1). After the 2-day expression period, cultures were selected for cloning based on their SG. After 10- 12 day incubation period, number of colonies/TFT and VC plates were determined and mutant frequency and induced mutant frequency calculated.

Analysis:

No. slides/plates/replicates/animals analyzed: replicates

Counting method: potentiometers were set so that all colonies were counted and then potentiometer setting adjusted so that 15 size groups were established for each plate.

Cytotoxic endpoints: relative cloning efficiency

Genetic toxicity endpoints/results: mutant frequency

Statistical methods:

Criteria for positive results: A response was considered positive if at least one culture had an mutant frequency (MF) that was 2 times or more greater than the average MF of the corresponding solvent control cultures and the response was dose dependent.

Criteria for a negative response: response considered negative if all of the cultures exhibiting total growth of culture (TG) of 20% and greater had MFs that were less than twice that of the mean MF of the corresponding control cultures and there was no evidence of a dose-dependent response.

Results: In the range finding test, concentrations of 10000 and 5000 ug/ml with activation had precipitate.

In the non-activated system, the relative suspension growth (RSG) for test article concentration ranging from — ug/ml ranged from 17% to 109%. Respective values for the activated system with concentrations ranging from —— ug/ml ranged from 0- 104%.

Table 50

	Without activation		With activation		Positive control			
	DMSO Solvent control	PPI-149 289-1446 ug/ml	DMSO solvent control	PPI-149 58-231 ug/ml	DMSO solvent control	HVC 5 and 10 ug/ml	Acetone Sovent control	DMBA 5 and 7.5 ug/ml
Av. mutant frequency (MF)/10^6	85 & 93	44 – 86	74 & 74	58-122	76 & 90	445 & 529	77 & 75	271 & NA
Coloning efficiency %	131 & 107	89 – 112	118 & 126	85 - 118	124 & 98	26 & 25	127 & 134	92 & NA
Relative total growth		13 – 103%		14 – 109%		5 & 7%		26%

Study validity: seems valid

Study outcome: The responses for cultures treated in the absence and presence of S-9 were negative. Mutant frequencies were less than 2 fold the mean MF of the corresponding solvent controls. The positive controls produced significantly positive responses with and without exogenous metabolic activation. Solvent controls were within the laboratory's historic control range.

Sponsor has presented graphs of the results of the colony sizing for cultures treated with the positive and solvent controls and stated that distribution for the cultures treated with positive controls HYC and DMBA exhibited acceptable positive responses and colony sizes. Graphs showed that pattern of colonies shifted to smaller sizes. Sponsor however, did not expand on the results. No data was presented for the drug treated cultures.

Conclusion: PPI-149-Depot was not genotoxic in the mouse lymphoma mutagenesis assay

Study title: **In vivo test for chemical induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells.**
Study No: ——— study 0482-1521
Study type: in vivo mutagenesis assay
Amendment #, volume # and page #: vol.27 p.172
Conducting laboratory: ———————
Date of study initiation/completion: 5-22-1998/10-2-1998 Revised final report 10-18-2000
GLP compliance: yes
QA- Reports Yes (*) No ( ):
Drug Lot number:030298g2 and 030498g2
Study endpoint: induction of micronucleated polychromatic erythrocytes

Methodology:
Strain/species/cell line: male and female mice/CD-1
Dose selection criteria: maximum recommended dose of 2000 mg/kg
Basis of dose selection: maximum recommended dose
Range finding studies: no
Test agent stability:
Metabolic activation system: NA
Controls:
Vehicle: saline
Negative controls: saline
Positive controls: cyclophosphamide, 80 mg/kg (8 mg/ml X 10ml/kg) oral
Exposure conditions:
Incubation and sampling time: bone marrow sampling time 24, 48 and 72 hour post dosing
Doses used in definitive study: Single SC 2000 mg/kg injection
Study design: Mice were placed into treatment groups of 5 mice/s. Five such groups (one per harvest time) were designated for PPI-149 dose level of 2000 mg/kg and the vehicle control. One group was designated for the positive control. Animals were treated with a single dose on Day 1, and sacrificed on Days 2, 3,4, 8 and 15. Mice treated with CP were sacrificed 24 hours after treatment. Blood was collected for PPI-149 concentration analysis, hematology and serum chemistry. The same mice used for plasma sampling were used for the preparation of bone marrow slides.
Analysis:
No. slides/plates/replicates/animals analyzed:
Counting method: Bone marrow slides were scored for number of polychromatic erythrocytes (PCE) and total erythrocytes (PCE +NCE) for each animal by counting 200 erythrocytes. The number of micronucleated polychromatic erythrocytes then was scored for 2000 PCE per animal.
Cytotoxic endpoints: micronucleated polychromatic erythrocytes
Genetic toxicity endpoints/results: a significant decrease in PCE
Statistical methods: Student's t-test

Criteria for positive results: Response was considered positive if PPI-149 showed a statistically significant increase in the number of MPCE at dose level for each harvest time over that of he concurrent vehicle control.

Results: The ranges of the mean number of MPCE in 2000 PCE are given in table below:
Table 51

Treatment	Mean numbers of MPCE in 2000 PCE in males				
	Day 2	Day 3	Day 4	Day 8	Day 15
Vehicle control (saline)	0.2	0.0	0.0	0.2	0.4
PPI-149 2000 mg/kg	0.0	0.2	0.0	0.4	0.0
Positive control CP	61.0*	N/A	N/A	N/A	N/A
Mean number of MPCE in2000 PCE in females					
Vehicle control (saline)	0.6	0.4	0.4	0.2	0.2
PPI-149 2000 mg/kg	0.6	0.4	0.2	0.0	0.0
Positive control CP	59.8*	N/A	N/A	N/A	N/A

The percent of PCE in vehicle and PPI-149 group at all harvest time ranged from 42 to 55 except on Day 3 when percent of PCE was significantly reduced (30.9%) at dose of 2000 mg/kg in male mice. According to OECD guidelines, a reduction more than 20% of vehicle in the number of PCE among total erythrocytes is used as an indication of toxicity. Sponsor suggested that since the percentage of the vehicle on Day 3 was 55% and higher than results of the other 4 days, the reduction might be due to variation of the vehicle values.
Sponsor however, ignored the fact that vehicle percentage was also 55 on Day 2 for the female mice and there was no reduction in the treated group. Also on Day 4 for male mice the reduction was 11.1% and on Day 8, reduction in PCE for female mice was 15.7%, suggesting that treatment might have toxic effects.

Study validity: Study as conducted seems valid
Study outcome: PPI-149-Depot was not genotoxic in the mouse micronucleus assay.

SPECIAL TOXICOLOGY STUDIES: none

OVERALL SUMMARY AND EVALUATION:

Introduction: Suppression of testosterone production by either medical or surgical means has proved beneficial in the management of prostate cancer.
One class of agents, the leutinizing hormone-relcasing (LHRH) superagonists, is considered to act by initially stimulating the pituitary LHRH receptor leading to an increased production of androgens, followed by subsequent desensitization of the receptor and eventual suppression of androgen production. The LHRH superagonists leuprolide acetate (Lupron Depot by TAP Pharmaceuticals) and goserelin acetate (Zoladex by AstrZeneca Pharmaceuticals) are widely and effectively used for the palliative treatment of prostate cancer. However, as a consequence of the agonist's mechanism of action, the onset of efficacy due to suppression of testosterone to castrate levels may be delayed for several weeks. Furthermore, the initial stimulation of the LHRH receptor may cause hormonal surge that has been associated with an exacerbation of prostate

cancer and accompanying severe adverse effects such as increased bone pain, urinary retention, and spinal cord compression.
Abarelix is a GnRH (LHRH) antagonist that achieves the goal of androgen suppression by preventing the binding of GnRH to gonadotrophic receptors, thereby inhibiting the secretion of LH and FSH.

Safety Pharmacology: Abarelix Depot increased sleeping time in mice, although there was no dose-response relationship. In rats, except for increased spontaneous activity, abarelix had no neurotoxic, psychotropic or neurobehavioral effects or effect on body temperature. The reference compound, Haloperidol induced typical depressant CNS effects with a decrease in body temperature.

Subcutaneous administration of abarelix in conscious normotensive rat at doses of up to 300 mg/kg had no effect on BP, heart rate, or ECG parameters.

In anesthetized dog, abarelix at a single IV dose of 10 mg/kg, induced a decrease in cardiac contractility, in arterial blood pressure and in vascular peripheral resistance and an increase in mean pulmonary artery pressure. Changes in these parameters of low magnitude were also seen at the 1 mg/kg dose level. These effects were marked and led in 1/5 dogs to a cardiac failure in the 10 mg/kg dose group. It was reported that cardiac output, regional blood flow, stroke volume and heart rate were not significantly affected. ECG was not affected. Plasma K was significantly greater in the 10 mg/kg group at 120 and 180 minutes post dosing.

In the monkey, SC doses of up to 25 mg/kg had no adverse effect on mean arterial pressure, heart rate and body temperature.

Based on the results of a study on the effect of abarelix on the action potential of piglet purkinje fibers, it was reported that abarelix at doses of 0.01 to 10 uM had no effect on resting potential, action potential amplitude, maximum rate of depolarization and on the duration of action potential. However, at a dose of 30 uM, it induced a shortening of the action potential and a reduction of the maximum rate of depolarization.

Serious adverse effects were reported in monkeys in a study where 1 mg/kg of labeled abarelix dose was used via IV, SC and IM route in the same 3 monkeys in a cross over design. 2/3 monkeys following IV dosing exhibited a transient lethargy characterized by a limp demeanor and limp tail. The third monkey began to appear lethargic 2 minutes after doing and within 15 minutes began to recover and appeared normal. However, after the 40 minute blood collection, the animal once again exhibited lethargy and became limp and slow with rapid heart rate and breathing. The animal appeared exhausted and tired and for all appearances was asleep. The monkey was treated with Lactated Ringer's solution and within minutes its condition improved, and it became alert and responsive. This animal exhibited similar lethargy after IM dosing but of much less severity. No noteworthy adverse effects were seen after SC administration. Sponsor attributed these effects to the use of tri-fluoroacetate salt of drug product, which was acidic. These adverse effects were dependent on the extent and speed of drug exposure (most pronounced after IV administration, less severe after IM administration and nonexistent after subcutaneous administration). As such it should have no significant clinical relevance.

A single SC administration of abarelix depot in unrestrained conscious guinea pigs, showed that a dose of 30 mg/kg had no significant effect on respiratory parameters. At doses of 100 and 300 mg/kg there was a transient increase in peak expiratory flow and minute volume indicating a respiratory stimulation, an increase in airway resistance and/or a decrease in pulmonary compliance. Codeine on the other hand induced a decrease in inspiratory flow, tidal volume and minute volume and an increase in inspiratory time, findings stated to be consistent with respiratory depression.

The effect of SC administration of abarelix on renal parameters was determined in rats. A dose of 300 mg/kg decreased urine pH and increased sp. gravity in female rats, increased the amount of protein in both sexes and decreased urine Na and increased urine K concentrations.
Abarelix was compared to Antide (a GnRH antagonist) for its ability to release histamine from rat peritoneal mast cells. At equal concentrations of 293 uM, abarelix and Antide stimulated the release of 1.3% and 1.7% of total cellular histamine, respectively. The positive control, PPTAA-LHRH, caused complete release of cellular histamine at 8.2 uM. This compares to the plasma concentration of 34 nM (48 ng/ml) of abarelix in humans given a therapeutic dose.

Histamine release in response to abarelix administered SC was also evaluated in monkeys in two 28-day studies. In the first study, abarelix was administered via osmotic pump at doses of 0, 30, 100 and 300 ug/kg/day while in the second study abarelix was injected SC twice a day with total doses of 0, 100, 1000 and 5000 ug/kg/day. These doses gave plasma abarelix levels in the first study about 10 fold higher than plasma levels reported in humans with a therapeutic dose based on C_{max}. In the second study the high dose of 5000 ug/kg/day gave 80 fold higher plasma levels based either on C_{max} or AUC. Before abarelix administration and at various time intervals during the 28 day study, systemic histamine levels were determined. Results of the first study which were submitted only in graphic form demonstrate that the high dose of abarelix increased histamine release approximately 2-3 fold compared to the control group, although the results were variable and the sponsor stated that the difference was not significant. In this same study, a SC injection of 0.2 mg/kg Lupron on day 29 after removal of osmotic pumps had no effect on histamine release. In the second study using 5 monkeys/sex per group, no treatment-related increase in histamine was observed when compared either to baseline values or to the control group at any time during the course of the 28 day study. To the best of my knowledge histamine release in response to various GnRH antagonists has been determined only in vitro using peritoneal mast cells. Since this is the first time that the histamine releasing activity of a GnRH antagonist has been investigated in vivo, there are no data to compare histamine releasing activity of abarelix to the approved GnRH antagonists, Citrorelix and Ganirelix.

Although the results of the two studies seem contradictory, the positive results from the first study may be an artifact of the use of an osmotic pump and the use of only 3 monkeys per group. The control pump alone caused essentially a doubling of histamine release while the high dose elevated histamine by about 3 fold (the high dose group had a higher baseline histamine level than the control group). Other explanations for the apparent difference between the two studies include a burst of abarelix from the pump on implantation resulting in a very high drug concentration or a different response to a continuous release of abarelix from the pump vs two injections/day.

Based on the negative results with the rat peritoneal mast cells, and the results of the two monkey studies, abarelix is inactive or only very slightly active as a releaser of histamine and should not pose more of a safety risk for histamine release than other approved GnRH antagonists.

In a 12-month safety study in dogs, abarelix doses up to 3.6 mg/kg/28 days had no significant effect on hematology and blood chemistry. The testes and prostate glands of all dogs allowed 3 or 6-month recovery period were of normal size and had normal spermatozoa development and progression. Although no histological changes were observed in the pituitary glands after 3 or 6 months treatment, minimal hyperplasia was reported in 2/3 and 3/3 dogs after 9 and 12 months of treatment.

Local tolerance of a single IM or SC dose of PPI-149-Depot was determined in rabbits. Results showed that the incidence and severity of granulomatous inflammation were slightly greater for the PPI-149-depot at both IM and SC sites, and inflammation was observed for a longer time period with PPI-149-depot than with Lupron.

ADME:

In monkeys SC doses of 30, 100 and 300 ug/kg/day administered by [redacted] osmotic pumps showed increased plasma abarelix concentrations with increasing dose, but had great within group variation. The 100 ug/kg/day dose induced a complete pharmacological castration and complete blockade of testosterone surge response to the depot formulation of Lupron (HTD is 50 ug/kg/day).

In another study, monkeys were given an implant designed to deliver 50 or 100 ug/kg/day and another implant on day 29 after removal of the first implant, which was designed to deliver 5 or 15 ug/kg/day. Mean plasma abarelix concentrations ranged from 20-52, 10 to 25, 1.8 to 8.9 and 0.8 to 3.5 ng/ml for implants with intended rates of release of 100, 50, 15 and 5 ug/kg/day. 5 ug/kg/day dose was ineffective and at 15 ug/kg/day, there was escape in testosterone suppression in 2/3 monkeys. Thus suppression of testosterone by a regimen of initial constant exposure to abarelix at high levels followed by constant exposure at levels several folds lower was ineffective.

In rats PPI-149 administered by SC route at dose levels of 260, 877 or 4390 ug/kg, showed dose proportionality with increasing dose levels for AUC and Cmax. The higher V_d with a 4390 ug/kg IM dose was attributed to a decreased elimination rate after IM administration. The duration of testosterone suppression was also dose-related. With all dose levels during the recovery phase, concentrations exceeded control levels. Similar dose-proportional increase was observed in rats after a single IM dose of abarelix depot.

When monkeys were administered abarelix via IV, IM or SC routes as a single 1 mg/kg dose, abarelix given IV was cleared rapidly with terminal T1/2 of 0.17 days.
The bioavailability after IM and SC dosing was 87 and 78% respectively. Serum radioactivity was mostly composed of abarelix and with minor amount of metabolite M-1. Majority of radioactivity was excreted in the feces. The major route of abarelix clearance were urinary excretion of unchanged abarelix and hepato-biliary elimination of abarelix and its hydrolytic

metabolites. The metabolites observed were M-1 (hepta-peptide), M-2 (penta-peptide), M-3 (nona-peptide) and M-4 (hexa-peptide).

The % of administered dose recovered in urine and feces after IV, IM and SC administration was 20.0 and 81.3, 17.8 and 69.5, and 17.3 and 71.3%, respectively.

In rats after a single IV and SC administration, urinary and fecal excretion were the major pathways for elimination and most of the administered dose was recovered equally in the urine and feces within the first 24 hours. In addition to abarelix, biliary radioactivity was composed of M-1 and M-3. In contrast urinary radioactivity was primarily composed of unchanged abarelix. Total recovery was about 90% with no differences in males and females.

Evaluation of abarelix metabolism after in vitro exposure to isolated rat, monkey and human hepatocyte suspensions, showed that human and monkey hepatocytes are capable of metabolizing abarelix. Although rat hepatocytes did not form metabolites M-1 and M-3, these were reported to be major components of the rat and monkey excreta.

Protein binding: Plasma protein binding of abarelix was shown to be independent of abarelix concentration in the range from 0.2 to 1.0 ug/ml in rat, monkey and human plasma. The average fraction bound across all species was about 98%. Therapeutic plasma concentration range was reported to be 48.6 +/- 13.7 ng/ml.

Toxicokinetics: Toxicokinetics of PPI-149-Depot was carried out in mice, rats and monkeys after SC administration. In mice the PPI-149-depot dose level was 30, 100, 300 and 1000 mg/kg, in rats 10, 30 and 100 mg/kg and in monkeys 5, 15 or 40 mg/kg. Systemic exposure expressed as multiples of AUC observed with human therapeutic dose for the high dose for male and female mice was 68 and 48 times, for the rats 51 and 43 times and for the monkeys 47 and 22 times, respectively.

Toxicology with PPI-149-Depot

28-day continuous SC toxicity in rats and monkeys, 13-week repeat dose SC toxicity in mice, 6-month SC toxicity in rats and 12-month chronic toxicity in monkeys, abarelix did not show any consistent, dose-dependent, across species adverse effects. Almost all clinical observations, macroscopic and microscopic findings were associated with depot administration site and reproductive system in both males and females. In the 12-month monkey study, significant alterations in ST-T appeared in 1/3 high dose female and 1/3 high dose males at terminal examination before 4 month and 13 month sacrifice, respectively. Sponsor indicated that these changes can be consistent with ventricular myocardial hypoxia/injury and suggested that it may be of neither physiological nor toxicological significance because of its infrequent occurrence.

Reproductive toxicology:

Results of the SC fertility and general reproductive toxicity studies in male and female rats with doses up to 10 mg/kg, demonstrated that fertility was returned after cessation of treatment.

In the development toxicity study in female rats at doses up to 2 mg/kg, SC abarelix proved to be highly embryolethal but not teratogenic. There was however, a significantly increased incidence of litters with incomplete ossified pelvis in the high dose group. The number of litters with fetuses having extra metacarpals was significantly increased in the 1 and 2 mg/kg dose groups.

In the SC development toxicity study in rabbits, 0.01 to 30 mg/kg abarelix reduced embryo-fetal viability with significant increases in fetal resorptions and an increased number of does with all conceptuses resorbed at doses of 0.01 mg/kg and higher, as compared to control group values. Although the average number of litters with fetuses with any alterations and average % of fetuses with any alteration did not differ significantly among the treated groups, a few malformations and variations observed occurred in the drug treated groups with no dose-response relationship. These included 1/179 (0.56%), 2/118 (1.69%) and 1/28 (3.57%) fetuses in control, 0.03 mg/kg and 0.3 mg/kg dose groups, respectively. Since no malformations were reported in the 0.1 and 1 mg/kg dose groups, the effect was not dose-related.

Genetic toxicology:

PPI-149 was not genotoxic in the in-vitro Ames/Salmonella typhimurium/Escherichia coli reverse mutation assay, in the mouse lymphoma mutagenesis assay or in the in-vivo mouse micronucleus test.

Safety Evaluation: Except for cardiovascular effects in dogs after an IV dose of 10 mg/kg and in monkeys after an IV dose of 1 mg/kg, no other significant, consistent, dose-related effects were observed across species. The severity of the cardiovascular findings was much less when abarelix was given IM and there were no effects when administered SC. The adverse effect thus seems to be due to bolus IV administration, a situation that is not expected to occur in clinical use.

The histamine release from mast cells, was negligible and was similar to Antide. No comparison was made with approved GnRH antagonists or superagonists. Also SC administration of abarelix in monkeys did not show any histamine releasing potential.

No hepatotoxicity was reported in the SC 6-month rat and in the 12-month monkey toxicity studies. Also review of the histopathology tables for the 2-year mouse and rat carcinogenicity studies did not reveal any treatment-related liver damage. However, in the 28 day continuous SC toxicity in monkeys where doses of 100, 1000 or 4650 ug/kg/day were administered via a catheter, significant changes in certain enzymes in abarelix-treated compared to controls were reported.
These included increases in GGT in low and high dose males on Day 7, elevated creatine kinase and sorbitol dehydrogenase in high dose males and females on Day 29. Serum transaminases were not increased with treatment in either sex and no histological damage was reported.

Clinical Relevance of Safety Issues: It is Pharmacology opinion that CV findings will not be applicable in clinical use of PPI-149-Depot. Also histamine-releasing activity of PPI-149-Depot was negligible in the routine assay conducted with mast cells and after SC administration in monkeys.

Other Clinically Relevant Issues: The rat and mouse carcinogenicity study data was received on 3-30-2001 and 4-20-2001, respectively and as such has not been reviewed and evaluated. Sponsor's provided summary however, indicates that no abnormal findings were observed in either study. Also these studies are still to be evaluated by Division of Biometrics.

Conclusions: Baring any unexpected findings in the mouse and rat carcinogenicity studies, there are no concerns for the use of PPI-149-Depot based on preclinical toxicology, pharmacokinetic and toxicokinetic studies in various animal species.

Communication Review:

- **Labeling Review** (NDA):

  Animal toxicology: Significant cardiovasular effects were reported in dogs and monkeys with IV administration of abarelix. In dogs 10 mg/kg abarelix intravenous dose induced a decrease in cardiac contractility, in arterial blood pressure and in vascular peripheral resistance and an increase in pulmonary artery pressure. Similar changes of lower magnitude were observed with a dose of 1 mg/kg. These effects were marked and led in 1/5 dogs to cardiac failure.
  In monkeys an intravenous dose of 1 mg/kg caused lethargy in 3/3 monkeys. In one monkey heart rate and breathing were rapid and animal had to be treated with Lactated Ringer's solution to recover. This animal exhibited similar transient lethargy after IM dosing but of much less severity. No noteworthy clinical signs were reported for animals following SC dosing. However, 1/3 monkeys had PK profile similar to that of IV dose animals suggesting part of the SC dose was inadvertently injected IV.

  In the 12-month chronic subcutaneous toxicity in monkeys, electrocardiographic changes were observed but ECG tracings were not submitted. Following statement was made by the consulting veterinarian:

  "All ECGs showed sinus rhythms or sinus tachycardias. There were frequent alterations in configurations of component deflections and in orientations of QRS and ST-T vectors when comparing baseline to pre-post mortem recordings, but these appeared just as frequently in monkeys serving as vehicle controls. It appeared that heart rates accelerated in many of the monkeys post-dosing, and apparently significant alterations in ST-T appeared in monkeys 407 and 422 just before post mortem examination. These changes are consistent with ventricular myocardial hypoxia/injury, particularly since they appeared in 2 monkeys receiving the highest dose of compound; however, they occurred so infrequently that they may be of neither physiological nor toxicological significance".

- **Carcinogenesis, Mutagenesis, Impairment of Fertility**
-
- Two-year rat and mouse carcinogenicity studies have not been reviewed.
-
- PPI-149 Depot was negative in the in-vitro Bacterial mutation assay (Salmonella and E.Coli), in the mouse lymphoma mutagenesis assay and in the in-vivo mouse micronucleus test.
-
- Single SC administration of PPI-149-Depot at dose level of 10 mg/kg (1.14 times the HTD on BSA basis) to female rats 14 days prior to co-habitation, resulted in infertility which was reversed by post-dosage day 154.
-
- In male rats, a single SC administration of 10 mg/kg PPI-149-Depot at a dose of 10 mg/kg 7 days before first cohabitation significantly reduced mating and fertility which, was returned to normal by post-dosage day 119.

Pregnancy Category X
Labeling recommendations will be communicated to sponsor.
(see **CONTRAINDICATIONS**) The following should go under contraindications.

-
- Development toxicity studies were conducted in female rats and rabbits.
-
- In female rats dose levels of PPI-149-Depot were 0.3, 1.0 and 2.0 mg/kg, which are equivalent to 0.03, 0.1, 0.2 times the human therapeutic dose of 100 mg/kg/70 kg person on body surface area basis, were administered as a single SC injection on Day 7 of gestation. Embryo-fetal viability was reduced in the 1 and 2 mg/kg dose groups but no malformations were reported.
-
- In female rabbits doses of 0.01 to 30 mg/kg which represent 0.002 to 7 times the human dose on body surface area were administered as a single SC injection on gestation day 7. Embryo-fetal viability was reduced. Significant increases in the means for resorptions and increased number of does with all conceptuses resorbed at doses of 0.01 mg/kg and higher were reported.
- Fetal malformations were reported in 1/179 controls (0.56%, short tail and fused and misaligned caudal vertebrae), 2/118 in the 0.03 mg/kg dose group (1.69%, one with umbilical hernia and another with small head, microphthalmia and hydrocephalus), and 1/28 in the 0.3 mg/kg dose group (3.57%, short tail and absent hind limb and pelvis). Since no malformations were reported in the 0.1 and 1 mg/kg dose groups, the drug-induced adverse effect was not dose-related.
-

RECOMMENDATIONS: Based on review of the pre-clinical data submitted, Pharmacology recommends approval of PPI-149-Depot for the palliative treatment of prostate cancer.

Internal comments:
External Recommendations (to sponsor):

Future development or NDA issues:

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

Reviewer: Krishan l. Raheja

Team leader: Alex Jordan

cc:

Original NDA: 21-320
HFD-580
HFD-580/A.Jordan/S. Monroe/J.Best
N21-320.000

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/s/

Krishan L. Raheja
6/11/01 09:27:47 AM
PHARMACOLOGIST

Alexander W. Jordan
6/11/01 10:09:31 AM
PHARMACOLOGIST

Statistical Review - Carcinogenicity Studies

NDA: 21320 Date: **August 6, 2003**

Applicant: Praecis Pharmaceuticals Incorporated

Name of Drug: Plenaxis™

Documents Reviewed: Original NDA volumes 1 and C11.1, dated March 30, 2001.

Reviewing Pharmacologist: Krishan Raheja, Ph.D.

Reviewing Statistician: Wen-Jen Chen, Ph.D.

I. Background

In this NDA submission two-year carcinogenicity studies in two rodent species, one in CD-1 mice and one in Sprague-Dawley rats, were included. These two studies were intended to assess the carcinogenic potential associated with subcutaneous exposure to PPI-149 Depot in CD-1 mice and Sprague-Dawley rats for at least 104 weeks.

II. Study Design

The designs of the carcinogenicity studies were similar with primary differences arising in the dose levels and rodent species. The current review evaluates and presents results separately for each species.

i.) Study in Mice (Study 081-001)

Studies were conducted in both males and females over a 104-week period. For each sex, four hundred and twenty CD-1 mice with ages seven to eight weeks old were randomly divided into six groups of 70 animals each to form three treated groups, two negative control groups and one positive control group (castrated/ovariectomized animals). A group of castrated/ovariectomized mice were also evaluated because the pharmacologic effect of the test material is similar to surgical castration or ovariectomy. The dose levels were 0, 0, 0, 30, 100, and 300 mg/kg, respectively for the two negative and the positive control groups, low, medium, and high treated groups. Non fasted mice were dosed subcutaneously in the dorsal thorax with the test or control material once every 28 days for a minimum of 104 weeks. The castrated or ovariectomized animals were treated for a minimum of 100 weeks.

An ophthalmological examination by a board-certified veterinary ophthatmologist was performed on ten mice/sex/group prior to necropsy. Mortality checks were performed twice daily and clinical

observations were done weekly. Palpation for tumors began after 26 weeks of treatment. Hematology evaluations were done on the first ten mice/sex/group during Weeks 26, 52, 78,and at necropsy.

ii.) Study in Rats (Study 081-002)

Studies were conducted in both males and females over a 104-week period. For each sex, four hundred and twenty CD-1 mice with ages seven weeks old were randomly divided into six groups of 70 animals each to form three treated groups, two negative control groups and one positive control group (castrated/ovariectomized animals). A group of castrated/ovariectomized rats were also evaluated because the pharmacologic effect of the test material is similar to surgical castration or ovariectomy. The dose levels were 0, 0, 0, 10, 30, and 100 mg/kg, respectively for the two negative and the positive control groups, low, medium, and high treated groups. Non fasted rats were dosed subcutaneously in the dorsal thorax with the test or control material once every 28 days (last dose during Week 97 or 101). The castrated or ovariectomized animals were also treated with saline on the same schedule.

An ophthalmological examination by a board-certified veterinary ophthatmologist was performed on ten mice/sex/group prior to necropsy. Mortality checks were performed twice daily and clinical observations were done weekly. Palpation for tumors began after 26 weeks of treatment. Hematology evaluations were done on the first ten rats/sex/group during Weeks 26, 52, 78,and prior to scheduled necropsy.

III. Statistical Analysis Methods

This reviewer conducted an independent analysis on the carcinogenicity data submitted by the sponsor. The analysis conformed to the Food and Drug Administration's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May, 2001). In addition, this reviewer's analysis was primarily conducted using eReview of Animal Carcinogenicity, a review tool developed for and utilized by CDER reviewers.

The initial interest was focused on the mortality data. Tests for homogeneity and dose-mortality trends were conducted via the Cox test (Cox, 1972; Thomas, Breslow, and Gart, 1977) and the Kruskal-Wallis test (Gehan, 1965; Breslow, 1970, Thomas, Breslow, and Gart, 1977) where the latter test weights early failures more heavily. The subsequent interest was focused on the analysis of tumor data. The sponsor classified tumors as fatal or incidental, and the data of these two tumor types were analyzed via the prevalence and death-rate methods (Peto et al, 1980), respectively. A combined test was utilized to analyze the data of a tumor classified as both fatal and incidental. In addition, an exact permutation test was utilized to correct the underestimation of p-values commonly when the number of tumor bearing animals occurred across treatment groups is small. In addition, the scores used in the reviewer's tumor trend analyses were zero (0) for the three control groups and ordinal scores 1, 2, and 3 for the low, medium, and high dose groups. The time intervals used were 0 - 52, 53 - 78, 79-92, 93-104 weeks, and terminal sacrifice. All tests were performed separately for males and females in both species.

Multiplicity was addressed employing a decision rule proposed in the guidance. Specifically, positive trends in incidence rates of rare and common tumors were tested at the 0.025 and 0.005 levels of significance, respectively. However, for pair-wise comparisons, the rare and common tumors were tested at the 0.05 and 0.01 levels of significance, respectively. Rare and common tumors were defined based on the tumor rate in the concurrent control groups. If the tumor rate in the concurrent control group was less than or equal to 1%, the tumor was classified as rare. Otherwise, the tumor was classified as common.

Lastly to further validate results, this reviewer evaluated the number of animals at risk in relation to the adequacy of exposure. Per the guidance document, "a 50% survival rate of the 50 initial animals in any treatment group between weeks 80-90 of a two year study may be considered as a sufficient number and adequate exposure".

IV. Analysis Results and Discussion

i.) Study in Mice (Study 081-001)

Mortality data analysis

At the termination of drug administration, the percent mortalities in males were 64, 63, 60, 56, 46, and 51% respectively for the two negative and the positive control groups with zero doses and three treated groups with dose levels 30, 100, 300 mg/kg/day. Similarly, the percent mortalities in females at the termination of drug administration were 56, 66, 63, 44, 40, and 51% for the respectively ascending dose groups (ie., 0, 0, 0, 30, 100, and 300 mg/kg/day). Table 1 presents the mortality results for both sexes.

The homogeneity of the survival distributions and the dose-mortality trend for the six treatment groups (two negative and one positive control groups, low, medium, and high treated groups) were tested separately for male and female mice using the Cox test and the Generalized Wilcoxon/Kruskal-Wallis test. Results of the tests were presented in Table 2. Additional investigations of the mortalities among dose groups were conducted via Kaplan-Meier product limit survival curves. Results of the investigations were depicted in Figure 1.

Only for females, tests yielded a significant dose-mortality trend for the six survival curves ($p= 0.02$) at 0.05 level, indicating that mortality rates in the six treatment groups were increasing/decreasing as dose levels increased. However, from Table 1 and Figure 1, one further noted that for females, the survival rates/curves for the three control groups were distinguishably lower than those of the three treated groups while the survival rates/curves for the three treated groups were comparable.

Finally, the pair-wise tests showed that the mortality rates for the two negative control groups were not significantly different for both sexes ($p > 0.2$). In addition, the mortality rate of the positive control group was also not significantly different from that of the pooled negative control group.

Tumor incidence rates analysis

Since the mortality rates for the two negative control groups were not significantly different, in the tumor trend analysis, tumor data for the two negative control groups were pooled together. Thus, in the performance of the tumor trend analysis, four treatment groups with the following dose levels were involved: zero (pooled negative-control), 30, 100,and 300 mg/kg/day. In addition, since mice in the positive control group were castrated for males and ovariectomized for females, they were considered different from those in the negative controls and were analyzed separately from the negative control group in the tumor trend analysis. As a consequence, for tumor trend analysis, two sets of tumor data analyses were performed: set 1) Crl1+Cntr2 (pooled negative control), low, medium, and high dose groups and set 2) Positive control, low, medium, and high dose groups.

Table 3 and Table 4 presented the results of the tumor trend analysis respectively for male and female mice using both tumor data set 1 (pooled negative control) and set 2 (positive control). The results indicated that on the basis of the Division's p-value adjustment rule, only for males, evidence suggested a significantly positive trend in the incidence of Lymphoma, Malignant in the Lymphoreticular System was detected using the pooled negative control data set (asymptotic adjusted p-value = 0.0042). This tumor was classified as common; therefore, conclusions were formulated using a 0.005 significance level. However, the pair-wise analysis showed that the difference in tumor incidence rate between the pooled negative control group and the high dose group for tumor type Lymphoreticular System/Lymphoma, Malignant was not significant on the basis of the Division's p-value adjustment rule for pair-wise comparisons.

Except the significant trend in the tumor type Lymphoreticular System/Lymphoma, Malignant in male mice, the reviewer's results are in general in agreement with those of the sponsor's tumor data analysis.

To further validate study results, this reviewer revisited the Kaplan-Meier survival curves to investigate the proportion of the surviving animals at the beginning of Week 90. For the three treated groups, more than 50% of the male and female animals were alive at the desired time interval. This suggests a sufficient number of animals with adequate exposure to the studied compound.

ii.) Study in rats (Study 081-002)

Mortality data analysis

At the termination of drug administration, the percent mortalities in males were 39, 54, 24, 21, 24, and 23% respectively for the two negative and the positive control groups with zero doses and the three treated groups with dose levels 10, 30, 100 mg/kg/day. Similarly, the percent mortalities in females at the termination of drug administration were 76, 69, 36, 10, 16, and 19% for the respectively ascending dose groups (ie., 0, 0, 0, 10, 30, and 100 mg/kg/day). Table 5 presented the mortality results for both sexes.

The homogeneity of the survival distributions and the dose-mortality trend for the six treatment

groups (two negative and one positive control groups, low, medium, and high treated groups) were tested separately for male and female rats using the Cox test and the Generalized Wilcoxon/Kruskal-Wallis test. Results of the tests were presented in Table 6. Additional investigations of the mortalities among dose groups were conducted via Kaplan-Meier product limit survival curves. Results of the investigations were depicted in Figure2.

For males and females, tests showed that both departure from trends and dose-mortality trends for the six survival curves were highly statistically significant at 0.05 level ($p < 0.01$ for both sexes). However, from Table 5 and Figure 2, one noted that for both sexes, the survival rates/curves for the three control groups were distinguishably lower than those of the three treated groups while the survival rates/curves for the three treated groups were comparable.

Finally, the pair-wise tests showed that for males, the mortality rates for the two negative control groups were significantly different ($p < 0.05$). For females, the mortality rates for the two negative control groups were not significantly different ($p > 0.30$) while the mortality rate of the positive control group was highly significantly different from that of the pooled negative control group ($p < 0.001$).

Tumor incidence rates analysis

For female rats, since the mortality rates for the two negative control groups were not significantly different, tumor data for the two negative control groups were pooled together in the tumor trend analysis as the reviewer did in the mouse study. Thus, for female rats, as the logic stated in the mouse study, the two sets of tumor data analysis were performed in the tumor trend analysis: set 1) Crl1+Cntr2 (pooled negative control), low, medium, and high dose groups and set 2) Positive control, low, medium, and high dose groups. However, for male rats, the mortality rates for the two negative control groups were significantly different. Thus, for tumor trend analysis in males, in addition to performing the above two sets of analysis, this reviewer also performed the following two sets of analysis: set 3) Cntr1 (negative control 1), low, medium, and high dose groups and set 4) Cntr2 (negative control 2), low, medium, and high dose groups. Table 7 and Table 8 presented the results of the tumor trend analysis respectively for males and females.

The results from Tables 7 and 8 showed that for females and males, there was no evidence to suggest the presence of any positive dose-tumor trends. The results are in general in agreement with those of the sponsor's tumor data analysis.

To further validate study results, this reviewer revisited the Kaplan-Meier survival curves to investigate the proportion of the surviving animals at the beginning of Week 90. For the three treated groups, more than 50% of the male and female animals were alive at the desired time interval. This suggests a sufficient number of animals with adequate exposure to the studied compound.

V. Summary

1.) Study in Mice (Study 081-001)

For the mortality data analysis, only for females, tests yielded a significant dose-mortality trend for the six survival curves (p=0.02) at 0.05 level. This indicates that mortality rates in the six treatment groups are increasing/decreasing as dose levels increased. However, from Table 1 and Figure 1, one further noted that for females, the survival rates/curves for the three control groups were distinguishably lower than those of the three treated groups while the survival rates/curves for the three treated groups were comparable. In addition, the pair-wise tests showed that the mortality rates for the two negative control groups were not significantly different for both sexes ($p > 0.2$). Likewise, for both sexes, the mortality rate of the positive control group was not significantly different from that of the pooled negative control group.

For tumor incidence rate analysis, on the basis of the p-value adjustment rule developed by Division of Biometrics, only for males, a significant positive trend in the incidence of Lymphoma, Malignant in the Lymphoreticular System was detected using pooled negative control data set (asymptotic adjusted p-value = 0.0042).

Except the finding of the significant trend in the tumor type Lymphoreticular System/Lymphoma, Malignant in male mice, the reviewer's results are in general in agreement with those of the sponsor's tumor data analysis.

Finally, for the three treated groups, more than 50% of the male and female animals were alive at the desired time interval (at the beginning of Week 90). This suggests a sufficient number of animals with adequate exposure to the studied compound.

2.) Study in rats (Study 081-002)

For the mortality data analysis, in males and females, tests showed that both departure from trends and dose-mortality trends for the six survival curves were highly statistically significant at 0.05 level ($p < 0.01$ for both sexes). However, from Table 5 and Figure 2, one noted that for both sexes, the survival rates/curves for the three control groups were distinguishably lower than those of the three treated groups while the survival rates/curves for the three treated groups were comparable. In addition, the pair-wise tests showed that for males, the mortality rates for the two negative control groups were significantly different ($p < 0.05$). For females, the mortality rates for the two negative control groups were not significantly different ($p > 0.30$) while the mortality rate of the positive control group was highly significantly different from that of the pooled negative control group ($p < 0.001$).

For tumor incidence rate analysis, on the basis of the p-value adjustment rule developed by Division of Biometrics, for males and females, there was no evidence to suggest the presence of any positive dose-tumor trends in the tumor types tested. This reviewer's results are in general in agreement with those of the sponsor's tumor data analysis.

Finally, for the three treated groups, more than 50% of the male and female animals were alive at the desired time interval (at the beginning of Week 90). This suggests a sufficient number of animals with adequate exposure to the studied compound.

Table 1. Analysis Results for Mortality Behavior in Mouse Study

Male

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	70	9	61	87.1	12.9
	53-78	61	15	46	65.7	34.3
	79-91	46	14	32	45.7	54.3
	92-103	32	7	25	35.7	64.3
	Terminal sacrifice	25	25	0		
CTR2	0-52	70	4	66	94.3	5.7
	53-78	66	11	55	78.6	21.4
	79-91	55	15	40	57.1	42.9
	92-103	40	14	26	37.1	62.9
	Terminal sacrifice	26	26	0		
LOW	0-52	70	6	64	91.4	8.6
	53-78	64	10	54	77.1	22.9
	79-91	54	10	44	62.9	37.1
	92-103	44	13	31	44.3	55.7
	Terminal sacrifice	31	31	0		
MED	0-52	70	7	63	90.0	10.0
	53-78	63	9	54	77.1	22.9
	79-91	54	9	45	64.3	35.7
	92-103	45	7	38	54.3	45.7
	Terminal sacrifice	38	37	1		
HIGH	0-52	70	6	64	91.4	8.6
	53-78	64	18	46	65.7	34.3
	79-91	46	6	40	57.1	42.9
	92-103	40	6	34	48.6	51.4
	Terminal sacrifice	34	34	0		
CTR0	0-52	70	6	64	91.4	8.6
	53-78	64	14	50	71.4	28.6
	79-91	50	13	37	52.9	47.1
	92-103	37	9	28	40.0	60.0
	Terminal sacrifice	28	28	0		

Female

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	70	4	66	94.3	5.7
	53-78	66	11	55	78.6	21.4
	79-91	55	16	39	55.7	44.3
	92-103	39	8	31	44.3	55.7
	Terminal sacrifice	31	31	0		
CTR2	0-52	70	10	60	85.7	14.3
	53-78	60	8	52	74.3	25.7
	79-91	52	10	42	60.0	40.0
	92-103	42	18	24	34.3	65.7
	Terminal sacrifice	24	23	1		
LOW	0-52	70	9	61	87.1	12.9
	53-78	61	5	56	80.0	20.0
	79-91	56	10	46	65.7	34.3
	92-103	46	7	39	55.7	44.3
	Terminal sacrifice	39	39	0		
MED	0-52	70	7	63	90.0	10.0
	53-78	63	4	59	84.3	15.7
	79-91	59	7	52	74.3	25.7
	92-103	52	10	42	60.0	40.0
	Terminal sacrifice	42	42	0		
HIGH	0-52	70	7	63	90.0	10.0
	53-78	63	10	53	75.7	24.3
	79-91	53	10	43	61.4	38.6
	92-103	43	9	34	48.6	51.4
	Terminal sacrifice	34	34	0		
CTR0	0-52	70	5	65	92.9	7.1
	53-78	65	25	40	57.1	42.9
	79-91	40	4	36	51.4	48.6
	92-103	36	10	26	37.1	62.9
	Terminal sacrifice	26	25	1		

Note: CTR1, CTR2, CTR0, LOW, MED, and HIGH respectively stand for the two negative and one positive control groups with zero doses and three treated groups with dose levels 30, 100, 300 mg/kg/day.

Table 2 Analysis of Homogeneity and Dose-Mortality Trend in Mouse Study
(as adapted from results produced by eReview)

Male

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	2.8922	0.5760	4.0312	0.4018
Dose-Mortality Trend	2.8923	0.0890	1.4073	0.2355
Homogeneity	5.7845	0.3278	5.4385	0.3647

Female

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	8.9190	0.0632	8.5294	0.0740
Dose-Mortality Trend	5.4469	0.0196	4.0793	0.0434
Homogeneity	14.3658	0.0134	12.6088	0.0273

Table 3: Report on Tumor Trend Test for Male Mice

Pooled negative control group (Tumor data set 1)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1010	ADRENAL GLANDS	1070	adenoma, cortical	6	0	0	0	1.0000	0.5860	1
1010	ADRENAL GLANDS	1450	pheochromocytoma	1	6	1	2	0.0948	0.0823	2 *
1050	BRAIN	1130	astrocytoma	1	0	0	0	1.0000	0.8896	3
1110	HARDERIAN GLAND	1010	adenocarcinoma	1	0	0	0	1.0000	0.8794	4
1110	HARDERIAN GLAND	1040	adenoma	12	7	2	7	0.4694	0.4941	5 *
1160	ILEUM	1010	adenocarcinoma	1	0	0	0	1.0000	0.8825	6
1200	KIDNEYS	1260	hemangiosarcoma	0	0	1	0	0.3846	0.4123	7 *
1220	LIVER	1090	adenoma, hepatocellular	22	7	9	1	0.9996	0.9993	8 *
1220	LIVER	1180	carcinoma, hepatocellular	4	2	1	0	0.8967	0.8986	9 *
1220	LIVER	1200	cholangiocarcinoma	0	0	1	0	0.3900	0.4120	10 *
1220	LIVER	1210	cholangioma	0	0	0	1	0.2857	0.1723	11 *
1220	LIVER	1250	hemangioma	2	1	0	1	0.6062	0.6334	12 *
1220	LIVER	1260	hemangiosarcoma	15	6	4	4	0.8737	0.8736	13 *
1230	LUNG	1060	adenoma, alveolar/bronchiolar	16	7	11	12	0.0721	0.0710	14 *
1230	LUNG	1160	carcinoma, alveolar/bronchiolar	9	4	1	1	0.9514	0.9474	15 *
1260	MUSCLE, SKELETAL	1250	hemangioma	0	0	0	1	0.3953	0.1864	16 *
1290	PANCREAS	1100	adenoma, islet-cell	2	0	1	0	0.7256	0.7700	17 *
1300	PITUITARY	1040	adenoma	12	0	1	2	0.2713	0.2715	18 *
1340	SPLEEN	1260	hemangiosarcoma	1	1	0	3	0.0796	0.0746	19 *
1360	STOMACH	1140	carcinoid	1	0	0	1	0.4533	0.4142	20 *
1360	STOMACH	1430	osteosarcoma, extra-osseous	1	0	0	0	1.0000	0.8916	21
1390	THYROID	1150	carcinoma, C-cell	1	0	0	0	1.0000	0.8773	22
1395	PARATHYROID	1040	adenoma	1	0	0	0	1.0000	0.8767	23
2110	PROSTATE	1400	osteogenic sarcoma, extra-osse	1	0	0	0	1.0000	0.9257	24
2130	TESTES	1540	tumor, interstitial-cell	48	0	0	0	1.0000	0.9683	25
3012	LYMPH NODE, MESENTERIC	1250	hemangioma	1	0	0	0	1.0000	0.8837	26
8020	EPIDIDYMIDES	1520	tumor, granular-cell	1	0	0	0	1.0000	0.8586	27
8040	SKIN, OTHER	1260	hemangiosarcoma	0	0	2	2	0.1374	0.1145	28 *
8040	SKIN, OTHER	1300	lipoma	0	0	2	0	0.4583	0.3935	29 *
8040	SKIN, OTHER	1350	malignant fibrous histiocytoma	2	0	2	0	0.7500	0.7472	30 *
8040	SKIN, OTHER	1430	osteosarcoma, extra-osseous	0	2	0	0	0.4000	0.5497	31 *
8040	SKIN (OTHER)	1440	papilloma	0	2	0	0	0.6250	0.7442	32 *
9998	LYMPH NODE, MESENTERIC	1250	hemangioma	1	0	0	0	1.0000	0.8996	33
9998	LYMPHORETICULAR SYSTEM	1290	leukemia, myelogenous	2	1	0	0	0.6778	0.5013	34 *
9998	LYMPHORETICULAR SYSTEM	1330	lymphoma, malignant	7	3	7	11	0.0050	0.0042 √	35 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).

CTR0, LOW, MED, and HIGH respectively stand for the pooled negative control group with zero dose and three treated groups with dose levels 30, 100, 300 mg/kg/day.

The check mark √ indicates statistically significant test results, based on the decision rule of FDA.CDER.Divisions of Biometrics.

Table 3: Report on Tumor Trend Test for Male Mice (Continued)

Positive control group (Tumor data set 2)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1010	ADRENAL GLANDS	1070	adenoma, cortical	24	0	0	0	1.0000	1.0000	1
1010	ADRENAL GLANDS	1450	pheochromocytoma	1	0	1	2	0.2907	0.2827	2 *
1110	HARDERIAN GLAND	1040	adenoma	7	7	2	7	0.7020	0.7028	3 *
1170	DUODENUM	1010	adenocarcinoma	1	0	0	0	1.0000	0.9522	4
1190	JEJUNUM	1010	adenocarcinoma	1	0	0	0	1.0000	0.9434	5
1200	KIDNEYS	1260	hemangiosarcoma	0	0	1	0	0.5147	0.5247	6 *
1220	LIVER	1090	adenoma, hepatocellular	8	7	3	1	0.8812	0.8825	7 *
1220	LIVER	1180	carcinoma, hepatocellular	1	2	1	0	0.8117	0.8243	8 *
1220	LIVER	1200	cholangiocarcinoma	0	0	1	0	0.5065	0.5173	9 *
1220	LIVER	1210	cholangioma	0	0	0	1	0.3600	0.2391	10 *
1220	LIVER	1250	hemangioma	1	1	0	1	0.5804	0.5939	11 *
1220	LIVER	1260	hemangiosarcoma	3	6	4	4	0.5091	0.5090	12 *
1230	LUNG	1060	adenoma, alveolar/bronchiolar	14	7	11	12	0.6612	0.6615	13 *
1230	LUNG	1160	carcinoma, alveolar/bronchiola	4	4	1	1	0.9448	0.9451	14 *
1260	MUSCLE, SKELETAL	1250	hemangioma	0	0	0	1	0.5397	0.2799	15 *
1290	PANCREAS	1100	adenoma, islet-cell	1	0	1	0	0.7166	0.7605	16 *
1300	PITUITARY	1020	adenocarcinoma	1	0	0	0	1.0000	0.9753	17
1300	PITUITARY	1040	adenoma	1	0	1	2	0.2237	0.2187	18 *
1340	SPLEEN	1260	hemangiosarcoma	2	1	0	5	0.4108	0.4079	19 *
1360	STOMACH	1140	carcinoid	0	0	0	1	0.4776	0.2632	20 *
1390	THYROID	1080	adenoma, follicular	2	0	0	0	1.0000	0.9709	21
6040	SKIN, OTHER	1250	hemangioma	2	0	0	0	1.0000	0.9567	22
6040	SKIN, OTHER	1260	hemangiosarcoma	0	0	2	2	0.1612	0.1382	23 *
6040	SKIN, OTHER	1300	lipoma	0	0	2	0	0.5000	0.4320	24 *
6040	SKIN, OTHER	1350	malignant fibrous histiocytoma	0	0	2	0	0.5000	0.4591	25 *
6040	SKIN, OTHER	1430	osteosarcoma, extra-osseous	0	2	0	0	0.5000	0.6185	26 *
6040	SKIN, OTHER	1440	papilloma	2	2	0	0	0.8807	0.9127	27 *
9998	LYMPHORETICULAR SYSTEM	1290	leukemia, myelogenous	0	1	0	0	0.6605	0.7686	28 *
9998	LYMPHORETICULAR SYSTEM	1330	lymphoma, malignant	9	3	7	11	0.2129	0.2121	29 *
9998	LYMPHORETICULAR SYSTEM	1340	lymphoma, thymic	1	0	0	0	1.0000	0.9395	30
9998	LYMPHORETICULAR SYSTEM	1490	sarcoma, histiocytic	1	1	2	2	0.2945	0.2909	31 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).

CTR0, LOW, MED, and HIGH respectively stand for the positive control group with zero dose and three treated groups with dose levels 30, 100, 300 mg/kg/day.

Table 4: Report on Tumor Trend Test for Female Mice

Pooled negative control group (Tumor data set 1)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1010	ADRENAL GLANDS	1070	adenoma, cortical	1	0	0	1	0.6107	0.4665	1 *
1010	ADRENAL GLANDS	1170	carcinoma, cortical	2	0	0	1	0.7181	0.6441	2 *
1010	ADRENAL GLANDS	1450	pheochromocytoma	1	0	0	1	0.6107	0.4665	3 *
1110	HARDERIAN GLAND	1010	adenocarcinoma	0	0	0	1	0.3365	0.1606	4 *
1110	HARDERIAN GLAND	1040	adenoma	5	2	3	5	0.1287	0.1260	5 *
1130	INJECTION SITE	1440	papilloma	0	0	0	1	0.1800	0.1024	6 *
1150	COLON	1030	adenocarcinoma, mucinous	1	0	0	0	1.0000	0.8688	7
1170	DUODENUM	1010	adenocarcinoma	1	0	0	0	1.0000	0.8756	8
1190	JEJUNUM	1010	adenocarcinoma	0	0	0	1	0.3820	0.1837	9 *
1220	LIVER	1090	adenoma, hepatocellular	3	1	2	3	0.2641	0.2616	10 *
1220	LIVER	1180	carcinoma, hepatocellular	1	0	2	0	0.4493	0.5216	11 *
1220	LIVER	1260	hemangiosarcoma	4	3	2	1	0.6871	0.6984	12 *
1230	LUNG	1060	adenoma, alveolar/bronchiolar	16	8	6	6	0.7018	0.7048	13 *
1230	LUNG	1160	carcinoma, alveolar/bronchiola	6	2	4	1	0.7163	0.7235	14 *
1250	MAMMARY GLAND	1010	adenocarcinoma	4	1	0	0	0.9911	0.9834	15 *
1290	PANCREAS	1100	adenoma, islet-cell	0	1	0	0	0.4468	0.6504	16 *
1300	PITUITARY	1010	adenocarcinoma	1	0	0	0	1.0000	0.9011	17
1300	PITUITARY	1040	adenoma	9	1	1	0	0.9998	0.9992	18 *
1340	SPLEEN	1250	hemangioma	2	0	0	0	1.0000	0.9393	19
1340	SPLEEN	1260	hemangiosarcoma	0	1	3	4	0.0083	0.0077	20 *
1360	STOMACH	1190	carcinoma, squamous-cell	0	0	0	1	0.1887	0.1034	21 *
1390	THYROID	1050	adenoma, C-cell	1	0	0	0	1.0000	0.9022	22
2010	CERVIX/VAGINA	1270	leiomyoma	1	1	0	0	0.8423	0.8764	23 *
2010	CERVIX/VAGINA	1460	polyp(s)	5	0	0	1	0.9423	0.9358	24 *
2020	OVARIES	1040	adenoma	2	0	0	0	1.0000	0.9379	25
2020	OVARIES	1110	adenoma, papillary	4	4	0	0	0.9844	0.9797	26 *
2020	OVARIES	1120	adenoma, tubulo-stromal	1	1	1	0	0.7713	0.7802	27 *
2020	OVARIES	1240	granulosa/theca-cell tumor	2	0	0	0	1.0000	0.9774	28
2020	OVARIES	1250	hemangioma	3	1	0	0	0.9719	0.9617	29 *
2020	OVARIES	1260	hemangiosarcoma	1	0	0	1	0.5049	0.5049	30 *
2020	OVARIES	1280	leiomyosarcoma	1	0	0	0	1.0000	0.9490	31
2020	OVARIES	1320	luteoma	1	0	0	0	1.0000	0.9011	32
2020	OVARIES	1440	papilloma	0	1	0	0	0.6826	0.7708	33 *
2020	OVARIES	1500	Sertoli-cell tumor	0	0	1	0	0.4491	0.4394	34 *
2020	OVARIES	1510	thecoma	1	0	0	0	1.0000	0.9007	35
2020	OVARIES	1530	tumor, granulosa-cell	0	0	1	0	0.4491	0.4394	36 *
2050	OVIDUCT(S)	1040	adenoma	2	0	0	0	1.0000	0.9775	37
2040	UTERUS	1020	adenocarcinoma, endometrial	2	0	0	0	1.0000	0.9770	38
2040	UTERUS	1250	hemangioma	3	0	0	0	1.0000	0.9810	39
2040	UTERUS	1260	hemangiosarcoma	1	0	0	0	1.0000	0.9268	40
2040	UTERUS	1270	leiomyoma	5	0	0	0	0.9976	0.9934	41 *
2040	UTERUS	1280	leiomyosarcoma	3	1	0	0	0.9904	0.9849	42 *
2040	UTERUS	1470	polyp, stromal	14	6	0	0	1.0000	0.9999	43
3011	LYMPH NODE, MANDIBULAR	1360	mastocytoma	0	0	1	0	0.5000	0.4331	44 *
3012	LYMPH NODE, MESENTERIC	1250	hemangioma	1	1	0	0	0.7101	0.8328	45 *
8040	SKIN, OTHER	1230	fibrosarcoma	0	0	0	2	0.3200	0.2487	46 *
8040	SKIN (OTHER)	1250	hemangioma	0	0	2	0	0.6000	0.6859	47 *
8040	SKIN, OTHER	1260	hemangiosarcoma	0	2	0	0	0.8667	0.9268	48 *
8040	SKIN, OTHER	1310	liposarcoma	2	0	0	0	1.0000	0.8763	49
8040	SKIN, OTHER	1370	melanoma, amelanotic	0	0	0	2	0.4000	0.3141	50 *
8040	SKIN, OTHER	1380	myxosarcoma	0	0	2	0	0.6000	0.6859	51 *
8040	SKIN (OTHER)	1420	osteosarcoma (primary undeterm	0	0	2	0	0.6429	0.5625	52 *
8998	LYMPH NODE, MESENTERIC	1250	hemangioma	1	1	0	0	0.7743	0.8568	53 *
9998	LYMPHORETICULAR SYSTEM	1330	lymphoma, malignant	29	16	17	13	0.4784	0.4825	54 *
9998	LYMPHORETICULAR SYSTEM	1340	lymphoma, thymic	1	0	1	0	0.6409	0.6797	55 *
9998	LYMPH NODE, MANDIBULAR	1360	mastocytoma	0	0	1	0	0.4144	0.4231	56 *
9998	LYMPHORETICULAR SYSTEM	1490	sarcoma, histiocytic	7	6	3	3	0.6205	0.6272	57 *

Note: The symbol "*" indicates that the p-values fall in (0, 1). CTRO: Pooled negative control group.
CTR0, LOW, MED, and HIGH respectively stand for the pooled negative control group with zero dose and three treated groups with dose levels 30, 100, 300 mg/kg/day.

Table 4: Report on Tumor Trend Test for Female Mice (Continued)

Positive control group (Tumor data set 2)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1010	ADRENAL GLANDS	1070	adenoma, cortical	41	0	0	1	1.0000	1.0000	1
1010	ADRENAL GLANDS	1170	carcinoma, cortical	2	0	0	1	0.8824	0.8410	2 *
1010	ADRENAL GLANDS	1450	pheochromocytoma	1	0	0	1	0.6826	0.6424	3 *
1050	BRAIN	1130	astrocytoma	1	0	0	0	1.0000	0.9335	4
1110	HARDERIAN GLAND	1010	adenocarcinoma	0	0	0	1	0.5072	0.2806	5 *
1110	HARDERIAN GLAND	1040	adenoma	8	2	3	5	0.8325	0.8339	6 *
1130	INJECTION SITE	1260	hemangiosarcoma	1	0	0	0	1.0000	0.9786	7
1130	INJECTION SITE	1440	papilloma	0	0	0	1	0.2647	0.1893	8 *
1140	CECUM	1030	adenocarcinoma, mucinous	1	0	0	0	1.0000	0.9449	9
1190	JEJUNUM	1010	adenocarcinoma	0	0	0	1	0.5574	0.3006	10 *
1220	LIVER	1090	adenoma, hepatocellular	1	1	2	3	0.3218	0.3110	11 *
1220	LIVER	1180	carcinoma, hepatocellular	2	0	2	0	0.8709	0.8857	12 *
1220	LIVER	1210	cholangioma	1	0	0	0	1.0000	0.9812	13
1220	LIVER	1260	hemangiosarcoma	2	3	2	1	0.8543	0.8586	14 *
1230	LUNG	1060	adenoma, alveolar/bronchiolar	13	8	6	6	0.9880	0.9878	15 *
1230	LUNG	1160	carcinoma, alveolar/bronchiola	5	2	4	1	0.9587	0.9602	16 *
1250	MAMMARY GLAND	1010	adenocarcinoma	0	1	0	0	0.8214	0.8565	17 *
1290	PANCREAS	1100	adenoma, islet-cell	2	1	0	0	0.9661	0.9729	18 *
1300	PITUITARY	1040	adenoma	2	1	1	0	0.9696	0.9687	19 *
1340	SPLEEN	1250	hemangioma	1	0	0	0	1.0000	0.9488	20
1340	SPLEEN	1260	hemangiosarcoma	1	1	3	4	0.1617	0.1593	21 *
1360	STOMACH	1190	carcinoma, squamous-cell	0	0	0	1	0.3226	0.2344	22 *
1360	STOMACH	1480	sarcoma, NOS	1	0	0	0	1.0000	0.9396	23
2010	CERVIX/VAGINA	1270	leiomyoma	0	1	0	0	0.8214	0.8565	24 *
2010	CERVIX/VAGINA	1460	polyp(s)	0	0	0	1	0.2273	0.1120	25 *
2020	OVARIES	1110	adenoma, papillary	0	4	0	0	1.0000	0.9963	26
2020	OVARIES	1120	adenoma, tubulo-stromal	0	1	1	0	0.8850	0.8942	27 *
2020	OVARIES	1250	hemangioma	0	1	0	0	1.0000	0.9660	28
2020	OVARIES	1260	hemangiosarcoma	0	0	0	1	0.3125	0.2601	29 *
2020	OVARIES	1440	papilloma	0	1	0	0	1.0000	0.9660	30
2020	OVARIES	1500	Sertoli-cell tumor	0	0	1	0	0.6579	0.7137	31 *
2020	OVARIES	1530	tumor, granulosa-cell	0	0	1	0	0.6579	0.7137	32 *
2040	UTERUS	1270	leiomyoma	0	1	0	0	0.8214	0.8565	33 *
2040	UTERUS	1280	leiomyosarcoma	0	1	0	0	0.8214	0.8565	34 *
2040	UTERUS	1470	polyp, stromal	1	6	0	0	0.9804	0.9799	35 *
3011	LYMPH NODE, MANDIBULAR	1360	mastocytoma	0	0	1	0	0.7143	0.6409	36 *
3012	LYMPH NODE, MESENTERIC	1250	hemangioma	0	1	0	0	0.6429	0.8019	37 *
8040	SKIN, OTHER	1230	fibrosarcoma	0	0	0	2	0.3200	0.2487	38 *
8040	SKIN, OTHER	1250	hemangioma	0	0	2	0	0.6875	0.6321	39 *
8040	SKIN, OTHER	1260	hemangiosarcoma	0	2	0	0	0.8125	0.8921	40 *
8040	SKIN, OTHER	1370	melanoma, amelanotic	0	0	0	2	0.3750	0.2869	41 *
8040	SKIN, OTHER	1380	myxosarcoma	0	0	2	0	0.6875	0.6321	42 *
8040	SKIN, OTHER	1420	osteosarcoma (primary undeterm	0	0	2	0	0.6429	0.5625	43 *
9998	LYMPH NODE, MESENTERIC	1250	hemangioma	0	1	0	0	0.6988	0.8176	44 *
9998	LYMPHORETICULAR SYSTEM	1330	lymphoma, malignant	8	16	17	13	0.4075	0.4063	45 *
9998	LYMPHORETICULAR SYSTEM	1340	lymphoma, thymic	0	0	1	0	0.3095	0.3285	46 *
9998	LYMPH NODE, MANDIBULAR	1360	mastocytoma	0	0	1	0	0.5542	0.5505	47 *
9998	LYMPHORETICULAR SYSTEM	1490	sarcoma, histiocytic	2	6	3	3	0.6416	0.6417	48 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).

CTR0, LOW, MED, and HIGH respectively stand for the positive control group with zero dose and three treated groups with dose levels 30, 100, 300 mg/kg/day.

Table 5. Analysis Results for Mortality Behavior in Rat Study

Males

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	70	2	68	97.1	2.9
	53-78	68	6	62	88.6	11.4
	79-91	62	12	50	71.4	28.6
	92-99	50	7	43	61.4	38.6
	Terminal Sacrifice	43	43	0		
CTR2	0-52	70	3	67	95.7	4.3
	53-78	67	6	61	87.1	12.9
	79-91	61	17	44	62.9	37.1
	92-99	44	12	32	45.7	54.3
	Terminal Sacrifice	32	32	0		
LOW	0-52	70	1	69	98.6	1.4
	53-78	69	4	65	92.9	7.1
	79-91	65	4	61	87.1	12.9
	92-99	61	6	55	78.6	21.4
	Terminal Sacrifice	55	55	0		
MED	0-52	70	1	69	98.6	1.4
	53-78	69	4	65	92.9	7.1
	79-91	65	4	61	87.1	12.9
	92-99	61	8	53	75.7	24.3
	Terminal Sacrifice	53	53	0		
MEDHI	0-52	70	2	68	97.1	2.9
	53-78	68	4	64	91.4	8.6
	79-91	64	8	56	80.0	20.0
	92-99	56	2	54	77.1	22.9
	Terminal Sacrifice	54	54	0		
CTR0	0-52	70	3	67	95.7	4.3
	53-78	67	6	61	87.1	12.9
	79-91	61	2	59	84.3	15.7
	92-99	59	6	53	75.7	24.3
	Terminal Sacrifice	53	53	0		

Females

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	70	3	67	95.7	4.3
	53-78	67	24	43	61.4	38.6
	79-91	43	12	31	44.3	55.7
	92-99	31	14	17	24.3	75.7
	Terminal Sacrifice	17	17	0		
CTR2	0-52	70	2	68	97.1	2.9
	53-78	68	17	51	72.9	27.1
	79-91	51	18	33	47.1	52.9
	92-99	33	11	22	31.4	68.6
	Terminal Sacrifice	22	22	0		
LOW	53-78	70	3	67	95.7	4.3
	79-91	67	1	66	94.3	5.7
	92-99	66	3	63	90.0	10.0
	Terminal Sacrifice	63	63	0		
MED	0-52	70	1	69	98.6	1.4
	53-78	69	3	66	94.3	5.7
	79-91	66	4	62	88.6	11.4
	92-99	62	3	59	84.3	15.7
	Terminal Sacrifice	59	59	0		
HIGH	0-52	70	1	69	98.6	1.4
	53-78	69	2	67	95.7	4.3
	79-91	67	5	62	88.6	11.4
	92-99	62	5	57	81.4	18.6
	Terminal Sacrifice	57	57	0		
CTR0	0-52	70	1	69	98.6	1.4
	53-78	69	5	64	91.4	8.6
	79-91	64	12	52	74.3	25.7
	92-99	52	7	45	64.3	35.7
	Terminal Sacrifice	45	45	0		

Note: CTR1, CTR2, CTR0, Low, MED, and HIGH respectively stand for the two negative and one positive control groups with zero doses and three treated groups with dose levels 10, 30, 100 mg/kg/day.

Table 6 Analysis of Homogeneity and Dose-Mortality Trend in Rat Study
(as adapted from results produced by eReview)

Male

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	18.8929	0.0008	17.2925	0.0017
Dose-Mortality Trend	8.3193	0.0039	7.9711	0.0048
Homogeneity	27.2122	0.0001	25.2636	0.0001

Female

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	83.0747	0.0000	78.1216	0.0000
Dose-Mortality Trend	61.2969	0.0000	59.5311	0.0000
Homogeneity	144.3716	0.0000	137.6527	0.0000

Table 7: Report on Tumor Trend Test for Male Rats

Pooled negative control group (Tumor data set 1)

Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1510	BRAIN	1129	Astrocytoma	5	0	1	0	0.9511	0.9453	1 *
1540	HEART	1181	Endocardial Schwannoma	1	0	0	1	0.5850	0.4776	2 *
1540	HEART	1293	Hemangiosarcoma	1	0	0	0	1.0000	0.8900	3
1570	LUNG	1142	Alveolar Bronchiolar Carcinoma	0	1	0	0	0.4681	0.7103	4 *
1570	LUNG	1279	Alveolar Bronchiolar Adenoma	0	0	0	1	0.3630	0.1984	5 *
1580	LIVER	1121	Hepatocellular Carcinoma	3	1	0	2	0.5684	0.6002	6 *
1580	LIVER	1253	Hemangiosarcoma	1	0	0	0	1.0000	0.9043	7
1590	SPLEEN	1293	Hemangiosarcoma	1	0	0	0	1.0000	0.8903	8
1600	ADRENAL	1108	Pheochromocytoma, Benign	26	3	1	5	0.9972	0.9963	9 *
1600	ADRENAL	1209	Cortical Adenoma	3	0	0	0	1.0000	0.9626	10
1600	ADRENAL	1211	Pheochromocytoma, Malignant	1	3	0	0	0.8631	0.8276	11 *
1600	ADRENAL	1325	Cortical Carcinoma	0	0	0	1	0.3673	0.1913	12 *
1610	PITUITARY	1028	Adenoma	87	51	54	45	0.8629	0.8630	13 *
1610	PITUITARY	1143	Carcinoma	3	1	0	0	0.9849	0.9782	14 *
1620	KIDNEY	1047	Tubular Cell Carcinoma	2	0	0	0	1.0000	0.9385	15
1620	KIDNEY	1126	Lipoma	1	0	0	0	1.0000	0.8982	16
1620	KIDNEY	1228	Mesenchymal Tumor, Malignant	0	1	0	0	0.4792	0.7138	17 *
1620	KIDNEY	1252	Tubular Cell Adenoma	0	0	1	0	0.4444	0.4434	18 *
1620	KIDNEY	1291	Liposarcoma	0	0	0	1	0.3750	0.1979	19 *
1630	STOMACH	1176	Squamous Cell Carcinoma	1	0	0	0	1.0000	0.9077	20
1640	PANCREAS	1011	Adenocarcinoma, Acinar	1	0	0	0	1.0000	0.8845	21
1640	PANCREAS	1109	Adenoma, Islet Cell	11	2	3	4	0.7575	0.7606	22 *
1640	PANCREAS	1123	Carcinoma, Islet Cell	4	1	0	1	0.8215	0.8614	23 *
1640	PANCREAS	1276	Adenoma, Mixed Acinar-Islet Ce	1	0	0	0	1.0000	0.8837	24
1650	LYMPH NODE, MESENTERIC	1293	Hemangiosarcoma	0	1	1	0	0.4513	0.4113	25 *
1650	LYMPH NODE, MESENTERIC	1369	Hemangioma	2	0	0	0	1.0000	0.9342	26
1670	INTESTINE-SMALL, JEJUNUM	1266	Sarcoma, Undifferentiated	1	0	0	0	1.0000	0.8896	27
1760	MAMMARY GLAND	1032	Adenoma	0	0	0	1	0.2105	0.0999	28 *
1760	MAMMARY GLAND	1064	Adenocarcinoma	1	0	0	0	1.0000	0.8673	29
1760	MAMMARY GLAND	1195	Fibroadenoma	1	0	0	0	1.0000	0.8673	30
1770	THYROID	1116	C-Cell Adenoma	12	0	0	9	0.4466	0.4498	31 *
1770	THYROID	1218	C-Cell Carcinoma	4	2	2	2	0.6263	0.6157	32 *
1770	THYROID	1253	Follicular Cell Carcinoma	1	0	0	1	0.4473	0.4056	33 *
1770	THYROID	1272	Follicular Cell Adenoma	7	0	0	0	1.0000	0.9949	34
1780	PARATHYROID	1012	Adenoma	4	0	0	2	0.7354	0.7048	35 *
1820	EYE W/OPTIC NERVE	1363	Amelanotic Melanoma	1	0	0	0	1.0000	0.8958	36
1940	URINARY BLADDER	1352	Transitional Cell Papiloma	0	1	0	0	0.4526	0.7039	37 *
1950	TESTIS	1196	Interstitial Cell Tumor	5	1	0	0	0.9409	0.9356	38 *
2060	ZYMBAL'S GLAND	1032	Adenoma	3	0	0	1	0.8226	0.7937	39 *
2060	ZYMBAL'S GLAND	1142	Carcinoma	1	0	1	0	0.6538	0.6780	40 *
2070	NASAL TURBINATE	1352	Malignant Schwannoma	0	1	0	0	0.4315	0.6730	41 *
2080	INJECTION SITE	1111	Keratoacanthoma	5	0	0	0	1.0000	0.9831	42
2090	INJECTION SITE	1285	Trichoepithelioma	0	1	0	0	0.4571	0.6203	43 *
2100	SPINAL CORD, CERVICAL	1129	Astrocytoma	1	0	0	0	1.0000	0.8903	44
2120	SPINAL CORD, LUMBAR	1129	Astrocytoma	1	0	0	0	1.0000	0.8903	45
2210	ADIPOSE TISSUE	1120	Lipoma	1	0	0	0	1.0000	0.9088	46
2220	SUBCUTANEOUS TISSUE	1205	Fibrosarcoma	1	0	0	4	0.0555	0.0453	47 *
2220	SUBCUTANEOUS TISSUE	1111	Keratoacanthoma	1	0	0	0	1.0000	0.9188	48
2220	SUBCUTANEOUS TISSUE	1120	Lipoma	1	0	0	0	1.0000	0.9186	49
2220	SUBCUTANEOUS TISSUE	1352	Malignant Schwannoma	1	0	0	0	1.0000	0.9061	50
2220	SUBCUTANEOUS TISSUE	1337	Fibroma	4	2	1	1	0.9714	0.9623	51 *
2220	SUBCUTANEOUS TISSUE	1324	Osteosarcoma	2	0	0	0	1.0000	0.9402	52
2220	SUBCUTANEOUS TISSUE	1278	Rhabdomyosarcoma	0	0	0	1	0.3333	0.1870	53 *
2230	SKIN, OTHER	1111	Keratoacanthoma	6	0	2	0	0.9963	0.9955	54 *
2230	SKIN, OTHER	1285	Trichoepithelioma	1	0	0	0	1.0000	0.9332	55
2230	SKIN, OTHER	1347	Sebaceous Gland Adenoma	1	0	0	0	1.0000	0.9548	56
2230	SKIN, OTHER	1356	Squamous Cell Papilloma	1	0	1	0	0.8042	0.8063	57 *
2230	SKIN, OTHER	1367	Basal Cell Carcinoma	1	1	0	0	0.9081	0.9309	58 *
2260	PREPUTIAL GLAND	1032	Adenoma	0	1	0	0	0.7500	0.8145	59 *
2260	PREPUTIAL GLAND	1142	Carcinoma	0	1	0	0	0.7143	0.6800	60 *
9998	LYMPHORETICULAR SYSTEM	1019	Lymphoma, Malignant	2	0	0	2	0.2196	0.1807	61 *
9998	LYMPHORETICULAR SYSTEM	1125	Histiocytic Sarcoma	4	0	1	0	0.9410	0.9349	62 *
9999	ALL ORGANS	1019	Lymphoma, Malignant	3	0	0	2	0.1895	0.1792	63 *
9999	ALL ORGANS	1125	Histiocytic Sarcoma	5	1	2	1	0.8743	0.8754	64 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).

CTR0, LOW, MED, and HIGH respectively stand for the pooled negative control group with zero dose and three treated groups with dose levels 10, 30, 100 mg/kg/day.

Table 7: Report on Tumor Trend Test for Male Rats (Continued)

Negative control 1 (Tumor data set 3)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1510	BRAIN	1129	Astrocytoma	2	0	1	0	0.9018	0.9085	1 *
1540	HEART	1181	Endocardial Schwannoma	0	0	0	1	0.4178	0.2413	2 *
1570	LUNG	1341	Alveolar Bronchiolar Carcinoma	0	1	0	0	0.6055	0.7959	3 *
1570	LUNG	1379	Alveolar Bronchiolar Adenoma	0	0	0	1	0.4954	0.2786	4 *
1580	LIVER	1131	Hepatocellular Carcinoma	2	1	0	2	0.6620	0.6793	5 *
1590	SPLEEN	1293	Hemangiosarcoma	1	0	0	0	1.0000	0.9338	6
1600	ADRENAL	1108	Pheochromocytoma, Benign	9	6	1	5	0.9278	0.9286	7 *
1600	ADRENAL	1209	Cortical Adenoma	1	0	0	0	1.0000	0.9384	8
1600	ADRENAL	1311	Pheochromocytoma, Malignant	0	3	0	0	0.8763	0.8440	9 *
1600	ADRENAL	1325	Cortical Carcinoma	0	0	0	1	0.4696	0.2661	10 *
1610	PITUITARY	1032	Adenoma	48	51	54	45	0.9406	0.9406	11 *
1610	PITUITARY	1143	Carcinoma	0	1	0	0	0.7857	0.8344	12 *
1620	KIDNEY	1047	Tubular Cell Carcinoma	1	0	0	0	1.0000	0.9387	13
1620	KIDNEY	1228	Mesenchymal Tumor, Malignant	0	1	0	0	0.6161	0.7987	14 *
1620	KIDNEY	1352	Tubular Cell Adenoma	0	0	0	0	0.5714	0.5483	15 *
1620	KIDNEY	1391	Liposarcoma	0	0	0	1	0.4821	0.2762	16 *
1640	PANCREAS	1011	Adenocarcinoma, Acinar	1	0	0	0	1.0000	0.9326	17
1640	PANCREAS	1109	Adenoma, Islet Cell	8	2	5	4	0.9068	0.9082	18 *
1640	PANCREAS	1133	Carcinoma, Islet Cell	2	1	0	1	0.7983	0.8410	19 *
1650	LYMPH NODE, MESENTERIC	1293	Hemangiosarcoma	0	1	1	0	0.6017	0.6024	20 *
1760	MAMMARY GLAND	1032	Adenoma	0	0	0	1	0.3077	0.1838	21 *
1770	THYROID	1138	C-Cell Adenoma	8	0	0	9	0.5514	0.5497	22 *
1770	THYROID	1213	C-Cell Carcinoma	3	2	2	2	0.8059	0.7987	23 *
1770	THYROID	1283	Follicular Cell Carcinoma	0	0	0	1	0.5000	0.2788	24 *
1770	THYROID	1312	Follicular Cell Adenoma	4	0	0	0	1.0000	0.9947	25
1780	PARATHYROID	1032	Adenoma	3	0	0	2	0.8129	0.7913	26 *
1820	EYE W/OPTIC NERVE	1263	Amelanotic Melanoma	1	0	0	0	1.0000	0.9376	27
1940	URINARY BLADDER	1395	Transitional Cell Papilloma	0	1	0	0	0.5905	0.7903	28 *
1950	TESTIS	1194	Interstitial Cell Tumor	1	1	0	0	0.9092	0.9192	29 *
2060	ZYMBAL'S GLAND	1032	Adenoma	1	0	0	1	0.7799	0.6675	30 *
2060	ZYMBAL'S GLAND	1143	Carcinoma	0	0	1	0	0.5728	0.5522	31 *
2070	NASAL TURBINATE	1152	Malignant Schwannoma	0	1	0	0	0.5986	0.7747	32 *
2090	INJECTION SITE	1111	Keratoacanthoma	1	0	0	0	1.0000	0.9714	33
2090	INJECTION SITE	1285	Trichoepithelioma	0	1	0	0	0.6957	0.7688	34 *
2120	SPINAL CORD, LUMBAR	1129	Astrocytoma	1	0	0	0	1.0000	0.9338	35
2210	ADIPOSE TISSUE	1120	Lipoma	1	0	0	0	1.0000	0.9088	36
2220	SUBCUTANEOUS TISSUE	1105	Fibrosarcoma	1	0	0	4	0.2231	0.2053	37 *
2220	SUBCUTANEOUS TISSUE	1120	Lipoma	1	0	0	0	1.0000	0.9683	38
2220	SUBCUTANEOUS TISSUE	1237	Fibroma	1	2	1	1	0.8968	0.8909	39 *
2220	SUBCUTANEOUS TISSUE	1378	Rhabdomyosarcoma	0	0	0	1	0.4444	0.2781	40 *
2230	SKIN, OTHER	1111	Keratoacanthoma	6	0	2	0	0.9994	0.9993	41 *
2230	SKIN, OTHER	1247	Sebaceous Gland Adenoma	1	0	0	0	1.0000	0.9751	42
2230	SKIN, OTHER	1358	Squamous Cell Papilloma	1	0	1	0	0.8721	0.8771	43 *
2230	SKIN, OTHER	1387	Basal Cell Carcinoma	0	1	0	0	0.7826	0.8518	44 *
2260	PREPUTIAL GLAND	1032	Adenoma	0	1	0	0	0.7500	0.8145	45 *
2260	PREPUTIAL GLAND	1143	Carcinoma	0	1	0	0	0.8000	0.8113	46 *
9998	LYMPHORETICULAR SYSTEM	1019	Lymphoma, Malignant	0	0	0	2	0.1577	0.1043	47 *
9998	LYMPHORETICULAR SYSTEM	1125	Histiocytic Sarcoma	1	0	1	0	0.8165	0.8231	48 *
9999	ALL ORGANS	1019	Lymphoma, Malignant	0	0	0	2	0.0635	0.0578	49 *
9999	ALL ORGANS	1125	Histiocytic Sarcoma	2	1	2	1	0.7335	0.7370	50 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).
CTR0, LOW, MED, and HIGH respectively stand for the negative control 1 group with zero dose and three treated groups with dose levels 10, 30, 100 mg/kg/day.

Table 7: Report on Tumor Trend Test for Male Rats (Continued)

Negative control 2 (Tumor data set 4)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table
1510	BRAIN	1129	Astrocytoma	3	0	1	0	0.9642	0.9676	1 *
1540	HEART	1181	Endocardial Schwannoma	1	0	0	1	0.7716	0.6837	2 *
1540	HEART	1293	Hemangiosarcoma	1	0	0	0	1.0000	0.9500	3
1570	LUNG	1341	Alveolar Bronchiolar Carcinoma	0	1	0	0	0.6735	0.8390	4 *
1570	LUNG	1379	Alveolar Bronchiolar Adenoma	0	0	0	1	0.5510	0.3195	5 *
1580	LIVER	1131	Hepatocellular Carcinoma	1	1	0	2	0.5980	0.6136	6 *
1580	LIVER	1293	Hemangiosarcoma	1	0	0	0	1.0000	0.9576	7
1600	ADRENAL	1108	Pheochromocytoma, Benign	17	9	1	5	0.9995	0.9995	8 *
1600	ADRENAL	1209	Cortical Adenoma	2	0	0	0	1.0000	0.9784	9
1600	ADRENAL	1311	Pheochromocytoma, Malignant	1	3	0	0	0.9679	0.9629	10 *
1600	ADRENAL	1325	Cortical Carcinoma	0	0	0	1	0.5192	0.3034	11 *
1610	PITUITARY	1032	Adenoma	39	51	54	45	0.7311	0.7313	12 *
1610	PITUITARY	1142	Carcinoma	3	1	0	0	0.9983	0.9965	13 *
1620	KIDNEY	1047	Tubular Cell Carcinoma	1	0	0	0	1.0000	0.9589	14
1620	KIDNEY	1120	Lipoma	1	0	0	0	1.0000	0.9589	15
1620	KIDNEY	1228	Mesenchymal Tumor, Malignant	0	1	0	0	0.6832	0.8412	16 *
1620	KIDNEY	1352	Tubular Cell Adenoma	0	0	1	0	0.6337	0.6025	17 *
1620	KIDNEY	1391	Liposarcoma	0	0	0	1	0.5347	0.3158	18 *
1630	STOMACH	1176	Squamous Cell Carcinoma	1	0	0	0	1.0000	0.9332	19
1640	PANCREAS	1109	Adenoma, Islet Cell	3	2	3	4	0.5977	0.5920	20 *
1640	PANCREAS	1133	Carcinoma, Islet Cell	2	1	0	1	0.8865	0.9234	21 *
1640	PANCREAS	1276	Adenoma, Mixed Acinar-Islet	1	0	0	0	1.0000	0.8959	22
1650	LYMPH NODE, MESENTERIC	1293	Hemangiosarcoma	0	1	1	0	0.6429	0.5859	23 *
1650	LYMPH NODE, MESENTERIC	1369	Hemangioma	2	0	0	0	1.0000	0.9848	24
1670	INTESTINE-SMALL, JEJUNUM	1268	Sarcoma, Undifferentiated	1	0	0	0	1.0000	0.9449	25
1760	MAMMARY GLAND	1032	Adenoma	0	0	0	1	0.3077	0.1838	26 *
1760	MAMMARY GLAND	1064	Adenocarcinoma	1	0	0	0	1.0000	0.9140	27
1760	MAMMARY GLAND	1195	Fibroadenoma	1	0	0	0	1.0000	0.9140	28
1770	THYROID	1138	C-Cell Adenoma	4	0	0	5	0.2577	0.2503	29 *
1770	THYROID	1213	C-Cell Carcinoma	1	2	2	2	0.6872	0.6636	30 *
1770	THYROID	1282	Follicular Cell Carcinoma	1	0	0	1	0.6362	0.5828	31 *
1770	THYROID	1312	Follicular Cell Adenoma	3	0	0	0	1.0000	0.9949	32
1780	PARATHYROID	1032	Adenoma	1	0	0	2	0.6351	0.5354	33 *
1940	URINARY BLADDER	1255	Transitional Cell Papilloma	0	1	0	0	0.6596	0.8343	34 *
1950	TESTIS	1194	Interstitial Cell Tumor	2	1	0	0	0.9101	0.9162	35 *
2060	ZYMBAL'S GLAND	1032	Adenoma	5	0	0	1	0.8714	0.8501	36 *
2060	ZYMBAL'S GLAND	1143	Carcinoma	1	0	1	0	0.8350	0.8430	37 *
2070	NASAL TURBINATE	1152	Malignant Schwannoma	0	1	0	0	0.6071	0.7799	38 *
2090	INJECTION SITE	1111	Keratoacanthoma	2	0	0	0	1.0000	0.9874	39
2090	INJECTION SITE	1285	Trichoepithelioma	0	1	0	0	0.6429	0.6915	40 *
2100	SPINAL CORD, CERVICAL	1129	Astrocytoma	1	0	0	0	1.0000	0.9547	41
2220	SUBCUTANEOUS TISSUE	1105	Fibrosarcoma	0	0	0	4	0.0220	0.0196	42 *
2220	SUBCUTANEOUS TISSUE	1111	Keratoacanthoma	1	0	0	0	1.0000	0.9495	43
2220	SUBCUTANEOUS TISSUE	1152	Malignant Schwannoma	1	0	0	0	1.0000	0.9260	44
2220	SUBCUTANEOUS TISSUE	1237	Fibroma	3	2	1	1	1.0000	0.9896	45
2220	SUBCUTANEOUS TISSUE	1324	Osteosarcoma	2	0	0	0	1.0000	0.9622	46
2220	SUBCUTANEOUS TISSUE	1378	Rhabdomyosarcoma	0	0	0	1	0.4000	0.2411	47 *
2230	SKIN, OTHER	1111	Keratoacanthoma	0	0	2	0	0.5397	0.5246	48 *
2230	SKIN, OTHER	1285	Trichoepithelioma	1	0	0	0	1.0000	0.9741	49
2230	SKIN, OTHER	1358	Squamous Cell Papilloma	0	0	1	0	0.6508	0.6143	50 *
2230	SKIN, OTHER	1387	Basal Cell Carcinoma	1	1	0	0	0.9816	0.9853	51 *
2260	PREPUTIAL GLAND	1032	Adenoma	0	1	0	0	1.0000	0.9669	52
2260	PREPUTIAL GLAND	1143	Carcinoma	0	1	0	0	0.6667	0.7339	53 *
5998	LYMPHORETICULAR SYSTEM	1019	Lymphoma, Malignant	1	0	0	2	0.3947	0.3555	54 *
5998	LYMPHORETICULAR SYSTEM	1125	Histiocytic Sarcoma	3	0	1	0	0.9731	0.9735	55 *
5999	ALL ORGANS	1019	Lymphoma, Malignant	1	0	0	2	0.3191	0.3094	56 *
5999	ALL ORGANS	1125	Histiocytic Sarcoma	3	1	2	1	0.8866	0.8886	57 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).
CTR0, LOW, MED, and HIGH respectively stand for the negative control 2 group with zero dose and three treated groups with dose levels 10, 30, 100 mg/kg/day.

Table 7: Report on Tumor Trend Test for Male Rats (Continued)

Positive control group (Tumor data set 2)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1510	BRAIN	1129	Astrocytoma	2	0	1	0	0.8915	0.8966	1 *
1540	HEART	1161	Endocardial Schwannoma	1	0	0	1	0.7001	0.6061	2 *
1570	LUNG	1241	Alveolar Bronchiolar Carcinoma	1	1	0	0	0.8037	0.8979	3 *
1570	LUNG	1279	Alveolar Bronchiolar Adenoma	0	0	0	1	0.4538	0.2488	4 *
1580	LIVER	1331	Hepatocellular Carcinoma	0	1	0	2	0.1748	0.2056	5 *
1600	ADRENAL	1208	Pheochromocytoma, Benign	7	3	1	5	0.8811	0.8625	6 *
1600	ADRENAL	1209	Cortical Adenoma	2	0	0	0	1.0000	0.9623	7
1600	ADRENAL	1211	Pheochromocytoma, Malignant	1	3	0	0	0.9199	0.8981	8 *
1600	ADRENAL	1225	Cortical Carcinoma	0	0	0	1	0.4320	0.2385	9 *
1610	PITUITARY	1032	Adenoma	37	51	54	45	0.1688	0.1687	10 *
1610	PITUITARY	1142	Carcinoma	0	1	0	0	0.7619	0.8198	11 *
1620	KIDNEY	1047	Tubular Cell Carcinoma	2	0	0	0	1.0000	0.9669	12
1620	KIDNEY	1228	Mesenchymal Tumor, Malignant	0	1	0	0	0.5656	0.7672	13 *
1620	KIDNEY	1352	Tubular Cell Adenoma	0	0	1	0	0.5246	0.5092	14 *
1620	KIDNEY	1291	Liposarcoma	0	0	0	1	0.4426	0.2472	15 *
1640	PANCREAS	1011	Adenocarcinoma, Acinar	1	0	0	0	1.0000	0.9183	16
1640	PANCREAS	1109	Adenoma, Islet Cell	7	5	3	4	0.7802	0.7821	17 *
1640	PANCREAS	1133	Carcinoma, Islet Cell	0	1	0	1	0.2889	0.4097	18 *
1650	LYMPH NODE, MESENTERIC	1293	Hemangiosarcoma	0	1	1	0	0.5573	0.5691	19 *
1760	MAMMARY GLAND	1012	Adenoma	0	0	0	1	0.5000	0.3609	20 *
1770	THYROID	1138	C-Cell Adenoma	7	0	0	5	0.3837	0.3806	21 *
1770	THYROID	1213	C-Cell Carcinoma	3	2	2	2	0.7175	0.7040	22 *
1770	THYROID	1263	Follicular Cell Carcinoma	1	0	0	1	0.7151	0.6073	23 *
1780	PARATHYROID	1032	Adenoma	0	0	0	2	0.2261	0.1222	24 *
1940	URINARY BLADDER	1195	Transitional Cell Papiloma	0	1	0	0	0.5439	0.7610	25 *
1950	TESTIS	1194	Interstitial Cell Tumor	0	1	0	0	1.0000	0.9826	26
2060	ZYMBAL'S GLAND	1012	Adenoma	0	0	0	1	0.4779	0.2550	27 *
2060	ZYMBAL'S GLAND	1143	Carcinoma	0	0	1	0	0.5221	0.5109	28 *
2070	NASAL TURBINATE	1032	Adenoma	1	0	0	0	1.0000	0.9177	29
2070	NASAL TURBINATE	1152	Malignant Schwannoma	0	1	0	0	0.5862	0.7672	30 *
2090	INJECTION SITE	1265	Trichoepithelioma	0	1	0	0	0.7273	0.7891	31 *
2220	SUBCUTANEOUS TISSUE	1105	Fibrosarcoma	2	0	0	4	0.5141	0.5015	32 *
2220	SUBCUTANEOUS TISSUE	1217	Fibroma	0	2	1	1	0.8143	0.8126	33 *
2220	SUBCUTANEOUS TISSUE	1178	Rhabdomyosarcoma	0	0	0	1	0.5000	0.3274	34 *
2230	SKIN, OTHER	1111	Keratoacanthoma	1	0	2	0	0.6344	0.6495	35 *
2230	SKIN, OTHER	1156	Squamous Cell Papilloma	0	0	1	0	0.4767	0.4370	36 *
2230	SKIN, OTHER	1267	Basal Cell Carcinoma	0	1	0	0	0.6279	0.7560	37 *
2260	PREPUTIAL GLAND	1012	Adenoma	0	1	0	0	1.0000	0.9669	38
2260	PREPUTIAL GLAND	1143	Carcinoma	0	1	0	0	1.0000	0.9342	39
5998	LYMPHORETICULAR SYSTEM	1019	Lymphoma, Malignant	1	0	0	2	0.3931	0.3540	40 *
5998	LYMPHORETICULAR SYSTEM	1125	Histiocytic Sarcoma	0	0	1	0	0.5267	0.5059	41 *
5999	ALL ORGANS	1019	Lymphoma, Malignant	1	0	0	2	0.3181	0.3085	42 *
5999	ALL ORGANS	1125	Histiocytic Sarcoma	0	1	2	1	0.2565	0.2501	43 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).

CTR0, LOW, MED, and HIGH respectively stand for the positive control group with zero dose and three treated groups with dose levels 10, 30, 100 mg/kg/day.

Table 8: Report on Tumor Trend Test for Female Rats

Pooled negative control group (Tumor data set 1)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1510	BRAIN	1129	Astrocytoma	0	0	1	0	0.4364	0.4438	1 *
1510	BRAIN	1230	Oligodendroglioma	1	0	0	1	0.3755	0.2449	2 *
1550	THYMUS/REGION	1302	Thymoma, Malignant	0	0	0	1	0.4958	0.2630	3 *
1580	LIVER	1131	Hepatocellular Carcinoma	0	0	1	0	0.5862	0.5705	4 *
1580	LIVER	1342	Hepatocellular Adenoma	0	0	0	1	0.4914	0.2883	5 *
1590	SPLEEN	1268	Sarcoma, Undifferentiated	0	1	0	0	0.6176	0.8065	6 *
1600	ADRENAL	1108	Pheochromocytoma, Benign	4	0	2	2	0.7058	0.7177	7 *
1600	ADRENAL	1209	Cortical Adenoma	5	0	0	3	0.8044	0.8013	8 *
1600	ADRENAL	1311	Pheochromocytoma, Malignant	0	0	0	2	0.2393	0.1495	9 *
1600	ADRENAL	1325	Cortical Carcinoma	1	0	0	1	0.7688	0.7029	10 *
1610	PITUITARY	1032	Adenoma	126	37	36	33	1.0000	1.0000	11
1610	PITUITARY	1143	Carcinoma	2	0	0	0	1.0000	0.9777	12
1620	KIDNEY	1120	Lipoma	0	0	1	0	0.6078	0.5787	13 *
1620	KIDNEY	1228	Mesenchymal Tumor, Malignant	1	0	0	0	1.0000	0.8833	14
1620	KIDNEY	1261	Nephroblastoma	0	1	0	0	0.4520	0.6822	15 *
1620	KIDNEY	1352	Tubular Cell Adenoma	1	0	0	0	1.0000	0.9446	16
1640	PANCREAS	1109	Adenoma, Islet Cell	4	0	0	1	0.9501	0.9208	17 *
1640	PANCREAS	1133	Carcinoma, Islet Cell	1	1	1	0	0.8502	0.7677	18 *
1670	INTESTINE-SMALL, JEJUNUM	1255	Leiomyosarcoma	0	0	1	0	0.2250	0.2047	19 *
1690	INTESTINE-LARGE, CECUM	1294	Cystadenocarcinoma	1	0	0	0	1.0000	0.9146	20
1720	SALIVARY GLAND, MANDIBULAR	1351	Mast Cell Tumor, Malignant	1	0	0	0	1.0000	0.9393	21
1760	MAMMARY GLAND	1032	Adenoma	1	1	0	0	0.8474	0.8591	22 *
1760	MAMMARY GLAND	1064	Adenocarcinoma	54	0	1	0	1.0000	1.0000	23
1760	MAMMARY GLAND	1195	Fibroadenoma	65	0	0	0	1.0000	1.0000	24
1770	THYROID	1138	C-Cell Adenoma	12	0	0	7	0.4114	0.4111	25 *
1770	THYROID	1213	C-Cell Carcinoma	11	0	0	0	1.0000	0.9996	26
1770	THYROID	1283	Follicular Cell Carcinoma	1	0	0	0	1.0000	0.9381	27
1770	THYROID	1312	Follicular Cell Adenoma	1	0	0	0	1.0000	0.9381	28
1780	PARATHYROID	1032	Adenoma	1	0	0	0	1.0000	0.8546	29
1920	OVARY	1208	Sertoli Cell Tumor	1	0	0	0	1.0000	0.8375	30
1920	OVARY	1319	Thecoma	1	0	0	0	1.0000	0.8551	31
1940	URINARY BLADDER	1395	Transitional Cell Papilloma	0	1	0	0	0.5938	0.8010	32 *
1990	UTERUS	1032	Adenoma	1	0	0	0	1.0000	0.9773	33
1990	UTERUS	1227	Endometrial Stromal Polyp	3	0	0	0	1.0000	0.9983	34
2006	CERVIX	1227	Endometrial Stromal Polyp	1	0	0	0	1.0000	0.8434	35
2000	CERVIX	1237	Fibroma	1	0	0	0	1.0000	0.9778	36
2060	ZYMBAL'S GLAND	1032	Adenoma	1	0	0	0	1.0000	0.8434	37
2180	EXTREMITIES	1334	Osteoma	0	0	0	1	0.5000	0.5000	38 *
2210	ADIPOSE TISSUE	1120	Lipoma	2	0	0	0	1.0000	0.9829	39
2220	SUBCUTANEOUS TISSUE	1105	Fibrosarcoma	2	0	0	0	1.0000	0.9464	40
2220	SUBCUTANEOUS TISSUE	1120	Lipoma	1	0	0	1	0.4000	0.1882	41 *
2220	SUBCUTANEOUS TISSUE	1152	Malignant Schwannoma	1	0	0	0	1.0000	0.8556	42
2220	SUBCUTANEOUS TISSUE	1237	Fibroma	3	0	0	1	0.7000	0.4778	43 *
2230	SKIN, OTHER	1111	Keratoacanthoma	0	1	0	0	0.9559	0.9503	44 *
2230	SKIN, OTHER	1176	Squamous Cell Carcinoma	1	1	0	0	0.9987	0.9974	45 *
2230	SKIN, OTHER	1414	Basal Cell Adenoma	0	0	0	1	0.2059	0.1999	46 *
2290	CLITORAL GLAND	1143	Carcinoma	0	1	0	0	0.7273	0.7235	47 *
2290	CLITORAL GLAND	1176	Squamous Cell Carcinoma	1	0	0	0	1.0000	0.9332	48
9998	LYMPHORETICULAR SYSTEM	1019	Lymphoma, Malignant	0	0	1	2	0.0567	0.0504	49 *
9999	ALL ORGANS	1019	Lymphoma, Malignant	0	0	1	2	0.0393	0.0347	50 *

Note: The symbol "*" indicates that the p-values fall in (0, 1).

CTR0, LOW, MED, and HIGH respectively stand for the pooled negative control group with zero dose and three treated groups with dose levels 10, 30, 100 mg/kg/day.

Table 8: Report on Tumor Trend Test for Female Rats (Continued)

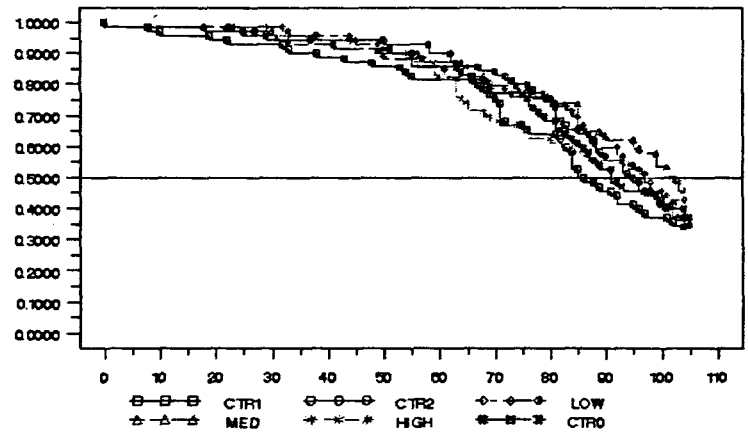
Positive control group (Tumor data set 2)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	Link 2XC Table >
1510	BRAIN	1129	Astrocytoma	4	0	1	0	0.9759	0.9737	1 *
1510	BRAIN	1230	Oligodendroglioma	0	0	0	1	0.4726	0.2555	2 *
1510	BRAIN	1412	Granular Cell Tumor	1	0	0	0	1.0000	0.9282	3
1550	THYMUS/REGION	1302	Thymoma, Malignant	0	0	0	1	0.5086	0.2716	4 *
1580	LIVER	1131	Hepatocellular Carcinoma	1	0	1	0	0.8110	0.8248	5 *
1580	LIVER	1342	Hepatocellular Adenoma	0	0	0	1	0.4672	0.2700	6 *
1590	SPLEEN	1268	Sarcoma, Undifferentiated	0	1	0	0	0.5833	0.7850	7 *
1600	ADRENAL	1108	Pheochromocytoma, Benign	2	0	2	2	0.5470	0.5641	8 *
1600	ADRENAL	1209	Cortical Adenoma	1	0	0	3	0.2941	0.2525	9 *
1600	ADRENAL	1311	Pheochromocytoma, Malignant	0	0	0	2	0.2162	0.1329	10 *
1600	ADRENAL	1325	Cortical Carcinoma	0	0	0	1	0.4672	0.2737	11 *
1610	PITUITARY	1032	Adenoma	40	37	36	33	0.9704	0.9704	12 *
1610	PITUITARY	1143	Carcinoma	2	0	0	0	1.0000	0.9917	13
1620	KIDNEY	1120	Lipoma	0	0	1	0	0.5741	0.5508	14 *
1620	KIDNEY	1261	Nephroblastoma	0	1	0	0	0.5817	0.7745	15 *
1640	PANCREAS	1109	Adenoma, Islet Cell	3	0	0	1	0.9373	0.9133	16 *
1640	PANCREAS	1133	Carcinoma, Islet Cell	0	1	1	0	0.7938	0.6563	17 *
1650	LYMPH NODE, MESENTERIC	1152	Malignant Schwannoma	1	0	0	0	1.0000	0.9270	18
1670	INTESTINE-SMALL, JEJUNUM	1255	Leiomyosarcoma	0	0	1	0	0.4091	0.3743	19 *
1760	MAMMARY GLAND	1032	Adenoma	0	1	0	0	0.7982	0.8380	20 *
1760	MAMMARY GLAND	1064	Adenocarcinoma	1	0	1	0	0.8428	0.8572	21 *
1760	MAMMARY GLAND	1195	Fibroadenoma	1	0	0	0	1.0000	0.9724	22
1770	THYROID	1138	C-Cell Adenoma	5	0	0	7	0.3426	0.3310	23 *
1770	THYROID	1213	C-Cell Carcinoma	2	0	0	0	1.0000	0.9642	24
1770	THYROID	1312	Follicular Cell Adenoma	1	0	0	0	1.0000	0.8998	25
1920	OVARY	1301	Luteoma	1	0	0	0	1.0000	0.9917	26
1920	OVARY	1410	Granulosa Cell Tumor	1	0	0	0	1.0000	0.9983	27
1940	URINARY BLADDER	1395	Transitional Cell Papilloma	0	1	0	0	0.5644	0.7823	28 *
1990	UTERUS	1255	Leiomyosarcoma	2	0	0	0	1.0000	0.9918	29
2060	ZYMBAL'S GLAND	1032	Adenoma	1	0	0	0	1.0000	0.8938	30
2180	EXTREMITIES	1324	Osteoma	0	0	0	1	0.5000	0.5000	31 *
2220	SUBCUTANEOUS TISSUE	1268	Sarcoma, Undifferentiated	1	0	0	0	1.0000	0.9088	32
2230	SKIN, OTHER	1111	Keratoacanthoma	0	1	0	0	0.8025	0.8499	33 *
2230	SKIN, OTHER	1176	Squamous Cell Carcinoma	0	1	0	0	0.8025	0.8499	34 *
2230	SKIN, OTHER	1414	Basal Cell Adenoma	0	0	0	1	0.1728	0.1650	35 *
2290	CLITORAL GLAND	1143	Carcinoma	0	1	0	0	0.8889	0.8116	36 *
9998	LYMPHORETICULAR SYSTEM	1019	Lymphoma, Malignant	0	0	1	2	0.1266	0.1180	37 *
9998	LYMPHORETICULAR SYSTEM	1125	Histiocytic Sarcoma	2	0	0	0	1.0000	0.9661	38
9999	ALL ORGANS	1019	Lymphoma, Malignant	0	0	1	2	0.0647	0.0630	39 *
9999	ALL ORGANS	1125	Histiocytic Sarcoma	2	0	0	0	1.0000	0.9894	40

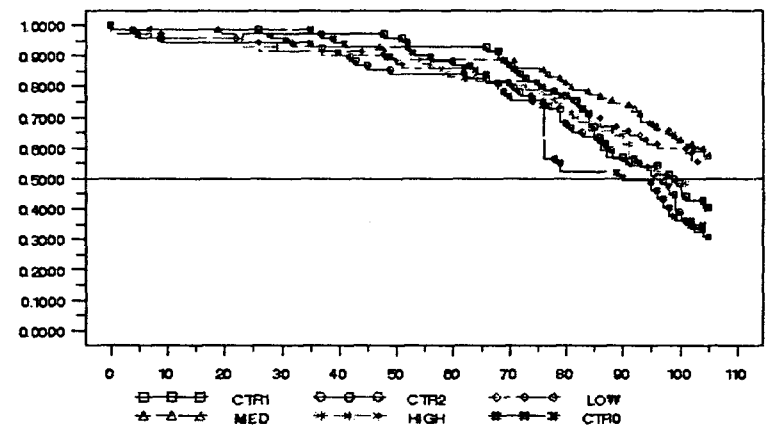
Note: The symbol "*" indicates that the p-values fall in (0, 1).
CTR0, LOW, MED, and HIGH respectively stand for the positive control group with zero dose and three treated groups with dose levels 10, 30, 100 mg/kg/day.

Figure 1. Kaplan-Mier estimates of Survival Curves in Mouse Study

Male



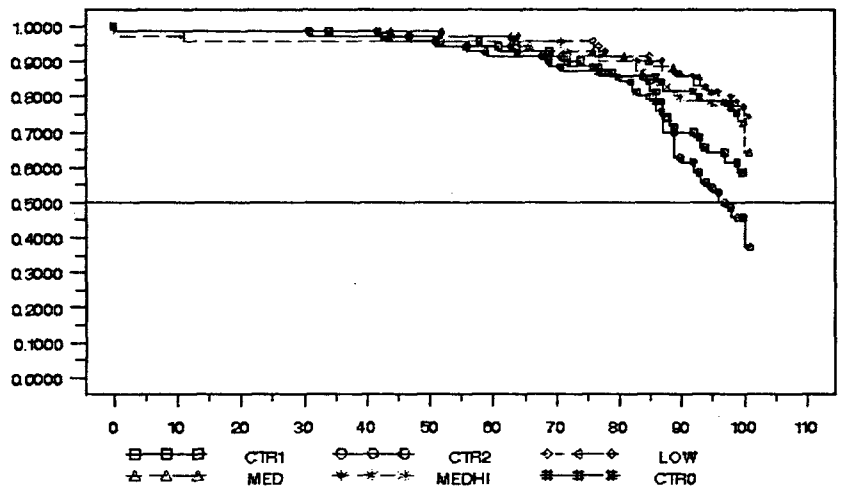
Female



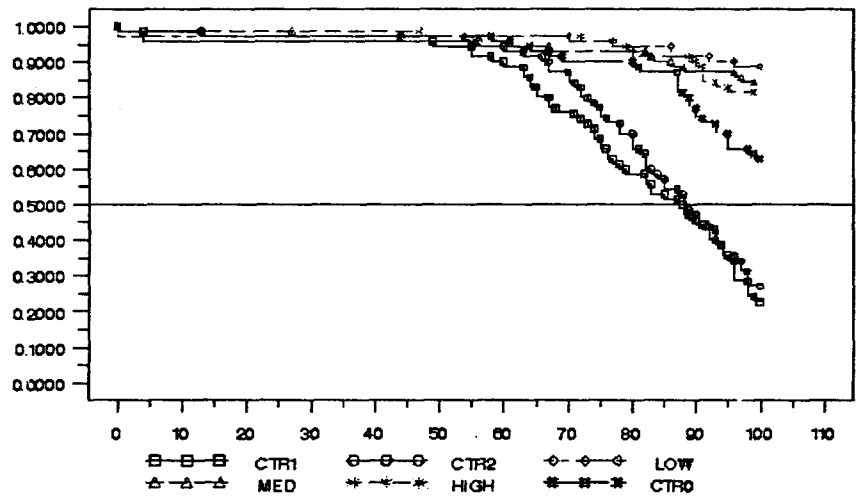
Note: CTR1, CTR2, CTR0, Low, MED, and HIGH respectively stand for the two negative and one positive control groups with zero doses and three treated groups with dose levels 30, 100, 300 mg/kg/day.

Figure 2. Kaplan-Mier estimates of Survival Curves in Rat Study

Male



Female



Note: CTR1, CTR2, CTR0, Low, MED, and HIGH respectively stand for the two negative and one positive control groups with zero doses and three treated groups with dose levels 10, 30, 100 mg/kg/day.

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/s/

Wen-Jen Chen
8/6/03 02:52:43 PM
BIOMETRICS

Karl Lin
8/6/03 03:13:21 PM
BIOMETRICS
Concur with review

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

The Statistical Review of Carci Studies is pending (ongoing) at this time.

/S/

5/7/04

Executive CAC
Date of meeting: July 22, 2003

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Abby Jacobs, Ph.D., HFD-540, Member
C. Joseph Sun, Ph.D., HFD-570, Alternate Member
Alex Jordan, Ph.D., HFD-580, Team Leader
Krishan Raheja, D.V.M., Ph.D., HFD-580, Presenting Reviewer

Author of the draft: Krishan Raheja

The following information reflects a brief summary of the committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA: 21-320
Drug name: Plenaxis (PPI-141, Abarelix acetate)
Proposed indication: Treatment of advanced prostate cancer
Sponsor: Praecis Pharmaceuticals Inc. Cambridge, MA

Subject: Results of 2-year subcutaneous carcinogenicity studies in mice and rats

Background information: Plenaxis is a GnRH antagonist which is indicated for the advanced symptomatic carcinoma of the prostate in patients with 1) impending neurological compromise l metastases, 2) urinary tract obstruction. 3 /or 3) bone pain from prostate cancer skeletal metastases necessitating narcotic analgesia.

Dose selection for the mouse and rat carcinogenicity studies: The dosage used in both the mouse and the rat carcinogenicity studies were based on the results of 13-week dose range-finding studies and were approved by the Exec-CAC on 3-18-1998. In both the mouse and the rat carcinogenicity studies 6 treatment groups i.e., 2 saline control, 3 drug-treated and 1 castrated or ovariectomized were used. In the mouse study PPI-141 dosage used were 30, 100 and 300 mg/kg/28days while in the rat study the doses were 10, 30 and 100 mg/kg/28days. These doses represent good multiples of the human therapeutic dose of 100 mg PPI-141 every 28 days.

Mouse carcinogenicity study: Significant PPI-141-related study finding in the mice carcinogenicity study were essentially similar to those observed in the castrated male and ovariectomized female mice. These consisted of atrophy of the reproductive organs and secondary sex organs and injection site reaction in the form of granuloma. No treatment-related neoplastic findings were reported except that adrenal cortical adenomas were observed predominantly in the surgically altered mice. The occurrence of adrenal adenoma was explained by the loss of negative feedback to he pituitary resulting from gonadectomy. Systemic exposure achieved with doses used represented high multiple of

the systemic exposure in humans with the therapeutic dose of 100 mg PPI-141 per administration.

Rat carcinogenicity study: As in the mouse carcinogenicity study, in the rat study gross and histological findings in the PPI-141 treated animals were similar to those observed in the castrated male and ovariectomized female rats. The systemic exposure achieved in rats represented good multiples of the systemic exposure achieved in humans with the therapeutic dose of 100 mg PPI-141 per administration.

Executive CAC Recommendations and Conclusions: For both the mouse and the rat carcinogenicity studies the committee considered the approved dose levels used to be adequate.
The Committee concluded that no carcinogenic effects were seen in either study.

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

cc

HFD-580
Alex Jordan, HFD-580
Krishan Raheja, HFD-580
Eufrecina Deguia, HFD-580
A.Seifried, HFD-024

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

The Carci Studies were received late in the this review cycle; submissions are under review; after review is complete, the information will be forwarded to the CAC for a Report.

S

5/7/01

APPEARS THIS WAY
ON ORIGINAL