

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-350

PHARMACOLOGY REVIEW(S)

Executive CAC

Date of Meeting: March 3, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barry Rosloff, Ph.D., DPP, Alternate Member
Todd Bourcier, Ph.D., DMEP, Team Leader/Presenting Reviewer

NDA # 22-350

Drug Name: Saxagliptin (Onglyza)

Sponsor: Bristol Myers Squibb

Background

Saxagliptin is a dipeptidyl peptidase-4 inhibitor currently under Agency review as a blood-glucose lowering therapy for type 2 diabetes. The ECAC concurred with 2-yr carcinogenicity study protocols in rats and mice in 2003, and the Division received final study reports in the NDA submitted in June 2008.

Mouse Carcinogenicity Study

CD-1 mice were dosed 50, 250, and 600mg/kg saxagliptin in a vehicle of 0.5% methylcellulose for 2 years. Dual controls consisted of vehicle alone. Reduced survival prompted termination of high dose males at week 90 and of all remaining male groups at week 100. Female groups survived to scheduled termination at week 104. The Division and ECAC were notified prior to termination of dose groups. There was no evidence of drug-related increases in the incidence of neoplastic lesions in any dose group. Exposure margins relative to AUC at the 5mg clinical dose ranged from ~20 to 1000x (low to high dose) for saxagliptin and ~15 to 300x for the active metabolite BMS-510849.

Rat Carcinogenicity Study

Sprague Dawley rats were dosed 25, 75, 150, and 300mg/kg saxagliptin in a vehicle of 0.5% methylcellulose for 2 years. Dual controls consisted of vehicle alone. Reduced survival prompted termination of high dose males at week 68; this dose group was excluded from statistical analysis of tumor incidence. All remaining male groups were terminated at week 99 when survival in the dual controls collectively reached ~ 22 animals. Female groups survived to scheduled termination at week 104. The Division and ECAC were notified prior to termination of dose groups. There was no evidence of drug-related increases in the incidence of neoplastic lesions in any dose group. Exposure margins relative to AUC at the 5mg clinical dose ranged from ~50 to 2200x (low to high dose) for saxagliptin and ~3 to 68x for the active metabolite BMS-510849.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee found that the study was adequate, noting prior Exec CAC concurrence with the doses.
- The Committee agreed that the study was negative for drug related tumor findings.

Rat:

- The Committee found that the study was adequate, noting prior Exec CAC concurrence with the doses.
- The Committee agreed that the study was negative for drug related tumor findings.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DMEP
/Todd Bourcier, DMEP
/Fred Alavi, DMEP
/Julie Marchick, DMEP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
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Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology
OND IO

NDA: 22-350

Submission date: June 30, 2008

Drug: saxagliptin (Onglyza)

Sponsor: Bristol Myers Squibb

Indication: type 2 diabetes

Reviewing Division: Division of Metabolism and Endocrine Products

Comments: The pharm/tox reviewer and supervisor found the nonclinical information submitted for saxagliptin to be sufficient to support approval for the indication as proposed above.

Developmental and Reproductive toxicity:

Saxagliptin was tested in rats and rabbits in oral embryofetal studies and no indication of teratogenicity was observed at doses of up to 500 mg/kg in rats and 200 mg/kg in rabbits. Saxagliptin was also tested in rats in combination with metformin. This study had three groups: one vehicle and two that received 200 mg/kg metformin and either 5 or 25 mg/kg saxagliptin. The group receiving 25 mg/kg saxagliptin and 200 mg/kg metformin exhibited malformations such as craniorachischisis, absent renal papilla, cleft palate and absent or shortened digits of forepaws/hindpaws. Since neither saxagliptin nor metformin has shown teratogenicity alone, it appears that the combination might be responsible for this signal, if it is a real signal. These two drugs may be used together in the patients; therefore, in order to better understand the teratogenic potential, the reviewer and supervisor recommend that the applicant conduct additional embryofetal studies in rats and rabbits studying the combination of saxagliptin with metformin as post marketing requirements. It was also recommended that these studies include saxagliptin and metformin alone arms to aid in interpretation.

The reviewer and supervisor have concluded that pregnancy category B is acceptable for the labeling of the product under consideration in this NDA, which contains saxagliptin as the sole active ingredient. Some incomplete ossification was observed in the rat reproductive toxicity studies but this occurred at exposures that were much higher than expected clinically.

Carcinogenicity:

No drug-related tumors were observed in carcinogenicity studies in rats or mice. These studies were considered adequate by the executive carcinogenicity assessment committee.

Other issues:

Saxagliptin produced cutaneous lesions in cynomolgus monkeys and erosive lesions in the paws of dogs. These lesions were only observed at exposures that were significantly higher than those expected in humans and no such lesions were observed in the clinical studies. Such lesions have also been described in studies with other compounds of the

class. Consequently, the reviewer and supervisor recommended including a description of these findings in the labeling.

Other nonclinical issues were adequately described and discussed in the primary and secondary reviews and will not be further discussed here as they have no further impact on approval or labeling.

Conclusions:

I concur with the Division pharm/tox conclusion that the nonclinical data support approval of this NDA. I agree that it is appropriate to collect additional information on the teratogenic potential of the combination of saxagliptin and metformin and that these may be postmarketing requirements. I agree that pregnancy category B is acceptable and that the labeling may contain a brief description of the cutaneous lesions noted in the animal studies.

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/s/

Paul Brown
7/23/2009 12:45:57 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health
Service
Food and Drug Administration

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research

Date: June 23, 09
From: Fred Alavi, Ph.D.

Subject: Rat and rabbits embryofetal development study protocols

Reference is made to the sponsor's rat and rabbit embryofetal development study protocols (Protocol DN09018 and DN09020) submitted on June 17, 2009 (sequence # 0036). The protocols were submitted in part to fulfill the Post Marketing Requirement (PMR) for the approval of saxagliptin (Onglyza®). It should be noted that both studies have been initiated and dosing has commenced or completed.

- Protocol DN09018 dated April 27, 2009 titled: Saxagliptin (MBS-477118) and Metformin (BMS-207 150): Oral combination Study of Embryo-Fetal Development in Rats
- Protocol DN09020 dated May 21, 2009 titled: Saxagliptin (BMS-4771 18) and Metformin (BMS-207150): Oral Combination Study of Embryo-fetal Development in Rabbits

The proposed studies were requested by the agency in March 25 of 2009 to determine whether malformations found in the rat saxagliptin/metformin combination (25/200 mg/kg) embryofetal development study were not coincidental and due to drug-drug pharmacodynamic interaction. Since the study also lacked separate arms for saxagliptin and metformin alone, the study was considered inadequate to support the sponsors claim that metformin was responsible for the malformations. The malformations identified in 2 fetuses from 1 litter at 25 /200 mg/kg of saxagliptin/metformin were craniochischisis, a type of neural tube defect (incomplete closure of the skull and spinal column) and absence of renal papillae.

Rat Embryofetal Development Study Protocol:

In the proposed rat study, 4 groups of pregnant SD rats (30/group) will be treated orally with the vehicle (water and 1.25% Avicel), saxagliptin (25 mg/kg), metformin (600 mg/kg) or combination of saxagliptin/metformin (25/600 mg/kg) from gestation Day 6 (GD6) through GD15. Standard clinical chemistry parameters including glucose will be measured from blood samples collected via jugular vein at 2 and 24 hrs from the first 15 rats in each group on GD 13.

The plasma chemistry analysis will not include analysis of Vit B12 or folate. The toxicokinetic analysis will be carried out on GD 15 on the second 15 rats in each group. Rats will be necropsied on GD 21 (May 19-22, 2009). The report is expected to be finalized by Oct 14, 2009.

In the original study pregnant rats were treated with two saxagliptin dose combination levels while metformin dose was kept the same (5/200 and 25 /200 mg/kg of saxagliptin/metformin). There were no separate saxagliptin and metformin treatment groups alone. The agency had asked the sponsor to repeat the study but to also include separate arms for saxagliptin and metformin alone. Based on the protocol, the sponsor appears to have added separate arms for saxagliptin and metformin but the dose of metformin is raised to 600 mg/kg from 200 mg/kg in the original study.

Although the study overall appears to be fine, the increase in metformin dose is likely to pose additional problems: a) metformin dose of 600 mg/kg may cause maternal toxicity thus confounding interpretation of any positive fetal findings, b) the higher dose of metformin may cause fetal toxicity and change reproductive parameters that excludes comparison to the lower metformin dose in the original study, c) the study does not include the metformin dose that produced craniochisis in the original study, d) the protocol does not include plasma analysis of glucose, Vit B12 and folate. The sponsor may have chosen 600 mg/kg of metformin to show that metformin was responsible for the malformations, but by doing so they have also introduced additional complexities to the study. The new study would only be interpretable if there is no maternal or excessive fetal toxicity, if reproductive parameters are comparable to the original rat study, and if no fetal abnormalities are observed. An outcome other than this would not adequately address our concern described in the PMR. The reviewer recommends repeating the study at dose levels of saxagliptin/metformin (25/200 mg/kg of saxagliptin/metformin) that caused malformation in the original rat study. The study also should include separate arms for saxagliptin (25 mg/kg) and metformin (200 mg/kg) alone.

Group No.	Identification	Saxagliptin/Metformin (or Respective Vehicle)			Number of Females Assigned
		Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg/day)	
1	Vehicle control ^a	0/0	0/0	1/4	30
2	Saxagliptin ^b	25/0	25/0	1/4	30
3	Metformin ^c	0/600	0/150	1/4	30
4	Saxagliptin + Metformin ^d	25/600	25/150	1/4	30

a - 1.25% Avicel will be dosed first and immediately followed by deionized water.

b - Deionized water will be administered first and immediately followed by saxagliptin formulation.

c - 1.25% Avicel will be administered first and immediately followed by metformin formulation.

d - Saxagliptin formulation will be administered first and immediately followed by metformin formulation.

Rabbit Embryofetal Development Study Protocol:

In the proposed rabbit study, 4 groups of pregnant New Zealand White Hra rabbits (30/group) will be treated orally with the vehicle (water and 1.25% Avicel), saxagliptin (40 mg/kg), metformin (50 mg/kg) or combination of saxagliptin/metformin (40/50 mg/kg) from gestation

Day 7 (GD7) through GD19. Standard clinical chemistry parameters including glucose will be measured from blood samples collected via the marginal ear vein at 1, 4 and 24 hrs from 5 rabbits in each group on GD 18. The plasma chemistry analysis will not include analysis of Vit B12 or folate. The toxicokinetic analysis will be carried out on GD 19 on designated animals for TK (5 /group). Rabbits will be necropsied on GD 29. The report is expected to be finalized by Nov. of 2009.

The dose selection for saxagliptin was based on studies in the saxagliptin NDA. The metformin dose was based on 13-day dose ranging study where pregnant rabbits were treated with 25, 50, 100 and 150 mg/kg from GD 7 through GD19. Metformin was maternally toxic at 100 and 150 mg/kg to the point that none of the pregnant rabbits survived to the scheduled C-section. In contrast, 50 mg/kg metformin dose was not maternally toxic, nor did it produce any gross external changes in fetuses. Based on that, the sponsor chose 50 mg/kg/d for the rabbit combination study. The reviewer concurs with the doses the sponsor has selected for saxagliptin/metformin combination embryofetal development study in rabbits.

Experimental Design

Group Number	Saxagliptin Daily Dose			Metformin Daily Dose			Number of Female Rabbits
	Dose (mg/kg)	Volume (mL/kg)	Conc. (mg/mL)	Dose (mg/kg)	Volume (mL/kg)	Conc. (mg/mL)	
1	0	4	0	0	2	0	30
2	0	4	0	50	2	25	30
3	40	4	10	0	2	0	30
4	40	4	10	50	2	25	30

External recommendation:

We have reviewed protocols #DN09018 and #DN09020 for the rat and rabbit embryofetal development studies with the saxagliptin/metformin combination and have the following comments:

The intent of repeating the rat embryofetal study was to assess the reproducibility of the neural tube malformation observed with the metformin/saxagliptin combination along with an evaluation of each component alone. The proposed 600mg/kg dose of metformin selected for the rat study is 3-fold greater than the metformin dose evaluated in the original rat study. Increasing the metformin dose to 600mg/kg may confound interpretation of the repeat study due to several factors, including unexpected maternal/fetal toxicity when combined with saxagliptin and alteration of C-section data that differs from the original study. Not including the dose combination associated with the neural tube malformation in the original study is also a deficiency of the current protocol. It is reasonable that a 'negative' study outcome would be interpretable and acceptable; however, a confounded outcome will not adequately address the PMR issue. Therefore, we request that you submit a new study protocol that incorporates the following elements, should additional studies be required:

- Include a 25/200 mg/kg saxagliptin/metformin combination group plus separate arms for saxagliptin and metformin in the rat embryofetal study. Additional combination groups at doses that bracket the 25/200mg/kg group are acceptable. Signs of maternal toxicity at the highest dose combination group is desirable. Doses of the separate saxagliptin and metformin arms should equal those in the highest combination dose group.
- Evaluate at least two combination dose levels in the rabbit study that enable identification of a NOAEL and a maternally toxic dose. Separate arms for metformin and saxagliptin should also be incorporated.
- Monitor blood glucose, folate and vitamin B12 in both rat and rabbit studies to determine the potential role of metformin in malformations observed in rats.

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/s/

Fred Alavi

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PHARMACOLOGIST

Brief review of the embryofetal development study protocols. Most
of the information was conveyed to the sponsor

(Dr. Smith, BMS) by Tcon on Wed June

24, 2009. We reserved the right to reject

the studies since they had already started the
studies witho

Reveiw of rat and rabbit embryofetal development study protocols-
part of the PMR

Todd Bourcier

6/25/2009 02:25:11 PM

PHARMACOLOGIST

I concur.



SUPERVISOR MEMO

Date:	20 May 2009
RE:	NDA 22-350
Sponsor:	Bristol Myers Squibb
Drug/Indication	Onglyza (saxagliptin, DPP4 inhibitor) Type 2 diabetes

Bristol Myers Squibb is seeking marketing approval for saxagliptin, proposed trade name Onglyza®, as a treatment option for Type 2 diabetes. Saxagliptin is a member of the DPP4 inhibitor class of compounds whose primary mode of action consists of extending the half-life of the incretin GLP-1, thereby enhancing glucose-induced insulin release from pancreatic beta cells.

only Januvia® (sitagliptin) is approved for US and global markets while Galvus® is approved for non-US markets.

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Dr. Fred Alavi, the primary nonclinical reviewer, concludes that the pharmacology and toxicology data support approval of saxagliptin (5 mg q.d.) with a post-marketing requirement to conduct embryofetal development studies in rats and rabbits administered saxagliptin and metformin in combination. I concur with Dr. Alavi's assessment.

Dr. Alavi's decision is based on reasonable exposure margins between animal toxicities and clinical exposure at the proposed maximum dose of 5mg/day. Toxicity in rats, dogs, and monkeys was largely dose-dependent, with no adverse effects observed at low multiples (≤ 8 fold) of clinical exposure. Adverse effects that were relatively minimal and reversible including splenic lymphoid proliferation and multi-organ lymphoid/monocytic infiltration in all species and non-necrotizing cutaneous lesions in monkeys were observed at 20 to 30-fold multiples of clinical exposure. Severe toxicity that exceeded tolerability in all test species occurred at higher multiples of clinical exposure. Saxagliptin did not alter tumorigenesis in rats and mice after lifetime (2 year) exposure to exceedingly high doses of saxagliptin and its active metabolite, BMS-510849 (>800 and 300 fold higher, respectively, than clinical exposure). Findings from the reproductive toxicology studies with saxagliptin alone did not reveal relevant toxicities without also producing signs of maternal toxicity. A Moderate increase in drug exposure at relevant clinical doses in susceptible patients (i.e. renal insufficiency) is unlikely to reproduce toxicities noted in animals and presents negligible risk to humans.

Dr. Alavi recommends a non-clinical post-marketing requirement to conduct additional embryofetal development studies based on findings of teratogenicity in rats co-administered saxagliptin and metformin. I agree with his recommendation. If approved, saxagliptin would be commonly prescribed as an add-on therapy to metformin; therefore, findings of teratogenicity

with the saxagliptin/metformin combination are concerning and are relevant to the monotherapy NDA. Craniochischisis identified in the saxagliptin/metformin combination study is a rare and serious neural tube malformation involving the incomplete closure of the skull and spinal cord. The relevance of this finding should not be dismissed, as yet, based on exposure margins alone. Alternative explanations for the apparent teratogenic interaction of saxagliptin and metformin were confounded by the lack of separate arms for saxagliptin and metformin alone in the study design. Arguments that metformin altered vitamin B12 and folate levels which caused the neural tube malformation were unconvincing because metformin exposure was equal in the two combination dose groups but teratogenicity occurred only in the group with the higher dose of saxagliptin. Also, the original embryofetal studies with metformin did not report craniochischisis. Dr. Alavi's and my recommendation are consistent with advice received from the Associate Director and Director of Pharmacology/Toxicology and the Reproductive Toxicology Subcommittee at FDA. Special contraindications in the monotherapy label are not recommended at this time, but will be reconsidered after review of the additional studies.

One issue of some concern during development of saxagliptin identified by Dr. Alavi was the finding of cutaneous lesions in cynomolgus monkeys. Since first reported to the FDA nearly five years ago, similar toxicity has been encountered in monkey studies with several other DPP4 inhibitors in development. Past clinical experience suggest that the findings in monkeys are relevant to human risk, and therefore should not be dismissed. Mechanistic data from several sponsors variably implicate off-target inhibition of DPPs 8 or 9, peripheral vasoconstriction, or ischemic vascular injury underlying the lesions, but as Dr. Alavi rightly states, the etiology remains unresolved. The lesions observed with saxagliptin are remarkably consistent with the class regarding the peripheral location, time-dependent emergence, and dose-related severity of the lesions. Saxagliptin at clinical exposure and low multiples thereof did not produce lesions in monkeys, and a further 20-fold increase in exposure was required to produce minimal, self-resolving lesions. Of note, saxagliptin also induced minimal erosive lesions of the paws in dogs after 12 months exposure at doses ≥ 35 times clinical exposure. This is unlike the case with vildagliptin, currently approved in non-US markets, whereby an equivalent 20-fold multiple of clinical exposure resulted in lesions of such severity in monkeys that amputation and humane sacrifice was required. The currently marketed DPP4 inhibitor sitagliptin does not induce cutaneous lesions in monkeys, which has been independently verified by several sponsors including the sponsor of saxagliptin. It is important to note that the cutaneous lesions described herein are separate from hypersensitivity reactions that have been reported from post-market experience with sitagliptin and vildagliptin. I agree with Dr. Alavi's assessment that the risk to human subjects is minimal based on the exposure margins to the no-effect and lowest-effect doses in monkeys. This assessment is further supported by the lack of adverse cutaneous events in human subjects given up to 400mg saxagliptin in phase I studies or given 5 to 10mg saxagliptin in phase 3 clinical studies.

Dr. Alavi discusses potential immunotoxicity issues with saxagliptin, concluding that the risk of severe adverse effects is minimal but that the risk of more subtle immune system-related AEs remains to be seen in the post-approval period. Preclinical signs of potential adverse effects on immunity generally occurred at high doses ($\geq 20x$) of saxagliptin, notably splenic lymphoid hyperplasia and multiorgan lymphoid or monocytic aggregates in rats and dogs. Saxagliptin at high exposure also partially inhibited the humoral response to KLH, but this effect likely reflects inhibition of DPP8/9 activity which is known to suppress lymphocyte proliferation. A small but consistent 5-10% reduction in circulating lymphocytes was reported in human subjects given 10mg saxagliptin, though without any clear clinical correlate. There are instances of reduced

lymphocytes in monkeys, dogs, and rats given high doses of saxagliptin, but the finding was not consistent across studies and did not follow a dose- or time-dependency; thus, the animal studies do not provide much insight to this observation in humans. I agree with Dr. Alavi that there appears to be minimal to no risk of severe immunotoxicity with saxagliptin. I also agree that the risk of more subtle changes in immunity cannot be excluded from the available preclinical data, particularly given the reported role of DPP4 in deactivating numerous chemokines and its role as CD26 in lymphocyte responses to antigen.

Another issue of some interest discussed by Dr. Alavi was the finding of severe lesions in various parts of the brain in male rats administered high doses of saxagliptin. The sponsor undertook a number of mechanistic studies which convincingly demonstrated that the brain lesions were secondary to release of cyanide from the saxagliptin structure (which contains a cyano group) by CYP2C11, an androgen-regulated metabolizing enzyme. As detailed in Dr. Alavi's review, the studies demonstrated that expression of CYP2C11 is highest in male rats, that methods to reduce or inhibit CYP2C11 also reduced development of brain lesions, and that notably high levels of cyanide were present in blood from male but not female rats, nor from any other species including dogs, monkeys, and humans. The molecular structure of several DPP4 inhibitors includes a cyano group, but the release of cyanide via a metabolic pathway has only been documented with saxagliptin. Studies comparing the metabolism of two cyano-containing DPP4 inhibitors, saxagliptin and vildagliptin, demonstrated cyanide release from the former but not the latter. Our preclinical experience with saxagliptin ensures that the potential release of cyanide from other cyano-containing DPP4 inhibitors in development would be detected in the course of regulatory toxicology studies.

Non-clinical labeling issues to be resolved prior to an 'approval' action include refining the post-marketing requirement and revising language in sections on Pregnancy, Nursing Mothers, and Animal Toxicology.

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/s/

Todd Bourcier
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PHARMACOLOGIST

**CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT
AND
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET**

P/T REVIEWER(s): Fred Alavi, Ph.D.
DATE: Feb 23, 2009

NDA: 22-350 (IND 63,634)
DRUG CODE#: BMS-477118
CAS#: 945667-22-1
DIVISION(s): DMEP
DRUG NAME(s): Saxagliptin (ONGLYZA®)

SPONSOR: Bristol Meyer and Squib Pharmaceuticals (BMS)
LABORATORY:
CARCINOGENICITY STUDY REPORT DATE: June 2008

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THERAPEUTIC CATEGORY: Type 2 Diabetes
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION:
Dipeptidylpeptidase IV (DPIV) inhibitor

MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay): No

Saxagliptin was not genotoxic in Ames assay, *in-vivo* rat micronucleus assay, *in-vivo/in-vitro* peripheral blood lymphocyte assay (1 month rat study) and oral DNA repair assay in male rats with BMS-477118 containing degradant . However, in an earlier clastogenicity assay using primary human lymphocyte assay saxagliptin containing degradant , saxagliptin was found to be clastogenic. The clastogenicity was attributed to degradant impurities. The impurities including which were as high as in preclinical and in clinical studies were later reduced to less than in commercial preparations (Process D). Overall saxagliptin was considered nongenotoxic.

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MOUSE CARCINOGENICITY STUDY:

MOUSE STUDY DURATION (weeks): 104 Weeks (DN03100)
STUDY STARTING DATE: Dec 30, 2003
STUDY ENDING DATE: Jan 16, 2006
MOUSE STRAIN: CrI:CD-1@(ICR)BR mice
ROUTE: Oral gavage, 5 ml/kg, acidified water

DOSING COMMENTS:

The carcinogenicity protocol was submitted to the agency (IND 63,634) and reviewed by Dr. Colerangle. The sponsor had proposed to use 0, 0, 50, 150 and 500 mg/kg/d for both sexes with two identical vehicle controls (acidified water). The dose selection was based on MTD determined by relatively mild toxicity seen at ≥ 1000 mg/kg/d in the 3-month mouse dose-ranging study (30, 100, 300, 600, 1000 and 1500 mkgd). The toxicology reviewer agreed with the sponsor's doses selection, however, the ECAC recommended 0, 0, 50, 250 and 600 mg/kg/d for both male and female mice due to mild toxicity of saxagliptin in the dose-ranging study.

NUMBER OF MICE:

- Control-1 (C1): 60 per sex
- Control-2 (C2): 60 per sex
- Low Dose (LD): 60 per sex
- Middle Dose (MD): 60 per sex
- High Dose-1 (HD1): 60 per sex

MOUSE DOSE LEVELS* (mg/kg/day):

- Low Dose: 50
- Middle Dose: 250
- High Dose-1: 600

BASIS FOR DOSES SELECTED: MTD, determined by relatively mild toxicity in mice

PRIOR FDA DOSE CONCURRENCE: Yes, Nov 4, 2003

MOUSE CARCINOGENICITY: Negative

There were no statistical significant differences in the incidence of tumors between control and saxagliptin treated groups. There was no statistically significant difference in survival rate in female mice. However, saxagliptin at 250 and 600 mg/kg/d significantly reduced survival rate in male mice. The analysis of mouse survival rate and tumor incidences was also carried out by Dr. Rahman which was in agreement with the sponsor's conclusion.

MOUSE TUMOR FINDINGS: There were no statistically significant drug-related tumor findings in mice.

MOUSE STUDY COMMENTS:

Mice were give saxagliptin doses of 50, 250 and 600 mg/kg/day for 2 years with 2 identical vehicle control (acidified water). The two controls were combined and compared to the treated mice. Study protocol was reviewed by the Division and approved by eCAC. The study design and statistical method used in the study appeared to be adequate and were similar to statistical methods used by FDA statistician.

Oral administration of 250 and 600 mg/kg/d to male mice produced significant increase in mortality leading to early termination of the MD and HD males at week 90 and all remaining males at week 100 when the survival rate was $\leq 25\%$. Final survival in male mice were 51%, 38%, 36%, 25% and 25% in Control 1, Control 2, 50, 250, and 600 mg/kg/day groups, respectively. There was no significant drug-related increase in mortality in female mice and reached scheduled necropsy. Final survival rate in female mice were 22%, 28%, 33%, 27%, and 27% in Control 1, Control 2, 50, 250, and 600 mg/kg/day groups, respectively.

Statistical analysis provided by the sponsor found no statistically significant difference in the incidence of tumors between control and saxagliptin treated male or female mice. There were no notable differences in gross and histopath findings between control and saxagliptin treated mice. The analysis carried out by the FDA statistician, Dr. Raman was in agreement with the sponsor analysis. There were no saxagliptin related increases in incidence of tumors in CD mice. Saxagliptin exposure in male mice at 50, 250 and 600 was 20, 428 and 870 fold the clinical dose of 5 mg based on AUC, respectively. Saxagliptin exposure in female mice was 32, 376 and 1165 fold the clinical dose of 5 mg based on AUC, respectively. The exposure to active metabolite, BMS-510849 at parent doses of 50, 250 and 600 mg/kg/day in male and female mice are shown in table below. BMS-510849 exposure in mice and humans were overestimated by 20% and 6.7%, respectively. Slightly lower safety margin for BMS-510849 is unlikely to change safety profile of saxagliptin or its active metabolite.

Safety margins:

Species	Dose, mg/kg/d	Saxagliptin AUC, ng.h/ml	BMS-510849 AUC, ng.h/ml	Safety margins based on AUC (Animal/Human)	
				Saxagliptin	BMS-510849
104-week Mouse Carci Study	50	M: 1605, F: 2615	M:6246, F:7643	M:20, F:32	M:14, F:17
	250	M:34661, F: 30483	M:76123, F:49443	M:428, F:376	M:174, F:113
	600	M: 70436, F:94393	M:147802,F:131654	M:870, F:1165	M:337, F:301
Clinical Dose: 5 mg (BMS-510849) *		81 438			

*Saxagliptin is metabolized in all species primarily to an active metabolite, BMS-510849. This metabolite is half as potent as the parent but more selective to DPPIV. The initial HPLC analysis used for AUC calculations apparently overestimated BMS-510849 exposure due to inadequate resolution of BMS-510849 peak from two minor metabolites, thus all submitted AUC values for BMS-510849 in mice, rats, pregnant rabbits, dogs, Cyno monkeys and humans were overestimated by 20%, 42.7%, 11.1%, 36.2%, 15.1% and 6.8%, respectively. Therefore the corrected safety margins for BMS-510849 are lower than safety margins shown in the table above. The safety margins for BMS-510849 in the table are from the original data and not corrected for lower BMS-510849 exposures.

RAT CARCINOGENICITY STUDY:

RAT STUDY DURATION: 104 weeks (DN05004)
STUDY STARTING DATE: Jan 10, 2005
STUDY ENDING DATE: Jan 30, 2007
RAT STRAIN: Hsd: Sprague Dawley
ROUTE: Oral gavage 5ml/kg

DOSING COMMENTS: The carcinogenicity study protocol for saxagliptin (IND 63,634) was reviewed by Dr. John Colerangle (DMEP) and eCAC recommendation was sent to the sponsor on Nov 4, 2003.

The carcinogenicity dose selection was based on MTD in the 3-month rat study (300, 600 and 1200 mkd). The sponsor had proposed to use 0, 0, 10, 35, 100 and 300 mg/kg/d for both male and female rats with two identical control vehicles (acidified water). The toxicology reviewer recommended 0, 0, 10, 35, 100 and 300 mg/kg/d. The committee recommended 0, 0, 25, 75 and 300 mg/kg/d for males and 0, 0, 25, 75 and 150 mg/kg/d for females based on MTD determined by decrease in body weight gain and mortality in the 3-month rat study. The committee recommended a lower top dose for females due to 2 fold greater exposure in female rats than males. The sponsor accepted eCAC recommendation but added additional group to males (150 mkd) and females (300 mkd) in the study. The top dose of 300 mg/kg/d was not well tolerated in male rats. Due to high mortality rate, all male rats at 300 mg/kg/d were euthanized during week 68. The data from the HD male rats was not used in statistical analysis. The sponsor also terminated the remaining male rats during week 99 due to poor survival rate in one of the controls (survival rate reaching 25%). All the female rats survived to the end of the scheduled necropsy.

NUMBER OF RATS:

- Control-1 (C1): 60 per sex
- Control-2 (C2): 60 per sex
- Low Dose (LD): 60 per sex
- Middle Dose (MD): 60 per sex
- High Dose-1 (HD1): 60 per sex
- High Dose-2 (HD2): 60 per sex

RAT DOSE LEVELS* (mg/kg/day):

- Low Dose: 25
- Middle Dose: 75
- High Dose-1: 150
- High Dose-2: 300

BASIS FOR DOSES SELECTED: MTD, determined by decrease in BW and mortality in the 3-month rat toxicology study

PRIOR FDA DOSE CONCURRENCE: Yes, Nov 4, 2003

RAT CARCINOGENICITY: Negative.

There were no statistically difference in the incidence of tumors between controls and saxagliptin treated rats.

RAT TUMOR FINDINGS:

The tumors identified in all groups were within the historical controls with no notable change in the incidence due to 2 year treatment with saxagliptin at doses up to 300 mg/kg/d. There were two incidences of astrocytomas in female rats treated with 300 mg/kg/d. The trend analysis by the sponsor reported a p-value of 0.0274 which is near the p-value for rare tumors. At the top dose of 300 mg/kg/d, the exposure to saxagliptin in rats was 847 (males) to 2217 (female) fold the clinical dose of 5 mg, based on AUC (81 ng.h/ml). Exposure in males at 150 mg/kg/d was approximately 355 fold the clinical dose. The corrected exposure to active metabolite (BMS-510849) at top saxagliptin dose was greater than 40 fold the clinical exposure to metabolite.

RAT STUDY COMMENTS:

Saxagliptin doses of 25, 75, 150 and 300 mg/kg/d were given to Hsd SD rats for 2 years. The study had two identical vehicle controls (acidified water). Controls were combined for statistical analysis. Study protocol was reviewed by the Division and eCAC. The study design and statistical method appeared to be adequate and were similar to statistical methods used by FDA statistician, Dr Rahman.

Oral administration of 300 mg/kg/d significantly increased mortality in males but not in female rats. Due to high mortality rate, HD males were terminated prematurely during week 68 thus removed from statistical analysis. The remaining male groups were terminated during week 99 due to poor survival rate in the 2nd control male rats. Final survival in male rats were 22%, 15%, 35%, 27%, and 27% for Control1, Control 2, 25, 75, and 150 mg/kg/day groups, respectively. All females survived with adequate numbers to reach scheduled termination at week 105. Final survivals in female rats were 43%, 42%, 45%, 50%, 47%, and 50% for two controls, 25, 75, 150, and 300 mg/kg/day groups, respectively.

The significant mortality noted in the HD males was suspected to be due to brain lesions caused by cyanide release from saxagliptin. Earlier studies had shown that a high prevalence of CYP2C11 in male rats is responsible for significant cyanide release leading to brain lesions.

Ascribed Cause of Death/Morbidity in Males (Unscheduled Necropsy)

	Group	Males					
		1	2	3	4	5	6
	BMS-477118 (mg/kg/day)	0	0	25	75	150	300
	No. Examined	47	51	39	44	44	46*
Brain necrosis/degeneration		0	1	0	1	0	5
Undetermined		7	6	9	6	6	30
Chronic progressive nephropathy		26	30	21	32	32	7
Neoplasia		9	6	8	4	5	0
Other non-neoplastic lesions		5	8	1	1	1	3
Accidental		0	0	0	0	0	1

* = Up to Week 68; all other groups up to Week 99.

Degenerative brain lesions noted in males at 150 and 300 mg/kg/day, occurred at 355 and 847 fold the clinical dose, respectively. CYP2C11 is less prominent in female rats and other species. Since there was no evidence of brain lesion in males at 75 mg/kg/day (175 fold the

clinical dose) or at any dose level in female, the risk to humans is very small. Analysis of plasma samples in humans found no notable change in cyanide release. Other notable drug related histology previously seen in rat studies were also seen in this study (lung, Harderian gland, epididymides and liver).

**Microscopic Incidence of Selected Brain Findings in Males
(Unscheduled and Scheduled Necropsies)**

	Group	Males					
		1	2	3	4	5	6
	BMS-477118 (mg/kg/day)	0	0	25	75	150	300
	No. Examined	60	60	60	60	60	60
Corpus Callosum, Degeneration/Rarefaction		0	0	0	0	<i>10</i>	<i>33</i>
Corpus Callosum, PAS-Positive Material, Intracytoplasmic, Glial/Gitter Cells		0	0	0	0	<i>10</i>	<i>32</i>
Caudate Putamen, Focal/Multifocal, Degeneration/Rarefaction with Gliosis		0	0	0	0	1	<i>15</i>
Caudate Putamen, PAS-Positive Material		1	0	0	0	<i>6</i>	<i>40</i>
Piriform/Temporal Cortex, Focal/Multifocal, Degeneration/Rarefaction with Gliosis		0	0	0	0	0	<i>5</i>
Piriform/Temporal Cortex, PAS-Positive Material, Intracytoplasmic, Glial/Gitter Cells		0	0	0	0	0	<i>4</i>
Thalamus, Focal/Multifocal Degeneration/Rarefaction with Gliosis		0	0	0	0	<i>1</i>	<i>3</i>

Values in bold italics indicate changes considered to be related to the oral administration of BMS-477118.

Statistical analysis provided by the sponsor found no statistically significant differences in the incidence of tumors between control and saxagliptin treated male or female rats. Histopath findings were limited to lung, harderian glands, liver, epididymides and urinary bladder. The analysis carried out by the FDA statistician, Dr. Raman, was in agreement with the sponsor analysis.

There were no saxagliptin related increases in incidence of tumors in SD rats. Saxagliptin exposure in male rats at 25, 75, 150 and 300 was 43, 175, 355 and 847 fold the clinical dose of 5 mg based on AUC, respectively. Saxagliptin exposure in females was 108, 380, 1012 and 2217 fold the clinical dose of 5 mg based on AUC, respectively. The exposure to active metabolite, BMS-510849 is shown in the table below. Since BMS-510849 exposure was overestimated by 42.7% in rats and 6.7% in humans, the safety margin for BMS-510849 was about 35% lower than the exposure multiple shown in the table below.

Safety margins:

Species	Dose, mg/kg/d	Saxagliptin AUC, ng.h/ml	BMS-510849 AUC, ng.h/ml	Safety margins based on AUC (Animal/Human)	
				Saxagliptin	BMS-510849
104-week Rat Study,	25	M: 3492, F:8763	M:1174, F:2658	M:43, F: 108	M:3, F:6
	75	M: 13993, F:30808	M:3843, F:7672	M:173, F:380	M:9, F:18
	150	M: 28742, F: 81962	M:9204, F:15226	M: 355, F: 1012	M:21, F:35
	300	M:68568, F: 179606	M:28569, F:29730	M:847, F:2217	M:65, F:68
Clinical Dose: 5 mg (BMS-510849) *		81 438			

*Saxagliptin is metabolized in all species primarily to an active metabolite, BMS-510849. This metabolite is half as potent as the parent but more selective to DP1V. The initial HPLC analysis used for AUC calculations was apparently overestimated BMS-510849 exposure due to in

adequate resolution of BMS-510849 peak from two minor metabolites, thus all submitted AUC values for BMS-510849 in mice, rats, pregnant rabbits, dogs, Cyno monkeys and humans were overestimated by 20%, 42.7%, 11.1%, 36.2%, 15.1% and 6.8%, respectively. Therefore the corrected safety margins for BMS-510849 are lower than safety margins shown in the table above. The safety margins for BMS-510849 in the table are from the original data and not corrected for lower BMS-510849 exposures.

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Study title: BMS-477118: 104-Week Oral Gavage Carcinogenicity Study in Mice

Key study findings:

- Due to extensive early incidence of deaths at 250 and 600 mg/kg/d in males, necropsies were conducted on WK 90 ($\geq 25\%$ survival) for MD and HD males and WK100 for the remaining. Females were terminated at scheduled necropsy.
- The final survival rate in the male mice were 51%, 38%, 36%, 25% and 25% in control 1, control 2, 50, 250 and 600 mg/kg/d groups, respectively.
- The final survival rate in the females were 22%, 28%, 33%, 27% and 27% in Control 1, control 2, 50, 250 and 600 mg/kg/d groups, respectively.
- There was no statistically significant difference in the incidence of neoplasms at any dose level, compared to controls, in male or female mice.
- The non-neoplastic findings in all male and female BMS-477118 treated groups were similar to controls. Furthermore, there was no evidence of target organ toxicity at any dose level.
- In conclusion, BMS-477118 was not carcinogenic when tested up to 600 mg/kg/d for 2 years in mice. The study did not identify a target organ of toxicity, although a dose related increase in mortality was noted in male mice at 250 and 600 mg/kg/d. There was sufficient number of animals surviving to week 90 to allow adequate statistical analysis. Exposure multiples at 600 mg/kg/d in mice were 869 and 1165 times the parent clinical dose of 5 mg, based on AUC. Exposure to BMS-510849 metabolite at high dose in mice was 337 (M) and 300 (F) fold the metabolite exposure in humans. If the exposure to the metabolite is reduced by 13%, the exposure at top dose in mice is still in excess of 260 fold.

Adequacy of the carcinogenicity study and appropriateness of the test model: The mouse carcinogenicity protocol and BMS-477118 doses were reviewed by toxicology reviewer, Dr. John Colerangle. Based on MTD of ≥ 600 mg/kg/d in the 3-month mouse study, eCAC recommended 50, 250 and 600 mg/kg/d in contrast to the sponsor's recommendation of 50, 150 and 500 mg/kg/d. The sponsor used ECAC-recommended doses, and overall survival of animals in the study was adequate for statistical analysis. The maximum tolerated dose was exceeded in males (evidenced by mortality), but was not attained in females. However, doses used in the study yielded extraordinarily high exposure multiples of the to-be-marketed clinical dose, based on AUC.

Evaluation of tumor findings:

Statistical analysis of tumor incidences by the sponsor found no difference between saxagliptin and control mice. Tumor incidence in mice was also analyzed by the FDA's preclinical statistician, D. Atiar Rahman which was in agreement with the sponsor's analysis. There was no statistically significant difference in the incidences of tumors between control and saxagliptin treated mice.

**Ascribed cause of death/morbidity in Males
(Dying or euthanatized during the course of the study)**

Group	Males				
	1	2	3	4	5
BMS-477118 (mg/kg/day)	0	0	50	250	600
No. Examined	32 ^a	39 ^a	38 ^a	45 ^a	45 ^b
Undetermined	2	2	4	5	22
Neoplasia	13	13	10	9	4
Other non-neoplastic lesions	14	23	24	28	15
Accidental (gavage-related/trauma/other)	3	1	0	3	4

a Terminal necropsy occurred during Week 100.

b Terminal necropsy occurred during Week 90.

Study no.: (6108-415) and BMS (DN03100)

Volume #, and page #: electronic format (eCTD)

Conducting laboratory and location:

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Date of study initiation: Dec 30, 2003 and ended Jan 16, 2006

GLP compliance: yes

QA report: yes (x) no ()

Drug, lot #, and % purity: 3D65912 (May 04, 90.8%), 3D65912 (Jan 05, 91.4%), 4J88286 (Jul 05, 92.6%), 4K85994 (Dec 05, 94.2%), 4J88286 (Jan 06, 94.5%)

CAC concurrence: Yes

Methods:

The mouse carci protocol was reviewed by eCAC. The eCAC meeting minutes is attached to the review (Appendix C, page). Mice were treated with free base BMS-477118 with purity of different batches ranging from 90.8 (May 04) to 94.5% (Nov 06). At , BMS-477118 was prepared every two weeks in acidified reverse osmosis water for oral gavage delivery (5 ml/kg). Drug solutions were sampled approximately every 3-month for HPLC analysis by using a method developed by BMS. Mice were house individually in suspended stainless-steel cages. Polycarbonate cages with bedding were used only when health conditions required such measures. Food (Harlan Teklad) and water (automatic watering system) were provided ad lib. Dose selection was based on 3-month oral range-finding toxicity study where mice were treated with 30, 100, 300, 600, 1000, and 1500 mg/kg/day (DN02016). In the dose-ranging study, there were no adverse findings at 30, 100 and 300 mg/kg/d. Drug-related effects consisting of increased liver weight (18%) in males, minimal or mild multifocal thymic atrophy, and minimal focal or multifocal pulmonary histiocytosis at 600 mg/kg/d. There were deaths at ≥ 1000 mkd. Due to thymic atrophy at doses >600 mg/kg, 300 mg/kg/day was selected as NOAEL and 600 mg/kg/day as MTD. Based on the 3-month dose-ranging study the sponsor had selected 50, 150 and 500 mg/kg/d for the mouse carcinogenicity study. The protocol was reviewed and eCAC recommended 50, 250 and 600 mg/kg/d. Microscopic slides were peer reviewed at

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Group	No. of Animals		Dose Level (mg/kg/day)	Dose Concentration ^a (mg/mL)
	Male ^b	Female		
Carcinogenicity Mice				
1 (Control 1) ^c	60	60	0	0
2 (Control 2) ^c	60	60	0	0
3 (Low)	60	60	50	10
4 (Mid)	60	60	250	50
5 (High)	60	60	600	120
Toxicokinetic Mice				
6 (Low)	19	19	50	10
7 (Mid)	19	19	250	50
8 (High)	19	19	600	120

a Concentrations were adjusted for lot specific purity.

b Males in Group 5 were dosed for at least 89 weeks and Groups 1 through 4 for at least 99 weeks.

c Animals in the control groups received reverse osmosis water only.

Test Article	Lot No	Storage	Date of Use On Study	Purity	Expiration Date ^a	Reserve (Archive) Sample
BMS-477118-11	3D65912	In a refrigerator, set to maintain 2 to 8°C	12-Jan-04 to 27 May-04	90.8%	30-May-04	Collected
	3D65912		28-May-04 to 20-Jan-05	91.4%	30-May-05	Collected
	4J88286		21-Jan-05 to 21-Jul-05	92.6%	30-Nov-06	Collected
	4K85994		23-Dec-05 to 05-Jan-06	94.2%	31-Dec-05	Collected
	4J88286		06-Jan-06 to 15-Jan-06	94.5%	30-Nov-06	Collected

a The terms expiration, use, and retest date are synonymous and indicate the date the test article should not be used beyond, without further testing

Doses: 0, 0, 50, 250 and 600 mg/kg/d

Basis of dose selection (MTD, MFD, AUC etc.): MTD

Species/strain: Crl:CD-1@(ICR)BR mice

Number/sex/group (main study): 60/sex/group, see table above

Route, formulation, volume: Oral gavage, acidified water, 5 ml/kg

Frequency of dosing: Once daily

Satellite groups used for toxicokinetics or special groups: Yes

Age: 38 to 44 days old males and 42 to 48 day old females

Animal housing: individually in stainless-steel cages

Restriction paradigm for dietary restriction studies: no (ad lib food and water)

Drug stability/homogeneity: yes The mean concentrations of BMS-477118 in dosing formulations prepared for use in Weeks 1, 14/15, 24/25, 26/27, 38/39, 52/53, 54, 55 (Groups 3 and 5 only), 56/57, 58/59, 64/65, 78/79, 90/91, and 104 (if applicable) were within acceptance criteria (+10% of target) and ranged from 97.5 to 106% of the target concentrations. These results demonstrate the formulations prepared and assayed were of the correct concentrations and suitable for dose administration. The formulation was stable for up to 17 days in refrigerator.

Results of Concentration Verification

Interval	BMS-477118 (Mean % of Target)			
	Groups 1/2	Groups 3/6	Groups 4/7	Groups 5/8
Week 1	a	104	105	102
Males Days 96-109/Females Weeks 14/15	a	100	101	101
Weeks 24/25	a	101	102	103
Males Days 180-193/Females Weeks 26/27	a	99.2	99.2	99.5
Males Days 264-277/Females Weeks 38/39	a	102	106	103
Week 52, 53	a	99.0	97.8	101
Males Days 390-403/Females Weeks 56/57	NA	101	103	102
Males Days 404-417/Females Weeks 58/59	NA	97.5	98.3	98.1
Males Days 446-459/Females Weeks 64/65	a	101	104	102
Males Days 544-557/Females Weeks 78/79	a	101	98.4	101
Males Days 628-641/Females Weeks 90/91	a	100	102	101
Week 104	a	103	102	105
		Group 3		Group 5
Week 54, 55	NA	101	NA	101

NA = Not applicable.

a <5.00 mg/mL detected.

Dual controls employed: yes

Interim sacrifices: no

Deviations from original study protocol:

Due to high mortality at high doses, MD and HD males were sacrificed at Week 90 at 25 % survival. The remaining male mice were sacrificed on Week 100. All females were sacrificed at scheduled week 104. Except for slight variations such as errors in data collection or data loss from individual animals with minimal impact on the study integrity, the protocol was closely followed.

Observation times

Mortality: twice daily

Clinical signs: twice daily

Body weights: weekly up to 14 weeks and every 4 weeks thereafter

Food consumption: weekly up to 13 weeks and every 4 weeks thereafter

Histopathology: Peer review: yes (x), no ()

Microscopic slides were peer reviewed by I _____, consultant pathologist for _____ The peer reviewer was in agreement with study pathologists _____ interpretation and conclusion.

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Toxicokinetics: Separate group of animals were used for TK only. Mice were TK analysis was made at week 26. The collected plasma samples were analyzed for saxagliptin (BMS-477118) and active metabolite, BMS-510849.

Results

Mortality:

- There was statistically significant dose-related mortality in male mice. A trend test that included all dose groups was significant (log-rank Z=4.61, P <0.0001). In addition, a stepped down trend test that included only the controls, the 50 mg/kg group, and the 250 mg/kg group was also significant (log-rank Z=2.19, P =0.0286). The survival of the 50 mg/kg group was not significantly different from that of the controls (long-rank Z=0.56, P=0.5789).

- The lowest survival was in the 600 mg/kg group, and the survival of the 250 mg/kg group was below that of both the control groups and the 50 mg/kg group. As noted earlier, the sponsor terminated and necropsied HD males when the survival reached 25% at week 90. The same rules also applied to males treated with 250 mg/kg/d (necropsies at week 100).
- The test for dose related trends in mortality was not significant for the female mice (log-rank Z=0.44, P=0.6601). Survival in the two female control groups was comparable during the study (log-rank Z=0.59, P=0.5566).
- There was no significant difference in survival between the two control groups (log-rank Z=1.29, P=0.1978).
- The two control groups were combined and treatment effects were compared to pooled controls.

**Ascribed cause of death/morbidity in Males
(Dying or euthanatized during the course of the study)**

	Group	Males				
		1	2	3	4	5
BMS-477118 (mg/kg/day)		0	0	50	250	600
	No. Examined	32 ^a	39 ^a	38 ^a	45 ^a	45 ^b
Undetermined		2	2	4	5	22
Neoplasia		13	13	10	9	4
Other non-neoplastic lesions		14	23	24	28	15
Accidental (gavage-related/trauma/other)		3	1	0	3	4

a Terminal necropsy occurred during Week 100.

b Terminal necropsy occurred during Week 90.

Male Mice: Mortality due to all causes, followed by Kaplan-Meier (KM) survival estimates at terminal sacrifice, life-table trend tests for dose related trends in mortality, and a pairwise life-table comparison between the two control groups. The survival estimate for the control groups is a pooled estimate.

Group:	1	2	3	4	5
Dose (mg/kg/day)	0	0	50	250	600
Natural Death / Moribund Sacrifice	29	38	38	42	41
Terminal Sacrifice	28	21	22	15	15
Accidental Death	3	1	0	3	4
TOTAL	60	60	60	60	60
KM Survival Estimate at Terminal Sac.	0.42		0.37	0.26	0.29
Two-Sided Trend Test P-Values ^a			P=0.5789	P=0.0286	P<0.0001
Pairwise Comparison P-Value	P=0.1978				

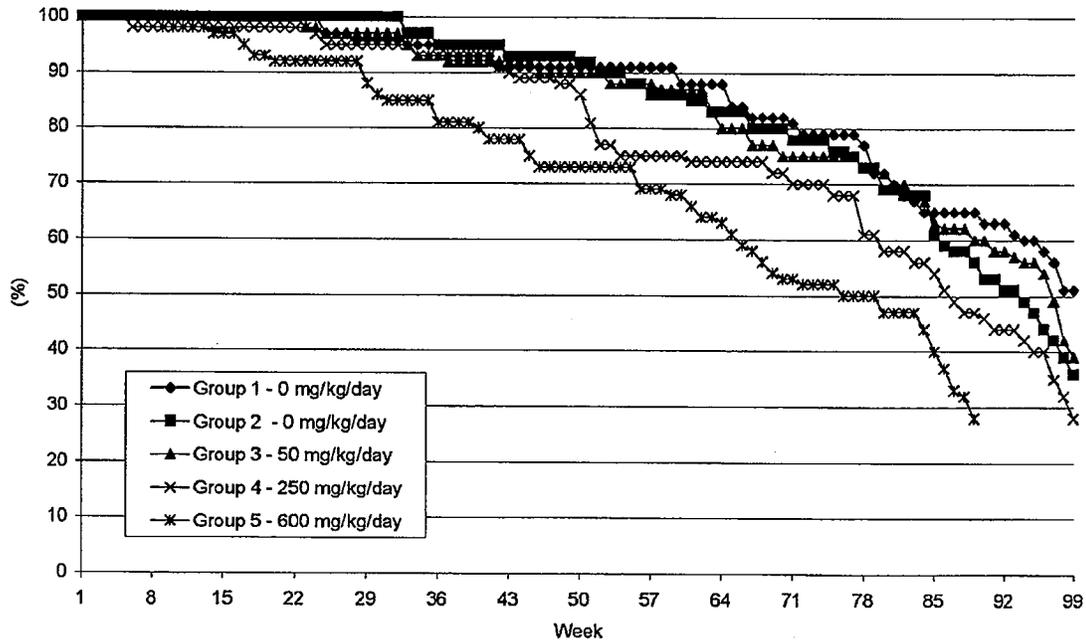
^a Trend test P-values are reported in the column of the highest dose-group included in the trend test.

Female Mice: Mortality due to all causes, followed by Kaplan-Meier (KM) survival estimates at terminal sacrifice, a life-table trend test for dose related trends in mortality, and a pairwise life-table comparison between the two control groups. The survival estimate for the control groups is a pooled estimate.

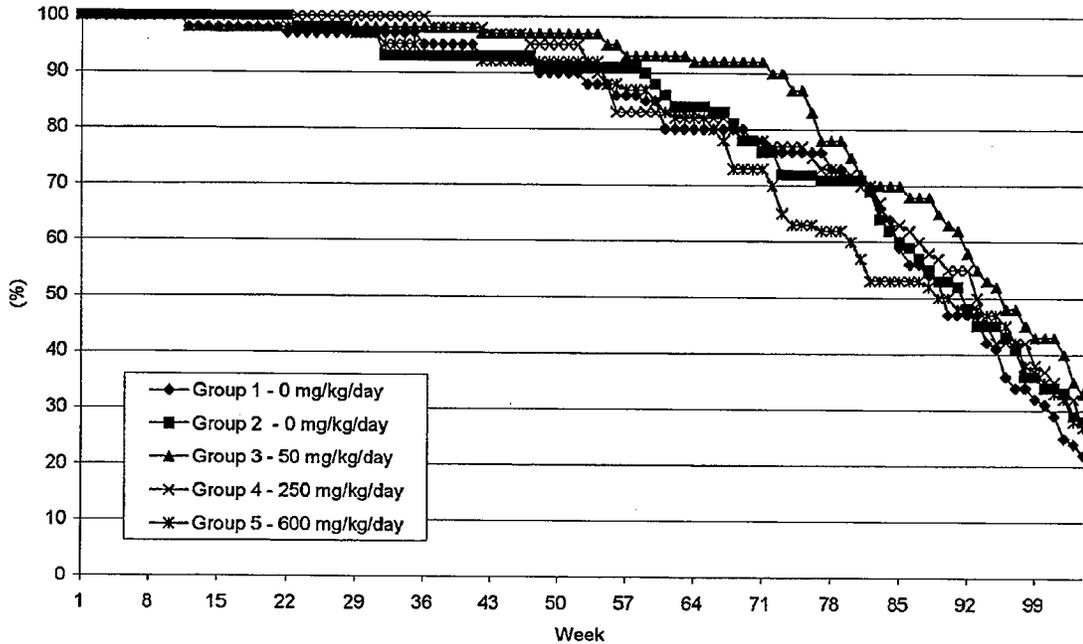
Group ¹	1	2	3	4	5
Dose (mg/kg/day)	0	0	50	250	600
Natural Death/Moribund Sacrifice	46	42	40	44	44
Terminal Sacrifice	13	16	20	16	15
Accidental Death	1	2	0	0	1
TOTAL	60	60	60	60	60
KM Survival Estimate at Terminal Sac.	0.25		0.33	0.27	0.25
Two-sided Trend Test P-Value ^a					P=0.6601
Pairwise Comparison P-Value	P=0.5566				

^a Trend test P-values are reported in the column of the highest dose-group included in the trend test.

Adjusted Survival Data (%) - Males



Adjusted Survival Data (%) - Females



Number of animals alive at the end of 10 week intervals

WEEK	MALE					FEMALE				
	GROUP					GROUP				
	DOSE (mg/kg/day)					DOSE (mg/kg/day)				
	1	2	3	4	5	1	2	3	4	5
0	60	60	60	60	60	60	60	60	60	60
10	59	60	60	59	59	60	60	60	60	60
20	58	60	60	59	55	59	59	59	60	60
30	55	60	58	56	51	58	57	59	60	58
40	53	56	55	54	47	56	55	59	59	56
50	52	54	54	49	43	53	53	58	57	55
60	50	53	52	43	40	50	51	56	50	51
70	47	47	45	41	31	46	45	55	47	44
80	41	41	43	33	27	42	41	45	43	36
90	36	31	36	26	15*	28	31	38	33	30
100	28*	21*	22*	15*		18	20	26	22	21

* = Number at Terminal Sacrifice

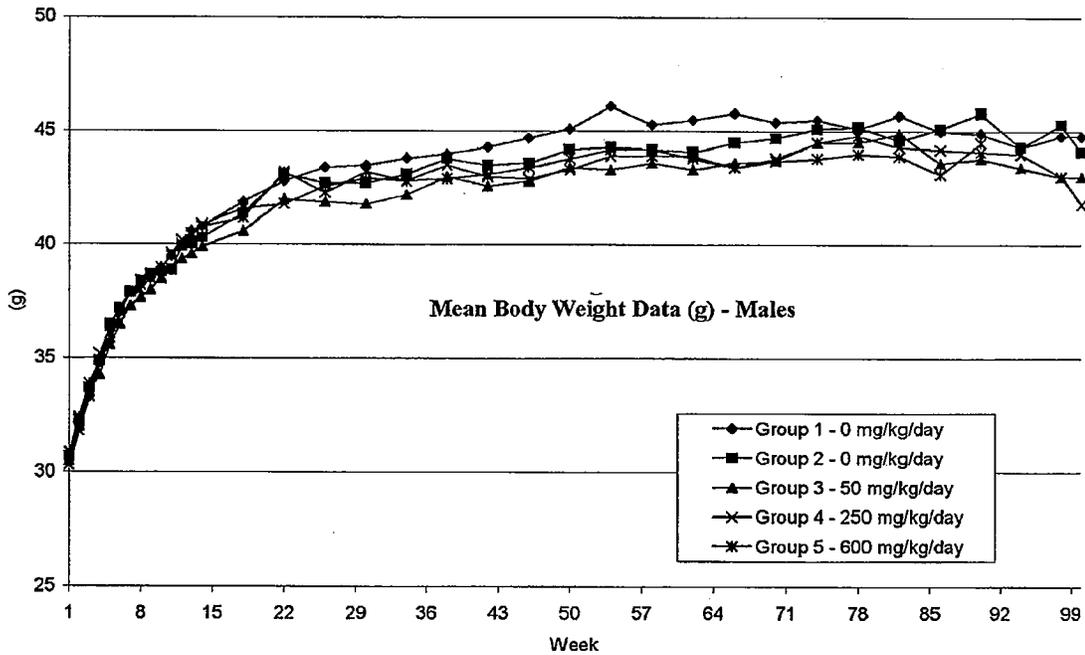
Clinical signs:

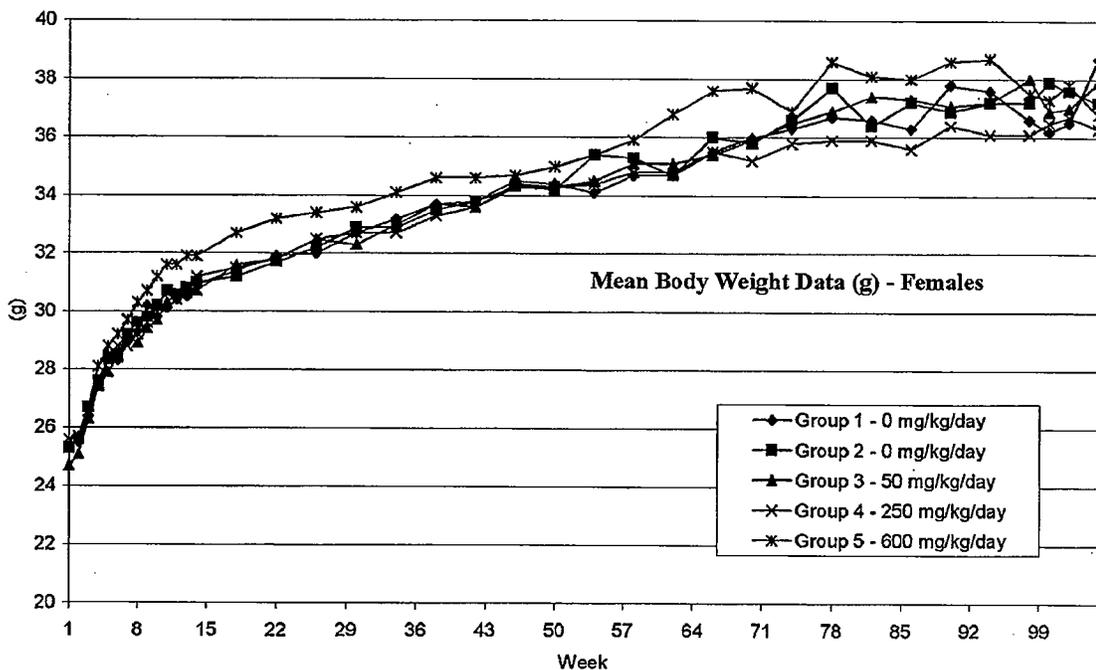
No clear drug-related clinical observations were noted in males or females dosed with up to 600 mg/kg/day. Rough haircoat in males dosed with 250 mg/kg/day was noted with a slightly increased incidence over both controls but was not increased at 600 mg/kg/day. A slightly increased incidence over both controls of swollen abdominal region was noted in females dosed with >50 mg/kg/day, but the increase was not seen in males. Given that rough haircoat or swollen abdomen was not seen in both genders and the lack of a clear dose response, these

changes are not considered drug related. Based on an initial concern for infection in early-sacrifice males, an evaluation for signs of infection was conducted under the direction of a clinical veterinarian during Week 92 on selected males that had concurrent signs of skin sore/scabs. The skin lesions observed in all dose groups, including controls, were generally consistent with mild ulcerative dermatitis syndrome (an expected finding for aged mice). No evidence of widespread infection was noted and, therefore, is not considered drug related.

Body weights:

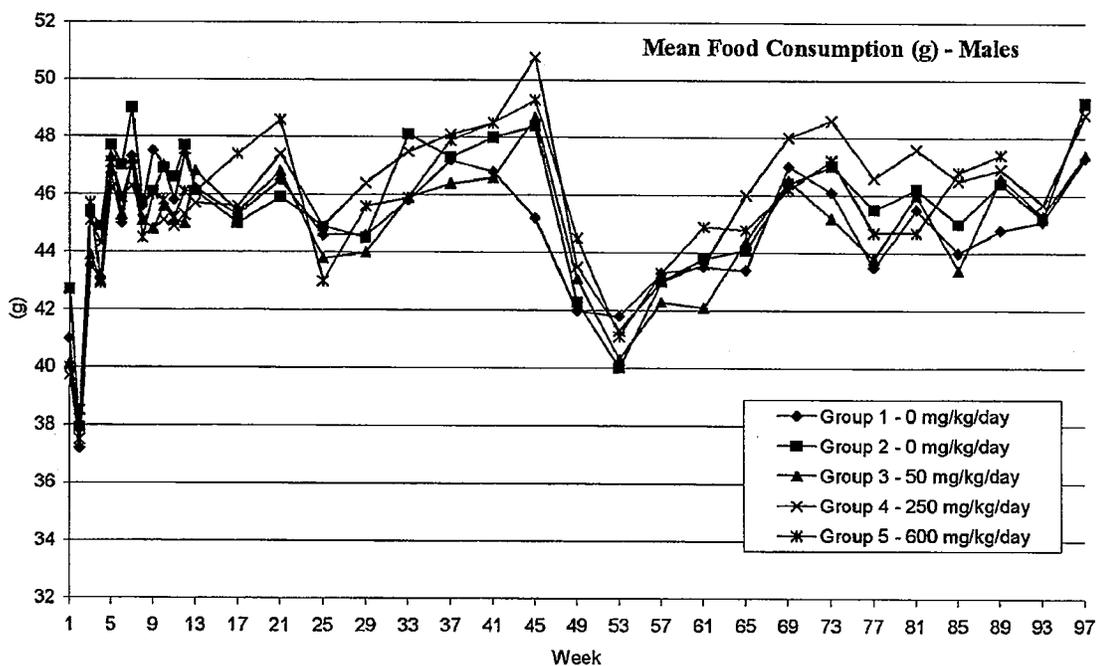
- There was no significant change in mean BW in males of all groups. However, HD females (600 mkd) had slightly higher BW than controls from week 10 to 22 (31.9 vs. 33.2 g). The final BW among female mice was similar (please see body weight graphs).
- BW changes were variable over the 2 years. There was no notable change in BW change at the end of the study.

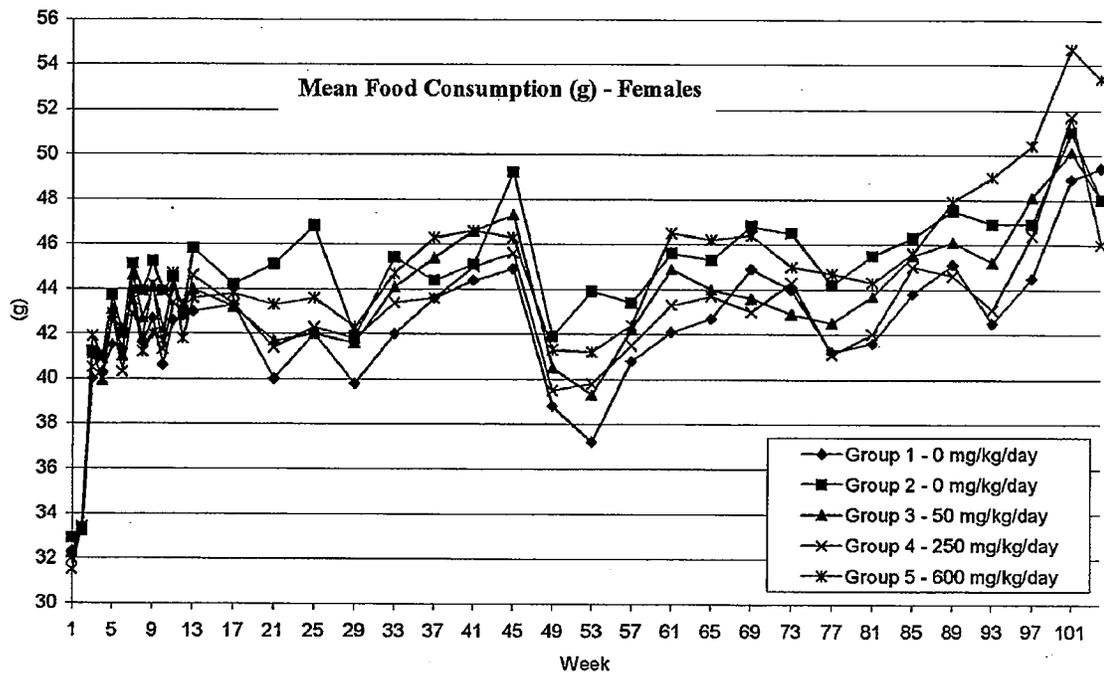




Food consumption:

- Overall, there was no notable drug dose-related effect on food intake in male mice. The food intake in HD females tend to be slightly (~ 5%) higher than controls during weeks 10 and 22 corresponding to slightly higher BW in HD females during that time. Food intakes during the final weeks of the study were higher in HD females but not in HD males.





Hematology:

- Blood samples collected at the study termination from the main study animals found no notable changes in hematology parameters in treated male and female mice relative to controls.

Gross pathology:

There were no notable drug-related macroscopic findings or increased incidence of masses in either males or females that died or were euthanatized during the course of the study or at the end of the treatment period. Findings noted in the saxagliptin treated mice were of low incidence, and/or their incidence was not dose dependent; therefore, they were considered unrelated to the test article. Tabulated macroscopic findings are located on page 52.

Summary of Mass Observations

CATEGORY KEYWORD QUALIFIER	NUMBER OF ANIMALS AFFECTED					CATEGORY KEYWORD QUALIFIER	NUMBER OF ANIMALS AFFECTED						
	SEX: GROUP: DOSE:	MALE					SEX: GROUP: DOSE:	FEMALE					
	1 0	2 0	3 50	4 250	5 600		1 0	2 0	3 50	4 250	5 600		
*** TOP OF LIST ***	NUMBER:	60	60	60	60	60	*** TOP OF LIST ***	NUMBER:	60	60	60	60	60
MASS (ES)							MASS (ES)						
AXILLARY REGION-LEFT		0	1	0	0	0	AXILLARY REGION-LEFT		0	0	0	0	2
AXILLARY REGION-RIGHT		0	1	0	1	2	AXILLARY REGION-RIGHT		1	0	1	0	0
DORSAL		1	1	3	0	0	DORSAL		2	3	0	1	0
DORSAL-CERVICAL		0	0	0	1	0	DORSAL-CERVICAL		1	1	2	0	1
DORSAL-CERVICAL-LEFT		0	2	1	0	0	DORSAL-CERVICAL-LEFT		0	0	0	1	0
DORSAL-CERVICAL-RIGHT		0	0	0	1	1	DORSAL-CERVICAL-RIGHT		0	1	0	0	0
EAR-LEFT		0	0	0	1	0	HEAD-MAXILLARY-LEFT		0	0	1	0	0
HEAD-MAXILLARY-RIGHT		0	0	1	0	0	INGUINAL REGION-LEFT		0	0	0	1	0
INGUINAL REGION-LEFT		1	1	6	2	0	INGUINAL REGION-RIGHT		0	0	1	1	0
INGUINAL REGION-RIGHT		0	0	3	4	0	LIMB-HIND-LEFT		1	0	0	0	0
LIMB-HIND-LEFT		1	0	0	0	0	LIMB-HIND-RIGHT		1	0	1	1	0
LIMB-HIND-RIGHT		1	0	1	1	0	SHOULDER-RIGHT		0	0	0	1	0
SHOULDER-RIGHT		0	0	0	1	0	TAIL-PROXIMAL		0	1	0	0	0
TAIL-PROXIMAL		0	1	0	0	0	VENTRAL-ABDOMINAL		3	3	5	11	5
VENTRAL-ABDOMINAL		3	3	5	11	5	VENTRAL-ABDOMINAL-LEFT		1	4	6	5	4
VENTRAL-ABDOMINAL-LEFT		1	4	6	5	4	VENTRAL-ABDOMINAL-RIGHT		4	5	4	5	8
VENTRAL-ABDOMINAL-RIGHT		4	5	4	5	8	VENTRAL-CERVICAL		0	1	1	0	0
VENTRAL-CERVICAL		0	1	1	0	0	VENTRAL-CERVICAL-LEFT		0	0	1	0	0
VENTRAL-CERVICAL-LEFT		0	0	1	0	0	VENTRAL-CERVICAL-RIGHT		1	1	0	0	0
VENTRAL-CERVICAL-RIGHT		0	0	0	2	1	LATERAL LEFT		0	0	2	0	2
LATERAL LEFT		0	0	2	1	1	LATERAL RIGHT		1	2	1	0	0
LATERAL RIGHT		0	0	1	0	0	PERINEAL		0	1	0	0	1
PERINEAL		2	0	2	1	1	PROTUDING VAGINAL AREA		0	0	0	1	1
PROTUDING VAGINAL AREA		0	0	1	0	0	WART LIKE LESION(S)						
WART LIKE LESION(S)							INGUINAL REGION-LEFT		0	0	0	0	1
INGUINAL REGION-LEFT		0	0	1	1	0	SHOULDER-LEFT		1	0	0	0	0
SHOULDER-LEFT		1	0	0	0	0	TAIL-MID		1	0	1	0	0
TAIL-MID		1	0	1	0	0	VENTRAL-ABDOMINAL-LEFT		0	0	0	0	1
VENTRAL-ABDOMINAL-LEFT		0	0	0	1	1	VAGINAL AREA		0	1	0	0	1
VAGINAL AREA		0	1	0	0	1							

Histopathology:

Non-neoplastic:

- There were no notable differences among groups in regards to microscopic evaluations. Any changes seen in treated groups did not appear to be dose related such as lenticular degeneration in females (4 in MD dose, 2 in HD and 1 in each control) and hepatocellular lipid vacuolation in males (11 in LD, 16 in MD and , 0 in HD and controls). It is not clear if absence of vacuolation in the HD males was related to earlier termination and higher mortality or not.
- There were no drug-related cardiac histopathology findings in male or female mice. In fact cardiomyopathy incidences appeared to be slightly higher in control males than saxagliptin treated mice.
- There was no drug-related increase in brain, lung, epididymis and harderian gland pathology in mice.

- Overall, microscopic findings present only in animals given the test article had a very low incidence, and/or their incidence was not dose dependent, and were therefore considered unrelated to the test article and incidental in this species and strain.
- The safety margin at the highest dose of saxagliptin (600 mkd) was over 800 fold the clinical dose of 5 mg, based on AUC. At the same dose, exposure to active metabolite, BMS-510849 was about 300 fold the clinical exposure. Correcting for slightly lower exposure (by 13%) is unlikely to significantly impact the overall safety margin for active metabolite, BMS-510849 (260x the clinical exposure).
- Tabulated mouse histopathology findings are in appendix A, Page 55

Neoplastic:

- Statistical analysis of incidence of neoplastic tissue in mice treated with saxagliptin found no significant difference in incidence of tumors among groups. Trend analysis found no P value that was less than 0.1 suggesting that there was no trend.
- Although there was significant drug-related mortality, the number of animals per group was sufficient to carry out statistical analysis.
- The incidences of tumors in male and female mice are shown in tables below. Again, there was no significant increase in tumor incidence in mice treated with saxagliptin doses as high as 600 mg/kg/d for 80 weeks in males and 104 weeks in females.
- Neoplastic findings in the mouse study are shown in the following pages.

Male Mice: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values

ORGAN/TISSUE	NEOPLASM	DOSE				
		0	0	50	250	600
Adrenal, Cortex	Adenoma, Subcapsular Cell	0/59	0/58	1/60	1/59	0/60
	Trend Test P-Values				0.1631	0.3176
Adrenal, Medulla	Pheochromocytoma	0/58	0/58	1/60	0/59	0/60
	Trend Test P-Values				0.4722	0.5347
Brain	Hemangioma	0/60	0/60	0/60	1/60	0/60
	Trend Test P-Values				0.1744	0.2808
Epididymis	Fibrosarcoma	0/60	1/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Gallbladder	Papilloma	0/50	0/51	0/53	1/51	0/45
	Trend Test P-Values				0.1786	0.2846
Harderian Gland	Adenoma	4/60	6/60	6/59	1/60	4/60
	Trend Test P-Values				0.9307	0.5754
Harderian Gland	Carcinoma	0/60	0/60	0/59	0/60	1/60
	Trend Test P-Values				1.0000	0.2857
Hemato Neoplasia	Lymphoma	5/60	2/60	2/60	1/60	1/60
	Trend Test P-Values				0.8803	0.8279
Hemato Neoplasia	Sarcoma, Histiocytic	3/60	0/60	0/60	1/60	0/60
	Trend Test P-Values				0.5684	0.7520
Kidney	Carcinoma, Tubular Cell	0/60	1/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Kidney	Hemangiosarcoma	1/60	0/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Kidney	Adenoma, Tubular Cell	1/60	0/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Liver	Carcinoma, Hepatocellular	5/60	5/60	1/60	1/60	0/60
	Trend Test P-Values				0.9317	0.9881
Liver	Hemangioma	0/60	0/60	1/60	1/60	1/60
	Trend Test P-Values				0.1505	0.1297
Liver	Hemangiosarcoma	3/60	3/60	4/60	3/60	1/60
	Trend Test P-Values				0.3226	0.6440
Liver	Adenoma, Hepatocellular	5/60	2/60	1/60	2/60	1/60
	Trend Test P-Values				0.6497	0.6913

Male Mice: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values.

ORGAN/TISSUE	NEOPLASM	DOSE				
		0	0	50	250	600
Lung	Carcinoma, Bronchiolar-Alveolar	6/60	13/60	5/60	7/60	0/60
	Trend Test P-Values				0.4792	0.9817
Lung	Adenoma, Bronchiolar-Alveolar	6/60	9/60	3/60	4/60	2/60
	Trend Test P-Values				0.7960	0.9224
Muscle, Skeletal	Fibrosarcoma	1/60	0/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Muscle, Skeletal	Hemangiosarcoma	0/60	0/60	0/60	0/60	1/60
	Trend Test P-Values				1.0000	0.1329
Pituitary	Adenoma	0/60	0/59	0/60	1/60	1/59
	Trend Test P-Values				0.2571	0.1845
Salivary GJ, Mandibular	Carcinoma	0/60	1/60	0/60	0/59	0/59
	Trend Test P-Values				1.0000	1.0000
Skin	Fibrosarcoma	0/60	0/59	0/59	1/60	0/60
	Trend Test P-Values				0.2270	0.3500
Skin	Histiocytoma	0/60	0/59	1/59	0/60	0/60
	Trend Test P-Values				0.5581	0.5278
Skin	Papilloma, Squamous Cell	0/60	2/59	0/59	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Skin & Pinna	Papilloma, Squamous Cell	0/60	2/60	0/60	1/60	0/60
	Trend Test P-Values				0.5784	0.8427
Spleen	Hemangioma	0/60	1/60	2/60	0/60	0/60
	Trend Test P-Values				0.7090	0.8486
Spleen	Hemangiosarcoma	1/60	0/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Stomach, Glandular	Adenoma	0/60	0/60	1/60	0/60	0/60
	Trend Test P-Values				0.5135	0.6471

Male Mice: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values.

ORGAN/TISSUE	NEOPLASM	DOSE				
		0	0	50	250	600
Stomach, Nonglandular	Papilloma, Squamous Cell	0/60	0/60	0/60	0/60	1/60
	Trend Test P-Values				1.0000	0.1027
Testis	Interstitial Cell Tumor	0/60	2/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Testis	Sertoli Cell Tumor	0/60	1/60	0/60	0/60	0/60
	Trend Test P-Values				1.0000	1.0000
Thymus	Hemangiosarcoma	0/40	0/34	0/44	1/37	0/44
	Trend Test P-Values				0.2857	0.2718
Tongue	Papilloma, Squamous Cell	0/60	0/60	1/60	0/60	0/60
	Trend Test P-Values				0.4834	0.5593
Urinary Bladder	Carcinoma, Transitional Cell	0/58	0/60	0/58	0/60	1/57
	Trend Test P-Values				1.0000	0.2800
Whole Body	Hemangioma	0/60	1/60	3/60	2/60	1/60
	Trend Test P-Values				0.1637	0.3810
Whole Body	Hemangiosarcoma	5/60	3/60	4/60	4/60	2/60
	Trend Test P-Values				0.2948	0.4543
Whole Body	Hemangioma / Hemangiosarcoma	5/60	4/60	7/60	6/60	3/60
	Trend Test P-Values				0.1645	0.3961
Penis ^a	Fibrosarcoma	0/1	0/4	1/5	0/2	0/1
Pinna ^a	Papilloma, Squamous Cell	0/7	0/9	0/9	1/10	0/4

^a Not analyzed statistically

Female Mice: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values

ORGAN/TISSUE	NEOPLASM	DOSE				
		0	0	50	250	600
Adrenal, Cortex	Adenoma	0/59	0/60	0/60	1/59	0/60
	Trend Test P-Values					0.3875
Adrenal, Cortex	Adenoma, Subcapsular Cell	2/59	1/60	0/60	0/59	1/60
	Trend Test P-Values					0.6071
Adrenal, Cortex	Carcinoma	1/59	1/60	0/60	0/59	0/60
	Trend Test P-Values					1.0000
Adrenal, Medulla	Pheochromocytoma	0/58	1/60	0/59	0/58	2/59
	Trend Test P-Values					0.1083
Cervix	Leiomyoma	0/57	0/59	2/58	1/58	0/59
	Trend Test P-Values					0.5054
Cervix	Polyp, Endometrial Stromal	1/57	0/59	2/58	1/58	0/59
	Trend Test P-Values					0.7440
Cervix	Sarcoma, Endometrial Stromal	2/57	0/59	1/58	0/58	0/59
	Trend Test P-Values					0.9489
Duodenum	Carcinoma	0/57	0/59	0/57	0/58	1/58
	Trend Test P-Values					0.1975
Gallbladder	Papilloma	0/53	0/52	0/50	0/48	1/47
	Trend Test P-Values					0.1974
Harderian Gland	Adenoma	3/59	2/59	2/60	1/60	2/60
	Trend Test P-Values					0.6248
Harderian Gland	Carcinoma	1/59	0/59	0/60	0/60	0/60
	Trend Test P-Values					1.0000
Heart	Rhabdomyosarcoma	0/59	0/60	1/60	0/60	0/60
	Trend Test P-Values					0.5254
Hemato Neoplasia	Lymphoma	10/60	9/60	5/60	13/60	7/60
	Trend Test P-Values					0.4929
Hemato Neoplasia	Sarcoma, Histiocytic	6/60	1/60	1/60	5/60	3/60
	Trend Test P-Values					0.3697
Jejunum	Adenoma	1/57	0/58	0/56	0/57	0/58
	Trend Test P-Values					1.0000

Female Mice: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values

ORGAN/TISSUE	NEOPLASM	DOSE				
		0	0	50	250	600
Liver	Carcinoma, Hepatocellular	0/60	0/60	1/60	0/60	0/60
	Trend Test P-Values					0.6375
Liver	Hemangioma	0/60	0/60	1/60	1/60	0/60
	Trend Test P-Values					0.4810
Liver	Hemangiosarcoma	0/60	2/60	0/60	1/60	0/60
	Trend Test P-Values					0.7508
Lung	Osteosarcoma	0/60	0/60	1/60	0/60	0/60
	Trend Test P-Values					0.6301
Lung	Adenoma, Bronchiolar-Alveolar	8/60	7/60	5/60	5/60	4/60
	Trend Test P-Values					0.8629
Lung	Carcinoma	6/60	6/60	9/60	4/60	5/60
	Trend Test P-Values					0.7314
Mammary, Female	Fibrosarcoma	1/50	0/52	0/50	0/50	0/51
	Trend Test P-Values					1.0000
Mammary, Female	Carcinoma	1/50	0/52	2/50	0/50	1/51
	Trend Test P-Values					0.5213
Muscle, Skeletal	Fibrosarcoma	1/60	1/59	1/60	1/60	1/60
	Trend Test P-Values					0.4608
Ovary	Cystadenoma	0/60	0/58	0/59	1/59	1/60
	Trend Test P-Values					0.1213
Ovary	Adenoma	0/60	0/58	0/59	1/59	0/60
	Trend Test P-Values					0.4366
Ovary	Luteoma	2/60	0/58	0/59	1/59	0/60
	Trend Test P-Values					0.7903
Pancreas	Adenoma, Islet Cell	1/60	1/60	0/60	0/60	0/60
	Trend Test P-Values					1.0000
Pituitary	Adenoma	4/59	2/59	3/58	2/58	2/58
	Trend Test P-Values					0.7264

Female Mice: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values

ORGAN/TISSUE	NEOPLASM	DOSE				
		0	0	50	250	600
Pituitary	Carcinoma	1/59	0/59	0/58	0/58	0/58
	Trend Test P-Values					1.0000
Skin	Carcinoma, Basal Cell	0/59	0/60	1/60	0/60	0/60
	Trend Test P-Values					0.6375
Skin	Carcinoma, Squamous Cell	0/59	1/60	0/60	0/60	0/60
	Trend Test P-Values					1.0000
Skin	Fibrosarcoma	0/59	1/60	0/60	1/60	0/60
	Trend Test P-Values					0.6440
Skin	Keratoacanthoma	0/59	0/60	0/60	1/60	0/60
	Trend Test P-Values					0.3333
Skin	Neurofibroma	0/59	0/60	0/60	0/60	1/60
	Trend Test P-Values					0.1356
Skin	Papilloma, Squamous Cell	0/59	1/60	0/60	0/60	0/60
	Trend Test P-Values					1.0000
Spleen	Hemangiosarcoma	0/59	1/60	1/60	0/60	1/60
	Trend Test P-Values					0.3996
Stomach, Nonglandular	Papilloma, Squamous Cell	0/59	0/60	0/60	0/60	1/59
	Trend Test P-Values					0.1918
Stomach, Nonglandular	Sarcoma, Spindle Cell	0/59	0/60	0/60	0/60	1/59
	Trend Test P-Values					0.2126
Thyroid	Adenoma, Follicular Cell	2/59	1/59	0/60	0/60	0/60
	Trend Test P-Values					1.0000
Uterus	Adenocarcinoma	0/60	0/60	0/60	1/60	0/60
	Trend Test P-Values					0.3875
Uterus	Hemangioma	0/60	0/60	2/60	0/60	0/60
	Trend Test P-Values					0.6417
Uterus	Leiomyoma	0/60	1/60	0/60	0/60	0/60
	Trend Test P-Values					1.0000
Uterus	Polyp, Endometrial, Stromal	1/60	3/60	3/60	1/60	1/60
	Trend Test P-Values					0.8077
Uterus	Sarcoma, Endometrial, Stromal	2/60	3/60	6/60	1/60	4/60
	Trend Test P-Values					0.4698

Female Mice: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values

ORGAN/TISSUE	NEOPLASM	DOSE				
		0	0	50	250	600
Whole Body	Hemangioma	0/60	0/60	3/60	1/60	0/60
	Trend Test P-Values					0.6675
Whole Body	Hemangiosarcoma	0/60	3/60	1/60	1/60	1/60
	Trend Test P-Values					0.5886
Whole Body	Hemangioma / Hemangiosarcoma	0/60	3/60	3/60	2/60	1/60
	Trend Test P-Values					0.5473
Adipose Tissue ^a	Mesothelioma	1/1	0/2	0/0	0/2	0/0
Bone, Other ^a	Osteosarcoma	0/0	0/0	1/1	0/0	0/0
Subcutaneous Tissue ^a	Fibrosarcoma	0/2	1/1	0/1	0/0	0/0
Subcutaneous Tissue ^a	Rhabdomyosarcoma	0/2	0/1	1/1	0/0	0/0

^a Not analyzed statistically

Toxicokinetics:

- For the carcinogenicity study, mice were treated with 50, 250 and 600 mg/kg/d for 6 months.
- Systemic exposure was dose-related. The increase in exposure was dose-related for the parent drug but was greater than dose-proportional for the active metabolite, BMS-510849.
- There were no notable gender effects
- Repeated dosing increased the AUC ratio of parent to BMS-510849 in males by 2.1 to 3.9 fold and 1.4 to 2.9 fold in females. It appears that mice were transforming more of the parent drug to the active metabolite with repeated dosing suggesting that parent drug was inducing its own metabolism.
- In the NDA submission the sponsor stated that BMS-510849 peak was not well resolved from two small metabolites, thus AUC calculated for BMS-510849 was overestimated by as much as 20% in mice and 6.8% in humans. Due to high safety margins for active metabolite ($\geq 300x$ the clinical exposure), the small decrease in BMS-510849 exposure (about 14%) in mice relative to humans will not affect the overall safety of BMS-510849 in humans. Furthermore, since BMS-510849 is more specific to DP-4, BMS-510849 may have safety advantage over saxagliptin itself.
- The PK values for the parent, BMS-477118 and prominent active metabolite, BMS-510849 are shown in table below.

Dose [mg/kg/day]	Study Day	BMS-477118		BMS-510849		BMS-477118		BMS-510849	
		Male	Female	Male	Female	Male	Female	Male	Female
		C _{max} [ng/mL]				AUC [ng.h/mL] ^a			
50	177 or 179 ^b	1834	2925	5022	7732	1605	2615	6246	7643
250	177 or 179 ^b	20888	36659	32414	31491	34661	30483	76123	49443
600	177 or 179 ^b	66631	92239	65319	59487	70436	94393	147802	131654

^a Calculated from time zero to the time of the last measurable plasma concentration, ranging from 8 to 24 h.

^b Day 177 for males and Day 179 for females.

Safety margins:

Species	Dose, mg/kg/d	Saxagliptin AUC, ng.h/ml	BMS-510849 AUC, ng.h/ml	Safety margins based on AUC (Animal/Human)	
				Saxagliptin	BMS-510849
104-week Mouse Carci Study	50	M: 1605, F: 2615	M:6246, F:7643	M:20, F:32	M:14, F:17
	250	M:34661, F: 30483	M:76123, F:49443	M:428, F:376	M:174, F:113
	600	M: 70436, F:94393	M:147802,F:131654	M:870, F:1165	M:337 F:301
Clinical Dose: 5 mg (BMS-510849) *		81 438			

*Saxagliptin is metabolized in all species primarily to an active metabolite, BMS-510849. This metabolite is half as potent as parent but more selective to DP1V. The initial HPLC analysis used for AUC calculations was apparently overestimated due to inadequate peak resolution from two small metabolite, thus all the submitted AUC values for BMS-510849 in mice, rats, pregnant rabbits, dogs, cynomolgus monkeys and humans were overestimated by 20%, 42.7%, 11.1%, 36.2%, 15.1% and 6.8%, respectively. Therefore the safety margins for BMS-510849 are lower than safety margin shown in the table above. The lower metabolite exposure was less than 2 fold therefore is unlikely to alter safety profile of saxagliptin and its metabolite

Study title: BMS-477118: 104-Week Oral Gavage Carcinogenicity Study in Rats

Key study findings:

- There was a significant increase in mortality in the HD males early in the study and therefore they were sacrificed prematurely during week 68 and excluded from the analysis. The remaining male rats were sacrificed during week 99 due to unexpected decrease in survival rate in one of the control groups. Female rats survived to scheduled necropsy.
- The final survival rates for males at week 99 were 22%, 15%, 35%, 27%, and 27% for the control1, control2, 25, 75, and 150 mg/kg/day groups, respectively.
- The final survival rates for females during week 105 were 43%, 42%, 45%, 50%, 47%, and 50% for the 2 control, 25, 75, 150, and 300 mg/kg/day groups, respectively.
- There were no drug-related increases in incidence of tumors in either male or female rats treated with BMS-477118.
- The target organs for non-neoplastic finding were brain, lung, Harderian gland, epididymis, urinary bladder and liver.
- Brain associated lesions seen at ≥ 150 mg/kg/day were localized to corpus callosum thalamus and caudate putamen in males at ≥ 150 . Brain lesions limited to males at 300 mg/kg/day were further extended to piriform/temporal cortex.
- In summary, BMS-477118 was not considered carcinogenic. The incidence of tumors between saxagliptin treated rats (up to 150 mkd M and 300 mkd F) and controls were similar. There was a significant increase in mortality in HD males but not in females leading to early termination of HD males. There were minimal histopath findings in females at high drug exposure levels. These lesions specific to male rats are due to liberation of cyanide from BMS-477118 by CYP2C11 which is highly expressed in male rats. The role of CYP2C11 and cyanide release has been characterized in earlier toxicology studies as well as in humans. The exposure to saxagliptin at 300 mg/kg/d was 847 and 2217 fold the clinical dose of 5 mg, based on AUC. The exposure in males at 150 mg/kg/d was 355 fold the clinical dose. The exposure to active metabolite was reduced based on new analysis from 68 to 42x the clinical exposure. Even at reduced levels, rats had significantly higher exposure to BMS-510849 than humans.

Adequacy of the carcinogenicity study and appropriateness of the test model: The rat carcinogenicity protocol was reviewed by the Division and concurred by the eCAC. The study design and the animal model were considered appropriate for testing the carcinogenicity of saxagliptin (saxagliptin). A maximum tolerated dose was exceeded in males based on the cyanide-related brain necrosis and early deaths, but was not reached in females. However, doses in rats attained extraordinary exposure multiples relative to the clinical dose of 5mg.

Evaluation of tumor findings:

- There was no statistically significant difference in tumor incidence in any of the treated groups compare to controls. However, there were non-neoplastic microscopic findings in the treated groups (brain, harderian gland, epididymis, urinary bladder and liver).

b(4)

Study no.: #6108-489, BMS#DN05004

Volume #, and page #: eCTD NDA

Conducting laboratory and location:

Date of study initiation: Jan 10, 2005 (End date, Jan 30, 2007)

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, and % purity: 98.4 to 99.9% purity

Test Article	Lot Nos.	Storage	Corrected Purity	Expiration Date ^a	Reserve (Archive) Sample
BMS-477118-11	4J88286	In a refrigerator, set to maintain 2 to 8°C	98.4%	30-Nov-05	Collected
	4K85994		99.42%	31-Jan-07	Collected
	4L78037		99.9%	30-Sep-07	Collected

^a The terms expiration, use, and retest date are synonymous and indicate the date beyond which, without further testing, the test article should not be used.

Results of Stability Analyses

Time Point	Storage Conditions	BMS-477118-11 (Mean % of Target)	
		Group 6 (60 mg/mL)	Change from Initial
Initial	NA	98.6	NA
8 Days	Refrigerated	93.7	-4.9
17 Days	Refrigerated	101	+2.4

NA Not Applicable.

Results of Concentration Verification

Interval	Groups 1 and 2 (0 mg/mL)	Group 3 (5 mg/mL)	Group 4 (15 mg/mL)	Group 5 (30 mg/mL)	Group 6 (60 mg/mL)
Week 1 & 2	ND ^a	99.7	98.7	98.6	98.6
Weeks 3 & 4	NA	102	99.0	99.6	99.1
Weeks 5 & 6	NA	100	100	101	103
Week 13	ND ^a	101	101	103	104
Week 26	ND ^a	102	100	99.2	101
Week 39	ND ^a	98.1	97.8	98.3	99.8
Week 52	ND ^a	101	100	99.0	101
Week 65	ND ^a	99.7	99.9	99.2	98.1
Week 78	ND ^a	98.9	98.3	98.4	99.3
Week 91	ND ^a	99.4	100	100	101
Week 104	ND ^a	101	99.4	102	102

ND = None detected.

NA = Not applicable.

^a Limit of quantitation is 2.00 mg/mL.

CAC concurrence: The carcinogenicity protocol was reviewed and approved by eCAC. The minutes of the meeting are attached to this review.

Methods

Doses: 0, 0, 25, 75, 150 or 300 mg/kg/day

Basis of dose selection (MTD, MFD, AUC etc.): MTD

Species/strain: Hsd: Sprague Dawley rats

Number/sex/group (main study): 60/sex/group

Route, formulation, volume: 5 ml/kg, oral gavage, acidified water

Frequency of dosing: Single daily gavage
Satellite groups used for toxicokinetics or special groups: TK rats were evaluated at 6 months
Age: 6 weeks old
Animal housing: individually housed in stainless steel cages
Restriction paradigm for dietary restriction studies: No, animals had free access to food and water at all times
Drug stability/homogeneity: BMS-477118 was stable
Dual controls employed: Yes
Interim sacrifices: No interim sacrifice; however, the 300 mg/kg/day dose was not well tolerated in males and were sacrificed early during week 68.

Deviations from original study protocol: As noted above, male rats treated with 300 mg/kg/d saxagliptin (BMS-477118) had high incidence of mortality and therefore had to be terminated early during week 68. One of the control males also had poor survival thus the remaining males were terminated by week 99. These animals were not included in statistical analysis. The survival rate in female rats was adequate to maintain the treatment until the scheduled terminal necropsy.

Statistical Analysis: The tumor data were analyzed using one-sided Peto-Pike trend tests. According to the sponsor, this method is sensitive to tumor rates that increase with dose. Tumors observed only in an incidental context were analyzed by the prevalence method. Tumors observed only in a fatal context were analyzed by the death rate method. When a tumor was observed in both fatal and incidental contexts, the fatal and incidental occurrences were analyzed and combined as described in Peto et al (1980). Mortality independent tumors, such as skin tumors, which were seen or palpated in 1 or more live animals, were analyzed by the onset rate method. The asymptotic version of the Peto-Pike test was used whenever the total number of tumor bearing animals, summed across all dose groups, was greater than 12. When the total number of tumor bearing animals was twelve or less, the exact permutation method was used (Lin & Ali 1994). A Peto-Pike trend test was considered statistically significant if the one-sided P-value was less than 0.025 for a rare tumor, or less than 0.005 for a common tumor. All these statistical analyses were carried out with SAS program (V.9.1)

Observation times

Mortality: twice daily

Clinical signs: daily

Body weights: weekly from week 1 to 14 and every 4 weeks thereafter

Food consumption: weekly from week 1 to 13 and every 4 weeks thereafter

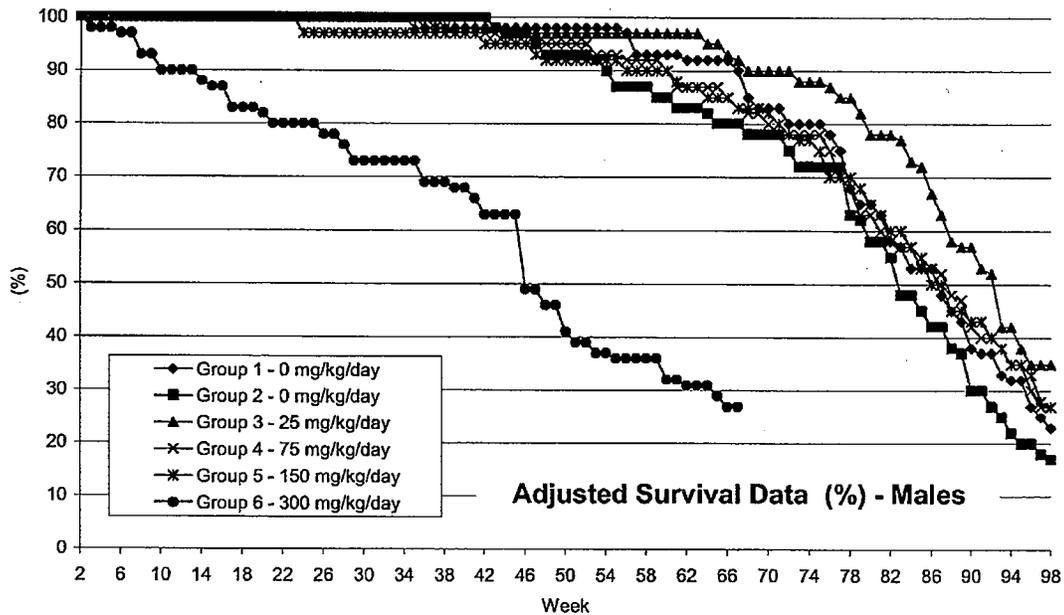
Histopathology: Peer review: yes (x), no ()

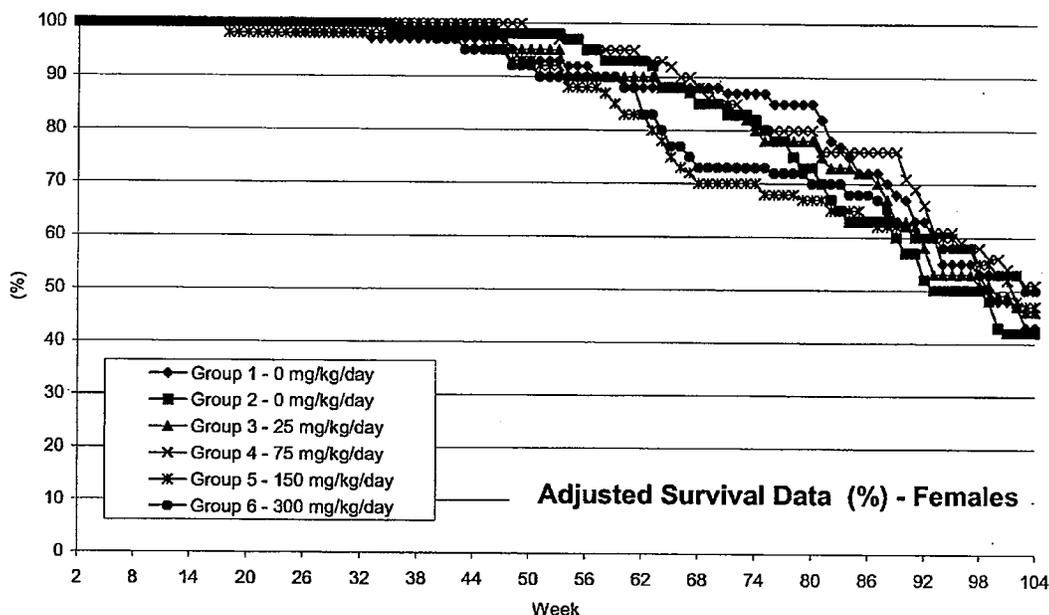
Toxicokinetics: yes. Toxicokinetic study of parent and active metabolites were evaluated at 0.5, 1, 2, 4, 8 and 24 hr at 6 months

Results

Mortality:

- Significant increase in incidence of mortality was noted in males treated with 300 mkd resulted in termination of HD males at week 68 (May 09, 2006). Increase in incidence of death in one control lead to termination of all males during week 99 (Dec 07, 2006).
- There was no notable difference in survival rate among female rats treated with BMS-477118 relative to controls (Jan 22-23, 2007). The most common cause of death in control as well as treated females was attributed to inflammatory uterine lesions and mammary gland tumors.
- Deaths in HD males were seen as early as week 8. Interestingly, in the 3-month dose-ranging study (300, 600 and 1200 mkd), there was one dead female at 300 mkd which was attributed to nephropathy and no deaths in males. There were no deaths at 600 mkd; however, 1200 mg/kg/d was overtly toxic (8 deaths). The most frequent finding at 600 mkd was decreased BW in males (19 to 27%). At 300 mkd minimal changes in RBC and alveolar histocytosis were noted in females. There were no drug-related deaths in the 6-month rat study (2, 20 and 100 mkd). In this study, 20 mkd reduced BW by 18% in males. It is not clear why there was no significant increase in mortality in the 3-month study at 300 mkd.





Ascribed Cause of Death/Morbidity in Males (Unscheduled Necropsy)

	Males						
	Group	1	2	3	4	5	6
	BMS-477118 (mg/kg/day)	0	0	25	75	150	300
	No. Examined	47	51	39	44	44	46*
Brain necrosis/degeneration		0	1	0	1	0	5
Undetermined		7	6	9	6	6	30
Chronic progressive nephropathy		26	30	21	32	32	7
Neoplasia		9	6	8	4	5	0
Other non-neoplastic lesions		5	8	1	1	1	3
Accidental		0	0	0	0	0	1

* = Up to Week 68; all other groups up to Week 99.

Male Rats: Mortality due to all causes, followed by Kaplan-Meier (KM) survival estimates at terminal sacrifice, life-table trend tests for dose related trends in mortality, and a pairwise life-table comparison between the two control groups. The survival estimate for the control groups is a pooled estimate.

Group	1	2	3	4	5	6
Dose (mg/kg/day)	0	0	25	75	150	300
Natural Death / Moribund Sacrifice	47	51	39	44	44	45
Terminal Sacrifice	13	9	21	16	16	14
Accidental Death	0	0	0	0	0	1
TOTAL	60	60	60	60	60	60
KM Survival Est. at Terminal Sac.	0.18		0.35	0.27	0.27	0.24
Two-Sided Trend Test P-Values ^a			P=0.0063	P=0.2743	P=0.5213	P<0.0001
Pairwise Comparison P-Value		P=0.2534				

^a Trend test P-values are reported in the column of the highest dose-group included in the trend test.

Female Rats: Mortality due to all causes, followed by Kaplan-Meier (KM) survival estimates at terminal sacrifice, a life-table trend test for dose related trends in mortality, and a pairwise life-table comparison between the two control groups. The survival estimate for the control groups is a pooled estimate.

Group	1	2	3	4	5	6
Dose (mg/kg/day)	0	0	25	75	150	300
Natural Death / Moribund Sacrifice	34	35	32	29	32	30
Terminal Sacrifice	26	25	27	30	28	30
Accidental Death	0	0	1	1	0	0
TOTAL	60	60	60	60	60	60
KM-Survival Est. at Terminal Sac.	0.42		0.46	0.51	0.47	0.50
Two-sided Trend Test P-Value ^a			P=0.7211	P=0.2909	P=0.7458	P=0.6932
Pairwise Comparison P-Value			P=0.6322			

^a Trend test P-values are reported in the column of the highest dose-group included in the trend test.

Number of animals alive at 10 week intervals

WEEK	MALE GROUP						FEMALE GROUP					
	DOSE (mg/kg/day)						DOSE (mg/kg/day)					
	1	2	3	4	5	6	1	2	3	4	5	6
0	60	60	60	60	60	60	60	60	60	60	60	60
10	60	60	60	60	60	54	60	60	60	60	60	60
20	60	60	60	60	60	49	60	60	60	60	59	60
30	60	60	60	60	58	43	59	60	60	60	59	60
40	59	60	59	58	58	40	58	59	60	60	59	58
50	59	56	58	57	55	24	56	59	57	59	56	55
60	56	51	58	54	54	19	53	56	54	56	50	53
70	50	47	54	48	49	14 ^a	53	51	51	50	42	44
80	39	35	47	38	39		51	44	47	47	40	42
90	23	18	34	25	26		40	34	38	42	37	37
100	13 ^a	9 ^a	21 ^a	16 ^a	16 ^a		29	26	29	33	32	32

^a Number alive at terminal sacrifice

Incidence and location of masses observed in control and saxagliptin treated rats:

- There were no statistically significant differences or dose-related increase in observed masses in rats.

Summary of Mass Observations

Category Sign	Sex:	M a s s e s					
	Group:	1	2	3	4	5	6
	Dose Level: Dose Units: Number in Group:	0.00 mg/kg/day 60	0.00 mg/kg/day 60	25.00 mg/kg/day 60	75.00 mg/kg/day 60	150.00 mg/kg/day 60	300.00 mg/kg/day 60
		N	N	N	N	N	N
MASS (ES)							
DISTAL DORSAL TAIL		1	0	0	0	0	0
LEFT EYE		1	0	2	0	0	0
LEFT, DORSAL ABDOMEN		1	5	2	1	1	0
LEFT, DORSAL HEAD		0	0	1	1	0	0
LEFT, DORSAL THORAX (CHEST)		1	0	0	0	0	0
LEFT, INGUINAL AREA (GROIN)		3	1	2	0	1	1
LEFT, PROXIMAL, VENTRAL HINDLEG		0	1	1	0	0	0
LEFT, VENTRAL ABDOMEN		4	2	0	2	1	0
LEFT, VENTRAL NECK		0	0	0	0	1	0
LEFT, VENTRAL NOSE		1	0	0	1	0	0
LEFT, VENTRAL THORAX (CHEST)		0	0	1	0	0	0
LEFT, VENTRAL THROAT		0	0	0	2	0	0
MIDLINE, DORSAL ABDOMEN (BACK)		1	0	0	0	0	0
MIDLINE, DORSAL THORAX (CHEST)		0	0	0	1	0	0
MIDLINE, VENTRAL ABDOMEN		19	9	24	17	11	2
MIDLINE, VENTRAL THORAX (CHEST)		0	0	0	0	2	0
PROXIMAL, DORSAL TAIL		0	1	0	0	0	0

N = Number of animals with observed sign

Summary of Mass Observations

Category Sign	Sex:	M a s s e s					
	Group:	1	2	3	4	5	6
	Dose Level: Dose Units: Number in Group:	0.00 mg/kg/day 60	0.00 mg/kg/day 60	25.00 mg/kg/day 60	75.00 mg/kg/day 60	150.00 mg/kg/day 60	300.00 mg/kg/day 60
		N	N	N	N	N	N
MASS (ES)							
RIGHT EYE		0	0	0	0	1	0
RIGHT, DISTAL, DORSAL HINDLEG		0	1	0	0	0	0
RIGHT, DORSAL ABDOMEN		2	2	0	0	1	0
RIGHT, DORSAL EAR		1	0	0	0	0	0
RIGHT, DORSAL HEAD		1	0	1	0	0	0
RIGHT, DORSAL NOSE		0	0	1	0	0	0
RIGHT, DORSAL THORAX (CHEST)		1	0	0	0	0	0
RIGHT, INGUINAL AREA (GROIN)		6	2	8	8	5	2
RIGHT, PROXIMAL, DORSAL FORELEG		0	0	0	0	1	0
RIGHT, PROXIMAL, VENTRAL HINDLEG		1	0	0	0	0	0
RIGHT, VENTRAL ABDOMEN		3	1	0	1	1	0
RIGHT, VENTRAL NECK		0	0	0	0	1	0
RIGHT, VENTRAL NOSE		1	0	0	0	1	0
RIGHT, VENTRAL THORAX (CHEST)		2	0	0	1	0	0
RIGHT, VENTRAL THROAT		0	1	0	1	0	0
NART-LIKE LESION(S)							
LEFT EYE		1	0	1	1	2	0
LEFT, DISTAL, DORSAL FORELEG		0	0	0	0	1	0
LEFT, DORSAL NECK		0	0	1	0	0	0
LEFT, DORSAL HEAD		0	0	0	1	0	0
LEFT, DORSAL NOSE		0	0	0	0	1	0
PROXIMAL, DORSAL TAIL		0	0	0	0	1	0
PROXIMAL, VENTRAL TAIL		0	0	1	0	1	0
RIGHT EYE		1	0	1	1	3	0
RIGHT, DORSAL ABDOMEN		1	0	0	0	0	0
RIGHT, DORSAL NOSE		1	0	1	1	2	0
RIGHT, PROXIMAL, DORSAL FORELEG		0	0	0	0	1	0
RIGHT, VENTRAL NECK		0	1	0	0	0	0
RIGHT, VENTRAL NOSE		0	0	1	0	0	0

N = Number of animals with observed sign

Summary of Mass Observations

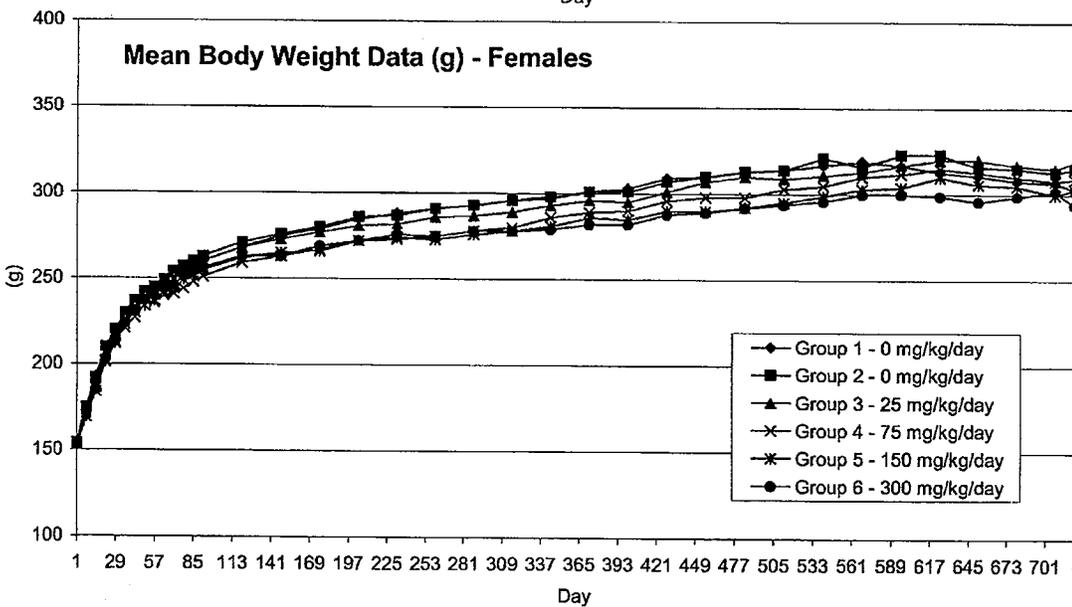
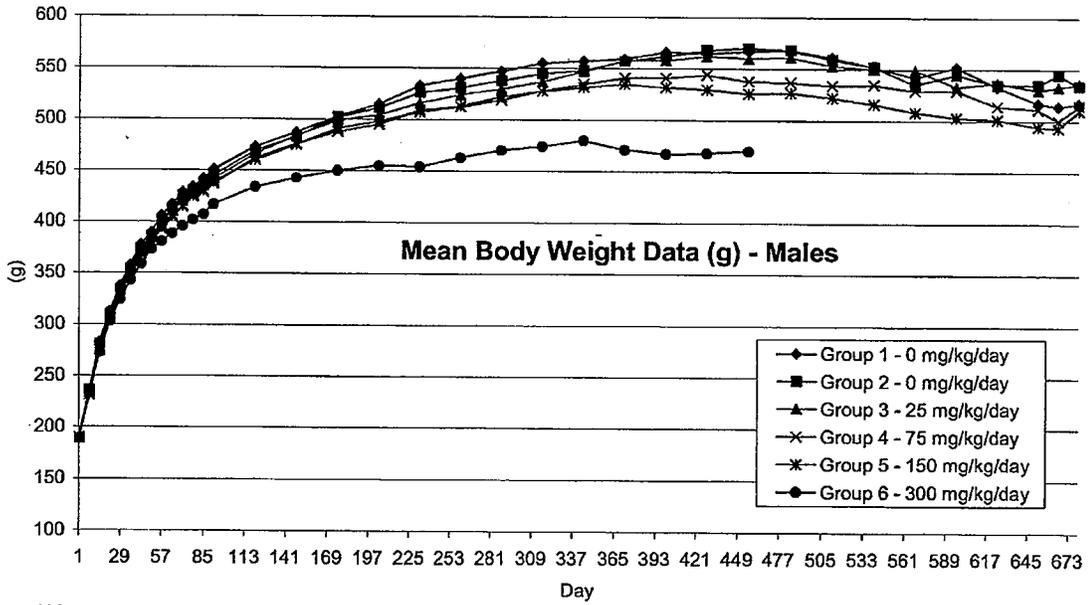
Category Sign	Sex: Group:		Females			
	1	2	3	4	5	6
	Dose Level:	Dose Level:	25.00	75.00	150.00	300.0
	Dose Units:	Dose Units:	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
	Number in Group:	Number in Group:	60	60	60	60
	N	N	N	N	N	N
MASS (ES)						
DISTAL, DORSAL TAIL	0	0	0	1	0	0
LEFT, DORSAL ABDOMEN,	0	0	1	0	0	0
LEFT, DORSAL HEAD,	0	0	0	1	0	0
LEFT, DORSAL NECK,	1	0	0	0	0	0
LEFT, DORSAL THORAX (CHEST)	0	1	0	2	0	1
LEFT, INGUINAL AREA (GROIN)	4	4	1	7	0	0
LEFT, VENTRAL ABDOMEN	4	3	4	4	4	2
LEFT, VENTRAL AXILLA (ARMPIT)	13	12	10	9	7	5
LEFT, VENTRAL EAR	1	0	0	0	0	0
LEFT, VENTRAL NECK	2	1	1	0	4	0
LEFT, VENTRAL THORAX (CHEST)	4	5	6	0	3	1
LEFT, VENTRAL THROAT	0	1	1	1	0	1
MIDLINE, VENTRAL ABDOMEN	18	19	15	13	16	8
MIDLINE, VENTRAL THORAX (CHEST)	1	1	2	0	0	0
PERI-VAGINAL AREA	2	14	5	3	3	5
RIGHT EYE,	0	0	0	1	0	0
RIGHT, DORSAL ABDOMEN	2	0	0	1	0	0
RIGHT, DORSAL HEAD	0	0	0	1	0	0
RIGHT, DORSAL THORAX (CHEST)	5	1	0	0	0	0
RIGHT, INGUINAL AREA (GROIN)	10	9	5	10	6	4
RIGHT, VENTRAL ABDOMEN	11	7	6	4	1	1
RIGHT, VENTRAL AXILLA (ARMPIT)	6	10	6	3	2	6
RIGHT, VENTRAL NECK	4	0	0	2	2	0
RIGHT, VENTRAL NOSE	0	0	1	0	0	0
RIGHT, VENTRAL THORAX (CHEST)	1	6	7	5	1	1
RIGHT, VENTRAL THROAT	0	0	0	0	1	0
WART-LIKE LESION(S)						
LEFT EYE	0	0	1	0	1	0
LEFT, DORSAL ABDOMEN	0	0	0	0	0	1
LEFT, DORSAL EAR	0	0	1	0	0	0
LEFT, DORSAL NECK	0	0	1	0	0	0
LEFT, DORSAL NOSE	0	0	0	1	0	0
LEFT, VENTRAL NOSE	0	0	0	0	1	0
PROXIMAL, DORSAL TAIL	0	0	0	1	0	0
PROXIMAL, VENTRAL TAIL	0	0	0	0	1	1
RIGHT, DORSAL HEAD	1	0	0	0	0	0
RIGHT, DORSAL NOSE	0	0	0	0	1	0
RIGHT, INGUINAL AREA (GROIN)	1	0	0	0	0	0

N = Number of animals with observed sign

Clinical signs: Clinical signs in HD males were sporadic tremors, respiratory changes (audible, irregular or labored) and recumbency. These clinical signs were thought to be related to acute cyanide toxicity and were notable as early as Day 16 in the study.

Body weights:

- There was a slight decrease in BW at ≥ 150 mg/kg/d in both male and female rats, but were only significant in the HD males at the time of necropsy by as much as 17%. The occasional decrease in BW at ≥ 75 mg/kg/day corresponded to food intake ($< 10\%$).



Food consumption: Food intake was lower (<10%) periodically in higher doses of BMS-477118

Gross pathology: There were no notable drug-related macroscopic findings in the schedules or unscheduled necropsies. Gross pathology findings appeared to be similar among groups. Tabulated macroscopic findings are listed on Appendix B, page 83.

Histopathology:

Non-neoplastic:

- The most significant histopath findings were **brain lesions seen in males**. These brain lesions have been shown to be the consequence of cyanide release, a by product of high expression of CYP2C11 in male rats. CYP2C11 enzyme is responsible for breakdown of saxagliptin to release cyanide which leads to brain lesions in male rats. The activity of CYP2C11 is minimal in other species thus there is minimal chance of cyanide release in other species. Cyanide release has not been seen in female rats or male and female mice and humans. Studies in humans found no measurable levels of cyanide. These brain lesions have been documented in males in earlier rat toxicology studies, and are likely responsible for death, tremor and respiratory problems in the HD male rats. These lesions especially in the HD males appeared to have been responsible to excessive mortality, tremor and respiratory difficulties as early as day 16. The high incidence of death in males treated with 300 mg/kg/day lead to premature termination of the HD males during week 68. The remaining male rats were also terminated during week 99 due to decrease in survival rate in one of the controls. The incidence of brain lesions in male rats are shown in table below.

**Microscopic Incidence of Selected Brain Findings in Males
(Unscheduled and Scheduled Necropsies)**

	Group	Males					
		1	2	3	4	5	6
	BMS-477118 (mg/kg/day)	0	0	25	75	150	300
	No. Examined	60	60	60	60	60	60
Corpus Callosum, Degeneration/Rarefaction		0	0	0	0	<i>10</i>	<i>33</i>
Corpus Callosum, PAS-Positive Material, Intracytoplasmic, Glial/Gitter Cells		0	0	0	0	<i>10</i>	<i>32</i>
Caudate Putamen, Focal/Multifocal, Degeneration/Rarefaction with Gliosis		0	0	0	0	1	<i>15</i>
Caudate Putamen, PAS-Positive Material		1	0	0	0	<i>6</i>	<i>40</i>
Piriform/Temporal Cortex, Focal/Multifocal, Degeneration/Rarefaction with Gliosis		0	0	0	0	0	5
Piriform/Temporal Cortex, PAS-Positive Material, Intracytoplasmic, Glial/Gitter Cells		0	0	0	0	0	4
Thalamus, Focal/Multifocal Degeneration/Rarefaction with Gliosis		0	0	0	0	<i>1</i>	<i>3</i>

Values in bold italics indicate changes considered to be related to the oral administration of BMS-477118.

- Additional target organs were lung, Harderian gland, epididymides and liver.
- The most significant finding besides the brain findings (males only) were minimal to marked dose-dependent increase in alveolar macrophage infiltrates in (at 75 mg/kg only in females) and inflammation in the lungs in both male and female rats. The severity and incidence of inflammation and macrophage infiltration increase in a dose dependent manner and tend to be higher in female rats which had greater drug exposure than males suggesting that lung findings were drug exposure related.
- Notable increase in lymphocyte infiltration (minimal to slight) in urinary bladder in both male and female rats at ≥ 150 mg/kg/day
- Notable increase in incidence of lymphocyte/macrophage infiltration (minimal to slight) in Harderian gland in female rats at ≥ 150 mg/kg/day
- Notable increase in mononuclear infiltration liver in males at 150 mg/kg/day but not at 300 mg/kg/day likely due to early mortality.
- Males dosed with 300 mg/kg/day of saxagliptin also had increased incidence and severity of mononuclear cell infiltration in the Epididymis and urinary bladder. Overall, there was no evidence of associated paranchymal cell injury in tissues with the increased mononuclear cell infiltrates and inflammation.
- Tabulated detailed histopathology findings in mice can be found in Appendix B, page 90

Microscopic Incidence of Selected Findings (Unscheduled and Scheduled Necropsies)									
		Group	1	2	3	4	5	6	
		BMS-477118 (mg/kg/day)	0	0	25	75	150	300	
Lung		Males							
	No. Examined	60	60	60	60	60	60*		
Alveolar Macrophage Infiltrates		20	27	19	27	<i>41</i>	<i>49</i>		
	Minimal	12	18	16	22	39	40		
	Slight	4	3	1	2	0	8		
	Moderate	3	5	1	3	2	1		
	Marked	1	1	1	0	0	0		
Inflammation		12	16	9	10	13	5		
	Minimal	8	10	6	6	11	4		
	Slight	2	5	3	1	1	1		
	Moderate	1	1	0	3	1	0		
	Marked	1	0	0	0	0	0		
Alveolar Macrophage Infiltrates		20	24	28	37	<i>58</i>	<i>59</i>		
	Minimal	17	21	20	17	10	19		
	Slight	3	3	7	12	34	33		
	Moderate	0	0	1	8	14	7		
Inflammation		7	7	8	17	<i>37</i>	<i>32</i>		
	Minimal	6	4	5	16	36	32		
	Slight	1	2	2	1	1	0		
	Moderate	0	1	0	0	0	0		
	Marked	0	0	1	0	0	0		
Urinary Bladder		Males							
	No. Examined	60	59	60	60	59	59*		
Lymphocyte Infiltrates		1	2	3	4	0	<i>12</i>		
	Minimal	1	1	2	3	0	12		
	Slight	0	1	1	1	0	0		
		Females							
	No. Examined	59	60	60	59	60	59		
Lymphocyte Infiltrates		0	2	0	7	<i>19</i>	<i>30</i>		
	Minimal	0	1	0	6	19	26		
	Slight	0	1	0	1	0	4		
Harderian Gland		Females							
	No. Examined	60	60	60	60	60	60		
Mononuclear Cell (Lymphocyte/Macrophage) Infiltrates		12	12	14	14	<i>29</i>	<i>39</i>		
	Minimal	12	12	13	14	28	36		
	Slight	0	0	1	0	1	3		
Epididymis		Males							
	No. Examined	60	60	60	59	60	60*		
Lymphocyte Infiltrates		7	2	6	5	11	<i>29</i>		
	Minimal	7	2	6	5	11	29		
Liver		Males							
	No. Examined	60	60	60	60	60	60*		
Mononuclear Cell (Lymphocyte/Macrophage) Infiltrates		5	7	8	8	<i>17</i>	<i>10</i>		
	Minimal	5	6	8	8	16	10		
	Slight	0	1	0	0	1	0		

* = Males given 300 mg/kg/day were sacrificed early during Week 68.

Values in bold italics indicate changes considered to be related to the oral administration of BMS-477118.

Neoplastic:

- Male rats treated with 300 mg/kg/d terminated early at week 68 were not included in the analysis.
- Statistical analysis using Peto-Pike method across the remaining male rats, the smallest p value of 0.061 was for whole/cavity; histiocytic sarcoma.
- For the female rats, none of the p-values were considered significant. There were two incidences of astrocytomas in females treated with 300 mg/kg/d. The trend analysis

p-value was 0.0274, which is near the p-value for rare tumors. The p-value for vagina polyp in endometrial stoma was 0.0931.

- Overall, there was no statistically significant difference in the incidence of neoplasms among different groups in the 2-year carcinogenicity study. Saxagliptin was concluded to be not a carcinogen in rats.
- The p-values and the list of animals with tumors and numbers evaluated for each tissue are shown in tables below:

Male Rats: Number of Tumor Bearing Animals / Number of Animals Evaluated, and Peto-Pike Trend Test P-Values.

ORGAN/TISSUE	NEOPLASM	DOSE					
		0	0	25	75	150	
Adrenal, Cortex	Adenoma	5/59	6/60	3/60	3/59	3/60	0.8298
Adrenal, Cortex	Carcinoma	1/59	0/60	1/60	0/59	0/60	0.8725
Adrenal, Medulla	Pheochromocytoma	8/59	15/60	15/60	7/59	6/60	0.9789
Body, Whole/Cavity	Hemangiosarcoma	0/60	1/60	0/60	1/60	1/60	0.2732
Body, Whole/Cavity	Histiocytic Sarcoma	0/60	0/60	1/60	0/60	2/60	0.0614
Body, Whole/Cavity	Large Granular Cell Leukemia	1/60	0/60	0/60	0/60	0/60	1.0000
Body, Whole/Cavity	Lymphosarcoma	3/60	2/60	1/60	0/60	0/60	0.9984
Brain	Granular Cell Tumor	0/60	0/60	0/60	1/60	1/60	0.1219
Brain	Malignant Astrocytoma	1/60	0/60	1/60	0/60	0/60	0.8582

**Male Rats: Number of Tumor Bearing Animals / Number of
Animals Evaluated, and Peto-Pike Trend Test P-Values.**

ORGAN/TISSUE	NEOPLASM	DOSE					
		0	0	25	75	150	
Brain	Malignant Oligodendroglioma	1/60	0/60	0/60	0/60	0/60	1.0000
Brain	Meningeal Sarcoma	1/60	1/60	0/60	0/60	0/60	1.0000
Eye	Fibrosarcoma	1/60	0/60	0/60	0/60	0/60	1.0000
Jejunum	Fibrosarcoma	0/54	0/56	0/54	0/54	1/55	0.2133
Jejunum	Carcinoma	0/54	0/56	0/54	1/54	0/55	0.3959
Kidney	Malignant Renal Mesenchyma	0/60	0/60	1/60	0/60	0/60	0.6463
Kidney	Nephroblastoma	0/60	0/60	0/60	0/60	1/60	0.2000
Liver	Adenoma, Hepatocellular	1/60	1/60	1/60	0/60	1/60	0.6300
Pancreas	Carcinoma, Islet Cell	0/60	0/60	1/60	0/59	0/60	0.5729
Pancreas	Adenoma, Acinar Cell	1/60	0/60	0/60	1/59	1/60	0.2685
Pancreas	Adenoma, Islet Cell	2/60	2/60	0/60	2/59	0/60	0.8817
Parathyroid	Adenoma	0/55	0/60	0/58	0/60	1/59	0.1895
Pituitary	Adenoma	9/60	5/60	10/60	6/60	4/60	0.8978

**Male Rats: Number of Tumor Bearing Animals / Number of
Animals Evaluated, and Peto-Pike Trend Test P-Values.**

ORGAN/TISSUE	NEOPLASM	DOSE					
		0	0	25	75	150	
Skin	Fibroma	0/60	1/60	0/60	1/60	1/60	0.2740
Skin	Fibrosarcoma	1/60	1/60	0/60	1/60	0/60	0.7672
Skin	Keratoacanthoma	3/60	1/60	0/60	0/60	2/60	0.5049
Skin	Malignant Basal Cell Tumor	0/60	0/60	0/60	1/60	0/60	0.3646
Skin	Sarcoma	0/60	0/60	1/60	0/60	0/60	0.5068
Stomach, Nonglandular	Carcinoma, Squamous Cell	0/60	0/60	1/60	0/60	0/60	0.7067
Testis	Interstitial Cell Tumor	0/60	1/59	0/60	0/59	2/60	0.1137
Thyroid	Carcinoma, C-cell	1/60	0/60	1/60	0/60	0/60	0.9168
Thyroid	Adenoma, C-cell	8/60	5/60	17/60	11/60	11/60	0.2298
Urinary Bladder	Carcinoma, Transitional Cell	0/60	0/59	1/60	0/60	0/59	0.7162
Zymbal's Gland	Carcinoma	0/58	2/55	0/59	0/53	1/57	0.5373
Cavity, Abdominal ^a	Lipoma	0/0	0/0	0/0	1/1	0/0	
Skin/SubQ, Other ^a	Fibrosarcoma	1/11	1/7	0/9	0/10	0/10	
Skin/SubQ, Other ^a	Keratoacanthoma	4/11	3/7	0/9	0/10	1/10	
Skin/SubQ, Other ^a	Papilloma, Squamous Cell	1/11	0/7	1/9	2/10	0/10	
Skin/SubQ, Other ^a	Carcinoma, Basal Cell	0/11	0/7	1/9	0/10	0/10	
Tail ^a	Keratoacanthoma	2/6	0/7	2/12	3/11	1/11	

^a Non-protocol specified tissue.

**Female Rats: Number of Tumor Bearing Animals / Number of
Animals Examined, and Peto-Pike Trend Test P-Values**

ORGAN/TISSUE	NEOPLASM	DOSE						
		0	0	25	75	150	300	
Adrenal, Cortex	Adenoma	1/60	8/60	5/60	6/60	6/60	6/60	0.2220
Adrenal, Cortex	Carcinoma	0/60	0/60	0/60	2/60	1/60	1/60	0.2059
Adrenal, Medulla	Malignant Pheochromocytoma	0/60	0/60	0/59	1/59	0/60	1/59	0.1605
Adrenal, Medulla	Pheochromocytoma	3/60	0/60	2/59	1/59	4/60	1/59	0.4504
Body, Whole/Cavity	Hemangioma	0/60	1/60	0/60	0/60	0/60	0/60	1.0000
Body, Whole/Cavity	Hemangiosarcoma	0/60	0/60	1/60	0/60	0/60	1/60	0.2064
Body, Whole/Cavity	Histiocytic Sarcoma	0/60	0/60	0/60	1/60	0/60	0/60	0.5318
Body, Whole/Cavity	Large Granular Cell Leukemia	2/60	0/60	0/60	0/60	0/60	0/60	1.0000
Body, Whole/Cavity	Lymphosarcoma	0/60	2/60	0/60	0/60	1/60	0/60	0.7570
Body, Whole/Cavity	Malignant Mesothelioma	0/60	0/60	0/60	0/60	1/60	0/60	0.3145
Brain	Malignant Astrocytoma	0/60	0/60	0/60	0/60	0/60	2/60	0.0274
Cervix	Polyp, Endometrial Stromal	0/60	3/60	1/60	2/59	1/60	2/59	0.3855
Cervix	Carcinoma	1/60	0/60	1/60	0/59	0/60	0/59	0.9069
Duodenum	Fibroma	0/59	0/60	0/57	0/57	1/59	0/59	0.3494
Duodenum	Sarcoma	0/59	0/60	0/57	0/57	1/59	0/59	0.3494

**Female Rats: Number of Tumor Bearing Animals / Number of
Animals Examined, and Peto-Pike Trend Test P-Values**

ORGAN/TISSUE	NEOPLASM	DOSE					
		0	0	25	75	150	300
Eye	Fibrosarcoma	0/60	1/60	0/59	0/60	0/60	0/60 1.0000
Heart	Endocardial Schwannoma	1/60	0/60	0/60	0/60	0/60	0/60 1.0000
Kidney	Fibrosarcoma	1/60	0/60	0/60	0/60	0/60	0/60 1.0000
Kidney	Adenoma, Tubule Cell	0/60	0/60	0/60	0/60	0/60	1/60 0.1807
Liver	Adenoma, Hepatocellular	3/60	3/60	1/60	1/60	0/60	1/60 0.9408
Mammary, Female	Adenoma	1/59	1/60	0/59	0/60	1/60	0/58 0.7241
Mammary, Female	Fibroadenoma	26/59	34/60	23/59	20/60	13/60	8/58 1.0000
Mammary, Female	Fibrosarcoma	0/59	0/60	0/59	1/60	0/60	0/58 0.3333
Mammary, Female	Sarcoma	0/59	1/60	0/59	0/60	0/60	0/58 1.0000
Mammary, Female	Schwannoma	0/59	0/60	0/59	1/60	0/60	0/58 0.4792
Mammary, Female	Carcinoma	11/59	4/60	2/59	0/60	3/60	1/58 0.9830
Ovary	Leiomyoma	0/60	0/60	0/60	0/59	0/59	1/59 0.1250
Ovary	Luteoma	0/60	0/60	1/60	0/59	0/59	0/59 0.6928

**Female Rats: Number of Tumor Bearing Animals / Number of
Animals Examined, and Peto-Pike Trend Test P-Values**

ORGAN/TISSUE	NEOPLASM	DOSE						
		0	0	25	75	150	300	
Kidney	Adenoma, Tubule Cell	0/60	0/60	0/60	0/60	0/60	1/60	0.1807
Liver	Adenoma, Hepatocellular	3/60	3/60	1/60	1/60	0/60	1/60	0.9408
Mammary, Female	Adenoma	1/59	1/60	0/59	0/60	1/60	0/58	0.7241
Mammary, Female	Fibroadenoma	26/59	34/60	23/59	20/60	13/60	8/58	1.0000
Mammary, Female	Fibrosarcoma	0/59	0/60	0/59	1/60	0/60	0/58	0.3333
Mammary, Female	Sarcoma	0/59	1/60	0/59	0/60	0/60	0/58	1.0000
Mammary, Female	Schwannoma	0/59	0/60	0/59	1/60	0/60	0/58	0.4792
Mammary, Female	Carcinoma	11/59	4/60	2/59	0/60	3/60	1/58	0.9830
Ovary	Leiomyoma	0/60	0/60	0/60	0/59	0/59	1/59	0.1250
Ovary	Luteoma	0/60	0/60	1/60	0/59	0/59	0/59	0.6928
Ovary	Malignant Granulosa/Theca	0/60	0/60	0/60	2/59	0/59	1/59	0.2299
Pancreas	Carcinoma, Islet Cell	0/60	0/60	1/60	0/60	0/60	0/60	0.6928
Pancreas	Adenoma, Islet Cell	3/60	2/60	1/60	1/60	3/60	0/60	0.9084
Pituitary	Adenoma	30/60	37/60	27/60	21/60	17/60	8/60	1.0000
Pituitary	Carcinoma	0/60	0/60	1/60	1/60	1/60	0/60	0.5485

**Female Rats: Number of Tumor Bearing Animals / Number of
Animals Examined, and Peto-Pike Trend Test P-Values**

ORGAN/TISSUE	NEOPLASM	DOSE						
		0	0	25	75	150	300	
Skin	Fibroma	1/60	0/60	0/60	1/60	0/60	0/60	0.7479
Skin	Fibrosarcoma	0/60	0/60	1/60	0/60	0/60	0/60	0.6463
Skin	Leiomyosarcoma	0/60	0/60	0/60	1/60	0/60	0/60	0.5187
Stomach, Nonglandular	Carcinoma, Squamous Cell	0/60	1/60	0/60	0/60	0/60	0/60	1.0000
Thymus	Adenoma	0/58	0/59	0/59	0/57	1/58	0/55	0.3476
Thyroid	Carcinoma, C-cell	0/60	0/60	1/60	2/60	1/60	0/60	0.5827
Thyroid	Adenoma, C-cell	10/60	18/60	22/60	11/60	10/60	13/60	0.8423
Uterus	Carcinoma, Squamous Cell	1/60	0/60	0/60	0/59	3/60	0/59	0.3635
Uterus	Leiomyosarcoma	0/60	0/60	0/60	0/59	0/60	1/59	0.1531
Uterus	Polyp, Endometrial Stromal	20/60	19/60	11/60	13/59	11/60	8/59	0.9967
Uterus	Sarcoma, Endometrial Strom	1/60	0/60	0/60	0/59	0/60	0/59	1.0000
Uterus	Carcinoma	1/60	1/60	0/60	2/59	1/60	3/59	0.0964
Vagina	Polyp, Endometrial Stromal	0/60	0/60	0/60	0/59	1/60	1/59	0.0931
Zymbal's Gland	Adenoma	0/54	0/57	0/58	0/54	0/57	1/57	0.1887

**Female Rats: Number of Tumor Bearing Animals / Number of
Animals Examined, and Peto-Pike Trend Test P-Values**

ORGAN/TISSUE	NEOPLASM	DOSE					
		0	0	25	75	150	300
Cavity, Abdominal ^a	Lipoma	0/1	0/0	0/0	0/0	1/2	0/0
Muscle, Other ^a	Schwannoma	1/1	0/1	0/0	0/0	0/0	0/0
Nerve, Other ^a	Malignant Schwannoma	0/0	1/1	0/0	0/0	0/0	0/0
Skin/SubQ, Other ^a	Fibrosarcoma	1/3	0/5	0/4	0/3	0/6	0/7
Skin/SubQ, Other ^a	Keratoacanthoma	1/3	0/5	0/4	0/3	0/6	0/7
Skin/SubQ, Other ^a	Papilloma, Squamous Cell	0/3	0/5	0/4	1/3	0/6	0/7
Skin/SubQ, Other ^a	Basal Cell Tumor	0/3	1/5	0/4	0/3	0/6	0/7
Skin/SubQ, Other ^a	Carcinoma, Basal Cell	0/3	0/5	1/4	0/3	0/6	0/7
Tail ^a	Leiomyosarcoma	0/2	0/1	0/0	1/9	0/4	0/4

^a Non-protocol specified tissue

Toxicokinetics:

- TK data was collected after 26 week of treatment with saxagliptin (25, 75, 150 and 300 mg/kg/d)
- C_{max} increased in dose-proportional manner for both saxagliptin and BMS-510849 in both males and females
- AUC increased in greater than dose-proportional manner for saxagliptin in both sexes and BMS-510849 in males. The increase in BMS-510849 exposure in females was dose-proportional.
- Systemic exposure to saxagliptin and BMS-510849 in females was 1.6 and 2.9x greater than those in male rats except at 300 mg/kg/d where exposures were similar suggesting that absorption and bioavailability were t was better in females.
- Exposure to major active metabolite, BMS-510849 was 26 to 40% of saxagliptin (BMS-477118) in males and 16 to 29% in females.
- According to the sponsor, initial HPLC methods failed to resolve BMS-510849 peak from couple of other metabolites leading to overestimation of BMS-510849 concentrations in rats by 42.7%. Exposure to BMS-510849 in humans was also

overestimated by as 6.8%. Since the exposure multiples were as much as 68 fold for BMS-510849 in rats at HD without correction, the small decrease in BMS-510849 exposure multiples in rats is unlikely to have a meaningful impact in the overall risk.

Dose [mg/kg/day]	Week	Cmax [ng/mL]				AUC(0-T) [ng·h/mL] ^a			
		BMS-477118		BMS-510849		BMS-477118		BMS-510849	
		Males	Females	Males	Female	Males	Females	Males	Females
25	26	1893	5600	550	1144	3492	8763	1174	2658
75	26	6153	24733	1523	3647	13993	30808	3843	7672
150	26	10863	60800	2187	5063	28724	81962	9204	15226
300	26	17600	92333	4563	9363	68568	179606	28569	29730

a Calculated from time zero to the time of last measurable concentration, ranging between 8 and 24 h.

Safety margins:

Species	Dose, mg/kg/d	Saxagliptin AUC, ng.h/ml	BMS-510849 AUC, ng.h/ml	Safety margins based on AUC (Animal/Human)	
				Saxagliptin	BMS-510849
104-week Rat Study,	25	M: 3492, F:8763	M:1174, F:2658	M:43, F: 108	M:3, F:6
	75	M: 13993, F:30808	M:3843, F:7672	M:173, F:380	M:9, F:18
	150	M: 28742, F: 81962	M:9204, F:15226	M: 355, F: 1012	M:21, F:35
	300	M:68568, F: 179606	M:28569, F:29730	M:847, F:2217	M:65, F:68
Clinical Dose: (BMS-510849) *	5 mg	81 438			

*Saxagliptin is metabolized in all species primarily to an active metabolite, BMS-510849. This metabolite is half as potent as parent but more selective to DPIV. The initial HPLC analysis used for AUC calculations was apparently overestimated due to inadequate peak resolution from two small metabolite, thus all the submitted AUC values for BMS-510849 in mice, rats, pregnant rabbits, dogs, Cyno monkeys and humans were overestimated by 20%, 42.7%, 11.1%, 36.2%, 15.1% and 6.8%, respectively. Therefore the safety margins for BMS-510849 are lower than the safety margin shown in the table above.

Appendix A

Macroscopic findings in mice

Incidence of Macroscopic Observations Terminal Sacrifice

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4,5
DEATH=T,SUBSET=ALL

SEX: -----MALE-----
GROUP: -1- -2- -3- -4- -5-

ORGAN AND KEYWORD(S) OR PHRASE	NUMBER	28	21	22	15	15
BRAIN (BR)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	28	21	22	15	15
SPINAL CORD (SC)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	28	21	22	15	15
KIDNEY (KD)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	11	12	16	13	13
LARGE PELVIS (ES)		8	5	2	1	0 A
ROUGH SURFACE, DIFFUSE		0	0	0	0	1
CYST(S)		15	7	5	1 B	2 A
RAISED FOCUS (I)/AREA(S)		0	1	0	0	0
MOTTLED		1	0	0	0	0
DIFFUSELY DARK		0	0	0	0	1
LIVER (LI)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	19	14	18	14	14
MASS (ES)		8	7	0 B	1	1
CYST(S)		0	0	3 A	0	0
RED FOCUS (I)/AREA(S)		1	0	0	0	0
ADHESION(S)		1	0	1	0	0
LUNG (LU)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	23	12	21	13	14
LIGHT FOCUS (I)/AREA(S)		2	4	0	0	1
MASS (ES)		2	3	1	2	0
MOTTLED		0	1	0	0	0
ADHESION(S)		1	0	0	0	0
MASS #2		0	1	0	0	0
RED FOCUS (I)/AREA(S)		0	1	0	0	0
HEART (HT)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	28	20	22	15	14
LIGHT FOCUS (I)/AREA(S)		0	1	0	0	0
ADHESION(S)		0	0	0	0	1
SPLEEN (SP)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	27	21	21	14	12
LARGE		0	0	0	1	2
ADHESION(S)		0	0	1	0	1
LIGHT FOCUS (I)/AREA(S)		0	0	1	0	0
MOTTLED		0	0	0	1	1
MASS (ES)		1	0	0	0	0
STOMACH, GL (ST)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	27	19	22	15	13
DARK FOCUS (I)/AREA(S)		1	1	0	0	0
THICKENED WALL		1	0	0	0	1
MASS (ES)		0	0	0	0	1
LIGHT FOCUS (I)/AREA(S)		0	1	0	0	0

		SEX: -----MALE-----					
		GROUP:	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	28	21	22	15	15	
STOMACH, NONGL (SU)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	28	21	22	15	14	
EROSION/ULCERATION		0	0	0	0	1	
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	28	20	21	15	15	
MASS (ES)		0	1	0	0	0	
LARGE		0	0	1	0	0	
SKIN (SK)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	27	20	21	14	15	
CRUSTED AREA(S)		1	0	1	1	0	
SUBCUTANEOUS EDEMA		0	1	0	0	0	
MASS (ES)		0	0	1	0	0	
MAMMARY, MALE (MM)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	28	21	22	15	15	
URINARY BLADDER (UB)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	21	15	17	13	11	
LARGE LUMEN		7	5	5	2	4	
SEMIFLUID MATERIAL		0	1	0	0	0	
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	11	10	7	7	7	
SMALL		0	1	0	0	0	
LARGE		17	7	14	8	8	
GELATINOUS		1	1	0	0	0	
DIFFUSELY DARK		2	2	2	1	1	
DIFFUSELY RED		1	1	1	0	0	
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	27	20	22	13	13	
LARGE		1	1	0	1	2	
MASS (ES)		0	0	0	1	0	
TAIL (TI)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	26	21	21	14	15	
CRUSTED AREA(S)		1	0	0	1	0	
RED FOCUS (I) / AREA(S)		1	0	1	0	0	
LN, ANT MES/PANC (AP)	NUMBER EXAMINED:	28	21	22	15	15	
	NOT REMARKABLE:	28	21	22	15	14	
LARGE		0	0	0	0	1	

Incidence of Macroscopic Observations
Terminal Sacrifice

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4,5;
DEATH=T;SUBSET=ALL

SEX: -----FEMALE-----

GROUP: -1- -2- -3- -4- -5-

ORGAN AND KEYWORD(S) OR PHRASE	NUMBER	13	16	20	16	15
KIDNEY (KD)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	12	15	19	14	13
DIFFUSELY LIGHT		0	0	0	0	1
CYST(S)		0	1	1	1	0
LARGE PELVIS(ES)		0	0	0	1	0
MOTTLED		0	0	0	0	1
MASS(ES)		1	0	0	0	0
LIVER (LI)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	16	17	14	14
MASS(ES)		0	0	0	0	1
LARGE		0	0	1	0	0
RED FOCUS(I)/AREA(S)		0	0	1	0	0
CYST(S)		0	0	1	2	0
LUNG (LU)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	10	12	18	14	13
MASS(ES)		2	4	1	1	1
LIGHT FOCUS(I)/AREA(S)		0	0	1	0	1
RED FOCUS(I)/AREA(S)		1	0	0	1	0
SPLEEN (SP)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	10	15	19	16	15
LARGE		2	0	1	0	0
LIGHT FOCUS(I)/AREA(S)		1	0	0	0	0
ADHESION(S)		0	1	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	16	20	16	14
MASS(ES)		0	0	0	0	1
PITUITARY (PI)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	11	16	19	16	14
MASS(ES)		2	0	1	0	1
STOMACH, GL (ST)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	16	19	16	13
DARK FOCUS(I)/AREA(S)		0	0	1	0	0
EROSION/ULCERATION		0	0	0	0	1
THICKENED WALL		0	0	0	0	1
STOMACH, NONGL (SU)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	16	20	16	14
THICKENED WALL		0	0	0	0	1

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4,5;WEEI
DEATH=T;SUBSET=ALL

SEX: -----FEMALE-----

GROUP: -1- -2- -3- -4- -5-

ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	13	16	20	16	15
SKIN (SK)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	10	16	18	16	14
SUBCUTANEOUS EDEMA		0	0	1	0	0
CRUSTED AREA(S)		1	0	1	0	1
ALOPECIA-FOCAL		2	0	0	0	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	12	16	18	16	15
MASS(ES)		1	0	2	0	0
OVARY (OV)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	3	4	6	3	6
CYST(S)		10	12	13	13	9
MASS(ES)		1	0	1	1	0
UTERUS (UT)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	2	2	6	4	2
CYST(S)		9	12	12	10	13
MASS(ES)		2	4	3	2	0
THICKENED WALL		1	0	0	2	0
CERVIX (CV)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	12	16	18	15	15
MASS(ES)		0	0	2	1	0
LARGE		1	0	0	0	0
VAGINA (VA)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	12	16	20	16	15
MASS(ES)		1	0	0	0	0

Histopath tables for male mice.

Incidence of Microscopic Observations Terminal Sacrifice

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

SEX: -----MALE-----

GROUP: -1- -2- -3- -4- -5-

ORGAN AND FINDING DESCRIPTION	NUMBER:	28	21	22	15	15
** TOP OF LIST **						
DEATH COMMENT (DC)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	0	0	0	0	0
--SCHEDULED SACRIFICE		28	21	22	15	15
MARROW, STERNUM (SE)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	26	20	21	11	9
--HYPERPLASIA, MYELOID, MARROW		0	1	1	3	2
--HYPERPLASIA, MEGAKARYOCYTIC, MARROW		2	0	0	0	3
--PIGMENT, MARROW		0	0	0	1	1
BONE, STERNUM (SB)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	28	21	22	15	14
--INFLAMMATION, VASCULAR		0	0	0	0	1
EYE (EY)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	22	19	11	4	13
--DEGENERATION, LENTICULAR		1	0	2	2	1
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE, CORNEAL		1	0	2	1	0
--INFLAMMATION, SUBACUTE		0	0	2	1	0
--MINERALIZATION, CORNEAL		1	0	2	1	0
--MINERALIZATION, IRIS		4	2	5	6	1

Incidence of Microscopic Observations
Terminal Sacrifice

TABLE INCLUDES:		SEX: -----MALE-----				
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=T; FIND=ALL; SUBSET=ALL		NUMBER: 28 21 22 15 15				
ORGAN AND FINDING DESCRIPTION	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	3	2	2	1	2
NERVE, OPTIC (ON)	NUMBER EXAMINED:	28	21	22	15	13
	NOT REMARKABLE:	3	2	2	1	2
--DEGENERATION, AXONAL		8	4	0	0	0
--ONE EXAMINED		2	0	0	0	1
--VACUOLATION, ARTIFACTUAL		18	15	20	14	11
BRAIN (BR)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	17	17	15	8	10
--B-HEMANGIOMA		0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	2	0	1
--MINERALIZATION		2	1	1	3	3
--VACUOLATION, WHITE MATTER, ARTIFACTUAL		9	4	6	6	2
KIDNEY (KD)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	0	0	0	0	0
--AMYLOID, GLOMERULAR/INTERSTITIAL		2	2	1	0	0
--B-ADENOMA, TUBULAR CELL		1	0	0	0	0
--CAST, PROTEINACEOUS		21	13	11	7	8
--DILATATION, PELVIC		8	6	2	2	1
--ECTASIA, TUBULAR		21	15	15	7	7
--HYPERPLASIA, TRANSITIONAL CELL		1	0	0	0	0
--INFARCT		0	0	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
--INFLAMMATION, VASCULAR		1	1	0	0	0
--INFLAMMATION, SUBACUTE		1	0	0	0	0
--NEPHROPATHY, CHRONIC		27	21	22	15	15
--OSSIFICATION, FOCAL/MULTIFOCAL		2	0	0	0	0
LIVER (LI)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	0	0	0	0	0
--AMYLOID		0	3	0	0	0
--B-ADENOMA, HEPATOCELLULAR		5	2	0	0	1
--B-HEMANGIOMA		0	0	1	0	0
--CYST, BILIARY		0	1	2	0	0
--FIBROSIS		0	0	1	0	0
--FOCUS, ALTERED HEPATOCELLULAR, BASOPHILIC		0	0	1	0	0
--GLYCOGEN, HEPATOCELLULAR, INCREASED		10	5	9	4	3
--HYPERPLASIA, BILE DUCT		1	0	1	0	0
--HYPERTROPHY, HEPATOCELLULAR		25	19	19	13	15
--MACROPHAGES, PIGMENT-LADEN, INCREASED		0	1	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		23	18	19	11	12
--INFLAMMATION, CHRONIC-ACTIVE		3	1	5	3	1
--M-CARCINOMA, HEPATOCELLULAR		3	3	0	0	0
--M-HEMANGIOSARCOMA		2	1	1	1	0
--MITOSIS, HEPATOCELLULAR, INCREASED		1	1	0	1	0
--NECROSIS, COAGULATIVE		2	4	3	1	0
--NECROSIS, INDIVIDUAL HEPATOCYTES/MULTIFOCAL		1	0	2	2	2
--THROMBUS		1	0	0	1	0
--VACUOLATION, HEPATOCELLULAR		1	1	0	0	0
--VACUOLATION, HEPATOCELLULAR, LIPID		0	0	6	11	0
--BARBITURATE LYSIS		0	1	0	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	28	19	22	15	14
	NOT REMARKABLE:	24	16	16	13	11
--B-PAPILLOMA		0	0	0	1	0
--CYST		0	0	3	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		4	3	4	1	2
LUNG (LU)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	10	4	9	4	4
--AMYLOID		0	1	0	0	0
--B-ADENOMA, BRONCHIOLAR-ALVEOLAR		4	4	0	0	0
--BLOOD, TERMINALLY INHALED		1	1	0	1	0
--BRONCHIECTASIS, WITH INTRALUMINAL MUCUS AND EXUDATE		2	1	1	0	1
--FIBROSIS, PLEURAL/SUBPLEURAL		2	0	1	0	1
--HYPERPLASIA, ALVEOLAR / BRONCHIOLAR		3	2	2	1	2
--INFILTRATE, LYMPHOHISTIOCYTIC		3	4	1	2	2
--INFILTRATE, MACROPHAGE, ALVEOLAR		13	11	7	10	10
--INFLAMMATION, CHRONIC-ACTIVE		2	1	4	3	4
--M-CARCINOMA, BRONCHIOLAR-ALVEOLAR		4	6	1	3	0
--N-CARCINOMA		1	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
THYROID (TY)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	20	16	17	11	9
--CYST, FOLLICULAR		4	4	2	2	4
--INFILTRATE, LYMPHOHISTIOCYTIC		3	2	3	3	4
--INFLAMMATION, VASCULAR		1	1	0	0	0
--ONE EXAMINED		1	0	0	0	0
--INFLAMMATION, ACUTE		0	0	0	0	1

Incidence of Microscopic Observations
Terminal Sacrifice

TABLE INCLUDES:		SEX: -----MALE-----				
SEX-ALL; GROUP-1, 2, 3, 4, 5; WEEKS-ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH-T; FIND-ALL; SUBSET-ALL		NUMBER: 28 21 22 15 15				
ORGAN AND FINDING DESCRIPTION	NUMBER EXAMINED:	28	21	22	15	15
HEART (HT)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	15	5	7	4	3
--AMYLOID		0	1	0	0	0
--CARDIOMYOPATHY		9	8	7	2	4
--INFILTRATE, LYMPHOHISTIOCYTIC		2	8	5	9	7
--INFLAMMATION, CHRONIC-ACTIVE		3	3	4	2	1
--INFLAMMATION, VASCULAR		1	1	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	24	21	22	15	12
--ATROPHY, MYOFIBER		0	0	0	0	1
--DEGENERATION/NECROSIS		0	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		3	0	0	0	1
SPLEEN (SP)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	0	0	9	3	6
--AMYLOID		0	1	0	0	0
--B-HEMANGIOMA		0	0	1	0	0
--DEPLETION, LYMPHOCTIC		0	0	1	0	0
--FIBROSIS, CAPSULAR		0	0	1	0	1
--HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED		28	20	12	12	9
--HYPERPLASIA, LYMPHORETICULAR		0	1	0	0	0
--N-HEMANGIOSARCOMA		0	0	0	2	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
--M-HEMANGIOSARCOMA		1	0	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	20	16	19	9	11
	NOT REMARKABLE:	10	6	10	5	3
--CYST		1	3	1	1	1
--DEPLETION, LYMPHOCTIC		6	8	8	4	6
--ECTOPIC THYROID		1	0	0	0	0
--HYPERPLASIA, LYMPHORETICULAR		1	0	1	0	2
--INFLAMMATION, VASCULAR		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
LN, MESENTERIC (MS)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	22	18	16	11	11
--AMYLOID		0	1	1	0	0
--CONGESTION		2	1	2	2	1
--DEPLETION, LYMPHOCTIC		0	1	1	1	0
--HEMORRHAGE		3	0	2	0	1
--HYPERPLASIA, LYMPHORETICULAR		0	0	1	1	1
--HYPERPLASIA, PLASMACYTIC		0	0	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	1	1	0	0
--N-HEMANGIOSARCOMA		0	0	0	2	0
--NEUTROPHILIA, SINUSOIDAL		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	10	8	4	2	8
--AMYLOID		0	1	0	0	0
--B-ADENOMA, SUBCAPSULAR CELL		0	0	0	1	0
--CYST		1	1	0	0	0
--DEGENERATION, LIPOFUSCIN, INNER CORTEX		8	8	10	10	5
--HYPERPLASIA, SPINDLE CELL		8	4	9	6	6
--INFILTRATE, LYMPHOCTIC		1	0	0	1	0
--INFILTRATE, NEUTROPHILS, FOCAL		0	0	0	1	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
--MINERALIZATION		0	0	0	3	0
--ONE EXAMINED		1	2	2	1	1
--HYPERPLASIA, CORTICAL		1	0	0	1	0
--HYPERTROPHY, CORTICAL CELL		6	0	5	7	1
--NECROSIS, COAGULATIVE		1	0	0	0	0
ADRENAL, MEDULLA (MA)	NUMBER EXAMINED:	28	20	22	15	15
	NOT REMARKABLE:	18	13	13	9	8
--DEGENERATION, LIPOFUSCIN		7	5	7	4	7
--INFILTRATE, LYMPHOHISTIOCYTIC		2	0	1	1	0
--ONE EXAMINED		3	2	1	1	1
PITUITARY (PI)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	1	0	0	0	1
--CYST		3	1	2	1	0
--PARS, INTERMEDIA		27	21	22	15	14

Incidence of Microscopic Observations
Terminal Sacrifice

TABLE INCLUDES:

SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL
DEATH=T; FIND=ALL; SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: -----MALE-----				
		GROUP: -1-	-2-	-3-	-4-	-5-
PANCREAS (PA)	NUMBER EXAMINED: 28	21	22	15	15	
	NOT REMARKABLE: 18	18	18	12	10	
--ATROPHY, ACINAR	1	0	0	0	0	0
--HYPERPLASIA, ACINAR	0	0	0	0	1	
--INFILTRATE, LYMPHOHISTIOCYTIC	5	2	4	3	4	
--INFLAMMATION, CHRONIC-ACTIVE	1	0	0	0	0	
--INFLAMMATION, VASCULAR	2	1	0	0	0	
--THROMBUS, MESENTERY	0	0	0	0	1	
--ZYMOGEN, DECREASED	1	1	0	0	0	
STOMACH, GL (ST)	NUMBER EXAMINED: 28	21	22	15	15	
	NOT REMARKABLE: 6	2	4	2	0	
--CYSTS, EPITHELIAL, SUBMUCOSA/TUNICA MUSCULARIS WITH INTRACYSTIC CELLULAR DEBRIS	1	2	0	1	1	
--ECTASIA, GASTRIC GLANDS	17	17	13	12	13	
--HYPERTROPHY / HYPERPLASIA, MUCOSAL	21	19	15	12	14	
--INFLAMMATION, CHRONIC-ACTIVE	0	1	2	2	0	
--INFLAMMATION, SUBACUTE	2	2	0	0	2	
--INFLAMMATION, VASCULAR	0	1	0	0	0	
--INFILTRATE, LYMPHOHISTIOCYTIC	0	1	4	3	3	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	0	0	0	0	
STOMACH, NONGL (SU)	NUMBER EXAMINED: 28	21	22	15	15	
	NOT REMARKABLE: 26	19	20	10	14	
--CYST, SQUAMOUS	1	0	1	1	0	
--HYPERKERATOSIS, NONGLANDULAR MUCOSA	0	2	2	5	0	
--HYPERPLASIA, SQUAMOUS, NONGLANDULAR	1	1	0	1	0	
--INFLAMMATION, CHRONIC-ACTIVE	1	0	0	0	0	
--B-PAPILLOMA, SQUAMOUS CELL	0	0	0	0	1	
--INFLAMMATION, SUBACUTE, SUBMUCOSA	0	0	0	0	1	
DUODENUM (DU)	NUMBER EXAMINED: 28	21	22	15	15	
	NOT REMARKABLE: 28	21	21	15	15	
--AMYLOID	0	0	1	0	0	
JEJUNUM (JE)	NUMBER EXAMINED: 28	21	22	15	15	
	NOT REMARKABLE: 28	20	21	15	14	
--AMYLOID	0	1	1	0	0	
--INFLAMMATION, CHRONIC-ACTIVE	0	0	0	0	1	
ILEUM (IL)	NUMBER EXAMINED: 28	21	22	15	15	
	NOT REMARKABLE: 25	19	19	15	15	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	0	0	0	0	
--AMYLOID	1	2	2	0	0	
--INFLAMMATION, SUBACUTE	1	0	1	0	0	
--NECROSIS/ULCERATION	0	0	1	0	0	
CECUM (CE)	NUMBER EXAMINED: 28	21	22	15	14	
	NOT REMARKABLE: 27	21	22	14	14	
--INFLAMMATION, CHRONIC-ACTIVE	0	0	0	1	0	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	0	0	0	0	
COLON (CO)	NUMBER EXAMINED: 28	21	22	15	14	
	NOT REMARKABLE: 28	21	22	15	14	
LN, MANDIBULAR (MN)	NUMBER EXAMINED: 27	21	22	15	15	
	NOT REMARKABLE: 22	15	17	10	10	
--HYPERPLASIA, LYMPHOPLASMATIC	0	0	1	1	0	
--HYPERPLASIA, LYMPHORETICULAR	0	0	0	0	1	
--INFLAMMATION, GRANULOMATOUS, SUBLINGUAL SALIVARY GLAND	1	0	0	0	0	
--ONE EXAMINED	3	5	4	5	4	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	0	0	0	0	
SALIV GL, MANDIB (SG)	NUMBER EXAMINED: 28	21	22	15	15	
	NOT REMARKABLE: 16	10	7	8	5	
--AMYLOID	0	1	0	0	0	
(PRESENT IN MANDIBULAR AND/OR OTHER SALIVARY GLANDS IN SECTION)						
--INFILTRATE, LYMPHOHISTIOCYTIC	11	10	15	7	10	
--INFLAMMATION, CHRONIC-ACTIVE	0	0	0	1	0	
--INFLAMMATION, VASCULAR	0	1	0	0	0	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	0	0	0	0	
--ONE EXAMINED	0	0	0	1	0	
HARDERIAN GLAND (HG)	NUMBER EXAMINED: 28	21	21	15	15	
	NOT REMARKABLE: 10	8	4	6	5	
--ATROPHY	1	0	0	0	0	
--B-ADENOMA	1	3	4	1	1	
--DEGENERATION/NECROSIS	0	0	1	0	0	
--ECTASIA, DUCTAL	13	7	9	6	4	
--HYPERPLASIA, GLANDULAR	0	0	1	1	0	
--INFILTRATE, LYMPHOHISTIOCYTIC	12	8	11	5	5	
--INFLAMMATION, CHRONIC-ACTIVE	0	0	1	1	0	
--PIGMENT, INTRADUCTAL, INCREASED	7	3	8	2	4	

Incidence of Microscopic Observations
Terminal Sacrifice

TABLE INCLUDES:		SEX: -----MALE-----				
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=T; FIND=ALL; SUBSET=ALL		-----				
ORGAN AND FINDING DESCRIPTION	NUMBER:	28	21	22	15	15
-----	-----	-----	-----	-----	-----	-----
SKIN (SK)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	27	21	20	13	12
--ACANTHOSIS/HYPERKERATOSIS		1	0	1	1	0
--COLONY, BACTERIAL		1	0	0	0	0
--EDEMA		1	0	0	1	0
--FIBROSIS		1	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	0	2
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	1	0
--INFLAMMATION, SUBACUTE		0	0	0	1	0
--INFLAMMATION, VASCULAR		0	0	0	0	1
--SUPERFICIAL CRUSTING		1	0	0	1	0
--ULCERATION		1	0	0	1	0
MAMMARY, MALE (MM)	NUMBER EXAMINED:	9	4	1	0	0
	NOT REMARKABLE:	9	4	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	1	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	27	21	21	15	15
	NOT REMARKABLE:	11	5	9	6	6
--DILATATION		7	7	6	3	6
--FIBROSIS		1	0	0	0	0
--HYPERPLASIA, TRANSITIONAL CELL		3	2	0	1	1
--HYPERTROPHY, SMOOTH MUSCLE		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		6	12	7	7	4
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	0
--INFLAMMATION, SUBACUTE		2	0	0	0	1
--PROTEINACEOUS MATERIAL, LUMINAL		0	0	2	1	0
--VACUOLATION, TRANSITIONAL EPITHELIUM		1	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	27	21	22	15	15
	NOT REMARKABLE:	12	12	9	5	10
--ATROPHY		0	0	1	0	1
--HYPERPLASIA, EPITHELIAL		0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		11	8	13	8	5
--INFLAMMATION, CHRONIC-ACTIVE		2	0	0	1	0
--INFLAMMATION, SUBACUTE		1	0	0	0	0
--INFLAMMATION, VASCULAR		1	1	0	0	0
--THROMBUS		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	1	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	6	4	6	2	4
--FIBROSIS		1	3	2	2	0
--INFILTRATE, LYMPHOHISTIOCYTIC		7	6	8	3	5
--INFLAMMATION, CHRONIC		0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		1	2	0	1	0
--INFLAMMATION, SUBACUTE		2	0	0	0	0
--INFLAMMATION, VASCULAR		1	0	0	0	0
--ONE EXAMINED		0	1	0	0	0
--SECRETION, INCREASED		18	10	16	10	10
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
TESTIS (TE)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	19	8	15	8	11
--ATROPHY / DEGENERATION, UNILATERAL		9	4	5	5	1
--ATROPHY / DEGENERATION, BILATERAL		0	5	0	1	1
--B-INTERSTITIAL CELL TUMOR		0	2	0	0	0
--ECTASIA, SEMINIFEROUS TUBULE, WITH HEMORRHAGE		0	1	0	0	0
--HYPERPLASIA, INTERSTITIAL CELL (LEYDIG CELL)		1	0	1	0	2
--MINERALIZATION		0	4	2	2	1
EPIDIDYMIS (EP)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	15	12	13	11	12
--ATROPHY		0	0	1	0	0
--GRANULOMA, SPERM		0	0	1	0	0
--HYOSPERMIA		4	4	2	1	1
--IMMATURE SPERM FORMS		5	7	5	2	1
--INFILTRATE, LYMPHOHISTIOCYTIC		5	1	2	0	2
--INFLAMMATION, CHRONIC-ACTIVE		1	2	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	28	21	22	15	15
	NOT REMARKABLE:	26	21	22	14	15
--M-LYMPHOMA		1	0	0	0	0
--M-SARCOMA, HISTIOCYTIC		1	0	0	1	0

Incidence of Microscopic Observations
Terminal Sacrifice

TABLE INCLUDES:
SEX-ALL; GROUP-1, 2, 3, 4, 5; WEEKS-ALL
DEATH-T; FIND-ALL; SUBSET-ALL

ORGAN AND FINDING DESCRIPTION	NUMBER:	SEX: -----MALE-----				
		GROUP: -1-	-2-	-3-	-4-	-5-
PINNA (PN)	NUMBER EXAMINED:	2	1	3	0	0
	NOT REMARKABLE:	0	0	0	0	0
PINNA (PN)	NUMBER EXAMINED:	2	1	3	0	0
	NOT REMARKABLE:	0	0	0	0	0
--ACANTHOSIS/HYPERKERATOSIS		2	1	3	0	0
--COLONY, BACTERIAL		1	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		2	1	1	0	0
--ULCERATION		2	1	1	0	0
--SUPERFICIAL CRUSTING		2	1	2	0	0
--MINERALIZATION, DERMAL		0	0	1	0	0
LN, AXILLARY (AX)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	1	1	1	2	2
	NOT REMARKABLE:	0	0	0	0	0
--ECTASIA, DUCTAL		1	1	0	1	2
--HYPERPLASIA		0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	1	2	1
--NECROSIS		1	0	0	0	0
LN, LUMBAR/ILIAC (LM)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
LN, OTHER (LN)	NUMBER EXAMINED:	2	0	0	0	0
	NOT REMARKABLE:	1	0	0	0	0
--N-CARCINOMA		1	0	0	0	0
URETER (UE)	NUMBER EXAMINED:	6	1	3	1	0
	NOT REMARKABLE:	0	0	0	0	0
--DILATATION		6	1	3	1	0
--ONE EXAMINED		2	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		1	0	0	0	0
--INFLAMMATION, SUBACUTE		1	0	0	0	0
LN, MEDIASTINAL (ML)	NUMBER EXAMINED:	0	0	0	0	1
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, PLASMACYTIC		0	0	0	0	1
LN, INGUINAL (IN)	NUMBER EXAMINED:	0	0	0	0	1
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, LYMPHOPLASMACYTIC		0	0	0	0	1
PENIS (PE)	NUMBER EXAMINED:	0	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	1	0	0	0
--EXUDATE, EPIDERMAL		0	1	0	0	0
LN, TRACHEOBRON (TB)	NUMBER EXAMINED:	1	0	1	0	0
	NOT REMARKABLE:	0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	0
TAIL (TI)	NUMBER EXAMINED:	2	0	1	1	0
	NOT REMARKABLE:	0	0	0	0	0
--INFLAMMATION, CHRONIC		1	0	0	0	0
--ACANTHOSIS / HYPERKERATOSIS		2	0	1	1	0
--ULCERATION		1	0	0	0	0
--INFLAMMATION, SUBACUTE, ADNEXAL/PERIADNEXAL		0	0	0	1	0
BONE, FEMUR (FE)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
COAGULATING GL (CG)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
FOOTPAD(S) (FP)	NUMBER EXAMINED:	0	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE, INVOLVING DERMIS, BONE AND JOINT		0	1	0	0	0
--ULCERATION, SKIN		0	1	0	0	0
LN, ANT MBS/PANC (AP)	NUMBER EXAMINED:	0	0	0	0	1
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, PLASMACYTIC		0	0	0	0	1

** END OF LIST **

Histopath tables for female mice (terminated at schedules week 104):

Incidence of Microscopic Observations
Terminal Sacrifice

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=T; FIND=ALL; SUBSET=ALL		NUMBER: 13 16 20 16 15				
ORGAN AND FINDING DESCRIPTION		-1-	-2-	-3-	-4-	-5-
** TOP OF LIST **						
DEATH COMMENT (DC)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--SCHEDULED SACRIFICE		13	16	20	16	15
MARROW, STERNUM (SE)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	12	16	19	14	15
--HYPERPLASIA, NYELOID, MARROW		1	0	0	1	0
--PIGMENT, INCREASED		0	0	1	1	0
BONE, STERNUM (SB)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	6	3	13	7	11
--OSTEODYSTROPHY, FIBROUS		7	13	7	9	4
--INFLAMMATION, VASCULAR		0	0	0	1	0
EYE (EY)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	9	9	13	7	5
--CYST, CORNEA		0	0	0	0	1
--DEGENERATION, LENTICULAR		1	1	1	4	2
--DEGENERATION, RETINAL		0	0	1	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC, SCLERA		0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	2
--INFLAMMATION, CHRONIC-ACTIVE, CORNEAL		0	5	2	1	3
--INFLAMMATION, SUBACUTE		1	2	0	1	2
--MINERALIZATION, CORNEA		2	3	2	1	3
--MINERALIZATION, IRIS		1	1	0	4	3
NERVE, OPTIC (ON)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	3	1	2	1	1
--ATROPHY		1	2	2	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	0	0	1
--VACUOLATION, ARTIFACTUAL		9	14	17	15	13
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	1
--DEGENERATION, AXONAL		13	15	20	16	14
--INFILTRATE, LYMPHOHISTIOCYTIC		2	1	3	2	0
BRAIN (BR)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	1	3	1	3	1
--COMPRESSION, VENTRAL		2	0	0	0	1
--I-CARCINOMA, PITUITARY		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		2	0	1	1	0
--MINERALIZATION		1	3	3	2	1
--VACUOLATION, WHITE MATTER ARTIFACTUAL		8	13	19	13	14
--MINERALIZATION, VASCULAR		0	0	1	0	0
KIDNEY (KD)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--AMYLOID, GLOMERULAR/INTERSTITIAL		2	1	3	3	0
--CAST, PROTEINACEOUS		4	4	7	2	3
--DILATATION, PELVIC		1	2	0	2	0
--ECTASIA, TUBULAR		5	8	10	7	8
--NECROSIS		0	0	0	0	1
--NEPHROPATHY, CHRONIC		13	16	20	15	15
--THROMBUS, WITH ISCHEMIC NECROSIS		0	0	0	0	1
--INFLAMMATION, VASCULAR		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	1	0
LIVER (LI)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--AMYLOID		0	0	1	2	0
--B-HEMANGIOMA		0	0	1	1	0
--CYST, BILIARY		0	0	2	2	1
--GLYCOGEN, HEPATOCELLULAR, INCREASED		5	4	7	6	2
--HYPERPLASIA, HEPATOCELLULAR, NODULAR		0	0	1	0	0
--HYPERTROPHY, HEPATOCELLULAR		9	13	17	10	14
--INFILTRATE, LYMPHOHISTIOCYTIC		12	15	15	14	13
--INFLAMMATION, CHRONIC-ACTIVE		0	3	6	2	1
--NECROSIS, COAGULATIVE, FOCAL/MULTIFOCAL		1	0	3	0	1
--NECROSIS, INDIVIDUAL HEPATOCYTES/MULTIFOCAL		1	3	3	2	1
--LEUKOCYTOSIS, SINUSOIDAL		0	0	1	0	0
--MITOSIS, HEPATOCELLULAR, INCREASED		1	1	1	1	2
--THROMBUS		0	0	1	0	0
--VACUOLATION, HEPATOCELLULAR, LIPID		8	10	6	3	10
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
--M-HEMANGIOSARCOMA		0	1	0	0	0
--M-CARCINOMA, HEPATOCELLULAR		0	0	1	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	13	16	16	16	15
	NOT REMARKABLE:	9	12	15	8	10
--B-PAPILLOMA		0	0	0	0	1
--CYST		0	1	0	3	0
--INFILTRATE, LYMPHOHISTIOCYTIC		4	3	1	5	4

Incidence of Microscopic Observations

Terminal Sacrifice

TABLE INCLUDES:
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL
DEATH=T; FIND=ALL; SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: -----FEMALE-----				
		GROUP: -1-	-2-	-3-	-4-	-5-
** TOP OF LIST **		13	16	20	16	15
DEATH COMMENT (DC)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--SCHEDULED SACRIFICE		13	16	20	16	15
MARROW, STERNUM (SE)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	12	16	19	14	15
--HYPERPLASIA, MYELOID, MARROW		1	0	0	1	0
--PIGMENT, INCREASED		0	0	1	1	0
BONE, STERNUM (SB)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	6	3	13	7	11
--OSTEODYSTROPHY, FIBROUS		7	13	7	9	4
--INFLAMMATION, VASCULAR		0	0	0	1	0
EYE (EY)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	9	9	13	7	5
--CYST, CORNEA		0	0	0	0	1
--DEGENERATION, LENTICULAR		1	1	1	4	2
--DEGENERATION, RETINAL		0	0	1	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC, SCLERA		0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	2
--INFLAMMATION, CHRONIC-ACTIVE, CORNEAL		0	5	2	1	3
--INFLAMMATION, SUBACUTE		1	2	0	1	2
--MINERALIZATION, CORNEA		2	3	2	1	3
--MINERALIZATION, IRIS		1	1	0	4	3
NERVE, OPTIC (ON)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	3	1	2	1	1
--ATROPHY		1	2	2	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	0	0	1
--VACUOLATION, ARTIFACTUAL		9	14	17	15	13
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	1
--DEGENERATION, AXONAL		13	15	20	16	14
--INFILTRATE, LYMPHOHISTIOCYTIC		2	1	3	2	0
BRAIN (BR)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	1	3	1	3	1
--COMPRESSION, VENTRAL		2	0	0	0	1
--I-CARCINOMA, PITUITARY		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		2	0	1	1	0
--MINERALIZATION		1	3	3	2	1
--VACUOLATION, WHITE MATTER ARTIFACTUAL		8	13	19	13	14
--MINERALIZATION, VASCULAR		0	0	1	0	0
KIDNEY (KD)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--AMYLOID, GLOMERULAR/INTERSTITIAL		2	1	3	3	0
--CAST, PROTEINACEOUS		4	4	7	2	3
--DILATATION, PELVIC		1	2	0	2	0
--ECTASIA, TUBULAR		5	8	10	7	8
--NECROSIS		0	0	0	0	1
--NEPHROPATHY, CHRONIC		13	16	20	15	15
--THROMBUS, WITH ISCHEMIC NECROSIS		0	0	0	0	1
--INFLAMMATION, VASCULAR		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	1	0
LIVER (LI)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--AMYLOID		0	0	1	2	0
--B-HEMANGIOMA		0	0	1	1	0
--CYST, BILIARY		0	0	2	2	1
--GLYCOGEN, HEPATOCELLULAR, INCREASED		5	4	7	6	2
--HYPERPLASIA, HEPATOCELLULAR, NODULAR		0	0	1	0	0
--HYPERTROPHY, HEPATOCELLULAR		9	13	17	10	14
--INFILTRATE, LYMPHOHISTIOCYTIC		12	15	15	14	13
--INFLAMMATION, CHRONIC-ACTIVE		0	3	6	2	1
--NECROSIS, COAGULATIVE, FOCAL/MULTIFOCAL		1	0	3	0	1
--NECROSIS, INDIVIDUAL HEPATOCYTES/MULTIFOCAL		1	3	3	2	1
--LEUKOCYTOSIS, SINUSOIDAL		0	0	1	0	0
--MITOSIS, HEPATOCELLULAR, INCREASED		1	1	1	1	2
--THROMBUS		0	0	1	0	0
--VACUOLATION, HEPATOCELLULAR, LIPID		8	10	6	3	10
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
--M-HEMANGIOSARCOMA		0	1	0	0	0
--M-CARCINOMA, HEPATOCELLULAR		0	0	1	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	13	16	16	16	15
	NOT REMARKABLE:	9	12	15	8	10
--B-PAPILLOMA		0	0	0	0	1
--CYST		0	1	0	3	0
--INFILTRATE, LYMPHOHISTIOCYTIC		4	3	1	5	4

Incidence of Microscopic Observations

Terminal Sacrifice

TABLE INCLUDES:

SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL
DEATH=T; FIND=ALL; SUBSET=ALL

SEX: -----FEMALE-----

ORGAN AND FINDING DESCRIPTION	NUMBER	GROUP: -1- -2- -3- -4- -5-				
		13	16	20	16	15
LUNG (LU)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	5	5	4	3	2
--AMYLOID		0	0	1	0	0
--B-ADENOMA, BRONCHIOLAR-ALVEOLAR		4	2	1	1	0
--BLOOD, TERMINALLY INHALED		0	0	1	0	0
--HYPERPLASIA, BRONCHIAL/BRONCHIOLAR		0	1	2	1	0
--HYPERPLASIA, LYMPHOCTIC, PERIBRONCHIOLAR/PERIVASCULAR		3	5	4	6	7
--INFILTRATE, MACROPHAGE, ALVEOLAR		5	8	10	9	10
--INFLAMMATION, CHRONIC-ACTIVE, MEDIASTINUM		1	4	6	6	7
--M-CARCINOMA		0	3	2	2	2
--MINERALIZATION, SEPTAL		0	0	1	0	0
--MINERALIZATION, SUBENDOTHELIAL, FOCAL		1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0
TRACHEA (TR)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	16	18	16	15
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	2	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0
ESOPHAGUS (ES)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	15	19	16	15
--INFLAMMATION, CHRONIC-ACTIVE, ADVENTITIA WITH INTRALESIONAL FRED MATERIAL AND BACTERIAL COLONIES		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	1	0	0
THYROID (TY)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	4	4	8	4	3
--AMYLOID		0	1	1	2	0
--B-ADENOMA, FOLLICULAR CELL		1	0	0	0	0
--CYST, FOLLICULAR		7	11	9	10	10
--ECTOPIC THYMUS		0	0	1	0	0
--INFILTRATE, LYMPHOPLASMACYTIC		2	3	3	3	4
--INFLAMMATION, CHRONIC-ACTIVE		0	1	1	0	1
--INFLAMMATION, VASCULAR		0	0	0	1	1
PARATHYROID (PT)	NUMBER EXAMINED:	10	13	16	12	13
	NOT REMARKABLE:	10	13	15	12	13
--AMYLOID		0	0	1	0	0
HEART (HT)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	7	7	5	5	5
--AMYLOID		0	0	0	1	1
--CARDIOMYOPATHY		1	0	1	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		5	6	12	7	6
--INFLAMMATION, CHRONIC-ACTIVE		1	3	3	2	4
--INFLAMMATION, VASCULAR		0	1	0	3	2
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	1	0
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	8	14	19	14	14
--DEGENERATION/NECROSIS		0	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		1	1	0	0	0
--INFLAMMATION, SUBACUTE		1	0	0	0	0
--INFLAMMATION, VASCULAR		0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC, PERIVASCULAR		3	2	1	1	1
--M-FIBROSARCOMA		1	0	0	0	0
TONGUE (TO)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	16	19	12	15
--DEGENERATION/NECROSIS		0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	1	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	0
--INFLAMMATION, VASCULAR		0	0	0	2	0
SPLEEN (SP)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	2	3	1	0	0
--AMYLOID		0	1	0	1	0
--FIBROSIS, CAPSULAR		0	1	0	0	0
--HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED		10	11	19	14	14
--HYPERPLASIA, LYMPHORETICULAR		1	0	0	0	3
--M-HEMANGIOSARCOMA		0	0	1	0	1
--PIGMENT, INCREASED		0	1	1	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	1	1	0
THYMUS (TH)	NUMBER EXAMINED:	7	16	17	14	14
	NOT REMARKABLE:	5	11	10	9	10
--CYST		0	0	0	1	1
--DEPLETION, LYMPHOCTIC		2	1	3	0	0
--ECTOPIC THYROID		0	0	1	0	0
--HEMORRHAGE		0	1	0	0	0
--HYPERPLASIA, LYMPHORETICULAR		0	2	3	3	2
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	2	1	1	1

Incidence of Microscopic Observations
Terminal Sacrifices

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX-ALL; GROUP=1, 2, 3, 4, 5; WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=T; FIND=ALL; SUBSET=ALL		NUMBER: 13 16 20 16 15				
ORGAN AND FINDING DESCRIPTION	NUMBER EXAMINED:	13	16	20	16	15
-----		---	---	---	---	---
LN, MESENTERIC (MS)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	8	10	12	7	10
--AMYLOID		1	2	1	2	0
--CONGESTION		3	3	3	2	2
--DEPLETION, LYMPHOCYTTIC		0	1	1	2	1
--HISTIOCYTOSIS, SINUSOIDAL/CORTICAL, INCREASED		1	1	1	2	2
--HYPERPLASIA, LYMPHORETICULAR		0	0	0	1	0
--INFLAMMATION, VASCULAR		0	0	0	1	1
--MASTOCYTOSIS, SINUSOIDAL		0	0	0	0	1
--NEUTROPHILIA, SINUSOIDAL		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	2	1	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--AMYLOID		0	0	2	1	0
--B-ADENOMA		0	0	0	1	0
--B-ADENOMA, SUBCAPSULAR CELL		2	1	0	0	0
--DEGENERATION, LIPOFUSCIN, INNER CORTEX		11	14	18	13	15
--HEMATOPOIESIS, EXTRAMEDULLARY		1	0	0	0	0
--HYPERPLASIA, SPINDLE CELL		9	13	18	14	13
--HYPERTROPHY, CORTICAL CELL		2	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTTIC		0	2	0	1	0
--POLYARTERITIS NODOSA, MESENTERY		0	0	1	0	0
--MINERALIZATION		3	2	3	2	2
--NECROSIS		1	0	0	0	0
--ONE EXAMINED		0	0	1	1	0
--VACUOLATION		1	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	1	0
ADRENAL, MEDULLA (MA)	NUMBER EXAMINED:	13	16	20	16	14
	NOT REMARKABLE:	8	11	11	9	9
--DEGENERATION, LIPOFUSCIN		2	3	8	6	5
--NECROSIS, COAGULATIVE, UNILATERAL, WITH MINERALIZATION		1	0	0	0	0
--ONE EXAMINED		2	2	1	3	0
AORTA (AO)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	11	15	16	13	14
--INFILTRATE, LYMPHOHISTIOCYTTIC, AORTIC ADVENTITIA		1	0	4	2	0
--INFLAMMATION, VASCULAR		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	1	0
PITUITARY (PI)	NUMBER EXAMINED:	13	16	19	15	15
	NOT REMARKABLE:	1	1	0	0	0
--B-ADENOMA		3	0	1	0	1
--CYST		0	2	2	2	1
--GRANULOMA, WITH ACICULAR CLEFTS AND MINERALIZATION		0	0	1	0	0
--HYPERPLASIA		0	1	0	1	0
--M-CARCINOMA		1	0	0	0	0
--PARS INTERMEDIA		11	15	18	15	15
PANCREAS (PA)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	8	10	13	8	6
--INFILTRATE, LYMPHOHISTIOCYTTIC		5	6	6	8	8
--ZYMOGEN, DECREASED		0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	0
--ATROPHY, ACINAR		0	0	0	1	0
--INFLAMMATION, VASCULAR		0	0	0	0	2
STOMACH, GL (ST)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	1	3	1	1	2
--AMYLOID		0	1	0	1	0
--CORPORA AMYLACEA		1	0	0	0	0
--CYST, SUBMUCOSA/TUNICA MUSCULARIS		1	0	1	2	1
--ECTASIA, GASTRIC GLANDS		10	11	16	10	12
--EROSION		0	0	0	1	0
--HYPERTROPHY/HYPERPLASIA, MUCOSAL		11	11	16	12	11
--INFILTRATE, LYMPHOHISTIOCYTTIC		1	8	6	6	6
--INFLAMMATION, CHRONIC-ACTIVE		4	1	3	4	2
--INFLAMMATION, VASCULAR		0	0	0	2	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	1	1	0
STOMACH, NONGL (SU)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	10	14	15	10	12
--HYPERKERATOSIS, NONGLANDULAR MUCOSA		3	2	4	6	3
--HYPERPLASIA, SQUAMOUS, NONGLANDULAR		0	0	1	1	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	0
--INFLAMMATION, SUBACUTE		1	0	0	0	0
DUODENUM (DU)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	12	12	18	14	15
--AMYLOID		0	3	0	2	0
--ECTASIA, INTESTINAL GLAND		1	0	1	0	0
--HYPERPLASIA, EPITHELIAL		0	1	2	0	0
--INFLAMMATION, VASCULAR		0	0	1	0	0

Incidence of Microscopic Observations

Terminal Sacrifice

TABLE INCLUDES:
SEX-ALL; GROUP-1, 2, 3, 4, 5; WEEKS-ALL
DEATH-T; FIND-ALL; SUBSET-ALL

ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: -----FEMALE-----				
		GROUP: -1-	-2-	-3-	-4-	-5-
JEJUNUM (JE)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	15	18	13	15
--AMYLOID		0	1	1	3	0
ILEUM (IL)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	10	12	15	10	13
--AMYLOID		3	4	5	5	2
--INFLAMMATION, VASCULAR		0	0	0	1	0
CECUM (CE)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	15	20	16	15
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0
COLON (CO)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	13	15	20	15	15
--INFLAMMATION, VASCULAR		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	12	16	19	16	15
	NOT REMARKABLE:	9	12	14	9	9
--HEMORRHAGE		0	1	0	0	0
--HYPERPLASIA, LYMPHOPLASMACYTIC		1	0	0	1	2
--ONE EXAMINED		1	3	4	6	4
--PIGMENT, INCREASED		1	0	1	0	0
SALIV GL, MANDIB (SG)	NUMBER EXAMINED:	13	15	20	16	15
	NOT REMARKABLE:	7	10	9	6	7
--AMYLOID		0	1	0	3	1
(PRESENT IN MANDIBULAR AND/OR OTHER SALIVARY GLANDS IN SECTION)						
--ATROPHY/DEGENERATION, SALIVARY GLAND, SUBLINGUAL		0	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		6	4	9	9	7
--INFLAMMATION, CHRONIC-ACTIVE, SUBLINGUAL		0	0	1	0	0
--SECRETORY GRANULES, DECREASED		0	1	2	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	1	0	0
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	1	4	5	4	4
--ATROPHY		0	0	1	0	0
--B-ADENOMA		1	1	1	0	1
--ECTASIA, DUCTAL		8	8	6	6	6
--HYPERPLASIA, GLANDULAR		1	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		8	9	13	11	8
--INFLAMMATION, SUBACUTE		0	0	1	0	0
--M-CARCINOMA		1	0	0	0	0
--PIGMENT, INTRADUCTAL, INCREASED		6	8	8	5	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	1	0
SKIN (SK)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	11	15	18	15	12
--ACANTHOSIS/HYPERKERATOSIS		0	0	1	0	1
--EDEMA		0	0	1	0	0
--FIBROSIS, DERMAL		0	0	0	1	0
--HAIR FOLLICLES, DECREASED		1	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	1	1	0	1
--INFLAMMATION, SUBACUTE		1	0	0	0	0
--INFLAMMATION, VASCULAR		0	0	0	0	1
--M-CARCINOMA, BASAL CELL		0	0	1	0	0
--SUPERFICIAL CRUSTING		0	0	0	0	1
--ULCERATION		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	12	16	20	11	15
	NOT REMARKABLE:	9	14	14	10	13
--ECTASIA, DUCTAL		1	0	1	0	1
--HYPERPLASIA, GLANDULAR		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		1	1	3	1	1
--INFLAMMATION, CHRONIC-ACTIVE		0	1	1	0	0
--M-CARCINOMA		1	0	1	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	3	5	11	4	7
--DILATATION		2	2	2	1	1
--HYPERPLASIA, TRANSITIONAL CELL		0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC, PERIVASCULAR		10	9	9	10	7
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	2	0	0	0
OVARY (OV)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	1	2	2	4
--AMYLOID		0	0	0	1	0
--B-LUTEOMA		1	0	0	1	0
--CYST		13	15	16	14	10
--HEMORRHAGE		3	0	2	1	2
--HYPERPLASIA, EPITHELIAL		2	0	0	1	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	3	2	1
--INFLAMMATION, VASCULAR		0	1	1	1	1
--ONE EXAMINED		0	0	2	0	0
--THROMBUS		0	1	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	1	0
--B-CYSTADENOMA		0	0	0	1	0
--ANGIECTASIS		1	0	0	0	0

Incidence of Microscopic Observations
Terminal Sacrifice

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=T;FIND=ALL;SUBSET=ALL						
ORGAN AND FINDING DESCRIPTION	NUMBER:	13	16	20	16	15
UTERUS (UT)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	1	0	0	0	0
--B-POLYP, ENDOMETRIAL, STROMAL		0	1	2	0	1
--HEMORRHAGE/NECROSIS		0	0	2	0	0
--HYPERPLASIA, CYSTIC, ENDOMETRIAL		12	16	20	16	15
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	0	0
--INFILTRATE, NEUTROPHILIC, MUCOSA		0	0	1	0	0
--INFLAMMATION, SUPERFICIAL		0	0	1	0	0
--M-SARCOMA, ENDOMETRIAL, STROMAL		1	2	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
--M-ADENOCARCINOMA		0	0	0	1	0
CERVIX (CV)	NUMBER EXAMINED:	13	16	19	15	15
	NOT REMARKABLE:	5	8	8	6	7
--B-LEIOMYOMA		0	0	1	0	0
--B-POLYP, ENDOMETRIAL STROMAL		1	0	2	1	0
--CYST, SUBMUCOSAL		0	1	0	1	0
--INFLAMMATION, SUBCUTE		1	0	0	0	0
--HYPERPLASIA, CYSTIC, ENDOMETRIAL		2	3	4	5	1
--HYPERPLASIA, MUCOSAL		0	0	0	1	0
--HYPERTROPHY, TUNICA MUSCULARIS		0	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		1	0	0	0	0
--INFILTRATE, NEUTROPHILIC, MUCOSAL		0	0	2	1	0
--INFLAMMATION, CHRONIC-ACTIVE, SEROSAL		2	1	1	1	0
--INFLAMMATION, VASCULAR		1	2	0	1	3
--MULTIPLICATION, EPITHELIAL		1	1	2	1	3
--THROMBUS		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	0	0
--HYPERPLASIA, STROMAL		1	1	1	0	0
VAGINA (VA)	NUMBER EXAMINED:	13	16	20	16	14
	NOT REMARKABLE:	12	9	10	7	9
--CYSTS, SUBMUCOSAL		0	0	0	1	0
--HYPERPLASIA, MUCOSAL		0	0	1	4	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	0	1
--INFLAMMATION, VASCULAR		0	0	0	1	0
--KERATINIZATION, MUCOSA		0	1	0	3	0
--LUMEN, EXUDATE		0	0	0	1	0
--MULTIPLICATION, EPITHELIAL		1	7	9	3	4
--THROMBUS		1	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	0
RECTUM (RE)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
NASAL TURBINATE (NT)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
LN, MEDIASTINAL (ML)	NUMBER EXAMINED:	1	2	1	2	2
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	2	0	1	1
--HYPERPLASIA, LYMPHORETICULAR		0	1	1	1	0
--THROMBUS		0	0	0	0	1
LN, RENAL (RL)	NUMBER EXAMINED:	2	0	0	0	1
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	0	0	0	0
--HYPERPLASIA, LYMPHORETICULAR		0	0	0	0	1
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	9	14	19	15	14
--M-LYMPHOMA		1	2	1	1	1
--M-SARCOMA, HISTIOCYTIC		3	0	0	0	0
LN, INGUINAL (IN)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
PINNA (PN)	NUMBER EXAMINED:	0	0	2	1	2
	NOT REMARKABLE:	0	0	0	0	0
--ACANTHOSIS/HYPERKERATOSIS		0	0	2	1	2
--INFLAMMATION, CHRONIC-ACTIVE		0	0	2	1	2
--SUPERFICIAL CRUSTING		0	0	2	1	2
--ULCERATION		0	0	2	1	2
--NECROSIS, DISTAL		0	0	0	1	0
LN, LUMBAR/ILIAC (LM)	NUMBER EXAMINED:	1	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
--HYPERPLASIA, LYMPHORETICULAR		0	1	0	0	0
LN, ANT MES/PANC (AP)	NUMBER EXAMINED:	1	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
--CYST		0	1	0	0	0
TAIL (TI)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0

Incidence of Microscopic Observations

Terminal Sacrifice

TABLE INCLUDES:
SEX=ALL; GROUP=1, 2, 3, 4, 5; WEEKS=ALL
DEATH=T; FIND=ALL; SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: -----FEMALE-----				
		GROUP: -1-	-2-	-3-	-4-	-5-
LN, TRACHEOBRON (TB)	NUMBER EXAMINED:	13	16	20	16	15
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, LYMPHORETICULAR		1	0	1	0	0
MESENTERY (MY)	NUMBER EXAMINED:	1	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
--CYST		0	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	1	0	0	0
--THROMBUS		1	0	0	0	0
BONE, OTHER (BO)	NUMBER EXAMINED:	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:	0	0	1	0	0
	NOT REMARKABLE:	0	0	0	0	0
--M-RHABDOMYOSARCOMA		0	0	1	0	0

** END OF LIST **