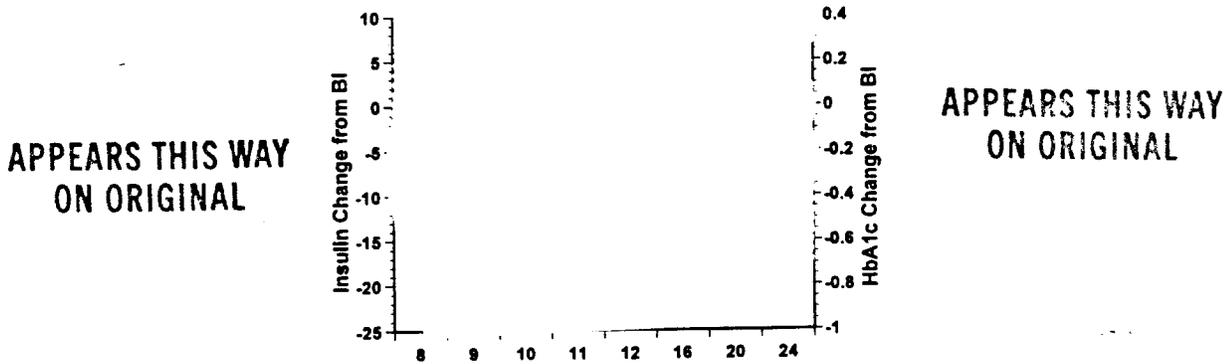


**Study 20 - HbA<sub>1c</sub> Change from Baseline, ITT**



The overlay of change from baseline of insulin dose and HbA<sub>1c</sub> are displayed in the following figure.

**Fig. HbA<sub>1c</sub> Change & Insulin Change**



APPEARS THIS WAY ON ORIGINAL

### Sponsor's Analysis

The results of covariance analysis with baseline (week 8) as covariate on change from baseline fasting blood glucose are displayed in Table 21.

**Table 21 Mean Fasting Glucose Levels and Mean Change from Baseline, Evaluable Patients (OC) – Study 20**

WEEK	Treatment	n	FBG	SD	n	Change from Bl	SD	p-value
8	Placebo	21	145.05	46.27	21	-	-	
8	Metformin	19	170.42	41.81	19	-	-	0.0778
16	Placebo	22	175.36	63.74	21	24.29	48.23	
16	Metformin	19	148.05	38.76	19	-22.37	42.11	0.0127
24	Placebo	20	144.50	37.88	19	4.95	39.83	
24	Metformin	19	152.32	50.23	18	-23.56	33.45	0.1754

APPEARS THIS WAY  
ON ORIGINAL

**Table 22 Change from Baseline Fasting Blood Glucose, ITT (LOCF) – Study 20**

WEEK	Treatment	n	FBG (mg/dl)	SD	n	Change from Bl	SD	p-value
8	Placebo	24	142.04	45.49	-	-	-	
8	Metformin	25	170.40	49.54	-	-	-	0.0422
16	Placebo	25	181.24	62.57	24	34.17	52.66	
16	Metformin	25	144.12	37.48	25	-26.28	46.02	0.0001
24	Placebo	25	158.08	48.42	24	16.42	50.29	
24	Metformin	26	148.96	49.07	25	-27.16	46.32	0.0028

The following tables display the sponsor's covariance analysis on weight for evaluable patients and all-treated patients.

**Table 23 Weight (lb.) and Weight Change from Baseline, Evaluable Patients – Study 20**

WEEK	Placebo					Metformin					p-value
	n	Weight	SD	Wt. Change	SD	n	Wt	SD	Wt Change	SD	
0	22	227.14	38.55	-	-	20	219.11	44.16	-	-	0.5326
8	22	225.98	37.34	-	-	20	217.46	43.66	-	-	0.4993
12	21	226.21	38.65	0.57	2.71	20	217.69	45.09	0.23	2.43	0.8356
16	22	226.26	38.72	0.28	4.37	19	212.33	43.33	-1.62	3.28	0.2069
24	22	227.28	38.59	1.30	6.08	20	214.35	46.14	-3.11	4.30	0.0146

APPEARS THIS WAY  
ON ORIGINAL

**Table 24 Weight (lb.) and Weight Change from Baseline, ITT - Study 20**

WEEK	Placebo					Metformin					p-value t-test
	n	Weight	SD	Wt. Change	SD	n	Wt	SD	Wt Change	SD	
8	25	233.87	43.14	-	-	26	224.50	46.07	-	-	0.4575
12	24	234.58	44.69	0.68	2.60	26	224.87	47.62	0.37	2.55	0.6758
16	25	234.24	44.10	0.37	4.16	25	221.10	47.29	-1.02	3.40	0.2009
24	25	235.98	45.17	2.11	6.15	26	221.89	48.45	-2.61	4.04	0.0021

The mean weight change from baseline to week 24 was significantly different between metformin and placebo treated patients with a treatment difference of ~5 lbs.

Sponsor's ANCOVA on blood pressure in all-treated patients are displayed in the following tables.

**Table 25 Diastolic Blood Pressure All- Treated Patients - Study 20**

WEEK	Placebo					Metformin					p-value	
	n	DBP	SD	DBP Change	SD	n	DBP	SD	DBP Change	SD	ANCOVA	t-test
0	25	75.52	9.10			26	74.46	7.76			-	
2	25	80.36	20.58			24	71.75	8.35			-	
4	25	74.72	8.22			25	71.68	7.50			-	
Baseline	25	71.44	11.44			26	70.38	9.16				0.7171
12	24	76.00	9.80	4.83	9.44	26	69.46	7.79	-0.92	9.52	0.0059	0.0371
16	25	74.32	9.64	2.88	8.40	26	71.31	6.81	0.92	6.98	0.1659	0.3693
24	25	73.28	11.59	1.84	11.30	26	71.77	7.85	1.38	9.33	0.6764	0.8757

**Table 26 Systolic Blood Pressure All-Treated Patients - Study 20**

WEEK	Placebo					Metformin					p-value	
	n	SBP	SD	SBP Change	SD	n	SBP	SD	SBP Change	SD	ANCOVA	t-test
0	25	142.88	18.78			26	137.46	9.63			-	
2	25	141.52	18.94			24	133.08	11.34			-	
4	25	138.96	16.22			25	136.44	17.16			-	
Baseline	25	133.68	20.26	-	-	26	134.23	11.71	-	-	-	0.905
12	24	137.96	18.52	5.79	18.49	26	129.92	12.32	-4.31	13.68	0.0275	0.032
16	25	140.08	15.68	6.40	16.55	26	131.04	11.59	-3.19	10.84	0.0048	0.018
24	25	138.56	12.75	4.88	19.58	26	132.38	12.88	-1.85	9.48	0.0509	0.123

For the all treated patients at week 24, t-tests on change from baseline of diastolic blood pressure and systolic blood pressure indicated no significant difference between the two treatment groups.

### Lipid parameters

The results from the sponsor's analysis of covariance on the evaluable patients and this reviewer's analysis of variance on the all-treated patients are displayed in the following tables:

**Table 27 Lipid Parameters, Evaluable Patients – Study 20**

LABTEST	Placebo								Metformin				p-value	
	Wk	n	Lab Value	SD	n	Change from bl	SD	n	Lab Value	SD	n	Change from bl	SD	ANCOV
CHOL/HDL	8	21	5.77	1.63	21	-	-	19	5.59	1.24	19	-	-	0.6956
CHOL/HDL	24	21	5.10	1.16	20	-0.62	0.74	19	4.92	1.23	18	-0.59	0.99	<b>0.900</b>
CHOLESTEROL	8	21	192.14	27.87	21	-	-	19	204.16	34.62	19	-	-	0.2321
CHOLESTEROL	24	21	184.90	32.36	20	-4.90	29.18	19	181.95	28.18	18	-20.28	29.12	<b>0.309</b>
C-PEPTIDE	8	22	384.43	295.59	22	-	-	20	433.25	419.53	20	-	-	0.6630
C-PEPTIDE	24	22	500.66	438.22	22	116.23	299.96	20	569.05	349.59	20	135.81	374.20	<b>0.723</b>
HDL	8	21	35.62	9.64	21	-	-	19	37.95	8.71	19	-	-	0.4296
HDL	24	21	39.00	10.02	20	3.50	4.67	19	38.63	8.17	18	0.61	3.22	<b>0.053</b>
LDL	8	20	122.85	25.76	20	-	-	19	131.58	39.22	19	-	-	0.4143
LDL	24	20	113.85	22.84	19	-5.58	13.89	18	107.61	26.87	17	-25.06	29.42	<b>0.048</b>
TRIGLYCERIDE	8	21	180.43	88.00	21	-	-	19	172.68	79.36	19	-	-	0.7725
TRIGLYCERIDE	24	21	192.76	93.20	20	8.40	58.09	19	202.42	133.66	18	25.11	81.81	<b>0.464</b>

**Table 28 Lipid Parameters, All-Treated Patients – Study 20**

LABTEST	Placebo								Metformin				p-value	
	Wk	n	Lab Value	SD	n	Change from bl	SD	n	Lab Value	SD	n	Change from bl	SD	t-test
CHOL/HDL	8	24	5.70	1.54	24	-	-	25	5.64	1.18	25	-	-	0.8873
CHOL/HDL	24	24	5.10	1.12	23	-0.55	0.71	25	4.82	1.14	24	-0.77	0.98	<b>0.3980</b>
CHOLESTEROL	8	24	190.25	26.53	24	-	-	25	206.60	33.82	25	-	-	0.0666
CHOLESTEROL	24	24	185.00	31.16	23	-3.13	28.26	25	183.08	27.87	24	-22.13	28.09	<b>0.0255</b>
C-PEPTIDE	8	25	352.16	291.87	25	-	-	26	437.11	376.85	26	-	-	0.3738
C-PEPTIDE	24	25	478.44	421.18	25	126.28	286.59	26	532.73	319.59	26	95.62	350.63	<b>0.7345</b>
HDL	8	24	35.50	9.11	24	-	-	25	37.96	8.59	25	-	-	0.3355
HDL	24	24	38.88	9.94	23	3.48	4.84	25	39.56	8.54	24	1.58	3.48	<b>0.1290</b>
LDL	8	23	121.00	24.85	23	-	-	25	134.48	36.02	25	-	-	0.1414
LDL	24	23	113.83	22.93	22	-4.14	14.14	24	104.67	31.31	23	-31.00	36.19	<b>0.0022</b>
TRIGLYCERIDE	8	24	178.83	84.89	24	-	-	25	170.68	72.87	25	-	-	0.7195
TRIGLYCERIDE	24	24	190.13	91.00	23	7.83	56.17	25	191.96	119.30	24	17.46	72.10	<b>0.6130</b>

Lipid parameters at baseline were not significantly different in the evaluable patients, but for the all-treated patients, the total cholesterol and LDL at baseline between treatment groups showed a trend ( $p \sim 0.1$ ) of difference. From the analysis of covariance on evaluable patients and the t-test on all-treated patients, the mean change from baseline to week 24 LDL was statistically

significantly different between treatment groups. The mean change of HDL cholesterol from baseline to week 24 showed a trend favoring placebo patients.

### Safety

The most common adverse event was hypoglycemia (100%, each treatment group) defined as blood glucose <70 mg/dl.

Incidences of drug-related adverse events involving the digestive system were significantly different ( $p < 0.001$ ) between treatment groups. 88% of metformin and 24% of placebo patients reported at least one such adverse event during the study. Diarrhea occurred in 69% and 20% ( $p < 0.001$ ), flatulence occurred in 31% and 8% ( $p = 0.075$ ) and nausea occurred in 23% and 4% ( $p = 0.099$ ) of the metformin and placebo treated patients, respectively.

### Conclusion of Study 20

The sponsor listed 4 primary efficacy variables, insulin dosage, HbA<sub>1c</sub>, change in body weight and change in blood pressure. The mean reduction of daily insulin dose from baseline (week 8) of metformin treated patients was statistically significantly different from placebo at week 24. The difference between treatment groups was ~25 units with the mean reduction of ~24 units (from 124 to 100) in the metformin group and a slight increase in the placebo group from baseline to week 24. The mean change of HbA<sub>1c</sub> from baseline was not different between treatment groups at week 24. The baseline HbA<sub>1c</sub> was 7.76% and 7.41% for metformin and placebo, respectively and at week 24 it was 7.10 and 7.04, respectively.

### Overall Conclusion:

The sponsor's analyses of covariance for both studies 16 and 20 were based on evaluable patient populations with ~20 patients per treatment group. The analysis of covariance method was not specified in either protocol. In study 16, the sponsor's result from ANCOVA on mean HbA<sub>1c</sub> change from baseline to week 24 was statistically significant ( $p = 0.03$ ) but was not significant when using the analysis of variance model ( $p = 0.26$ ). In study 20, four primary efficacy variables were designated: insulin dosage, HbA<sub>1c</sub>, change in body weight and change in blood pressure. HbA<sub>1c</sub> was not statistically significantly different between treatment groups at week 24 but it was statistically significant at week 16. The mean change from baseline of total daily insulin dose was statistically significantly different between treatment groups at weeks 6, 20 and 24. At week 24, the reduction from baseline in the metformin group was 22 units (from 122 to 100 units.) There was a slight increase in daily insulin dose in the placebo group.

The mean change from baseline of HbA<sub>1c</sub> to week 24 in study 16 does not show consistent results between the two-sample t-test and the sponsor's analysis of covariance. For study 20, both methods showed statistically significant results in insulin reduction favoring metformin. For HbA<sub>1c</sub>, there was a statistically significant treatment difference at week 16 but not at week 24.

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/S/

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Concur: Dr. Sahlroot

/S/ 7/24/98

Dr. Nevius

/S/ 10/11/98

cc: Arch NDA 20-357

HFD-510

HFD-510/SSobel

HFD-510/RMisbin

HFD-510/EGalliers

HFD-510/JWeber✓

HFD-715/Division file, LPian, TSahlroot, ENevius  
Chron.

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