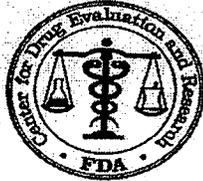


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-044**

**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:	22-044
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	31 May 2006
PRODUCT:	Janumet (Sitagliptin/Metformin Fixed-Dose Combination)
INTENDED CLINICAL POPULATION:	Type 2 Diabetics
SPONSOR:	Merck
DOCUMENTS REVIEWED:	eCTD
REVIEW DIVISION:	Division of Metabolic and Endocrine Products
PHARM/TOX SUPERVISOR:	Todd Bourcier, Ph.D.
DIVISION DIRECTOR:	Mary Parks, M.D.
PROJECT MANAGER:	Lina Aljuburi, Pharm. D., M.S.

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

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**TABLE OF CONTENTS**

**EXECUTIVE SUMMARY ..... 3**

- I. Recommendations..... 3**
- II. Summary of non-clinical findings ..... 4**
  - A. Brief overview of non-clinical findings..... 4
  - B. Non-clinical safety issues relevant to clinical use ..... 7

**2.6 PHARMACOLOGY/TOXICOLOGY REVIEW ..... 8**

**2.6.1 INTRODUCTION AND DRUG HISTORY..... 8**

- 2.6.6.8 Special toxicology studies ..... 10
  - MK-0431 + Metformin: Combination Toxicity Studies in Dogs..... 10**
  - MK-0431 + Metformin: 14 week oral toxicity study in dogs..... 10**
  - Exploratory 5-week oral tolerability study with Metformin in female dogs ..... 21**
  - MK-0431 + Metformin: 16 week oral toxicity in female dogs..... 25**

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## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

#### **A. Recommendation on approvability**

##### AP (Approval)

Pharmacology/Toxicology recommends approval of NDA 22-044 (Janumet)

#### **B. Recommendation for nonclinical studies**

No additional nonclinical studies are required.

#### **C. Recommendations on labeling**

The proposed labeling language relevant to pharmacology/toxicology has been accurately reproduced from the approved labels for Januvia and Glucophage. No further changes are recommended.

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## II. Summary of non-clinical findings

### A. Brief overview of non-clinical findings

Non-clinical studies with the fixed-dose combination product were not performed. Potential toxicity unique to the combination of sitagliptin phosphate (MK-0431) and metformin was evaluated in dogs co-administered each drug separately. The combination of MK-0431 and high-dose metformin (50 mg/kg) in dogs may have resulted in more numerous and earlier deaths than observed with metformin alone. The combination of MK-0431 and a lower dose of metformin (20 mg/kg) that better approximates human exposure of 2,500mg/day resulted in no deaths and yielded no evidence of exacerbated toxicity. Convincing evidence is provided that the deaths at 50 mg/kg are due to metformin toxicity and not to the combination. Nevertheless, there is a slight possibility of exacerbated toxicity in the setting of high metformin exposure ( $\geq 400\mu\text{M}\cdot\text{h}$  AUC) and clinical exposure to MK-0431 ( $\sim 10\mu\text{M}\cdot\text{h}$  AUC).

*The following summary is taken from the pharmacology/toxicology review for Januvia, NDA 21-995.*

#### *Pharmacology*

MK-0431 (sitagliptin phosphate) is a competitive inhibitor of dipeptidyl peptidase 4 (DPP4), an enzyme principally responsible for degrading incretin peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). MK-0431 prolongs incretin half-life and biological activity and thus potentiates glucose-dependent insulin release and delays gastric emptying. In non-clinical models of diabetes, MK-0431 moderates glucose excursion and improves insulin release and islet cell function/mass without provoking hypoglycemia. MK-0431 is body weight-neutral, unlike marketed glitazones (weight gain) and GLP-1 analogues (weight loss).

Immunomodulatory effects of DPP4 (aka CD26) are reportedly not altered by MK-0431, based on normal responses of murine T- and B-cells to antigens and mitogens. However, rodent DPP4/CD26 differs in some aspects from human DPP4/CD26 (e.g., binding of adenosine deaminase) and Merck's experiments did not directly test the T-helper memory function ascribed to CD26. Therefore, the non-clinical data do not adequately predict potential effects of MK-0431 on DPP4/CD26's role in human immunity.

Safety pharmacology assessment of neurological, renal, pulmonary, and gastrointestinal effects of MK-0431 did not identify any significant liabilities.

#### *Absorption, Distribution, Metabolism, and Excretion*

An oral dose of MK-0431 is rapidly absorbed and is 60-90% bioavailable in rats and dogs. MK-0431 distributes to most rat tissues with low amounts distributing to the brain, eyes, and bone. Plasma protein binding is moderate (30%). Metabolism of MK-0431 is minimal with 80% of unchanged parent compound being eliminated in the urine of rats,

dogs, and humans. Oxidative metabolism by CYP3A4 and 2C8 is a minor metabolic pathway. MK-0431 has a longer plasma half-life in humans (13hrs) than in rats and dogs (2-5hrs) probably due to different rates of renal elimination. MK-0431 slightly accumulates in humans but not in dogs or rats after multiple dosing.

MK-0431 is a P-glycoprotein and hOAT3 substrate, but does not interfere in the shuttling of other substrates via these transporters *in vitro*. MK-0431 does not inhibit CYP450 enzymes or induce CYP3A4. The results predict a low probability for pharmacokinetic drug interactions via these pathways.

*General Toxicology (MRHD, Maximum Recommended Human Dose, or 100mg)*

Single dose studies identified minimum lethal doses of 2000mg/kg (200-400x MRHD) in mice and 3000mg/kg (150-300x MRHD) in rats. Little other toxicological information was obtained in these studies.

Repeat dose studies were conducted in Sprague-Dawley rats and Beagle dogs up to 6 months and 12 months duration, respectively.

A high-dose 3-month study in rats identified kidney and liver necrosis, myocardial degeneration, bone marrow necrosis, and death at 1500 and 2000mg/kg (150-200x MRHD). Kidney toxicity was also observed in mice at 500mg/kg. Note that exposure at these high doses is theoretically sufficient to inhibit off-target enzymes DPP8/9, proteases that are associated with these toxicities.

Administration of doses up to 20x the MRHD for 6 months in rats did not elicit significant toxicity.

Studies in dogs identified NOAEL doses based on clinical signs that consisted of reduced activity, hunched posture, ataxia, tremor, and sporadic emesis observed at 50mg/kg (20x MRHD). Respiratory distress, described as audible and labored breathing and open-mouthed breathing, was also reported. No consistent target organs were identified in these studies.

Administration of doses up to 5x the MRHD for up to 12 months in dogs did not elicit significant toxicity.

*Special Toxicology*

MK-0431 did not produce vascular/skin lesions in rhesus monkeys, as seen with some DPP4 inhibitors, after three months administration of doses up to 25x the MRHD. Mechanistic data provided by Merck suggests that inhibiting DPP4 activity alone is not sufficient to produce this toxicity.

*Reproductive Toxicology*

Exposure to MK-0431 in the definitive studies ranged from 12x to 90x MRHD in the rat and 6x to 50x in the rabbit. Resorptions and post-implantation losses increased in

females in a fertility study at ~25x MRHD; male fertility was not effected. MK-0431 was not teratogenic but increased the incidence of skeletal malformations in rat pups at maternally toxic doses. At maternally non-toxic doses, a single rat pup had multiple skeletal abnormalities (incidence within historical range), and a single rabbit pup had multiple cardiovascular abnormalities, but a relationship to drug treatment is not conclusive. MK-0431 crosses the placenta in rats and rabbits and is excreted in maternal milk at a 4:1 ratio to plasma. As with other oral hypoglycemic agents, MK-0431 should not be given to pregnant or nursing mothers and Merck will maintain a pregnancy register. Pregnancy Category 'B' is recommended.

There were no conclusive drug-related effects on embryonic/post-natal development in rats at 125mg/kg (12x MRHD) or in rabbits at 125mg/kg (20x MRHD).

#### *Genetic Toxicology*

MK-0431 was not mutagenic or clastogenic in three *in vitro* assays (Ames, hepatocyte alkaline elution, and chromosome aberration) and one *in vivo* assay (murine micronucleus induction).

#### *Carcinogenicity*

Carcinogenic potential of MK-0431 was evaluated in 2 year studies in mice and rats. Both studies adequately assessed carcinogenesis. MK-0431 significantly increased the incidence of combined liver adenoma/carcinoma in male and female rats, and increased liver carcinomas in female rats at 500mg/kg (62x MRHD). Non-genotoxic, chronic hepatotoxicity is the suggested etiological event but this is based on weak correlative evidence of liver toxicity. MK-0431 did not produce any drug-related tumors in CD-1 mice up to 500mg/kg (72x MRHD). MK-0431 poses a minimal carcinogenic risk to humans.

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**B. Non-clinical safety issues relevant to clinical use**

1. DPP4 cleaves several substrates in addition to GLP-1. Therefore, MK-0431 may have undesirable effects related to inhibiting cleavage of non-incretin substrates. Effects on human immunity, specifically recall responses to antigens and immune cell trafficking, may be adversely affected by DPP4 inhibition. This risk is an unavoidable characteristic of MK-0431 and the drug class. There is currently no clinical evidence of such effects with Januvia or with Janumet.
2. MK-0431 presents a marginal clinical risk of producing skin lesions with prolonged administration. This conclusion is based on the absence of skin findings in the 3-month monkey study, on mechanistic data suggesting that inhibiting DPP4 activity alone is not sufficient to produce this toxicity, and on the high DPP4 selectivity of MK-0431 at clinical exposure. Risk assessment for skin lesions must be done on a case-by-case basis and is not evidence of similar safety with other DPP4 inhibitors currently in clinical development.
3. Issues specific for the combination of Januvia and metformin include the finding of excess deaths of dogs administered pharmacologically high doses of metformin and a clinically relevant dose of sitagliptin. Convincing evidence is provided that the deaths at 50 mg/kg are due to metformin toxicity and not to the combination. Nevertheless, there is a slight possibility of exacerbated toxicity in the setting of high metformin exposure ( $\geq 400\mu\text{M}\cdot\text{h}$  AUC) and clinical exposure to MK-0431 ( $\sim 10\mu\text{M}\cdot\text{h}$  AUC).

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## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 22-044

**Review number:** 1

**Sequence number/date/type of submission:** SN000 / 31 May 2006

**Information to sponsor:** Yes (X) No ( )

**Sponsor and/or agent:** Merck Research Laboratories

**Manufacturer for drug substance:** Merck Facilities

**Reviewer name:** Todd Bourcier

**Division name:** Metabolic and Endocrine Products

**HFD #:** 510

**Review completion date:** 28 Feb 2007

**Drug:**

Trade name: Janumet

Generic name: Sitagliptin phosphate and Metformin HCl

Fixed Dose Combination

**Sitagliptin phosphate:**

Trade name: Januvia

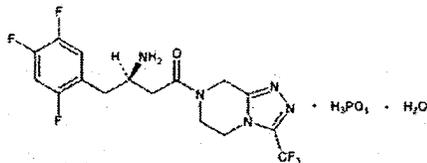
Code name: MK-0431, sitagliptin phosphate

Chemical name: 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate

CAS registry number: 654671-77-9

Molecular formula/molecular weight:  $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$  / 523.32 MW

Structure:



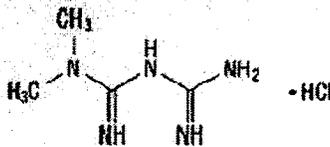
**Metformin HCl:**

Chemical name: *N,N*-dimethylimidodicarbonimidic diamide hydrochloride

CAS registry number:

Molecular formula/molecular weight:  $C_4H_{11}N_5 \cdot HCl$  / 165.6 MW

Structure:



**Relevant INDs/NDAs/DMFs:**

1. NDA 21-995 (Januvia)
2. NDA 20-357 (Glucophage)

**Drug class:** Oral antihyperglycemic agents

**Intended clinical population:** Type II diabetics

**Clinical formulation:** Film-coated tablets containing 50 mg sitagliptin phosphate and 500 mg metformin hydrochloride (Janumet 50/500) or 1000 mg metformin hydrochloride (Janumet 50/1000). Inactive ingredients include microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulfate, and sodium stearyl fumarate.

**Route of administration:** Oral

**Maximum Recommended Human Dose:** Twice daily dosing of Janumet 50/1000 will provide 100mg sitagliptin phosphate and a maximum of 2000mg metformin.

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

**Studies reviewed within this submission:**

MK-0431 + Metformin: Combination Toxicity Studies in Dogs  
MK-0431 + Metformin: 14 week oral toxicity study in dogs  
Exploratory 5-week oral tolerability study with Metformin in female dogs  
MK-0431 + Metformin: 16 week oral toxicity in female dogs

**Studies not reviewed within this submission:**

All other pharmacology/toxicology studies relevant to evaluation of Janumet have been reviewed previously and are publicly available under NDA 21,995 for Januvia (sitagliptin) and under NDA 20,357 for Glucophage (metformin).

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### 2.6.6.8 Special toxicology studies

#### **MK-0431 + Metformin: Combination Toxicity Studies in Dogs**

##### **Summary**

A series of studies evaluated the potential toxicity of MK-0431 administered in *combination* with metformin to dogs. The combination of MK-0431 and high-dose metformin (50 mg/kg) in dogs may have resulted in more numerous and earlier deaths than observed with metformin alone (Study #TT 06-6000). The combination of MK-0431 and a lower dose of metformin (20 mg/kg) that better approximates human exposure resulted in no deaths and yielded no evidence of exacerbated toxicity (Study #TT 06-6017). Convincing evidence is provided that the deaths at 50 mg/kg are due to metformin toxicity and not to the combination (Study #TT 06-6018). Nevertheless, there is a slight possibility of exacerbated toxicity in the setting of high exposure to metformin ( $\geq 400\mu\text{M}\cdot\text{h}$  AUC) and clinical exposure to MK-0431 ( $\geq 10\mu\text{M}\cdot\text{h}$  AUC).

#### **MK-0431 + Metformin: 14 week oral toxicity study in dogs**

50 mg/kg Metformin and 2, 10, 50 mg/kg MK-0431

##### **Key study findings:**

- Mortality occurred in females of all combination groups and the metformin-alone group. Deaths with the combination appear more numerous and occur earlier than with the metformin-alone group.
- Mortality occurred in females only; all males survived to termination.
- The metformin-alone death may be due to lactic acidosis, indicated by high plasma lactate and low bicarbonate.
- Earlier deaths with the combination are not adequately explained.
- Three deaths in the MD and HD combination groups showed vacuolation in the brain with one of the three also showing neuronal necrosis; degenerative changes in brain are reported in dogs administered metformin (NDA 20-537).
- Exposure to MK-0431 is not altered by co-administration of metformin.
- Exposure to Metformin tends to be 50% higher in females co-administered MK-0431 than metformin alone. However, TK comes from a single female in the MD and HD groups, so only tentative conclusions can be drawn. There is no difference in males.

*Reviewer Comments*

Merck concludes that all deaths are related to metformin toxicity and not to exacerbated toxicity with the combination. The data in this study do not support that conclusion because earlier deaths with the combination are not adequately explained. To the contrary, the death of one female given metformin alone was associated with a 50% higher metformin AUC than the females given the combination, yet deaths were observed in all groups except control.

Nevertheless, it is feasible that the deaths are related to metformin toxicity for the following reasons:

1. Plasma lactate tended to be higher in surviving dogs and was clearly higher in 2 dogs in the HD combination group, though this may be related to morbidity.
2. The minimally toxic dose of metformin in dogs is 50mg/kg, with death in 50% to 100% of animals at  $\geq 100$ mg/kg (IND 5934, NDA 20,357), indicating a sharp dose response curve.
3. Metformin exposure in females was higher in this study ( $\geq 500$   $\mu$ g\*h/ml) than reported in the metformin NDA ( $\sim 300$   $\mu$ g\*h/ml). Exposure in males was similar to females on day 1 but decreased by week 8.

Exacerbated toxicity of the MK-0431/Metformin combination cannot be excluded based on this data, but neither can it be confirmed.

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**Study no.:** TT 06-6000

**Volume #, and page #:** eCTD

**Conducting laboratory and location:** MRL, Chibret, France

**GLP compliance:** French Ministry of Health GLP standard

**QA report:** yes (x) no ( )

**Drug, lot #, and % purity:**

MK-0431, lot L-000224715-010X029

Metformin, lot L-000282095-001L012, from \_\_\_\_\_  
 \_\_\_\_\_ purity by HPLC (manufacturer's data)

**Methods**

<u>Doses:</u>	Control (vehicles) <sup>a</sup>	Females	Males
	MK-0431 + Metformin	3	3
	0 + 50 mg/kg/day <sup>b</sup>	3	3
	2 + 50 mg/kg/day <sup>c</sup>	3	3
	10 + 50 mg/kg/day <sup>c</sup>	3	3
	50 + 50 mg/kg/day <sup>c</sup>	3	3
<sup>a</sup> Control animals received 5 mL/kg of acidified deionized water followed by 5 mL/kg of 0.5% (w/v) methylcellulose in deionized water daily. <sup>b</sup> Animals received 5 mL/kg of acidified deionized water followed by 5 mL/kg of Metformin dosing formulation daily. <sup>c</sup> Animals received 5 mL/kg of MK-0431 dosing formulation followed by 5 mL/kg of Metformin dosing formulation daily.			
<u>Species/source</u>	Beagle dogs from _____		
<u>Age:</u>	40-42 weeks		
<u>Weight:</u>	6.8-9.6 kg		
<u>Toxicokinetic groups</u>	Blood collected after the first dose and in drug week 8		
<u>Recovery groups:</u>	No recovery		
<u>Route, formulation, dose volume</u>	Oral gavage of both drugs, MK-0431 first, then metformin MK-0431 in acidified water Metformin in 0.5% methylcellulose in water		

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**Observation and Times:**

<u>Clinical Findings:</u>	Daily observations
<u>Body weights:</u>	Pretest and then weekly
<u>Food consumption:</u>	Four times per week
<u>Ophthalmoscopy</u>	Pretest, drug weeks 6 and 12
<u>EKG:</u>	Pretest, drug weeks 6 and 12
<u>Hematology:</u>	Pretest, drug weeks 4, 9, and 12, fasted state
<u>Clinical chemistry:</u>	Pretest, drug weeks 4, 9, and 12 Lactate and bicarbonate done on week 6, 9, and 12 Some frozen samples from week 4 analyzed in week 6 for bicarbonate and serum electrolytes
<u>Urinalysis:</u>	Overnight urines collected in drug weeks 9 and 12
<u>Gross pathology:</u>	Complete necropsies on all scheduled/unscheduled deaths
<u>Organ weights:</u>	adrenals, brain, heart, ovaries, kidneys, thymus, liver, pituitary, prostate, spleen, testes, thyroid
<u>Histopathology:</u>	From control, metformin alone, and high dose MK-0431/metformin Also from found dead/early sacrifice animals
<u>Adequate Battery:</u>	yes ( X ), no ( )
<u>Peer review:</u>	yes ( ), no ( X )

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**Results:**

**Mortality:** Deaths occurred in all treated groups including metformin alone (Table 1). There was one death each in the metformin alone group and the low dose MK-0431/metformin group, and two deaths each in the mid- and high-dose MK-0431/metformin groups. Deaths in the combination groups occurred earlier (1-4 weeks) than the metformin alone group (week 6).

Note that only females were effected; mortality did not occur in males.

Females 05-0121 and 05-0143 showed severe physical signs, including lateral recumbency, limb paddling, rigidity, labored breathing and prostration.

Females 05-0133 and 05-0137 showed body weight loss, markedly reduced food intake, and anorexia.

**Table 1: Mortality in female dogs administered MK-0431 and Metformin**

Group (Dose in mg/kg/day)	Animal Number	Drug Week of Death	Found Dead or Early Sacrifice	Cause of Death/Reason Killed
Metformin (50)	05-0133F	6	ES	Body weight loss and persistent anorexia
MK-0431 + Metformin (2 + 50)	05-0137F	3	FD	Undetermined
MK-0431 + Metformin (10 + 50)	05-0121F 05-0111F	1 4	FD FD	Undetermined Undetermined
MK-0431 + Metformin (50 + 50)	05-0125F 05-0143F	4 4	FD FD <sup>a</sup>	Undetermined Undetermined
<sup>a</sup> Animal died prior to euthanasia for early sacrifice. ES = Early Sacrificed. F = Female. FD = Found Dead.				

**Histological** changes in early sacrifice females #05-0121, -0111, and -0143 included vacuolation of the brain in all three and neuronal necrosis in #05-0143. Note that two of these dogs are in the MD combo group and the one with vacuolation and neuronal necrosis is in the HD combo group. Hemorrhage was not reported in these individuals. No other early death or surviving dogs showed histological changes in brain. Metformin administration to dogs has been associated with degenerative changes in the brain, among other organs (ref. NDA .

Other histological changes found only in early sacrifice females include lymphoid depletion of Peyer's patch, lymph nodes, and thymus, and adrenal vacuolation (1f).

Merck concludes that the deaths are related to metformin alone and not to co-treatment with MK-0431, citing lactic acidosis as a likely mechanism. As evidence, the metformin-

alone death was associated with high plasma lactate and low bicarbonate prior to sacrifice in week 6 compared to the control group. Unfortunately, plasma lactate was not measured in 3 other combination-group deaths where frozen samples were available from week 4. Bicarbonate tended to be lower in those samples, but not substantially. Changes in lactate/bicarbonate in surviving animals is discussed under the clinical chemistry section.

The data indicate lactic acidosis as a possible cause of death in the metformin-alone group, but is not conclusive as to the cause of deaths in the combination groups.

Plasma Lactate and Bicarbonate from Unscheduled Deaths			
	Dog number	Plasma Lactate (mg/dL)	Bicarbonate (mM)
<i>CONTROL</i>	<i>group average</i>	9.9	23.9
Metformin	05-0133F	90	12.1
LD MK-0431/metformin	05-0137F	nd	nd
MD MK-0431/metformin	05-0121F	nd	nd
	05-0111F	nd	20.1
HD MK-0431/metformin	05-0125F	nd	17.8
	05-0143F	nd	21.6

nd = sample not taken (05-0137 & -0121) or not analyzed (05-0111, -0125, & -0143)

#### Clinical signs:

Males and females in all treatment groups (excluding control) showed physical signs starting in drug weeks 1/2. Signs included salivation and occasional emesis shortly after dosing, and an increased incidence of unformed stools. There was no difference noted between the dose groups relative to these clinical signs.

In the high dose MK-0431/metformin group, ataxia and tremors were observed in 2 females and 1 male shortly after dosing but the signs subsided within 4-6 hours. The transient ataxia/tremors associated with dosing were observed from drug weeks 1 to 3. This CNS effect has been identified in several previous toxicity studies in beagle dogs administered 50 mg/kg.

Body weights:

Death of females #05-0133 and 05-0137 from the metformin-alone and LD MK-0431/metformin group was associated with a 1 to 2 kg loss in body weight by drug week 2 and 5, respectively, consistent with reduced food intake and anorexia in these individuals.

Treated females generally gained less weight than the control females except for the individual in the HD MK-0431/metformin group. Males administered the combination tended to gain less weight than the control of metformin-alone males, but the data is variable and not dose-dependent.

The data are not conclusive as to an effect on BW in surviving dogs, though the data in males suggests some effect with combination treatment.

Change in BW in surviving dogs			
Study Time	Dose, mg/kg	Females BW gain (kg)	Males BW gain (kg)
13 weeks	Control	+0.6	0.5
	Metformin	+0.1 (n=2)	0.5
	LD MK-0431/metformin	-0.1 (n=2)	-0.3
	MD MK-0431/metformin	-0.3 (n=1)	0 (-0.8 to 0.9)
	HD MK-0431/metformin	+0.6 (n=1)	0.1

Food consumption: Aside from reduced food consumption in the moribund females described above, there was no difference in food intake between the treated and control groups.

Ophthalmoscopy: There were no treatment-related changes reported.

EKG: There were no treatment-related changes reported. Note that primary data was not submitted.

Hematology: There were no treatment-related changes relative to RBC, WBC, and coagulation variables.

Plasma Lactate in Male Dogs (all survived, n=3/group)			
	Week 6	Week 9	Week 12
CONTROL	8.1	10.2	8.3
Metformin	7.9	11.6	10.1
LD MK-0431/metformin	7.9	11.2	9.7
MD MK-0431/metformin	9.1	16.8	13.2
HD MK-0431/metformin*	9.1	24.1*	20.2*

\*Plasma lactate in dog #05-0138 was 37 and 31 mg/dL at weeks 9, 12 respectively, skewing the mean upward.

Historical Control Values for Dogs, Plasma Lactate and Bicarbonate

Historical Control Values for Dog (06-Feb-2006 to 20-Feb-2006)							
Age	No. of Tests	No. of Animals	Median Value	Range of Actual Values	2.5%	95% Spread	97.5%
Bicarbonate mmol/L							
Female							
26 to 39 Weeks	73	73	23.4	18.7 - 26.6	19.5		26.4
Combined Ages	73	73	23.4	18.7 - 26.6	19.5		26.4
Male							
26 to 39 Weeks	74	74	24.0	20.7 - 27.7	20.8		27.2
Combined Ages	74	74	24.0	20.7 - 27.7	20.8		27.2
Both Sexes							
26 to 39 Weeks	147	147	23.8	18.7 - 27.7	20.0		26.9
Combined Ages	147	147	23.8	18.7 - 27.7	20.0		26.9
Lactate mg/dl							
Female							
26 to 39 Weeks	53	53	12.1	5.4 - 28.8	5.5		28.7
Combined Ages	53	53	12.1	5.4 - 28.8	5.5		28.7
Male							
26 to 39 Weeks	54	54	13.0	4.5 - 33.4	4.8		33.2
Combined Ages	54	54	13.0	4.5 - 33.4	4.8		33.2
Both Sexes							
26 to 39 Weeks	107	107	12.7	4.5 - 33.4	5.4		32.1
Combined Ages	107	107	12.7	4.5 - 33.4	5.4		32.1

Urinalysis: Treated and control groups showed no difference in urinary volume, specific gravity, urobilinogen, glucose, protein, blood, ketones, or sediments.

Gross pathology: Treated and control groups showed no difference. (scheduled sacrifices)

Organ weights: Treated and control groups showed no difference. (scheduled sacrifices)

Histopathology:

**Histological** changes were present only in early sacrifice females, and are described under the 'Mortality' section above.

To summarize, females #05-0121 and -0111 had brain vacuolation and female 05-0143 showed brain vacuolation and neuronal necrosis. Although these dogs are in the MD and HD combo groups, such changes in brain have been previously described in dogs following administration of metformin (ref. NDA \_\_\_\_\_)

Other histological changes found only in early sacrifice females include lymphoid depletion of Peyer's patch, lymph nodes, and thymus, and adrenal vacuolation (1f).

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**Toxicokinetics:**

**MK-0431:** Exposure as AUC at all dose groups is consistent with TK from prior studies. There is no sex difference, and exposure slightly decreases by drug week 8. Co-administration of metformin did not alter TK of MK-0431.

**Metformin:** Exposure as AUC was ~50% higher in females given metformin alone compared to females given the combination, which may suggest some PK interaction in females. This was not seen in males. In addition, exposure in females tends to be higher than in males by drug week 8, though not substantially. Note that TK comes from a single female in the MD and HD groups, so only tentative conclusions can be drawn.

**Exposure to MK-0431**

Mean Plasma MK-0431 Toxicokinetic Parameters – Drug Day 1

	MK-0431 + Metformin (mg/kg/day)			
	Females			
	2a + 50b	10a + 50b	50a + 50b	
AUC <sub>0-24 hr</sub> (µM•hr)	11.0 ± 1.61	59.8 ± 9.65	315 ± 37.4	
C <sub>max</sub> (µM)	2.24 ± 0.391	11.3 ± 1.02	66.6 ± 9.56	
T <sub>max</sub> (hr)	1.0 ± 0.0	0.8 ± 0.2	0.5 ± 0.0	
	Males			
	2a + 50b	10a + 50b	50a + 50b	
	AUC <sub>0-24 hr</sub> (µM•hr)	12.2 ± 0.593	71.0 ± 4.35	368 ± 30.9
C <sub>max</sub> (µM)	2.36 ± 0.130	11.6 ± 0.578	58.7 ± 0.623	
T <sub>max</sub> (hr)	1.0 ± 0.0	0.8 ± 0.2	0.7 ± 0.2	
	Sexes Combined			
	2a + 50b	10a + 50b	50a + 50b	
	AUC <sub>0-24 hr</sub> (µM•hr)	11.6 ± 0.815	65.4 ± 5.35	342 ± 24.8
C <sub>max</sub> (µM)	2.30 ± 0.186	11.4 ± 0.529	62.7 ± 4.63	
T <sub>max</sub> (hr)	1.0 ± 0.0	0.8 ± 0.1	0.6 ± 0.1	

a Dose of MK-0431.  
b Dose of Metformin.  
Values are the mean ± SEM.

Mean Plasma MK-0431 Toxicokinetic Parameters – Drug Week 8

	MK-0431 + Metformin (mg/kg/day)			
	Females			
	2a + 50b	10a + 50b	50a + 50b	
AUC <sub>0-24 hr</sub> (µM•hr)	9.12 ± ID	56.3* ± ID	252* ± ID	
C <sub>max</sub> (µM)	1.47 ± ID	7.08* ± ID	35.8* ± ID	
T <sub>max</sub> (hr)	0.8 ± ID	2.0* ± ID	1.0* ± ID	
	Males			
	2a + 50b	10a + 50b	50a + 50b	
	AUC <sub>0-24 hr</sub> (µM•hr)	7.84 ± 2.20	42.9 ± 16.5	313 ± 29.1
C <sub>max</sub> (µM)	1.24 ± 0.358	7.54 ± 3.30	46.5 ± 4.33	
T <sub>max</sub> (hr)	1.0 ± 0.0	0.8 ± 0.2	0.8 ± 0.2	
	Sexes Combined			
	2a + 50b	10a + 50b	50a + 50b	
	AUC <sub>0-24 hr</sub> (µM•hr)	8.35 ± 1.40	46.2 ± 12.2	298 ± 25.6
C <sub>max</sub> (µM)	1.35 ± 0.254	7.43 ± 2.34	43.9 ± 4.07	
T <sub>max</sub> (hr)	0.9 ± 0.1	1.1 ± 0.3	0.9 ± 0.1	

a Dose of MK-0431.  
b Dose of Metformin.  
\* The data reported is from 1 animal (n=1).  
ID = Insufficient data available for calculation.  
Values are the mean ± SEM.

**Exposure to Metformin**

Mean Plasma L-000282095 (Metformin) Toxicokinetic Parameters – Drug Day 1

	MK-0431 + Metformin (mg/kg/day)			
	Females			
	0a + 50b	2a + 50b	10a + 50b	50a + 50b
AUC <sub>0-24 hr</sub> (µM•hr)	755 ± 72.6	519 ± 57.1	592 ± 59.3	528 ± 63.6
C <sub>max</sub> (µM)	205 ± 13.0	159 ± 25.3	154 ± 13.2	134 ± 10.5
T <sub>max</sub> (hr)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	0.7 ± 0.2
	Males			
	0a + 50b	2a + 50b	10a + 50b	50a + 50b
	AUC <sub>0-24 hr</sub> (µM•hr)	445 ± 75.8	558 ± 39.4	585 ± 34.4
C <sub>max</sub> (µM)	142 ± 33.6	182 ± 17.6	190 ± 15.5	164 ± 18.8
T <sub>max</sub> (hr)	1.3 ± 0.3	1.0 ± 0.0	1.0 ± 0.0	0.7 ± 0.2
	Sexes Combined			
	0a + 50b	2a + 50b	10a + 50b	50a + 50b
	AUC <sub>0-24 hr</sub> (µM•hr)	600 ± 83.7	539 ± 32.2	588 ± 30.7
C <sub>max</sub> (µM)	158 ± 26.4	171 ± 14.8	172 ± 12.1	149 ± 11.8
T <sub>max</sub> (hr)	1.2 ± 0.2	1.0 ± 0.0	1.0 ± 0.0	0.7 ± 0.1

a Dose of MK-0431.  
b Dose of Metformin.  
Values are the mean ± SEM.

Mean Plasma L-000282095 (Metformin) Toxicokinetic Parameters – Drug Week 8

	MK-0431 + Metformin (mg/kg/day)			
	Females			
	0a + 50b	2a + 50b	10a + 50b	50a + 50b
AUC <sub>0-24 hr</sub> (µM•hr)	807 ± ID	517 ± ID	503* ± ID	330* ± ID
C <sub>max</sub> (µM)	141 ± ID	136 ± ID	65.7* ± ID	49.3* ± ID
T <sub>max</sub> (hr)	1.5 ± ID	1.0 ± ID	3.0* ± ID	2.0* ± ID
	Males			
	0a + 50b	2a + 50b	10a + 50b	50a + 50b
	AUC <sub>0-24 hr</sub> (µM•hr)	432 ± 96.3	363 ± 121	358 ± 132
C <sub>max</sub> (µM)	124 ± 45.2	91.9 ± 38.9	80.7 ± 28.9	99.9 ± 18.2
T <sub>max</sub> (hr)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.0 ± 0.0
	Sexes Combined			
	0a + 50b	2a + 50b	10a + 50b	50a + 50b
	AUC <sub>0-24 hr</sub> (µM•hr)	582 ± 165	424 ± 81.0	394 ± 100
C <sub>max</sub> (µM)	131 ± 37.0	109 ± 27.7	76.9 ± 20.8	87.3 ± 18.1
T <sub>max</sub> (hr)	1.4 ± 0.2	1.2 ± 0.2	1.8 ± 0.5	1.3 ± 0.3

a Dose of MK-0431.  
b Dose of Metformin.  
\* The data reported is from 1 animal (n=1).  
ID = Insufficient data available for calculation.  
Values are the mean ± SEM.

**Exploratory 5-week oral tolerability study with Metformin in female dogs**

Control and 50mg/kg

**Key study findings:**

- One female was found dead on day 16 following body weight loss and reduced food intake.
- One female was sacrificed on day 23 for physical signs; plasma lactate was markedly elevated and bicarbonate reduced just prior to sacrifice, likely an effect of morbidity than true drug-related lactic acidosis.
- The timing of deaths is similar to deaths in response to the combination with MK-0431 in study #TT 06-6000.
- Mean plasma lactate increased  $\leq 2$  fold in metformin-treated females (high end of historical range), but bicarbonate was unchanged.

*Reviewer Comments:*

This study shows that 50mg/kg metformin is not well-tolerated in dogs, with 2 of 5 females dying by drug day 23. Merck suggests that metformin-induced lactic acidosis underlies morbidity/mortality in the dogs, but the reviewer concludes that morbidity in the dogs may be responsible for elevations in plasma lactate. The NDA \_\_\_\_\_ (Glucophage) review states that animal (rodent) studies have provided conflicting results relative to lactate production, and that death of dogs administered metformin are associated with symptoms of GI distress, vascular lesions, and degenerative changes in the brain, heart, kidney, and skeletal muscle (NDA \_\_\_\_\_), which are reasonable alternative explanations for the deaths.

The mechanism of metformin-related death is less important than the occurrence of death; a 50mg/kg dose with an exposure of  $\geq 400 \mu\text{M}\cdot\text{h}$  appears too high for combination toxicity studies in dogs.

The reviewer concludes that the deaths of female dogs given the combination of MK-0431 and metformin may be due to metformin toxicity rather than exacerbated toxicity of the combination.

**Study no.:** TT-06-6018

**Volume #, and page #:**

**Conducting laboratory and location:** MRL, Chibret, France

**GLP compliance:** No

**QA report:** yes ( ) no ( x )

**Drug, lot #, and % purity:**

Metformin, lot L-000282095-001L012, from \_\_\_\_\_

### Methods

<u>Doses:</u>	Control and 50 mg/kg groups
<u>Species/source</u>	Beagle Dogs from _____
<u>Age:</u>	34-38 weeks
<u>Weight:</u>	5.5-9.6 kg
<u>Number/sex/group:</u> (main study)	5 females
<u>Toxicokinetic groups</u>	After first dose and drug week 3
<u>Route, formulation, dose volume</u>	Oral gavage of drug in 0.5% methylcellulose/water

### Results:

**Mortality:** Two females died during the study. One female (#05-0277) was found dead before dosing on drug day 16, and the other (#06-0047) was sacrificed after dosing on drug day 23 due to marked physical signs.

***Female 05-0277:*** This female lost 1.2 kg body weight and food intake decreased markedly before death. Plasma lactate was elevated, but not substantially.

***Female 06-0047:*** This female had labored breathing and lateral recumbency prior to sacrifice. Plasma lactate was markedly increased (177 mg/dL), bicarbonate decreased (13mM), and glucose, potassium, and chloride decreased prior to its sacrifice on day 23. These findings may be secondary to morbidity rather than directly drug-related.

**Clinical signs:** Surviving females showed emesis and peri-dose salivation. The incidence of emesis was greatest during week 1.

Body weights: Female 05-0277 lost 1.2 kg BW (above). No other female showed a change in BW relative to pre-test values.

Food consumption: Female 06-0047 showed reduced food intake in drug weeks 1 and 2 prior to death. No other female showed a change in food intake.

Clinical chemistry:

*Blood samples were collected 24 hours post-dose (trough drug levels) on all days except day 17, where samples were taken at 1 hour post-dose (near-peak drug levels).*

*Blood was also drawn immediately before sacrifice of female #06-0047 of the metformin group prior to its sacrifice on day 23.*

There were no changes in the standard clinical chemistry panel. Plasma lactate and bicarbonate require detailed evaluation:

*Plasma Bicarbonate:* No change is seen in control or metformin groups up to drug day 29.

*Plasma Lactate:* Plasma lactate in metformin-treated females tended to be higher relative to pre-test values and to the control group, particularly during the first 2-3 weeks of dosing. The magnitude of the increase is ~2-fold compared to pre-test values and is in the high end of the historical range. Plasma lactate did not exceed ~3.5mM; clinical lactic acidosis is defined by a plasma lactate concentration of 5mM.

Plasma lactate reportedly increased to 177 mg/dL (20mM) in female #06-0047 (metformin group) and bicarbonate reportedly decreased (13mM) prior to sacrifice on day 23. These values, which are not obvious in the Table below, came from a blood sample taken just prior to sacrifice of the dog. This suggests that large acute changes in plasma lactate are associated with the moribund condition rather than directly related to drug treatment.

Plasma Bicarbonate

TREATMENT GROUP & ANIMAL NUMBER	PRETEST PERIOD	DRUG DAY	4	15	17	23	29
<b>Control</b>							
05-0229F	23.2	23.9	24.3	31.8	22.4	23.3	
06-0013F	23.2	24.0	25.3	26.1	33.6	24.0	
06-0043F	22.3	23.2	23.8	32.7	23.2	22.5	
06-0045F	25.1	23.7	25.9	28.0	24.1	24.4	
06-0049F	22.2	23.5	23.8	22.9	21.4	23.6	
MEAN	23.0	23.9	24.6	24.3	23.0	23.6	
STD DEV	1.2	0.7	0.9	2.6	0.9	0.7	
<b>50 mg/kg/day</b>							
05-0241F	21.3	19.4	21.1	20.1	20.7	22.3	
05-0263F	22.8	24.3	24.0	24.2	25.2	24.6	
05-0277F		23.0	21.6				
06-0011F	22.5	25.0	23.5	27.8	16.4	24.9	
06-0047F	21.1	24.0	23.3	35.4	22.6		
MEAN	21.9	23.1	24.7	24.4	23.7	23.9	
STD DEV	0.9	1.2	2.8	3.2	2.6	1.4	

**Plasma Lactate**

TREATMENT GROUP & ANIMAL NUMBER	PRETEST PERIOD	DRUG DAY				
		2	15	17	23	29
<b>Control</b>						
05-0229F	12.9	9.2	8.7	11.7	17.4	28.2
06-0013F	12.0	6.4	9.6	4.6	10.0	8.8
06-0043F	12.0	8.7	7.5	6.8	13.2	9.2
06-0045F	11.8	12.4	13.1	6.4	12.9	18.4
06-0049F	8.4	12.5	11.6	6.1	23.4	9.0
MEAN	11.4	9.8	10.1	7.0	15.4	14.7
STD DEV	1.7	2.6	2.3	2.7	5.2	8.5
<b>50 mg/kg/day</b>						
05-0241F	7.4	25.8	17.1	10.7	30.9	12.2
05-0263F	6.6	11.7	15.5	22.6	14.9	17.2
05-0277F		28.0	16.0			
06-0011F	17.9	14.2	14.6	7.8	18.8	19.6
06-0047F	10.9	15.2	12.0	18.2	15.8	
MEAN	10.7	19.0	14.2	14.8	20.1	16.3
STD DEV	5.2	7.4	1.5	4.8	7.4	3.8

**Historical Control Data for Female Dogs: Lactate and Bicarbonate**

Historical Control Values for Dog (04-Feb-2006 to 20-Feb-2006)

Age	No. of Tests	No. of Animals	Median Value	Range of Actual Values	2.5%	97.5%
Bicarbonate mmol/L						
Female 26 to 39 Weeks	74	74	23.4	18.7 - 26.6	19.5	26.4
Lactate mg/dL						
Female 26 to 39 Weeks	54	54	12.3	5.4 - 28.8	5.5	28.7

**Gross pathology:** There were no gross changes in the early sacrifice/found dead animals.

**Histopathology:** No histopathology was performed.

**Toxicokinetics:** Exposure was somewhat lower than in the combination toxicity study (402 vs.  $\geq 500 \mu\text{M}\cdot\text{h}$ ), but still somewhat higher than reported in NDA 20,357 ( $300 \mu\text{M}\cdot\text{h}$ ).

**Mean Plasma Metformin Toxicokinetic Parameters - Drug Week 3**

	Metformin (mg/kg/day)	
	Females	
	50	
AUC <sub>0-24 hr</sub> ( $\mu\text{M}\cdot\text{hr}$ )	402	$\pm 77.2$
C <sub>max</sub> ( $\mu\text{M}$ )	119	$\pm 36.2$
T <sub>max</sub> (hr)	0.88	$\pm 0.13$
Values are the mean $\pm$ SEM.		

**MK-0431 + Metformin: 16 week oral toxicity in female dogs**

Control, 20 mg/kg metformin alone or with MK-0431 at 2, 10, 50 mg/kg

**Key study findings:**

- The dose of metformin was lowered to 20 mg/kg based on lethality observed in prior studies at 50 mg/kg.
- There were no findings in dogs administered MK-0431 + metformin that substantially differed from dogs administered metformin alone or the control vehicles.

*Reviewer Comments:*

Dogs tolerated the 20mg/kg dose of metformin, evidenced by no reduction in body weight or food intake, and no resultant deaths. Exposure at 20mg/kg metformin in dogs is similar to exposure at 2000 mg metformin in humans, which is a more appropriate design for combination toxicity studies with an unapproved entity (MK-0431).

The lack of any difference between the control, metformin-alone, and combination treatment groups suggests that the combination of MK-0431 and metformin does not exacerbate existing toxicities (e.g., tremors/ataxia at 50mg/kg MK-0431) or produce new toxicities not seen with either drug alone. This study provides further evidence that deaths observed in study #TT 06-6000 were due to metformin toxicity at 50 mg/kg, and not to co-administration with MK-0431. There is a slight possibility that the earlier deaths with MK-0431 + metformin in study #TT 06-6000 express exacerbated toxicity.

**Study no.:** TT 06-6017**Volume #, and page #:** eCTD**Conducting laboratory and location:** MRL, Chibret, France**Date of study initiation:****GLP compliance:** Compliant with French Ministry of Health GLP regulations**QA report:** yes ( X ) no ( )**Drug, lot #, and % purity:**

MK-0431: lot L-000224715-010X029

Metformin: lot L-000282095-001L012, from \_\_\_\_\_

**Methods**

<u>Doses:</u>	Control (vehicles) <sup>a</sup>	Females
	MK-0431 + Metformin	5
	0 + 20 mg/kg/day <sup>b</sup>	5
	2 + 20 mg/kg/day <sup>c</sup>	5
	10 + 20 mg/kg/day <sup>c</sup>	5
	50 + 20 mg/kg/day <sup>c</sup>	5
NOTE: Dogs were administered metformin alone for the first 2 weeks to assess tolerability. Combination treatment commenced on week 3		
<u>Species/source</u>	Beagle Dogs, female, from _____	
<u>Age:</u>	32-35 weeks	
<u>Weight:</u>	5.9-8.8kg	
<u>Number/sex/group:</u> (main study)	5 females per group	
<u>Toxicokinetic groups</u>	Drug day 1 (metformin alone) and drug weeks 3 and 15 (combination)	
<u>Recovery groups:</u>	None	
<u>Route, formulation, dose volume</u>	Oral gavage of MK-0431, then metformin MK-0431 in 0.1mM HCl in water Metformin in 0.5% methylcellulose in water	

**Observation and Times:**

<u>Clinical Findings:</u>	Daily
<u>Body weights:</u>	Pretest and then weekly
<u>Food consumption:</u>	2-4 times weekly
<u>Ophthalmoscopy</u>	Pretest, drug weeks 8, 14
<u>EKG:</u>	Pretest, drug weeks 8, 14
<u>Hematology:</u>	Blood collected from fasted dogs: Pretest, drug weeks 6, 10, 14 Standard panel
<u>Clinical chemistry:</u>	Blood collected from fasted dogs: Pretest, drug weeks 2, 6, 10, 14 Week 2 analysis limited to serum bicarbonate, sodium, potassium, chloride, and lactate
<u>Urinalysis:</u>	Overnight urines collected in drug weeks 10, 14
<u>Gross pathology:</u>	Necropsies on all animals
<u>Organ weights:</u>	adrenals, brain, heart, liver, pituitary, spleen, ovaries, kidneys, thymus, thyroid
<u>Histopathology:</u>	Control, metformin alone, and high dose combination evaluated
Adequate Battery:	yes ( X), no ( )

**Results:**

Mortality: None

Clinical signs:

Ataxia, tremors, or both occurred in all dogs in the HD combination group starting in drug week 3 (first week of combination treatment). The signs occurred within 30 minutes of dosing and lasted about 3 hours post-dose. Transient, dose-related ataxia/tremor has been documented in dogs administered 50 mg/kg MK-0431 in standard toxicology studies. The Sponsor states that such signs were not exacerbated by metformin compared to historical experience with MK-0431 alone, but note that a concurrent 50mg/kg MK-0431 group was not employed.

Body weights: No change in BW was observed.

Food consumption: No change in food intake was observed.

Ophthalmoscopy: No findings observed. (primary data not shown)

EKG: No changes observed. (primary data not shown)

Hematology: No changes observed. (Red cell mass, coagulation, white cell differential)

Clinical chemistry: No changes observed. (Liver and kidney markers; serum proteins)

Serum bicarbonate: No changes; values ranged from 23-25 mg/dL for all groups.

Serum lactate: No changes; values ranged from 5-21 mg/dL for all groups without a dose- or time-dependence.

Urinalysis: No changes observed. (volume, pH, specific gravity, protein, bilirubin, glucose, blood, sediments)

Gross pathology: No changes observed.

Organ weights: No changes observed. (see *Methods* for organ list)

Histopathology:

Control, metformin-alone, and the HD combination groups were evaluated. No treatment-related change was observed.

Findings considered not treatment-related:

- Minimal focal adhesion in the heart of 1 HD combination female.

Toxicokinetics:

*Metformin exposure:* Exposure to metformin was similar in all groups on day 1 and week 5, but tended to increase in the combination groups by week 15 (~200  $\mu\text{M}\cdot\text{h}$  in control vs. 287  $\mu\text{M}\cdot\text{h}$  in HD combo group). Metformin PK does not appear to change substantially with co-administration of MK-0431, despite the small increase in AUC.

Note that metformin exposure in dogs administered 20 mg/kg (~200 $\mu\text{M}\cdot\text{h}$ ) is similar to humans administered 2000 mg (160  $\mu\text{M}\cdot\text{h}$ ).

Mean Plasma L-000282095 (Metformin) Toxicokinetic Parameters – Drug Day 1

	MK-0431 + Metformin (mg/kg/day)			
	Females			
	0 <sup>a</sup> + 20 <sup>b</sup>	2 <sup>a</sup> + 20 <sup>b</sup>	10 <sup>a</sup> + 20 <sup>b</sup>	50 <sup>a</sup> + 20 <sup>b</sup>
AUC <sub>0-24 hr</sub> ( $\mu\text{M}\cdot\text{hr}$ )	182 ± 16.4	196 ± 7.48	192 ± 11.0	212 ± 18.4
C <sub>max</sub> ( $\mu\text{M}$ )	43.9 ± 8.47	53.3 ± 3.10	45.1 ± 2.78	58.1 ± 5.53
T <sub>max</sub> (hr)	1.1 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	0.9 ± 0.1
<sup>a</sup> Dose of MK-0431. <sup>b</sup> Dose of Metformin. Values are the mean ± SEM.				

Mean Plasma L-000282095 (Metformin) Toxicokinetic Parameters – Drug Week 3

	MK-0431 + Metformin (mg/kg/day)			
	Females			
	0 <sup>a</sup> + 20 <sup>b</sup>	2 <sup>a</sup> + 20 <sup>b</sup>	10 <sup>a</sup> + 20 <sup>b</sup>	50 <sup>a</sup> + 20 <sup>b</sup>
AUC <sub>0-24 hr</sub> ( $\mu\text{M}\cdot\text{hr}$ )	187 ± 24.8	201 ± 10.2	191 ± 11.3	220 ± 10.9
C <sub>max</sub> ( $\mu\text{M}$ )	39.6 ± 7.57	45.7 ± 6.03	44.5 ± 4.64	51.9 ± 6.30
T <sub>max</sub> (hr)	1.1 ± 0.2	1.2 ± 0.5	1.1 ± 0.2	1.3 ± 0.4
<sup>a</sup> Dose of MK-0431. <sup>b</sup> Dose of Metformin. Values are the mean ± SEM.				

## Mean Plasma L-000282095 (Metformin) Toxicokinetic Parameters – Drug Week 15

	MK-0431 + Metformin (mg/kg/day)			
	Females			
	0a + 20b	2a + 20b	10a + 20b	50a + 20b
AUC <sub>0-24 hr</sub> (μM•hr)	191 ± 23.8	224 ± 19.3	239 ± 13.1	287 ± 7.77
C <sub>max</sub> (μM)	44.9 ± 9.05	50.7 ± 6.21	67.7 ± 9.00	73.8 ± 3.58
T <sub>max</sub> (hr)	1.3 ± 0.3	1.3 ± 0.3	1.1 ± 0.2	1.1 ± 0.2
<sup>a</sup> Dose of MK-0431. <sup>b</sup> Dose of Metformin. Values are the mean ± SEM.				

*MK-0431 Exposure:* Exposure to MK-0431 increased with dose in a near-linear manner. AUC did not change substantially from the first to last week of administration, and did not change with co-administration of metformin.

## Mean Plasma MK-0431 Toxicokinetic Parameters – Drug Week 3

	MK-0431 + Metformin (mg/kg/day)		
	Females		
	2a + 20b	10a + 20b	50a + 20b
AUC <sub>0-24 hr</sub> (μM•hr)	10.2 ± 0.368	50.7 ± 1.78	307 ± 18.9
C <sub>max</sub> (μM)	1.64 ± 0.159	9.62 ± 0.729	56.6 ± 3.86
T <sub>max</sub> (hr)	1.2 ± 0.5	0.6 ± 0.1	0.7 ± 0.1
<sup>a</sup> Dose of MK-0431. <sup>b</sup> Dose of Metformin. Values are the mean ± SEM.			

## Mean Plasma MK-0431 Toxicokinetic Parameters – Drug Week 15

	MK-0431 + Metformin (mg/kg/day)		
	Females		
	2a + 20b	10a + 20b	50a + 20b
AUC <sub>0-24 hr</sub> (μM•hr)	10.4 ± 0.404	52.9 ± 1.56	310 ± 12.1
C <sub>max</sub> (μM)	1.80 ± 0.155	11.1 ± 0.609	58.1 ± 2.65
T <sub>max</sub> (hr)	0.9 ± 0.3	0.7 ± 0.1	0.6 ± 0.1
<sup>a</sup> Dose of MK-0431. <sup>b</sup> Dose of Metformin. Values are the mean ± SEM.			

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