Medical Officer Safety Review of an Original NDA Submission

NDA 20-357
Metformin

rev 2.1

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1. INTRODUCTION:

NIDDM (non-insulin dependent diabetes mellitus) accounts for 90-95% of the total number of patients with diabetes mellitus [1]. It is certainly less homogeneous than IDDM (insulin-dependent diabetes mellitus) although the majority (70%) of patients who comprise NIDDM manifest obesity as some basis of their pathophysiology. The evidence for this is: (1) not only are they obese at diagnosis[2], but (2) their disease dissipates with weight loss significant to the order of 5.00 to 10.00 kg/m^2 of Body Mass Index (BMI)[3]; [4,5,6,7] and (3) it is more difficult for obese NIDDM patients to lose weight than their obese non-diabetic counterparts[8]. Nutritional status is therefore a key pathogenic component of a majority of patients with NIDDM. Nevertheless, insufficient insulin secretion to overcome hepatic [and peripheral] insulin resistance seems to be the common pathophysiologic thread weaving its way throughout disorders c urrently classified as NIDDM[9].

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1 Harris MI, in National Diabetes Data Group, eds. Diabetes in America:diabetes data compiled in 1984. Bethesda, .:National Institutes of Health, Chapter VI, 1985: publication no. 85-1468

2Everhart J, Knowler WC, and Bennett PH, in National Diabetes Data Group, eds. Diabetes in America: Chapter IV, loc.cit.

3 Bistrian BR, Blackburn GL, Flatt JP, Sizer J, Scrimshaw NS, and Sherman M, *Diabetes* **25**:494, 1976

4Genuth SL, *Am. J. Clin. Nutr* **32**:2579, 1979

5 Hughes TA, Gwynne JT, Switzer BR, Herbst C, and White G, *Am J Med* **77**:7, 1984

6 Hadden DR, Montgomery DAD, Skelley RJ, Tremble RR, Weaver SA, Wilson FA, and Buchanan KD, *Br Med J* **3**:276, 1975

7 Bogardus C, Ravusin E, Robbins DC, Wolfe RR, Horton ES, and Sims EAH, *Diabetes* **33**:311, 1984

8 Henry RR, Wiest-Kent TA, Scheaffer L, Kolterman OG, and Olefsky JM, *Diabetes* **35**:155,1986

9Haffner SM, Stern MP, Hazuda HP, Mitchell BD, and Patterson JK, *NEJM* **319**:1297, 1988

Since the genetic/concordance data are much stronger for NIDDM, than for IDDM [10,11], investigators are feverously searching for the molecular basis of the defect [or defects] in NIDDM. Obesity itself, though, has also been shown to have a very strong genetic predisposition,[12,13] Given the above data relating obesity to NIDDM, perhaps a significant genetic link which has been observed in nondiabetic offspring of NIDDM patients might associate more closely with obesity [which in turn correlates with hyperinsulinemia] than with glycemia, per se (Haffner et al, Table 1, loc.cit[9]).

What might make a particular obese individual predisposed to NIDDM? In addition, is it possible that the route to NIDDM could represent a normal physiologic escape from what otherwise might develop into the pathophysiologic state of "morbid obesity?" Are there any lines of evidence which might lend support to such a hypothesis? What is the nature of the relationships which exist between insulin resistance, hyperinsulinemia, and obesity? Is there a form of nutritional saturation present at the cellular [and sub-cellular] level which may be operative in these inter-relationships? If so, can this kind of pathophysiology be safely and appropriately rectified?

Watanabe[14] first noted the hypoglycemic effect of guanidines early this century. Since guanidine was quite toxic, substituted guanidines (Synthalin A and B) were synthesized around 1928 and utilized. These, too, proved very toxic. This led to the synthesis of biguanides in 1929. However, some initial investigators believed even the most active of these biguanides (N1,N1-dimethylbiguanide or metformin) to be not indicated for use as an insulin substitute in humans[15]. Phenformin (phenylethylbiguanide) was synthesized by USV in 1956, developed and then widely used until the latter 1970's when its lethal association with lactic acidosis forced its elimination from the market in most of the civilized world. Metformin, however, is still fairly widely marketed and used in the treatment of NIDDM.

Prof. Med. Günter Schäfer of the Department of Biochemistry at the Medizinische

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10Newman B, Selby JV, King MC, Slemenda C, Fabsitz R, and Friedman GD, *Diabetologia* **30**:763, 1987

11Barnett AH, Eff C, Leslie RD, and Pyke DA, *Diabetologia* **20**:87, 1981

12Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Theriault G, Dussault J, Moorjani S, Pinault A, and Fournier G, *NEJM* **322:**1477, 1990

13Stunkard AJ, Harris JR, Pedersen NL, and McClearn GE, *NEJM* **322**:1483, 1990

14 Watanabe Studies in the metabolic changes by administration of guanidine bases - I. Influence of injected guanidine hydrochloride upon blood sugar content. *J. Biol. Chem.* **33**:253-265, 1918

15Hesse E; Taubman G. *Arch. Exp. Pathol. Pharmacol. Naunyn-Schmiedberg's* **142**: 290, 1929

Hochschule in Hannover, Germany described how biguanides intercalate into all lipid membranes.[16] Pursuant to this activity, biguanides appear to (1) inhibit shuttling of reducing equivalents(Ibid.) [at pharmacologic, non-toxic levels-see **Figure 0**] and also possibly via glyceraldehyde-3-phosphate/dihydroxyacetone phosphate or malate/aspartate conversions thereby resulting in increased cytoplasmic NADH[H+]:NAD+ ratios and (2) inhibit fatty acid ß-oxidation by limiting mitochondrial expansion thereby diminishing the mitochondrial flux coefficient while inhibiting gluconeogenesis[17,18];

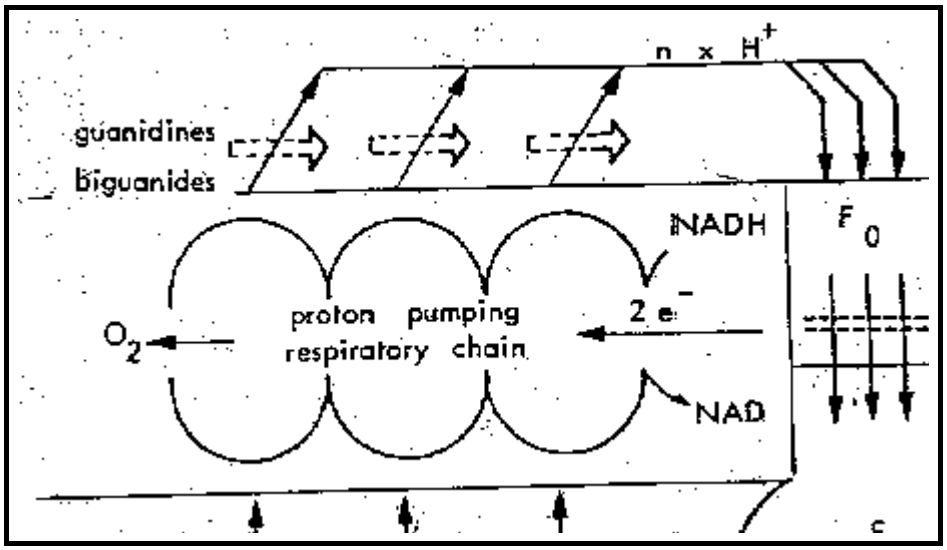


Figure 0 (from Schäfer[16], p.28)

16 Schäfer G. "Biguanides:molecular mode of action" *Research and Clinical Forums* **1**:22-32 [NDA Vol 1.99 Section 8.12.2.284]

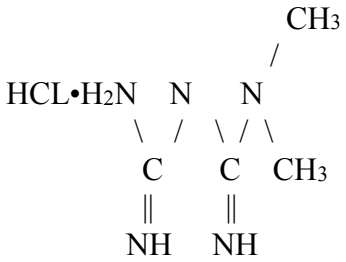
17 Muntoni S: Inhibition of fatty acid oxidation by biguanides: implications for metabolic physiopathology. *Adv Lip Res* **12**:311-377, 1974

18 Pryor HJ; Smyth JE; Quinlan PT; Halestrap AP; Evidence that the flux control coefficient of the respiratory chain is high during gluconeogenesis in hepatocytes from starved rats: implications for the hormonal control of gluconeogensis and action of hypoglycaemic agents. *Biochem J.* **247**:449-457, 1987

18[a]Owen MR; Halestrap AP; The mechanisms by which mild respiratory chain inhibitors inhibit hepatic gluconeogenesis. *Biochim Biophys Acta* **1142**:11-22, 1993

Is the toxicity profile of these biguanides a manifestation of their mechanism of action? In his review "Biguanides:molecular mode of action" [16] Prof. Schäfer also concluded:- "We have to assume that no different molecular mechanisms underlie the desirable drug effects, or their toxic effects, respectively. We may consider this point ainly as a matter of biguanide concentration in the specific tissues....Of course, the dominating toxic reaction which may lead to lactic acidosis is an inhibition of cellular respiration and of ATP production. Unfortunately, two unfavourable circumstances coincide, if respiratory inhibition causes a stimulation of glycolysis and of peripheral lactate production, while theremoval of lactate by hepatic and renal gluconeogenesis is also inhibited; lactic acidosis will be the result."

2. CHEMISTRY:



Metformin is a white to off-white crystalline compound whose molecular weight is 165.63. It is the hydrochloride salt of N,N-dimethylimidodicarbonimidic diamide. It is very hydrophilic and virtually insoluble in acetone, ether, and chloroform, but is readily dialyzable. Its pKa is 12.4 and a 1% aqueous solution of metformin hydrochloride has a pH of 6.68. (See also **Chemistry Officer Review** of Dr. Xavier Ysern.)

3. PRECLINICAL TOXICOLOGY:

3.1 Acute toxicity:-

Oral LD50 for the dog was ~375 mg/kg and for the mouse was ~2400 mg/kg. Sensitivity was greatest in rabbits and dogs and least in mice or rats. Major clinical signs were decreased activity, ataxia, and diarrhea. Convulsions were seen prior to death. In primates (monkeys) a single metformin dose of 250 mg/kg showed "no clinical signs." However, higher doses produced vomiting. The lethal dose of 693.75 mg/kg led to a "subconvulsive state" with loss of righting reflex, decreased respiration, decreased activity, and ptosis.

3.2 Multidose Toxicity:-

A 1-year study in mice showed no adverse effects up to and including the 450 mg/kg dose level. The highest dose of 1500 mg/kg showed decreased weight and some renal tubular abnormalities. According to the **Pharmacology Officer Review** of Dr. David Hertig :

> **The incidence and severity of Gp4** [1500mg/kg/day] **male and female kidney cystic tubular dilation and Gp4 male kideny tubular vacuolization showed a drug-related increase.**

A 91-week study showed no carcinogenicity but an increased mortality in males treated at the 450 and 1500 mg/kg/day levels. This death rate was ascribed to "an increase in urogenital lesions resulting from the renal toxicity." Again, according to the **Pharmacology Officer Review**:

> **Amyloid cystic nephropathy caused deaths (Gps 1-4:** 0, 150, 450, 1500mg/kg/day**) in 0, 0, 7, 11 males and 0, 0, 5, 10 females....**
>
> **Kidneys however, showed treatment related changes. Cystic nephropathy (cystic tubular dilation)...showed a dose related increase....**
> **All male treatment groups and intermediate and high dose females showed an increased incidence and severity of cystic nephropathy. A polycystic appearance (usually present at necropsy), often accompanied by a shortening of the renal papilla and dilation of the renal pelvis (hydronephrosis) was present in the more extensive cases. Cystic nephropathy was frequently associated with amyloidosis. Deaths of several were attributed to amyloid/cystic nephropathy and renal papillary necrosis.**

Other rodent studies showed only reductions in weight gain. A 99-week study in female rats showed no hormonal effects of metformin.

A 6-month study in dogs showed toxicity at 100 or 500 mg/kg/day levels with salivation, emesis, diarrhea, and CNS "effects, including convulsions." Although no clinical signs were seen at the 50 mg/kg/day dose, gross and tissue changes were noted in brain, heart, kidney, stomach, and small intestine. The high dose group manifested cerebral edema and "neuronal necrosis" questionably secondary to some form of vascular hyperplasia.

There was no apparent mutagenic or teratologic disposition uncovered. (See also **Pharmacology Officer Review** of Dr. David Hertig.)

4. PHARMACOLOGY:

4.1 ADME:-
Although the dog excretes an oral dose primarily in the urine, monkeys excrete almost equal amounts in urine and stool. Apparently absorbed drug is excreted primarily via the kidneys (79-98% of an IV dose) in all species tested. Only one metabolite has been found (N-desmethyl metformin) and that only in rabbits.

Favorable anti-atherogenic effects were seen in cholesterol-fed animals. (See also **Pharmacology Officer Review** of Dr. David Hertig.)

5. HUMAN PHARMACOKINETICS:

Although most single dose studies show a half life of ~2-4 hours, multiple dosing significantly and reproducibly increases the t½ to 5-21 hours after 6 days. This increase in half-life after multiple dosing also occurs in animals. Most of the variability appears to be a function of delayed gastrointestinal absorption.

Dose proportionality above 500mg was not observed in humans or in animals. Glybenclamide seemed to increase metformin levels especially at the lower metformin doses in the long-term clinical trials - but not in single dose PK studies.

Metformin, once absorbed, is primarily excreted. The renal clearance is in excess of 500 ml/min (greater than 4x the mean glomerular filtration rates) implying significant tubular secretion via the cationic pathway. Not unexpectedly, therefore, the similarly cationically-secreted cimetidine significantly interacts with metformin resulting in elevated metformin levels. (See also **Biopharmaceutical Officer Review** of Drs. Dan Gordin and John Hunt.)

6. EFFICACY REVIEW

6.1 DCCT
The DCCT has demonstrated that tight control of IDDM reduces microvascular complications. These microvascular complications are predominantly renal, retinal, and neurologic. Review of the DCCT data suggests that the error would be suitably small in predicting that none of these complications would arise within a range of glycohemoglobins of less than 7%[25].

Most of the morbidity and mortality (~80%) from NIDDM is macrovascular and secondary to enhanced atherosclerosis or coronary heart disease (CHD) seen in this population. **There is no data that suggests any correlation of CHD with**

glycemia.[19] The primary microvascular mortality in NIDDM, as in IDDM, derives from renal disease. It is possible, then, to assess the incidence of microvasculopathy, and, therefore also the death rate, which would accrue from a modality which would decrease the glycohemoglobin to less than 7% (see **Figure 1**).

6.2 End-Stage Renal Disease (ESRD)

6.2.1 There were 4535 cases of ESRD felt to be secondary to "diabetes mellitus" reported to the CDC from January-June 1988. Of these, 2,577 (56.8%) cases of ESRD were ascribed to non-insulin dependent diabetes mellitus (NIDDM), 1,836 (40.5%) cases to insulin dependent diabetes mellitus (IDDM), and 122 (2.7%) were unclassified. This equates to 5154 cases of ESRD per year from NIDDM, 3672 cases of ESRD per year from IDDM, and 9070 cases per year from diabetes mellitus as a whole.[20]

6.2.2 The estimated prevalence of NIDDM in the US was 14,400,000 DM cases in 1991[22,23] of which 5% - 720,000 - are felt to have IDDM and the remaining 95% or 13,680,000 felt to have NIDDM[21]. This figure is based on an estimate of 7,200,000 diabetic patients from the National Center for Health Statistics, Health Information Survey quoted by Harris.[22] As part of that study, a subset of responders were administered oral glucose tolerance tests. Only half of those patients with World Health Organization (WHO) OGTT criteria diagnostic for diabetes reported the diagnosis on the original survey. Therefore, the survey statistic was doubled.

6.2.3 Cowie[23] calculated the total yearly ESRD incidence in the general diabetic population of Michigan as 144.5 per hundred thousand (127.2 to 161.8) among blacks and 60.4 per hundred thousand (53.7 to 67.1) among whites. Additional data from Harris[21] would suggest that 70% of NIDDM patients are white, 20% black, 6% hispanic, and 4% "other." Since only 5% of DM is IDDM these ratios may approximate those in the general diabetic population. In that case the total US black diabetic population base would be 20% x

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19Lebovitz HL. The DCCT and its implications for NIDDM. *Clinical Diabetes* **12**(1):3-4, 1994

20 USRDS, "Incidence and Causes of Treated ESRD" (Chapter 3) 1993 Annual Data Report, pp 19-28

21Harris MI, Personal Communication, 3/7/94

22 Harris MI; Hadden WC; Knowler WC; Bennett PH. Prevalence of diabetesand impaired glucose tolerance and glucose levels in U.S. population aged 20-74 yr. *Diabetes* **36**:523-34, 1987

23Cowie CC; Port FK; Wolf RA; Savage PJ; Moll PP; Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *NEJM* **321**: 1074-9, 1989

14,400,000 or 2,880,000 patients. Likewise, the total US white diabetic population base would be 70% x 14,400,000 or 10,080,000 patients.

Cowie further estimated 108.2 per 100,000 black NIDDM patients (93.5 to 123.0 per 100,000 black NIDDM patients) cases of ESRD a year in black NIDDM based on the ratio observed in southeastern Michigan from 1974 through 1983. [By the 1991 NCHS-HIS statistics doubled according to Harris[22]] this should amount to 108.2 x 28.8(hundred thousand) or 3116 black NIDDM ESRD cases per year (1.082 cases per thousand black diabetics). However, this point estimate (mean) yields about a 20% under-representation of the actual reports of ESRD incidence/death rate according to the USRDS. Using the upper bound of the [Cowie] confidence interval would yield 123.3 x 28.8(hundred thousand) or 3551 black NIDDM ESRD cases per thousand black diabetics per year. This combined with the figure of 2974 derived from using the upper limits of the confidence interval for whites yields a total rate of 6525 cases per year which is more in line with actual reports particularly given the extra 10% of diabetic patients (hispanics, others) not previously accounted for. [Keep in mind that this under-representation of projected diabetic ESRD cases is even based upon the "diagnosed plus undiagnosed" population estimate ofHarris (14,400,000) and not just upon that of the "diagnosed" diabetics that resulted in Cowie's original estimates.]

6.2.4 The USRDS recorded 51,665 ESRD cases from DM from 1987 to 1990[20]. This equates to 12,916 new diabetic ESRD cases per year from DM over that 4 year period (and is 29.8% more than the 4535 cases [over 6 months in 1988 from DM] reported to the CDC, see **Section 6.2.1**). Using this larger figure to avoid underestimating the true incidence of ESRD from NIDDM, 56.8% (2° to NIDDM, see **Section 6.2.1**) of 12,916 comes out to 7336 cases of ESRD per year 2° to NIDDM.

6.2.5 **The incidence of ESRD emerging from the NIDDM population in 1991 would then be 7,336/13,680,000 or 0.53625 cases per thousand (NIDDM).**

6.2.6 The CDC suggests a [Medicare] base of 147,000 ESRD patients and USRDS[20] estimates 32.9% of those are 2° to diabetes. Based on USRDS data, the death rate from ESRD 2° to DM would appear to be 25.8% per year.[20] This, then, calculates out to 12,478 deaths per year (approximately the incidence of new cases as might be expected at steady state).[24]

6.2.7 **The death rate from ESRD 2° to NIDDM would then appear to be** 56.8% of 12,478 or 7,087 divided by a base of 13,680,000 NIDDM patients or **0.51806 cases per thousand** (NIDDM). Again, utilizing the somewhat higher i*ncidence* rate (rather than the slightly lower *mortality* rate) should avoid underestimating true

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24CDC: End-stage renal disease associated with diabetes - United States. *MMWR* **38**:546-548, 1988 [Based on data from January through June, 1988]

NIDDM ESRD mortality.

6.2.8 NDA US Data - All races

EOT	metformin	control
A1c>=7	354	294
A1c <7	212	60

Only 60 of 354 control (16.9%) patients dropped their HbA1c's to less than 7% as opposed to 212 of 566 metformin (37.5%) patients. This amounts to a drug-attributable benefit of 20.5% 99%CI(13.2 to 27.9%). Assuming that a HbA1c of less than 7% may not associate with microangiopathy[25] (See Figure 1) ,

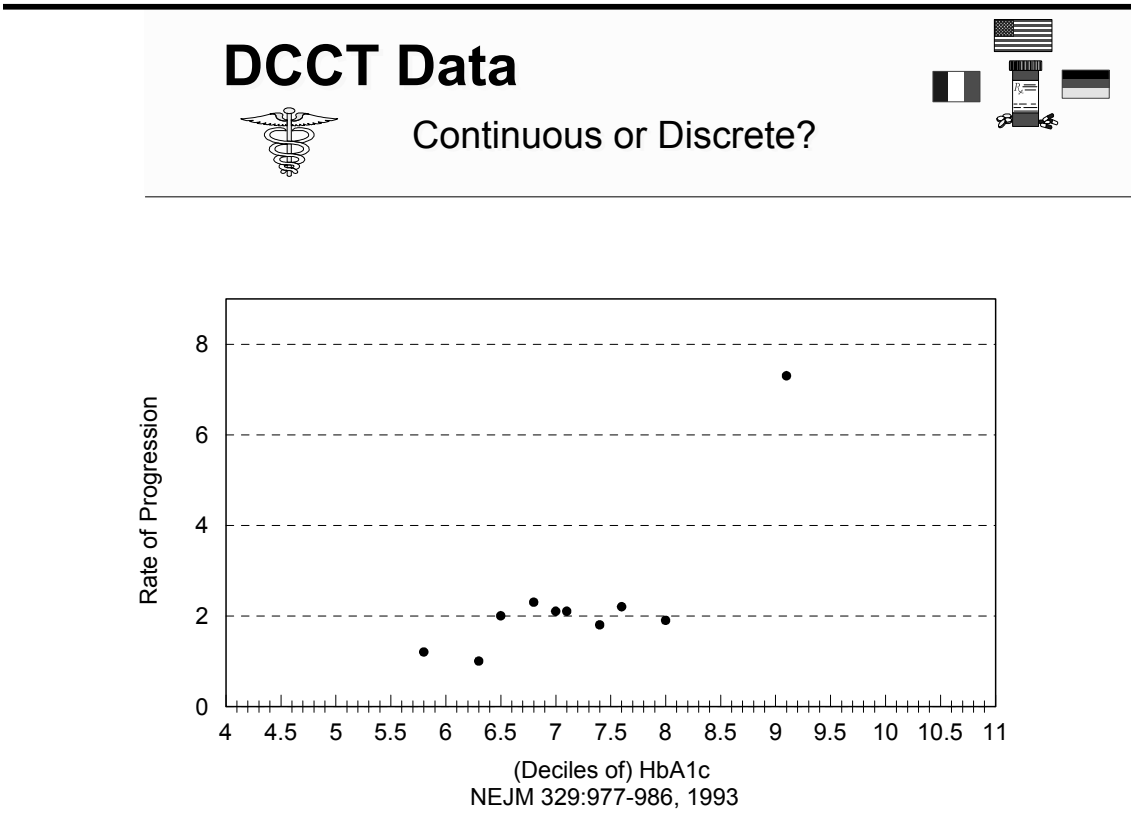


Figure 1

that 385,000 NIDDM patients will be taking metformin [as were taking phenformin in

25 DCCT Research Group, The effect of intensive treatment of diabetes onthe development and progression of long-term complications in insulin-dependent diabetes mellitus. *NEJM* **329**:977-986, 1993

1976[26]], and that one-fourth of these will be switched from insulin [for which no additional glycemic benefit of metformin is to be expected], then one can calculate that the net reduction of death or incidence of ESRD from NIDDM attributable to metformin would be 385 x 0.53625 x 20.5% x 75% or about 32 (deaths or new cases) per year. **This metformin-attributable *savings* rate is 0.08 deaths/1000 PYE.**

6.2.9 **The annual death rate from ESRD in black NIDDM should approximate the incidence rate of 1.233 cases per thousand (**see **Section 6.2.3).**

6.2.10 NDA US Data - Blacks

EOT	**metformin**	**control**
A1c>=7	**47**	**48**
A1c <7	**33**	**4**

Only 4 of 52 black control (7.7%) patients dropped their HbA1c's to less than 7% as opposed to 33 of 80 metformin (41.2%) patients. This amounts to a drug-attributable benefit of 33.6% 99%CI(16.5 to 50.7%). Assuming that a HbA1c of less than 7% may not associate with microangiopathy[25], that 385,000 black NIDDM patients will be taking metformin [reflective of the total population taking phenformin in 1976[26]], that 100% of these will be black, and that one-fourth of these will be switched from insulin [for which no additional glycemic benefit of metformin is to be expected], then one can calculate that the net reduction of death or incidence of ESRD from NIDDM attributable to metformin would be 385 ÷ 95% (to yield the respective total diabetic population in hundreds of thousands) x 1.233 (upper bound of 95% CI for ESRD incidence in black NIDDMS per hundred thousand diabetics) x 33.6% (who get a net benefit from metformin therapy) x 75% (excluding the population that was switched from insulin) -
385 ÷ 95% x 1.233 x 33.6% x 75% - or about 126 (deaths or new cases) per year if the total population taking metformin were limited to blacks. **This metformin-attributable *savings* rate is 0.33/1000 PYE**.

6.2.11 **The death rate from ESRD in white NIDDM should approximate the incidence rate of 0.295 cases per thousand (**see **Section 6.2.3)**.

26Lowenstein J, Presentation to 15 October 1981 DMEDP Advisory Committee on metformin

6.2.12 NDA US Data - Whites

EOT	**metformin**	**control**
A1c>=7	**238**	**198**
A1c <7	**147**	**52**

Only 52 of 250 white control (20.8%) patients dropped their HbA1c's to less than 7% as opposed to 147 of 385 metformin (38.2%) patients. This amounts to a drug-attributable benefit of 17.4% 99%CI(8.18 to 26.6%). Assuming that a HbA1c of less than 7% may not associate with microangiopathy[25], that 385,000 NIDDM patients will be taking metformin [as were taking phenformin in 1976[26]], that 100% of these will be white, and that one-fourth of these will be switched from insulin [for which no additional glycemic benefit of metformin is to be expected], then one can calculate that the net reduction of death or incidence of ESRD from NIDDM attributable to metformin would be 385 ÷ 95% (to yield the respective total diabetic population in hundreds of thousands) x 0.295 (upper bound of 95% CI for ESRD incidence in white NIDDMS per hundred thousand diabetics) x 17.4% (who get a net benefit from metformin therapy) x 75% (excluding the population that was switched from insulin) - 385 ÷ 95% x 0.295 x 17.4% x 75% - or about 16 (deaths or new cases) per year if the total population taking metformin were limited to whites. **This metformin-attributable *savings* rate is 0.04/1000 PYE.**

6.2.13 At first glance, then it would appear that by limiting the population at inference to just blacks the increase in lives saved could be almost fourfold. Treating homogeneous black populations saves more than eightfold the lives gained by treating homogeneous white populations.

Remember that this also assumes that all patients - diagnosed and undiagnosed - would be treated. If one treated only the diagnosed, as seems likely, the savings estimate is proportionately lowered.

6.2.14 ***NB***: A significant treatment-by-baseline interaction elucidated by the sponsor has demonstrated more glycohemoglobin reduction the worse the baseline glycemic control. The number of black patients randomized to metformin in these studies was relatively small - 80 (15%) - and the baseline for these patients was quite significantly higher (9.65 ± 1.75%) than that of the 385 white patients (8.54 ± 1.59) exposed to metformin (mean racial difference of 1.11 ± 0.199% SED with a 99%CI around that difference of 0.596 to 1.62%).

==> **In summary, therefore, the difference attributed to race may actually reflect a difference in baseline control which may be independent of race.**

6.3 METFORMIN AND POSSIBLE INHIBITION OF GLYCATION:

The primary efficacy variable in the US trials was the mean change in HbA1c from baseline. There may be some reason to believe that metformin may directly inhibit glycosylation. The rationale includes:

Opportunity: Metformin has a significant life-span (half-life) within the erythrocyte which is longer than in plasma

Weaponry: As a guanidine derivative with protein-denaturant activity it has much in common with aminoguanidine which is being developed solely for its anti-glycation properties

Circumstantial data:

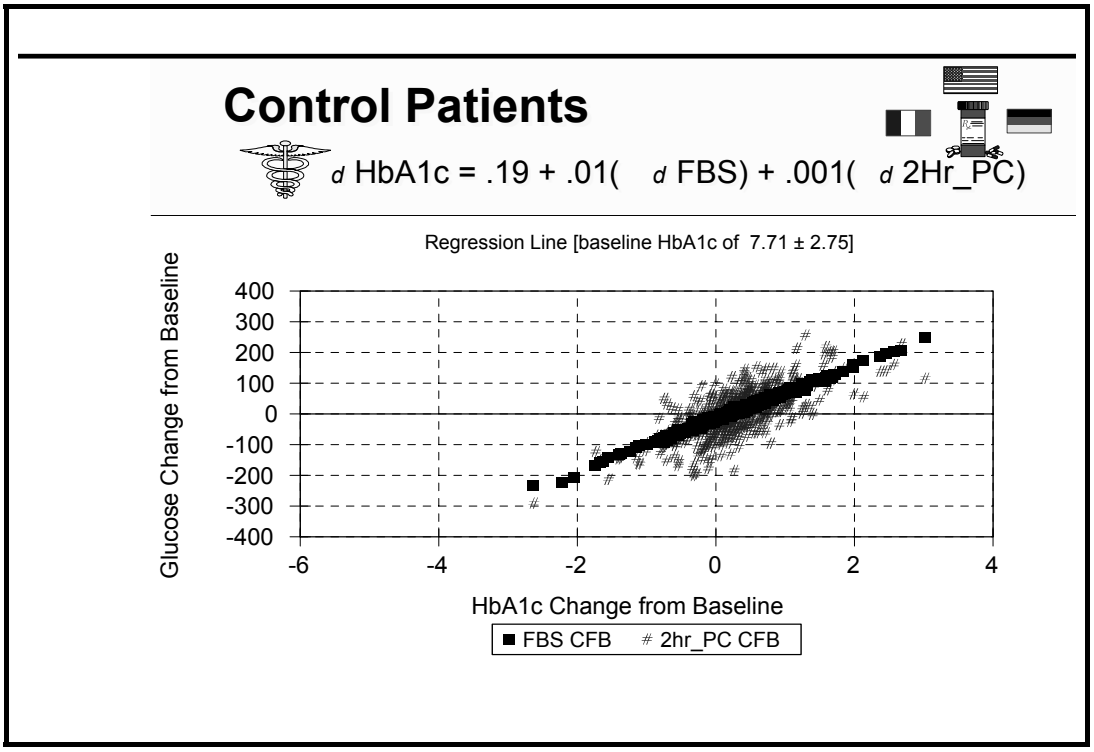


Figure 2

In control patients, the intersection of the X-axis (no change in either fasting or prandial glucose levels) with the regression curve shows that for this control population the HbA1c has increased by 0.19%. Note the basline of HbA1c for this population is 7.71%.

In metformin patients, however, the intersection of the X-axis (no change in either fasting or prandial glucose levels) with the regression curve shows that for this control population the HbA1c has decreased by 0.54%. Note the baseline of HbA1c for this population

is even higher than that of the controls at 8.14%.

What this means is that when there is no change in fasting or prandial sugars, control patients increase their glycohemoglobin while metformin patients decrease theirs for a mean treatment difference of -0.73% ± 0.186. This regression difference has a 99% CI of 0.25 to -1.21.

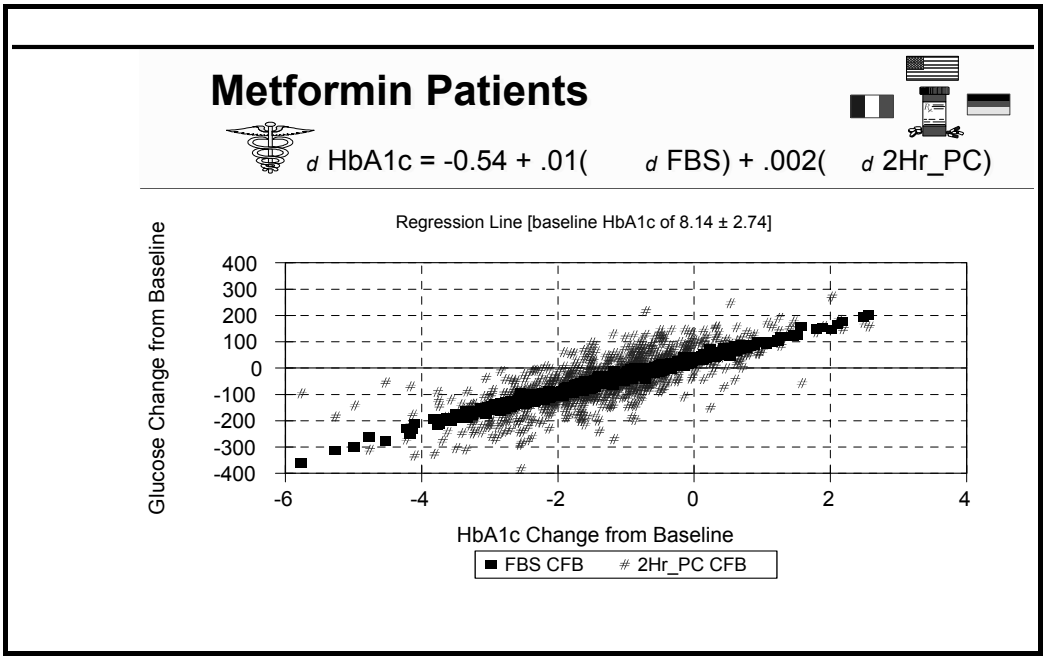


Figure 3

This evidence may appear somewhat circumstantial, however the metformin monotherapy arm of the 87-2D trial had essentially nochange in glycemia. What happened to the glycohemoglobin?

dFBS (mg/dl) from b/l	d2hr_pc (mg/dl) from b/l	dHbA1c (%Hb) from b/l	b/l HbA1c (%Hb)	n ±SD
-0.43	-4.29	***-0.38***	8.28	217
71.24	84.3	1.58	2.82	

Primary Failure with Metformin Monotherapy in the 87-2D Study

The 99%CI for HbA1c change of -.38% is from -.10 to -.66%. [This effect should be magnified when compared to control data.] Thus it may be safe to assume that at least some of the efficacy shown by metformin may be due to direct inhibition of intracorpuscular glycation independent of an effect upon glycemic control. Assuming a *net* -0.7%

contribution from inhibition of glycation, the point estimate of the net treatment difference in the 87-1D study of dietary failure would then be (+0.4)placebo -(-1.4)metformin +(-0.7)glycation or 1.1%. Assuming this very same contribution from inhibition of glycation, the point estimate of the net treatment difference in the 87-2D study of sulfonylurea failure would then be (+0.2)glybenclamide -(-1.7)metformin&glibenclamide combination +(-0.7)glycation or 1.2%. Given especially that the primary analysis was based on the intention-to-treat population, these results remain both clinically and statistically robust.

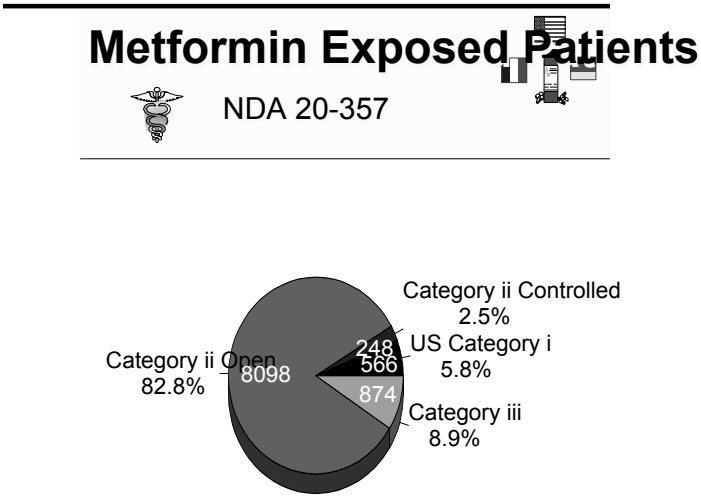
7. SAFETY REVIEW

7.1 METHODS:

This submission comes with little or no useful pooling of safety data.

Short-term [clinical trial] safety data presented in this NDA has been compartmentalized into three (3) categories. The first segregation consists of the two "pivotal" US Studies: 87-1D and 87-2D. These studies comprise 566 patients treated with metformin (213 were concomitantly on glibenclamide). Of these 566 patients, 471 (83.2%) were treated with metformin for a full 24 weeks and 434 (76.7%) received a dose higher than or equal to 2g/day at the last treatment visit.

A small portion of the patients exposed were in controlled clinical trials. **Figure 4**



There were 403 males (43%) and 454 females (57%) in controlled portions of pooled Category i and ii trials of which 814 were felt by this reviewer to be evaluable (c.f. **BERGIS STUDY**).

Only a small percentageof the 857 patients enrolled in controlled clinical trials and exposed to metformin for whom age information is available were over age 65 (15.8%). The mean age of all of these patients who were exposed to metformin was 54.5 years. In the US 87-1D trial there were143 patients randomized to metformin and 146 to placebo. In the 87-2D study, 210 were randomized to monotherapy with metformin, 209 to monotherapy with glibenclamide, and 213 to combination therapy. Pooling by exposure sults in 566 metformin patients and 355 controls. In the European (Category ii) controlled trials, safety data is available on176 were randomized to metformin monotherapy , 83 to

placebo, 87 to monotherapy with sulfonylurea, and 72 to combination sulfonylurea plus metformin. Again pooling results in 248 metformin patients and 170 controls. NDA wide pooling yields 814 metformin patients and 525 controls.

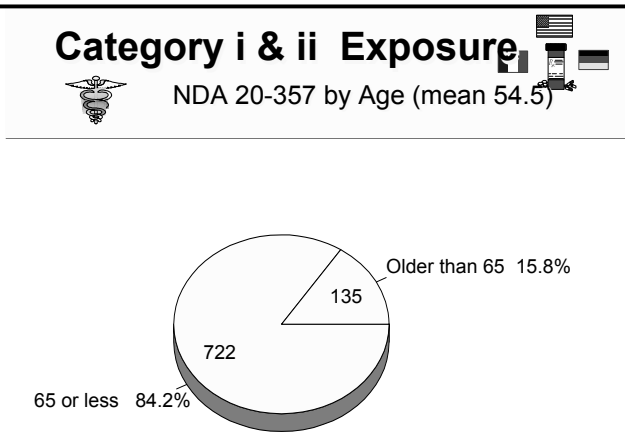


Figure 5

Only 15% of the US study population was black as opposed to at least 20% of the US NIDDM population which is black.

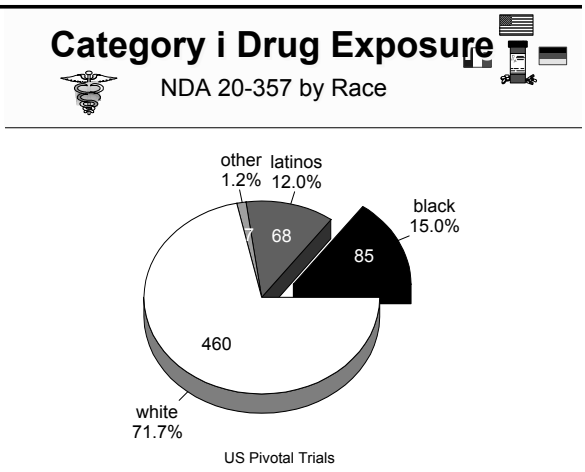
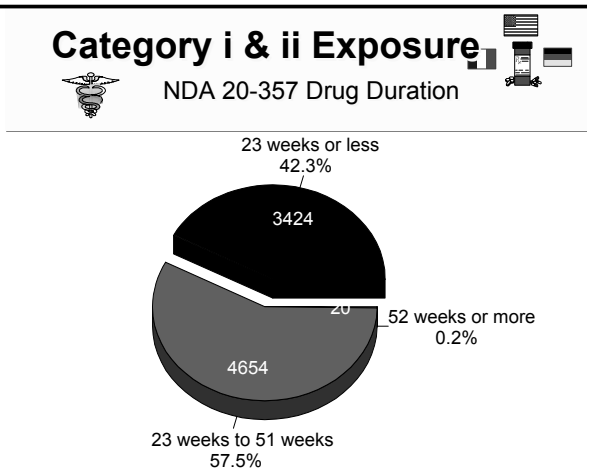


Figure 6

The second segregation ("Category II") comprises nine (9) non-US studies with "reasonable" safety data, i.e., (1) AM/84/DORF1 (2) AM/86/DORF2 (3) GB/85/DORNA (4) D/86/BERGI (5) GB/86/CAMP1 (6) AM/88/DUCHI (7) S/86/HERMA (8) D/86/HAUPT and (9) AM/87/PHASE. Study D/86/BERGI, however, was a two-year, open-labeled study at 800mg/day of metformin versus diet initiated and completed at a hospital setting in Germany but followed at primary care centers in the field. "Minimal information relative to safety was available for this study: no data on concurrent medications, adverse experiences/intercurrent medical events, or creatinine levels was collected" (NDA 8.8.6 p.1453). This study (D/86/BERGI) will therefore not be included in the subsequent summary of the non-US studies.

Most of the patients presented in the NDA had very short durations of exposure, with only 0.2% on therapy for over a year. There were 57.5% on therapy for 23-51 weeks, and 42.3% on therapy for 23 weeks or less.



There appears to be dose information available for 8992 patients exposed to metformin and included in the safety database:

½g-1g/day: 1532 patients
>1g-2g/day: 3844 patients
>2g-3g/day: 696 patients

Figure 7

Relatively fewer patients have been exposed to very high doses. This situation has improved with preliminary submission of data from the open enrollment 89-1C-6023 study. However, a final and complete study report is open and still pending submission to this NDA.

The third compartmentalization included studies which were non-US, poorly designed, poorly-controlled, and/or poorly-executed, and therefore not pooled in any coherent fashion in this NDA.

7.2 DEATHS:

CRF's are available for nine (9) of the 20 deaths in the Catgeory i and Category ii trials combined as well as in the open-enrollment study. One of these patients for which CRF's are available died in the US controlled study 87-2D-6023, six died in in the US (open-enrollment) study 89-1C-6023 (see also **Section 7.3.3**), one died in the non-US study MET/GB/86/CAMP1, and one died in the non-US study MET/S/86/HERMA. Eighteen (18) of the 20 patients were on metformin, one was on glipizide, and one on glibenclamide. Despite the lack of a complete study report for the open-enrollment trial, there have been no other deaths which have occurred in that trial (confirmed in a tele-phone conversation with the sponsor on 22 Mar 1994.)

Of the 11 patients who died for whom no CRF's are available - all in the non-US study MET/AM/87/PHASE) - one (M,56) died from the "result of an automobile accident", one (M,53) died of "decompensation of alcoholic cirrhosis", one

(M,63) died of "esophageal cancer", one (M,58) died of "pulmonary embolism", two (M,71; M,51) died of "myocardial infarction", one (F,78) died of "cranial trauma", one (M,70) died "during a coronary artery bypass", two (M,67; M,52) died of "cerebrovascular disease", and one (F,81) died of "pulmonary edema".

One patient on glipizide in study MET/GB/86/CAMP1 (F,61) developed carcinoma of the stomach, liver, and omentum on study day 306 and died four days later.

One patient on glibenclamide in study MET/S/86/HERMA (M,63) had a prior history of angina, myocardial infarction, and atrial fibrillation. He had mild to moderate chest pain throughout the study and died 4 months later of a "myocardial infarction." No post-mortem, however, was obtained.

7.2.1 The single patient in the controlled portion of the US trials to die (V01-20006, a 51 y.o. white male, Vignati site) had an 11-year history of NIDDM. He was enrolled onto metformin monotherapy in study 87-2D-6023. On study day 31 after having been titrated up to 2500 mg/day of metformin from 2000 mg/day he developed a "flu syndrome" which progressed into "abdominal discomfort - lower abdominal discomfort - cramps" and "lower abdominal suprapubic pain" and associated with "nausea/vomiting" on day 55. These symptoms apparently lasted until study day 61. By study day 67 he had a blood level of 629 ng/ml on 2500 mg of metformin per day. His creatinine had increased to 1.3 from 1.0, and he had proteinuria and microscopic hematuria [which had been there at baseline.] There were no associated changes in acid-base balance. He apparently developed "chest pains" on study day 97. Advised earlier to go to the emergency room, he nevertheless was later brought there in full cardiac arrest with electromechanical dissociation and pronounced after resuscitative measures had failed. Notably, this gentleman had no prior history of cardiovascular disease. The NDA describes him as "obese, diabetic, and a former smoker." His total duration of exposure to metformin was 97 days.

7.2.2 The first patient who died in the open-enrollment study (89-1C-6023) to be discussed (T01-06021, a 65 y.o. black female, Taylor site) had previously been enrolled onto metformin monotherapy in study 87-2D. Her past medical history included hypertension and arthritis. She had one episode of diarrhea on study day 124 and also developed "asthenia" and "lethargy" which lasted until study day 152. These latter reoccurred on study day 187 through the end-of-study. Her HbA1c had dropped 2.1% to from 8.5% to 6.4% during the course of therapy. On study day 97 her bicarbonate dropped transiently (2.72 SD) down to 18.3 from a baseline of 25.7 associated with an increased anion gap of 2.7 meq but a decrease in lactate of 0.3 mm/L to 0.9. These were the only abnormal acid-base disturbances during double-blind therapy. Blood metformin levels were 873 ng/ml on 2500 mg of metformin day. By the end of double-blind her FBS was 167mg/dl (up 19 mg/dl from baseline) but her HbA1c was 6.4 (down 2.1% from baseline). Persistent fatigue/lethargy continued through study 89-1C-6023 on 2500 mg metformin/day.

Concomitant therapy initially included glibenclamide 10 mg bid, verapamil SR 240mg qd, and ascorbate 1000 mg qd. Ten days before the patients demise she was seen on glibenclamide 10mg qd and 1500 mg of metformin day complaining, again, solely of "lethargy". The site apparently called "to repeat some labs and a U/A" - only to be informed that the
patient had just been found dead in her apartment. The exact nature of the labs which needed repeating were not described. A slight increase in creatinine (0.2 mg/dl) and decrease in bicarbonate (2.4 meq/L) was all that was noted. No post-mortem was performed. Her total duration of metformin exposure was 754 days.

7.2.3 The second patient (G04-07026, a 60 y.o. white male, Gerich site) enrolled onto metformin monotherapy in the 87-2D-6023 study. By the end of double-blind his FBS was 285 mg/dl (up 54 mg/dl from baseline) but his HbA1c was 8.9 (down 2.0% from baseline). In the 1C-6023 extension was placed on concomitant glipizide therapy at 10 mg bid. He later died of steroid-requiring pulmonary fibrosis apparently secondary to an inoperative non-small cell carcinoma of the lung. His total duration of exposure to metformin was 510 days.

7.2.4 The third patient to die in the open-extension US study (F02-10023, a 67 y.o. hispanic female, Fischer site) had been on metformin/glibenclamide in the 2D study. Adverse experiences in that study included heel pain (SD 0-14), left deltoid shoulder pain/myalgia (SD 56-70), diarrhea (SD 89-89), and laser surgery of the left eye (SD 178-178). By the end-of-treatment (SD 201), however, her HbA1c had dropped 4.6% from 10.9 to 6.3% (!) and her FBS dropped 137 mg/dl to 148 mg/dl. She then had blood levels of 2140 ng/ml of metformin and 193 ng/ml of glibenclamide on 2500 and 20 mg/day, respectively. Her B12 had dropped 206 pg/ml to 294 pg/ml and folate 2.2 ng/ml to 6.4 ng/ml with an increase in MCV of 7 to 84 from an abnormally low baseline of 77. Lactates increased 0.3 mM/L to 1.3 mM/L. Open-enrollment was complicated by:
(V2): dental infection requiring erythromycin and penicillin
(V4): UTI requiring norfloxacin
(V8): muscle strain and ankle edema
(V10.1): URI
(V12): hand burn and hypoglycemia
(~V14): ST-T wave changes developed on routine EKG. Unbeknownst to the site she was referred to a cardiologist who performed an echocardiogram which "suggested severe coronary artery disease." [Review of the actual cardiologist's notes determined that the echo, performed on 04/08/91, "did reveal diminished LV function with evidence of multiple regional wall motion abnormalities." This echo has been requested from the site.]
(V15.1): UTI requiring TMP/SFX
(V16): dry cough requiring Tussar SF, myalgias, fatigue, head tremor
(V16.1): mid-back pain
(V17): pedal edema requiring furosemide 20 mg/qd

(V18): blurring of vision requiring laser surgery x 3
(V19.1): herpetic lesions right leg requiring acyclovir 200mg q3h x5/d x10d
(V20): "cardiac prophylaxis" with isorbide dinitrate
At V20.2 she was seen with chest pain, nausea, vomiting, and weakness x 24 hours, found to be "in extreme distress" with "profound wide-QRS arrhythmia." "Attempts were made to catheterize her...." She presented in severe lactic acidosis. [Review of the admission H&P: Admission chemistries showed a CPK of 3200, a glucose of 628, a BUN of 36, a creatinine of 2.2, a potassium of 5.7, a bicarbonate of 9, a pH of 7.05, pO2 of 203, and pCO2 of 13, and an elevated lactic acid level (actual results unavailable at the current time) that was elevated. The cardiologist did not ascribe the acidosis to circulatory causes but rather appeared to feel that the acidosis was on a diabetic basis, i.e., - "diabetic ketoacidosis." The patient's condition deteriorated and she expired. Her total duration of exposure to metformin was 825 days.

7.2.5 The fourth open-enrollment expiration (J01-13002, a 61 y.o. white male, Johnson site) had a past medical history of hypertension, aneurysm OD, redwood allergy, arthritis, and left pulmonary nodule-stable. He had a 5 year history of NIDDM complicated by neuropathy and retinopathy. He was on lisinopril 10 mg qd and ASA 2 gr qd. In the 87-2D study he was randomized to therapy with metformin and glibenclamide. By study day 63 on 2500 mg of metformin and 20 mg glibenclamide blood levels were 756 and 128 ng/ml, respectively. Creatinine had increased 0.3mg/dl to 1.4 mg/dl. By SD 91, trace proteinuria and ketonuria had appeared. On SD 93 he developed small ulcers on the right leg attributed to "spider bites." On this day metformin level was 3343 ng/ml and glibenclamide levels were non-detectable. These bites resolved by SD 104. At that time blood levels of metformin had decreased to 725 ng/ml and those of glibenclamide increased to 38.5 ng/ml. MCV had increased 9 points to 92 and Hb had dropped 1.3 to 14.8. At double-blind end-of-treatment HbA1c had decreased 2.3% to 7.1 and FBS had decreased 104 mg/dl to 132. By then, blood levels of metformin had increased to 1044 ng/ml and those of glibenclamide to 63 ng/ml. MCV had increased by 12 to 95 and B12 decreased by 124 pg/ml to 232. No acid-base changes were noted. He had eight relatively uneventful months of open-enrollment on maximum doses of metformin and glibenclamide. However, his ultimate EKG had shown "non-specific ST-T wave abnormalities, consistent with ischemia, drugs, etc." (This EKG had apparently even improved since the previous tracing!) He expired quite suddenly twelve days later without any well-documented diagnosis. The total duration of his metformin exposure had been 343 days.

7.2.6 The fifth open-enrollment expiration (F03-11024, a 68 y.o. white female, Flood site) with a BMI of 22.26 had a past medical history of renal tuberculosis s/p left nephrectomy, malignant melanoma s/p right radical neck, right hip replacements x 3, bilateral breast carcinoma/mastectomy, hypertension, osteoarthritis, retinopathy s/p laser infarction. She had had NIDDM for 11 years at one point requiring insulin therapy. She was enrolled onto metformin

and glibenclamide in the 2D study also taking ibuprofen 800mg bid and enalapril maleate 5 mg qd. Baseline alkaline phosphatase was slightly elevated at 118 with a normal creatinine of 0.9. She was diagnosed with lower respiratory tract infection from SD 11-24. Hip and right thigh pains occurred on SD 28-36. On SD 73 on 2500 mg metformin and 20 mg glibenclamide she had metformin levels of 74 ng/ml and glibenclamide levels of 65.9 ng/ml. On SD 122-136 she suffered from a lacerated left hand. By SD 133 she had metformin levels of 748 ng/ml and glibenclamide levels of 131 ng/ml. Her hematocrit had fallen 4% to 34 with an MCV decrease of 7 points. Creatinine had fallen to 0.8. On SD 233 at end-of-treatment she had developed a left carotid bruit. Her HbA1c had fallen by 4.4% to 7.7 and FBS 92 mg/ml to 255. Hematocrit was 36 with an MCV of 96, an RBC count of 3,700,000, and an MCV of 192 (down 195 pg/ml). Her bicarbonate was 21.8 (down 3.3 meq/l) , but lactates had only increased by 0.3 mM/L to 1.6 with negligeable (0.8) increase in anion gap to 13. Creatinine was 0.7 at this time. However, by two months (V2) of the open-enrollment her creatinine clearance was found to be 42.7 ml/min. Lactate at V3 was apparently 0.8 mM/L. Calling to terminate the patient from the study the site was informed of the patients sudden expiration. Her total duration of metformin exposure was 252 days.

7.2.7 The sixth and final patient who expired during open-enrollment (S01-18018, a 53 y.o. white male, Saudek site) was also in the 2D study during double-blind enrolled on metformin and glibenclamide. No adverse experiences were noted, however at end-of-treatment on 2500 mg of metformin and 20 mg of glibenclamide he had an increase of 0.1% in the HbA1c to 6.7% with a 46 mg/dl drop in FBS to 180 with metformin levels of 527 ng/ml and glibenclamide levels of 89.7 ng/ml and a BMI of 26.75. Of note was a 55 pg/ml drop in B12 to 233, a 5.8 mEq/L increase in anion gap to 18.5, a 6.8 mEq/L decrease in bicarbonate to 22.5, and a 0.5 mM/L increase in lactate to 2.2. Twelve and some months into the open-enrollment phase the patient apparently committted suicide by "ingestion of chemicals." The total duration of his exposure to metformin was 461 days.

7.2.8 **Summary Breakdown of Deaths in this NDA**

	Suicide	Accident	Cancer	Pulm Emb	MI CABG	Sudden Death	CVD	CHF	Meta bolic
met	**1**	**2**	**2**	**1**	**3**	**4**	**2**	**1**	**2**
glyb			**1**		**1**				

	Total	Non_CV	Deaths	Total	CV	Deaths
met		**5 (27.8%)**			**13 (72.2%)**	
glyb		**1 (50%)**			**1 (50%)**	

7.2.9 It is true that (7%) more of the metformin patients elected to be followed in the

open-extension than did glibenclamide patients. **Nevertheless, it is of no small note that all 7 of the deaths in the US trials emanated not only from the 87-2D study, but only from the metformin arms of that trial**. On an intent-to-treat basis there were 7 deaths out of 426 patients exposed to metformin in that trial versus 0 deaths in 209 patients not originally randomized to metformin but randomized rather to monotherapy with glibenclamide. The mean treatment difference of having been randomized to metformin (alone or in combination with glibenclamide) versus having been randomized to glibenclamide alone was 1.64% - 99% CI (0.0541 to 3.23%) - i.e., significant at the $p < 0.01$ level. Considering that 1 death was due to cancer and another to suicide, then excluding these deaths from analysis reveals a mean treatment difference of 1.17% with a 95% CI of 0.151% to 2.20% and a 99% CI of -0.173% to +2.52% - i.e., still significant at the $p<0.05$ level. The same levels of significance apply to consideration of ITT evaluation of deaths in all patients in the pooled Category i trials by exposure to metformin. At any rate, all six of the deaths in the open-enrollment phase were on combination therapy at the time of death. **A Kaplan-Meier analysis revealed that the event rate was enriched at the end of observation to its maximum of 29.22 deaths/1000/year**. [Over the entire observation period the mortality rate averaged 14.58 ± 8.03 deaths/1000/year.]

7.2.9.1 Two major questions emerge from such an analysis:

1) Were patients originally randomized to metformin in the 1D study protected and, if so, by what mechanism?

2) Were patients originally randomized to glibenclamide monotherapy in the 2D study also protected and, if so, by what mechanism? Duration of exposure may not be the answer. The smallest duration of exposure to metformin in this group was 14 days. The longest was 783 days. The mean was 498.28 ± 209.70 days. These compare quite favorably to the statistics manifested by those patients from the other two groups in the 2D study who died.

The answer to the first question may have to do with lack of enough power to detect a difference in that arm.

The answer to the second question may not be so readily apparent. The major bug-a-boo relates to the notion that the glibenclamide-monotherapy patients had relatively similar and sufficient durations of metformin exposure to the other two groups and came from the same sulfonylurea-failure population at risk. The simplest solution would be to say that there was not enough power in that arm alone to warrant any conclusion of protection. Nevertheless, the difference between the glybenclamide lack of deaths and the seven deaths in the other two arms was statistically significant at a $p < 0.01$. What other possible explanations exist as to why no mortality was seen in that arm, if valid? A conceivable answer may lie in the design features of the double-blind portion of the study. The patients on metformin in the double-blind study had to be rapidly titrated up to, and, for the most part kept on, maximum doses of

metformin (i.e., 2500 mg day) on top of maximum doses of glibenclamide. When glibenclamide-monotherapy patients entered the 1C study the following occurred:

1) a time lag was likely from the cessation of the 2D study
2) whatever sulfonylurea patients were taking at the time needed to be completely discontinued
3) no retitration of metformin would have been necessary
4) these patients would have been forced to discontinue sulfonylurea completely, then have metformin titrated upward in biweekly 850mg increments, and then have their previous sulfonylurea - which was not necessarily glibenclamide - retitrated upwards. This strategy is unlike the 2D combination arm in which metformin was titrated upward more gradually in weekly 500mg increments on top of maximum glybenclamide therapy (which could not be reduced.)

Another intriguing lead relates to selection bias, the argument being that glybenclamide-randomized patients who elected open-enrollment were somehow more resistant to metformin toxicity than those who opted out. There has, unfortunately, not been enough time to fully explore this mechanism. Yet, here is some preliminary analysis:

Did Glyburide-Randomized Patient Enter Open-Enrollment?	**n**	**Age**	**BMI**	**HbA1c**
==> No	**70**			
[Mean:]	**55.66**	**28.33**	***7.10***	
[Standard Deviation:]		**8.86**	**3.62**	**3.56**
==>Yes	**146**			
[Mean:]		**56.51 NS**	**29.03 NS**	***8.16****
[Standard Deviation:]		**8.50**	**4.47**	**2.86**

*95% CI for 1.06 difference ± 0.451 (SED) -> 0.171 to 1.95

The (1) selective self-removal of better controlled [glibenclamide] patients from open enrollment and the (2) decreased incidence of death in that arm followed in open enrollment taken with the (3) highly significant increase in hypoglycemia seen with combination therapy suggests that hypoglycemia may be a significant contributing factor to the deaths seen in the other two arms. If this is the case than it renders somewhat less credible the sponsor's argument that the hypoglycemia seen in the double-blind phase of the trials was an ersatz

function of the design which kept maximum sulfonylurea therapy fixed while only allowing titration of metformin.

All this may suggest:

a) some possible sensitization-withdrawal-rechallenge mechanism
b) some possible higher metformin dose + maximum glibenclamide dose interaction
c) some possible interaction based on hypoglycemia or,
d) some combination of the above operative in this population of sulfonylurea-failure patients.

7.2.9.2 ITT Statistics
==>: There is a highly statistically significant increase in the number of deaths in patients randomized to prescription for metformin than to prescription for glibenclamide alone or than to prescription with either glibenclamide alone or placebo alone. The predominant population at risk was patients with sulfonylurea-failure (excess risk 1.65% with 99% CI of 0.0545% to 3.26%). The earliest duration of exposure to metformin resulting in a death was 97 days. The latest was 825 days. The mean was 463.14 ± 242.26 days.

Of the metformin deaths, 72.22% were due to cardiovascular related causes, yet only 16.67% were directly attributable to coronary heart disease, which usually claims 75 to 80% of NIDDM patients[21].

7.2.10 Lactic acidosis, a known sequel to therapy with metformin was seen in one patient with sudden death (F02-10023, see **Section 7.2.4**), and renal failure which is known to predispose to lactic acidosis in patients taking metformin, was seen to develop in another patient on metformin who had a sudden, unexplained death (F03-11024, see **Section 7.2.6**).

However, considering one lactic acidosis death in the clinical trials yields a death rate of 0.88/1000 PYE. This death rate is about threefold our point estimate of 0.3/1000 PYE (see **Section 7.17.1.2**) In addition, both of these events have occurred in females. Moreover, there were no episodes of lactic acidosis ascribable to patients taking placebo or glibenclamide monotherapy in the US clinical trials.

==> The death rate estimated from metformin-associated lactic acidosis in the US clinical trials is slightly greater than one-third that of the highest FDA estimate (2.5/1000 PYE) of phenformin-associated lactic acidosis mortality at the time phenformin was removed from the market for "imminent hazard."

7.2.11 Thirdly, at least two of the patients who died (F02-10023, and J01-13002, see **Sections 7.2.4-5**) had EKG ST-T wave changes which developed on therapy with metformin. There was a statistically significant increase in "clinically-significant EKG changes from baseline" in patients exposed to metformin in the US clinical trials (see **Sections 7.7, 7.12.2**). It may also be that 8/18 (44.4%) metformin deaths although cardiovascular, were non-CHD, non ASCVD related. If that is the case, then: the associated increase in total (primarily cardiovascular) mortality manifested by phenformin in the University Group Diabetes Program[27] (UGDP) study may have been revalidated and operative with metformin, and, perhaps, with other biguanides as well.

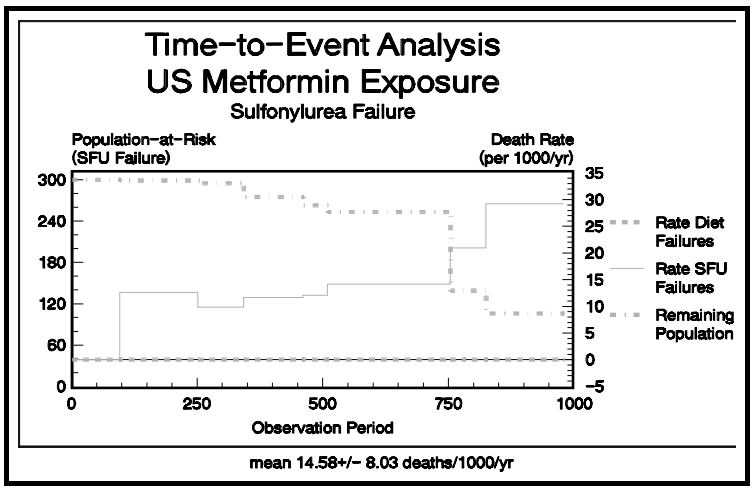
==>: There appears to be an increase in sudden deaths in patients exposed to metformin. Some of these sudden deaths may be a function of hypoglycemia seen with combined metformin-sulfonylurea therapy, others may be related to conductive disturbances (see also **Section 7.12.2**).

7.2.12 Sulfonylurea Failure Population and Deaths
==> The patients at risk of metformin-induced mortality in the US trials appear to be solely those with sulfonylurea-failure. It is difficult to sort out the precise mechanisms which may underlie this association. The University Group Diabetes Program[27] (UGDP) showed significant excess mortality independently in both the sulfonylurea and biguanide arms - but no study was made of the potential additive effects of the two classes of medication taken simultaneously. The significant excess mortality displayed by the combination therapy among patients with sulfonylurea-failure in the comparatively well-underpowered US trials may, indeed, be a function of this additive phenomenon.

Once again, the predominant population at risk from death in these US trials was patients with sulfonylurea-failure (excess risk 1.65% with 99% CI of 0.0545% to 3.26%). A Kaplan-Meier analysis revealed that the event rate was enriched at the end of observation to its maximum of 29.22 deaths/1000/year. [Over the entire observation period the mortality rate averaged 14.58 ± 8.03 deaths/1000/year.]

27University Group Diabetes Program, A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes V. Evaluation of phenformin therapy. *Diabetes* **24** (Suppl 1):65-184, 1975

Figure 8



So far as B12 associations may be concerned, B12 abnormalities were so prevalent among metformin users that it is difficult to attribute any prognostic import to changes seen along this axis amongst the patients who died.

7.3 DROP-OUTS:

7.3.1 **ALL PATIENTS**

Of the total of 566 "pivotal" Category I patients on metformin, 105 patients (18.6%) withdrew from the studies. Of these 105 patients, 24 (4.2%) withdrew for lack of efficacy, and 81 (14.3%) for "non-efficacy related" reasons with 23 (4.1%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 353 patients on metformin alone, a total of 84 patients (21.4%) withdrew from the studies. Of these 84 patients, 23 (6.5%) withdrew for lack of efficacy, and 61 (17.3%) for "non-efficacy related" reasons with 19 (5.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 213 patients on metformin plus glibenclamide, a total of 21 (9.9%) patients withdrew from the study. Of these 21 patients, only 1 (0.5%) patient withdrew for lack of efficacy, and 20 (9.4%) for "non-efficacy related" reasons with 4 (1.9%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

This first compartment also had 355 comparators, i.e., 146 on placebo and 209 on glibenclamide alone. Of these 355 controlled patients a total of 76 (21.4%) patients withdrew from the study. Of these 76 patients, 24 (6.8%) patients withdrew for lack of efficacy, and 52 (14.6%) for "non-efficacy related"

reasons with 7 (1.1%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 146 patients on placebo alone, a total of 41 (28.1%) patients withdrew from the study. Of these 41 patients, 18 (12.3%) patients withdrew for lack of efficacy, and 23 (15.8%) for "non-efficacy related" reasons with 2 (1.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 209 patients on glybenclamide alone, a total of 35 (16.7%) patients withdrew from the study. Of these 35 patients, 6 (2.9%) patients withdrew for lack of efficacy, and 29 (12.4%) for "non-efficacy related" reasons with 5 (2.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The second segregation ("Category II") includes the other eight (8) non-US studies (excluding D/86/BERGI) and comprises 8346 patients treated with metformin (72 were concomitantly on glipizide, glibenclamide, or glicazide). Of these 8346 patients, 248 patients were in controlled clinical trials and 8,098 were uncontrolled in open-labeled trials.

Of the controlled 248 Category II patients, 20 (8.1%) were treated with metformin for a full 52 weeks (versus glipizide in GB/86/CAMP1), 23 (9.3%) patients for at least 24 weeks, and 67 (27.0%) received a dose higher than or equal to 2g/day at the last treatment visit.

Of the total of 248 controlled Category II patients on metformin, 34 patients (13.7%) withdrew from the studies. Of these 34 patients, 0 (0.0%) withdrew for lack of efficacy, and 34 (13.7%) for "non-efficacy related" reasons with 24 (9.7%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 176 patients on metformin alone, a total of 30 patients (17.0%) withdrew from the studies. Of these 30 patients, 0 (0.0%) withdrew for lack of efficacy, and 30 (17.0%) for "non-efficacy related" reasons with 20 (11.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 72 controlled Category II patients on metformin plus sulfonylureas, a total of 4 (5.6%) patients withdrew from the studies. Of these 4 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 4 (5.6%) for "non-efficacy related" reasons with 4 (5.6%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

This second compartment had 170 comparators, i.e., 83 on placebo and 87 on sulfonamides (34 on glibenclamide, 25 on glipizide, and 28 on glicazide). Of

these 170 controlled patients a total of 24 (14.1%) patients withdrew from the studies. Of these 24 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 24 (14.1%) for "non-efficacy related" reasons with 11 (6.5%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 83 patients on placebo alone, a total of 15 (18.1%) patients withdrew from the study. Of these 15 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 15 (18.1%) for "non-efficacy related" reasons with 7 (6.5%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 87 patients on sulfonylureas alone a total of 9 (10.3%) patients withdrew from the study. Of these 9 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 9 (10.3%) for "non-efficacy related" reasons with 4 (4.6%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The second compartment also had 8,098 uncontrolled patients. Of these, no patients (0.0%) were treated with metformin for a full 52 weeks, 4160 (51.8%) patients were treated for at least 24 weeks, and 4406 (5.4%) received a dose higher than or equal to 1.7g/day at the last treatment visit. One hundred fifty two patients (1.9%) received a dose higher than or equal to 2g/day and 211 patients (2.6%) received a dose higher than or equal to 2.55g/day at the last treatment visit. Of the total 8,098 uncontrolled patients on metformin, 488 patients (6.0%) withdrew from the studies. Of these 488 patients, 33 (0.4%) withdrew for lack of efficacy, and 455 (5.6%) for "non-efficacy" reasons with 170 (2.1%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

7.3.2 **POOLED PATIENTS FROM CONTROLLED TRIALS**

There were a total of 814 controlled patients on metformin. Of these 814, 139 patients (17.1%) withdrew from the studies. Of these 139 patients, 24 (2.9%) withdrew for lack of efficacy, and 115 (14.1%) for "non-efficacy related" reasons with 47 (5.8%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 529 controlled patients on metformin alone, a total of 114 patients (21.6%) withdrew from the studies. Of these 114 patients, 23 (4.3%) withdrew for lack of efficacy, and 91 (17.2%) for "non-efficacy related" reasons with 39 (7.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 285 controlled patients on metformin plus sulfonylureas, a total of 25 (8.8%) patients withdrew from the studies . Of these 25 patients, 1 (0.4%) patient withdrew for lack of efficacy, and 24 (8.4%) for "non-efficacy related" reasons with 8 (2.8%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The pooled controlled studies had 525 comparators, i.e., 229 on placebo and 296 on sulfonamides (243 on glibenclamide, 25 on glipizide, and 28 on glicazide). Of these 525 controlled patients a total of 100 (19.0%) patients withdrew from the study. Of these 100 patients, 29 (5.5%) patients withdrew for lack of efficacy, and 71 (13.5%) for "non-efficacy related" reasons with 18 (3.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 229 patients on placebo alone, a total of 56 (24.5%) patients withdrew from the study. Of these 56 patients, 18 (7.9%) patients withdrew for lack of efficacy, and 38 (16.6%) for "non-efficacy related" reasons with 11 (4.8%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 296 patients on sulfonylureas alone a total of 44 (14.9%) patients withdrew from the study. Of these 44 patients, 6 (2.0%) patients withdrew for lack of efficacy, and 38 (12.8%) for "non-efficacy related" reasons with 9 (3.0%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The pooled (Category I and II controlled) relative risk of dropping out on metformin or placebo alone versus that on metformin in combination with sulfonylurea was 3.18 (99%CI of 1.90 to 5.33; $p<0.001$).

7.3.3 **PATIENTS FROM THE OPEN-ENROLLMENT TRIAL**
Concerning the 89-1C-6023 open-extension trial the sponsor states on page 08A-1669 of Volume 1.75 of this NDA:-

> **Of the 604 patients enrolled in this study, *preliminary* data review indicates that 164 patients were terminated from the study prior to the potential termination time. A complete analysis of patient disposition will be provided with the complete study report *(to be submitted with the first safety update of this NDA)*.** [Italics mine]

A "complete study report" of this trial has yet to be submitted(!) Nevertheless, it would appear that six hundred four (604) patients enrolled into the 89-1C-6023 open-extension trial to receive metformin with or without sulfonylureas. Of these, 217 were from control arms in the 87-1D or 87-2D trials with 75 emanating from placebo in the 1D trial and 142 from glybenclamide in the 2D trial. This amounts to 75/145 placebo patients, 142/209 glybenclamide patients, 217/351 metformin (monotherapy) patients, and 168/213 metformin/glybenclamide (combination) patients. This (385/564 or 68.3% of metformin patients minus 217/354 or 61.3% of control patients) amounts to a mean treatment difference of 6.96% with a 95%CI of 0.599 to 13.3% [and a $p<0.05$]. (The open-enrollment study increased

the total duration of metformin exposure during all of the US open and controlled trials to 1136 patient years.)

Of the 604 patients enrolled into 89-1C, 164 (27.15%) patients discontinued prematurely. There were 74 (12.23% of the total enrolled) discontinuations secondary to an adverse event/intercurrent medical event (AE/IME), significant laboratory abnormality, or death.

Adverse Events/Intercurrent Medical Illnesses/Significant Labs/Deaths Resulting in Withdrawal from Study 89-1C

Total		**74**
GI		**26**
Abdominal pain	**3**	
Bloody stools/diarrhea	**2**	
Diarrhea	**11**	
Colon Carcinoma	**3**	
Pancreatitis	**2**	
Cirrhosis	**1**	
Abnormal LFT's+Sx	**1**	
Abnormal LFT's..(Lab only)	**3**	
GU		**24**
Pyelonephritis	**1**	
Stones/UTI	**1**	
Increased Pcr/Decreased Ccr	**19**	
Prostate Ca/BPH	**3**	
CNS		**4**
Suicidal Deaths	**1**	
Neuropathy	**1**	
Toe infection/gangrene	**2**	
Cardiovascular		**17**
Deaths	**4**	
EKG changes/Arrhythmias/CHF	**6**	
Angina/MI	**4**	
Surgery/Catheterization	**3**	
Respiratory		**1**
Carcinoma of the lung/Deaths	**1**	
GYN		**1**
Breast Carcinoma	**1**	
Metabolic		**1**
Increased lactates/risk of lactic acidosis	**1**	

7.4 INCIDENCE OF ADVERSE EXPERIENCES:

Adverse events or intercurrent medical illnesses in the US pooled Category i randomized trials either reported by at least 9% of the patients in one treatment group or for whom the mean treatment differences in incidence between any two treatment groups was at least 5% follows:

7.4.1 Category i Pooled Adverse Events/Intercurrent Medical Illnesses

AE/IME	metformin	placebo	glyburide	combination
n	*351*	*145*	*209*	*213*
any AE/IME**	**86%**	**79%**	**82%**	**88%**
diarrhea**	**50%**	**14%**	**12%**	**45%**
nausea/vomiting**	**28%**	**10%**	**8%**	**25%**
URI	**21%**	**22%**	**22%**	**31%**
asthenia	**13%**	**11%**	**10%**	**11%**
headache	**12%**	**12%**	**8%**	**14%**
abdominal discomfort	**11%**	**6%**	**11%**	**13%**
accidental injury	**9%**	**6%**	**8%**	**8%**
flatulence	**9%**	**6%**	**7%**	**10%**
flu syndrome	**9%**	**6%**	**8%**	**8%**
back pain	**8%**	**7%**	**10%**	**6%**
arthralgia	**7%**	**10%**	**7%**	**10%**
indigestion*	**7%**	**4%**	**6%**	**12%**
UTI	**7%**	**9%**	**6%**	**8%**
myalgia	**7%**	**8%**	**10%**	**6%**
pharyngitis	**6%**	**5%**	**5%**	**9%**
vaginitis++	**3%**	**8%**	**8%**	**2%**
paresthesia	**3%**	**8%**	**4%**	**5%**
thirst+	**2%**	**6%**	**4%**	**1%**
hypoglycemia##	**2%**	**<1%**	**3%**	**18%**

+p<0.05 higher in control pool than metformin pool
++p<0.01 higher in control pool than metformin pool
*p<0.05 higher in metformin pool than control pool
**p<0.01 higher in metformin pool than control pool
##p<0.01 higher in combination than SFU

Adverse events or intercurrent medical illnesses in the non-US pooled Category ii randomized trials either reported by at least 9% of the patients in one treatment group or for whom the mean treatment differences in incidence between any two treatment groups was at least 5% follows:

7.4.2 Category ii Pooled Adverse Events/Intercurrent Medical Illnesses

AE/IME	metformin	placebo	SFU	combination
n	*176*	*83*	*87*	*72*
any AE/IME**	63%	39%	57%	85%
diarrhea**	32%	14%	1%	17%
nausea/vomiting**	17%	5%	5%	4%
abdominal discomfort**	13%	6%	3%	13%
AE/IME	**metformin**	**placebo**	**SFU**	**combination**
indigestion	7%	4%	2%	4%
asthenia	7%	1%	8%	31%
URI	5%	2%	8%	13%
hypoglycemia##	5%	0%	13%	33%
taste disorder	5%	0%	2%	3%
constipation	4%	8%	3%	7%
headache##	4%	4%	2%	15%
sweating	4%	0%	6%	7%
dizziness#	3%	4%	9%	24%
bronchitis	4%	0%	3%	6%
UTI	4%	0%	2%	4%
thirst*	3%	1%	1%	8%
abnormal vision	2%	0%	3%	7%
pruritus	1%	1%	0%	6%
tremulousness#	1%	0%	16%	32%
polyuria	1%	0%	5%	7%
appetite increased	1%	0%	13%	8%
anxiety/tension	1%	0%	1%	6%
angina pectoris*	<1%	0%	0%	4%

#p<0.05 higher in combination than SFU
##p<0.01 higher in combination than SFU
*p<0.05 higher in metformin pool than control pool
**p<0.01 higher in metformin pool than control pool

With the exception of thirst the statistical tests were all confirmatory in these pooled studies separated across the wide Atlantic. In the US the significant differences favoring metformin for vaginitis or thirst undoubtedly reflect the differences in efficacy manifested. This, apparently, was not quite so profound in Europe. Note the hypoglycemic symptom complex of combination therapy versus sulfonylurea alone was highly significant for "hypoglycemia or headache" and significant for "tremulousness or dizziness."

The highly significant gastrointestinal profile of "diarrhea" or "nausea/vomiting" with "abdominal discomfort" (Non-US) or "indigestion" (US) undoubtedly reflects some portion of the mechanism of action of the drug by which it induces carbohydrate as well

as protein and B12 malabsorption[28];[29];[30];[31];[32];[33];[34](see **Section 7.5**).

The significant treatment difference in angina pectoris (1.61% with 95% CI of 0.0451% to 3.18%,) seen in the pooled European studies must be taken particularly seriously in light of:

a) the statistically significant difference in clinically significant changes from baseline seen in EKG's during the US controlled trials (see **Section 7.7**) and the mandate of the 18 March 1994 DMEDP Advisory Committee to completely follow that up

b) the highly significant treatment increase in deaths reported during the US trials on an intent-to-treat basis (only among the two groups originally randomized to metformin - see **Section 7.2**), and

c) the significant increase in hospitalizations seen in the UK Prospective Diabetes Study (see **Section 7.17.2**)[35]

28Walter-Sack I. Reduction and delay in resorption as a pathogenetic and therapeutic principle. *Z Gastroenterol* [Verh] **16**:54-61, 1979

28[a]Leroy Guerin V. Acidose lactique induite par la metformine. Revue de littérature à propos de 2 cas. *THESIS MED.*:1-81, 1979 (see page 17) reprinted in *NDA 20-357*, Vol. 1.102, p 08A-08951

29Caspary WF. Effect and side effects of drugs on digestive and resorptive function of small intestine. *Dtsch Med Wochenschr* **102**(5):167-73 1977

30Longstreth GF ; NewcomerAD. Drug-induced malabsorption. *Mayo Clin Proc* **50**(5):284-93, 1975

31Kendall MJ ; Chan K. Drug-induced malabsorption. *Xenobiotica* **3**(11):727-44, 1973

32Gray GM. Drugs, malnutrition, and carbohydrate absorption. *Am J Clin Nutr* **26**(1):121-4, 1973

33Olsen WA ; Rasmussen HK. Effect of phenformin on carbohydrate absorption in man. *Diabetes* **23**(8):716-8, 1974

34Tomkin GH ; Hadden DR ; Weaver JA ; Montgomery DA. Vitamin-B12 status of patients on long-term metformin therapy. *Br Med J* **19**;2(763):685-7, 1971

35UK Prospective Diabetes Study Group, UK Prospective Disabetes Study (UKPDS): 14. Relative efficacy of randomly allocated diet, sulfonylurea, insulin, or metformin therapy in patients with newly diagnosed type 2 diabetes followed for three years. Manuscript enclosed in *NDA Amendment #19*, 11 Feb 1994, Table 4, p 17 [slated for BMJ 20 Dec 1993]

7.5 LABORATORY ABNORMALITIES:

Changes in the following safety laboratory variables were reviewed for mean changes, treatment-emergent lows or highs, and movement of at least 1 standard deviation at any time during double-blind therapy in the US trials:

Hematocrit (Hct), Red Blood Cells (RBC), Hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), White Blood Cells (WBC), Granulocytes, Stabs, Eosinophils, Lymphocytes, Basophils, Monocytes, Platelets, Creatinine, BUN, Bilirubin, Uric_Acid, ALT (SGPT), AST (SGOT), Alkaline Phosphatase, Albumin, Total Protein, Folic Acid, Vitamin B12, Anion Gap, Bicarbonate, Calcium, Chloride, Phosphate, Potassium, Sodium, Urinary Specific Gravity, Urinary pH, Urinary Glucose, Urinary Protein, Urinary Ketones, Urinary Blood, Serum Lactate, Plasma Metformin, Plasma Glybenclamide [in 87-2D Study].

There were no clinically significant differences in laboratory safety variables reviewed with the exception of the red cell series and vitamin B12 levels [or drug levels, themselves]. There did appear to be a slightly statistically significant but clinically insignificant difference in lactate levels across pooled treatment groups (0.07 mM/L with 90% CI ranging from 0.00956 to 0.130mM/L) at end-of-treatment (EOT).

Patients randomized to metformin (564) dropped their B12 levels a mean of 131.89 pg/ml from a baseline average of 530.68 pg/ml. Control patients (354) increased their B12 a mean of 12.59 from a baseline average of 518.71 pg/ml. This is a mean treatment difference of 144.48 pg/ml. There were 6.89% of metformin patients with normal B12 levels at baseline who dropped their B12 below the normal range of 200 pg/ml during double-blind therapy as opposed to 0.28% of controls. This mean treatment difference (excess risk) of 6.61% has a 99% CI of 3.77 to 9.45% or a relative risk of 24.4 with a 99%CI of 1.8 to 333. Interestingly enough this did not translate into any meaningful treatment difference in MCV (0.65 ± 4.5NS). Nevertheless, this did translate into a mean treatment difference of -1.15 in the hematocrit with a 99% CI around this difference of -0.63 to -1.67. Likewise for hemoglobin (-0.418, 99%CI -0.265 to -0.571) and RBC (-169,000/cc, 99%CI -107,000 to -231,000/cc). Looked at categorically, Hb displayed drops of over 1 gram in 126 patients on metformin but only in 32 controlled patients. This 13.3% difference had a 99%CI of 7 to 19%). Moreover, Hb displayed drops of over 2 grams in 23 patients on metformin but only in a single controlled patient. This 3.8% difference had a 99%CI of 1.5 to 6.1%). Hb displayed drops of over 3 grams in 5 patients on metformin but still only in a single controlled patient. This last difference was not statistically significant.

There were 34/564 metformin patients (6.03%) with treatment-emergent low RBC counts

as opposed to 8/354 controls (2.26%) for a mean treatment difference of 3.77 ± 1.27% SED with 99% CI of 0.462 to 7.03%. There were 18/564 metformin patients (3.19%) with treatment-emergent low hemoglobins as opposed to 4/354 controls (1.13%) for a mean treatment difference of 2.06 ± 0.93% SED with 95% CI of 0.233 to 3.87%. The difference in hematocrit (a volume parameter) was significant only at the $p<0.1$ level. Therefore significantly more patients on metformin had both meaningful hemoglobin drops and treatment-emergent anemias than did patients on controlled therapy.

"Malabsorption" was defined as the adverse event "diarrhea" in association with the laboratory change "B12 drop from baseline of over 150 pg/ml" occurring in the same patient during therapy. There were 100 pooled patients on metformin with malabsorption thus defined as opposed to 5 pooled patients on controlled treatment. This is an excess risk for malabsorption on metformin of 16.6% with a 99% CI of 12.1 to 22.2% [or a relative risk of 12.6 with a 99% CI of 3.9 to 40.4].

Cross-associations of changes in laboratory variables in particular sub-populations defined by specific adverse experiences or other laboratory abnormalities were also reviewed and are attached as appendices.

1) B12 vs lactate in all patients, by treatment group, in patients with and without diarrhea:
Conclusions: no significant findings

2) drug levels vs dose vs BMI in patient visits ± ADR's, ± diarrhea:
Conclusions: there were significantly higher drug levels of metformin ($p<0.05$) in patients also on glibenclamide at both the 1000 (MTD 195 µg/ml with 95% CI of 3.69 to 386 µg/ml) and 2500mg (MTD 112 µg/ml with 95% CI of 6.2 to 218 µg/ml) metformin dose levels when compared to patients at the same doses on metformin monotherapy (in the 87-2D study).

3) GFR Changes vs Urinary pH vs potassium changes vs sodium changes vs phosphate changes vs anion gap changes vs treatment group:
Conclusions: no significant findings

4) hematocrit changes vs lactate changes:
Conclusions: no significant findings

5) lactate changes vs creatinine changes vs treatment group:
Conclusions: no significant findings

6) urinary pH vs lactate changes vs treatment group
Conclusions: no significant findings

7) anion gaps vs lactate changes
Conclusions: no significant correlations

8) diarrhea vs Hb drops vs treatment group
Conclusions: no significant findings

7.6 VITAL SIGNS:

Because the sponsor felt that by relieving insulin resistance in patients (putatively with "Syndrome X") that hypertension could then be ameliorated, only reductions in pressure were analyzed and not elevations (as might reasonably be expected given the phenformin experience as reported in the Federal Register, 06 April 1979.)

This analysis although requested from the sponsor in February, has not yet been received. It is to be noted, however, that in the US open-enrollment 89-1C Study there were 17 reported events of "blood pressure increased" (6 moderate) and 115 reported events of "hypertension" (2 severe/ 53 moderate) while only 3 events of "hypotension" were reported.

Nevertheless, this reviewer's analysis of patients reporting "hypertension" as a treatment-emergent AE (hypertension that occurred on treatment which was either absent or present at a lower level of severity at baseline) which was "sustained" (present at that new level or higher on two or more visits) reveals the following significant findings:

TREATMENT EMERGENT SUSTAINED HYPERTENSION

drug \study	**87-1D**		**87-2D**	
	whites	**blacks**	**whites**	**blacks**
metformin	**3/100**	**0/26**	**5/151**	**4/28**
placebo	**5/101**	**2/29**	**--**	**--**
glibenclamide	**--**	**--**	**12/160#**	**1/30**
combination	**--**	**--**	**3/149**	**3/30**

#p<0.05 vs metformin pool MTD +4.83% 95%CI from +1.07% to +8.6% (whites 2D)

The overall changes either pooled (metformin vs control) or in the 2D study (metformin

vs glibenclamide) showed no significant differences. However, there was a significant decrease (4.83%) in reports of sustained treatment-emergent hypertension in white patients with sulfonylurea-failure, and a trend in the opposite direction among blacks in this population.

7.7 EKG's:

On page 08A-01592 (Vol 1.74) of the NDA the sponsor noted clinically "significant EKG changes from baseline" occurred as follows (Sponsor Table 242):

		Significant Change From Baseline	
Study No.	**Treatment**	**Yes**	**No**
87-1D	**Metformin**	**19 (15%)**	**110 (85%)**
	Placebo	**9 (7%)**	**117 (93%)**
87-2D	**Metformin**	**14 (8%)**	**169 (92%)**
	Glyburide	**13 (7%)**	**175 (93%)**
	Combination	**24 (12%)**	**180 (88%)**
Pooled (Sic!)	**Metformin (Monotherapy)**	**33 (11%)**	**279 (89%)**

Only "pooling" metformin monotherapy patients does not make much sense, especially when true pooling based on exposure reveals 57 (10.1%) significantly changed EKG's in patients exposed to metformin as opposed to 22 (6.2%) in unexposed patients. This amounts to an excess risk of +3.9% which has a [significant] 95% CI around it of +0.324% to +7.3%). All of these EKG's as well as similarly significantly changed EKG's from the open-enrollment 1C study were requested from the sponsor on 22 Mar 1994 as decreed by the DMEDP Advisory Committee 4 days prior.

7.8 WITHDRAWAL PHENOMENA:

There does not appear to be any evidence for tolerance or withdrawal.

7.9 ABUSE POTENTIAL:

The only abuse potential may relate to whether or not a suicidal predisposition exists.

7.10 HUMAN REPRODUCTION:

No data is presented in this NDA

7.11 OVERDOSE EXPERIENCE:

There was 1 suicide in the US trials which was described previously and not definitely attributed to ingestion of metformin.

Review of 255 cases of lactic acidosis did reveal 12 suicides (4.71 ± 1.33%, 99% CI 1.28 to 8.13%). These comprised 5 men and 7 women whose ages ranged from 16 to 83 (44.67 ± 16.66 years) on metformin anywhere from 0.25 to 8395 days (1687.72 ± 3353.68 days) taking from 1700 to 38250 mg of metformin (15695.45 ± 10161.35 mg) with metformin blood levels ranging from 39.10 to 110 µg/ml (65.42 ± 23.4 µg/ml). Of the ensuing deaths, 2 were female and 1 was male. Of the survivors, 5 were female and 4 were male. The metformin blood levels trended lower (59.41 ± 17.05 µg/ml) in the 5/9 survivors with drug level data available than in the 2/3 deceased patients with that data available (80.45 ± 29.55 µg/ml). Most of the cases seemed to respond to alkalinization and/or hemodialysis.

(See the sections on "*LACTIC ACIDOSIS*" in "**POTENTIALLY SERIOUS DRUG-RELATED AE'S**", **Section 7.12**and "**OTHER HUMAN SAFETY DATA**", **Section 7.17**)

7.12 POTENTIALLY SERIOUS DRUG-RELATED ADVERSE EVENTS:

7.12.1 LACTIC ACIDOSIS: ****(See also Section 7.17.1)****
The following metabolic, non-hypoglycemic events were noted in the US open-enrollment 89-1C study:

AE/IME	total	mild	moderate	severe
BUN increased[1]	**2**	**2**	**0**	**0**
creatinine clearance decr[1]	**9**	**4**	**5**	**0**
creatinine serum increased[1]	**8**	**6**	**2**	**0**
dehydration[1]	**6**	**0**	**3**	**3**
hyperchloremic acidosis[3]	**1**	**1**	**0**	**0**
ketoacidosis[3]	**1**	**0**	**0**	**1**
ketonuria[2]	**4**	**1**	**1**	**2**
kidney function abnormal[1]	**2**	**1**	**0**	**1**
lactate blood increased[2]	**15**	**2**	**12**	**1**
lactic acidosis[3]	**1**	**0**	**0**	**1**
renal insufficiency[1]	**1**	**0**	**1**	**0**
[1]Renal-related	**28**	**13**	**11**	**4**
[2]Lactatemia/Ketonemia	**19**	**3**	**13**	**3**
[3]Acidosis	**3**	**1**	**0**	**2**
TOTAL	**50**	**17**	**24**	**9**

Please note that there were at least 28 renal-related events all which occurred while on therapy, all but four of which were mild or moderate, and all of which could potentially predispose toward lactic acidosis. In fact 19 patients were removed from this study for this very reason (See **Sections 7.3.3, 7.17.1**).

Nevertheless, despite these preventive withdrawals there were at least two events which classify as lactic acidosis and at least one fatality among the 15 cases of hyperlactatemia seen in this study. The first event was imputational based upon the removal of patient 89-1C-T01-06006 from the study because of:

1) increasing lactates
2) decreasing bicarbonates
3) increased risk of developing lactic acidosis

The second case was 89-1C-F02-10023 [described in great detail earlier in the section dealing with deaths.] She was noted to have documented lactic acidosis

during her final hospitalization. That hospitalization record is pending at the this time.

Lactic acidosis, a known sequel to therapy with metformin, was therefore seen in one patient with sudden death (F02-10023), and renal failure which is known to predispose to lactic acidosis in patients taking metformin, was seen to develop in another patient on metformin who had a sudden, unexplained death (F03-11024). [If this latter case were ascribed to lactic acidosis, a not unlikely scenario, then given 781 patients exposed to metformin for a total of 1136 patient years, there would have been 3 events (see the section on premature terminations for the third patient) and 2 deaths for an event rate of 2.64/1000 PYE and a death rate of 1.76/1000 PYE. This death rate is about sixfold our point estimate of 0.3/1000 PYE and greater than 70% that of the highest FDA estimate (2.5/1000 PYE) of phenformin-associated lactic acidosis mortality at the time phenformin was removed from the market for "imminent hazard."(see **Section 7.17.1.2**)]

Considering two events of lactic acidosis and one death in the clinical trials yields an event rate of 1.76/1000 PYE and a death rate of 0.88/1000 PYE. This death rate is about threefold our point estimate of 0.3/1000 PYE (see **Section 7.17.1.2**). In addition, both of these events have occurred in females. Moreover, there were no episodes of lactic acidosis ascribable to patients taking placebo or glibenclamide monotherapy in the US clinical trials.

7.12.2 CARDIOVASCULAR EVENTS:
Several lines of evidence point to an increased association of metformin therapy and enhanced cardiovascular morbidity and mortality, particularly in patients with sulfonylurea failure:

1) the UGDP[27] noted an excess cardiovascular mortality (6.55/1000 patient years over placebo) with the related drug, phenformin

2) despite the small power and metformin exposure of the US trials in this NDA (1136 pt-years), there was a highly significant excess mortality seen here in [sulfonylurea-failure] patients originally randomized to metformin (see **Section 7.2**)

3) despite the small power and metformin exposure of the US controlled trials in this NDA (305 patient-years), there was a statistically meaningful excess in "significant EKG changes from baseline" seen in patients randomized to metformin (see **Section 7.7**)

4) the UK Prospective Diabetes Study noted an annual hospital admissions rate of 4.4% of 262 obese patients exposed to metformin versus 1.75% of 994 patients unexposed (291 on diet alone, 187 on chlorpropamide, 212 on glibenclamide, and 304 on insulin) - an excess yearly morbidity of 2.83% with 95% CI of this point estimate at 0.195% to 5.46% (see also section **7.17.2**)

5) despite the small power and metformin exposure of the pooled non-US trials in this NDA, there was a significant excess of patients with angina pectoris ($p < 0.05$) in patients exposed to metformin (see **Section 7.4.2**).

The following cardiovascular events were noted in the 89-1C open-enrollment study:

AE/IME	total	mild	moderate	severe
angina pectoris[1]	19	11	5	3
arrhythmia[2]	7	2	4	1
arteriosclerosis[1]	1	1	0	0
atrial fibrillation[2]	4	2	1	1
bundle branch block[2]	1	0	1	0
cardiomegaly[3]	1	1	0	0
cardiomyopathy[3]	1	0	1	0
cardiovascular disorder[4]	2	0	2	0
congestive heart failure[3]	1	1	0	0
coronary artery disorder[1]	10	3	7	0
coronary artery occlusion[1]	2	0	0	2
chest discomfort[1]	6	5	0	1
chest pain[1]	30	17	8	5
chest pain - substernal[1]	3	3	0	0
chest pain -> L arm[1]	1	0	0	1
dizziness[2]	39	17	21	1
dyspnea[3]	7	3	4	0
edema[3]	8	6	2	0
edema extremities[3]	21	15	5	1
edema legs[3]	13	9	4	0
edema peripheral[3]	3	1	2	0
EKG abnormal[2]	1	0	1	0
extrasystoles[2]	1	1	0	0
fluid retention[3]	2	2	0	0
generalized edema[3]	2	0	2	0
heart fluttering[2]	1	0	1	0
infarct[1]	1	0	0	1
ischemia myocardial[1]	1	0	0	1
light-headed[2]	11	7	4	0
myocardial infarction[1]	3	0	2	1
palpitation[2]	10	6	4	0
PVC's[2]	2	1	1	0
shortness of breath[3]	13	9	3	1
SV tachycardia[2]	1	0	1	0
syncope[2]	6	1	3	2
tachycardia[2]	10	7	3	0
tachycardia ventricular[2]	1	0	1	0
tightness in chest[1]	4	3	1	0
TIA[1]	3	1	1	1
ventricular arrhythmia[2]	1	1	0	0

EVENT CLASSES (Pooled):				
AE/IME	**total**	**mild**	**moderate**	**severe**
[1]Ischemic	**84**	**44**	**24**	**16**
[2]Conductive	**96**	**45**	**46**	**5**
[3]Contractile	**72**	**47**	**23**	**2**
[4]Unclassifiable	**2**	**0**	**2**	**0**
TOTAL:	**254**	**136**	**95**	**23**

There appears to be somewhat of an excess in conductive and contractile dysfunction from what might reasonably be expected in this coronary disease prone population. This is reinforced by the increase in EKG abnormalities noted. Keep in mind that a majority of the events were classified as conductive and that 51/96 (53%) of these were either moderate or severe. The contractile disturbances may be a function of the drug's mechanism of action whereby it both inhibits fatty acid oxidation and decreases the shuttling of reducing equivalents from the cytoplasm to the mitochondria. Certainly the tendency of sulonylureas alone to decrease the coronary vasodilatory response to ischemia has been well documented.

The function of the heart depends critically on an adequate oxygen supply through the coronary arteries. Coronary arteries dilate when the intravascular oxygen tension decreases. Hypoxic vasodilation in isolated, perfused guinea pig hearts can be prevented by glibenclamide, a blocker of adenosine triphosphate (ATP)-sensitive potassium channels, and can be mimicked by cromakalim, which opens ATP-sensitive potassium channels. Opening of potassium channels in coronary smooth muscle cells and the subsequent drop in intracellular calcium is probably the major cause of hypoxic and ischemic vasodilation in the mammalian heart.[36,37];

Nevertheless, the potential synergic effects of metformin and sulfonylureas have never been studied under this paradigm.

36Daut J ; Maier-Rudolph W ; von Beckerath N ; Mehrke G ; G:unther K ; Goedel-Meinen L Hypoxic dilation of coronary arteries is mediated by ATP-sensitive potassium channels. [Physiologisches Institut der Technischen Universit:at M:unchen, Biedersteiner, Federal Republic of Germany] *Science* **247**(4948):1341-4, 1990

37Grover GJ ; McCullough JR ; Henry DE ; Conder ML ; Sleph PG Anti-ischemic effects of the potassium channel activators pinacidil and cromakalim and the reversal of these effects with the potassium channel blocker glyburide. Department of Pharmacology, Squibb Institute for Medical Research, Princeton, New Jersey. *J Pharmacol Exp Ther* Oct;**251**(1):98-104, 1989

7.12.3 PANCREATITIS:

Since cases of pancreatitis have been associated with metformin in the lactic acidosis database, it is not unreasonable to ascribe some possible link which might be related to acidosis.[38]

AE/IME	total	mild	moderate	severe
pancreatitis	**3**	**0**	**0**	**3**

7.12.4 HYPOGLYCEMIA:

As seen previously, there was a highly significant increase in hypoglycemia manifested by patients taking combined metformin-sulfonylurea therapy in all controlled trials submitted in this NDA. Combined therapy had an 14.5% excess in hypoglycemia compared with controls for which the 99% CI was 7 to 22%. Though none of these in the short-duration double blind phase appeared to be severe, there were 5 severe and 94 moderate hypoglycemic episodes seen in the US open enrollment 1C trial.

AE/IME	total	mild	moderate	severe
diaphoresis	**15**	**6**	**8**	**1**
glucose_blood_decreased	**6**	**4**	**2**	**0**
hunger_abnormal	**1**	**0**	**0**	**1**
hypoglycemia	**124**	**80**	**42**	**2**
hypoglycemic_reaction	**24**	**14**	**0**	**0**
irritability	**1**	**0**	**1**	**0**
jitteriness	**1**	**0**	**1**	**0**
night sweat	**4**	**3**	**1**	**0**
shakiness	**10**	**8**	**2**	**0**
sweating increased	**17**	**10**	**7**	**0**
tension nervous	**14**	**3**	**10**	**1**
tingling	**7**	**6**	**1**	**0**
tremor	**25**	**17**	**8**	**0**
tremulousness	**3**	**2**	**1**	**0**
TOTAL	**252**	**153**	**94**	**5**

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38 Kahler SG; Sherwood WG; Woolf D; Lawless ST; Zaritsky A; Bonham J; Taylor CJ; Clarke JTR; Durie P; Leonard JV. Pancreatitis in patients with organic acidemias. *J Ped* **124**(2):240-243, 1994

As discussed previously, the (1) selective self-removal of better controlled [glibenclamide] patients from open enrollment (see **Section 7.2.9.1**) and the (2) absent incidence of death in that arm contrasted with the highly significant increase in the other two arms (see **Section 7.2.9.1**) taken with the (3) highly significant increase in hypoglycemia seen with combination therapy (see **Sections 7.4.1-2**) suggests that hypoglycemia might very well be a meaningful factor contributing to the deaths seen in those ther two arms (see **Section 7.17.4**).

7.12.5 DEPRESSION:
Although depression in the open enrollment was only noted 26 times with 12 events classified as mild, 13 as moderate, and 1 severe. Suicidal attempts comprise 11/255 or 4.3% of the lactic acidosis cases on record here [as of 18 Mar 1994]. Therefore, depression could possibly be drug-related.

7.12.6 WEAKNESS/LETHARGY/ASTHENIA:
This lack of energy complex was seen frequently enough in all trials to suggest some possible association. Most of the events were mild to moderate.

AE/IME	total	mild	moderate	severe
asthenia	**15**	**5**	**10**	**0**
fatigue	**69**	**37**	**30**	**2**
lethargy	**18**	**14**	**4**	**0**
malaise	**8**	**5**	**3**	**0**
myasthenia	**5**	**3**	**2**	**0**
tiredness	**8**	**6**	**2**	**0**
weakness-generalized	**24**	**12**	**8**	**4**
weakness-muscle	**1**	**1**	**0**	**0**
TOTAL	**148**	**83**	**59**	**6**

7.13 SERIOUS ADVERSE EVENTS UNLIKELY TO BE DRUG-RELATED:

The following serious AE's/IME's seen in clinical trials were not felt to have enough discriminatory power within the context of the relatively few events seen in this NDA to be causally asssociated with metformin therapy at this time:

BODY AS A WHOLE
accidental injury
ascites
back pain
cellulitis

flank pain
flu (syndrome)
gangrene
infections
lumbo-sacral pain
neck pain
neoplasm (nos)
pain
pain foot
pain leg

CARDIOVASCULAR
aortic stenosis

ENDOCRINE
hypercholesterolemia

MUSCULOSKELETAL
arthritis
bursitis
carpal tunnel syndrome
leg cramps
joint disorder
strain
trigger finger

NERVOUS SYSTEM
insomnia
muscle spasm

RESPIRATORY SYSTEM
bronchitis
carcinoma of the lung
cough
pneumonia
rhinitis
sinusitis
sore throat
upper respiratory tract infection

SKIN
basal cell carcinoma
genital herpes
hives

nail disorder
psoriasis aggravated
rash
skin scaly
ulcer skin

SPECIAL SENSES
cataract
ear disorder (nos)
eye inflamed
macula degeneration
otitis media
retinal hemorrhage
uveitis
vision loss

UROGENITAL SYSTEM
breast carcinoma
calculus ureteral
carcinoma prostatic
cystitis
impotence
kidney pain
kidney stone
menorrhagia
nocturia
polyuria
pyelonephritis
urethral disorder
urinary tract infection

7.14 DRUG-DEMOGRAPHIC INTERACTIONS:

7.14.1 AGE:
Patients over age 65 (n=69) vs those under age 65 (n=495) reported more:

AE's/IME's (52% vs 43%)
asthenia (22% vs 11%)
hypoglycemia (12% vs 7%)
musculoskeletal symptoms (29% vs 22%)
nervous system symptoms (25% vs 16%)
GI symptoms and malabsorption (74% vs 66%)

7.14.2 RACE:

Blacks (84) vs whites (405) experienced *less*:

AE's/IME's (74% vs 89%)
GI symptoms (56% vs 69%)
abdominal discomfort (7% vs 14%)
indigestion (4% vs 11%)
diarrhea (37% vs 50%)
musculoskeletal symptoms (13% vs 25%)
nervous system symptoms (8% vs 18%)
respiratory symptoms (27% vs 37%)

Blacks vs whites experienced *more*:

back pain (9% vs 1%)
lowering of HbA1c (? <-significantly higher baseline , see **Section 6.2.14**)

Accounting for 119/566 (21%) of the US population exposed to metformin, blacks and hispanics had 2/7 (28.6%) of the deaths seen in that population.

The sponsor states on page 02 000464 of Volume 1.1 of this NDA, "**No clear racial differences in occurrence of AE/IMEs were noted excepted** (sic!) **for a greater incidence of Digestive System symptoms in whites compared to blacks.**" The author of another MOR of this NDA mimes on page 55, "**No clear racial differences in occurrence of AE/IMEs were noted excepted** (sic!) **for a greater incidence of Digestive System symptoms in whites compared to blacks**."

Nevertheless, this reviewer's analysis of patients reporting "hypertension" as an AE reveals the following significant finding(where treatment-emergent hypertension had to be present on at least two-visits in order to be "sustained"):

TREATMENT EMERGENT SUSTAINED HYPERTENSION

drug \study	**87-1D**		**87-2D**	
	whites	**blacks**	**whites**	**blacks**
metformin	**3/100**	**0/26**	**5/151**	**4/28**
placebo	**5/101**	**2/29**	**--**	**--**
glibenclamide	**--**	**--**	**12/160#**	**1/30**
combination	**--**	**--**	**3/149**	**3/30**

#p<0.05 vs metformin pool MTD +4.83% 95%CI from +1.07% to +8.6% (whites 2D)

The overall changes either pooled (metformin vs control) or in the 2D study (metformin vs glibenclamide) showed no significant differences. However, there was a significant decrease (4.83%) in reports of sustained treatment-emergent hypertension in white

patients with sulfonylurea-failure, and a trend in the opposite direction (8.74% increase) among blacks in this very same population. These opposing effects, if confirmed, could partially explain the seemingly greater acceptance of biguanides in European countries.

7.14.3 SEX:
Women (309) vs men (255) experienced *more*:
GI symptoms (72% vs 62%)
diarrhea (53% vs 43%)
nausea/vomiting (34% vs 19%)
musculoskeletal symptoms (28% vs 18%)
urogenital events (22% vs 10%)

The 7 deaths in the US trials were evenly distributed among 4 males and 3 females.

7.15 DRUG-DISEASE INTERACTIONS:

7.15.1 SEVERITY OF DIABETES AT BASELINE:
Patients with FBS <200 (n=120) vs >=200 (n=381) had *more*:
respiratory symptoms (40% vs 4%)

Patients with FBS <200 vs >=200 had *less*:
reduction in HbA1c at EOT from baseline (-0.76±1.42 vs -1.27±1.83)
difference -0.51% with 99% CI 0.0388 to 0.981%
reduction in MTD from control HbA1c at EOT (-1.26±1.60 vs -1.45±1.78) (NS)

7.15.2 DIABETES WITH SULFONYLUREA FAILURE:
The highly significant major toxicity, morbidity, and mortality seen in this NDA from therapy with metformin were all seen in patients with sulfonylurea-failure ($p < 0.01$).

7.15.3 RENAL IMPAIRMENT (DECREASED GFR)
Sirtori[39] showed a significant inverse correlation between creatinine clearance and plasma half life for metformin. Study 90-13-6023 showed a significant inverse correlation between age and plasma renal clearance of metformin resulting in a positive correlation between age and plasma levels in the elderly.

Renal impairment appears to correlate significantly with lactic acidosis (see **Section 7.17.1.6**)

39Sirtori CR; Franceschini G; Galli-Kienle M; Cighetti G; Galli G; Bondioli A; Conti F; Disposition of metformin (N,N,-dimethylbiguanide) in man *Clin Pharm Ther* **24**:683-93, 1978

7.15.4 INTERSTITIAL NEPHRITIS/PYELONEPHRITIS/TUBULAR DYSFUNCTION:-
Since metformin is extensively secreted in the renal tubule (over fourfold the filtered load), disorders which impair this function place the individual patient at increased risk of lactic acidosis. Several patients with lactic acidosis and normal creatinine levels who were non-alcoholics had evidence of interstitial types of nephritis (see **Section 7.17.1.6**).

7.15.5 ALCOHOLISM/LIVER DISEASE:-
A significant percentage of patients with metformin associated lactic acidosis (MALA) and low plasma levels of metformin had a history of ethanolism or significant hepatic disease (see **Section 7.17.1.6**). This may also associate with a hepatorenal syndrome. This interaction has been well documented in the fasted guinea pig model.

Although lactic acidosis has been recognized as a potential hazard in biguanide therapy, this complication has been claimed to be extremely rare with dimethylbiguanide (DMBG) (metformin). In the present studies, using the fasted guinea pig, DMBG (125-500 mg/kg i.p.) caused marked dose-related changes in both plasma glucose (43-88% reduction) and blood lactate (3.5-13 fold increase). Lactate/pyruvate ratios were substantially increased. While i.p. doses of 100 mg/kg of DMBG or of 1 g/kg of ethanol produced no changes in plasma glucose, lactate or pyruvate, the two drugs administered conjointly at the indicated doses produced a 53% decrease in plasma glucose and 2 and 10-fold increases in pyruvate and lactate levels respectively, and correspondingly, an increase in the lactate/pyruvate ratio. Ethanol decay curves indicated that DMBG did not significantly influence the disappearance of ethanol from the blood. These results indicate that: (1) doses of DMBG which produce hypoglycemia are associated with lactic acidosis, and (2) this effect of DMBG can be markedly potentiated by ethanol.[40]

7.16 DRUG-DRUG INTERACTIONS:

7.16.1 SULFONYLUREAS:
The highly significant major toxicity, morbidity, and mortality seen in this NDA from therapy with metformin were all seen in patients with sulfonylurea-failure ($p < 0.01$).

As mentioned previously, glibenclamide appeared to significantly increase plasma metformin levels in clinical trials despite the lack of effect in a single dose interaction study. [There were significantly higher drug levels of metformin ($p < 0.05$) in patients also on glibenclamide at both the 1000 (MTD 195 µg/ml with 95% CI of 3.69 to 386 µg/ml) and 2500mg (MTD 112 µg/ml with 95% CI of 6.2 to 218 µg/ml) metformin dose levels when compared to patients at the same doses on metformin monotherapy (in the 87-2D study).]

The major mortality was seen in this population among patients who were not random-

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40Dubas TC ; Johnson W. Metformin-induced lactic acidosis: potentiation by ethanol. *Res Commun Chem Pathol Pharmacol* **33**(1):21-31, 1981.

ized to treatment with glibenclamide alone ($p < 0.01$), but who were treated in open-enrollment with combination metformin-sulfonylurea therapy.

That death was not seen in patients randomized to glibenclamide alone but who took combination therapy in open-enrollment may relate to a major morbidity seen in this NDA, i.e. hypoglycemia. (The (1) selective self-removal of better controlled [glibenclamide] patients from open enrollment and the (2) decreased incidence of death in that arm followed in open enrollment taken with the (3) highly significant increase in hypoglycemia seen with combination therapy suggests that hypoglycemia may be a significant contributing factor to the deaths seen in the other two arms. If this is the case than it renders somewhat less credible the sponsor's argument that the hypoglycemia seen in the double-blind phase of the trials was an ersatz function of the design which kept maximum sulfonylurea therapy fixed while only allowing titration of metformin.)

Metformin appeared to decrease glibenclamide absorption by roughly 25%.

N.B. No other sulfonylureas - all of which have increased renal handling as compared to glibenclamide - had interactions studied.

7.16.2 DRUGS (CATIONIC) SECRETED BY TUBULAR SECRETION:
Studied: cimetidine
Result: "significant increase in plasma and whole blood metformin levels"

7.16.3 DRUGS (ANIONIC) SECRETED BY TUBULAR SECRETION:
Studied: furosemide
Result: increased plasma and whole blood levels (15-22%) despite unchanged urinary excretion and unchanged plasma half-life implying increased filtration secondary to increased Km for secretion, i.e., competitive inhibition of secretion. There was a concomitant decrease (13-31%) in the plasma levels of furosemide.

There were 27/139 or 19.42% patients with lactic acidosis [who had any concomitant therapy listed] taking furosemide at the time of the event.

7.16.4 OTHER DRUGS:
Studied: nifedipine
Result: increased plasma and whole blood levels despite increased urinary excretion and unchanged plasma half-life implying increased absorption from the GI tract

Studied: propranolol
Result: no interactions

Studied: ibuprofen

Result: no interactions

7.17 OTHER HUMAN SAFETY DATA:

Two major sources of safety information with respect to metformin relate to (1) surveillance and journal reports of lactic acidosis and (2) the UK Prospective Study of Diabetes (UKPDS). The UGDP data will be discussed as it relative to phenformin; hypoglycemia will also be discussed relative to sulfonylureas.

7.17.1 Metformin-Associated Lactic Acidosis (MALA)

7.17.1.1 The most recent data available from the Läkesmedelswerket - the Swedish regulatory authority[41] - records 24 cases of acidosis and 19 deaths with metformin therapy. This translates to 0.12045 cases per thousand per year and 0.09 deaths per thousand per year. The comparable incidence rate for phenformin-associated acidosis was 5.3 fold higher at 0.63838 cases per thousand per year and the mortality rate was 4.6 fold higher at 0.41825 deaths per thousand per year.

7.17.1.2 Joseph Lowenstein, a member of the DMEDP Advisory Committee in 1981, summarized the available ratio data at the time[26] for MALA and PALA (phenformin associated lactic acidosis) world-wide which ranged from 1:13 to 2:1 and believed that a ratio of 1:8 appeared to be the most conservative estimate. At the time phenformin was withdrawn and based on prospective studies where spontaneous reports were tabulated retrospectively, FDA had calculated a very high but presumably likely "true incidence" for PALA in the United States of 5 cases per thousand per year ibid. **Based on this figure, a ratio of MALA to PALA of 1:8 suggested a reasonably likely "true incidence" of MALA in the US would be about 0.6 cases per thousand per year**. Lowenstein calculated a mortality rate of 50% from the 18 deaths in 37 cumulative reports over the 24 years from 1968 to 1981 - amply confirmed in this review of 129 fatalities in 255 cases (50.6% [99%CI 42.5 to 58.7]) of MALA reported to date (2/94). Over that ensuing 13 years the reporting rate increased almost sixfold (5.89x) by some 218 cases. (At any rate, 385(,000) x 0.3(deaths per thousand per year) would amount to 115 projected deaths per year from MALA.)

41Benson L, Data from SWEDIS, Läkesmedelswerket, Uppsala, 17 Nov 1993

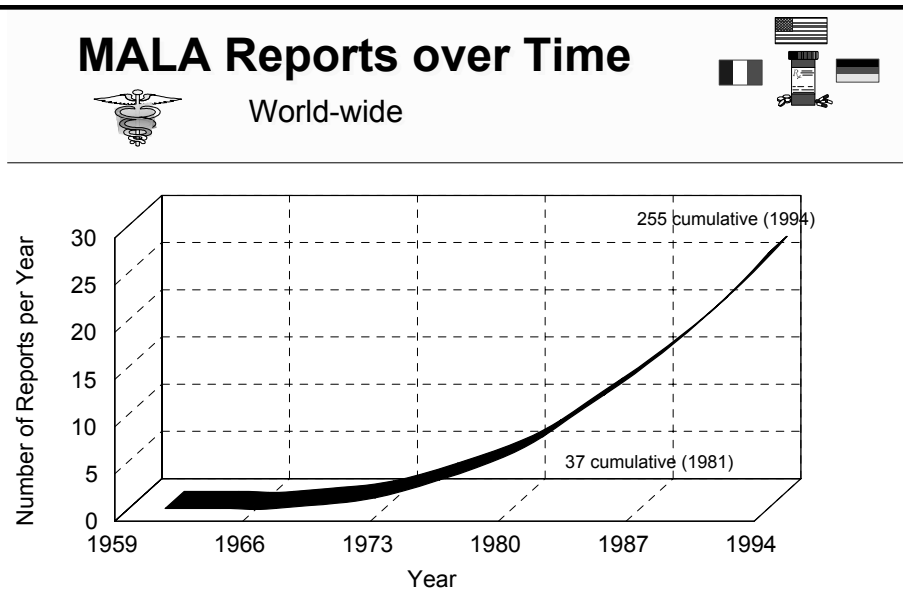
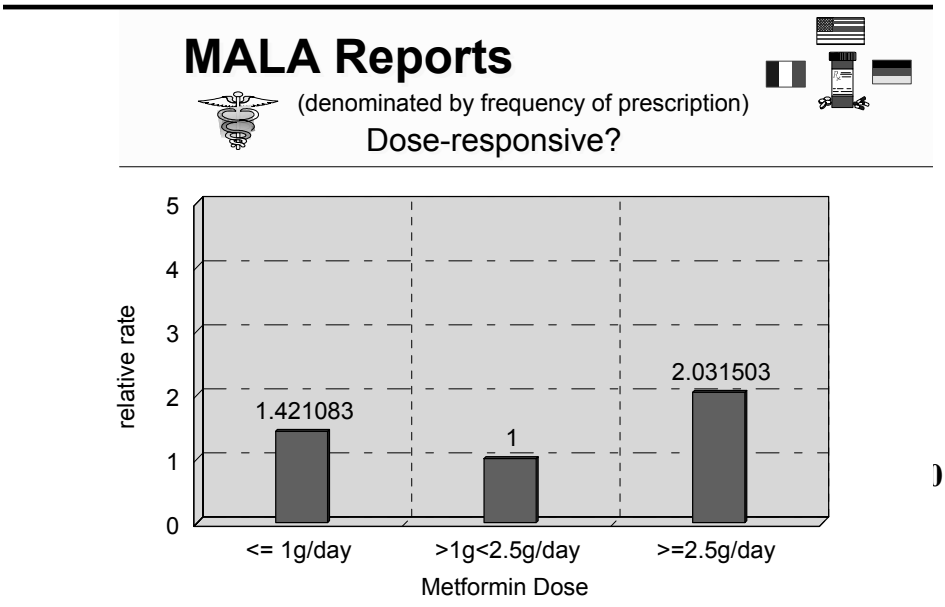


Figure 9

7.17.1.3 MALA reports have been steadily increasing since the drug was marketed in 1959

7.17.1.4 There does not appear to be dose-reponsiveness in MALA , but rather a "U-shaped" curve with increased frequency at both the lower and higher doses.



	n(age)	Age	metformin level	dose	glucose
Total	250	65.39±12.3	22.07±27.0	2.604±3.8	267±225
Men	107	63.90±12.1	24.74±30.4	2.7098±3.3	260±213
Women	143	66.51±12.3	19.80±23.6	2.547±4.2	273±236
Deceased	127	67.63±11.0	19.02±28.4	2.303±4.0	294±233
Men	50	65.90±10.9	26.53±34.7	2.427±3.4	260±188
Women	77	68.75±11.0	13.00±20.2	2.223±4.4	327±265
Survived	123	63.11±13.1	24.58±25.6	2.912±3.5	244±215
Men	57	62.14±12.9	23.35±26.4	2.961±3.2	261±232
Women	66	63.89±13.4	25.68±25.8	2.925±3.8	229±198

7.17.1.5 **The 255 cases in the database current as of the advisory committee does not include the open label death, nor does it include 17 more cases from the UK and 2 more cases from Canada** reported by Robert Turner at the DMEDP Advisory Committee meeting of 18 Mar 1994. That database (of 255 cases) provides the basis for the ensuing discussion.

7.17.1.6 As can be seen from some of these statistics, the "average" patient with MALA
was 65.390 ±12.3 years old (99% CI 63.4 to 67.4)
taking 2.604 ±3.8 grams (99% CI 1.98 to 3.23) of metformin per day
for a 1275.880 ±1870.36 day (99% CI 844 to 1708) duration
with a 22.070 ± 27 µg/ml (99% CI 17.6 to 26.5) metformin blood level
and a 267.000 ± 225 mg/dl (99% CI 230 to 304) glucose level
and a 4.625 ±6.29 mg/dl (99% CI 3.19 to 6.06) creatinine level
and a 7.053 ± 0.254 (99% CI 7.00 to 7.10) pH
and a 24.24 ±10.29 mmHg (99% CI 21.9 to 26.6) pCO2
and a 8.65 ±5.3964 mEq/L (99% CI 7.50 to 9.81) bicarbonate level
and a 16.499 ±32.093 mM/L (99% CI 10.7 to 22.3) lactic acid level
and a 50.800 ±3.16% death rate (99%CI 42.6 to 59).

Women with lactic acidosis tended be highly significantly overrepresented (by 14.4 ± 4.43% [99%CI 2.98 to 25.8]), 2.6 ± 1.56 years older taking 161 ± 491 mg/day less metformin with blood levels 4.94 ± 3.42 µg/ml lower, glucose 13 ± 28.9 mg/dl higher and a death rate 7.12 ± 6.38% higher than men with lactic

acidosis.

Men and women combined who died were significantly older (4.52 ± 1.53 years [99%CI 0.553 to 8.49]) than those who survived. Women who died were significantly older (4.86 ± 2.04 years [95%CI 0.826 to 8.89]) than women who survived, with highly significantly lower metformin blood levels (-12.7 ± 3.85 µg/ml [99%CI -2.63 to -22.7]), significantly higher glucose levels (+98 ± 39.7 [95%CI +19.6 to +176]), significantly lower partial pressures of pCO2 (-4.36 ± 2.07 [95%CI -0.231 to -8.49]), and somewhat lower doses of metformin (-702 ± 693 mg/day) being taken.

Of 140 patients for whom concomitant medication information was provided, 91 (65 ± 4.03% [99% CI 54.6 to 75.4%]) were taking concomitant sulfonylureas, 27 (19.3 ± 3.33% [99% CI 10.7 to 27.9%]) taking digoxin, 66 (47.1 ± 4.22% [99% CI 36.3 to 58.0%]) were taking diuretics (including amiloride, triamterene, spironolactone, furosemide, and others), 12 (8.57 ± 2.37% [99% CI 2.47 to 14.7%]) were taking cimetidine or ranitidine, 14 (10 ± 2.54% [99% CI 3.46 to 16.5%]) were taking calcium channel blockers, 7 (5 ± 1.84% (99%CI 1.47 to 11.8%) had urinary tract infections, and 4 (2.86 ± qns% 99% CI (0.482 to 8.72%) were taking NSAID's.

If this data is representative, it can be estimated with reasonable certainty that 35% (at least 24.6% to at most 45.4%) of patients with MALA (100 - limits of 99% CI for concomitant SFU therapy) come from a population of diabetic *mono*therapy with metformin.

	["GP-normal" creatinines are <2 mg/dl] (Elevated creatinines are >=2mg/dl)		
	[Metformin] >=5	**[Metformin] <5**	**Totals**
Ethanolics	**11**	**11**	**22**
Creatinine data	**9**	**8**	**17**
GP-normal	**2**	**6**	**8**
Elevated	**7**	**2**	**9**
Non-ethanolics	**60**	**41**	**101**
Creatinine data	**43**	**17**	**60**
GP-normal	**11**	**5**	**16**
Elevated	**32**	**12**	**44**
TOTALS	**71**	**52**	**123**
Creatinine data	**52**	**25**	**77**
GP-normal	**13**	**11**	**24**
Elevated	**39**	**14**	**53**

For some reason there is greater deficiciency of metformin drug level data and creatinine data available together in the same patient for those non-ethanolic patients with normal metformin levels.

For those MALA patients who have metformin blood level information available (123/255), it was above normal (>=5 µg/ml) in 71 (57.7 ± 4.45%) and normal (<5 µg/ml) in 52 (42.3 ± 4.45% [99% CI 30.8 to 53.8%]). Of these 123 patients, 22 (17.9 ± 3.46% [99% CI 8.97 to 26.8%) patients had a history of ethanolism and 101 (82.1 ± 3.46%) patients had no such history.

Of those 22 patients with ethanol history, 11 (50 ± 10.7% [99% CI 22.5 to 77.5%]) had normal metformin levels and the other 11 (same statistics) had elevated levels. The patients with ethanolism and elevated metformin levels had worse acidosis and significantly less [CNS] respiratory compensation than the other groups with a mean pH of 6.87 ± 0.31, a mean pCO2 of 27.99 ± 11.16 mmHg, and a mean bicarbonate of 6.14 ± 4.96 mEq/L. Of those patients, the 6 who died had the very worst acidosis ($p < 0.01$) and the most ($p < .05$) CNS respiratory depression with a mean pH of 6.75 ± 0.31, a mean pCO2 of 31.51 ± 10.07 mmHg, and a mean bicarbonate of 4.80 ± 2.66 mEq/L. The 5 alcoholics who survived had better ABG's with a mean pH of 7.01 ± 0.23, a mean pCO2 of 23.76 ± 10.94 mmHG, and a mean bicarbonate level of 7.74 ± 6.40 mEq/L.

Of the 22 ethanolic patients, 8 had creatinine levels < 2mg/dl (here defined as "GP-normal"): 6 of those had normal metformin levels and 2 had elevated metformin levels - a difference of 50 ± 21.7% [95% CI 7.56 to 92.4%]).

Of the 101 non-ethanolic patients, 16 had GP-normal creatinine levels:
5 of those had normal metformin levels and 11 had elevated metformin levels - a difference of -37.5 ± 16.4% [95% CI -5.38 to -69.6%]).

Of those patients with normal metformin and GP-normal creatinine levels, there were significantly more ethanolics (6/8) than non-ethanolics (5/16) by 43.8 ± 19.2% [95% CI 6.12 to 81.4%] and vice-versa for those patients with elevated metformin levels.

Of those 13 patients with elevated metformin levels and GP-normal creatinines, there were sigificantly more non-ethanolics (11) than ethanolics (2) by a difference of 69.2 ± 14.2% [95% CI 41.5 to 97%].

Of the eleven patients with normal metformin levels and GP-normal creatinines, 6 were ethanolics. These were significantly more than the 2 ethanolics from the 13 patients with elevated metformin levels and GP-normal creatinines and by a difference of 39.2 ± 18% [95% CI 3.8 to 74.5%]. This situation is vice-versa for the non-ethanolics.

How is it that metformin levels were increased in 11/16 non-ethanolics with GP-normal creatinines? Was tubular secretion impacted in these patients? Only 2/8 ethanolic patients had elevated metformin levels and GP-normal creatinines - a difference as seen above (*) of 43.8 ± 19.2% [95% CI 6.12 to 81.4%]. A review of the 11/16 non-ethanolics reveals only the following:

A) nifedipine, nicardipine in 2 patients
cimetidine, spironolactone in 1 patient
loop diuretics in 5 patients
digitoxin in 1 patient with dig toxicity (also on loop diuretic)

B) UTI, pyelonephritis in 2 patients

C) overdose in 2 patients

Of the 17 non-ethanolic patients with normal metformin levels, 12/14 had elevated creatinines versus 5/11 who had GP-normal creatinines - a difference of 40.3 ± 17.7% [95% CI 5.59 to 74.9%]. How is it the metformin levels were not elevated in these patients most of whom had abnormal creatinine clearance? Does this imply some synergic effect of renal failure on lactic acidosis (as seen with alcohol) before metformin concentrations elevate?

Most of the events occured in the population (53/77) with elevated creatinines - 68.8 ± 5.28% [99% CI 53.7 to 81.5%]. This excess was enriched in the 39/52 patients with elevated metformin levels - 75 ± 6% [99% CI 56.8 to 88.5%].

There were 19/604 patients who developed elevated creatinines in open-enrollment and who had to be removed from the study for that very reason. This is an event rate of 3.15% with a 99%CI of 1.61 to 5.46%.

==> **Elevations of previously normal creatinines into the abnormal range do occur while patients are on metformin**.

Lowenstein presented further data that metformin inhibits the excretion of an acid load[26] and that many patients with elevated creatinines at the time of MALA normalized after treatment. The Pharmacology Officer Reviewer has documented dose-related amyloid-cystic nephropathy with associated mortality in mice (see also **Section 3.2**).

Women appear to be at increased risk for development of and death from MALA.

Considering two events of lactic acidosis and one death in the clinical trials yields an event rate of 1.76/1000 PYE and a death rate of 0.88/1000 PYE. This death rate is about threefold our point estimate of 0.3/1000 PYE[26] In addition, both of these events have

occurred in females. Moreover, there were no episodes of lactic acidosis ascribable to patients taking placebo or glibenclamide monotherapy in the US clinical trials.

7.17.2 The UK Prospective Diabetes Study(UKPDS)[35]:
The UK Prospective Diabetes Study is a 15-center, prospective, randomized, intervention trial of 2,520 NIDDM patients aged 25 to 65. The UKPDS began in 1977 to determine whether *improved* glycemic control could prevent diabetic complications together with their associated morbidity and mortality. If diet therapy could not lower the fasting glucose to108 mg/dl or below then patients were randomized to either placebo chlorpropamide, glibenclamide, basal ultralente insulin, or, if obese, to all of the preceding plus metformin.

This study noted an annual hospital admissions rate of 4.4% of 262 obese patients exposed to metformin versus 1.75% of 994 patients unexposed (291 on diet alone, 187 on chlorpropamide, 212 on glibenclamide, and 304 on insulin) - an excess yearly morbidity of 2.83% with 95% CI of this point estimate at 0.195% to 5.46%.

7.17.3 The UGDP Data[27]
7.17.3.1 In the phenformin arm of the UGDP, there were 33 non-lactic acidosis deaths out of 204 patients enrolled into that arm. Over the eight years of the study, this amounted to 161.76 deaths per thousand or 20.22 deaths per thousand per year. There were 27 cardiovascular deaths or 132.35 deaths per thousand or 16.544 cardiovascular deaths per thousand per year.

7.17.3.2 In the tolbutamide arm of the UGDP, there were 30 non-lactic acidosis deaths out of 204 patients enrolled into that arm. Over the eight years of the study, this amounted to 147.06 deaths per thousand or 18.38 deaths per thousand per year. There were 26 cardiovascular deaths or 127.45 deaths per thousand or 15.93 cardiovascular deaths per thousand per year.

7.17.3.3 In the insulin arm of the UGDP, there were 10 non-lactic acidosis deaths out of 133 patients enrolled into that arm. Over the eight years of the study, this amounted to 75.19 deaths per thousand or 9.40 deaths per thousand per year. There were 9 cardiovascular deaths or 67.67 deaths per thousand or 8.46 cardiovascular deaths per thousand per year.

7.17.3.4 In the placebo arm of the UGDP, there were 7 non-lactic acidosis deaths out of 64 patients enrolled into that arm. Over the eight years of the study, this amounted to 109.37 deaths per thousand or 13.68 deaths per thousand per year. There were 3 cardiovascular deaths or 46.88 deaths per thousand or 5.86 cardiovascular deaths per thousand per year.

7.17.3.5 The excess total mortality of phenformin over placebo was 6.55 deaths per thousand per year. Assuming that metformin has 1/8th the excess mortality of phenformin, and that 385,000 patients will be taking phenformin of whom ¼ would come from

diet-alone, the excess total mortality over diet-alone attributable to metformin would be 6.55 x 385 x 0.125 x ¼ or 79 patients per year. [The excess cardiovascular mortality of phenformin over placebo was 10.68 deaths per thousand per year.]

7.17.3.6 The excess total mortality of phenformin over tolbutamide was 1.84 deaths per thousand per year. Assuming that metformin has 1/8th the excess mortality of phenformin, and that 385,000 patients will be taking phenformin of whom ½ would come from sulfonylureas, the excess total mortality over sulfonylureas attributable to metformin would be 1.84 x 385 x 0.125 x ½ or 44 patients per year. [The excess cardiovascular mortality of phenformin over tolbutamide was 0.613 deaths per thousand per year.]

7.17.3.7 The excess total mortality of phenformin over insulin was 10.83 deaths per thousand per year. Assuming that metformin has 1/8th the excess mortality of phenformin, and that 385,000 patients will be taking phenformin of whom ¼ would come from insulin, the excess total mortality over insulin attributable to metformin would be 10.83 x 385 x 0.125 x ¼ or 130 patients per year. [The excess cardiovascular mortality of phenformin over insulin was 8.083 deaths per thousand per year.]

7.17.4 Comparative Risks of Hypoglycemia

7.17.4.1 Campbell[42] has calculated that according to SADRAC (Swedish Adverse Drug Reactions Advisory Committee) data, the difference between the attributable risk for mortality from MALA (Metformin-Associated Lactic Acidosis) of 0.0240 deaths per thousand per year and that from glibenclamide-associated hypoglycemia of 0.0332 deaths per thousand per year was negligeable, i.e., 0.0092 deaths per thousand patients per year. This was based on 7 cases of MALA and 2 deaths from 1972-1981.

7.17.4.2 The most recent data available from the Swedish regulatory authorities[41] records 24 cases of MALA and 19 deaths. This translates to 0.12045 cases per thousand per year and 0.09 deaths per thousand per year. This suggests an excess mortality of MALA over that of glibenclamide-hypoglycemia (0.062 deaths per thousand per year.)

7.17.4.3 For the sake of argument, grant that for all practical purposes the rates are equivalent. Data from the NDA[43] show that 7 glibenclamide patients out of 209 (3.35%) in study 87-2D reported hypoglycemic episodes as opposed to 38 combination metformin + glibenclamide patients out of 213 (17.85%). The net difference of 14.5% attributable to adding metformin was highly statistically significant - 99% CI's (7 to 22%).

42Campbell IW. Metformin and the sulfonylureas: the comparative risk. *Horm Metab Res* Suppl **15**:105-11, 1985

43*NDA 20-357*, Volume 1.1, p.02 000426, (Table 56)

7.17.4.4 Lowenstein[26] estimated US MALA mortality at 0.3 deaths per thousand per year. Assume that ½ the 385,000 patients taking metformin will be switched from sulfonylureas (SFU's), of which half again (¼ x 385,000) will be on monotherapy with the other (¼ x 385,000) on combination therapy. This implies a mortality savings of ¼ x 385 x 0.3 or 29 lives. **The projected excess risk attributable to sulfonylurea hypoglycemia would then be** 0.3 x ¼ or **0.075 deaths /1000 PYE**. However, since the incidence of hypoglycemia in the combination therapy patients is higher by 14.5%, it is reasonable to expect some comparable increase in mortality. Campbell, himself[42], suggested a mortality of 9% of the reported cases of sulfonylurea-induced hypoglycemia. The incidence of hypoglycemia in SFU-monotherapy should then be 3.333 cases per thousand per year. Using the lower bounds of the 99% CI of 7% for the attributable difference the projected incidence attributable to combination therapy should be
70 per thousand plus 3.333 per thousand or 73.333 cases per thousand per year. Again using Campbell's figure of 9% for mortality yields an estimate of 6.6 deaths per thousand per year. [This may be confirmed by using Campbell's figure, and using the lower bounds of the 99% CI of 7% for the attributable difference the projected excess mortality attributable to combination therapy should be (0.07 x .09) or 6.3 cases per thousand per year which, when added to the 0.3 deaths per thousand per year yields 6.6 deaths per thousand per year.] This amounts to 385 x 6.6 x ¼ or 635 deaths per year. Assuming Campbell has exaggerated the hypoglycemic mortality fivefold still yields 127 excess hypoglycemic deaths per year from combination. **The projected excess risk attributable to metformin+sulfonylurea combination induced hypoglycemia would then be** 6.6 x ¼ x 0.2 or **0.33 deaths /1000 PYE**.

8. DOSAGE AND INDICATIONS:

The use of metformin, if approved in NIDDM as monotherapy, should be placed in the context of targetable lowering and/or maintenance of HbA1c to below 7% within two-years of initiation of therapy.

[See MOR of John Gueriguian valuable mainly for some dose-ranging considerations. Nevertheless, lactic acidosis appears even at the lowest metformin doses, particularly in alcoholics, cirrhotics, or others with synergistic inhibition of NADH[H+] oxidation or its mitochondrial shuttling.]

If approved, metformin should only be indicated in diabetics who are obese (BMI males >=27, females>=25).

If approved, metformin should be absolutely contraindicated in patients with sulfonylurea failure or in those who are taking concomitant sulfonylurea therapy.

If approved, metformin should be absolutely contraindicated in patients with existing CHD or who are at any increased risk therefrom.

If approved, hemoglobin A1c, creatinine, and electrolytes, blood pressure, and EKG's should be performed every 8 weeks. A line on a date chart (plotted against A1c) should be drawn connecting the before-therapy A1c to a value of 7% exactly 730 days (2 years) later. That line should never lie below the line A1c=7 (parallel to the X-axis) or have any slope >0. Then:

If any two successive values lie above the line, therapy with metformin should be discontinued.

If creatinine values increase above 1.5 therapy with metformin should be ceased.

If any EKG changes develop, therapy with metformin should be ceased.

If blood pressure elevates, therapy with metformin should be discontinued.

If any intercurrent illnesses develop, therapy with metformin should cease until the illness is completely resolved.

If approved, metformin should be contraindicated in patients over age 53 (1 standard deviation below the mean age of patients with lactic acidosis).

If approved, metformin should be contraindicated in patients whose alcoholic intake may exceed 1 oz. on any given day.

If approved, metformin should be contraindicated in patients with clinically significant depression.

If approved, large black box warnings should appear for lactic acidosis, UGDP data, [as well as the findings within this NDA of significantly increased] death, EKG changes, angina, hypoglycemia, and hospitalizations.

9. LABELING REVIEW:

Not applicable *pro-tempore*

10. SPECIAL CONSIDERATIONS:

1) The sponsor has submitted an exceedingly poor application which has required extensive effort to integrate data in order to discover problems which should have been readily apparent. The most revealing data is to be found in the US open-enrollment study (89-1C-6023) for which a complete study report has yet to be finalized or submitted (see **Section 7.3.3**).

2) It would have been better, perhaps, if proper dose-ranging studies and more meaningful drug-interaction studies had been required before NDA submission.

11.1 CONCLUSIONS:

1) The UGDP Study[27] suggested increased mortality, predominantly cardiovascular in nature, associated with phenformin monotherapy. The excess (non-lactic acidosis) mortality was 6.55/1000 over placebo, 1.84/1000 over tolbutamide, and 10.83/1000 over insulin. This was over 1632 patient-years of long- (8 years-)duration, continuous exposure (PYE).

2) This NDA has in its US trials 1136 PYE with more patients exposed but over relatively shorter-duration, and yet therein associated with metformin therapy can be found:

a) **Highly significant excess mortality** (+***6.16 deaths/1000 PYE***, $p<0.01$) in the patients randomized to metformin, and only in those patients randomized to metformin, particularly among the patients with sulfonylurea-failure. At the end of the observation period the death rate exceeded 29/1000 PYE (see **Section 7.2**).

b) **Significant excess in clinically meaningful EKG changes** (+***78/1000 PYE***, $p<0.05$, see **Section 7.7**). There appeared to be somewhat of an excess in moderate to severe conductive and contractile dysfunction than the expected ischemic events in this coronary disease-prone population (see also **Section 7.12.2**).

c) **Highly significantly excess hypoglycemia** (+***290 cases/1000 PYE***, $p<0.01$) in patients taking concomitant sulfonylureas compared with sulfonylurea alone (see **Sections 7.4, 7.12.4**)

d) **Lactic acidosis deaths** occurring at a rate (**0.88/1000 PYE**) which approximates some of the estimates (based on *reports*) for phenformin-associated lactic acidosis deaths in the US (0.90 to 1.05/1000 PYE)[44].

3) The European NDA (**Category ii**) controlled trials with less than 124 PYE has manifested:

Significant excess angina pectoris in pooled patients randomized to therapy with metformin (+***32 cases/1000 PYE***, $p<0.05$, see **Sections 7.4.2, 7.12.2**)

4) The **UKPDS** with 786 PYE has noted:

Significant excess annual hospitalization rates in patients randomized to *mono*therapy with metformin compared to pooled controls (+***28 hospitalizations/1000***

44Lowenstein, *Loc.Cit*, p.128 (reports estimates of 1.8 to 2.1 cases/1000 PYE) and 50% death rate is estimated on page 145

PYE, p <0.05, see **Section 7.17.2**)

5) The patients at most risk of metformin-induced mortality in the US clinical trials appear to be those with sulfonylurea-failure (see **Sections 7.2.12, 7.15.2, 7.16.1**). It is difficult to sort out the precise mechanisms which may underlie this association. The University Group Diabetes Program[27] (UGDP) showed significant excess mortality independently in both the sulfonylurea and biguanide arms - but no study was made of the potential additive effects of the two classes of medication taken simultaneously. The significant excess mortality displayed by the combination therapy among patients with sulfonylurea-failure in the comparatively well-underpowered US trials may, indeed, be a function of this additive phenomenon. Any benefits obtained in patients with sulfonylurea failure - increased compliance (? <= delay of insulin therapy), improved control, decreased treatment emergent sustained hypertension in whites - are far outweighed by the above risks. **Therefore this population of sulfonylurea-failures and/or sulfonylurea concomitants certainly ought to be absolutely excluded from any indication.**

6) *Should this drug be approved for only obese diabetics with dietary-failure who are not taking concurrent therapy with sulfonylureas*?

1) **Pro**:

a) The savings rate for deaths due to ESRD would be 0.08/1000 PYE. (see **Section 6.2.8**)

b) The savings rate for blacks due to ESRD would be 0.33/1000 PYE. (see **Section 6.2.10**)

c) None of the deaths or hypoglycemia occurred in this population. (see **Section 7.2.9**)

d) A registry is likely to be in place to improve the detection of any adverse mortality

2) **Con**:

a) EKG changes were significant only by pooling across *both* populations (see **Section 7.7**)

b) The significant increase in hospitalizations in the UKPDS was demonstrated by just this *mono*therapy population (see **Section 7.17.2**)

c) It can be estimated with reasonable certainty that 35% (at least 24.6% to at most 45.4%) of patients with MALA come from this population of diabetic *mono*therapy with metformin (see **Section 7.17.1.6**)

d) The savings in blacks may only reflect a sampling error with a population manifesting poorer glycemic control at baseline (see **Section 6.2.14**)

e) The UGDP Study showed increased total and cardiovascular mortality in a similar population treated with phenformin *mono*therapy (see **Section 7.17.3**)

f) The projected mortality of metformin in this *mono*therapy population (estimated at 20.2 deaths/1000 PYE) amongst a background estimated at 16 deaths/1000 PYE (see **Section 7.17.3**) is such that not only would 10,000 metformin patients have to

be registered, but so also would 10,000 of their matched controls in order to detect a difference in mortality of 42 patients per year with 95% CI of 5 to 80 excess deaths/year. The logistics of accomplishing this might be a bit cumbersome.

g) **The excess mortality seen in the US trials is still highly significant** (12.4 excess deaths/1000 with 99% CI of 0.4 to 24.4 excess deaths/1000) **when all metformin-randomized patients from both populations are pooled against all patients randomized to a control.**

7) This morbidity and mortality information was *not* available to the advisory committee when it recommended approval of metformin on March 18, 1994.

8) The burden of proof in ***removing*** phenformin from the market for "imminent hazard", according to the Administrative Law Judge at the time, was that FDA

> **..need only raise significant doubts as to the prior showing of safety. Once this threshold burden is met, the manufacturers are required to prove the safety of phenformin.**[45]

This threshold has been far exceeded already, and we are only considering approval. The burden is now upon the sponsor to "prove the safety" of metformin in any given population.

12. RECOMMENDATIONS:

The simplest, safest, and most expedient solution is for approval as monotherapy and non-approval in combination with sulfonylureas.

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Ronald Jay Innerfield, M.D.
Medical Officer
Apr 18, 1994

20-357
HFD-510/20-357/Fleming/Gueriguian/Innerfield
HFD-510/Chiu/Ysern
HFD-510/Jordan/Hertig
HFD-510/Short

45Federal Register, 6 April 1979