CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-748

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-748
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**4/27/2004**
PRODUCT:	**Glumetza®**
INTENDED CLINICAL POPULATION:	**Type 2 diabetes**
SPONSOR:	**Biovail Laboratories Inc.**
DOCUMENTS REVIEWED:	**Vol.**
REVIEW DIVISION:	**Division of Metabolic Endocrine Drug Products (HFD-510)**
PHARM/TOX REVIEWER:	**Herman Rhee, Ph.D.**
PHARM/TOX SUPERVISOR:	**Jeri El-Hage, Ph.D.**
DIVISION DIRECTOR:	**David Orloff, M.D.**
PROJECT MANAGER:	**Jena Weber**

Date of review submission to Division File System (DFS):

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APPENDIX/ATTACHMENTS .....

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval

Preclinical pharmacology and toxicology recommends approval of NDA 21-748, based on the preclinical findings for Glumetza as reviewed in this document.

B. Recommendation for nonclinical studies

The following preclinical findings should be included in labeling instructions as indicated under "Pharmacology Recommendation Section", which is briefly summarized below.

C. Recommendations on labeling:

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times therapeutic exposures based AUC values with the maximum recommended human daily dose of 2000 mg/kg/day. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and in vivo mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at dose up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparison.

Pregnancy:
Teratogenic Effects: Pregnancy Category B

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which result in 3 and 6 times , the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl Oral Solution should not be used during pregnancy unless clearly needed.

Nursing Mothers: Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Metformin hydrochloride (N,N-dimethylbiguanide) is a guanidine derivative that is used to lower blood glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM). Metformin ER is an extended-release (ER) tablet formulation of metformin hydrochloride that is intended for the treatment of NIDDM at dosages up to 2000 mg/day. As NIDDM is a chronic condition, the clinical use of Metformin ER will be long-term. Metformin has been approved in the United States for the treatment of NIDDM since 1994 and has been in use in Europe since 1970. The sponsor conducted a 3-month oral toxicity study in dogs and rodent carcinogenicity studies with the ER formulation. The main findings in the studies did not differ from those obtained with the immediate release formulation and are summarized below.

A 3-month dog study was performed to compare the GI tolerability and toxicity of metformin-ER with metformin-IR (glucophage). Seven dogs per sex received metformin-ER orally at doses of 250, 500, and 1000 mg per day with an additional group dosed with 1000 mg of glucophage. Toxicological evaluations indicate that there were no remarkable differences between metformin-ER and metformin-IR. Pharmacokinetic studies indicate that the rate of drug absorption was slower in metformin-ER than glucophage with a significant reduction in Cmax values. NOAEL appeared to be 250 mg per dog based on GI intolerance.

A two-year carcinogenicity study in rats was performed under acceptable conditions. However, the top dose for female rats (1,200 mg/kg/day) did not represent the MTD, based on body weight decrease. The eCAC did review and concur with the doses evaluated in the study. Based on toxicokinetic data obtained from the 26-week chronic study in female rats, the AUC ratio at the high dose was estimated to be approximately 10-fold human therapeutic exposures. In the 2-year carcinogenicity study, the increased incidence of parathyroid adenomas and diffuse hyperplasia in male rats was not statistically significant. There were no positive carcinogenic findings in female rats.

B. Pharmacologic activity

The pharmacology activity of metformin has been well documented both in animals and humans. The sponsor summarized the main pharmacological properties of metformin in the NDA, based entirely on reports in the scientific literature.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

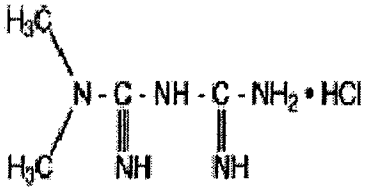
NDA number: 21-748
Review number: 1
Sequence number/date/type of submission: 000/April 27, 2004/Commercial
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: **Biovail Laboratories Inc.**

Manufacturer for drug substance: [redacted]

Reviewer name: Herman Rhee, Ph.D.
Division name: **Division of Metabolic Endocrine Drug Products**
HFD #: 510
Review completion date: Jan. 31, 2005

Drug:

Trade name: **Glumetza®**
Generic name: Metformin HCl Extended Release Tablets 500 and 1000 mg
Code name: NA
Chemical name: Dimethylbiguanide Hydrochloride or *N,N*-dimethylimidodicarbonimidic diamide hydrochloride
CAS registry number: 1115-70-4
Molecular formula: $C_4H_{11}N_5 \cdot HCl$
Molecular weight: 165.63 g/mol
Structure:



Relevant INDs/NDAs/DMFs: IND [redacted], 57,548 [redacted] NDA 20-357; DMF No [redacted]

Drug class: Metformin

Intended clinical population: An adjunct to diet and exercise to improve glycemic control in adult patients (18 years and older) with type 2 diabetes

Clinical formulation: 500 mg tablet contains coloring, hypromellose, magnesium stearate, microcrystalline cellulose and polyethylene oxide while 1000 mg tablet contains crospovidone, dibutyl sebacate, ethylcellulose, glyceryl behenate, polyvinyl alcohol, polyvinylpyrrolidone, and silicon dioxide.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of [NDA 21-748] are owned by [**Biovail Laboratories Inc.**] or are data for which [**Biovail Laboratories Inc.**] has obtained a written right of reference. Any information or data necessary for approval of [NDA 21-748] that [**Biovail Laboratories Inc.**] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that [**Biovail Laboratories Inc.**] does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of [NDA 21-748].]

Studies reviewed within this submission:

1). **A 3-Month Oral Toxicity Study of Metformin ER in Beagle Dogs (Study# 80-0001)**

2). 104-Week Gavage Carcinogenicity Study with Metformin HCl ir [redacted] CD (SD) IGS BR rats (Study Report# [redacted] BIO 00001MET)

Studies <u>not</u> reviewed within this submission: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Metformin has been approved in the United States for the treatment of Type 2 diabetes mellitus (NIDDM) since 1994 and has been in use in Europe since 1970. For this reason, the sponsor did not perform additional nonclinical pharmacology studies with metformin. The antihyperglycemic mechanism of metformin is not completely understood and probably several actions are involved. At therapeutic doses, metformin does not lower plasma glucose levels in non-diabetic animals or humans. However, oral administration of metformin effectively decreased plasma glucose levels in several different animal models such as streptozotocin-induced mice, genetically diabetic KK mice, obese female *fa/fa* rats, and alloxan-induced diabetic rats.

Several studies have been conducted, both *in vitro* and *in vivo*, to determine the effects of metformin on glucose uptake into tissues, glucose oxidation, and glycogen synthesis. In general, metformin potentiates insulin-mediated glucose uptake into tissues, with the skeletal muscle being the most important site. This effect of metformin appears to be due to facilitation of a post-receptor sensitivity to insulin. Metformin was shown to have no effect on basal or insulin stimulated glucose oxidation in muscle from non-diabetic mice but potentiated glucose oxidation in muscle from streptozotocin-diabetic mice in the presence of insulin. Metformin also increased basal glucose oxidation in adipocytes from non-diabetic rats.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. The following mechanisms of action have been suggested: 1) increased insulin receptor binding; 2) decreased intestinal glucose absorption; 3) increased cellular glucose uptake; 4) decreased hepatic gluconeogenesis; 5) stimulation of anaerobic glycolysis; and 6) potentiation of insulin action at the receptor or post-receptor level.

A direct effect of metformin on insulin secretion has been ruled out as a mechanism for the antihyperglycemic effects because metformin does not increase circulating levels of insulin nor has it been shown experimentally to stimulate insulin secretion. Some studies have demonstrated that metformin produces an increase in insulin receptor binding or an increase in low-affinity receptor number. Animal studies have demonstrated that metformin inhibits intestinal glucose absorption in both normal and diabetic animals, although the concentrations necessary to produce this effect are usually higher than the therapeutic range. The inhibition of intestinal glucose absorption does not appear to account for the full ability of metformin to reduce glycemia, indicating that other mechanisms of action play a role. The effect of metformin on glucose absorption has not been confirmed in diabetic patients. Studies at the cellular level indicate that metformin

potentiates insulin action and results from *in vitro* studies support a post-receptor mechanism of action.

Drug activity related to proposed indication:

In addition to antihyperglycemic effects, metformin has been shown to have hypolipidemic effects and to significantly improve the progression and regression of atherosclerotic lesions in animal models. Metformin has been shown to be effective in inhibiting fructose- and fat-induced hypertriglyceridemia; it appears that metformin inhibits the transfer of dietary triglyceride from the gastrointestinal tract into plasma and reduces the uptake of the absorbed lipid by adipose tissue. Metformin also altered lipid metabolism in the aortic wall, inhibiting intramural lipid biosynthesis.

2.6.2.3 Secondary pharmacodynamics

In normal rats, metformin had no effect on either hepatic enzyme, while intestinal ACAT was significantly decreased. Diabetic rats showed significantly higher intestinal HMG-CoA reductase activity when compared with normal controls, while intestinal ACAT activity was similar to control values. Metformin treatment caused a marked decrease in both intestinal HMG-CoA reductase and ACAT activity. These results suggest that metformin exerts its effect on cholesterol metabolism at the intestinal level, resulting in reduced HMG-CoA reductase and ACAT activities in alloxan-diabetic rats.

The effect of metformin on plasma cholesterol and high-density lipoprotein (HDL)-cholesterol were studied in normal male Sprague-Dawley rats treated for 8 weeks with IP injections of metformin (60 mg/kg/day). Neither plasma cholesterol, HDLcholesterol, nor the total cholesterol:HDL-cholesterol ratio was significantly altered by metformin treatment throughout the 8-week period. Metformin significantly lowered plasma cholesterol and phospholipids, but not triglycerides in control rabbits. In the cholesterol + metformin group, cholesterol was lowered by approximately 30% as compared with the cholesterol group, but levels remained generally high. Triglycerides in the cholesterol + metformin group were higher than in the cholesterol group, while phospholipids were significantly decreased.

2.6.2.5 Pharmacodynamic drug interactions

There were no significant changes in N-demethylation or hydroxylation, epoxide hydrase activity, or levels of cytochrome P450 at 36 hours after the last treatment of 25 mg/kg/day metformin PO twice a day for 10 days. However, liver blood flow was significantly increased in treated animals. Therefore, it was postulated that an increase in liver blood flow might explain the drug interaction between metformin and phenprocoumon that has been observed in diabetic patients where the therapeutic dose of phenprocoumon needed to be increased

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Metformin alone or in combination with other antidiabetic drugs such as sulfornyl ureas or thiazolindediones has been used for the control of type 2 diabetes mellitus. The primary and secondary pharmacodynamics, safety pharmacology, pharmacokinetics, toxicokinetics and toxicology of metformin are well characterized. Therefore, the sponsor was requested to submit a 3-month oral toxicity study of metformin ER in Beagle dogs to bridge this new ER formulation with conventional metformin preparations for the NDA. The sponsor submitted the results of the 3-month oral toxicity study with metformin in dogs and carcinogenicity data.

2.6.6.3 Repeat-dose toxicity:

Sponsor's ID #/study#: 80-0001
Sponsor's original title: A 3-Month Oral Toxicity Study of Metformin ER in Beagle Dogs
Study Number: Study NO. 3530.1
Conducting laboratory:

Date of study initiation: June 19, 2000
GLP compliance: Yes
QA Report: Yes (x) No ()
Methods:
Dosing information

- **Species: Beagle dogs**
- **#/sex/group or time point:** Total 7 dogs/sex/group (4 dogs/sex/day for main study and 3 dog/sex/day for interim sacrifice on Day 28). Group 1 was a placebo control group. Group 2, 3, and 4 had Metformin ER at doses of 250, 500, and 1000 mg/day, respectively, while group 5 had glucophage 500 mg/day as shown in a table below.

- **Age**: 5 months
- **Weight:** Male: 6.0-7.7 kg; Female 5.3-6.4 kg
- **Satellite groups used for toxicokinetics or recovery: NA**
- **Dosage groups in administered units:** Metformin-ER at doses of 250, 500, 1000 mg/dog/day and glucophage (1000 mg)
- **Route, form, volume, and infusion rate (if i.v.):** Oral

Group	No. of Animals		Dosage Material	No. of Tablets/Day[a]	
	Male	Female		a.m.	p.m.
1	7	7	Metformin ER Placebo	1	1
2	7	7	Metformin ER	½	0
3	7	7	Metformin ER	1	0
4	7	7	Metformin ER	1	1
5	7	7	Glucophage®	1	(1[b])

Note: Three males and three females from each group were necropsied following 28 days of dosing. Females in Groups 3, 4 and 5 were dosed for 28 days, and females that remained following the interim necropsy (four dogs, two dogs and two dogs, respectively) were placed on recovery for 29 days and euthanized on Day 58/59. The remaining males in all groups and females in Groups 1 and 2 were dosed a minimum of 91 days.

[a]Each tablet contained 500 mg of the appropriate active material; animals dosed twice a day received doses approximately 7 hours apart each day.
[b]Beginning on Day 3, Group 5 animals received one tablet in the morning only.

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Drug, lot#, radiolabel (if applicable), and % purity: Metformin ER 500 mg tablets, 000012

Formulation/vehicle: Inactive ingredients are commonly used in pharmaceutical oral tablets marketed in the U.S.A. as listed under "Clinical formulation (and components)" above.

Times at which Observations are made:

- **Clinical signs:** Twice daily: once prior to dosing and within 2 hours after dosing
- **Body weights:** Days –3, 1 and then weekly
- **Food consumption**: Days –8 to –1 and then daily
- **Ophthalmoscopy**: Day –16 and Days 26 and 53 and 88
- **EKG:** Days –7 or –6 and Days 4, 54 or 85 1 hour after dosing
- **Hematology:** Days –5 or –4 and Days 26, 57 and 88
- **Clinical chemistry:** Days –5 or –4 and Days 26, 57 and 88
- **Urinalysis:** Days –5 or –4 and Days 26, 57 and 88
- **Gross pathology:** At the time of death or sacrifice
- **Organs weighed:** At the time of death, sacrifice, or necropsy
- **Histopathology:** At the time of death or sacrifice
- **Toxicokinetics:** Days 0, 26, and 88 at 1, 2, 4, 6, 8, 12, and 24 hours after the dose

RESULTS:

• Clinical signs and mortality: Two high-dose females (1000 mg Metformin ER group 4 #539 and #D560) were euthanized on days 11 and 20. Two glucophage-treated females (Group 5) were euthanized on day 3 (group 5 #D567) and day 23 (group 5 #D552). One Group 3 male (#D524) died on Day 77 accidentally. Due to body weight decreases in groups 3, 4, and 5 females were euthanized on Day 58 and 59.

With the exception of vomitus in the low-dose females, clinical signs noted in the low-dose group were generally unremarkable and comparable to the signs noted in the control group. Clinical signs noted in these animals were vomitus, mucoid materials in the cage or tray, lateral recumbency, slow and congested breathing, pale mucosal membranes, and diarrhea as shown below. It appears that the clinical signs slightly increased as the doses increased in males so that the clinical signs in the HD were comparable to those in group 5. Black stools and tremors were also noted in some drug-treated animals. A dose-related increase in vomitus in the females treated with Metformin ER was also noted in the high-dose males and glucophage–treated animals. In general, the clinical effects of Metformin-ER in the MD dose group were similar to those observed in the group 5.

TABLE 1

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN PJ
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS AND PHYSICAL EXAMINATION DATA
(OCCURRENCE/ANIMALS AFFECTED)

----- M A L E -----

TABLE RANGE:	DAY 1 TO DAY 30				
GROUP:	1	2	3	4	5
LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:	2	1	1	2	1
TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
NORMAL					
-NO CLINICAL SIGNS	31/ 7	23/ 6	25/ 7	22/ 7	20/ 7
DEAD					
-SCHEDULED EUTHANASIA	3/ 3	3/ 3	3/ 3	3/ 3	3/ 3
ACTIVITY					
-ACTIVITY DECREASED	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
EXCRETA					
-MUCOID STOOLS	8/ 4	10/ 3	9/ 2	30/ 7	9/ 3
-SOFT STOOLS	12/ 3	19/ 4	22/ 6	19/ 7	23/ 4
-VOMITUS	8/ 4	5/ 3	8/ 5	40/ 7	23/ 7
-PARTIAL TABLET(S) FOUND IN CAGE/TRAY	1/ 1	0/ 0	1/ 1	3/ 3	0/ 0
-FEW FECES	0/ 0	0/ 0	7/ 3	37/ 6	20/ 6
-NO FECES	0/ 0	0/ 0	3/ 1	8/ 5	7/ 4
-COLORED MUCOID MATERIAL IN CAGE/TRAY	0/ 0	0/ 0	3/ 2	16/ 5	3/ 2
-DIARRHEA	1/ 1	1/ 1	2/ 1	4/ 2	11/ 6
-RED MATERIAL IN CAGE/TRAY	1/ 1	0/ 0	0/ 0	0/ 0	1/ 1
-BLACK STOOLS	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-PARTIAL TABLET FOUND IN FECES	0/ 0	0/ 0	1/ 1	2/ 2	0/ 0
-MUCOID MATERIAL IN CAGE/TRAY	1/ 1	1/ 1	1/ 1	2/ 2	1/ 1
BODY					
-SCAB(S)	1/ 1	2/ 2	1/ 1	3/ 2	1/ 1

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN PA
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS AND PHYSICAL EXAMINATION DATA
(OCCURRENCE/ANIMALS AFFECTED)

----- M A L E -----

TABLE RANGE:	DAY 1 TO DAY 30				
GROUP:	1	2	3	4	5
LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:	2	1	1	2	1
TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
BODY					
-LESION(S) ON FOOTPAD(S)	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-DEHYDRATION	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
EYES					
-OCULAR DISCHARGE	0/ 0	0/ 0	2/ 1	1/ 1	4/ 1
NOSE/MOUTH					
-LOCALIZED AREA OF RED	0/ 0	5/ 1	0/ 0	0/ 0	0/ 0
-SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
QUALT FOOD/WATER					
-FOOD FED	7/ 7	7/ 7	7/ 7	7/ 7	0/ 0
-FOOD REMOVED	7/ 7	7/ 7	7/ 7	7/ 7	0/ 0
POST-DOSE					
-VOMITUS	0/ 0	1/ 1	0/ 0	0/ 0	11/ 5
-MUCOID STOOLS	2/ 1	5/ 4	2/ 2	1/ 1	2/ 1
-MUCOID MATERIAL IN CAGE/TRAY	2/ 1	1/ 1	0/ 0	1/ 1	1/ 1
-COLORED MUCOID MATERIAL IN CAGE/TRAY	0/ 0	1/ 1	2/ 1	2/ 2	0/ 0
-SOFT STOOLS	1/ 1	3/ 2	1/ 1	0/ 0	2/ 2
-SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
PHYSICAL EXAM					
-NORMAL	5/ 5	4/ 4	5/ 5	6/ 6	6/ 6

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN PAG
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS AND PHYSICAL EXAMINATION DATA
(OCCURRENCE/ANIMALS AFFECTED)

----- M A L E -----

TABLE RANGE:	DAY 31 TO DAY 92				
GROUP:	1	2	3	4	5
LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:	2	1	1	2	1
TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
NORMAL					
-NO CLINICAL SIGNS	30/ 4	18/ 3	23/ 4	15/ 4	15/ 4
DEAD					
-FOUND DEAD	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
-SCHEDULED EUTHANASIA	4/ 4	4/ 4	3/ 3	4/ 4	4/ 4
ACTIVITY					
-ACTIVITY DECREASED	0/ 0	0/ 0	0/ 0	10/ 2	0/ 0
-IMPAIRED MOBILITY	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
EXCRETA					
-MUCOID STOOLS	9/ 3	31/ 4	24/ 4	54/ 4	11/ 3
-SOFT STOOLS	8/ 4	62/ 4	20/ 4	9/ 3	8/ 3
-VOMITUS	11/ 3	11/ 4	15/ 4	31/ 4	12/ 4
-PARTIAL TABLET(S) FOUND IN CAGE/TRAY	1/ 1	0/ 0	0/ 0	1/ 1	0/ 0
-FEW FECES	0/ 0	2/ 1	2/ 2	17/ 4	1/ 1
-NO FECES	0/ 0	2/ 1	0/ 0	3/ 2	0/ 0
-COLORED MUCOID MATERIAL IN CAGE/TRAY	0/ 0	0/ 0	4/ 2	24/ 3	0/ 0
-DIARRHEA	0/ 0	11/ 3	5/ 4	0/ 0	1/ 1
-RED MATERIAL IN CAGE/TRAY	0/ 0	0/ 0	2/ 1	0/ 0	0/ 0
-PARTIAL TABLET FOUND IN FECES	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
-MUCOID MATERIAL IN CAGE/TRAY	0/ 0	2/ 1	0/ 0	2/ 2	0/ 0
-TABLET(S) FOUND IN CAGE/TRAY	3/ 2	0/ 0	0/ 0	0/ 0	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN BEAGLE DOGS
CLIENT: DEPOMED, INC.
CLIENT NO.: 80-0001 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS AND PHYSICAL EXAMINATION DATA (OCCURRENCE/ANIMALS AFFECTED)

----- F E M A L E -----

TABLE RANGE:	DAY 1 TO DAY 30				
GROUP:	1	2	3	4	5
LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:	2	1	1	2	1
TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
NORMAL					
-NO CLINICAL SIGNS	27/ 7	29/ 7	16/ 6	16/ 7	15/ 7
DEAD					
-FOUND DEAD	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-EUTHANIZED MORIBUND	0/ 0	0/ 0	0/ 0	2/ 2	1/ 1
-SCHEDULED EUTHANASIA	3/ 3	3/ 3	3/ 3	3/ 3	3/ 3
ACTIVITY					
-LATERAL RECUMBENCY	0/ 0	0/ 0	1/ 1	2/ 2	0/ 0
-PROSTRATION	0/ 0	0/ 0	1/ 1	2/ 2	0/ 0
-ACTIVITY DECREASED	0/ 0	0/ 0	0/ 0	1/ 1	1/ 1
-ANIMAL STRUGGLED DURING DOSING	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
RESPIRATORY					
-SLOW BREATHING	0/ 0	0/ 0	0/ 0	2/ 2	0/ 0
-CONGESTED BREATHING	0/ 0	0/ 0	0/ 0	2/ 2	0/ 0
EXCRETA					
-MUCOID STOOLS	16/ 5	9/ 5	19/ 5	16/ 6	10/ 6
-SOFT STOOLS	16/ 5	9/ 3	8/ 5	10/ 6	15/ 5
-VOMITUS	6/ 4	7/ 4	21/ 5	24/ 7	12/ 6
-PARTIAL TABLET(S) FOUND IN CAGE/TRAY	0/ 0	1/ 1	3/ 2	5/ 4	0/ 0
-FEW FECES	0/ 0	0/ 0	44/ 6	23/ 6	34/ 5

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN PAGE 8
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS AND PHYSICAL EXAMINATION DATA
(OCCURRENCE/ANIMALS AFFECTED)

----- F E M A L E -----

TABLE RANGE:	DAY 1 TO DAY 30				
GROUP:	1	2	3	4	5
LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:	2	1	1	2	1
TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
EXCRETA					
-NO FECES	0/ 0	0/ 0	7/ 3	6/ 4	13/ 4
-COLORED MUCOID MATERIAL IN CAGE/TRAY	2/ 2	3/ 1	3/ 2	23/ 7	6/ 4
-DIARRHEA	2/ 2	0/ 0	0/ 0	0/ 0	7/ 4
-RED MATERIAL IN CAGE/TRAY	0/ 0	0/ 0	1/ 1	1/ 1	1/ 1
-BLACK STOOLS	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-PARTIAL TABLET FOUND IN FECES	1/ 1	0/ 0	1/ 1	2/ 2	0/ 0
-MUCOID MATERIAL IN CAGE/TRAY	1/ 1	1/ 1	4/ 3	5/ 4	2/ 2
BODY					
-SCAB(S)	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-COOL TO TOUCH	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
-LESION(S) ON FOOTPAD(S)	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-DEHYDRATION	0/ 0	0/ 0	3/ 2	1/ 1	4/ 2
EYES					
-OCULAR DISCHARGE	0/ 0	2/ 1	0/ 0	2/ 2	0/ 0
NOSE/MOUTH					
-MUCOSAL MEMBRANES PALE IN COLOR	0/ 0	0/ 0	1/ 1	2/ 2	0/ 0
-SLOW TO NO CAPILLARY REFILL	0/ 0	0/ 0	1/ 1	2/ 2	0/ 0
-SALIVATION	0/ 0	0/ 0	0/ 0	1/ 1	6/ 3
QUALT FOOD/WATER					
-FOOD FED	7/ 7	7/ 7	7/ 7	7/ 7	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN PAGE 12
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS AND PHYSICAL EXAMINATION DATA
(OCCURRENCE/ANIMALS AFFECTED)

----- F E M A L E -----

TABLE RANGE:	DAY 60 TO DAY 93				
GROUP:	1	2	3	4	5
LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:	2	1	1	2	1
TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
NORMAL					
-NO CLINICAL SIGNS	15/ 4	17/ 4			
DEAD					
-SCHEDULED EUTHANASIA	4/ 4	4/ 4			
EXCRETA					
-MUCOID STOOLS	20/ 4	5/ 3			
-SOFT STOOLS	11/ 3	2/ 2			
-VOMITUS	4/ 2	7/ 3			
-COLORED MUCOID MATERIAL IN CAGE/TRAY	1/ 1	0/ 0			
-DIARRHEA	2/ 2	1/ 1			
-MUCOID MATERIAL IN CAGE/TRAY	0/ 0	1/ 1			
BODY					
-SCAB(S)	2/ 2	1/ 1			
POST-DOSE					
-TABLET FOUND IN CAGE/TRAY - READMINISTERED	0/ 0	1/ 1			
-MUCOID STOOLS	3/ 2	5/ 3			
-DIARRHEA	1/ 1	1/ 1			
-PARTIAL TABLET(S) WITHIN NORMAL STOOLS	0/ 0	1/ 1			
PHYSICAL EXAM					
-NORMAL	4/ 4	4/ 4			

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.
SURVIVING FEMALES IN GROUPS 3, 4 AND 5 WERE EUTHANIZED ON DAY 58/59.

APPEARS THIS WAY ON ORIGINAL

• Body weights: Body weight decreased in a week after the test article treatment for both sexes in mid-, high-dose and glucophage-treated groups, which was due to reduction in food consumption. At the end of 4 weeks of study, high-dose males had lost 10% of their original body weight and weighed 23% less than placebo controls. Body weights in the HD group males reduced from Days 36 to78 as shown in tables below. Mean body weight in the Glucophage group was significantly decreased from Days 64 through 78.

In females, Metformin ER reduced body weight significantly in the MD on Days 29 and in the HD on Days 8, 22, and 29. Glucophage also reduced body weight on Days 22, and 29. The sponsor euthanized surviving females in groups 3, 4, and 5 on Days 58 and 59 due to weight loss-related moribundity.

TABLE 2

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN PAGE
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF BODY WEIGHT DATA (GRAMS)

----- M A L E -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
	NUMBER OF DOSES/DAY:	2	1	1	2	1
	TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
DAY 1	MEAN	6872	6797	6828	6865	6778
	S.D.	414.1	433.1	398.3	372.9	568.2
	N	7	7	7	7	7
DAY 8	MEAN	7161	6837	6514	6201**	6285*
	S.D.	478.7	528.5	405.5	631.1	392.2
	N	7	7	7	7	7
DAY 15	MEAN	7585	7318	6956	6414*	6634
	S.D.	605.5	717.7	522.5	964.4	795.0
	N	7	7	7	7	7
DAY 22	MEAN	7925	7657	7277	6280#	7137
	S.D.	563.7	740.9	523.0	835.2	720.2
	N	7	7	7	7	7
DAY 29	MEAN	8011	7642	7408	6122#	7424
	S.D.	686.4	702.5	555.6	816.1	779.3
	N	7	7	7	7	7
DAY 36	MEAN	8908	8394	7826	6366**	7485
	S.D.	554.7	698.7	826.9	1208.6	797.1
	N	4	4	4	4	4
DAY 43	MEAN	9263	8606	8223	6287**	7747
	S.D.	508.1	706.4	651.0	1548.9	671.0
	N	4	4	4	4	4

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01; # = P<0.001

APPEARS THIS WAY
ON ORIGINAL

TABLE 2

STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN PAGE
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF BODY WEIGHT DATA (GRAMS)

----- M A L E -----

		GROUP:	1	2	3	4	5
		LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
		NUMBER OF DOSES/DAY:	2	1	1	2	1
		TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
DAY	50	MEAN	9573	8831	8594	7234**	8188
		S.D.	573.8	682.3	485.3	1246.6	860.0
		N	4	4	4	4	4
DAY	57	MEAN	9731	8863	8718	7226**	8242
		S.D.	577.3	532.7	580.7	879.1	905.2
		N	4	4	4	4	4
DAY	64	MEAN	10027	9128	8756	7685**	8320*
		S.D.	533.2	744.2	435.1	744.8	911.7
		N	4	4	4	4	4
DAY	71	MEAN	10528	9663	9220	8363**	8632*
		S.D.	634.9	913.1	553.6	625.2	941.6
		N	4	4	4	4	4
DAY	78	MEAN	10480	9661	9230	8376**	8742*
		S.D.	476.9	831.9	566.4	624.4	880.4
		N	4	4	3	4	4
DAY	85	MEAN	10754	9790	9202	8764*	8932*
		S.D.	613.3	918.3	550.3	696.9	964.8
		N	4	4	3	4	4
DAY	92	MEAN	10577	9963	8905	8685	8960
		S.D.	786.6	1171.8	761.1	381.3	1203.4
		N	4	4	3	4	4

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01

APPEARS THIS WAY
ON ORIGINAL

TABLE 2
STUDY NO.: 3530.1 A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN
CLIENT: DEPOMED, INC. BEAGLE DOGS
CLIENT NO.: 80-0001 SUMMARY OF BODY WEIGHT DATA (GRAMS)

----- F E M A L E -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
	NUMBER OF DOSES/DAY:	2	1	1	2	1
	TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
DAY 1	MEAN	5731	5771	5799	5736	5735
	S.D.	281.2	326.5	273.6	242.8	339.7
	N	7	7	7	7	5
DAY 8	MEAN	5999	5809	5462	5031**	5906
	S.D.	302.1	343.8	432.4	400.3	821.1
	N	7	7	7	7	6
DAY 15	MEAN	6379	6224	5637	5415	5469
	S.D.	334.4	413.0	886.4	541.0	775.1
	N	7	7	7	6	6
DAY 22	MEAN	6599	6510	5572	5256*	5364*
	S.D.	339.4	416.4	995.4	542.2	821.6
	N	7	7	7	5	6
DAY 29	MEAN	6666	6444	5582*	5298*	5448*
	S.D.	362.6	386.4	1073.6	507.4	826.0
	N	7	7	7	5	5
DAY 36	MEAN	6867	6839	5840	6423	5814
	S.D.	546.0	612.1	860.1	--	--
	N	4	4	4	2	2
DAY 43	MEAN	7041	6974	6009	6765	6383
	S.D.	630.5	714.4	1113.9	--	--
	N	4	4	4	2	2

SIGNIFICANTLY DIFFERENT FROM CONTROL: * - P<0.05; ** - P<0.01
NOTE: STANDARD DEVIATIONS WERE NOT CALCULATED AND STATISTICAL ANALYSES WERE NOT PERFORMED WHEN N < 2.

APPEARS THIS WAY
ON ORIGINAL

3-Month Oral Toxicity Study of Metformin ER in Male Dogs: Body Weight (Gram)					
Group	Control	250 m/k/d	500 m/k/d	1000 m/k/d	Glucophage@
Day 36	8908	8394	7826	6366*	7485
Day 50	9573	8831	8594	7234*	8188
Day 64	10027	9128	8756	7685*	8320*
Day 78	10480	9661	9230	8376*	8742*
Day 92	10577	9963	8905	8685	8960
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Body Weight (Gram)					
Day 36	6867	6839	5840^	6423^	5814^
Day 50	7325	7110	6395^	7138^	6788^
Day 64	7410	7002			
Day 78	7649	7501			
Day 92	7717	7545			
@Dose = 500 m/k/d. *P<0.05 and ^ indicates that the animals were in recovery without drug treatment after 4-week study due to excessive loss of body weight with reduced food consumption.					

Food consumption: Food consumption was not significantly impaired in male dogs in Metformin ER groups. However, Glucophage reduced body weights in males on Days 36 and 64 as shown below. Significant reduction in food consumption was observed even in the LD female dogs from Day 64 to the end of the study.

3-Month Oral Toxicity Study of Metformin ER in Male Dogs: Food Consumption in gram/day					
Group	Control	250 m/k/d	500 m/k/d	1000 m/k/d	Glucophage@
Days 36-42	335	317	335	363	293*
Days 50-56	352	292	341	358	313
Days 64-70	354	332	347	346	327*
Days 71-77	342	341	362	340	329
Days 78-84	333	333	321	318	333
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Food Consumption@					
Days 36-42	311	277	199	211*	247
Days 50-56	325	255	327	311	276
Days 64-70	325	285*			
Days 71-77	318	291*			
Days 78-84	318	285*			
@Dose = 500 m/k/d. *P<0.05. There were only two animals from day 36 in females.					

A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN BEAGLE DOGS
SUMMARY OF FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

----- M A L E -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
	NUMBER OF DOSES/DAY:	2	1	1	2	1
	TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
DAYS 1 TO 7	MEAN	241.0	202.6	159.9#	97.5#	143.6#
	S.D.	58.96	53.21	85.11	82.41	90.43
	N	7	7	7	7	7
DAYS 8 TO 14	MEAN	278.8	262.8	210.8**	98.8#	174.3#
	S.D.	60.09	52.51	111.34	125.39	103.73
	N	7	7	7	7	7
DAYS 15 TO 21	MEAN	281.7	295.4	220.4**	138.5#	218.0**
	S.D.	73.01	48.37	73.91	105.58	118.80
	N	7	7	7	7	7
DAYS 22 TO 28	MEAN	310.5	299.5	204.2#	29.9#	181.4#
	S.D.	55.45	40.68	67.10	51.75	84.47
	N	7	7	7	7	7

SIGNIFICANTLY DIFFERENT FROM CONTROL: ** = P<0.01; # = P<0.001

A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN BEAGLE DOGS
SUMMARY OF FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

----- F E M A L E -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
	NUMBER OF DOSES/DAY:	2	1	1	2	1
	TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
DAYS 1 TO 7	MEAN	240.2	187.8#	139.0#	69.7#	140.4#
	S.D.	45.90	49.26	71.93	65.22	67.29
	N	7	7	7	7	7
DAYS 8 TO 14	MEAN	277.7	245.1	120.5#	98.1#	99.4#
	S.D.	54.94	53.99	123.29	102.70	84.24
	N	7	7	7	7	7
DAYS 15 TO 21	MEAN	292.4	269.7	110.5#	117.1#	79.0#
	S.D.	64.93	67.92	108.23	94.40	89.83
	N	7	7	7	7	7
DAYS 22 TO 28	MEAN	310.3	281.1	55.1#	31.1#	54.3#
	S.D.	39.49	52.17	69.27	48.81	62.95
	N	7	7	7	7	7

SIGNIFICANTLY DIFFERENT FROM CONTROL: # = P<0.001

• Ophthalmoscopy: The eyes of all dogs were examined by Dr. David Wilkie, Board certified veterinary ophthalmologist. All dogs that were treated with metformin-ER had no ocular disease. One dog from group 5 that was treated with glucophage had persistent pupillary membrane, which was a congenital lesion.

• Electrocardiography: ECGs were within normal limits on Days 4, 54 and 85. Multiple animals in all dose groups including controls had systolic and/or diastolic blood pressures less than 50 mmHg on both assessment days. The low blood pressure readings displayed no relation to treatment since many low measurements were obtained prior to dosing.

• Hematology: Most of hematological parameters in the treated-animals were not remarkably different from those of the control group. Mean corpuscular hemoglobin counts were reduced in the high-dose group male at Day 26. The low- and mid-doses had no effect on MCH counts. Reticulocyte counts were also similarly reduced on Day 26 in the high-dose group male as shown below. Eosinophils counts were significantly reduced in Glucophage group on Day 88 in males. Activated partial thromboplastin time (PTT) was increased in female dogs of the MD group on Day 26.

3-Month Oral Toxicity Study of Metformin ER in Male Dogs: Hematology					
Group	Control	250 m/k/d	500 m/k/d	1000 m/k/d	Glucophage@
MCH, Day –5	23	22*	23	22	22
MCH, Day 26	23	22	23	22*	22
Reticul D26	0.6	0.4	0.4	0.1*	0.5
Eosino D88	0.3	0.1	0.1	0.1	0.1*
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Hematology					
PTT, D26	11	11	13*	12	12
@Dose = 500 m/k/d, *P<0.05. MCH, Reticul, Eosino, PTT and D stand for mean corpuscular hemoglobin, reticulocyte count, eosinophil count, prothrombin time and day, respectively.					

A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN BEAGLE DOGS
SUMMARY OF HEMATOLOGY AND COAGULATION DATA

----- F E M A L E -----

GROUP:		1	2	3	4	5
LEVEL (MG/DOG/DOSE):		1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:		2	1	1	2	1
TOTAL (MG/DOG/DAY):		1000	250	500	1000	500
PROTHROMBIN TIME SCNDS						
DAY -4	MEAN	8.6	8.8	8.6	8.6	8.6
	S.D.	0.44	0.69	0.21	0.34	0.11
	N	7	7	7	7	7
DAY 26	MEAN	8.6	8.8	8.3	8.2	8.3
	S.D.	0.53	0.57	0.45	0.29	0.37
	N	7	7	7	5	5
ACTIVATED PTT SCNDS						
DAY -4	MEAN	10.8	10.3	10.6	10.2	10.6
	S.D.	0.33	0.41	0.48	0.52	0.75
	N	7	7	7	7	7
DAY 26	MEAN	10.6	10.6	12.5*	12.0	11.9
	S.D.	0.53	0.47	1.42	1.29	2.06
	N	7	7	7	5	5
RED CELL MORPHOLOGY						
DAY -4	NORMAL	7/ 7	7/ 7	7/ 7	7/ 7	7/ 7
DAY 26	NORMAL	7/ 7	7/ 7	7/ 7	5/ 5	5/ 5

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05
NOTE: THE MEANS AND STANDARD DEVIATIONS WERE CALCULATED USING NONROUNDED VALUES.

TABLE 5
A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN BEAGLE DOGS
SUMMARY OF HEMATOLOGY AND COAGULATION DATA

----- M A L E -----

GROUP:			1	2	3	4	5
LEVEL (MG/DOG/DOSE):			1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:			2	1	1	2	1
TOTAL (MG/DOG/DAY):			1000	250	500	1000	500
MEAN CORPUS VOL		FL					
DAY	-5	MEAN	65.5	63.4	65.2	63.2	64.6
		S.D.	1.60	1.87	1.95	1.71	1.18
		N	7	7	7	7	7
DAY	26	MEAN	65.0	63.2	65.1	63.0	64.4
		S.D.	1.13	2.00	1.57	1.49	1.27
		N	7	7	7	7	7
MCH		PG					
DAY	-5	MEAN	22.8	21.9*	22.5	22.0	22.3
		S.D.	0.44	0.72	0.64	0.66	0.42
		N	7	7	7	7	7
DAY	26	MEAN	22.7	21.9	22.5	21.8*	22.1
		S.D.	0.56	0.76	0.47	0.50	0.69
		N	7	7	7	7	7
MCHC		G/DL					
DAY	-5	MEAN	34.9	34.5	34.5	34.8	34.5
		S.D.	0.52	0.28	0.39	0.28	0.29
		N	7	7	7	7	7
DAY	26	MEAN	35.0	34.6	34.6	34.5	34.4
		S.D.	0.43	0.42	0.23	0.29	0.56
		N	7	7	7	7	7

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P<0.05$
NOTE: THE MEANS AND STANDARD DEVIATIONS WERE CALCULATED USING NONROUNDED VALUES.

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----- M A L E -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
	NUMBER OF DOSES/DAY:	2	1	1	2	1
	TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
PLATELETS	10*3/CMM					
DAY -5	MEAN	369	360	369	339	393
	S.D.	54.3	42.8	46.7	55.2	62.4
	N	7	7	7	7	7
DAY 26	MEAN	330	310	340	301	331
	S.D.	36.5	74.8	31.6	57.9	44.1
	N	7	7	7	7	7
NUCLEATED RBC'S	#/100WBC					
DAY -5	MEAN	0	0	0	0	0
	S.D.	0.0	0.0	0.0	0.0	0.0
	N	7	7	7	7	7
DAY 26	MEAN	0	0	0	0	0
	S.D.	0.0	0.0	0.0	0.0	0.0
	N	7	7	7	7	7
RETICULOCYTES	% RBC					
DAY -5	MEAN	0.4	0.4	0.3	0.6	0.6
	S.D.	0.29	0.21	0.42	0.35	0.28
	N	7	7	7	7	7
DAY 26	MEAN	0.6	0.4	0.4	0.1**	0.5
	S.D.	0.32	0.25	0.21	0.11	0.26
	N	7	7	7	7	7

SIGNIFICANTLY DIFFERENT FROM CONTROL: ** = P<0.01
NOTE: THE MEANS AND STANDARD DEVIATIONS WERE CALCULATED USING NONROUNDED VALUES.

• Clinical chemistry: Significant increases in potassium values were noted on Day 26 in high-dose male as shown below. The high potassium values were also observed in mid and high-dose females, including glucophage-treated group. Other findings included decrease in calcium in females, slight decreases in phosphorus in the LD males. The changes in sodium in the HD males and chloride in the HD female may not be biologically significant. TG values were elevated in LD females on Day 88 as shown below.

3-Month Oral Toxicity Study of Metformin ER in Male Dogs: Clinical Chemistry					
Group	Control	250 m/k/d	500 m/k/d	1000 m/k/d	Glucophage @
Sodium, 26D	144	144	144	142*	145
Potassium, 26D	4.38	4.49	4.71	5.13*	4.56
Phosphorus, D88	5.7	6.9*	6.5	6.8	6.3
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Clinical Chemistry					
Chloride, 26D	113	112	109*	109*	112
Potassium, 26D	4.15	4.33	4.80	5.02*	4.85*
Calcium, 26D	10.85	10.39*	10.02*	10.31*	9.55*
Phosphorus, D88	5.3	6.1*			
Triglyceride, D88	23	32*			
@Dose = 500 m/k/d, *P<0.05. D stands for the day when the parameters were determined.					

APPEARS THIS WAY
ON ORIGINAL

A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN BEAGLE DOGS
SUMMARY OF BIOCHEMISTRY DATA

----- M A L E -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
	NUMBER OF DOSES/DAY:	2	1	1	2	1
	TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
POTASSIUM	MMOL/L					
DAY -5	MEAN	4.57	4.79	4.74	4.67	4.74
	S.D.	0.224	0.274	0.293	0.557	0.334
	N	7	7	7	7	7
DAY 26	MEAN	4.38	4.49	4.71	5.13**	4.56
	S.D.	0.198	0.267	0.616	0.376	0.285
	N	7	7	7	7	7
CHLORIDE	MMOL/L					
DAY -5	MEAN	109	110	111	110	110
	S.D.	1.5	1.6	1.3	1.3	0.9
	N	7	7	7	7	7
DAY 26	MEAN	111	112	112	110	113
	S.D.	2.0	1.0	1.7	1.3	1.3
	N	7	7	7	7	7
CALCIUM	MG/DL					
DAY -5	MEAN	11.05	11.11	10.97	11.20	11.14
	S.D.	0.372	0.201	0.209	0.243	0.128
	N	7	7	7	7	7
DAY 26	MEAN	10.97	10.63	10.10#	9.98#	10.05#
	S.D.	0.215	0.262	0.250	0.296	0.184
	N	7	7	7	7	7

SIGNIFICANTLY DIFFERENT FROM CONTROL: ** = P<0.01; # = P<0.001
NOTE: THE MEANS AND STANDARD DEVIATIONS WERE CALCULATED USING NONROUNDED VALUES.

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A 3-MONTH ORAL (TABLET) TOXICITY STUDY OF METFORMIN ER IN BEAGLE DOGS
SUMMARY OF BIOCHEMISTRY DATA

----- F E M A L E -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/DOG/DOSE):	1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
	NUMBER OF DOSES/DAY:	2	1	1	2	1
	TOTAL (MG/DOG/DAY):	1000	250	500	1000	500
POTASSIUM	MMOL/L					
DAY -4	MEAN	4.63	4.78	4.76	4.88	4.90
	S.D.	0.261	0.200	0.221	0.448	0.371
	N	7	7	7	7	7
DAY 26	MEAN	4.15	4.33	4.80*	5.02**	4.85*
	S.D.	0.187	0.292	0.545	0.150	0.378
	N	7	7	7	5	5
CHLORIDE	MMOL/L					
DAY -4	MEAN	111	111	109	110	110
	S.D.	1.3	1.1	1.3	1.2	0.9
	N	7	7	7	7	7
DAY 26	MEAN	113	112	109**	109*	112
	S.D.	1.3	1.8	1.3	2.9	2.0
	N	7	7	7	5	5
CALCIUM	MG/DL					
DAY -4	MEAN	11.05	11.09	11.08	11.16	11.07
	S.D.	0.335	0.167	0.291	0.217	0.149
	N	7	7	7	7	7
DAY 26	MEAN	10.85	10.39*	10.02#	10.31*	9.55#
	S.D.	0.244	0.280	0.337	0.093	0.302
	N	7	7	7	5	5

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01; # = P<0.001
NOTE: THE MEANS AND STANDARD DEVIATIONS WERE CALCULATED USING NONROUNDED VALUES.

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----- M A L E -----

GROUP:		1	2	3	4	5
LEVEL (MG/DOG/DOSE):		1 X 500	1 X 250	1 X 500	1 X 500	1 X 500
NUMBER OF DOSES/DAY:		2	1	1	2	1
TOTAL (MG/DOG/DAY):		1000	250	500	1000	500
PROTHROMBIN TIME SCNDS						
DAY -5	MEAN	8.6	8.4	8.7	8.3	8.4
	S.D.	0.22	0.16	0.41	0.15	0.23
	N	7	7	7	7	7
DAY 26	MEAN	8.5	8.4	8.6	8.2	8.4
	S.D.	0.31	0.11	0.36	0.21	0.16
	N	7	7	7	7	7
ACTIVATED PTT SCNDS						
DAY -5	MEAN	10.3	10.2	10.1	10.3	10.5
	S.D.	0.46	0.59	0.33	0.56	0.47
	N	7	7	7	7	7
DAY 26	MEAN	10.3	10.1	10.6	12.3#	10.9
	S.D.	0.23	0.44	0.37	1.06	0.62
	N	7	7	7	7	7
RED CELL MORPHOLOGY						
DAY -5	NORMAL	7/ 7	7/ 7	7/ 7	7/ 7	7/ 7
DAY 26	NORMAL	7/ 7	7/ 7	7/ 7	7/ 7	7/ 7

SIGNIFICANTLY DIFFERENT FROM CONTROL: # = P<0.001
NOTE: THE MEANS AND STANDARD DEVIATIONS WERE CALCULATED USING NONROUNDED VALUES.

• Urinalysis: No statistically significant differences were noted among the groups treated with the drug and in control group after 3-month treatment with Metformin ER or Glucophage in the study.

• Organ weight: The sponsor determined weights of the following organs: brain, adrenal, thyroid, pituitary, heart, spleen, liver, kidneys and testes. There were no significant differences between the control and drug-treated groups when organ weights relative to body weights were analyzed except the weight of ovaries that was reduced significantly even at a dose of 250 mg/kg/day (LD group). The liver and kidney weights of the high-dose groups of both sexes were significantly ($P<0.05$) reduced in comparison to the relevant control, which appeared to be related to test-article dosages, in particular , in females, as shown in two tables below. Glucophage (Group 5) also reduced liver weight (238 vs. 182) and kidneys (43 vs. 32), respectively. The differences in absolute liver and kidney weights in males and females, and ovary weights in females appeared to be due to the differences in body weights. An increase in adrenal weight relative to body weight was detected for the high-dose males as shown below. But, there was no such difference when the absolute adrenal weight was compared.

3-Month Oral Toxicity Study of Metformin ER in Male Dogs: Organ Weight on Day 30					
Group	Control	250 m/k/d	500 m/k/d	1000 m/k/d	Glucophage @
Liver	252	219	219	177*	258
Kidney	44	42	48	32*	43
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Organ Weight on Day 29					
Ovaries	0.74	0.44*	0.42*	0.48	0.46*
Liver	238	201	184*	177*	182*
Kidney	43	41	36	33*	32*
Each value represents the mean of 2-4 dogs. @Dose = 500 m/k/d, *P<0.05. D stands for the day when the parameters were determined.					

Effects of Metformin ER on Organ Weight in 13-Week Toxicity Study on Day 90(#3530-1)@						
Group	Sex	1	2	3	4	5#
Dose (mg/kg/day)		0	250	500	1000	500
Brain	M	79	75	73	75	77
	F	70	79	68	68	74
Adrenal	M	0.72	0.85	0.74	0.76	0.80
	F	0.67	0.67	0.82	0.67	0.68
Thyroids	M	0.90	0.74	0.70	0.64	0.66
	F	0.66	0.64	0.63	0.52	0.53
Pituitary	M	0.067	0.065	0.057	0.050	0.067
	F	0.056	0.063	0.049	0.056	0.056
Heart	M	63	59	59	50	60
	F	57	58	52	44	50
Spleen	M	44	41	31	34	43
	F	45	38	34	27	29
Liver	M	252	220	219	177*	258
	F	238	201	184*	177*	182*
Kidneys	M	44	42	48	32*	43
	F	43	41	37	33*	32*
Testes	M	3.6	4.4	3.2	2.6	4.0
Ovaries	F	0.74	0.44*	0.42*	0.49	0.46*
@Organ weight in gram. *Indicates P<0.05. #Indicate the dose of glucophage.						

. Gross pathology: The main pathological findings were hematocyst, color changes in liver and lung. Hematocyst was observed in one dog in the control group, which was observed in a few animals in the groups 4 and 5 animals. There were dark red areas in the lung in one dog from each treated group in males on Day 30, which was not observed on Day 92 as shown below. The dark red areas in lung were also observed in females in groups 3, 4 and 5.

3-Month Oral Toxicity Study of Metformin ER in Male Dogs: Gross pathology on Day 30					
Group	Control	250 m/k/d	500 m/k/d	1000 m/k/d	Glucophage@
Heart(Hematocyst)	1	0	1	2	2
Liver(Tan area)	0	0	0	1	0
Lung(Dark red area)	0	0	0	1	1
Lung(Tan area)	0	1	1	1	1
Thymus(small)	0	0	0	2	0
3-Month Oral Toxicity Study of Metformin ER in Male Dogs: Gross pathology on Day 92					
Mandibular LN(large)	0	0	0	1	0
Mediastinal LN(red)	0	0	0	1	0
Mesenteric LN(red)	0	0	0	1	0
Stomach(foci)	0	1	0	0	0
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Gross pathology on Day 29					
Kidney(red medulla)	0	1	0	0	0
Liver(tan area)	0	0	0	1	0
Thymus(small)	0	0	1	0	0
Body fat depletion	0	0	1	0	0
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Gross pathology on Day 59					
Heart(hematocyst)	No data	No data	0	1	0
Liver(tan area)	No data	No data	0	0	1
Lung(dark red area)	No data	No data	1	2	1
Lung(tan area)	No data	No data	0	1	0
Pituitary(cyst)	No data	No data	1	0	0
3-Month Oral Toxicity Study of Metformin ER in Female Dogs: Gross pathology on Day 93					
Heart(hematocyst)	0	1	No data	No data	No data
Liver(tan area)	0	3	No data	No data	No data
Spleen(gray area)	0	1	No data	No data	No data
@Dose = 500 m/k/d. Data are expressed in numbers of dogs that had symptoms on indicated date.					

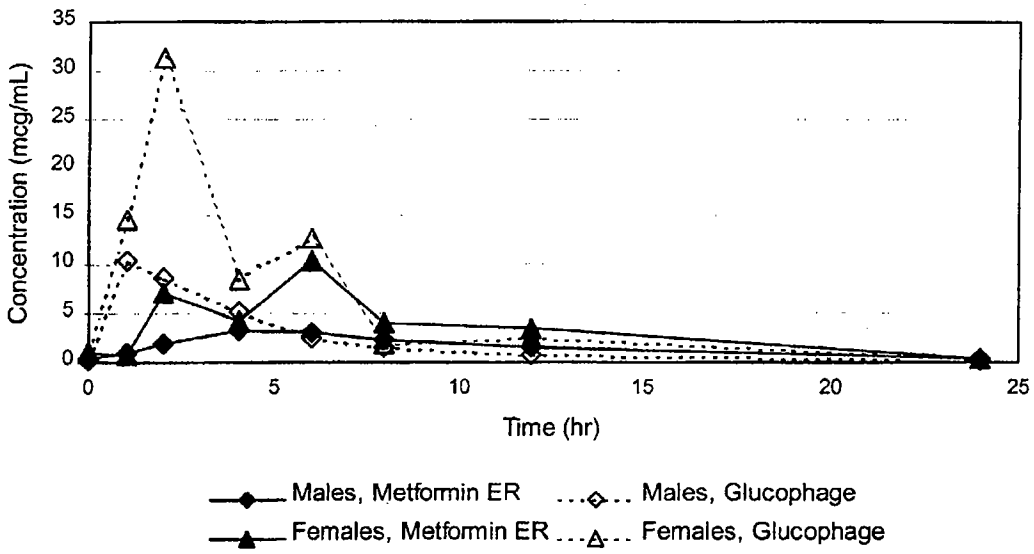
• Histopathology: The histopathological findings from the interim sacrifice were: Adrenal vacuolar changes were observed in males and females at the HD and Glucophage groups. Bone marrow hypocellularity of minimal to moderate severity was noted in mid-dose females and high-dose males and females. Cysts in cecum were observed in the HD group of both sexes, although the cysts in rectum were observed only in males.

The histopathological findings from the final necropsy were documented only in males because females in groups 3, 4 and 5 were euthanized earlier. Adrenal cysts were still there in one dog. There were hemorrhagic incidences in submandibular lymph nodes in 2 dogs from both sexes in the group 2(LD). There was also testes-atrophy in the groups 2, 3, and 4 males. Altered foci in liver and fibrosis in the spleen were noted in the group 5 with Glucophage treatment as shown below.

Histopathologic Findings in 3-Month Dog Study with Metformin ER: Interim Euthanasia@										
Tissues	Group 1		Group 2		Group 3		Group 4		Group 5	
	M	F	M	F	M	F	M	F	M	F
Adrenal, Vacuolar changes	0	0	0	0	0	0	2	1	1	1
Femur, Hypocellularity	0	0	0	0	0	1	1	2	0	0
Sternum, Hypocellularity	0	0	0	0	0	1	1	2	0	0
Cecum, Cysts	0	0	0	0	0	0	2	3	0	0
Kidney, Vacuolation	0	0	0	0	0	1	1	1	1	1
Rectum, Cysts	0	0	0	0	0	0	2	0	0	0
Thymus, Atrophy	0	0	0	0	0	1	3	1	0	0
Histopathologic Findings in 3-Month Dog Study with Metformin ER: Final Euthanasia@										
Adrenal, Cysts	0	0	0	0	0	-	1	-	0	-
Esophagus, Lymphocytic infilt.	0	0	0	1	1	-	1	-	0	-
Kidney, Hyaline casts	0	0	0	0	1	-	0	-	0	-
Liver, Altered foci	0	0	0	2	0	-	1	-	1	-
Lung, Chronic pleuritis	0	0	0	0	0	-	1	-	0	-
Submandibular LN, hemorrhage	0	0	2	2	0	-	1	-	0	-
Submandibular LN, Hyperplasia	0	0	0	0	0	-	1	-	0	-
Skin, Chronic dermatitis	0	0	0	0	0	-	2	-	0	-
Spleen, Fibrosis	0	0	0	0	0	-	0	-	1	-
Testes, Sperm stasis	0	0	1	0	0	-	0	-	0	-
Testes, Tubular atrophy	0	0	1	0	2	-	2	-	0	-
Thymus, Atrophy	1	0	0	0	0	-	1	-	0	-
Thymus, Hemorrhage	0	0	1	0	0	-	1	-	0	-
@Metformin ER doses for Groups 2, 3, and 4 were 250, 500, 1000 mg/kg/day, respectively and Group 5 had glucophage 500 mg/kg/day. M, F, infilt. and LN stand for male, female, infiltration, and lymph node, respectively. "-" Indicates no data were available due to early sacrifice on Day 59 in females.										

• Toxicokinetics: The mean values for the PK parameters for animals receiving metformin-ER and metformin-IR (GP) were compared in table below. In general, the mean values for Cmax of glucophage were 2- to 3-fold higher than the levels of metformin-ER in all studies. Metformin-ER had 2 to 3 times longer duration of action as indicated by Tmax, although there was an exception in female dogs on Day 26. The relationships were graphically illustrated in two figures below.

. Mean Plasma Concentrations of Metformin in Dogs Receiving Metformin ER or Glucophage®, 500 mg, on Day 26



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Comparison of Pharmacokinetic Parameters for Metformin after Administration of Metformin ER and Glucophage to Dogs

Group	Drug*	Sex	Day	Dose (mg/kg)	Mean and Standard Deviation Values for Pharmacokinetic Parameters				
					AUC_{0-24} (µg•hr/mL)	$NAUC_{0-24}$ (ng•hr/mL)	C_{max} (µg/mL)	NC_{max} (ng/mL)	T_{max} (hr)
4	ER	M	1	146.0 ± 7.5	82.1 ± 23.3	563 ± 161	6.0 ± 0.9	41.1 ± 5.0	6.3 ± 1.4
5	GP	M	1	148.4 ± 12.3	106.2 ± 28.8	712 ± 170	11.2 ± 4.3	75.4 ± 29.8	2.7 ± 2.4
		% Difference		1.6%	29.4%	26.5%	86.7%	83.5%	
4	ER	F	1	174.6 ± 7.4	123.6 ± 45.7	714 ± 272	10.6 ± 1.8	61.2 ± 11.6	9.4 ± 3.4
5	GP	F	1	173.2 ± 9.1	140.8 ± 31.9	811 ± 169	15.5 ± 4.0	89.9 ± 24.9	4.6 ± 3.4
		% Difference		-0.8%	13.9%	13.6%	46.2%	46.9%	
3	ER	M	26	69.0 ± 4.9	38.2 ± 9.7	552 ± 122	3.8 ± 0.9	55.2 ± 12.9	5.4 ± 3.0
5	GP	M	26	70.7 ± 7.4	51.0 ± 15.0	720 ± 210	11.3 ± 5.8	159.4 ± 87.4	1.9 ± 1.1
		% Difference		2.4%	33.5%	30.4%	197.4%	188.8%	
3	ER	F	26	92.2 ± 16.3	88.8 ± 54.4	913 ± 452	8.5 ± 5.1	88.0 ± 42.6	5.1 ± 2.0
5	GP	F	26	96.3 ± 16.0	145.0 ± 63.2	1,462 ± 461	25.1 ± 10.6	256.0 ± 86.0	5.0 ± 4.4
		% Difference		4.4%	63.3%	60.1%	195.3%	190.9%	

* Group 3 and 4 animals received metformin ER (ER). Group 5 animals received Glucophage (GP)

AUC Values of Metformin ER and AUC Ratios in 3-Month Toxicity Study in Male Dogs@								
Assay Day	AUC_{0-24} for Metformin ER (µg.hr/ml)				Therapeutic AUC ratio at indicated Day#			
	G2	G3	G4	G5	G2	G3	G4	G5
1	25.8	51.0	82.1	711.6	1.06	2.08	3.36	29.07
26	17.5	38.2	102.3	51.0	0.72	1.56	4.18	2.08
88	14.5	33.4	70.1	52.7	0.59	1.37	2.86	2.15
AUC Values of Metformin ER and AUC Ratios in 3-Month Toxicity Study in Female Dogs								
1	28.3	55.3	123.6	140.7	1.16	2.26	5.05	5.73
26	21.5	88.8	161.8	159.0	0.88	3.63	6.61	6.50
88	21.1	*	*	*	0.86	*	*	*
@G2, 3, 4, and 5 indicate groups for metformin ER 250, 500, 1000 mg/kg/day and glucophage 500 mg/kg/day. #Calculated based on human AUC values (24.48 µg.hr/ml) after Metformin ER (2000 mg/day) administration. *Indicate no data due to sacrifice on day 59 and the numbers of dog in each group were 3 to 7 dogs.								

Key Study Observations: Metformin-ER may produce severe toxicity like metformin-IR at doses above 1000 mg/kg/day in dogs. It appears that NOAEL is 250 mg/kg/day. The mean Cmax values of metformin after metformin-ER was significantly lower than those of active drug after the same dose of glucophage.

Overall Toxicology Summary: A 3-month dog study was performed to compare the GI tolerability and toxicity of metformin-ER with metformin-IR and glucophage. Seven dogs per sex received metformin-ER orally at doses of 250, 500, and 1000 mg per day with an additional group dosed with 1000 mg of glucophage. Toxicological evaluations indicate that there were no remarkable differences between metformin-ER and metformin-IR after 90 days of dosing. Pharmacokinetic studies indicate that the rate of drug absorption was slower in metformin-ER than glucophage with a significant reduction in Cmax values. NOAEL appeared to be 250 mg per dog.

2.6.6.5 Carcinogenicity

Study title: 104-Week Gavage Carcinogenicity Study with Metformin HCl in CD (SD) IGS BR rats

Key study findings:

Metformin, an antihyperglycemic agent used to treat non-insulin-dependent diabetes mellitus is currently marketed as an immediate and extended release oral formulation as glucophage (Bristol-Meyers Squibb). Biovail Technologies Ltd. proposes a long acting form of metformin under 505 (b)1. The maximum human dose (2550 mg) and indication is identical to glucophage. ECAC has concurred with the sponsor's dose selection for a two year rat bioassay and the proposal for a TG.AC alternative assay.

Rat Dose Finding:

In brief, the committee concurred with the doses of 0, 150, 300, and 450 mg/kg/day for males. But, they could not concur on a maximum of 450 mg/kg/day for females because there was no evidence of an MTD and there was no dose relationship in the toxicity (reduction in body weight gain) at doses up to 900 mg/kg/day. The decreases in bodyweight gains for females were virtually the same for all dose levels. The sponsor proposed doses for females in the carcinogenicity study of 0, 150, 450, 900, and 1200 mg/kg/day to ensure inclusion of an MTD.

Mouse Dose Finding:

As to the dose selection for mouse study, eCAC concurred with the acceptability of a transgenic Tg.AC mouse study in lieu of a 2-year mouse carcinogenicity study considering the fact that the drug is non-genotoxic (negative in the Ames test, mouse lymphoma assay and the micronucleus test). It is important to demonstrate significant exposure through the skin rather than by oral ingestion of the drug. Thus, the committee recommended using collared animals in the one-month study to ensure the dermal absorption of the article.

An increased incidence of benign parathyroid adenomas in all treated male rats relative to the untreated control group was observed as shown in a table below.

Incidence of Histopathological Findings in the Male and Female Rat Parathyroid									
	Males				Females				
Dose(m/k/d)	0	150	300	450	0	150	450	900	1200
#Examined	58	59	60	58	59	38	40	37	57
Adenomas@	1	9*	8*	7*	3	0	0	0	1
Hyperplasia, diffuse	5	6	10	12	0	0	0	0	1
Hyperplasia, focal	0	4	2	1	0	0	0	0	0
@Indicates number of rats affected and *P<0.05.									

Study/Report Number: — BIO 00001MET

Volume#, and Page# N-000-SX A5.1 to 5.6, Page 1-2599
Conducting Laboratory and Location:
1. —
Combined histopathology: —
Combined histopathology: —
Compilation of neoplatic lesions in control rats: —
Consulted by —

Date of study Initiation: Oct. 29, 1999
GLP compliance: yes
QA report: yes(x) no( )
Drug, lot#, radiolabel, and % purity: METP01, 202899MF1 and 202100MF1, all lots of the test material are — pure.
Formulation/vehicle: /Reverse Osmosis water was used as control and vehicle.
Methods (unique aspects):

Dosing:
Species/strain: Male and female CD(SD)IGS BR rats (—
#/sex/group or time point (main study): 520 (60/sex/dose)
Satellite groups used for toxicokinetics: (3 rats/sex/dose)
Age: 35-41 days old
Weight: 153-219 g for males and 118-175 g for females
Doses in administered units: 0, 150, 300, 450 mg/kg/day for males; 0, 150, 450, 900 and 1200 mg/kg/day for females.
Route, form, volume, and infusion rate: Gavage in a volume of 10 ml/kg

Observations and times:

Clinical signs: Twice daily
Body weights: Before initiation, Day 1, weekly for 14 weeks, once every 4 weeks thereafter, and at week 105
Food consumption: Weekly for Weeks 1 through 13, once every 4 weeks thereafter, and at Week 104.
Ophthalmoscopy: Before initiation (day –3) and during Weeks 26, 52, and 104 EKG: not performed.

Hematology: Before initiation and Weeks 52 and 104 and blood was analyzed at —

Clinical chemistry: Before initiation and Weeks 52 and 104
Urinalysis: not performed
Gross pathology: At necropsy and unscheduled deaths (see table)
Organs weighed: At the time of deaths or necropsy, the following organs weights were determined: adrenals, brain, epididymis, ovaries, heart, kidneys, liver, prostate, testes, uterus and cervix, and thyroid with parathyroid.

Histopathology: At necropsy (see table for the list of tissues)
Toxicokinetics: 1, 4, 10, 24 h post last dose during Day 29-29
Data Evaluation: One-way analysis of variance was used to analyze body weights, food consumption and Dunnett's t-test was used for control versus treated group comparisons. Incidental tumors were analyzed by Dinse-Lagakos logistic prevalence methods for tread and heterogeneity.

Results:

Mortality: Survival rate in the LD male group was increased significantly while the rate in females was not affected by the treatment as shown below.

Survival Analysis in 104-Week Carcinogenicity Study in Rats									
Sex	Males				Females				
Dose@	0	150	300	450	0	150	450	900	1200
Death#	46	34	39	39	37	39	39	40	41
%	77	57	65	65	62	65	65	67	70
S.E.	0.055	0.064	0.062	0.062	0.063	0.062	0.062	0.061	0.060
p-Value	0.2001	0.0175 *	0.1040	0.1372	0.0979	0.4583	0.3508	0.2079	0.2145
@, # and % indicate dose in mg/kg/day, number of death based on 60 dogs and percentage of death out of 60 dogs, respectively. *Statistically significant.									

Clinical signs: Test article-related clinical signs were yellow staining of the hair coat in the ventral-abdominal and perineal areas of both sexes in the HD groups. There were also high incidences of treatment-related diarrhea or soft feces in the HD groups as shown below.

Clinical Signs in 104-Week Carcinogenicity Study in Rats@									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Appearance, head tilt to right	0	1	1	4	0	0	0	0	0
Appearance, dehydrated	0	0	0	0	0	0	0	0	1
Appearance, missing tail	0	0	0	0	0	1	0	1	1
Protruding penis	0	0	1	3					
Swollen limb, right hind	0	1	1	2	0	0	0	0	0
Swollen, perineal area					0	1	0	1	1
Genital, red discharge	2	3	3	6	2	1	1	5	5
Genital, mucoid discharge	0	0	0	1	0	2	2	3	0
Discharge, clear oral	8	5	15	12	2	1	7	9	4

Excretion, nonformed feces	6	13	4	19	2	4	2	7	25
Eyes, red, right	0	0	0	1	0	0	0	0	0
Eyes, clear discharge	0	0	0	0	1	0	3	1	3
Eyes, dilated pupil	0	0	1	1	0	1	2	1	0
Skin, alopecia	0	0	0	1	0	0	0	0	0
Skin, brown, entire head	0	1	1	5	0	0	0	0	0
Skin, brown, perineal area	2	1	3	7	1	1	3	8	6
Skin, brown, ventral-abdominal	0	0	0	0	0	0	1	1	4
Skin, blue, ventral-abdominal	0	0	0	0	0	2	2	0	2
Skin, pale, entire body	0	0	0	0	0	2	2	1	4
Skin, brown hair, scrotum	1	0	0	4					
Skin, red, perineal area	0	0	0	0	0	2	2	1	0
Skin, sore, lateral-left	0	0	1	1	0	0	0	0	0
Skin, sore, perineal area	0	0	0	1	0	0	0	0	0
Skin, sore, scrotum-left	0	0	0	1					
Skin, yellow coat, penis	0	1	1	3					
Skin, yellow, perineal area	2	1	8	19	2	5	17	37	47
Skin, yellow, ventral abdominal	0	0	0	0	1	0	1	2	5
Stains, perineal/perianal	8	3	16	19	3	5	19	22	28
Stains, skin/haircoat	5	7	7	12	5	9	5	6	4
@Indicates number of animals affected.									

Body weight:

Mean body weights were reduced statistically at various times at Weeks 30, 34, and 39 for males given 150, 300, or 450 mg/kg/day, respectively. The weight values ranged from 91 to 95%, 93 to 94% and 88 to 96% of the mean values of control males. The weight data in females were also reduced at Weeks 18 and 34 for females given 900 or 1200 mg/kg/day, respectively. The weight values ranged from 87 to 96% and 90 to 94% of the mean values of control females. At study completion, there were no statistically significant decreases in mean body weight for both sexes in all treated groups. In that sense, the top doses in both sexes were not an MTD based on body weight reduction.

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Figure 3: Mean Body Weight Data (g) - Males

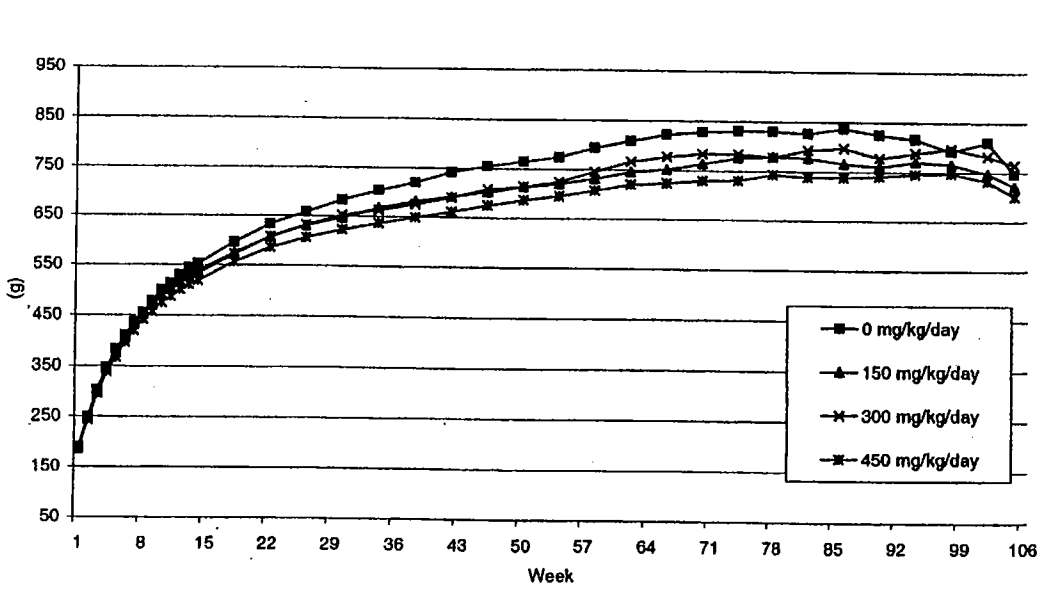

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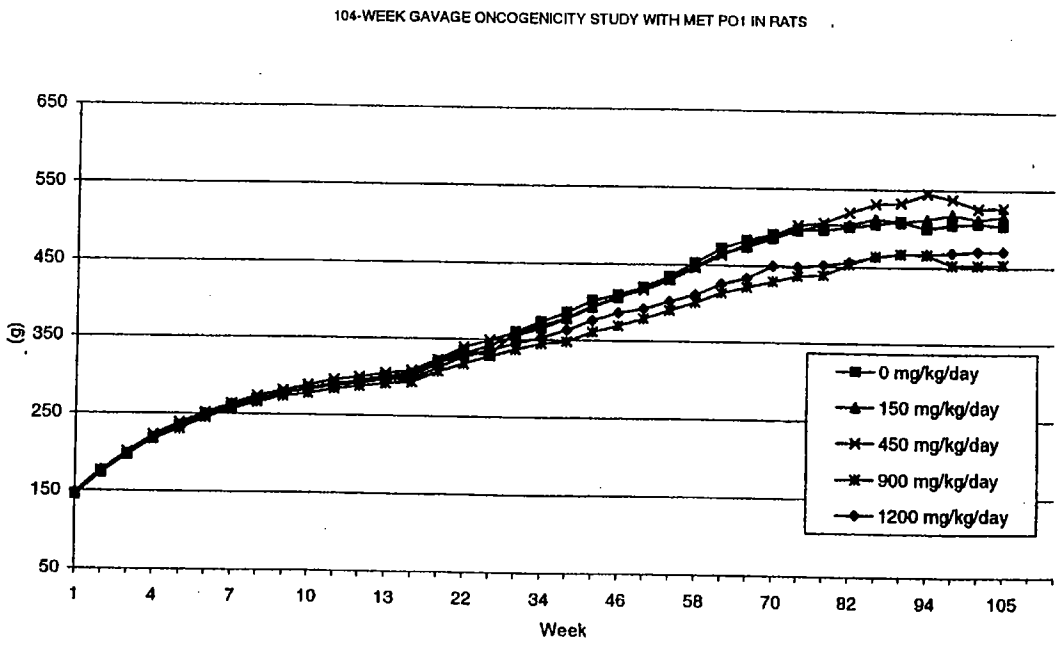
Figure 4: Mean Body Weight Data (g) - Females



Food consumption:

Mean food consumption for males given the test article was similar throughout most of the study compared with control group. In males, the food consumption was test-article dose dependent and ranged 93 to 96% of the control group values. Mean food consumption in females fluctuated sporadically with respect to treatment period without clear pattern as illustrated below.

Figure 5: Mean Food Consumption Data (g) - Males

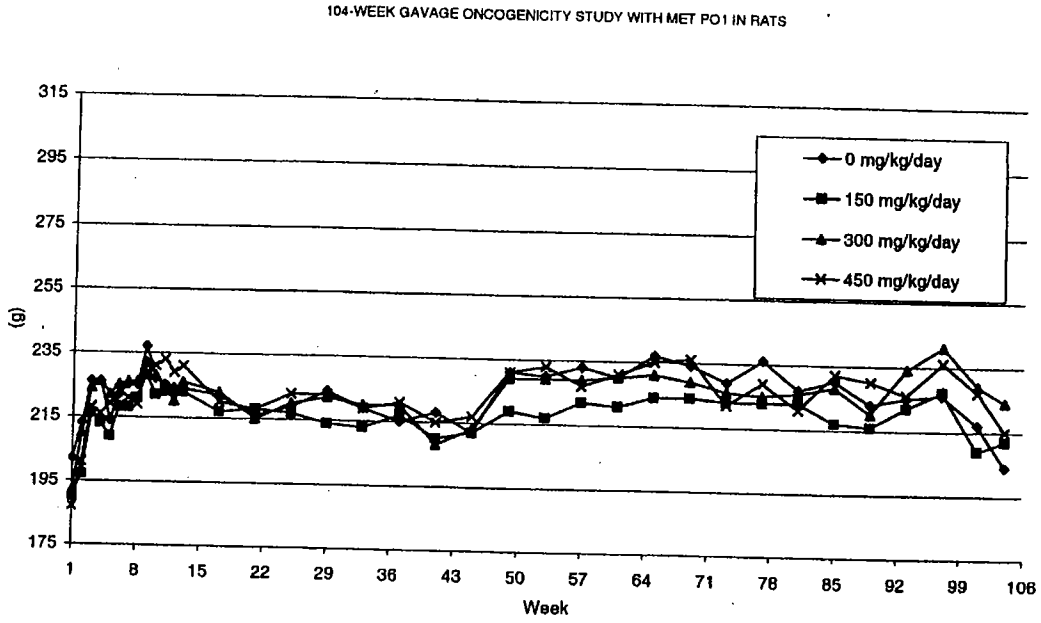


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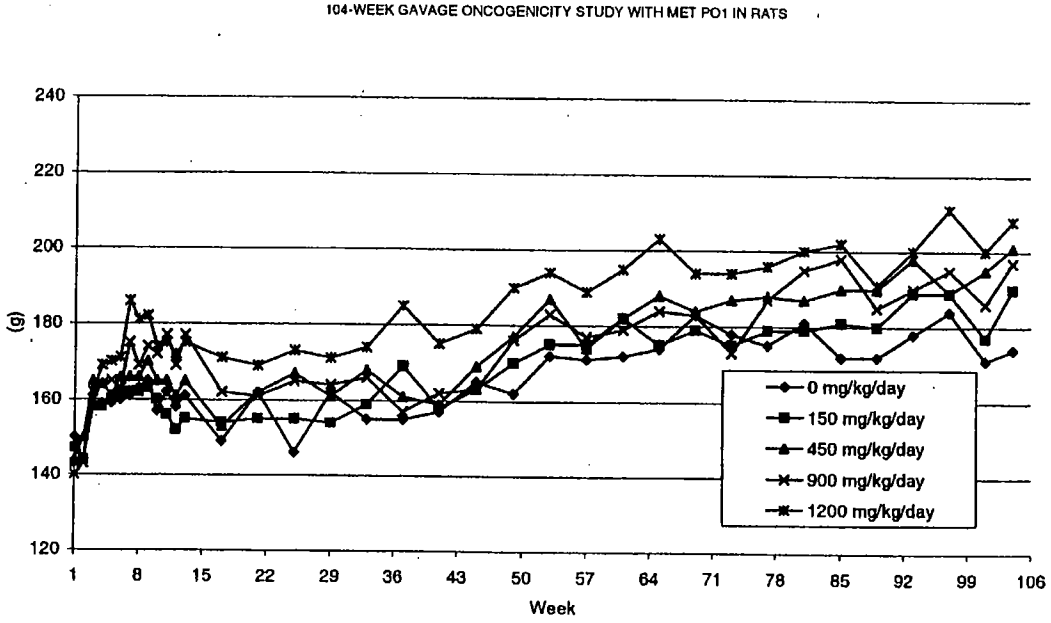
Figure 6: Mean Food Consumption Data (g) - Females



Tissue mass examinations:

Pronounced tissue masses were examined, which were summarized below. Remarkable tissue masses or warts were not related to the dose of test-article, although the incidences appear to be high in the treated groups in males.

Tissue Mass Observations in 104-Week Carcinogenicity Study in Rats@									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Mass(es), axillary region	0	0	2	1	13	12	12	9	11
Mass(es), dorsal-cervical	0	1	0	1	0	1	0	0	0
Mass(es), head-maxillary	0	2	1	3	0	0	0	0	0
Mass(es), tail	0	0	3	2	0	1	0	0	1
Mass(es), ventral-cervical	0	0	1	1	4	0	6	0	4
Mass(es), lateral left	1	1	1	3	5	3	12	6	7
Wart, paw, front right	0	0	1	0	0	0	0	0	0
Wart, ear, right	0	0	0	0	0	0	0	0	1
@Indicates number of animals affected.									

Ophthalmic Examinations: Remarkable ophthalmic observations are summarized below, which appear to be not related to the dose of test article.

Ophthalmic Signs in 104-Week Carcinogenicity Study in Rats@									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
No visible lesions	54	57	59	58	60	56	56	56	55
Cornea, Keratitis, eye-left	0	0	0	0	0	3	5	3	1
Lens, posterior capsular cataract	2	4	4	0	2	1	3	0	0
Retina, retinal degeneration-focal	2	2	1	1	0	4	3	3	1
Eye, pale vasculature	0	0	0	1	0	0	0	0	1
@Indicates number of animals affected.									

Organ weight:

There were no test article-related effects on mean terminal body weights. In males, adrenal weights were significantly reduced in the HD group as shown below. There were test article dose-related increases in mean weights of heart, liver, and kidney in female rats, which were all statistically significant in the HD female group. In the HD female rats, the ratios of organ weight to body weight or brain weight were also increased proportionally, which were not observed in males.

Organ Weight in 104-Week Carcinogenicity Study in Rats@									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Terminal body weight	730	684	733	673	472	492	495	420	426
Adrenal	0.22	0.16	0.10	0.12*	0.13	0.22	0.15	0.19	0.14
Heart	2.29	2.30	2.33	2.35	1.60	1.72	1.74	1.85	1.96*
Liver	18.9	17.8	18.6	19.1	12.5	13.8	14.4	14.6	15.1*
Kidney	4.96	5.15	4.81	5.15	2.90	3.17	3.01	3.29*	3.55*
@All weights are expressed in gram. *indicates $p<0.05$ compared to control group.									

Gross pathology:

Gross abnormalities of animals at terminal necropsy were observed in both males and females with no clear patterns, although some incidences were high in treated groups compared to vehicle control group as shown below. There was an increased incidence and severity of chronic progressive nephropathy in the kidney of females given 900 or 1200 mg/kg/day, suggesting a possible test article related effect, which was not confirmed in the males.

Macroscopic Observations in 104-Week Carcinogenicity Study in Rats@									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Number of rat examined	14	26	21	21	23	21	21	20	18
Lung, dark, red focus/area	0	0	1	1	0	0	0	0	0
Lung, light focus/area	1	0	2	1	0	1	0	1	2
Kidney, mottled	0	1	1	1	2	1	3	0	0
Kidney, mass(es)	0	1	0	0	0	0	0	0	1
Muscle, skeletal, mass+atrophy	0	0	0	0	0	0	0	0	2
Liver, light focus/area	1	0	2	1	0	0	1	1	3
Spleen, adhesion	0	0	0	1	0	0	1	0	1
Adrenal, cortex, red focus	0	1	0	1	1	0	0	0	0
Testis, red/yellow, focus	0	1	1	0					
Testis, contains fluid	0	0	1	0					
@Indicates number of animals affected.									

Microscopic Observations:

The incidence of parathyroid adenomas in male appeared to be increased in all treated groups including the LD and MD groups as shown below. The incidence of parathyroid adenomas in male controls in this study (1.7%) was comparable to Covance historical controls (3.4% with similar group size, study duration, and strain of rats). The effect was not dose-related and was not observed in female rats. There were no other statistically significant microscopic findings in the 2-year carcinogenicity study in rats as presented below.

Microscopic Observations in 104-Week Carcinogenicity Study in Rats@									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Number of rat examined	60	60	60	60	60	60	60	60	60
Adrenal, medulla, pheochromcytoma benign	5	3	0	7	4	0	1	0	0
Liver, adenoma/carcinoma	1	1	3	2	0	0	0	0	0
Thyroid, c-cell adenoma/carcinoma	7	11	9	5	6	2	3	4	4
Thyroid, follicular cell adenoma	2	1	2	4	3	0	0	0	1
Parathyroid, adenoma	1	9*	8*	7*	2	0	0	0	0
Pituitary: adenoma	35	26	37	42	51	49	47	38	49
Pancreas, acinar cell adenoma/carcinoma	1	0	2	3	0	0	0	0	2
Mammary, adenoma	4	9	5	3	0	0	0	0	0
Skin, keratoacanthoma	1	3	4	4	0	0	0	0	0
Organ, hemangiosarcoma	0	3	1	0	0	0	0	0	0
Organ, fibrosarcoma	2	1	2	0	0	0	0	0	0
Organ, leiomyoma					0	0	0	0	2
Organ, endometrial polyp					4	5	2	4	7
Organ, endometrial stromal sarcoma					5	5	2	4	9
@Indicates number of animals affected out of total 60 dogs, but the number was less than 60 in some tissues.									

According to historical control data that were generated by several
around the world, per cent incidences of parathyroid adenoma were 0.8 to 8.3% in male
CD (SD)BR rats as shown below. Per cent incidence of parathyroid adenoma in the present study in the control group was 2% while the incidences in treated group were 15, 13, and 12% in LD, MD, and HD groups, respectively as summarized in a table below. The incidences of these findings are above the historical control range. However, the statistical review revealed no significant increase in parathyroid tumors, either by trend test (P = 0.1043) or by pair-wise comparison (P=0.04).

Incidence of Parathyroid Hyperplasia and Adenomas in Untreated CD®(SD)BR Rats

		Males		Females	
	No. of Studies	**Minimum % Found**	**Maximum % Found**	**Minimum % Found**	**Maximum % Found**
Hyperplasia, parathyroid					
— (gavage)	10	3.8	24.0	0.0	3.9
— (dietary)	6	9.1	15.6	0.0	8.5
— (gavage)	5	0.0	58.2	0.0	16.4
Adenoma, parathyroid					
— (gavage)	10	0.0	3.4	0.0	5.1[a]
— dietary)	6	0.0	3.3	0.0	2.1
— (gavage)	5	0.0	5.9	0.0	2.1
— compilation	13/12[b]	0.8	8.3	1.0	4.4

[a] Found in control group of current study

[b] 13 studies were examined for male rats and 12 studies for female rats

Incidence of Parathyroid Adenoma in 104-Week Carcinogenicity Study in Rats									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Number of rat examined	60	60	60	60	60	60	60	60	60
Parathyroid, adenoma(#)	1	9*	8*	7*	2	0	0	0	0
Parathyroid, adenoma (%)	1.7	15.0	13.3	11.7	3.3	-	-	-	-
*Indicate P<0.05.									

Toxicokinetic Study:

The sponsor did not include toxicokinetic data in the 2-year carcinogenicity study, which are necessary for the estimation of drug exposure comparison. In particular, it is difficult to justify the top female dose (1200 mg/kg/day) as the MTD because there was no significant decrease in body weight in female rats in the 2-year carcinogenicity study as presented previously. Therefore, the sponsor provided toxicokinetic data that were generated for 26-week gavage toxicity study (Biovail Study#B98-PC037-MET P01). The chronic toxicity study was performed in the same strain of rats at doses of 150, 450, and 900 mg/kg/day as summarized in a table below.

Summary of Mean Toxicokinetic Parameters of Metformin in Rats

Dose Group		Gender	AUC0-∞ µg*hr/ml	AUClast µg*hr/ml	Clast µg/ml	Cmax µg/ml	t1/2 hr	Tlag hr	Tmax hr
150 mg/kg/day	Day 1	Female	63.74	60.05	0.49	11.01	5.22	0	1
		Male	37.32	36.38	0.15	6.07	4.31	0	2
	Day 14	Female	26.34	26.08	0.04	7.83	4.15	0	0.5
		Male	53.54	49.14	0.49	6.20	6.23	0	2
	Day 182	Female	36.16	33.44	0.96	8.96	1.97	0	0.5
		Male	54.43	50.73	1.36	13.24	1.89	0	2
	Day 182*	Female	51.57	41.88	0.96	8.96	NV	0	0.5
		Male	70.83	65.89	0.50	13.24	NV	0	2
450 mg/kg/day	Day 1	Female	122.57	118.83	0.50	18.70	5.22	0	1
		Male	105.31	103.33	0.32	18.48	4.23	0	1
	Day 14	Female	74.18	72.15	0.27	12.73	5.28	0	2
		Male	130.38	123.91	0.73	22.03	6.12	0	2
	Day 182	Female	86.89	75.36	3.08	18.81	2.60	0	1
		Male	94.75	75.81	4.07	17.84	3.23	0	0.5
	Day 182*	Female	110.08	105.34	0.67	18.81	4.91	0	1
		Male	123.11	114.98	0.83	17.84	6.78	0	0.5
900 mg/kg/day	Day 1	Female	227.56	201.66	2.05	34.80	8.76	0	2
		Male	215.54	197.87	1.67	23.01	7.32	0	2
	Day 14	Female	132.24	126.33	0.74	12.27	5.54	0	2
		Male	288.94	258.01	2.67	28.99	8.04	0	1
	Day 182	Female	160.48	107.10	8.22	22.42	4.50	0	2
		Male	204.86	132.29	11.00	29.98	4.57	0	1
	Day 182*	Female	208.13	186.06	1.65	22.42	7.17	0	2
		Male	255.14	235.54	1.91	29.98	7.12	0	1

Day 182* The concentration at time 0 was used to estimate 24 hr. post dose value
NV = Not able to estimate kel for half-life

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The sponsor also provided relevant toxicokinetic data that were obtained from human study (Biovail PK study#2624) after extended release metformin tablets (2 x 500 mg, q.d.). The PK data such as steady state human metformin concentrations, Cmax, tmax, and AUC values were obtained from 30 subjects, which are summarized below. In this clinical study, the AUC0-24 hr was 12.9 μg.h/ml, which was used for the calculation of therapeutic exposure ratios as summarized below.

BIOVAIL CONTRACT RESEARCH
A Division of Biovail Corporation
Study # 2624_Prelim (81-0018)
Table 8 SUMMARY OF Metformin PARAMETERS FOR EACH SUBJECT GIVEN THE TREATMENT A EXTENDED RELEASE TABLETS (2x500 mg q.d.)
(Depomed. Inc. (A). Batch Number: xxxxx, Manufacturing Date: mmddyy)

Subject No.	SEQ	PERIOD	Cmax (µg/mL)	Tmax (hrs)	AUC(0-24) (µg.hr/mL)	Cmin (µg/mL)	Degree of Fluctuation (%)	Cave (µg/mL)
01	BCA	3	1.32	8.00	13.62	0.09	216.39	0.57
02	ACB	1	0.96	8.00	9.38	0.08	224.78	0.39
03	CAB	2	1.41	6.00	14.60	0.12	210.88	0.61
04	BAC	2	1.30	8.00	12.34	0.07	239.66	0.51
05	ACB	1	1.27	8.00	13.65	0.08	210.08	0.57
06	BAC	2	1.34	8.00	16.22	0.12	180.52	0.68
07	DCA	3	1.11	6.00	11.57	0.07	215.35	0.48
08	ABC	1	0.86	10.00	9.00	0.07	212.27	0.38
09	CBA	3	1.96	8.00	16.51	0.08	273.37	0.69
10	CBA	3	1.44	8.00	14.68	0.13	213.79	0.61
11	BAC	2	1.31	8.00	14.84	0.10	195.74	0.62
12	BCA	3	1.37	6.00	14.62	0.10	209.19	0.61
13	ACB	1	1.18	8.00	12.23	0.11	210.09	0.51
14	BAC	2	1.10	6.00	11.59	0.09	210.57	0.48
17	CBA	3	0.99	8.00	11.88	0.11	177.75	0.49
20	ABC	1	1.23	8.00	11.83	0.08	233.48	0.49
21	BAC	2	1.41	6.00	15.65	0.11	198.74	0.65
23	ABC	1	1.05	8.00	12.24	0.10	187.76	0.51
24	CAB	2	1.62	6.00	14.49	0.10	250.47	0.60
25	CAB	2	1.08	8.00	12.64	0.07	192.63	0.53
26	BCA	3	1.52	8.00	12.85	0.06	273.06	0.54
27	CBA	3	0.98	6.00	10.34	0.07	211.54	0.43
29	CAB	2	1.02	8.00	11.36	0.12	191.10	0.47
30	BCA	3	1.13	3.00	11.49	0.20	192.68	0.48
MEAN			1.25	7.29	12.90	0.10	213.83	0.54
SD(±)			0.25	1.40	2.02	0.03	25.29	0.08
CV (%)			19.67	19.17	15.63	31.38	11.83	15.63
Range (Min.)				3.00	9.00		177.75	0.38
(Max.)				10.00	16.51		273.37	0.69
Num of Subjects			24	24	24	24	24	24

NC = No Calculation.

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ON ORIGINAL

The sponsor did not perform PK/TK analysis in the 104-week carcinogenicity study to estimate the therapeutic ratio of test article at the top dose of female rats.
Based on the provided data from the 26-week toxicology data in male and female rats, the therapeutic exposure ratios were calculated, although there were differences in the duration in the estimation of AUC values between animals (AUC0-∝) and human subjects (AUC0-24). The results are summarized below in a table. The therapeutic ratio in the top dose of female group was less than 25. Considering the fact that the top dose in female rat in 26-week toxicological study was 1200 mg/kg/day and both AUC and therapeutic ratio are fairly linear with respect to dose, the dose-dependent changes in the parameters were plotted for the estimation of AUC and therapeutic ratio at the top dose. As illustrated below, the therapeutic ratio was still under 20. The maximum recommended human daily dose is 2000 to 2500 mg. In this case, human AUC would be 26 μg.hr/ml, which will reduce the ratio by half. Thus, the ratio will be well below 25.

Therapeutic Exposure Ratio (AUC) in 26-Week Toxicological Study in Rats*

Dose (mg/ kg/day)	Tested Day	Male		Female	
		AUC0-∝	AUC ratio	AUC0-∝	AUC ratio
150	1	37	3	64	5
	14	53	4	26	2
	182	54	4	36	3
450	1	105	8	123	10
	14	130	10	74	6
	182	945	7	87	7
900	1	216	17	228	18
	14	288	22	132	10
	182	205	16	161	12

*Calculated based on human AUC0-24 value (12.90 μg.hr/ml) after a daily dose of 1000 mg (2 x 500 mg), which is not significantly different from AUC0-∝ value.

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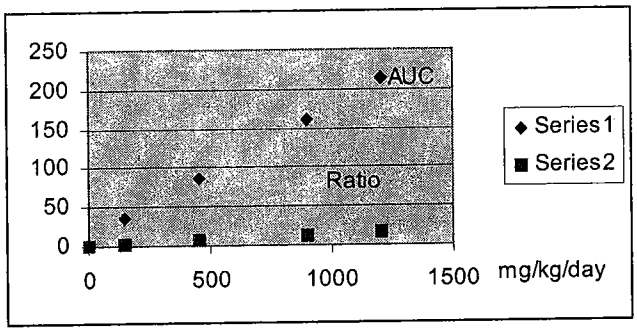

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Finally, the sponsor performed another human pharmacokinetic study because the maximum human dose is 2500 mg per day, although they used 1000 mg (2 x 500 mg) for their previous human PK study as described under Biovail PK study#2624. The new study (Biovail PK study#2625/81-0019) was performed by the same investigators under similar conditions, using the same formulation. In this study total 36 male and female subjects were used as shown in a table below. According to the preliminary report, the AUC0-t value was 13.5 μg.hr/ml, which is not really different the value (12.9 μg.hr/ml) that was obtained from the previous study. Thus, the therapeutic AUC ratio is still below 25.

According to the communication with Dr. Alex Rochefort, the report is final because the accuracy was verified by the sponsor. He also pointed out that the duration of AUC estimation was 0-36 hours, although it was listed AUC 0-t initially as shown in the table below. Thus, the therapeutic AUC ratios would be even lower than those values obtained from the previous human PK study (Biovail PK study#2624).

BIOVAIL TECHNOLOGIES LTD Study # 2625 (81-0019)

Table 8 SUMMARY OF METFORMIN PARAMETERS FOR EACH SUBJECT GIVEN METFORMIN ER TABLETS **(5x500 mg; Total Dose = 2,500 mg)**

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Subject	Gender	Cmax (ng/mL)	Tmax (hrs)	AUC (0-t) (ng.hr/mL)
1	M		4.00	14402.26
2	F		4.00	23217.75
4	F		4.00	17315.13
5	M		3.00	8215.25
6	F		4.00	13326.16
7	M		4.00	11289.39
8	F		4.00	9641.11
9	M		3.00	9662.7
10	F		4.00	16724.48
11	M		4.00	11342.78
12	F		4.00	19660.85
13	M		3.00	8789.54
14	F		4.00	14986.86
15	M		3.00	10531.61
16	F		4.00	16878.9
17	M		3.00	11934.76
18	F		3.00	12913.14
19	M		4.00	15602.66
20	F		4.00	13785.99
21	M		4.00	7254.98
22	F		4.00	9112.05
23	M		4.00	8871.65
24	F		4.00	21712.81
25	M		4.00	21075.06
26	F		4.00	18117.33
27	M		4.00	8489.23
28	F		4.00	21873.26
29	M		4.00	13486.26
30	F		4.00	12126.6
31	M		3.00	6975.92
32	F		4.00	13658.63
33	M		4.00	9597.97
34	F		4.00	20598.47
35	M		4.00	6948.99
36	F		4.00	11076.67
MEAN		1629.9	3.80	13462.78
SD		398.69	0.41	4718.78
MEDIAN		1646.4	4.00	12913.14
CV(%)		24.46	10.68	35.05
Range(Min.)			3.00	6948.99
(Max.)			4.00	23217.75
Num of Subjects		35	35	35

PRELIMINARY DATA

Summary of Pathology Report:

There were no statistically significant or treatment-related increases in mortality in any of the groups of either sex in this study. There were no test article-related effects on mean terminal body weights in both sexes. Test article-related decreases in mean absolute adrenal weights were observed in males at all dose levels. The adrenal weight decreases might be attributable to increased angiectasis/cystic degeneration in the adrenal cortex and an increased frequency, size, and bilateral occurrences of adrenal medullary neoplasms in the control group rather than to an effect of the test-article in males, which was not observed in females.

Test article-related increases in mean absolute and relative heart, kidney, and liver weight in the HD female groups were observed. The increases in the three organs were not observed in male rats. There was an increased incidence and severity of chronic progressive nephropathy in the kidney of females given 900 or 1200 mg/kg/day, suggesting a possible test article related effect. The incidence and severity of chronic progressive nephropathy in females were summarized below.

Incidence and Mean Severity of the Microscopic Finding in Chronic Progressive Nephropathy in 104-week Carcinogenicity Study in Rat@									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Number of rat examined	60	60	60	60	60	60	60	60	60
Incidence	49	55	54	54	33	31	36	46	43
Mean Severity	2.0	2.3	2.5	2.5	0.7	0.8	0.9	1.3	1.4
@Indicates number of animals affected.									

The incidence of parathyroid adenomas in male appeared to be increased in all treated groups including the LD and MD groups. The microscopic observational incidence of parathyroid adenomas in male controls in this study (1.7%) was comparable to historical controls (3.4%), which were obtained from comparable studies with similar group size, study duration, and strain of rats. The increased incidence of parathyroid adenomas in the males was significant, but not associated with a significant trend ($p = 0.0936$). The adenomas, diffuse and focal parathyroid hyperplasia were not test article-dose related and were not observed in female rats as summarized below.

Incidence of the Microscopic Finding in Parathyroid Hyperplasia and Adenoma									
Sex	Males				Females				
Dose (mg/kg/day)	0	150	300	450	0	150	450	900	1200
Number of rat examined	58	59	60	58	59	38	40	37	57
Adenomas@	1	9*	8*	7*	3	0	0	0	1
Hyperplasia, diffuse	5	6	10	12	0	0	0	0	1
Hyperplasia, focal	0	4	2	1	0	0	0	0	0
@Indicates number of animals affected. *P<0.05, compared to the control group.									

Statistical Review: Adenoma in the parathyroid gland is a common tumor, which will be considered significant by trend test if P<0.005 according to the FDA statistical significance guidance (May 2001). The level of significance of total incidence rate of adenoma in parathyroid gland was 0.1043, which is not significant as presented in a table below. In addition, for common tumors to be considered significantly increased by pair-wise comparison P values must be ≤ 0.01. Therefore, parathyroid adenomas were not significantly increased by trend test or T-test.

Incidence of histopathological findings in the parathyroid in the males

	Group 1	Group 2	Group 3	Group 4
Parathyroid – Adenoma				
Total Incidence Rate	1/58	9/59	8/60	7/58
One-sided (Upper-tailed) p	0.1043	0.0538	0.0404	0.0400
Parathyroid – Hyperplasia, Diffuse				
Total Incidence Rate	5/58	6/59	10/60	12/58
One-sided (Upper-tailed) p	0.0222	0.5121	0.1503	0.0567
Parathyroid – Hyperplasia, Focal				
Total Incidence Rate	0/58	4/59	2/60	1/58
One-sided (Upper-tailed) p	0.4337	0.0614	0.2564	0.5000

Conclusions:

A two-year carcinogenicity study in rats was performed under acceptable conditions. However, the top dose for female rats (1,200 mg/kg/day) did not represent the MTD, based on body weight decrease. The eCAC did review and concur with the doses evaluated in the study. Based on toxicokinetic data obtained from the 26-week chronic study in female rats, the AUC ratio at the high dose was estimated to be approximately 10-fold human therapeutic exposures. In the 2-year carcinogenicity study, the incidence of parathyroid adenomas and diffuse hyperplasia in male rats was not significantly increased. There were no positive carcinogenic findings in female rats.

Proposed Labeling: OK Carried / Changes 2/25/15

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times therapeutic exposures based AUC values with the maximum recommended human daily dose of 2000 mg/kg/day. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and in vivo mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at dose up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy:
Teratogenic Effects: Pregnancy Category B

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl should not be used during pregnancy unless clearly needed.

Nursing Mothers: Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.

2.6.7 TOXICOLOGY TABULATED SUMMARY

(PLEASE SEE THE TABLE BELOW)

Biovail Laboratories, Inc. NDA 21-748
GLUMETZA™ (metformin hydrochloride) Extended Release Tablets 500 mg and 1000 mg
2.6 Nonclinical Written and Tabulated Summaries

2.6.7.1 Toxicology — Overview — Test Article: Metformin Hydrochloride

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Dosex (mg/kg)	GLP Compliance	Testing Facility	Study Number	Location Vol.	Location Page
Single-Dose Toxicity	None								
Repeat-Dose Toxicity	FVB/N Mice	Dermal	5 days	0, 125, 250, 500, 1000	Yes		AA14YD.2D32.06.BTL	N/A	N/A
	FVB/N Mice	Dermal	28 days	0, 125, 250, 500, 1000, 2000	Yes		AA14YD.2D32.06.BTL	N/A	N/A
	SD Rats	Gavage	4 weeks	0, 150, 450, 900	Yes		6802-113	N/A	N/A
	SD Rats	Gavage	13 weeks	0, 150, 450, 900	Yes		6802-119	N/A	N/A
	SD Rats	Gavage	26 weeks	0, 150, 450, 900	Yes		6802-122	N/A	N/A
	Beagle Dogs	Capsule	4 weeks	0, 50, 100, 150	Yes		6802-116	N/A	N/A
	Beagle Dogs	Tablet	3 months	0, 250, 500, 1000/dog	Yes		3530.1	N/A	N/A
	Beagle Dogs	Capsule	39 weeks	0, 20, 40, 60, 80	Yes		6802-125	N/A	N/A
Genotoxicity	S. typhimurium and E. coli	*In vitro*	–	0, 100, 333, 1000, 3333, 5000 mcg/plate	Yes		G98AW49.502	N/A	N/A
	L5178Y/TK+/- cells	*In vitro*	–	0, 1000, 2000, 3000, 4000, 5000 mcg/mL	Yes		G98AW49.704	N/A	N/A
	ICR Mice	Gavage	Single	0, 500, 1000, 2000	Yes		G98AW49.123	N/A	N/A
Carcinogenicity	Tg.AC Mice	Dermal	26 weeks	0, 500, 1000, 2000	Yes		6802-163	N/A	N/A
	SD Rats	Gavage	104 weeks	M: 0, 150, 300, 450 F: 0, 150, 450, 900, 1200	Yes		6802-128	N/A	N/A
Reproduction Toxicity	SD Rats	Gavage	[a]	0, 150, 300, 600, 900	Yes		2102-005P	N/A	N/A
	SD Rats	Gavage	[b]	0, 150, 450, 900	Yes		2102-005	N/A	N/A
	NZW Rabbits	Stomach tube	G6-G18[c]	0, 25, 50, 100, 200	Yes		2102-004P	N/A	N/A
	NZW Rabbits	Stomach tube	G6-G18[c]	0, 30, 60, 90	Yes		2102-004	N/A	N/A
	SD Rats	Gavage	G7-L6[c]	0, 150, 300, 600, 900	Yes		2102-006P	N/A	N/A
	SD Rats	Gavage	G7-L20[c]	0, 150, 300, 600	Yes		2102-006	N/A	N/A

N/A, Not applicable

[a] Males: 15 days prior to mating. Females: 15 days prior to mating through Gestation Day 17
[b] Male: 28 days prior to mating. Females: 15 days prior to mating through Gestation Day 17
[c] G = Gestation Day; L = Lactation Day

APPEARS THIS WAY
ON ORIGINAL

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There are no preclinical pharmacology and toxicology issues with this metformin extended release (ER) formulation.

Unresolved toxicology issues (if any): None.

Recommendations: Pharmacology and toxicology data support approval of this NDA.

Suggested labeling: Please see "Pharmacology Recommendation" above.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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

/s/

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