

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-202

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-202 / N-000

SUBMISSION DATE:

12-NOV-99, 18-FEB-00(BZ),
11-AUG-00(BC)

BRAND NAME:

Glucophage ® XR

GENERIC NAME:

Metformin HCL 500mg extended release oral tablets

REVIEWER:

Robert M. Shore, Pharm.D.

SPONSOR:

Bristol-Myers Squibb Co.,
Princeton, NJ

TYPE OF SUBMISSION:

Original Application
Code: 3S**TERMS AND ABBREVIATIONS:**

AUCa-b Area under the plasma-concentration-time curve from time a to time b
Cmax..... Maximal observed plasma concentration
DMEDP Division of Metabolic and Endocrine Drug Products
OCPB.. Office of Clinical Pharmacology and Biopharmaceutics

SYNOPSIS:**What is the formulation of Glucophage XR?**

In addition to the active ingredient, Glucophage XR 500mg tablets contain sodium carboxymethylcellulose and hydroxypropyl methylcellulose _____ microcrystalline cellulose _____
_____ and magnesium stearate

Are the assays used to quantify metformin in the NDA acceptable?

Three assays were used; one was _____ method for urine and the two others _____ methods for plasma. The two plasma assays used similar methods and had only minor differences. All three assays were found to be acceptable.

What is the dissolution method and specification for Glucophage XR?

The sponsor has proposed the following:

Medium: _____

Apparatus 2: _____

Time: _____

Tolerances -- _____

After reviewing dissolution data, it is recommended that only the 10 hour tolerance be changed to _____

How do the pharmacokinetics of Glucophage XR and Glucophage immediate release oral tablets compare?

Generally, the Cmax is decreased by about 20%, Tmax is increased to about 7 hours, and AUC is comparable with Glucophage.

Does food have an effect on the bioavailability of Glucophage XR?
Food increased the AUC of Glucophage XR by 50% but had no effect on Cmax or Tmax

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-202/N-000 submitted 12-NOV-99, 18-FEB-00, and 11-AUG-00. The overall Human Pharmacokinetic Section is acceptable to OCPB. This recommendation, comments (p. 14), and labeling comments (p. 14) should be sent to the sponsor as appropriate.

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BACKGROUND:

Glucophage (metformin) 500mg and 850mg immediate release oral tablets were approved under NDA 20-357 on 03-MAR-95; the 1gm tablet was approved on 05-NOV-98. Glucophage, as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed on diet alone. Glucophage may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. These tablets are indicated to be taken in divided doses with meals up to a maximum daily dose of 2550mg/day. With NDA 21-202/N-000 the sponsor seeks approval of a 500mg extended release oral tablet. Extended release metformin tablets are available in many countries worldwide. The absolute bioavailability of a 500mg immediate release tablet is approximately 50-60% and the bioavailability decreases as the dose increases.

**APPEARS THIS WAY
ON ORIGINAL**

STUDY SUMMARY INDEX

Protocol Number	Title	Page
CV138-021	Pharmacokinetics and bioavailability of _____ metformin tablets relative to Glucophage®	p. 47
CV138-028	Steady state pharmacokinetics of metformin _____ tablet	p. 53
CV138-031	Evaluation of the effect of food on the pharmacokinetics of metformin _____ tablet	p. 59
CV138-035	The pharmacokinetics and pharmacodynamics of the _____ controlled release versus immediate release metformin tablet in type 2 diabetics	p. 63

DRUG FORMULATION:

What is the formulation of Glucophage XR?

Study CV138-021 examined the pharmacokinetics of four different experimental formulations of extended-release metformin after a single dose in healthy volunteers. The table below summarizes the pharmacokinetic parameters from each of these experimental formulations ($T_{90\%}$ is the time required for 90% dissolution *in vitro*).

Mean (SD) Pharmacokinetic Parameters of Metformin					
Treatment*	A	B	C	D	E
C _{MAX} (ng/ml)	1124 (280)	905 (220)	978 (131)	1285 (129)	1226 (191)
AUC(0-T) (ng.hr/ml)	10316 (2658)	9198 (2580)	10361 (2252)	10000 (1445)	9818 (1295)
T _{MAX} # (hr)	6.00 _____	7.00 _____	5.00 _____	4.00 _____	3.50 _____
%UR	39.88 (7.87)	38.62 (9.56)	42.72 (7.82)	43.31 (8.71)	43.28 (8.73)

- * A=2x metformin HCl 500 mg _____ A tablets ($T_{90\%}$ =7 hours)
 B=2x metformin HCl 500 mg _____ B tablets ($T_{90\%}$ =10 hours)
 C=2x metformin HCl 500 mg _____ tablets ($T_{90\%}$ =7 hours)
 D=2x metformin HCl 500 mg _____ tablets ($T_{90\%}$ =5-6 hours)
 E=2x metformin HCl 500 mg Glucophage® tablets
 # Median (range)

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The sponsor indicated that the _____ tablet had a plasma profile similar to Glucophage and was not suitable for a once daily formulation. The _____ A product had a delayed T_{max} but did not lower C_{max} and was not pursued. Both the _____ B and _____ tablet showed lower C_{max} with no decrease in AUC relative to Glucophage. Since the _____ tablet had less variability in its pharmacokinetic parameters it was chosen for further development as a once daily formulation.

The Glucophage XR tablet will be manufactured by Bristol-Myers Squibb Company in Evansville, Indiana. _____ different formulations have been used throughout the development of Glucophage XR. The only ingredient difference between the prototype product and clinical/commercial products was that the prototype product contained _____. The proposed commercial batch size will be _____ depending on market requirements.

**Composition of Metformin Hydrochloride MR Tablet
 Prototype Clinical Product (Product Identification Number
 207150-V500-014), Clinical Product (Product Identification
 Number 207150-V500-038) and Stability/Commercial Product
 (Product Identification Number 207150-V500-046)**

INGREDIENT	mg per tablet		
	Prototype Clinical Product (Product No. 207150-V500-014)	Clinical Product (Product No. 207150-V500-038)	Commercial Product (Product No. for tablets 207150-V500-046)
Metformin hydrochloride/ Magnesium stearate			
Sodium carboxymethylcellulose			
Hydroxypropyl methylcellulose			
Hydroxypropyl methylcellulose			
Microcrystalline cellulose			
Magnesium stearate			
TOTAL WEIGHT			1023.5
TABLET APPEARANCE	Biconvex, capsule shape, debossed with "SQUIBB" on one side	Biconvex, capsule shape, no debossing	Biconvex, capsule shape, debossed with "BMS 6063" on one side and "500" on the other side

Source: Section 4, Part II DP.T07
 q.s. quantity sufficient

In addition to the active ingredient, Glucophage XR 500mg tablets contain sodium carboxymethylcellulose and hydroxypropyl methylcellulose microcrystalline cellulose and magnesium stearate

The tablet is not film coated. Glucophage XR is a white to off-white, capsule shaped, biconvex tablet, debossed with "BMS 6063" on one side and "500" on the other side.

DISSOLUTION:

What is the dissolution method and specification for Glucophage XR?

The sponsor claims that metformin is a class 3 drug under the Biopharmaceutical Classification System. The solubility is about between 0.1M HCl and pH 7.5 SIF and the bioavailability of a 500mg immediate release tablet is about 50-60%.

The sponsor has proposed the following:

Proposed Product Dissolution Method and Specification

Dosage Form	Tablets
Strengths	500 mg metformin HCl
Apparatus	USP <711> Dissolution Apparatus 2 (paddles)
Media/Temperature	
Volume	
Speed of Rotation	
Sampling Times	
Brief Description of the Dissolution Analytical Method	
Recommended Dissolution Specifications*	

* As defined in USP <724> Drug Release (Extended Release Articles).

** Dissolution analytical method for drug products described in Attachment E employed

The justifications for this method include the following:

Preliminary results of dissolution testing are presented in the table below. The batches are from biostudies submitted in Section 6 of the NDA. Batches 8MBN119 and 8MDN203 were at least — of the proposed commercial size and were manufactured at the commercial site. The other two batches were less than — tablets in size and were not manufactured at the commercial site. However, it is noted that F2 values for each small batch as compared to each of the larger batches are between 85 and 96; an F2 between 50 and 100 indicates that the dissolution profiles are similar.

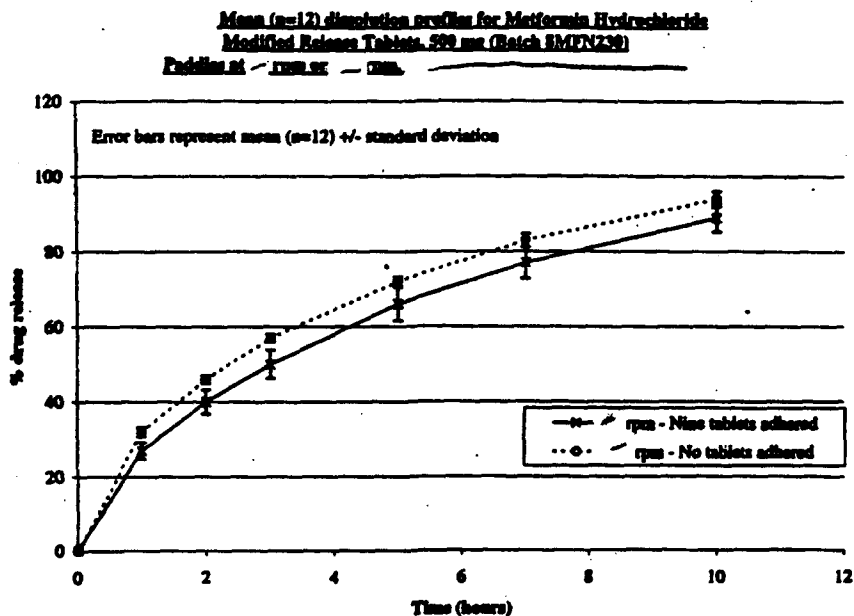
Drug Product Dissolution Testing

Date Tested	Strength/ Dosage Form	Batch Number	Dissolution Method*	Units Tested	Dissolution (% Dissolved)						
					Time (hours)	1	2	3	5	7	12
August 1997	500 mg modified release tablet	M97041	*	6	Mean	32	47	58	73	86	96
					Range	—	—	—	—	—	—
January 1998	500 mg modified release tablet	M97057	*	6	Mean	32	47	58	73	84	94
					Range	—	—	—	—	—	—
March 1998	500 mg modified release tablet	8MBN119	*	6	Mean	32	46	57	73	84	93
					Range	—	—	—	—	—	—
June 1998	500 mg modified release tablet	8MDN203	*	6	Mean	31	46	57	73	85	96
					Range	—	—	—	—	—	—

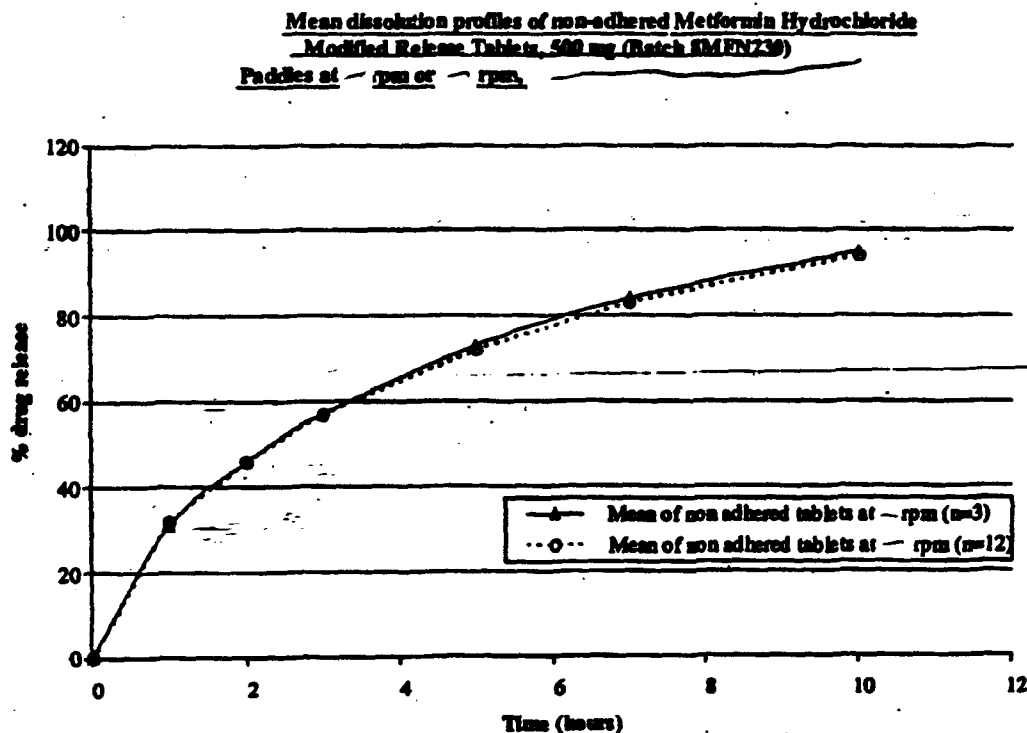
* Dissolution method can be found in Attachment F.

At a pre-NDA meeting on 24-MAY-99 additional dissolution data was requested; this data was submitted under IND — on 01-OCT-99 but was not reviewed. This same data were requested to be submitted under the current NDA and are presented here. Batches 8MFN230, 8MBS105, and 8MEN204 are of commercial size and were produced at the commercial manufacturing site.

The plot below shows the mean dissolution profiles of Glucophage XR tablets that adhered to the vessel wall at $\sim$ rpm (9 out of 12 tablets) and all Glucophage XR tablets at $\sim$ rpm (no tablets adhered; n=12).



It can be seen that those tablets that did adhere had an overall lower % drug release than the tablets that did not adhere. Below is a plot of the remaining 3 tablets at $\sim$ rpm that did not adhere to the vessel. Along with the $\sim$ rpm data again.



The 3 tablets that did not adhere at — rpm show a similar dissolution profile as compared with all tablets at — rpm. The individual data for these plots is presented below.

Batch Number 8MFN230

rpm paddle speed

Vessel	% Dissolved at (hours)						Tablet adhesion during dissolution test
	1	2	3	5	7	10	
1							Yes
2							Yes
3							Yes
4							No
5							Yes
6							Yes
7							Yes
8							No
9							Yes
10							Yes
11							Yes
12							No
Mean (n = 12)	27	40	50	66	71	89	-
Standard deviation (n = 12)	2.2	3.2	3.8	4.4	4.3	3.7	-

Batch Number 8MFN230

rpm paddle speed

Vessel	% Dissolved at (hours)						Tablet adhesion during dissolution test
	1	2	3	5	7	10	
1							No
2							No
3							No
4							No
5							No
6							No
7							No
8							No
9							No
10							No
11							No
12							No
Mean (n = 12)	32	46	57	72	83	94	-
Standard deviation (n = 12)	1.3	1.0	1.0	1.3	1.8	2.0	-

Two other commercial size batches were tested also and showed similar results - adhered tablets had lower % drug release than non-adhered tablets. The individual dissolution data for these two batches using the — rpm method are presented below. There is often a concern as to whether the — rpm speed is degrading the tablet too fast and just ripping it apart by force. Since metformin is being released over many hours from the Glucophage XR tablet and the % drug release is comparable between tablets that did not adhere at —rpm and —rpm, this concern is allayed.

Batch Number 8MBS105

rpm paddle speed

Vessel	% Dissolved at (hours)						Tablet adhesion during dissolution test
	1	2	3	5	7	10	
1							No
2							No
3							No
4							No
5							No
6							No
7							No
8							No
9							No
10							No
11							No
12							No
Mean (n = 12)	30	44	55	71	82	92	-
Standard deviation (n = 12)	1.5	2.1	1.8	1.9	2.2	2.1	-

Batch Number SMEN204

rpm paddle speed

Vessel	% Dissolved at (hours)						Tablet adhesion during dissolution test
	1	2	3	5	7	10	
1							No
2							No
3							No
4							No
5							No
6							No
7							No
8							No
9							No
10							No
11							No
12							No
Mean (n = 12)	29	43	53	69	80	89	-
Standard deviation (n = 12)	2.2	2.5	2.7	2.8	2.5	2.9	-

Therefore, it is reasonable to accept the — rpm rotation speed since there would be wider variability at the — rpm speed.

The average % drug released for the 3 batches combined is 30%, 55%, and 92% at 1, 3, and 10 hours, respectively. The proposed specification is acceptable at the 1 and 3 hour times, but the proposed 10 hour time point tolerance is too loose. It is recommended that it be changed to — dissolved at 10 hours' since the average for the three batches was 92% at three hours and the minimum for an individual tablet was —

ANALYTICAL METHODOLOGY:

All assays were found to be acceptable.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

II. Pharmacokinetics

How do the pharmacokinetics of Glucophage XR and Glucophage immediate release oral tablets compare?

Study CV138-028 explored the steady-state pharmacokinetics of 4 doses of Glucophage XR. Sixteen

healthy volunteers were dosed with 500mg Glucophage XR as a single dose following dinner and pharmacokinetic samples were taken. Subjects then received nightly doses of 500mg Glucophage XR for a week and pharmacokinetic samples were again obtained after the week of dosing. After the first week subjects received 2x500mg Glucophage XR tablets and had pharmacokinetic samples taken after a week at this dose. The 500mg dose increments continued each week up to 2000mg QD. All subjects also received 2x500mg BID Glucophage immediate release tablets for one week so as to provide comparative pharmacokinetic parameters.

The table below summarizes the pharmacokinetic parameters.

Treatment	N	C _{max} (ng/ml)	T _{max} ^a (hr)	AUC (ng hr/ml) ^a
500 mg — single dose	16	645(115)	7	6466(1751)
500 mg QD —	16	603(166)	6	6316(1996)
1000 mg QD —	16	1080(259)	7	12587(3164)
1500 mg QD —	15	1441(362)	7	16820(4160)
2000 mg QD —	14	1780(288)	7	20451(4114)
1000 mg BID Glucophage®	15	1321(234)	31	20544(4445)

^a Median (range)

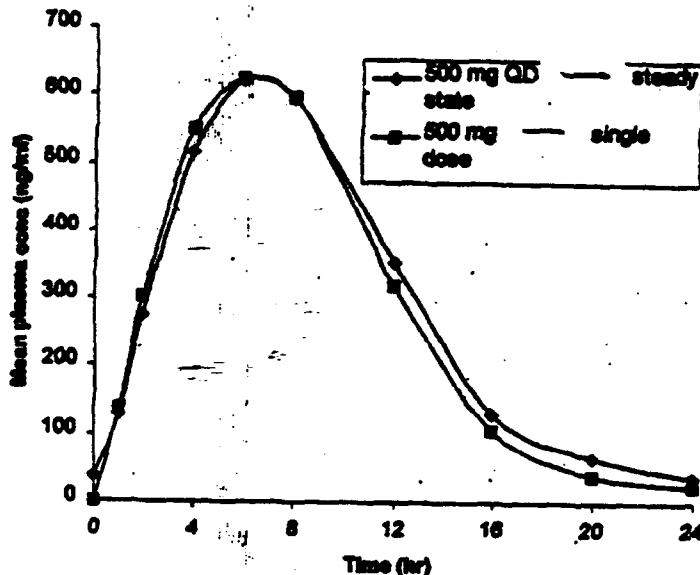
^a AUC(INF) for 500 mg single dose; all others AUC(0-24).

C_{MAX} and T_{MAX} for the Glucophage® treatment are from the PM dose.

For doses of Glucophage XR in the ratio 1:2:3:4 the means for C_{max} were in the ratio of 1:1.8:2.4:3.0 and the means for AUC increased in the ratio 1:2.0:2.7:3.2. There is less than proportional increases in the pharmacokinetic parameters as the dose of Glucophage increases. This is consistent with the current labeling of Glucophage which states 'there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.'

There appears to be no accumulation after a week of dosing. At the 500mg dose the AUC after a week of dosing is slightly less than, but comparable to, the AUC after a single dose (see plot below)

Mean plasma concentration time profiles of metformin after a single 500 mg dose and at steady state as the — tablet



The bioavailability of metformin administered as immediate release Glucophage 1000mg BID and

extended release Glucophage XR 2000mg QD was compared and is presented in the table below.

Parameter	Adjusted geometric means		Ratio of geometric means	
	2000 mg QD	1000 mg Glucophage® BID	Point estimate	90% CI
C _{MAX} (ng/ml)	1763	1297	1.36	(1.29, 1.44)
AUC(TAU) (ng.hr/ml)	19926	20053	1.00	(0.93, 1.07)

The AUCs are comparable between the two dosage forms. A difference in C_{max} may be expected since twice the dose is being administered at once.

The intra-subject variability was estimated by comparing day 6 and day 7 C_{max} and AUC values and the results are shown in the table below.

Estimates of Within-Subject Standard Deviations

	Log(C _{MAX})	Log(AUC(TAU))
500 mg — tablet QD	0.24 (19.7)*	0.24 (17.2)
1000 mg — tablet QD	0.12 (11.9)	0.12 (9.1)
1500 mg — tablet QD	0.16 (15.9)	0.11 (10.3)
2000 mg — tablet QD	0.13 (13.3)	0.14 (11.9)
1000 mg Glucophage® AM	0.17 (19.2)	0.14 (13.9)
1000 mg Glucophage® PM	0.09 (8.5)	0.09 (9.8)

*The number in parenthesis is the coefficient of variation for C_{MAX} and AUC(TAU) on the original scale.

Source: Appendix 6.3.2

Study CV138-035 investigated the pharmacokinetics and pharmacodynamics of Glucophage XR. This was a pilot, 5 arm, parallel group study in which diabetic patients were administered Glucophage 500mg BID for 2 weeks then randomized to one of 5 dosing groups for another 2 weeks. Pharmacokinetic and pharmacodynamic evaluations were done after each of the two week periods. Glucophage was administered with an ADA dinner. The pharmacokinetic results are listed in the table below.

Mean (SD) Pharmacokinetic Parameters for Metformin in Study CV138-035

Treatment	N	C _{MAX} (ng/ml)	T _{MAX} * (h)	AUC(TAU) (ng.hr/ml)	T-HALF (h)
500 mg BID Glucophage®	7	1048 (191)	3.0	17396 (3998)	4.4 (0.9)
500 mg QD	7	789 (222)	8.0	8828 (2630)	10.6 (6.3)
1000 mg QD	7	1261 (158)	6.0	14488 (1916)	13.2 (8.8)
2000 mg QD	5	2251 (358)	8.0	26667 (5140)	15.6 (5.2)
500 mg BID	7	790 (215)	8.0	13755 (3608)	6.8 (3.4)

CV138-035

Source: Supplemental Table S.11.2.2

Note: Median (range)

C_{MAX}, T_{MAX} and T-HALF values for the BID treatments are from the PM dose.

T_{max} is consistent at about 7 hours. For the QD doses in a ratio of 1:2:4 the C_{max} increased in a ratio of 1:1.6:2.9 and the AUC ratio was 1:1.6:3.0. This is consistent with other studies that showed a less than proportional increase in the pharmacokinetic parameters as doses of metformin increase.

The table below shows a comparison of the same daily dose administered with various dosage forms. The AUC of 1000mg Glucophage XR QD is, on average, about 13% less than 500mg Glucophage BID.

However, it is already known that as dose increases bioavailability decreases.

Statistical Comparison of CMAX and AUC(TAU) in Study CV138-035

Comparison	Adjusted Geometric Means	Ratio of Geometric Means Relative to Glucophage® BID	
		Point Estimate	90% CI
CMAX (ng/ml)			
500 mg BID Glucophage®	1020		
1000 mg QD —	1280	1.25	(1.11, 1.41)
500 mg BID —	783	0.77	(0.68, 0.86)
AUC(TAU) (ng.h/ml)			
500 mg BID Glucophage®	17032		
1000 mg QD —	14787	0.87	(0.77, 0.98)
500 mg BID —	14237	0.84	(0.74, 0.94)

CV138-035

Source: Appendix 6.4.2

The table below summarizes the pharmacodynamic biomarker changes between the lead-in (Glucophage 500mg BID) and each dose group. It is noted that the groups are small (N≤7) and therefore the results are exploratory.

Mean (90% CI) changes from Glucophage® Lead-in Baseline after Two Weeks of Randomized Treatment

Pharmacodynamic Parameter	*Adjusted Mean Change from Glucophage® Baseline, By Treatment (90% CI)				
	500mg BID Glucophage®	500mg QD MR	1000mg QD MR	2000mg QD MR	500mg BID MR
Glucose AUC(0-24) (mg.h/dL)	215 (-41, 471)	755 (499, 1011)	503 (247, 759)	119 (-184, 422)	463 (207, 719)
Mean Glucose (mg/dL)	9.68 (-1.97, 21.3)	30.7 (19.0, 42.3)	21.5 (9.89, 33.2)	4.05 (-9.73, 17.8)	14.0 (2.31, 25.6)
Pre-Breakfast Glucose (mg/dL)	3.86 (-11.0, 18.7)	13.0 (-3.02, 29.0)	-5.14 (-20.0, 9.7)	-7.00 (-24.5, 10.6)	11.7 (-4.36, 27.7)
Pre-dinner Glucose (mg/dL)	6.62 (-19.3, 32.6)	38.6 (14.6, 62.6)	13.9 (-10.1, 37.9)	11.0 (-17.4, 39.4)	6.50 (-19.4, 32.4)
Fructosamine (µmole/L)	3.23 (-6.38, 12.9)	11.6 (1.28, 21.9)	-5.14 (-15.4, 5.15)	-9.60 (-21.8, 2.58)	4.14 (-6.15, 14.4)
Nonesterified free fatty acids (nmol/L)	-0.01 (-0.16, 0.14)	-0.13 (-0.28, 0.03)	-0.19 (-0.35, -0.04)	0.04 (-0.15, 0.22)	-0.05 (-0.20, 0.11)
Glycated albumin (%)	0.15 (0.03, 0.27)	0.10 (-0.03, 0.23)	-0.20 (-0.33, -0.08)	-0.16 (-0.31, -0.01)	0.11 (-0.01, 0.24)
Lipoprotein (a) (mg/dL)	0.33 (-1.68, 2.73)	-2.28 (-4.82, 0.26)	-2.13 (-4.48, 0.22)	0.62 (-2.16, 3.40)	-0.56 (-2.91, 1.80)
Triglycerides (mg/dL)	26.3 (-11.3, 63.8)	-6.50 (-49.9, 36.9)	23.6 (-16.6, 63.7)	-42.8 (-90.3, 4.73)	17.6 (-22.6, 57.7)

Application Summary

* Adjusted mean change from Glucophage® Lead-in Baseline = End of Period B value - End of Period A value

CI = Confidence Interval

Basically, there is a dose response relationship between the QD Glucophage XR doses. The biomarker changes move toward improvement as the doses go from Glucophage XR 500mg QD to 2000mg QD. It is noted that the sponsors analysis indicated no significant differences between any of the pharmacodynamic parameters except for glycated albumin when comparing Glucophage 500mg BID with Glucophage XR 1000mg QD.

Does food have an effect on the bioavailability of Glucophage XR?

The current labeling of Glucophage indicates 'food decreases the extent and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting.

Study CV138-031 was undertaken to investigate the effect of food on the pharmacokinetics of Glucophage XR. Eighteen healthy volunteers were administered a single dose of 4x500mg Glucophage XR tablets in each of three conditions:

- after a 6.5 hour fast;
- 5 minutes after a high fat dinner;
- 5 minutes after a low fat dinner.

The table below summarizes the mean pharmacokinetic parameters.

Mean (SD) Pharmacokinetic Parameters for Metformin in Study CV138-031

Parameter	Fasted	High Fat Dinner	Low Fat Dinner
C _{MAX} (ng/mL)	1648 (357)	1580 (400)	1864 (383)
T _{MAX} (h)*	4.0 —	4.0 —	4.0, —
AUC (INF) (ng.h/mL)	14793 (5715)	21148 (5913)	21077 (4327)
T- _{HALF} (h)	9.5 (3.9)	8.3 (4.0)	9.3 (3.2)

* Median (range)

Source: Appendix 6.3.2

T_{max} was not affected when Glucophage XR was dosed under fasted or fed conditions. A formal comparison was made between the fasted condition and each of the fed conditions. This comparison is presented below.

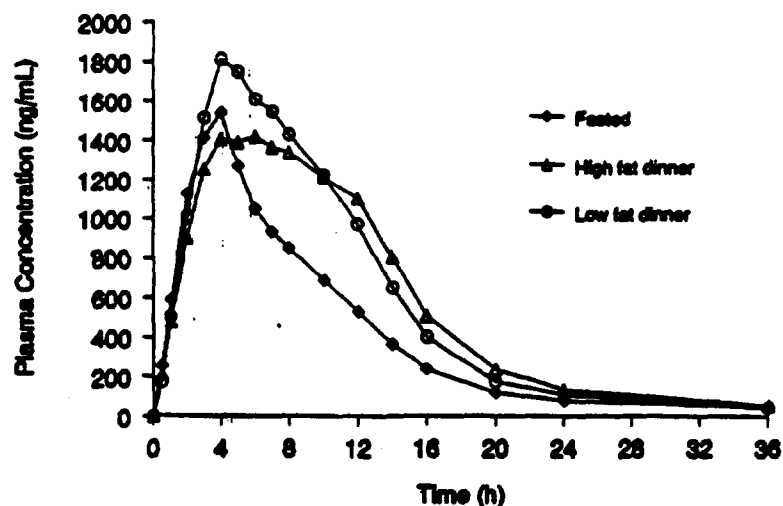
Results of Statistical Comparisons on Pharmacokinetic Parameters of Metformin in Study CV138-031

	Adjusted Geometric Mean	Ratio of Geometric Means relative to Fasted	
		Point Estimate	90% CI
C _{MAX} (ng/mL)			
Fasted	1609		
High fat dinner	1529	0.95	(0.89, 1.02)
Low fat dinner	1824	1.13	(1.06, 1.22)
AUC(INF) (ng.h/mL)			
Fasted	13835		
High fat dinner	20234	1.46	(1.30, 1.65)
Low fat dinner	20744	1.50	(1.33, 1.69)

Source: Appendix 6.3.2

Cmax is not affected by food. Both the high and low fat dinners increased the AUC of metformin by approximately 50%.

Mean plasma metformin concentrations under fasted condition and after a high fat and low fat dinner



Food increased the AUC of Glucophage by 50% but had no effect on Cmax or Tmax. The clinical trials submitted in the NDA were conducted with Glucophage administered with meals. The proposed labeling indicates that Glucophage and Glucophage XR be taken with meals.

COMMENTS FROM THE MEDICAL OFFICER:

The MO has provided the following table from a clinical trial submitted in support of this NDA.

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 = 63
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)

Application Summary

Source: Final Study Report CV138-012

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

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

Although slightly less effective, the 1000mg QD Glucophage XR (MR) dose is clinically comparable with the 500mg BID Glucophage dose. Also, it is noted that patients are titrated to the proper dose based on

clinical endpoints.

COMMENTS TO BE SENT TO MEDICAL OFFICER:

- 1) There is less than proportional increase in systemic exposure of metformin as the dose of Glucophage XR increases from 500mg to 2000. This is consistent with Glucophage immediate release tablets (as per current labeling).

COMMENTS TO BE SENT TO SPONSOR:

- 1) For the proposed dissolution specification, it is recommended that the 10 hour tolerance be changed to _____

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ~~✗~~ indicates an explanation only and is not intended to be included in the labeling)

- 1) Pharmacokinetics: Although the extent of metformin absorption from the GLUCOPHAGE XR tablet _____ increased by approximately _____ 50% when given _____ with food, there was no effect of food on Cmax and Tmax of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of GLUCOPHAGE XR.

☒ Consistent with current labeling.

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/

25-AUG-00

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 13-AUG-00

CPB Briefing 25-AUG-00

attendees: Hae-Young Ahn, Frank Pelsor, Robert Misbin, John Hunt.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader _____

/S/

8/25/00

CC: NDA 21-202/N-000 (orig., 1 copy), HFD-510(Weber), HFD-870(Ahn, HuangS), HFD-850(Lesko) CDR.

DFS Code: AE

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Appendix 1. Draft labeling

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Appendix 2. Study summaries (b) (4) "Appendix 2. Study summaries}

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METFORMIN

Indication: Non-Insulin Dependent Diabetes Mellitus (NIDDM)

Protocol No.: CV138-021

Report No: 910068379

Phase: I

Study Initiation Date: 15-Sept-97

Study Completion Date: 08-Oct-97

Report Date: 20-May-98

PHARMACOKINETICS AND BIOAVAILABILITY OF METFORMIN TABLETS RELATIVE TO GLUCOPHAGE®

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Name and Affiliation of Principal Investigator:

[Redacted Signature]

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Department of Metabolism and Pharmacokinetics
Pharmaceutical Development
Bristol-Myers Squibb Pharmaceutical Research Institute
Bristol-Myers Squibb Company

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May 20, 1998

Princeton, NJ 08543-4000

BRISTOL-MYERS SQUIBB
PHARMACEUTICAL RESEARCH INSTITUTE

PHARMACOKINETICS AND BIOAVAILABILITY OF
METFORMIN TABLETS RELATIVE
TO GLUCOPHAGE®

CONTRIBUTORS

MEDICAL MONITOR: _____ M.D.

CLINICAL MONITOR: _____ B.S.

PHARMACOKINETICIST: _____ Ph.D.

BIostatistician: _____ B.S.

REPORT PREPARATION: _____ B.S.

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BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS**TITLE OF STUDY:** Pharmacokinetics and Bioavailability of _____
_____ metformin tablets relative to Glucophage®.**INVESTIGATOR:** _____**STUDY CENTER:** []**PUBLICATIONS:** None**STUDY PERIOD:** September 15, 1997 to October 8, 1997.**CLINICAL PHASE:** I**OBJECTIVES:**The objective of this study was to assess the pharmacokinetics and bioavailability of _____
_____ metformin tablets relative to Glucophage®.**METHODOLOGY:**

A single site, five treatment, four period, open-label, single oral dose study was conducted to evaluate the pharmacokinetics and bioavailability of _____ metformin tablets relative to Glucophage® in healthy volunteers. Sixteen subjects who fulfilled the inclusion and exclusion criteria were admitted to the clinic and randomized to one of 16 sequences. Each subject was randomly assigned to Treatment E during one of the periods and to three of four treatments (A, B, C, or D) in the three remaining study periods. A brief description of all the treatments is provided below. Serial plasma and urine samples were obtained for 36 hours following dosing. Plasma and urine samples were analyzed for metformin using validated _____ methods respectively.

Treatment	Formulation
A	2 x Metformin HCl 500 mg — A tablets ($T_{90\%} \approx 7$ hrs)
B	2 x Metformin HCl 500 mg — B tablets ($T_{90\%} \approx 10$ hrs)
C	2 x Metformin HCl 500 mg — tablets ($T_{90\%} \approx 7$ hrs)
D	2 x Metformin HCl 500 mg — tablets ($T_{90\%} \approx 5-6$ hrs)
E	2 x Glucophage 500 mg tablets

* $T_{90\%}$: Time required for 90% dissolution *in vitro*.**NUMBER OF SUBJECTS:**

A total of 16 subjects were enrolled, 15 subjects completed the study, and 1 subject discontinued.

MAIN CRITERIA FOR INCLUSION:

Healthy young men and women between 18 and 40 years of age, within $\pm 15\%$ of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception.

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CLINICAL REPORT SYNOPSIS

Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

_____ A (Batch # N97103), _____ B (Batch # N97104), _____ (Batch # M97041), and _____
(Batch # 970704) tablets of metformin HCl were supplied by Bristol-Myers Squibb. Subjects were dosed 2 x 500 mg metformin HCl (total of 1000 mg) tablets of the appropriate product.

DURATION OF TREATMENT: Four single doses were administered, with at least one week washout between doses.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

The reference Glucophage[®] tablets were provided by the investigator (Lot # H7J033A). All subjects received 2 x 500 mg (total of 1000 mg) metformin HCl Glucophage[®] tablets.

CRITERIA FOR EVALUATION:

Serial plasma and urine samples for pharmacokinetic analysis were collected for 36 hours after each dose. C_{MAX}, T_{MAX}, AUC (0-T), T_{1/2} and % UR of metformin from Treatments A, B, C, and D were compared to that from Treatment E. Safety was assessed by monitoring vital signs, ECGs and clinical laboratory tests.

STATISTICAL METHODS:

Sample Size:

The objective of this study was to assess the pharmacokinetics and bioavailability of _____ metformin tablets relative to Glucophage[®]. Based on the sample size of 16 subjects and the results from a previous study (CV138-013) it was calculated that there would be 80% power to detect a 23% difference in mean AUC(0-T) values and a 24% difference in mean C_{MAX} values at the two-sided 0.05 significance level.

Statistical Methods:

Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term. The distributions of the pharmacokinetic variables were summarized by treatment. An analysis of variance appropriate for a 4-period, 5-treatment controlled balanced residual effects design was performed. A carryover effect variable was included in the statistical comparisons of T_{MAX}. Prior to analysis, C_{MAX} and AUC(0-T) were log transformed and T_{MAX} was rank transformed.

Analysis:

All available data from all subjects who completed the study were included in the statistical analysis of pharmacokinetic parameters. All available data from all subjects who received study medication were included in the analysis of safety data.

PHARMACOKINETIC RESULTS:

The pharmacokinetic results were determined using a validated noncompartmental analysis protocol. Metformin pharmacokinetic parameters are summarized in the following table:

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CLINICAL REPORT SYNOPSIS

Mean (SD) Pharmacokinetic Parameters of Metformin					
Treatment*	A	B	C	D	E
C _{MAX} (ng/ml)	1124 (280)	905 (220)	978 (131)	1285 (129)	1226 (191)
AUC(0-T) (ng.hr/ml)	10316 (2658)	9198 (2580)	10361 (2252)	10000 (1445)	9818 (1295)
T _{MAX} # (hr)	6.00	7.00	5.00	4.00	3.50
%UR	39.88 (7.87)	38.62 (9.56)	42.72 (7.82)	43.31 (8.71)	43.28 (8.73)

- * A=2x metformin HCl 500 mg ——— A tablets (T_{90%} — hours)
 B=2x metformin HCl 500 mg ——— B tablets (T_{90%} — hours)
 C=2x metformin HCl 500 mg ——— (T_{90%} — hours)
 D=2x metformin HCl 500 mg ——— tablets (T_{90%} — hours)
 E=2x metformin HCl 500 mg Glucophage® tablets

Median (range)

All modified release dosage form treatments (A, B, C, and D) showed a longer T_{MAX} relative to Glucophage® (treatment E). No statistically significant differences were observed in C_{MAX}, AUC(0-T), and %UR for treatment A (——— A tablet, T_{90%} = 7 hours) in comparison to treatment E (Glucophage® tablet). C_{MAX} and %UR were significantly lower (p<0.001 and p=0.03 respectively) for treatment B (——— B tablet, T_{90%} = 10 hours) in comparison to treatment E (Glucophage® tablet). Although AUC(0-T) was 11% smaller for treatment B with reference to treatment E, the difference was not statistically significant (p=0.06). For the comparison of treatment C (——— tablet, T_{90%} = 7 hours) to treatment E (Glucophage® tablet), a statistically significant decrease in C_{MAX} (p<0.001) was observed. There were no statistically significant differences in AUC(0-T) and %UR for treatment C in comparison to treatment E. Finally, a comparison of treatments D (——— tablet, T_{90%} = 5-6 hours) and E (Glucophage® tablet) indicated no significant differences for the variables C_{MAX}, AUC(0-T), and %UR.

SAFETY AND TOLERABILITY RESULTS:

There were no Serious Adverse Events (SAE's). A total of 28 Adverse Events (AE's) were reported in this study. None of these AE's were considered certain to be related to administration of the various drug treatments. There were 1, 2, 5, 11, and 9 AE's reported for treatments A, B, C, D, and E respectively. The most frequently reported AE's were gastrointestinal disorders. No clinically relevant abnormalities were found in the vital signs and ECGs during or post treatment. There were three marked abnormalities in the laboratory values during or post treatment. Two subjects had high lymphocyte counts and one subject had high monocytes.

CONCLUSIONS:

1. The ——— tablet had a plasma profile similar to Glucophage® and was therefore not suitable for development as a once daily formulation.

Final Study Report: Protocol CV138-021

Report No. 910068379

May 20, 1998

**BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS**

2. ——— A formulation showed a delayed TMAX but did not lower CMAX relative to Glucophage®. Based on this observation, it was concluded that this formulation was also not optimal for further development.
3. Both ——— B and the ——— tablet formulation showed a lower CMAX, with no decrease in AUC, relative to Glucophage®. Since the ——— tablet demonstrated less variability in its pharmacokinetics, it was chosen for further evaluation as a once daily formulation.

DATE OF REPORT: May 20, 1998.

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S10872814

METFORMIN

Indication: Non-Insulin Dependent Diabetes Mellitus (NIDDM)

Protocol No.: CV138-028

Phase: I

Study Initiation Date: February 1, 1998

Study Completion Date: March 9, 1998

Report Date: October 23, 1998

STEADY STATE PHARMACOKINETICS OF METFORMIN TABLET

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Name and Affiliation of Principal Investigator:

[Redacted Signature]

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Final Study Report: CV138-028

Report No. 910072014

October 23, 1998

**STEADY STATE PHARMACOKINETICS OF METFORMIN
TABLET**

CONTRIBUTORS

MEDICAL MONITOR: _____ M.D.

CLINICAL MONITOR: _____ B.S.

PHARMACOKINETICIST: _____ Ph.D.

BIostatistician: _____ Ph.D.

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BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: Steady state pharmacokinetics of metformin ——— tablet

INVESTIGATOR: _____

STUDY CENTER: _____

PUBLICATIONS: None

STUDY PERIOD: February 1, 1998 to March 9, 1998

CLINICAL PHASE: I

OBJECTIVES:

The objectives of this study were:

- To assess the steady state pharmacokinetics of metformin when administered as the ——— (modified release) tablet upon multiple dosing.
- To assess dose proportionality in the pharmacokinetics of metformin as the ——— tablet at doses to be studied in clinical safety and efficacy studies.
- To compare the plasma concentrations of metformin obtained after multiple dosing of the ——— tablet (2000 mg QD) relative to Glucophage® (1000 mg BID).
- To assess the intra-subject variability in the pharmacokinetics of metformin as the ——— tablet.
- To assess accumulation of metformin at steady state as the ——— tablet relative to a single dose at the lowest dose.

METHODOLOGY:

This was an open-label, multiple-dose, five-treatment, five-period study in sixteen healthy male/female subjects. The study schematic is shown below:

	Week 1 (days 1-7)	Week 2 (days 8-14)	Week 3 (days 15-21)	Week 4 (days 22-28)	Week 5 (days 29-35)
Treatment*	A	B	C	D or E	E or D
Serial sampling for Days 1, 6, 7 pharmacokinetics	Days 1, 6, 7	Days 13, 14	Days 20, 21	Days 27, 28	Days 34, 35
Predose sampling	Days 4, 5†	Days 11, 12	Days 18, 19	Days 25, 26	Days 32, 33
* Treatment A	1x500 mg ——— tablet QD				
Treatment B	2x500 mg ——— tablet QD				
Treatment C	3x500 mg ——— tablet QD				
Treatment D	4x500 mg ——— tablet QD				
Treatment E	2x500 mg Glucophage® tablet BID				

Treatments A, B, C and D were administered once daily at 7:30 PM, 5 minutes after completing a 7:00 PM dinner. Treatment E was administered BID at 7:30 PM following dinner and at 7:30 AM after breakfast. During weeks 1, 2 and 3, all subjects received treatments A, B and C, respectively. During week 4, 8 subjects received treatment D while the remaining 8 received treatment E. During week 5, each subject received the alternate treatment. Serial blood samples were collected on two consecutive days at steady state on each treatment. In addition, single dose pharmacokinetics were assessed on day 1. Plasma metformin concentrations were determined by ——— assay and metformin pharmacokinetic parameters were calculated by noncompartmental analysis.

Final Study Report: CV138-028

Report No. 910072014

October 23, 1998

NUMBER OF SUBJECTS:

A total of 16 subjects were enrolled and 14 completed all periods of the study. Two subjects dropped out due to personal reasons.

MAIN CRITERIA FOR INCLUSION:

Healthy young men and women between 18 and 40 years of age, within $\pm 15\%$ of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Metformin hydrochloride — tablets 500 mg (Batch No. M97057, Formulation code 207150-V500-014) were supplied by Bristol-Myers Squibb.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

The reference Glucophage® tablets 500 mg (Batch No. A8J097A) were provided by the investigator.

DURATION OF TREATMENT: Five treatments were administered with each treatment administered for one week. There was no washout between treatments. Total duration of study was 37 days.

CRITERIA FOR EVALUATION:

Serial plasma samples for pharmacokinetic analysis were collected for 24 hours after drug administration on days 1, 6, 7, 13, 14, 20, 21, 27, 28, 34 and 35. In addition predose samples were collected on days 4, 5, 11, 12, 18, 19, 25, 26, 32 and 33. CMAX, TMAX, AUC and T-HALF of metformin for — tablets given once daily and for 1000 mg Glucophage® tablets given BID were calculated. Safety was assessed by monitoring vital signs, ECGs and clinical laboratory tests.

STATISTICAL METHODS:

Sample Size:

Since no formal statistical tests were proposed for this study, the sample size was not based on statistical power. The sample size of 16 subjects (8 per sequence) was to provide 90% confidence intervals for the difference between the 2000 mg — formulation QD and 1000 mg Glucophage® tablets BID of ± 0.087 for log(CMAX) and ± 0.12 for log(AUC(TAU)).

Statistical Methods:

Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term. The distributions of the pharmacokinetic variables were summarized by treatment. An analysis of variance appropriate for a 2-period, 2-treatment crossover design was performed to compare 2000 mg — tablets QD and 1000 mg Glucophage® tablets BID for CMAX, AUC(TAU) and T-HALF. Prior to analysis, CMAX and AUC were log transformed. TMAX was analyzed by a nonparametric procedure. To assess dose proportionality, plots of CMAX, AUC(TAU) and T-HALF by day after dosing were provided. To estimate within subject variability for CMAX and AUC(TAU), an analysis of variance was done with time(day) of dosing as a factor and blocked by subjects.

Analysis:

All available data from all subjects who received study medication were included in the analysis of safety and pharmacokinetic data.

October 23, 1998

PHARMACOKINETIC RESULTS:

The pharmacokinetic results were determined using a validated noncompartmental analysis protocol. Mean (SD) pharmacokinetic parameters are summarized by treatment in the following table:

Treatment	N	C _{max} (ng/ml)	T _{max} ^a (hr)	AUC (ng hr/ml) ^a
500 mg — single dose	16	643(115)	7	6666(1751)
500 mg QD	16	603(166)	6	6316(1596)
1000 mg QD	16	1060(259)	7	12587(3164)
1500 mg QD	15	1441(362)	7	16820(4160)
2000 mg QD	14	1780(288)	7	20431(4114)
1000 mg BID Glucophage®	15	1521(234)	31	20344(4443)

^a Median (range)

^a AUC(INF) for 500 mg single dose; all others AUC(0-24).

C_{MAX} and T_{MAX} for the Glucophage® treatment are from the PM dose.

For doses of the — tablet in the ratio of 1:2:3:4, the means for C_{MAX} were in the ratio of 1:1.8:2.4:3.0, and the means for AUC(TAU) increased in the ratio of 1:2.0:2.7:3.2, implying that both C_{MAX} and AUC(TAU) showed a less than dose proportional increase. The results of the ANOVA comparing 2000 mg — tablets QD to 1000 mg Glucophage® tablets BID are presented in the table below.

Parameter	Adjusted geometric means		Ratio of geometric means	
	2000 mg QD	1000 mg Glucophage® BID	Point estimate	90% CI
C _{MAX} (ng/ml)	1763	1297	1.36	(1.29, 1.44)
AUC(TAU) (ng hr/ml)	19986	20053	1.00	(0.93, 1.07)

As seen from the table above, it is clear that the bioavailability of metformin at the 2000 mg QD dose was 100% relative to the same total daily dose of metformin administered as 1000 mg BID Glucophage®. In addition, the relative C_{MAX} from the — tablet was 36% higher than that at the same daily dose of Glucophage®. It is important to note that the C_{MAX} values for the Glucophage® regimen were from the PM dose and that the C_{MAX} values after the AM dose of Glucophage® were consistently higher than the PM dose thus making the difference in C_{MAX} values for the two formulations at the same total daily dose even smaller.

The median T_{MAX} for the 2000 mg — tablets QD was 7 hours and was significantly greater than the median for 1000 mg Glucophage® tablets BID (3 hours). Estimates of within-subject variability for C_{MAX} and AUC(TAU) were in the range of — (coefficients of variation 9.1% to 19.7%) for the — tablet at doses ranging from 500 mg QD to 2000 mg QD and were in the range of — (coefficients of variation 8.5% to 19.2%) for Glucophage® BID.

SAFETY AND TOLERABILITY RESULTS:

There were no serious or severe adverse events (AEs). All AEs were mild or moderate. A total of 137 AEs were reported in this study. There were 22, 30, 27, 27 and 31 AEs reported for 500 mg QD — 1000 mg QD — 1500 mg QD — 2000 mg QD — and 1000 Glucophage® BID treatments. The most frequently reported AEs were gastrointestinal disorders such as abdominal pain, diarrhea, nausea/vomiting and flatulence. Headache was another common adverse event. The number of total AEs reported did not appear to be related to the dose of metformin administered as the — tablet and the frequency of their occurrences was similar between the — tablet and Glucophage® tablet.

October 23, 1998

No clinically relevant abnormalities were found in the vital signs and ECG recordings during or post treatment. There were 10 marked abnormalities (MAs) found in the laboratory test results. There were five MAs in hematology and these included low hematocrit, low hemoglobin, low erythrocytes and high lymphocytes. The other five MAs were in serum chemistry and were associated with elevated total bilirubin and blood urea nitrogen. None of the MAs were considered to be clinically significant by the investigator and were not reported as AEs.

CONCLUSIONS:

- The — tablet was well tolerated at doses up to 2000 mg QD for 7 days.
- No significant accumulation was observed in the metformin exposure at steady state when dosed as the — tablet.
- Absorption of metformin from the — tablet was slower compared to that from Glucophage® with peak concentrations from the — tablet occurring 3 hr later.
- The — tablet as a 2000 mg single dose exhibited an equivalent extent of absorption of metformin as the immediate release Glucophage® tablet administered BID at the same total daily dose.
- Administering the daily dose as a single dose of the — tablet versus the BID administration of Glucophage® increased the peak plasma concentrations only by 36%.
- Within-subject variability in C_{MAX} and AUC of metformin from the — tablet was comparable to that with conventional Glucophage®.
- The significantly altered plasma concentration profile along with a low within-subject variability in C_{MAX} and AUC make the — tablet suitable for evaluation as a once-a-day dosing regimen.

DATE OF REPORT: October 23, 1998.

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METFORMIN



Indication: Type 2 Diabetes

Protocol No.: CV138-031

Phase: I

Study Initiation Date: November 2, 1998

Study Completion Date: November 18, 1998

Report Date: June 10, 1999

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**EVALUATION OF THE EFFECT OF FOOD ON THE PHARMACOKINETICS
OF METFORMIN TABLET**

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BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: Evaluation of the effect of food on the pharmacokinetics of metformin — tablet

INVESTIGATOR: _____

STUDY CENTER: _____

PUBLICATIONS: None

STUDY PERIOD: November 2, 1998 to November 18, 1998

CLINICAL PHASE: I

OBJECTIVES:

The objective of this study was to determine the effect of a high fat and low fat dinner on the pharmacokinetics of the — tablet form of metformin relative to the fasted condition

METHODOLOGY:

This was an open-label, randomized, single-dose, three-treatment, crossover study in 18 healthy men/women. Subjects who fulfilled the inclusion and exclusion criteria were admitted to the clinic and randomized to one of 6 sequences. The three treatments were:

Treatment 1	4x 500 mg metformin	—	tablet 5 min after a 6.5 h fast
Treatment 2	4x 500 mg metformin	—	tablet 5 min after a high fat dinner
Treatment 3	4x 500 mg metformin	—	tablet 5 min after a low fat dinner

All treatments were administered at around 6:30 PM. ~~Serial plasma samples were obtained for 36 hours following dosing and were analyzed for metformin using ————— method.~~

NUMBER OF SUBJECTS:

A total of 18 subjects were enrolled and 17 completed the study. One subject withdrew due to personal reasons.

MAIN CRITERIA FOR INCLUSION:

Healthy young men and women between 18 and 40 years of age, within $\pm 15\%$ of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Metformin HCl — tablets containing 500 mg metformin HCl (Lot # 8MDN203) were supplied by Bristol-Myers Squibb. The total dose was 2000 mg metformin (4 tablets) administered orally in each of the three treatments.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Not applicable.

DURATION OF TREATMENT: Three single doses were administered, with at least one week washout between doses.

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June 10, 1999

CRITERIA FOR EVALUATION:

Serial plasma samples for pharmacokinetic analysis were collected for 36 hours after each dose. CMAX, TMAX and AUC of metformin were compared between the three treatments. Safety was assessed by monitoring vital signs, ECGs and clinical laboratory tests.

STATISTICAL METHODS:

Sample Size:

The sample size of 18 subjects was to provide at least 90% power with respect to both CMAX and AUC(INF) to conclude an absence of food effect on metformin after a 0.5 h fast, a high fat dinner and a low fat dinner when there is no effect. These calculations were based on the assumptions that CMAX and AUC(INF) are log normally distributed and the within-subject coefficients of variation are similar to 15% for CMAX and 12% for AUC(INF).

Statistical Methods:

An analysis of variance model appropriate for a three-by-three crossover design was used for CMAX and AUC(INF). The factors in the analysis were sequence, subject(sequence), period, treatment and crossover. A second analysis of variance model was done with crossover deleted from the analysis. A priori, CMAX and AUC(INF) were log transformed and the resulting point and interval estimates of means and mean differences were exponentiated to express the results as geometric means and ratios of geometric means on the original scale of measurement. An absence of food effect was concluded when the 90% confidence interval for the ratio of means fell within ———— for AUC(INF) and within ———— for CMAX. The presence of a food effect was concluded when the 90% confidence interval for the ratio of means fell completely outside ———— for AUC(INF) and ———— for CMAX. When neither absence of a food effect nor the presence of a food effect was concluded, the food effect was indeterminate. No analysis other than descriptive statistics was done on TMAX and TMIN.

Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term.

Analysis:

All available data from all subjects who received study medication were included in the analysis of safety data. Subjects 14 discontinued the study after period 1 and data from this subject were not included in the pharmacokinetic analysis.

PHARMACOKINETIC RESULTS:

The pharmacokinetic results were determined using a validated noncompartmental analysis protocol. Mean (SD) metformin pharmacokinetic parameters along with the results of statistical analysis on CMAX and AUC are summarized in the following tables:

	Mean (SD)	Adjusted Geometric Mean	Ratio of Geometric Means*	
			Point Estimate	90% Confidence Interval
CMAX (ng/mL)				
Fasted	1648(357)	1609		
High Fat Dinner	1580(400)	1529	0.95	(0.89, 1.02)
Low Fat Dinner	1864(383)	1824	1.13	(1.06, 1.22)
AUC(INF) (ng.h/mL)				
Fasted	14793(5715)	13835		
High Fat Dinner	21148(5913)	20234	1.46	(1.30, 1.65)
Low Fat Dinner	21077(4327)	20744	1.50	(1.33, 1.69)

* Relative to fasted treatment based on adjusted means derived from ANOVA.

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Final Study Report: CV138-031

Report No. 910074244

June 10, 1999

The median metformin TMAX was 4 h for all three treatments. Both a high fat dinner and a low fat dinner increased the AUC(INF) of metformin from the ——— tablet relative to the fasted treatment. There was no effect on CMAX. There was no significant difference in pharmacokinetic parameters between the high fat and low fat dinner treatments.

SAFETY AND TOLERABILITY RESULTS:

There were no serious or severe adverse events (AEs). All AEs were mild or moderate. A total of 34 treatment emergent AEs were reported in this study. The most frequently reported AEs were diarrhea, dyspepsia, nausea, dizziness, abdominal pain, flatulence and musculoskeletal pain. The number of total AEs reported was similar between the high fat meal, low fat meal and fasted treatments. No clinically relevant abnormalities were found in the vital signs and ECG recordings during or post treatment. There were 5 marked abnormalities in the laboratory tests observed at discharge. These included one subject with elevated ALT, AST, creatine kinase and blood urea nitrogen and another with elevated creatinine. The elevated ALT, AST and creatine kinase values were considered clinically significant and were reported as AEs by the investigator. The subject was followed until the AST, ALT, creatine kinase and blood urea nitrogen returned to values within normal range.

CONCLUSIONS:

AUC(INF) of metformin from the ——— tablet was significantly increased after a high fat dinner and a low fat dinner.

DATE OF REPORT: June 10, 1999.

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METFORMIN

Indication:

Protocol No.: CV138-035

Phase: I

Study Initiation Date: 04-April-1998

Study Completion Date: 01-June-1998

Report Date: 21-June-1999

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PHARMACEUTICAL RESEARCH INSTITUTE

THE PHARMACOKINETICS AND PHARMACODYNAMICS OF THE
CONTROLLED RELEASE VERSUS IMMEDIATE RELEASE METFORMIN
TABLETS IN TYPE 2 DIABETICS

CONTRIBUTORS

MEDICAL MONITOR: _____ M.D.

CLINICAL SCIENTIST: _____ B.S.

CLINICAL SCIENTIST: _____ B.S., MBA

BIostatistician: _____ Ph.D

PHARMACOKINETICIST: _____ Ph.D

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**BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
FINAL REPORT SYNOPSIS**

TITLE OF STUDY: The Pharmacokinetics and Pharmacodynamics of the — Controlled Release Versus Immediate Release Metformin Tablets in Type 2 Diabetics

INVESTIGATORS: _____

STUDY CENTERS: _____

STUDY PERIOD: Sept 1997 to May 1998

CLINICAL PHASE: I

OBJECTIVES: Primary: To assess differences between treatments in the mean change from baseline of the glucose AUC(0—24). Glucose AUC(0—24) is the 24 hour area under the serum glucose concentration-time curve measured during the 24 hour period beginning at 1.0 hr post-dinner dose on Day 14 of each period.

Secondary: Pharmacodynamics:

- To assess differences between treatments (five separate groups of type 2 diabetics treated with either metformin as immediate release or various regimens of — tablets) in the change from baseline of mean serum glucose. Mean serum glucose is the average of the pre-breakfast, 2 hour post-breakfast, pre-lunch, 2 hour post-lunch, pre-dinner, 2 hour post-dinner, 10:30 PM, and 2:30 AM serum glucose measurements beginning at 1.0 hr post-dinner dose on Day 14 of each period.
- To assess differences between treatments in the change in pre-dinner (e.g. 1730 hour) serum glucose from Period B-Day 1 to Period B-Day 15.
- To obtain pilot data assessing the effect of different regimens of the — metformin tablet on fructosamine, fasting serum glucose, glycated serum albumin, free fatty acids (FFA), lipoproteins, and triglycerides.

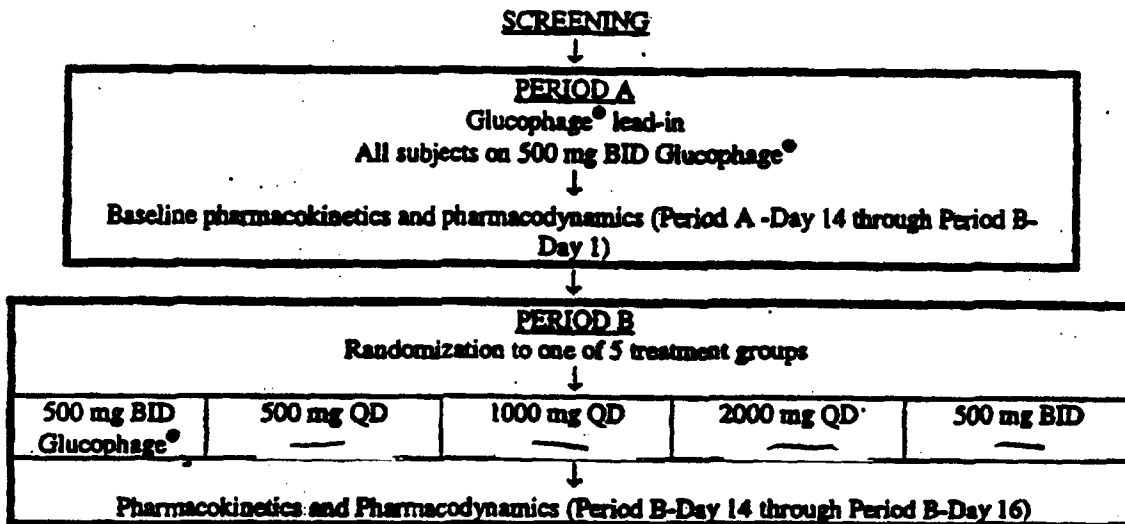
Pharmacokinetics:

- Assess dose proportionality and pharmacokinetic parameters of the metformin — tablet in diabetics.

METHODOLOGY: An open-label, randomized, parallel group, multiple oral dose design was used in this study. A total of 50 type 2 diabetics, aged 30-70 years, whose diabetes was inadequately controlled by either diet or diet plus an antihyperglycemic agent (excluding thiazolidinediones), with a HbA1c in the range of 6%-10%, and a fasting blood glucose (FBG) < 240 mg/dL, were to be enrolled in this study.

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Subjects reported to the Investigator's clinic within 14 days prior to enrollment for a medical history, 12-lead ECG, physical exam, and initial screening clinical labs. Subjects who met the screening criteria and were not currently receiving drug therapy for diabetes were enrolled in Period A of the study. Subjects who met the screening criteria and were currently receiving antihyperglycemic agents were first required to go through a 3-7 day washout period.



Period A:

On Day 1 subjects received in the clinic 500 mg Glucophage® along with a standardized American Diabetes Association (ADA) breakfast, and were discharged. They received 500 mg BID Glucophage® along with standardized ADA meals on an out-patient basis for 13 days (Period A-Days 1-13).

Subjects visited the clinic on Period A-Days 10 and 12 for fasted clinical laboratory tests.

Subjects returned to the clinic on Period A-Day 13, and they received their Period A-Day 13 evening and Period A-Day 14 doses of 500 mg BID Glucophage® while in the clinic. Subjects were maintained on an individually standardized ADA diet, with breakfast, lunch, and dinner meals served at 0700, 1200, and 1800 h. Fasted labs were drawn prior to the breakfast dose on Day 14 for baseline (post-Glucophage® lead-in) fructosamine, glycated serum albumin, FFA, lipoproteins [Lp(a)], and triglycerides. Subjects received 500 mg Glucophage® along with their Period A-Day 14 dinner, and serial blood samples were collected at 0 h (pre-dose) and for the next 24 h for determination of metformin pharmacokinetics. Baseline serum glucose pharmacodynamic measurements were collected prior to the dinner meal, and for the next 25 h. The first day of Period B began immediately following Period A-Day 14.

Period B:

At the time of the Period B-Day 1 dinner dose and the 25 h glucose sample, subjects were randomized to receive either 500 mg BID Glucophage®, 500 mg QD —, 1000 mg QD —, 2000 mg QD —, or 500 mg BID — in open-label fashion, along with standardized ADA meals. Following the Period B-Day 1 dinner dose, patients were counseled regarding pill compliance and were discharged from the clinic.

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Subjects visited the clinic on Days 5 and 9 for fasted clinical laboratory tests.

Subjects were readmitted to the clinic on Period B-Day 13. Fasted labs were drawn on Day 14 for fructosamine, glycated serum albumin, free fatty acids (FFA), lipoprotein (a) [Lp(a)], and triglycerides. Subjects received randomized study treatment along with their Period B-Day 14 dinner, and serial blood samples were collected at 0 (predose) and for the next 48 h for determination of metformin pharmacokinetics. Serum glucose (SG) was collected prior to the dinner meal, and for the next 48 h for pharmacodynamic determination. On the evening of Period B-Day 16, subjects were discharged from the clinic if no additional follow up was required.

Throughout Periods A and B of this study subjects were maintained on an individually standardized ADA diet. While in the clinic, breakfast, lunch, and dinner meals were served at 0700, 1200, and 1800 h. The daily caloric intake for all subjects was composed of 55% carbohydrate, 20% protein and 25% fat, and was normalized by subject body weight to contain approximately 25-30 Kcal/kg.

NUMBER OF SUBJECTS: A total of 53 subjects were enrolled into this study and 34 subjects completed the entire study. Nineteen (19) subjects (including both randomized and non-randomized subjects) discontinued; 3 discontinued due to adverse events; 4 due to patient request; and 4 due to other personal reasons. Seven subjects discontinued due to inadequate glycemic control; their serum glucose measurements were > 240 mg/dL on study Days A10, A12, B5, or B9.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects met the following criteria for inclusion in the study: signed study specific informed consent prior to study enrollment; established diagnosis of Type 2 diabetes mellitus; treatment with diet or diet plus oral diabetes medication (excluding thiazolidinediones); HbA_{1c} in the range of 6%-10%; fasting serum glucose < 240 mg/dL; 30 to 70 years of age; body mass index less than 40 kg/m²; and otherwise no clinically significant deviation from a "normal" classification in medical history, physical exam, ECG, and clinical laboratory tests performed at screening.

One subject was improperly enrolled with a history of major gastrointestinal surgery, and this subject's pharmacokinetic and pharmacodynamic data were omitted from analysis. He was included in the safety analysis.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Glucophage[®] (500 mg) marketed product was provided by the Investigator. — metformin tablets (500 mg) were provided by BMS. Glucophage[®] lot number for Site 001 was B8J216A. Glucophage[®] lot numbers for site 002 were B8J228A and B8J192A. The lot number for the — metformin tablets for both sites 001 and 002 was CMBN119.

DURATION OF TREATMENT: During Period A all subjects received 500 mg BID Glucophage[®] along with a standard ADA diet for 14 days. Those subjects permitted were randomized to receive one of five treatments for 14 days during Period B: 500 mg Glucophage[®] tablets BID, 500 mg — metformin tablets QD, 2x500 mg — metformin tablets QD, 4x500 mg — metformin tablets QD, and 500 mg — metformin tablets BID. There was no washout period in between treatments. The total duration of the study was 30 days.

CRITERIA FOR EVALUATION:

Efficacy: Not applicable.

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Safety: Monitoring for the occurrence of AEs, physical examinations, vital signs, ECGs and clinical laboratory tests.

Pharmacokinetics: Parameters evaluated for metformin included CMAX, AUC (TAU), TMAX and T-HALF.

Pharmacodynamics: Serum glucose measurements were made at predetermined times after the Day 14 PM dose for both Periods A and B. Based on these, a serum glucose AUC was calculated. The mean of the following eight serum glucose measurements was calculated; 10:30 PM, 2:30 AM, pre-breakfast (fasting), 2-hours post-breakfast, pre-lunch, 2-hours post-lunch, pre-dinner, and 2-hours post-dinner. In addition, fructosamine, glycated serum albumin, nonesterified fatty acids, lipoprotein (a) [Lp(a)], and triglycerides were obtained.

STATISTICAL METHODS:

Sample Size: Since no formal statistical tests were proposed for this study, the sample size was not based on statistical power. The proposed sample size, after allowance for dropouts, of 8 subjects per group would result in confidence intervals for a difference in group change in glucose AUC(0-24) means of ± 3.25 mg/dLoh. Assuming a 20% dropout rate, a total sample size of 50 was proposed for this study.

Statistical Methods and Analysis: Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term. The distributions of the pharmacokinetic variables were summarized by treatment.

Data listings are presented and summary statistics are tabulated for the pharmacokinetic variables by treatment, Period A or B and Time of Day (AM or PM). To obtain single values for 500 mg Glucophage[®] tablets BID and 500 mg metformin tablets BID, the AM and PM AUC(TAU)s were added. For CMAX, TMAX and T-HALF, the PM dose was used. Summary statistics were tabulated by treatment and Period A or B. No further analysis was done on T-HALF.

A one-way analysis of covariance model was used for Period B CMAX and AUC(TAU) using the Period A values as the covariate. A priori, the variables CMAX and AUC(TAU) were log transformed and the resulting point and interval estimates of means were exponentiated to express the results as adjusted geometric means on the original scale of measurement. To assess pairwise differences among treatment groups, 90% confidence intervals of the ratios of CMAX and AUC(TAU) adjusted geometric means were obtained. For TMAX, a one-way analysis of variance was done on the Period B rank transformed data. No adjustment was made for multiplicity.

Pharmacodynamic variables and their change from Period A baseline were summarized for each treatment. A one-way analysis of variance was used for the change from Period A to Period B. To assess pairwise treatment differences, 90% confidence intervals were obtained. No adjustment was made for multiplicity.

PHARMACOKINETIC RESULTS:

The pharmacokinetic results were determined using a validated noncompartmental analysis protocol. Arithmetic Mean (standard deviation) pharmacokinetic parameters are summarized by treatment in the following table:

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Treatment	N	C _{MAX} (ng/ml)	T _{MAX} * (h)	AUC(TAU) (ng.h/ml)	T-HALF (h)
500 mg BID Glucophage®	7	1048 (191)	3.0 —	17396 (3998)	4.4 (0.9)
500 mg QD —	7	789 (222)	8.0 —	8828 (2630)	10.6 (6.3)
1000 mg QD —	7	1261 (158)	6.0 —	14488 (1916)	13.2 (8.8)
2000 mg QD —	5	2251 (358)	8.0 —	26667 (5140)	15.6 (5.2)
500 mg BID —	7	790 (215)	8.0 —	13755 (3608)	6.8 (3.4)

* Median (range).

C_{MAX}, T_{MAX} and T-HALF values for the BID treatments are from the PM dose.

For QD doses (500, 1000, 2000 mg) of the — tablet in a ratio of 1 : 2 : 4, the geometric means for C_{MAX} increased in the ratio of 1 : 1.7 : 2.9 and geometric means for AUC(TAU) increased in a ratio of 1 : 1.8 : 3.0.

The geometric mean C_{MAX} for the 1000 mg QD — was 25% greater than the 500 mg BID Glucophage®. The geometric mean AUC(TAU) for the 1000 mg QD — was 87% of that for 500 mg BID Glucophage®.

PHARMACODYNAMIC RESULTS:

Mean values for glucose AUC increased with all regimens in Period B. Based on the confidence intervals of the differences:

The adjusted change in mean glucose AUC(0-24) for 500 mg — metformin tablets QD was significantly greater than that for 500 mg Glucophage® tablets BID, and 2000 mg — metformin tablets QD.

Pre-breakfast glucose increased for the 500 mg — metformin tablets QD group relative to the 1000 mg and 2000 mg — metformin tablets QD groups.

No statistically significant differences in pre-dinner glucose means among the five treatments were found (p=0.52).

Fructosamine increased for the 500 mg — metformin tablets QD group relative to the 1000 mg and 2000 mg — metformin tablets QD groups.

The adjusted mean change in glycated albumin for 500 mg Glucophage® tablets BID, 500 mg — metformin tablets QD and 500 mg — metformin tablets BID were all significantly greater than that for 1000 mg — metformin tablets QD and 2000 mg — metformin tablets QD.

The adjusted mean change in triglycerides for 500 mg Glucophage® tablets BID and 1000 mg — metformin tablets QD were significantly greater than that for 2000 mg — metformin tablets QD.

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No statistically significant differences in mean change of nonesterified fatty acids was found among the five treatments ($p=0.48$).

No statistically significant differences in mean change of [Lp(a)] was found among the five treatments ($p=0.46$).

Pharmacodynamic results are summarized by Period B treatment in the following table. The mean (and 90% confidence interval) changes from Glucophage® Lead-in baseline values are presented below:

Pharmacodynamic Parameter	*Adjusted Mean Change from Glucophage® Baseline, By Treatment (90% CI)				
	500mg B'D Glucophage®	500mg QD	1000mg QD	2000mg QD	500mg BID
Glucose AUC(0-24) (mg·h/dL)	215 (-41, 471)	755 (499, 1011)	503 (247, 759)	119 (-184, 422)	463 (207, 719)
Mean Glucose (mg/dL)	9.68 (-1.97, 21.3)	30.7 (19.0, 42.3)	21.5 (9.89, 33.2)	4.05 (-9.73, 17.8)	14.0 (2.31, 25.6)
Pre-Breakfast Glucose (mg/dL)	3.86 (-11.0, 18.7)	13.0 (-3.02, 29.0)	-5.14 (-20.0, 9.7)	-7.00 (-24.5, 10.6)	11.7 (-4.36, 27.7)
Pre-dinner Glucose (mg/dL)	6.67 (-19.3, 32.6)	38.6 (14.6, 62.6)	13.9 (-10.1, 37.9)	11.0 (-17.4, 39.4)	6.50 (-19.4, 32.4)
Fructosamine (μmole/L)	3.25 (-6.38, 12.9)	11.6 (1.28, 21.9)	-5.14 (-15.4, 5.15)	-9.60 (-21.8, 2.58)	4.14 (-6.15, 14.4)
Nonesterified free fatty acids (nmol/L)	-0.01 (-0.16, 0.14)	-0.13 (-0.28, 0.03)	-0.19 (-0.35, -0.04)	0.04 (-0.15, 0.22)	-0.05 (-0.20, 0.11)
Glycated albumin (%)	0.15 (0.03, 0.27)	0.10 (-0.03, 0.23)	-0.20 (-0.33, -0.08)	-0.16 (-0.31, -0.01)	0.11 (-0.01, 0.24)
Lipoprotein (a) (mg/dL)	0.53 (-1.68, 2.73)	-2.28 (-4.82, 0.26)	-2.13 (-4.48, 0.22)	0.62 (-2.16, 3.40)	-0.56 (-2.91, 1.80)
Triglycerides (mg/dL)	26.3 (-11.3, 63.8)	-6.50 (-49.9, 36.9)	23.6 (-16.6, 63.7)	-42.8 (-90.3, 4.73)	17.6 (-22.6, 57.7)

*Adjusted mean change from Glucophage® Lead-in Baseline = End of Period B value - End of Period A value

CI = Confidence Interval

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EFFICACY RESULTS: Not applicable.

SAFETY RESULTS: There were no deaths in this study. There was one serious adverse event (SAE) which was of severe grade but unrelated to the study drugs. This subject had a cerebrovascular accident and received thrombolytic therapy. Three other Adverse Events lead to the discontinuation of three subjects. The Investigators considered all of these events to be of mild intensity. Of the five gastrointestinal AEs reported after randomization, two occurred in the Glucophage® treatment group in 1 out of 7 subjects (14%), while three occurred in the metformin — groups in 3 out of 29 subjects (10%). The only subject to develop diarrhea after randomization was in the Glucophage® treatment group.

CONCLUSIONS:

- Increases in metformin exposures from the — tablet were slightly less than proportional to increases in doses from 500mg to 2000mg QD.
- The TMAX from the — metformin tablet was delayed by 3-5 hours relative to TMAX from Glucophage®.
- Compared to Glucophage® 500mg BID, the metformin — tablet at 1000mg QD resulted in:
 - a) nonsignificant increases in Glucose AUC, predinner glucose, and mean glucose.
 - b) nonsignificant decreases in fasting glucose, fructosamine, triglycerides and free fatty acids.
 - c) significant decreases in glycated albumin.
- Dose related changes in mean glucose AUC, fasting glucose, and fructosamine were seen with the metformin — tablet administered at 500 – 2000mg QD.
- The metformin — tablet was well tolerated.

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