connective tissue tumors. Inflammatory stimulation induced cellular and tissue hyperplasia at injection sites may also play some roles in the development of the neoplastic lesions.

Study no.: 77006
Volume #, and page #: Vol A3.55 to A3.67, and page 1 to 4878
Test Facility:

Date of study initiation: 04/03/2003
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: Lanreotide (acetate salt) refrigerated — dissolved in 0.9% NaCl for injection, U.S.P.; Lot # P60029, P60025, P60026, P60018, P60014, P60015, P60028, P60032, P60040, P60057, P60012, and P60013; and purity — to —
CAC concurrence: None

Methods

Doses: 0, 0, 0.5, 1.5, 5, 10, and 30 mg/kg/d

Basis of dose selection (MTD, MFD, AUC etc.): 30 mg/kg/d seems to be a MTD or exceeding the MTD based on clinical pathology findings and injection site inflammation in the dose ranging study, and premature sacrifice due to severe skin lesions in the 2-year assay.

Species/strain: Mouse/CD-1

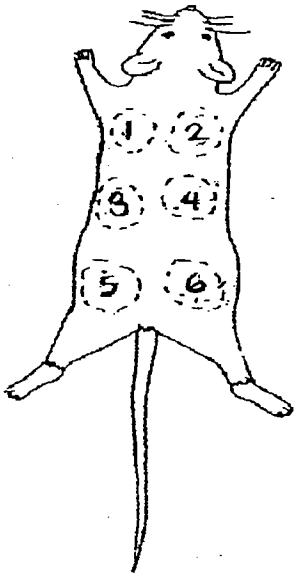
Number/sex/group (main study): 60/s/g for the two vehicle control groups and 70/s/g for the 5 treatment groups

Study Design

Group No. Identification	Dose Level (mg/kg/day)	Number of Animals			
		Main Study		Toxicokinetic	
		Males	Females	Males	Females
1. Vehicle Control	0	60	60	-	-
2. Vehicle Control	0	60	60	-	-
3. BIM23014	0.5	70	70	63	63
4. BIM23014	1.5	70	70	63	63
5. BIM23014	5	70	70	63	63
6. BIM23014	10	70	70	63	63
7. BIM23014	30	70	70	63	63

Route, formulation, volume: s.c. injection of vehicle or lanreotide (acetate salt, refrigerated — dissolved in 0.9% NaCl for injection, U.S.P.) into the dorsal region at a dosing volume of 10 ml/kg/d. The 6 predetermined dosing sites as illustrated below were used alternatively.

Treatment Site #1 Scapular Left
Treatment Site #2 Scapular Right
Treatment Site #3 Dorsal Thoracic Left
Treatment Site #4 Dorsal Thoracic Right
Treatment Site #5 Lumbar Left
Treatment Site #6 Lumbar Right



Frequency of dosing: once daily, 7 days a week for a minimum of 104-week

Satellite groups used for toxicokinetics or special groups: 63 mice/s/g at the 5 treatment dose levels for TK

Age: 6 weeks

Animal housing: housed 1 per cage in stainless steel wire mesh bottomed cage during the treatment period; each animal was uniquely identified using a tail tattoo system.

Restriction paradigm for dietary restriction studies: n/a

Drug stability/homogeneity: stability was examined when stored at room temperature for 36 hrs. For homogeneity and concentration tests duplicate samples were collected from the middle of the container of each dose formulation on the day of preparation from Weeks 1, 13, 26, 38, 52, 65, 78, 91 and 104. The results showed that all samples analyzed were within the acceptance criteria of ±10% of their nominal concentrations

Dual controls employed: yes, both control groups were given daily s.c. injections with the vehicle (0.9% NaCl for injection U.S.P.)

Interim sacrifices: none; however due to low survival, males treated at 30 mg/kg/d, were terminated during Week 87 and females at 30 mg/kg/d were terminated during Week 98.

Deviations from original study protocol: occasional minor deviations from the protocol occurred, and were documented in the study report. Misdosings were recorded

during treatment as shown in the table below; these misdosings were considered minor and did not show adverse impact on the study.

Table 5 Misdosings during Treatment Period

Day of misdosing	Animals affected	Reason for error	Percent deviation from intended dose
Day 92	1501-1506	Inadvertently dosed with volumes belonging to animals 1501-1506 from project 77005	Ranged from -3.33% to 28.6 %.
Day 112	3540	Received the dose volume of animal 3538 due to technical oversight	22.5%
Days 147 to 158	1518, 1519	Inadvertently dosed with volumes based on body weights performed during the previous month	-6.7% and 3.3%, respectively
Day 164	5099, 5100, 5103	Were misdosed with the volumes of 5098, 5099 and 5102, respectively	4.9%, 13.9% and 48.5%, respectively.
Day 235	6071-6097	Were dosed with dose formulation of Group 5 instead of dose formulation of Group 6	50%.
Day 487	4013	Received the dose of animal 4012 due to technical oversight	12.8%
Day 488	6037	Received the dose of animal 6036 due to technical oversight	4.9%
Day 682	3011	Received the dose of animal 3009 due to technical oversight	12.8%

Observation times

Mortality: twice daily

Clinical signs: twice daily

Body weights: once weekly from pretest through Week 13, then once every 4 weeks (i.e. Weeks 17, 21, 25, etc), and each main study animal was weighed before scheduled necropsy.

Food consumption: weekly from pretest through Week 13, thereafter once every 4 weeks till the end of study (i.e. Weeks 17, 21, 25, etc).

Histopathology: All tissues from all main study animals were embedded in paraffin wax, sectioned, stained with H & E and examined microscopically, except tissues from animals 5009 and 6011, which were misplaced each other due to a technical error and were therefore excluded. Peer review was not specified.

Toxicokinetics: samples were collected on Day 1 and during Weeks 26, 52 and 104 from 3 TK animals/sex in dosed groups/time point at normally 0 (predose), 0.25, 3, 12, and 24 hrs after dosing. Drug concentration was analyzed by a validated radioimmunoassay. Non-specific binding (NSB) was also evaluated if enough samples were available. If NSB was > 30% for a given group, remaining samples corresponding to the same dose level were pooled to determine putative lanreotide antibodies provided sufficient sample was available. Cmax and $AUC_{t\ (0\text{-}t)}$ were determined.

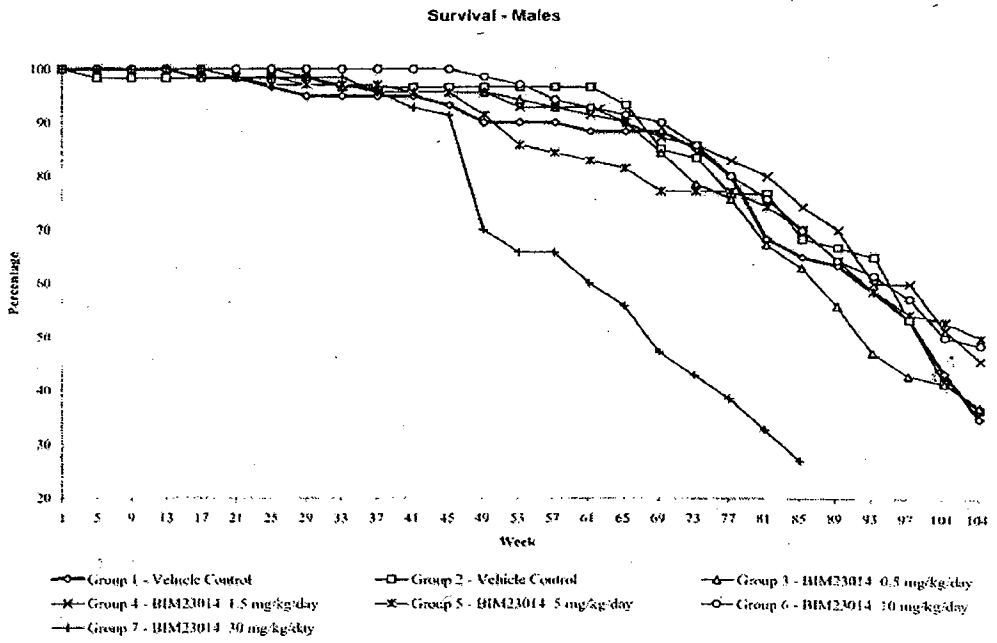
Results

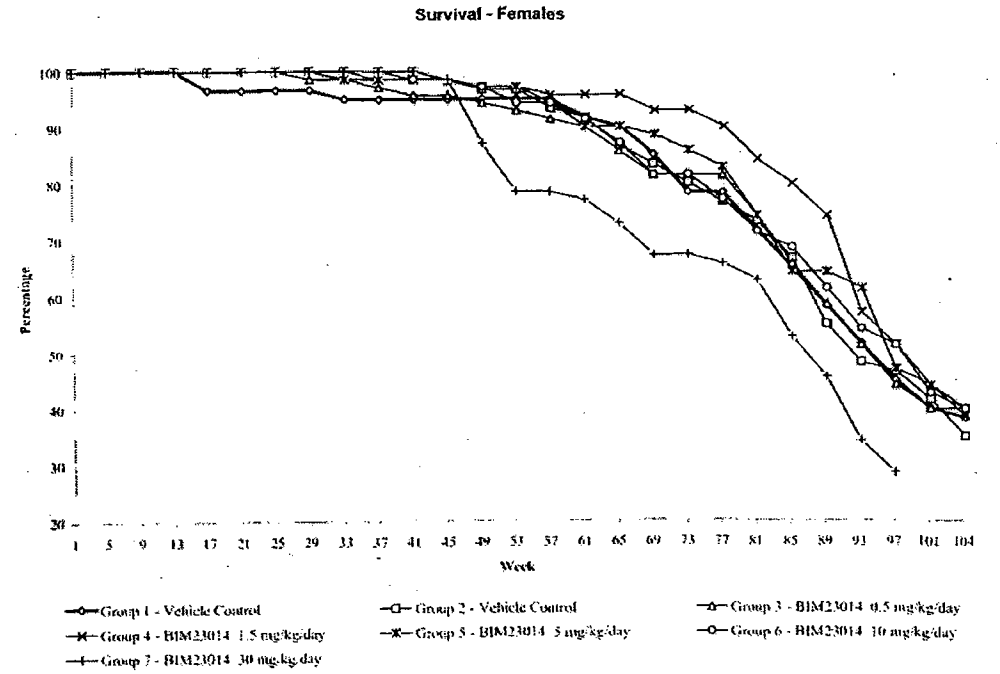
Mortality: Primarily at the 30 mg/kg/d, a notable proportion of animals died as a consequence of the presence of masses at injection sites. Mortality rate in other groups was not affected by the treatment (comparable to that of controls). The mortality data at Week 104 are shown in the table below:

Group		Dose (mg/kg/d)	MALE	FEMALE
			Number per 60 or 70 (%)	Number per 60 or 70 (%)
1	Control 1	0	39/60 (65%)	37/60 (62%)
2	Control 2	0	38/60 (63%)	39/60 (65%)
3	Lanreotide	0.5	44/70 (63%)	42/70 (60%)
4	Lanreotide	1.5	38/70 (54%)	43/70 (61%)
5	Lanreotide	5	35/70 (50%)	42/70 (60%)
6	Lanreotide	10	36/70 (51%)	42/70 (60%)
7*	Lanreotide	30	51/70 (73%)	50/70 (71%)

* early terminated on Weeks 87 (M) and 97.

Survival curves also indicate that reduced survival was observed in both male and female animals at 30 mg/kg/d, mainly due to compound-related dermal changes at the injection sites leading to premature euthanasia from Week 87.





Clinical signs: Palpable masses at injection sites were major findings in a similar proportion of animals from control and treated groups with the exception of males dosed at 30 mg/kg/d, which had much higher incidence than controls and lower dose groups. Incidences of palpable masses are shown in the scanned table 8 below:

Text Table 8 Animals with Clinically Observed Masses

Group No. Identification	Dose Level (mg/kg/day)	Masses			
		Males	%	Females	%
1 Vehicle Control	0	0/60	0	13/60	22
2 Vehicle Control	0	7/60	12	7/60	12
3 BIM23014	0.5	1/70	1	8/70	11
4 BIM23014	1.5	5/70	7	11/70	16
5 BIM23014	5	4/70	6	12/70	17
6 BIM23014	10	4/70	6	3/70	4
7 BIM23014	30	35/70	50	14/70	20

At the injection sites and the surrounding areas including interscapular and dorsal cervical areas, an increased incidence of thin fur cover was noted in males at 30 mg/kg/d when compared to controls. A higher incidence of fur loss, skin lesions with and/or without discharge, skin scabs and redness of the skin at the injection sites, dorsal cervical and/or thoracic areas, interscapular and/or mass sites were also noted in this HD group when compared to controls.

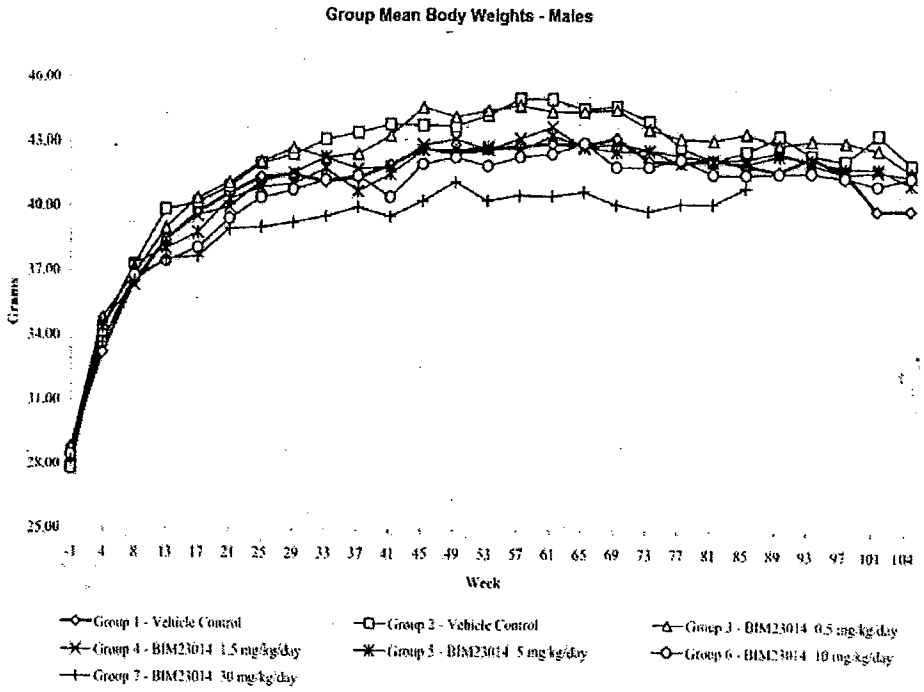
Additionally, some females at 30 mg/kg/ were noted to be hypersensitive (shows an exaggerated reaction to skin touch, toe pinch or tail pinch). An increased incidence of skin scabs at the treatment sites, dorsal cervical and/or dorsal thoracic areas was also noted in females at 5 and/or 10 mg/kg/d when compared to the control groups.

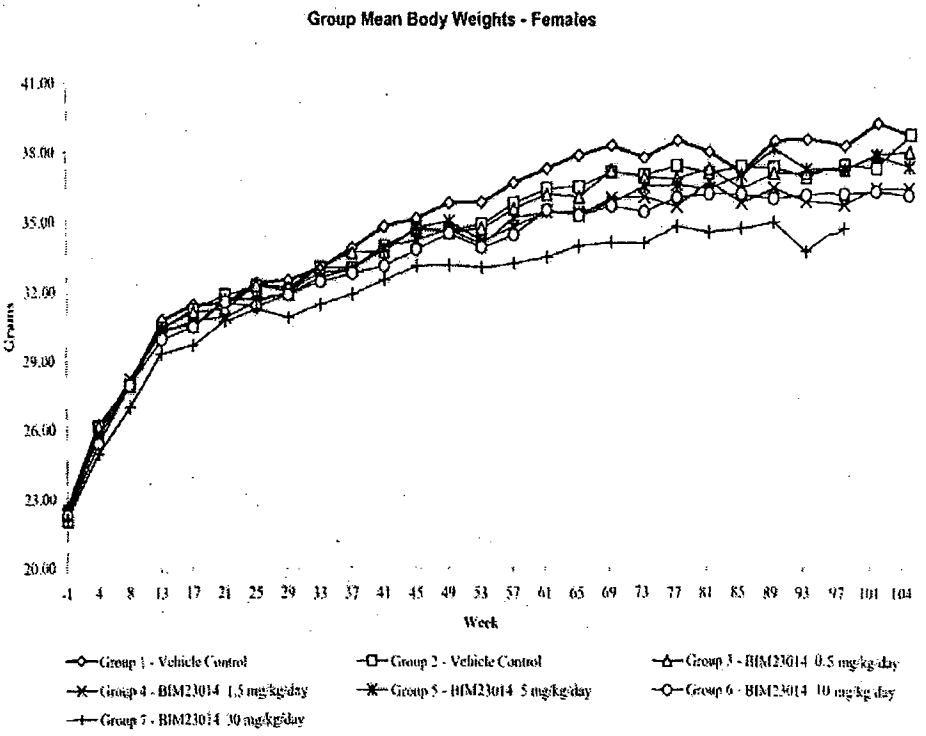
Body weights: Statistically significant decreases in mean BW were predominantly seen in females at ≥ 1.5 mg/kg/d on Week 104 (or Week 97 for 30 mg/kg/d group) and in males at 30 mg/kg/d after 10 weeks of treatment, compared to controls.

Text Table 9 Group Mean Body Weights at Week 104

Group No. Identification	Dose Level (mg/kg/day)	Mean Body Weight Week 104			
		Males (g)	% from control	Females (g)	% from control
Mean Groups 1 and 2	0	41.11	-	38.78	-
3 BIM23014	0.5	41.80	+2	38.03	-2
4 BIM23014	1.5	41.63	+1	36.43	-6
5 BIM23014	5	41.23	0	37.38	-4
6 BIM23014	10	41.56	−1	36.14	-7
7 BIM23014	30	40.97*	0	34.70*	-11

* Week 85 for males and Week 97 for females.





Food consumption: Unremarkable

Gross pathology: At a majority of injection sites (I.S.) of the animals at 30 mg/kg/d, cutaneous swelling or thickening was observed as well as a lesser incidence of cutaneous

scabs. Some animals from the 1.5, 5 and 10 mg/kg/d groups showed similar lesions but at a lower incidence or in fewer injection sites. In a small number of animals from the 30 mg/kg/d groups, masses or nodules were noted at injection sites. Minor lesions of similar description were occasionally reported in control animals. Apparently, the majority of these lesions occurred as a consequence of the drug dosing.

Text Table 11 **Incidence of BIM23014 related Macroscopic Finding at Injections Sites**

Tissue/Finding	Sex	Male							Female						
Dose (mg/kg/day)		0	0	0.5	1.5	5	10	30	0	0	0.5	1.5	5	10	30
No. of animals examined		60	60	70	70	70	70	70	60	60	70	70	70	70	70
I.S. Dorsal thoracic right															
Mass or nodule		—	—	—	—	—	—	6	—	1	1	—	1	1	1
Scab		1	—	—	—	3	3	—	1		1		—	1	6
Swelling/thickening		2	2	1	3	1	4	23	3	1	1	3	6	4	25
I.S. Dorsal thoracic left															
Mass or nodule		1	—	—	—	—	—	15	—	—	2		2		6
Scab		—	—	—	—	1	1	4	2	1	1	—	1	1	5
Swelling/thickening		2	2	1	2	2	4	22	3	1	4	6	6	5	33
I.S. Lumbar right															
Mass or nodule		—	1	—	—	—	—	4	—	1	3	—	2	—	2
Scab		—	—	—	—	2	—	3	1	1	—	—	—	—	1
Swelling/thickening		2	3	3	3	1	5	25	3	1	1	4	8	5	28
I.S. Lumbar left															
Mass or nodule		1	—	—	—	—	—	8	1	—	2		—	1	2
Scab		—	—	—	—	1	—	1	—	—	—	—	—	1	3
Swelling/thickening		4	3	2	2	1	4	28	5	1	3	5	6	9	34
I.S. Scapular, right															
Mass or nodule		—	—	—	1	—	—	3	4			1	—	—	
Scab		—	—	—	1	2	4	7	1	—	—	—	1	5	7
Swelling/thickening		—	2	2	1	1	4	11	3	2	2	5	9	3	13
I.S. Scapular left															
Mass or nodule		—	—	—	2	1	1	1	3	—	1		—	—	1
Scab		—	1	—	1	1	2	9	—	—	3	1	1	3	5
Swelling/thickening		1	3	2	1	1	4	15	3	—	3	4	7	7	24

Histopathology:

Non-neoplastic: Non-neoplastic, treatment-related changes were observed at the injection sites, liver and spleen (please see "Attachment 2: Incidence of non-neoplastic lesions by organ/group/sex for all animals" at the end of this review for all non-neoplastic lesion summary)

1. Injection sites - A range of non-neoplastic lesions were observed and were considered to be consequent upon the prolonged and repetitive injection of the test article, and likely to be the cellular and tissue basis for the neoplastic development. The incidence and severity of these lesions increased with increasing dose of lanreotide. The average severities illustrated in the scanned Table 13 below were calculated as the mean severity in animals with the findings; animals without finding were not included in the calculation.

- Subcutaneous fibrosis: The incidence and/or severity increased with a clear dose relationship in animals at 1.5. 5, 10 and 30 mg/kg/d.

- Dermal fibrosis: The incidence and/or severity were increased in animals at 5, 10 and 30 mg/kg/d.

- Epidermal hyperplasia: Increased thickness of the epidermis with an increasing occurrence of moderate or marked hyperplasia at 1.5, 5, 10 and 30 mg/kg/d.

- Vascular inflammation/degeneration/necrosis: This lesion was seen predominantly in animals from the 10 and 30 mg/kg/d and mainly affected the vessels of the subcutis.

- Vascular intimal thickening/medial hypertrophy: This lesion predominantly seen in animals at 10 and 30 mg/kg/d and in some controls mainly affected the vessels of the subcutis (mainly the small arteries) and was characterized by thickening of the vascular wall either the intima or the media layer.

- Panniculus muscle degeneration: The incidence and/or severity of this change were increased in animals at 5, 10 and 30mg/kg/d.

- Epidermal ulceration: Infrequently seen, and frequently focal in nature. Only in more severe instances. Overlying scab formation was commonly present and the lesions also included varying degrees of acute inflammation with or without edema of the superficial dermis and occasionally subepidermal cleft formation. The incidence of this change was increased in animals at 10 and 30mg/kg/d.

Text Table 13 **Incidence of BIM23014-related Histopathological Changes at Injection Sites**

Tissue/Finding Sex	Male							Female						
Dose (mg/kg/day)	0	0	0.5	1.5	5	10	30	0	0	0.5	1.5	5	10	30
No. of animals examined	60	60	70	70	70	70	70	60	60	70	70	70	70	70
I.S. Dorsal thoracic right														
Fibrosis: dermis	1	5	3	4	7	9	21	1	2	3	3	4	8	29
Average severity	1.0	1.0	1.0	1.0	1.4	1.7	1.3	2.0	1.5	1.3	2.3	1.3	1.1	1.2
Fibrosis: subcutis	12	8	17	7	17	42	57	13	6	17	30	30	44	62
Average severity	1.2	1.0	1.0	1.0	1.1	1.4	2.3	1.2	1.2	1.4	1.1	1.3	1.5	2.6
Degeneration: panniculus muscle	2	2	1	1	6	19	35	6	—	1	2	7	20	34
Average severity	1.0	1.0	1.0	1.0	1.3	1.4	1.9	1.3	—	1.0	1.0	1.1	1.8	1.7
Hyperplasia: epidermis	1	2	—	4	3	5	18	—	1	2	3	2	5	20
Average severity	1.0	1.0	—	1.0	2.3	2.0	1.4	—	2.0	1.0	1.7	1.0	1.2	1.5
Ulceration: epidermis	—	1	—	—	3	3	5	—	1	—	—	—	2	5
Average severity		2.0	—	—	2.3	3.0	2.8	—	1.0	—	—		2.5	2.4
Inflammation/degeneration/necrosis: vascular	—	—	—	—	1	2	8	1	—	1	—	—	2	6
Average severity	—		—	—	1.0	1.0	1.1	2.0	—	1.0	—	—	1.5	1.2
Intimal thickening/ medial hypertrophy: vascular	—	—	—	—	—	1	7		—	—	—	—	—	4
Average severity	—	—	—	—		1.0	1.3	—	—	—	—	—	—	1.3
I.S. Dorsal thoracic left														
Fibrosis: dermis	2	2	2	5	12	9	21	2	3	2	6	4	7	30
Average severity	1.0	1.0	2.0	1.2	1.2	1.4	1.3	1.5	1.7	1.5	1.7	1.5	1.6	1.2
Fibrosis: subcutis	18	8	11	9	27	48	55	16	8	19	27	28	50	58
Average severity	1.1	1.0	1.2	1.1	1.3	1.5	2.4	1.2	1.5	1.3	1.4	1.5	1.7	2.6
Degeneration: panniculus muscle	2	1	—	2	7	14	33	—	1	1	1	4	23	37
Average severity	1.0	1.0	—	1.0	1.3	1.1	1.6	—	2.0	1.0	3.0	1.3	1.5	1.8
Hyperplasia: epidermis	3	1	1	2	4	1	13	2	1	2	5	2	6	15
Average severity	1.3	1.0	3.0	1.0	2.3	2.0	1.7	1.0	3.0	2.0	2.0	1.0	1.8	1.8
Ulceration: epidermis	—	—	1	—	1	1	3	—	1	2	2	—	3	10
Average severity	—	—	2.0	-	3.0	4.0	3.0	—	3.0	1.5	3.5	—	3.3	2.3
Inflammation/degeneration/necrosis: vascular	—	1	—	2	—	2	13	—	—	2	1			7
Average severity	—	1.0	—	1.5	—	1.0	1.2	-	—	1.0	1.0	—	—	1.0
Intimal thickening/ medial hypertrophy: vascular		—	—	—	—	—	8	—		—	—	—	—	1
Average severity	—	—	—	—		—	1.4	—	—	—		—	—	1.0

Tissue/Finding Sex	Male							Female						
Dose (mg/kg/day)	0	0	0.5	1.5	5	10	30	0	0	0.5	1.5	5	10	30
No. of animals examined	60	60	70	70	70	70	70	60	60	70	70	70	70	70
I.S. Lumbar right														
Fibrosis: dermis	—	2	2	—	7	10	22	3	2	2	2	3	4	21
Average severity	—	1.0	1.0	—	1.0	1.2	1.1	1.0	1.0	1.0	1.0	1.0	1.3	1.1
Fibrosis: subcutis	18	12	19	25	39	59	59	19	15	25	44	46	58	65
Average severity	1.1	1.0	1.1	1.1	1.3	1.8	2.7	1.4	1.2	1.4	1.2	1.5	1.8	2.6
Degeneration: panniculus muscle	2	2	3	8	10	31	36	2	—	2	2	5	27	46
Average severity	1.0	1.0	1.0	1.3	1.3	1.4	1.7	1.0	—	1.5	1.0	1.0	1.4	1.8
Hyperplasia: epidermis	1	1	—	—	1	3	4	3			3	2	—	9
Average severity	1.0	1.0	—	—	1.0	1.0	1.0	1.0	—	—	1.0	1.0	—	1.3
Ulceration: epidermis	—			—	1	1	2	—	—	1	—	—	—	2
Average severity	—	—	—	—	3.0	3.0	3.0	—	—	1.0	—	—	—	3.5
Inflammation/degeneration/necrosis: vascular	—	—	—	1	—	5	8	—	—	—	—		2	4
Average severity	—	—	—	1.0	—	1.0	1.0	—	—			—	1.5	1.0
Intimal thickening/ medial hypertrophy: vascular	—	—	1	—	—	3	4	2	—	1		—	—	3
Average severity	—	—	1.0		—	1.0	1.3	1.5	—	1.0	—	—		1.3
I.S. Lumbar left														
Fibrosis: dermis	—	5	4	3	10	15	19	3	—	2	7	5	6	29
Average severity	—	1.0	1.0	1.3	1.2	1.2	1.5	1.0	—	1.5	1.6	1.4	1.0	1.3
Fibrosis: subcutis	23	6	19	23	41	60	53	20	11	22	44	52	62	63
Average severity	1.0	1.0	1.1	1.2	1.2	1.9	2.6	1.3	1.2	1.3	1.3	1.4	2.0	2.6
Degeneration: panniculus muscle	7	—	3	2	5	31	30	1	1	1	6	6	24	44
Average severity	1.0	—	1.3	1.0	1.0	1.5	1.8	1.0	1.0	1.0	1.2	1.5	1.4	1.8
Hyperplasia: epidermis	1	2	—	1	—	5	5	—	—	1	3	1	3	15
Average severity	1.0	1.5	—	1.0	—	1.4	1.4	—	—	1.0	2.0	1.0	1.3	1.6
Ulceration: epidermis	—	—	—	1	1	2	5	—		—	2	—	1	3
Average severity	—	—	—	4.0	4.0	2.5	2.8	—	—	—	3.5	—	3.0	2.0
Inflammation/degeneration/necrosis: vascular	—	—	—	—	2	3	8	—	—	—	—		—	6
Average severity	—	—	—	—	1.0	1.7	1.1	—	—	—	—	—	—	1.5
Intimal thickening/ medial hypertrophy: vascular	—	—	—	—	—	4	8	—	—	—		—	—	2
Average severity	—	—	—	—	—	1.8	1.5	—	—	—	—	—	—	1.5

Tissue/Finding Sex	Male							Female						
Dose (mg/kg/day)	0	0	0.5	1.5	5	10	30	0	0	0.5	1.5	5	10	30
No. of animals examined	60	60	70	70	70	70	70	60	60	70	70	70	70	70
I.S. Scapular, right														
Fibrosis: dermis	1	2	4	6	13	16	42	7	1	7	4	7	15	34
Average severity	1.0	1.5	1.5	1.7	1.4	1.5	1.5	1.6	2.0	1.4	1.8	1.7	1.4	1.4
Fibrosis: subcutis	12	8	17	16	14	41	58	9	5	13	15	19	25	62
Average severity	1.2	1.1	1.1	1.1	1.1	1.5	2.3	1.2	1.2	1.5	1.4	1.4	1.3	2.2
Degeneration: panniculus muscle	—	1	—	3	1	12	20	1	—	—	1	1	2	23
Average severity	—	1.0	—	1.3	1.0	1.1	1.5	1.0	—	—	1.0	1.0	1.5	1.6
Hyperplasia: epidermis	3	1		5	4	6	20	5	1	6	3	8	13	21
Average severity	1.3	2.0	—	1.6	2.0	2.2	1.7	1.4	3.0	1.3	2.3	1.5	1.5	1.6
Ulceration: epidermis	—	—	—	—	—	5	5	2	—	3	1	2	3	2
Average severity	—	—	—	—	—	3.0	2.2	3.0	—	2.3	3.0	2.0	1.3	2.5
Inflammation/degeneration/necrosis: vascular	—	1	—	1	3	4	10		—	1	—	1	2	14
Average severity	—	2.0	—	2.0	1.3	1.0	1.4	—	—	2.0	—	1.0	2.5	1.4
Intimal thickening/ medial hypertrophy: vascular	—	—	—	—	—	1	7	—		—	—	—	—	4
Average severity	—	—	—	—	—	2.0	1.4	—	—	—	—	—	—	1.8
I.S. Scapular, left														
Fibrosis: dermis	3	5	8	9	8	16	41	4	1	7	5	5	8	45
Average severity	1.0	1.2	1.3	1.3	1.8	1.1	1.6	1.0	1.0	1.7	1.8	1.6	1.6	1.4
Fibrosis: subcutis	19	17	21	18	37	58	60	14	8	12	14	26	41	65
Average severity	1.1	1.0	1.1	1.2	1.3	1.7	2.4	1.4	1.1	1.5	1.4	1.3	1.5	2.5
Degeneration: panniculus muscle	3	—	—	3	8	9	14	2	—	1	—	2	8	19
Average severity	1.0	—	—	1.0	1.1	1.4	1.5	1.0	—	2.0	—	1.0	1.5	1.6
Hyperplasia: epidermis	3	3	3	6	3	6	31	4	1	7	3	5	10	26
Average severity	1.3	1.3	1.0	1.3	2.7	2.0	1.4	1.5	1.0	1.7	2.3	1.4	1.4	1.6
Ulceration: epidermis	—	—	—	2	1	2	4	—	—	2	1	1	1	3
Average severity	—		—	2.0	3.0	1.5	2.5		—	2.0	3.0	3.0	2.0	2.0
Inflammation/degeneration/necrosis: vascular	2	1	—	-	2	10	23	—	1	1	—	1	—	16
Average severity	1.0	1.0	-	—	1.0	1.2	1.1	—	1.0	3.0	—	1.0	—	1.3
Intimal thickening/ medial hypertrophy: vascular	—	—	—	-	1	4	11	—	—	—	—		1	5
Average severity	—	-	—	—	1.0	1.0	1.5	—	—	—	—	—	1.0	1.2

2. Liver - changes consisted of centrilobular hypertrophy, single cell necrosis and mitotic figures. These changes were also observed in control animals. There was an increased incidence of centrilobular hypertrophy of the hepatocytes observed at all dose levels but most notably in animals at 10 and 30 mg/kg/d, males being more severely affected than females. Increases in single cell necrosis, particularly in the centrilobular area, as well as an increased number of mitotic figures were observed in animals (mostly males) treated at 30mg/kg/d (see scanned Table 14 below). In a few animals, the single cell necrosis was accompanied by degeneration of the centrilobular hepatocytes characterized by enlarged, granular and hypereosinophilic cells with indistinct cellular borders.

3. Spleen - there was an increased incidence of extramedullary hematopoiesis that was most notable in males at 30 mg/kg/d and in females at ≥ 1.5 mg/kg/d. The sponsor proposed that this change may be secondary to the sustained inflammatory process and/or chronic blood loss at the injection sites.

Text Table 14 Incidence of BIM23014–related Histopathological Changes in Liver and Spleen

Tissue/Finding Sc	Male							Female						
Dose (mg/kg/day)	0	0	0.5	1.5	5	10	30	0	0	0.5	1.5	5	10	30
No. of animals examined	60	60	70	70	70	70	70	60	60	70	70	70	70	70
Liver														
Hypertrophy: centrilobular	2	6	10	13	15	22	23	—	—	1	2	2	2	3
Necrosis: single cell	7	5	4	3	3	5	18	1	3	4	4	5	1	7
Increased mitotic figures	—	—	—	—	—		4	—	1	—	—	1	1	1
Hematopoiesis: extramedullary	6	5	2	7	5	8	16	6	7	5	10	11	10	2
Spleen														
Hematopoiesis: extramedullary	18	24	23	15	25	22	43	30	25	31	40	46	45	43

Neoplastic: The primary finding was drug-related effect on the incidence of cutaneous/subcutaneous tumors derived from fibrous connective tissues at the injection sites. The distribution and incidence of the tumors are shown in the scanned Table 12 below. All other neoplastic lesions were commonly encountered in animals of this strain and age compared to the NTP historical control data (historical data from the testing facility were not submitted except that of the fibrous connective tissues) without statistical significance, and therefore they were considered to be spontaneous and non-treatment related tumors.

- At HD 30 mg/kg/d, significantly increased incidence in malignant tumors of fibrous connective tissue (mainly fibrosarcoma and malignant fibrous histiocytoma) developed at injection sites (refer to the scanned summary Text Table 12 below); these tumors were found in 44/140 animals (M & F combined) corresponding to 79/840 potential injection sites (sex combined); males had higher incidence than females:

  Males: 29/70 animals with tumors corresponding to 55/420 potential injection sites;
  Females: 15/70 animals with tumors corresponding to 24/420 potential injection sites.

  Mean incidence of animals with tumor: 41.4% in males (29/70) and 21.4% in females (15/70) vs the testing lab's 0.25% for males and 1.86% for females.
  Mean tumor incidence per animal: 0.78 tumors/male and 0.34 tumors/female (vs 0.002 tumors/male and 0.018 tumors/female in historical controls)

- At lower dose levels (≤ 10 mg/kg/d), the incidence of fibrosarcoma was very low (occasionally seen, see table 12 below) and more incidence in females than in males, but these tumors did not show any dose relationship. Though tumor incidence at lower doses was higher than that in concurrent controls, they fell within the historical incidence range and mean value (ranged from 0-1.67% in males and 0-4.17% in females, and mean percentage 0.25% in males and 1.86% in females, see the testing facility's "Historical Data" in Appendix), which suggests that the effect is not treatment-related.

- In addition to the above, metastasis of fibrosarcoma were seen in the draining lymph nodes of 2/70 males at 30 mg/kg/d.

- Bone: Osteosarcoma was seen at the injection site of one male at 1.5 mg/kg/d and one female at 10 mg/kg/d. This tumor is known to occur spontaneously in the subcutaneous tissue of mice at a low incidence (historically, 0% for males and 0.12% for females). In the absence of tumors at the HD 30 mg/kg/d and the low incidence observed, the osteosarcoma appears to be spontaneous.

Text Table 12 Incidence/Group of Principal Injection Site Neoplasms

Tissue/Finding Se	Male							Female						
Dose (mg/kg/da	0	0	0.5	1.5	5	10	30	0	0	0.5	1.5	5	10	30
No. of animals examine	60	60	70	70	70	70	70	60	60	70	70	70	70	70
I.S. Dorsal thoracic right														
Fibrosarcoma	—	—	—	—	—	—	6	—	—	—	—	—	1	4
Malignant Fibrous Histiocytoma	—	—	—	—	—	—	2	—	—	—	—	—	—	—
I.S. Dorsal thoracic left														
Fibrosarcoma	—	—	—	—	—	—	13	—	—	1	—	—	—	9
Malignant Fibrous Histiocytoma	—	—	—	—	—	—	3	—	—	—	—	—	—	—
I.S. Lumbar right														
Fibrosarcoma	—	—	—	—	—	—	9	—	—	—	—	1	—	4
Malignant Fibrous Histiocytoma	—	—	—	—	—	—	1	—	—	—	—	—	—	—
I.S. Lumbar left														
Fibrosarcoma	—	—	—	—	—	—	10	—	—	—	—	1	1	2
Osteosarcoma	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Malignant Fibrous Histiocytoma	—	—	—	—	—	—	2	—	—	—		—	—	—
I.S. Scapular, right														
Fibrosarcoma	—	—	—	—	—	—	4	—	—	—	—	1	—	1
Malignant Fibrous Histiocytoma	—	—	—	—		—	1	—	—	—	—	—		
I.S. Scapular, left														
Fibrosarcoma	—	—	—	—	—	1	4	—	—	1	—	—	—	3
Osteosarcoma	—	—	—	1	—	—	—	—	—	—	—	—	—	—
Malignant Fibrous Histiocytoma	—	—	—	—		—	—	—	—	—	—	—	—	1
TOTAL no. of tumours	—	—	—	1	—	1	55	—	—	2	—	3	3	24
No. of animals with tumors at injection site	—	—	—	1	—	1	29	—	—	2	—	3	3	15

Incidence of neoplastic lesions in all animals is shown in the following scanned tables (Table 13); male and female data were summarized separately. Incidence of neoplastic lesions for preterminal (Table 11) and terminal (Table 12) animals in the mouse is shown in Attachment 1.

Table 13 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
All Animals

MALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 69	6 69	7 70
ADRENAL	NO.EXAM.:	-	3	-	1	2	-	1
- Hemangiosarcoma		-	1	-	-	-	-	-
- Carcinoma: metastasis		-	-	-	-	1	-	-
ADRENAL	NO.EXAM.:	59	60	70	69	68	68	70
- Adenoma: subcapsular		-	1	3	1	2	1	2
- Carcinoma: cortical		-	-	-	-	-	1	-
- Adenoma: cortical		2	-	1	-	-	-	-
- Benign pheochromocytoma		-	-	-	2	-	-	1
- Malignant pheochromocytoma		1	-	-	-	-	1	-
AORTA	NO.EXAM.:	60	60	70	70	69	69	70
- Carcinoma: metastasis		-	-	-	-	1	-	-
BILE DUCT	NO.EXAM.:	1	-	-	-	-	-	-
BLOOD VESSEL	NO.EXAM.:	-	1	-	-	-	-	-
BONE-FEMUR	NO.EXAM.:	60	60	70	70	69	69	70
- Sarcoma: metastasis		1	1	3	-	1	-	-
BONE MARROW	NO.EXAM.:	60	60	70	70	69	69	70
- Mast cell tumor (malignant)		-	-	-	-	-	1	-
BONE MISCELLANEOUS	NO.EXAM.:	-	-	-	1	-	-	-
BONE-STERNUM	NO.EXAM.:	60	60	70	70	69	69	70
- Sarcoma: metastasis		-	-	2	-	2	-	-
BRAIN	NO.EXAM.:	60	60	70	70	69	69	70
BULBOPENIS	NO.EXAM.:	4	3	6	4	-	1	1
CAVITY CRANIAL	NO.EXAM.:	-	-	-	-	-	1	-
CAVITY PELVIC	NO.EXAM.:	1	1	1	-	1	1	1
CECUM	NO.EXAM.:	60	60	70	69	69	69	70
- Adenocarcinoma		2	-	-	-	-	-	-
COLON	NO.EXAM.:	60	60	70	69	69	69	70

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
DIAPHRAGM	NO.EXAM.:	-	-	-	-	1	-	-
- Carcinoma: metastasis		-	-	-	-	1	-	-
DUODENUM	NO.EXAM.:	60	60	70	69	68	68	69
EPIDIDYMIS	NO.EXAM.:	60	60	70	70	70	70	70
- Hemangiosarcoma		-	-	-	-	1	-	-
- Sarcoma (not otherwise specified)		-	-	-	2	-	-	-
- Carcinoma: interstitial cell		-	-	-	-	1	1	-
ESOPHAGUS	NO.EXAM.:	60	60	70	70	70	70	70
EYE	NO.EXAM.:	60	60	70	70	70	70	70
FAT	NO.EXAM.:	-	1	-	-	-	1	-
GALLBLADDER	NO.EXAM.:	56	54	65	69	66	69	67
HARDERIAN GLAND	NO.EXAM.:	60	60	70	70	70	70	70
- Adenoma		5	3	5	5	1	7	-
- Adenocarcinoma		-	1	2	1	2	1	-
HEART	NO.EXAM.:	60	60	70	70	69	69	70
HEMOLYM. TISSUE	NO.EXAM.:	5	12	3	6	14	8	1
- Malignant lymphoma		4	9	2	4	12	7	1
- Histiocytic sarcoma		1	3	1	2	2	-	-
- Leukemia (not otherwise specified)		-	-	-	-	-	1	-
ILEUM	NO.EXAM.:	60	59	70	69	69	69	70
I.S. DORS.THO. LT	NO.EXAM.:	60	60	70	70	69	69	70
- Fibrosarcoma		-	-	-	-	-	-	13
- Malignant fibrous histiocytoma		-	-	-	-	-	-	3
I.S. DORS.THO. RT	NO.EXAM.:	60	60	70	70	69	69	69
- Fibrosarcoma		-	-	-	-	-	-	6
- Malignant fibrous histiocytoma		-	-	-	-	-	-	2
I.S. LUMBAR, LEFT	NO.EXAM.:	60	60	70	70	69	69	69
- Fibrosarcoma		-	-	-	-	-	-	10
- Malignant fibrous histiocytoma		-	-	-	-	-	-	2

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. LUMBAR, RIGHT	NO.EXAM.:	60	60	70	70	69	69	69
- Fibrosarcoma		-	-	-	-	-	-	9
- Malignant fibrous histiocytoma		-	-	-	-	-	-	1
I.S. SCAPULAR, LEFT	NO.EXAM.:	60	60	70	70	69	69	69
- Fibrosarcoma		-	-	-	-	-	1	4
- Osteosarcoma		-	-	-	1	-	-	-
- Lipoma		-	-	-	1	-	-	-
I.S. SCAPULAR, RIGHT	NO.EXAM.:	60	60	70	70	69	69	69
- Fibrosarcoma		-	-	-	-	-	-	4
- Malignant Fibrous Histiocytoma		-	-	-	-	-	-	1
JEJUNUM	NO.EXAM.:	60	60	70	70	69	69	70
- Adenocarcinoma		-	1	2	-	-	2	-
JOINT	NO.EXAM.:	-	-	1	1	1	-	-
KIDNEY	NO.EXAM.:	60	60	70	70	70	70	70
- Adenoma: tubular cell		-	-	-	-	-	-	1
- Carcinoma: tubular cell		-	1	-	-	-	-	-
- Sarcoma: metastasis		-	-	-	-	-	-	1
- Carcinoma: metastasis		-	-	-	-	1	-	-
LACRIMAL GLAND	NO.EXAM.:	60	60	69	69	70	68	69
LARYNX	NO.EXAM.:	60	60	70	70	69	69	70
LIVER	NO.EXAM.:	60	60	70	70	70	70	70
- Adenoma: hepatocellular		23	18	10	17	4	15	4
- Carcinoma: hepatocellular		2	3	4	2	9	1	2
- Hemangiosarcoma		3	2	4	3	3	3	-
- Sarcoma: metastasis		3	-	4	1	2	-	-
- Carcinoma: metastasis		1	-	-	-	-	-	-
LUNG	NO.EXAM.:	60	60	70	70	70	70	70
- Carcinoma: alveolar/bronchiolar		4	6	3	7	7	11	2
- Adenoma: alveolar/bronchiolar		5	10	17	12	6	13	9

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
LUNG	CONT'D.	60	60	70	70	70	70	70
- Carcinoma: metastasis		-	-	-	1	-	-	-
LYMPH NODE	NO.EXAM.:	9	24	16	12	21	10	27
- Sarcoma: metastasis		-	-	1	-	-	-	2
- Carcinoma: metastasis		1	-	-	-	3	-	-
L. NODE MANDIBULAR	NO.EXAM.:	57	50	61	60	59	64	62
L.NODE MESENTERIC	NO.EXAM.:	59	60	69	68	68	68	69
- Carcinoma: metastasis		-	-	2	-	-	-	-
- Sarcoma: metastasis		-	-	-	-	1	1	-
MENINGES	NO.EXAM.:	-	-	-	-	-	1	-
MUSCLE SKELETAL	NO.EXAM.:	60	59	69	68	68	67	69
- Sarcoma: metastasis		-	-	-	-	-	-	1
NERVES OPTIC	NO.EXAM.:	58	56	68	68	67	68	69
NERVE SCIATIC	NO.EXAM.:	58	60	70	70	69	70	70
- Sarcoma: metastasis		-	-	-	-	-	-	1
PANCREAS	NO.EXAM.:	60	60	70	70	70	70	70
- Adenoma: islet cell		-	1	-	-	-	-	-
- Carcinoma: metastasis		1	-	-	-	-	-	-
PARATHYROID GLAND	NO.EXAM.:	38	36	42	49	42	48	40
- Adenoma		-	-	-	1	-	-	-
PENIS	NO.EXAM.:	-	-	-	-	1	1	-
PITUITARY	NO.EXAM.:	59	60	67	68	68	68	68
- Adenoma: pars distalis		-	1	-	-	-	-	1
- Adenoma: pars intermedia		-	-	1	-	-	-	-
PREPUTIAL GLAND	NO.EXAM.:	59	60	69	68	67	68	69
- Hemangioma		-	-	-	1	-	-	-
PROSTATE	NO.EXAM.:	60	60	70	70	70	69	69
- Adenocarcinoma		-	-	-	-	1	1	-

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

MALE

DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
RECTUM	NO.EXAM.:	1	-	-	-	-	1	-
SALIV.GL. MANDIBULAR	NO.EXAM.:	60	60	70	70	70	70	70
SALIV. GLAND PAROTID	NO.EXAM.:	-	1	-	-	-	-	-
SEMINAL VESICLE	NO.EXAM.:	60	60	70	70	70	70	69
SKIN	NO.EXAM.:	60	60	70	69	69	69	70
SKIN MISCELLANEOUS	NO.EXAM.:	17	15	20	18	23	21	18
- Mast cell tumor		-	-	-	-	-	-	1
SPINAL CORD CERVICAL	NO.EXAM.:	60	60	70	70	69	69	70
SPLEEN	NO.EXAM.:	60	60	70	70	70	70	70
- Hemangioma		1	-	1	2	-	-	-
- Hemangiosarcoma		5	2	6	2	4	3	-
STOMACH	NO.EXAM.:	60	60	70	70	69	69	70
SUBCUTANEOUS TISSUE	NO.EXAM.:	5	7	5	5	3	6	2
- Hemangiosarcoma		-	1	-	-	-	-	-
- Fibrosarcoma		-	1	-	-	-	-	2
- Hemangioma		-	2	-	-	-	-	-
TAIL	NO.EXAM.:	2	-	2	-	-	1	1
- Hemangioma		2	-	1	-	-	-	-
- Hemangiosarcoma		-	-	1	-	-	-	-
TESTIS	NO.EXAM.:	60	60	70	70	70	70	70
- Adenoma: interstitial cell		1	1	-	-	1	-	-
THORAX	NO.EXAM.:	1	-	-	-	2	-	-
THYMUS	NO.EXAM.:	50	48	58	59	61	56	62
THYROID	NO.EXAM.:	60	60	70	69	68	69	70
- Adenoma: follicular cell		1	-	-	-	-	-	-

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

MALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
TONGUE	NO.EXAM.:	60	60	70	70	70	70	70
TRACHEA	NO.EXAM.:	60	60	70	69	70	70	69
URETER	NO.EXAM.:	13	13	11	11	15	11	9
URETHRA	NO.EXAM.:	-	-	-	1	-	-	-
URINARY BLADDER	NO.EXAM.:	60	60	70	70	70	70	70
- Submucosal mesenchymal tumor (M)		2	-	1	-	-	1	1
- Carcinoma: transitional cell		1	-	-	1	1	-	-
VAS DEFERENS	NO.EXAM.:	-	-	-	-	-	1	-
ZYMBAL'S GLAND	NO.EXAM.:	60	60	69	70	68	68	69

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

FEMALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
ABDOMEN	NO.EXAM.:	-	1	2	2	1	1	1
- Hemangiosarcoma		-	-	-	1	-	-	-
ADRENAL	NO.EXAM.:	60	60	70	69	68	70	70
- Adenoma: subcapsular		3	1	2	2	1	-	-
- Carcinoma: cortical		-	-	1	-	-	-	-
- Adenoma: cortical		-	-	-	-	-	-	1
- Benign pheochromocytoma		-	-	1	3	-	3	-
- Malignant pheochromocytoma		2	1	1	1	1	2	-
- Carcinoma: metastasis		-	-	-	-	1	-	-
AORTA	NO.EXAM.:	60	60	69	70	70	70	70
BLOOD VESSEL	NO.EXAM.:	-	1	-	-	-	-	-
BONE-FEMUR	NO.EXAM.:	60	59	70	70	70	70	70
- Sarcoma: metastasis		-	-	-	-	1	-	1
- Osteosarcoma		-	-	-	1	-	-	-
- Chondroma		-	-	-	1	-	-	-
BONE MARROW	NO.EXAM.:	60	60	70	70	70	70	70
- Mast cell tumor (malignant)		2	-	-	-	-	-	-
BONE MISCELLANEOUS	NO.EXAM.:	1	2	1	-	1	-	-
- Osteosarcoma		1	1	-	-	-	-	-

Table 13 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
BONE-STERNUM	NO.EXAM.:	60	60	69	70	70	69	70
- Sarcoma: metastasis		-	-	-	-	1	-	-
- Hemangiosarcoma		-	1	-	-	-	-	-
BRAIN	NO.EXAM.:	60	60	70	70	70	70	70
CAVITY CRANIAL	NO.EXAM.:	-	-	-	-	-	1	-
CAVITY ORAL	NO.EXAM.:	-	-	-	1	-	1	-
CECUM	NO.EXAM.:	60	60	70	70	70	70	70
CLITORAL GLAND	NO.EXAM.:	58	58	67	67	64	67	65
COLON	NO.EXAM.:	60	60	70	69	70	70	70
DUODENUM	NO.EXAM.:	60	60	70	70	70	70	70
- Sarcoma: metastasis		1	-	-	-	-	-	-
ESOPHAGUS	NO.EXAM.:	60	60	70	70	70	70	70
- Carcinoma: squamous cell		-	-	-	-	-	-	1
EYE	NO.EXAM.:	60	60	70	70	70	70	70
FAT	NO.EXAM.:	8	3	2	-	1	3	4
- Carcinoma: metastasis		1	-	-	-	-	-	-
- Sarcoma: metastasis		1	-	-	-	-	-	-
- Hemangioma		1	-	-	-	-	-	-
- Liposarcoma		-	-	-	-	-	-	1
GALLBLADDER	NO.EXAM.:	59	59	68	69	70	69	69
HARDERIAN GLAND	NO.EXAM.:	60	60	70	70	70	70	70
- Adenoma		2	1	1	1	6	-	-
HEAD	NO.EXAM.:	-	-	1	-	-	-	-
- Carcinoma (not otherwise specified)		-	-	1	-	-	-	-
HEART	NO.EXAM.:	60	60	70	70	70	70	70
- Carcinoma: metastasis		-	-	-	-	1	-	-
HEMOLYM. TISSUE	NO.EXAM.:	24	20	17	16	22	24	15
- Malignant lymphoma		23	15	11	13	17	15	10
- Histiocytic sarcoma		2	5	6	4	6	10	5

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
ILEUM	NO.EXAM.:	60	60	70	70	70	70	70
I.S. DORS.THO. LT	NO.EXAM.:	60	60	70	70	70	70	70
- Fibrosarcoma		-	-	1	-	-	-	3
- Mast cell tumor		-	-	-	1	-	-	-
I.S. DORS.THO. RT	NO.EXAM.:	60	60	70	70	70	70	70
- Fibrosarcoma		-	-	-	-	-	1	4
- Mast cell tumor		-	-	-	-	1	-	-
I.S. LUMBAR, LEFT	NO.EXAM.:	60	60	70	70	70	70	70
- Fibrosarcoma		-	-	-	-	1	1	2
- Osteosarcoma		-	-	-	-	-	1	-
I.S. LUMBAR, LEFT	CONT'D.	60	60	70	70	70	70	70
- Fibroma		-	-	-	-	1	-	-
I.S. LUMBAR, RIGHT	NO.EXAM.:	60	60	70	70	70	70	70
- Fibrosarcoma		-	-	-	-	1	-	4
- Sarcoma: metastasis		1	-	-	-	-	-	-
I.S. SCAPULAR, LEFT	NO.EXAM.:	60	60	70	70	70	70	70
- Fibroma		-	-	-	-	-	1	-
- Fibrosarcoma		-	-	1	-	-	-	3
- Malignant fibrous histiocytoma		-	-	-	-	-	-	1
- Hemangioma		-	-	-	-	-	-	1
I.S. SCAPULAR, RIGHT	NO.EXAM.:	60	60	70	70	70	70	70
- Fibrosarcoma		-	-	-	-	1	-	1
JEJUNUM	NO.EXAM.:	60	60	70	70	70	70	70
- Adenocarcinoma		1	-	-	-	-	1	-
JOINT	NO.EXAM.:	-	1	-	1	-	-	-
KIDNEY	NO.EXAM.:	60	60	70	70	70	70	70
LACRIMAL GLAND	NO.EXAM.:	57	59	69	70	70	69	70
LARYNX	NO.EXAM.:	60	60	70	70	70	70	70

Table 13 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
All Animals

FEMALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
LIVER	NO.EXAM.:	60	60	70	70	70	70	70
- Adenoma: hepatocellular		2	2	3	4	1	2	-
- Carcinoma: hepatocellular		1	-	-	-	1	-	1
- Hemangiosarcoma		-	4	1	3	1	-	-
- Sarcoma: metastasis		2	-	1	2	1	1	1
- Carcinoma: metastasis		-	-	-	-	1	-	-
LUNG	NO.EXAM.:	60	60	70	69	70	70	70
- Carcinoma: alveolar/bronchiolar		4	5	5	4	3	4	1
- Adenoma: alveolar/bronchiolar		10	7	12	5	6	8	3
- Carcinoma: metastasis		-	1	1	1	1	-	-
- Sarcoma: metastasis		1	-	-	1	1	1	-
LYMPH NODE	NO.EXAM.:	22	20	20	22	31	25	24
- Sarcoma: metastasis		1	-	-	-	-	-	1
- Carcinoma: metastasis		-	-	1	-	-	-	-
- Hemangiosarcoma		1	-	-	-	-	-	-
L. NODE MANDIBULAR	NO.EXAM.:	56	54	64	62	64	53	64
- Carcinoma: metastasis		-	-	1	-	-	-	-
L.NODE MESENTERIC	NO.EXAM.:	60	60	70	69	70	68	70
- Sarcoma: metastasis		-	-	-	-	1	-	1
MAMMARY GLAND	NO.EXAM.:	56	58	68	69	68	66	70
- Adenocarcinoma		4	1	4	2	4	-	-
- Adenoma		1	2	-	-	-	-	-
MUSCLE SKELETAL	NO.EXAM.:	60	58	68	69	68	70	70
MUSCLE SKELETAL MISC	NO.EXAM.:	-	2	-	1	-	1	1
NERVES OPTIC	NO.EXAM.:	59	59	70	68	66	66	68
NERVE SCIATIC	NO.EXAM.:	60	59	70	69	70	70	70

Table 13 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
OVARY	NO.EXAM.:	60	60	70	70	70	70	70
- Cystadenoma		1	-	1	-	1	1	-
- Cystadenocarcinoma		-	-	1	-	-	-	-
- Benign granulosa-theca cell tumor		-	-	2	-	-	1	-
- Malignant granulosa-theca cell tumor		1	-	-	-	1	2	-
- Benign sertoli cell tumor		-	-	-	-	1	-	-
- Adenoma: tubulostromal		1	-	-	-	-	-	-
- Hemangioma		-	-	-	-	-	1	-
OVIDUCT	NO.EXAM.:	60	60	70	70	70	70	69
PANCREAS	NO.EXAM.:	60	60	70	70	70	69	69
- Adenoma: islet cell		-	1	-	1	-	-	-
- Mesothelioma (B)		-	-	1	-	-	-	-
- Sarcoma: metastasis		1	-	-	-	-	-	-
PARATHYROID GLAND	NO.EXAM.:	39	38	52	51	47	51	46
PERICARDIUM	NO.EXAM.:	1	-	-	-	-	-	-
PITUITARY	NO.EXAM.:	59	60	69	70	69	69	67
- Adenoma: pars distalis		1	2	3	2	1	-	-
- Adenoma: pars intermedia		-	-	-	1	-	-	-
RECTUM	NO.EXAM.:	-	-	-	1	-	-	-
SALIV.GL. MANDIBULAR	NO.EXAM.:	59	59	70	69	70	69	70
SKIN	NO.EXAM.:	60	60	70	70	70	70	70
SKIN MISCELLANEOUS	NO.EXAM.:	9	9	16	16	10	10	16
- Papilloma: squamous cell		-	1	-	-	-	-	-
- Carcinoma: squamous cell		1	1	-	-	-	-	-
- Hemangioma		-	-	1	-	-	-	-
SPINAL CORD CERVICAL	NO.EXAM.:	60	60	70	70	70	70	70

Table 13 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
SPLEEN	NO.EXAM.:	60	60	70	70	70	70	70
- Mast cell tumor: metastasis		1	-	-	-	-	-	-
- Hemangiosarcoma		-	1	1	-	3	1	2
- Carcinoma: metastasis		-	-	-	-	1	-	1
- Sarcoma: metastasis		-	-	-	1	-	-	1
STOMACH	NO.EXAM.:	60	60	70	70	70	70	70
- Osteosarcoma		-	-	-	-	-	1	-
- Mesothelioma (B)		-	-	1	-	-	-	-
- Adenoma		-	-	1	-	-	-	-
SUBCUTANEOUS TISSUE	NO.EXAM.:	5	6	5	8	5	5	3
- Hemangiosarcoma		-	1	-	-	-	-	-
- Fibrosarcoma		1	-	2	4	1	-	1
- Myxoma		-	-	-	-	1	-	-
- Osteosarcoma		1	-	-	-	1	-	-
TAIL	NO.EXAM.:	3	-	1	1	-	1	1
THORAX	NO.EXAM.:	1	1	1	-	3	3	-
THYMUS	NO.EXAM.:	56	51	64	61	61	62	67
THYROID	NO.EXAM.:	60	59	70	70	70	70	70
- Adenoma: follicular cell		1	-	-	2	1	-	-
TONGUE	NO.EXAM.:	60	60	70	70	70	70	70
TRACHEA	NO.EXAM.:	60	60	69	68	70	70	70
URETER	NO.EXAM.:	2	4	2	2	1	1	1
URINARY BLADDER	NO.EXAM.:	60	60	70	68	70	70	69
- Submucosal mesenchymal tumor (N)		-	-	1	-	1	-	-
- Carcinoma: transitional cell		-	-	-	1	-	-	-
- Sarcoma: metastasis		1	-	-	-	-	1	-
- Leiomyosarcoma		-	-	1	-	-	-	-

Table 13 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
UTERUS	NO.EXAM.:	60	60	70	70	70	70	70
- Sarcoma: endometrial stromal		1	1	-	1	3	1	1
- Benign granular cell tumor		1	-	1	1	2	-	1
- Leiomyoma		6	3	4	7	4	2	3
- Leiomyosarcoma		3	-	2	2	3	1	1
- Hemangioma		-	-	-	-	-	1	-
- Hemangiosarcoma		1	2	-	-	2	3	-
- Adenoma: endometrial		-	-	-	1	-	-	-
- Adenocarcinoma: endometrial		-	3	7	4	5	1	4
- Carcinoma: squamous cell		-	1	-	-	-	-	-
- Sarcoma: metastasis		-	1	-	-	-	-	-
VAGINA	NO.EXAM.:	59	58	70	69	69	70	70
- Polyp		1	-	-	-	-	-	-
ZYMBAL'S GLAND	NO.EXAM.:	59	60	70	70	70	70	70

Toxicokinetics: Cmax values were less than proportional to the dose increase on Week 104. However AUC_{0-t} values increased more than proportional to the dose increase on Week 104, mean AUC_{0-t} at this time point were 155 and 203, 298 and 855, 1003 and 2184, 1530 and 4009 ng/ml/h in male and female mice, respectively, at doses of 0.5, 1.5, 5 and 10 mg/kg/d. At the HD 30 mg/kg/d, animals were died or moribund sacrificed from Week 87 prior to the end of the study, the AUC_{0-t} values at this dose level on Week 52 were 7242/14745 ng/ml/h in males and females, respectively (scanned Table 10 below).

Text Table 10 **Exposure (C_{max} ng/ml, AUC ng/ml.h-1) Values After Daily Treatment in Both Genders**

			DOSES (mg/kg/day)				
			0.5	1.5	5	10	30
Day 1	Males	Cmax	106.1	476.5	1198.9	2179.6	7780.3
		AUCt	103	452	1155	1971	8780
	Females	Cmax	113.6	379.6	1430.0	2616.2	5810.4
		AUCt	101	299	1319	2040	7104
Week 26	Males	Cmax	105.2	350.3	1805.0	5057.8	5545.6
		AUCτ	131	325	1504	3794	8811
	Females	Cmax	118.5	343.4	3372.1	5649.0	3755.6
		AUCτ	131	565	2842	8109	12356
Week 52	Males	Cmax	117.4	358.6	1600.5	4879.6	6844.9
		AUCτ	111	342	1465	3494	7242
	Females	Cmax	116.9	349.7	1430.0	2194.5	4592.4
		AUCτ	123	320	1613	2417	14745
Week 104	Males	Cmax	183.1	454.1	1411.9	2010.2	-
		AUCτ	155	298	1003	1530	-
	Females	Cmax	199.8	404.8	2268.4	4510.5	-
		AUCτ	203	855	2184	4009	-

Putative lanreotide antibody: There was no evidence that administration of lanreotide in the rat induces the production of putative antibodies.

Attachment 1: Incidence of neoplastic lesions by organ/group/sex for preterminal (Table 11) and terminal (Table 12) animals in the mouse

Table 11 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex

Preterminal Animals

MALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 40	2 38	3 44	4 38	5 35	6 36	7 51
ABDOMEN	NO.EXAM.:	-	2	-	-	1	-	1
- Hemangiosarcoma		-	1	-	-	-	-	-
ADRENAL	NO.EXAM.:	39	38	44	38	35	35	51
- Adenoma: subcapsular		-	-	2	3	-	-	-
- Adenoma: cortical		2	-	-	-	-	-	-
- Benign pheochromocytoma		-	-	-	1	-	-	-
- Malignant pheochromocytoma		1	-	-	-	-	1	-
AORTA	NO.EXAM.:	40	38	44	38	35	36	51
- Carcinoma: metastasis		-	-	-	-	1	-	-
BILE DUCT	NO.EXAM.:	1	-	-	-	-	-	-
BLOOD VESSEL	NO.EXAM.:	-	1	-	-	-	-	-
BONE-FEMUR	NO.EXAM.:	40	38	44	38	35	35	51
- Sarcoma: metastasis		1	-	2	-	-	-	-
BONE MARROW	NO.EXAM.:	40	38	44	38	35	36	51
BONE-STERNUM	NO.EXAM.:	40	38	44	38	35	36	51
- Sarcoma: metastasis		-	-	2	-	-	-	-
BRAIN	NO.EXAM.:	40	38	44	38	35	36	51
BULBOPENIS	NO.EXAM.:	4	3	6	4	-	1	1
CAVITY CRANIAL	NO.EXAM.:	-	-	-	-	-	1	-
CAVITY PELVIC	NO.EXAM.:	1	1	1	-	1	1	1
CECUM	NO.EXAM.:	40	38	44	37	35	36	51
- Adenocarcinoma		1	-	-	-	-	-	-
COLON	NO.EXAM.:	40	38	44	37	35	36	51
DIAPHRAGM	NO.EXAM.:	-	-	-	-	1	-	-
- Carcinoma: metastasis		-	-	-	-	1	-	-
DUODENUM	NO.EXAM.:	40	38	44	37	35	36	50
EPIDIDYMIS	NO.EXAM.:	40	38	44	38	35	36	51
- Hemangiosarcoma		-	-	-	-	1	-	-

Table 11 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
Preterminal Animals

MALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 40	2 38	3 44	4 38	5 35	6 36	7 51
ESOPHAGUS	NO.EXAM.:	40	38	44	38	35	36	51
EYE	NO.EXAM.:	40	38	44	38	35	36	51
FAT	NO.EXAM.:	-	1	-	-	-	1	-
GALLBLADDER	NO.EXAM.:	37	37	42	37	33	35	50
HARDERIAN GLAND	NO.EXAM.:	40	38	44	38	35	36	51
- Adenoma		1	2	-	1	-	4	-
- Adenocarcinoma		-	-	1	-	1	-	-
HEART	NO.EXAM.:	40	38	44	38	35	36	51
HEMOLYM. TISSUE	NO.EXAM.:	4	11	3	3	6	4	1
- Malignant lymphoma		3	8	2	2	6	3	1
- Histiocytic sarcoma		1	3	1	1	-	-	-
- Leukemia (not otherwise specified)		-	-	-	-	-	1	-
ILEUM	NO.EXAM.:	40	37	44	37	35	36	51
I.S. DORS.THO. LT	NO.EXAM.:	40	38	44	38	35	36	51
- Fibrosarcoma		-	-	-	-	-	-	12
- Malignant fibrous histiocytoma		-	-	-	-	-	-	2
I.S. DORS.THO. RT	NO.EXAM.:	40	38	44	38	35	36	50
- Fibrosarcoma		-	-	-	-	-	-	6
- Malignant fibrous histiocytoma		-	-	-	-	-	-	2
I.S. LUMBAR, LEFT	NO.EXAM.:	40	38	44	38	35	36	50
- Fibrosarcoma		-	-	-	-	-	-	8
- Malignant fibrous histiocytoma		-	-	-	-	-	-	2
I.S. LUMBAR, RIGHT	NO.EXAM.:	40	38	44	38	35	36	50
- Fibrosarcoma		-	-	-	-	-	-	8
- Malignant fibrous histiocytoma		-	-	-	-	-	-	1

Table 11 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Preterminal Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		40	38	44	38	35	36	51
I.S. SCAPULAR, LEFT	NO.EXAM.:	40	38	44	38	35	36	50
- Fibrosarcoma		-	-	-	-	-	-	1
- Lipoma		-	-	-	1	-	-	-
I.S. SCAPULAR, RIGHT	NO.EXAM.:	40	38	44	38	35	36	50
- Fibrosarcoma		-	-	-	-	-	-	1
- Malignant Fibrous Histiocytoma		-	-	-	-	-	-	1
JEJUNUM	NO.EXAM.:	40	38	44	38	35	36	51
- Adenocarcinoma		-	1	2	-	-	1	-
JOINT	NO.EXAM.:	-	-	1	1	-	-	-
KIDNEY	NO.EXAM.:	40	38	44	38	35	36	51
- Adenoma: tubular cell		-	-	-	-	-	-	1
- Sarcoma: metastasis		-	-	-	-	-	-	1
- Carcinoma: metastasis		-	-	-	-	1	-	-
LACRIMAL GLAND	NO.EXAM.:	40	38	43	38	35	34	50
LARYNX	NO.EXAM.:	40	38	44	38	35	36	51
LIVER	NO.EXAM.:	40	38	44	38	35	36	51
- Adenoma: hepatocellular		14	9	4	11	1	6	2
- Carcinoma: hepatocellular		2	3	3	1	4	-	1
- Hemangiosarcoma		3	1	2	3	2	2	-
- Sarcoma: metastasis		1	-	4	1	-	-	-
- Carcinoma: metastasis		1	-	-	-	-	-	-
LUNG	NO.EXAM.:	40	38	44	38	35	36	51
- Carcinoma: alveolar/bronchiolar		3	3	2	2	5	4	-
- Adenoma: alveolar/bronchiolar		4	6	9	6	2	6	6
LYMPH NODS	NO.EXAM.:	8	17	14	8	12	9	22
- Sarcoma: metastasis		-	-	1	-	-	-	2
- Carcinoma: metastasis		1	-	-	-	2	-	-

Table 11 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Preterminal Animals

MALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 40	2 38	3 44	4 38	5 35	6 36	7 51
L. NODE MANDIBULAR	NO.EXAM.:	39	33	37	31	32	33	47
L.NODE MESENTERIC	NO.EXAM.:	39	38	43	36	34	35	50
- Carcinoma: metastasis		-	-	2	-	-	-	-
- Sarcoma: metastasis		-	-	-	-	-	1	-
MENINGES	NO.EXAM.:	-	-	-	-	-	1	-
MUSCLE SKELETAL	NO.EXAM.:	40	38	44	37	34	34	51
- Sarcoma: metastasis		-	-	-	-	-	-	1
NERVES OPTIC	NO.EXAM.:	39	35	43	36	34	36	51
NERVE SCIATIC	NO.EXAM.:	39	38	44	38	35	36	51
- Sarcoma: metastasis		-	-	-	-	-	-	1
PANCREAS	NO.EXAM.:	40	38	44	38	35	36	51
- Carcinoma: metastasis		1	-	-	-	-	-	-
PARATHYROID GLAND	NO.EXAM.:	25	23	25	24	23	28	28
PITUITARY	NO.EXAM.:	39	38	42	38	34	36	50
- Adenoma: pars distalis		-	1	-	-	-	-	-
- Adenoma: pars intermedia		-	-	1	-	-	-	-
PREPUTIAL GLAND	NO.EXAM.:	40	38	43	36	34	35	50
PROSTATE	NO.EXAM.:	40	38	44	38	35	35	50
RECTUM	NO.EXAM.:	1	-	-	-	-	1	-
SALIV.GL. MANDIBULAR	NO.EXAM.:	40	38	44	38	35	36	51
SEMINAL VESICLE	NO.EXAM.:	40	38	44	38	35	36	50
SKIN	NO.EXAM.:	40	38	44	37	35	36	51
SKIN MISCELLANEOUS	NO.EXAM.:	12	12	15	13	15	15	15
- Mast cell tumor		-	-	-	-	-	-	1
SPINAL CORD CERVICAL	NO.EXAM.:	40	38	44	38	35	36	51
SPLEEN	NO.EXAM.:	40	38	44	38	35	36	51
- Hemangioma		1	-	-	1	-	-	-
- Hemangiosarcoma		3	1	4	1	-	1	-

Table 11 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Preterminal Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		40	38	44	38	35	36	51
STOMACH	NO.EXAM.:	40	38	44	38	35	36	51
SUBCUTANEOUS TISSUE	NO.EXAM.:	5	4	6	4	1	6	2
- Hemangiosarcoma		-	1	-	-	-	-	-
- Fibrosarcoma		-	1	-	-	-	-	2
TAIL	NO.EXAM.:	1	-	-	-	-	-	1
- Hemangioma		1	-	-	-	-	-	-
TESTIS	NO.EXAM.:	40	38	44	38	35	36	51
- Adenoma: interstitial cell		1	-	-	-	-	-	-
THORAX	NO.EXAM.:	1	-	-	-	1	-	-
THYMUS	NO.EXAM.:	34	30	39	30	30	28	43
THYROID	NO.EXAM.:	40	38	44	37	34	36	51
- Adenoma: follicular cell		1	-	-	-	-	-	-
TONGUE	NO.EXAM.:	40	38	44	38	35	36	51
TRACHEA	NO.EXAM.:	40	38	44	38	35	36	51
URETER	NO.EXAM.:	10	12	9	10	9	6	6
URETHRA	NO.EXAM.:	-	-	-	1	-	-	-
URINARY BLADDER	NO.EXAM.:	40	38	44	38	35	36	51
- Submucosal mesenchymal tumor (M)		1	-	1	-	-	-	-
- Carcinoma: transitional cell		1	-	-	1	1	-	-
VAS DEFERENS	NO.EXAM.:	-	-	-	-	-	1	-
ZYMBAL'S GLAND	NO.EXAM.:	40	38	43	38	34	35	50

Table 11 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Preterminal Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		37	39	42	44	42	44	56
ABDOMEN	NO.EXAM.:	-	1	2	1	1	1	-
- Hemangiosarcoma		-	-	-	1	-	-	-
ADRENAL	NO.EXAM.:	37	39	42	43	40	44	56
- Adenoma: subcapsular		-	-	1	1	-	-	-
- Adenoma: cortical		-	-	-	-	-	-	1
- Benign pheochromocytoma		-	-	-	2	-	2	-
- Malignant pheochromocytoma		1	1	1	1	-	-	-
AORTA	NO.EXAM.:	37	38	41	44	42	44	56
BLOOD VESSEL	NO.EXAM.:	-	1	-	-	-	-	-
BONE-FEMUR	NO.EXAM.:	37	38	42	44	42	44	56
- Sarcoma: metastasis		-	-	-	-	-	-	1
- Osteosarcoma		-	-	-	1	-	-	-
- Chondroma		-	-	-	1	-	-	-
BONE MARROW	NO.EXAM.:	37	39	42	44	42	44	56
- Mast cell tumor (malignant)		1	-	-	-	-	-	-
BONE MISCELLANEOUS	NO.EXAM.:	-	2	1	-	-	-	-
- Osteosarcoma		-	1	-	-	-	-	-
BONE-STERNUM	NO.EXAM.:	37	39	41	44	42	43	56
- Sarcoma: metastasis		-	-	-	-	1	-	-
BRAIN	NO.EXAM.:	37	39	42	44	42	44	56
CAVITY ORAL	NO.EXAM.:	-	-	-	1	-	1	-
CECUM	NO.EXAM.:	37	39	42	44	42	44	56
CLITORAL GLAND	NO.EXAM.:	36	37	40	41	38	41	51
COLON	NO.EXAM.:	37	39	42	43	42	44	56
DUODENUM	NO.EXAM.:	37	39	42	44	42	44	56
- Sarcoma: metastasis		1	-	-	-	-	-	-
ESOPHAGUS	NO.EXAM.:	37	39	42	44	42	44	56
- Carcinoma: squamous cell		-	-	-	-	-	-	1

Table 11 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Preterminal Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		37	39	42	44	42	44	56
EYE	NO.EXAM.:	37	39	42	44	42	44	56
FAT	NO.EXAM.:	7	2	2	-	1	2	4
- Carcinoma: metastasis		1	-	-	-	-	-	-
- Sarcoma: metastasis		1	-	-	-	-	-	-
- Liposarcoma		-	-	-	-	-	-	1
GALLBLADDER	NO.EXAM.:	36	38	41	44	42	43	55
HARDERIAN GLAND	NO.EXAM.:	37	39	42	44	42	44	56
- Adenoma		-	1	-	1	-	-	-
HEAD	NO.EXAM.:	-	-	1	-	-	-	-
- Carcinoma (not otherwise specified)		-	-	1	-	-	-	-
HEART	NO.EXAM.:	37	39	42	44	42	44	56
HEMOLYM. TISSUE	NO.EXAM.:	16	15	12	10	15	16	13
- Malignant lymphoma		15	10	9	7	10	11	8
- Histiocytic sarcoma		2	5	3	3	6	5	5
ILEUM	NO.EXAM.:	37	39	42	44	42	44	56
I.S. DORS.THO. LT	NO.EXAM.:	37	39	42	44	42	44	56
- Fibrosarcoma		-	-	1	-	-	-	9
- Mast cell tumor		-	-	-	1	-	-	-
I.S. DORS.THO. RT	NO.EXAM.:	37	39	42	44	42	44	56
- Fibrosarcoma		-	-	-	-	-	1	4
- Mast cell tumor		-	-	-	-	1	-	-
I.S. LUMBAR, LEFT	NO.EXAM.:	37	39	42	44	42	44	56
- Fibrosarcoma		-	-	-	-	1	-	2
- Osteosarcoma		-	-	-	-	-	1	-
- Fibroma		-	-	-	-	1	-	-
I.S. LUMBAR, RIGHT	NO.EXAM.:	37	39	42	44	42	44	56
- Fibrosarcoma		-	-	-	-	1	-	3
- Sarcoma: metastasis		1	-	-	-	-	-	-

Table 11 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Preterminal Animals

FEMALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 37	2 39	3 42	4 44	5 42	6 44	7 56
I.S. SCAPULAR, LEFT	NO.EXAM.:	37	39	42	44	42	44	56
- Fibroma		-	-	-	-	-	1	-
- Fibrosarcoma		-	-	1	-	-	-	2
- Malignant fibrous histiocytoma		-	-	-	-	-	-	1
- Hemangioma		-	-	-	-	-	-	1
I.S. SCAPULAR, RIGHT	NO.EXAM.:	37	39	42	44	42	44	56
- Fibrosarcoma		-	-	-	-	1	-	-
JEJUNUM	NO.EXAM.:	37	39	42	44	42	44	56
- Adenocarcinoma		1	-	-	-	-	-	-
JOINT	NO.EXAM.:	-	1	-	-	-	-	-
KIDNEY	NO.EXAM.:	37	39	42	44	42	44	56
LACRIMAL GLAND	NO.EXAM.:	34	39	41	44	42	43	56
LARYNX	NO.EXAM.:	37	39	42	44	42	44	56
LIVER	NO.EXAM.:	37	39	42	44	42	44	56
- Adenoma: hepatocellular		1	1	-	2	1	2	-
- Carcinoma: hepatocellular		-	-	-	-	1	-	-
- Hemangiosarcoma		-	2	-	2	1	-	-
- Sarcoma: metastasis		2	-	1	2	-	-	1
LUNG	NO.EXAM.:	37	39	42	44	42	44	56
- Carcinoma: alveolar/bronchiolar		1	2	3	3	2	4	1
- Adenoma: alveolar/bronchiolar		2	6	8	3	3	6	2
- Carcinoma: metastasis		-	1	1	1	1	-	-
- Sarcoma: metastasis		1	-	-	1	1	1	-
LYMPH NODE	NO.EXAM.:	17	15	12	18	20	20	23
- Sarcoma: metastasis		1	-	-	-	-	-	1
L. NODE MANDIBULAR	NO.EXAM.:	35	35	39	38	38	38	50
- Carcinoma: metastasis		-	-	1	-	-	-	-

Table 11 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Preterminal Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		37	39	42	44	42	44	56
L.NODE MESENTERIC	NO.EXAM.:	37	39	42	43	42	44	56
- Sarcoma: metastasis		-	-	-	-	1	-	1
MAMMARY GLAND	NO.EXAM.:	34	37	40	44	41	41	56
- Adenocarcinoma		2	1	2	1	1	-	-
- Adenoma		1	-	-	-	-	-	-
MUSCLE SKELETAL	NO.EXAM.:	37	37	40	43	40	44	56
MUSCLE SKELETAL MISC	NO.EXAM.:	-	1	-	1	-	1	1
NERVES OPTIC	NO.EXAM.:	36	38	42	42	38	40	54
NERVE SCIATIC	NO.EXAM.:	37	39	42	44	42	44	56
OVARY	NO.EXAM.:	37	39	42	44	42	44	56
- Cystadenoma		1	-	-	-	1	1	-
- Malignant granulosa-theca cell tumor		-	-	-	-	-	1	-
- Benign sertoli cell tumor		-	-	-	-	1	-	-
- Hemangioma		-	-	-	-	-	1	-
OVIDUCT	NO.EXAM.:	37	39	42	44	42	44	55
PANCREAS	NO.EXAM.:	37	39	42	44	42	43	55
- Adenoma: islet cell		-	1	-	1	-	-	-
- Mesothelioma(B)		-	-	1	-	-	-	-
- Sarcoma: metastasis		1	-	-	-	-	-	-
PARATHYROID GLAND	NO.EXAM.:	25	23	31	34	26	32	38
PERICARDIUM	NO.EXAM.:	1	-	-	-	-	-	-
PITUITARY	NO.EXAM.:	37	39	41	44	41	43	53
- Adenoma: pars distalis		-	1	1	1	-	-	-
- Adenoma: pars intermedia		-	-	-	1	-	-	-
RECTUM	NO.EXAM.:	-	-	-	1	-	-	-
SALIV.GL. MANDIBULAR	NO.EXAM.:	37	38	42	43	42	43	56
SKIN	NO.EXAM.:	37	39	42	44	42	44	56

Table 11 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
Preterminal Animals

FEMALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 37	2 39	3 42	4 44	5 42	6 44	7 56
SKIN MISCELLANEOUS	NO.EXAM.:	5	7	8	10	8	7	16
- Papilloma: squamous cell		-	1	-	-	-	-	-
- Carcinoma: squamous cell		1	1	-	-	-	-	-
SPINAL CORD CERVICAL	NO.EXAM.:	37	39	42	44	42	44	56
SPLEEN	NO.EXAM.:	37	39	42	44	42	44	56
- Mast cell tumor: metastasis		1	-	-	-	-	-	-
- Hemangiosarcoma		-	1	1	-	1	-	2
- Sarcoma: metastasis		-	-	-	1	-	-	1
STOMACH	NO.EXAM.:	37	39	42	44	42	44	56
- Mesothelioma(B)		-	-	1	-	-	-	-
SUBCUTANEOUS TISSUE	NO.EXAM.:	4	4	5	6	4	5	3
- Hemangiosarcoma		-	1	-	-	-	-	-
- Fibrosarcoma		-	-	2	2	1	-	1
- Osteosarcoma		1	-	-	-	1	-	-
TAIL	NO.EXAM.:	1	-	-	-	-	-	1
THORAX	NO.EXAM.:	1	1	1	-	2	2	-
THYMUS	NO.EXAM.:	34	32	37	37	33	38	55
THYROID	NO.EXAM.:	37	38	42	44	42	44	56
- Adenoma: follicular cell		1	-	-	1	-	-	-
TONGUE	NO.EXAM.:	37	39	42	44	42	44	56
TRACHEA	NO.EXAM.:	37	39	42	43	42	44	56
URETER	NO.EXAM.:	2	3	-	2	-	1	1
URINARY BLADDER	NO.EXAM.:	37	39	42	42	42	44	55
- Submucosal mesenchymal tumor (M)		-	-	1	-	-	-	-
- Sarcoma: metastasis		1	-	-	-	-	-	-

Table 11 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
Preterminal Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		37	39	42	44	42	44	56
UTERUS	NO.EXAM.:	37	39	42	44	42	44	56
- Sarcoma: endometrial stromal		-	1	-	1	2	1	-
- Benign granular cell tumor		1	-	-	-	2	-	1
- Leiomyoma		2	1	1	4	3	1	2
- Leiomyosarcoma		2	-	1	2	1	-	1
- Hemangiosarcoma		1	-	-	-	2	1	-
- Adenocarcinoma: endometrial		-	-	-	1	4	-	4
- Carcinoma: squamous cell		-	1	-	-	-	-	-
- Polyp: endometrial stromal		1	2	3	4	2	3	4
- Sarcoma: metastasis		-	1	-	-	-	-	-
VAGINA	NO.EXAM.:	36	39	42	43	42	44	56
- Polyp		1	-	-	-	-	-	-
ZYMBAL'S GLAND	NO.EXAM.:	36	39	42	44	42	44	56

Table 12 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
Terminal Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		20	22	26	32	35	34	19
ABDOMEN	NO.EXAM.:	-	1	-	1	1	-	-
- Carcinoma: metastasis		-	-	-	-	1	-	-
ADRENAL	NO.EXAM.:	20	22	26	31	33	33	19
- Adenoma: subcapsular		-	4	-	1	2	1	2
- Carcinoma: cortical		-	-	-	-	-	1	-
- Adenoma: cortical		-	-	1	-	-	-	-
- Benign pheochromocytoma		-	-	-	-	-	-	1
AORTA	NO.EXAM.:	20	22	26	32	34	33	19
BONE-FEMUR	NO.EXAM.:	20	22	26	32	34	34	19
- Sarcoma: metastasis		-	1	1	-	1	-	-
BONE MARROW	NO.EXAM.:	20	22	26	32	34	33	19
- Mast cell tumor (malignant)		-	-	-	-	-	1	-
BONE MISCELLANEOUS	NO.EXAM.:	-	-	-	1	-	-	-
BONE-STERNUM	NO.EXAM.:	20	22	26	32	34	33	19
- Sarcoma: metastasis		-	-	-	-	2	-	-
BRAIN	NO.EXAM.:	20	22	26	32	34	33	19
CECUM	NO.EXAM.:	20	22	26	32	34	33	19
- Adenocarcinoma		1	-	-	-	-	-	-
COLON	NO.EXAM.:	20	22	26	32	34	33	19
DUODENUM	NO.EXAM.:	20	22	26	32	33	32	19
EPIDIDYMIS	NO.EXAM.:	20	22	26	32	35	34	19
- Sarcoma (not otherwise specified)		-	-	-	2	-	-	-
- Carcinoma: interstitial cell		-	-	-	-	1	1	-
ESOPHAGUS	NO.EXAM.:	20	22	26	32	35	34	19
EYE	NO.EXAM.:	20	22	26	32	35	34	19
GALLBLADDER	NO.EXAM.:	19	17	26	32	33	34	17
HARDERIAN GLAND	NO.EXAM.:	20	22	26	32	35	34	19
- Adenoma		4	1	5	4	1	3	-
- Adenocarcinoma		-	1	1	1	1	1	-

Table 12 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Terminal Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		20	22	26	32	35	34	19
HEART	NO.EXAM.:	20	22	26	32	34	33	19
HEMOLYM. TISSUE	NO.EXAM.:	1	1	-	3	8	4	-
- Malignant lymphoma		1	1	-	2	6	4	-
- Histiocytic sarcoma		-	-	-	1	2	-	-
ILEUM	NO.EXAM.:	20	22	26	32	34	33	19
I.S. DORS.THO. LT	NO.EXAM.:	20	22	26	32	34	33	19
- Fibrosarcoma		-	-	-	-	-	-	1
- Malignant fibrous histiocytoma		-	-	-	-	-	-	1
I.S. DORS.THO. RT	NO.EXAM.:	20	22	26	32	34	33	19
I.S. LUMBAR, LEFT	NO.EXAM.:	20	22	26	32	34	33	19
- Fibrosarcoma		-	-	-	-	-	-	2
I.S. LUMBAR, RIGHT	NO.EXAM.:	20	22	26	32	34	33	19
- Fibrosarcoma		-	-	-	-	-	-	2
I.S. SCAPULAR, LEFT	NO.EXAM.:	20	22	26	32	34	33	19
- Fibrosarcoma		-	-	-	-	-	1	-
- Osteosarcoma		-	-	-	1	-	-	-
I.S. SCAPULAR, RIGHT	NO.EXAM.:	20	22	26	32	34	33	19
JEJUNUM	NO.EXAM.:	20	22	26	32	34	33	19
- Adenocarcinoma		-	-	-	-	-	1	-
JOINT	NO.EXAM.:	-	-	-	-	1	-	-
KIDNEY	NO.EXAM.:	20	22	26	32	35	34	19
- Carcinoma: tubular cell		-	1	-	-	-	-	-
LACRIMAL GLAND	NO.EXAM.:	20	22	26	31	35	34	19
LARYNX	NO.EXAM.:	20	22	26	32	34	33	19
LIVER	NO.EXAM.:	20	22	26	32	35	34	19
- Adenoma: hepatocellular		9	9	6	6	3	9	2
- Carcinoma: hepatocellular		-	-	1	1	5	1	1
- Hemangiosarcoma		-	1	2	-	1	1	-
- Sarcoma: metastasis		2	-	-	-	2	-	-

Table 12 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Terminal Animals

MALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 20	2 22	3 26	4 32	5 35	6 34	7 19
LUNG	NO.EXAM.:	20	22	26	32	35	34	19
- Carcinoma: alveolar/bronchiolar		1	3	1	5	2	7	2
- Adenoma: alveolar/bronchiolar		1	4	8	4	4	7	3
- Carcinoma: metastasis		-	-	-	1	-	-	-
LYMPH NODE	NO.EXAM.:	1	7	2	4	9	1	5
- Carcinoma: metastasis		-	-	-	-	1	-	-
L. NODE MANDIBULAR	NO.EXAM.:	18	17	24	29	27	31	15
L.NODE MESENTERIC	NO.EXAM.:	20	22	26	32	34	33	19
- Sarcoma: metastasis		-	-	-	-	1	-	-
MUSCLE SKELETAL	NO.EXAM.:	20	21	25	31	34	33	18
NERVES OPTIC	NO.EXAM.:	19	21	25	32	33	32	18
NERVE SCIATIC	NO.EXAM.:	19	22	26	32	34	34	19
PANCREAS	NO.EXAM.:	20	22	26	32	35	34	19
- Adenoma: islet cell		-	1	-	-	-	-	-
PARATHYROID GLAND	NO.EXAM.:	13	13	17	25	19	20	12
- Adenoma		-	-	-	1	-	-	-
PENIS	NO.EXAM.:	-	-	-	-	1	1	-
PITUITARY	NO.EXAM.:	20	22	25	30	34	32	18
- Adenoma: pars distalis		-	-	-	-	-	-	1
PREPUTIAL GLAND	NO.EXAM.:	19	22	26	32	33	33	19
- Hemangioma		-	-	-	1	-	-	-
PROSTATE	NO.EXAM.:	20	22	26	32	35	34	19
- Adenocarcinoma		-	-	-	-	1	1	-
SALIV.GL. MANDIBULAR	NO.EXAM.:	20	22	26	32	35	34	19
SALIV. GLAND PAROTID	NO.EXAM.:	-	1	-	-	-	-	-
SEMINAL VESICLE	NO.EXAM.:	20	22	26	32	35	34	19
SKIN	NO.EXAM.:	20	22	26	32	34	33	19
SKIN MISCELLANEOUS	NO.EXAM.:	5	3	5	5	8	6	3

Table 12 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Terminal Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		20	22	26	32	35	34	19
SPINAL CORD CERVICAL	NO.EXAM.:	20	22	26	32	34	33	19
SPLEEN	NO.EXAM.:	20	22	26	32	35	34	19
- Hemangioma		-	-	1	1	-	-	-
- Hemangiosarcoma		2	1	2	1	4	2	-
STOMACH	NO.EXAM.:	20	22	26	32	34	33	19
SUBCUTANEOUS TISSUE	NO.EXAM.:	-	3	-	1	2	-	-
- Hemangioma		-	2	-	-	-	-	-
TAIL	NO.EXAM.:	1	-	2	-	-	1	-
- Hemangioma		1	-	1	-	-	-	-
- Hemangiosarcoma		-	-	1	-	-	-	-
TESTIS	NO.EXAM.:	20	22	26	32	35	34	19
- Adenoma: interstitial cell		-	1	-	-	1	-	-
THORAX	NO.EXAM.:	-	-	-	-	1	-	-
THYMUS	NO.EXAM.:	16	18	19	29	31	28	19
THYROID	NO.EXAM.:	20	22	26	32	34	33	19
TONGUE	NO.EXAM.:	20	22	26	32	35	34	19
TRACHEA	NO.EXAM.:	20	22	26	31	35	34	18
URETER	NO.EXAM.:	3	1	2	1	6	5	3
URINARY BLADDER	NO.EXAM.:	20	22	26	32	35	34	19
- Submucosal mesenchymal tumor (M)		1	-	-	-	-	1	1
ZYMBAL'S GLAND	NO.EXAM.:	20	22	26	32	34	33	19

Table 12 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
Terminal Animals

FEMALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 23	2 21	3 28	4 26	5 28	6 26	7 14
ABDOMEN	NO.EXAM.:	-	-	-	1	-	-	1
ADRENAL	NO.EXAM.:	23	21	28	26	28	26	14
- Adenoma: subcapsular		3	1	1	1	1	-	-
- Carcinoma: cortical		-	-	1	-	-	-	-
- Benign pheochromocytoma		-	-	1	1	-	1	-
- Malignant pheochromocytoma		1	-	-	-	1	2	-
- Carcinoma: metastasis		-	-	-	-	1	-	-
AORTA	NO.EXAM.:	23	21	28	26	28	26	14
BONE-FEMUR	NO.EXAM.:	23	21	28	26	28	26	14
- Sarcoma: metastasis		-	-	-	-	1	-	-
BONE MARROW	NO.EXAM.:	23	21	28	26	28	26	14
- Mast cell tumor (malignant)		1	-	-	-	-	-	-
BONE MISCELLANEOUS	NO.EXAM.:	1	-	-	-	1	-	-
- Osteosarcoma		1	-	-	-	-	-	-
BONE-STERNUM	NO.EXAM.:	23	21	28	26	28	26	14
- Hemangiosarcoma		-	1	-	-	-	-	-
BRAIN	NO.EXAM.:	23	21	28	26	28	26	14
CAVITY CRANIAL	NO.EXAM.:	-	-	-	-	-	1	-
CECUM	NO.EXAM.:	23	21	28	26	28	26	14
CLITORAL GLAND	NO.EXAM.:	22	21	27	26	26	26	14
COLON	NO.EXAM.:	23	21	28	26	28	26	14
DUODENUM	NO.EXAM.:	23	21	28	26	28	26	14
ESOPHAGUS	NO.EXAM.:	23	21	28	26	28	26	14
EYE	NO.EXAM.:	23	21	28	26	28	26	14
FAT	NO.EXAM.:	1	1	-	-	-	1	-
- Hemangioma		1	-	-	-	-	-	-
GALLBLADDER	NO.EXAM.:	23	21	27	25	28	26	14
HARDERIAN GLAND	NO.EXAM.:	23	21	28	26	28	26	14
- Adenoma		2	-	1	-	6	-	-

Table 12 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Terminal Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		23	21	28	26	28	26	14
HEART	NO.EXAM.:	23	21	28	26	28	26	14
- Carcinoma: metastasis		-	-	-	-	1	-	-
HEMOLYM. TISSUE	NO.EXAM.:	8	5	5	6	7	8	2
- Malignant lymphoma		8	5	2	6	7	4	2
- Histiocytic sarcoma		-	-	3	1	-	5	-
ILEUM	NO.EXAM.:	23	21	28	26	28	26	14
I.S. DORS.THO. LT	NO.EXAM.:	23	21	28	26	28	26	14
I.S. DORS.THO. RT	NO.EXAM.:	23	21	28	26	28	26	14
I.S. LUMBAR, LEFT	NO.EXAM.:	23	21	28	26	28	26	14
- Fibrosarcoma		-	-	-	-	-	1	-
I.S. LUMBAR, RIGHT	NO.EXAM.:	23	21	28	26	28	26	14
- Fibrosarcoma		-	-	-	-	-	-	1
I.S. SCAPULAR, LEFT	NO.EXAM.:	23	21	28	26	28	26	14
- Fibrosarcoma		-	-	-	-	-	-	1
I.S. SCAPULAR, RIGHT	NO.EXAM.:	23	21	28	26	28	26	14
- Fibrosarcoma		-	-	-	-	-	-	1
JEJUNUM	NO.EXAM.:	23	21	28	26	28	26	14
- Adenocarcinoma		-	-	-	-	-	1	-
JOINT	NO.EXAM.:	-	-	-	1	-	-	-
KIDNEY	NO.EXAM.:	23	21	28	26	28	26	14
LACRIMAL GLAND	NO.EXAM.:	23	20	28	26	28	26	14
LARYNX	NO.EXAM.:	23	21	28	26	28	26	14
LIVER	NO.EXAM.:	23	21	28	26	28	26	14
- Adenoma: hepatocellular		1	1	3	2	-	-	-
- Carcinoma: hepatocellular		1	-	-	-	-	-	1
- Hemangiosarcoma		-	2	1	1	-	-	-
- Sarcoma: metastasis		-	-	-	-	1	1	-
- Carcinoma: metastasis		-	-	-	-	1	-	-

Table 12 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
Terminal Animals

FEMALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 23	2 21	3 28	4 26	5 28	6 26	7 14
LUNG	NO.EXAM.:	23	21	28	25	28	26	14
- Carcinoma: alveolar/bronchiolar		3	3	2	1	1	-	-
- Adenoma: alveolar/bronchiolar		8	1	4	2	3	2	1
LYMPH NODE	NO.EXAM.:	5	5	8	4	11	9	1
- Carcinoma: metastasis		-	-	1	-	-	-	-
- Hemangiosarcoma		1	-	-	-	-	-	-
L. NODE MANDIBULAR	NO.EXAM.:	21	19	25	24	26	25	14
L.NODE MESENTERIC	NO.EXAM.:	23	21	28	26	28	24	14
MAMMARY GLAND	NO.EXAM.:	22	21	28	25	27	25	14
- Adenocarcinoma		2	-	2	1	3	-	-
- Adenoma		-	2	-	-	-	-	-
MUSCLE SKELETAL	NO.EXAM.:	23	21	28	26	28	26	14
MUSCLE SKELETAL MISC	NO.EXAM.:	-	1	-	-	-	-	-
NERVES OPTIC	NO.EXAM.:	23	21	28	26	28	26	14
NERVE SCIATIC	NO.EXAM.:	23	20	28	25	28	26	14
OVARY	NO.EXAM.:	23	21	28	26	28	26	14
- Cystadenoma		-	-	1	-	-	-	-
- Cystadenocarcinoma		-	-	1	-	-	-	-
- Benign granulosa-theca cell tumor		-	-	2	-	-	1	-
- Malignant granulosa-theca cell tumor		1	-	-	-	1	1	-
- Adenoma: tubulostromal		1	-	-	-	-	-	-
OVIDUCT	NO.EXAM.:	23	21	28	26	28	26	14
PANCREAS	NO.EXAM.:	23	21	28	26	28	26	14
PARATHYROID GLAND	NO.EXAM.:	14	15	21	17	21	19	8

Table 12 **Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex**
Terminal Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		23	21	28	26	28	26	14
PITUITARY	NO.EXAM.:	22	21	28	25	28	26	14
- Adenoma: pars distalis		1	1	2	1	1	-	-
SALIV.GL. MANDIBULAR	NO.EXAM.:	22	21	28	26	28	26	14
SKIN	NO.EXAM.:	23	21	28	26	28	26	14
SKIN MISCELLANEOUS	NO.EXAM.:	4	2	8	5	2	3	-
- Hemangioma		-	-	1	-	-	-	-
SPINAL CORD CERVICAL	NO.EXAM.:	23	21	28	26	28	26	14
SPLEEN	NO.EXAM.:	23	21	28	26	28	26	14
- Hemangiosarcoma		-	-	-	-	2	1	-
- Carcinoma: metastasis		-	-	-	-	1	-	1
STOMACH	NO.EXAM.:	23	21	28	26	28	26	14
- Osteosarcoma		-	-	-	-	-	1	-
- Adenoma		-	-	1	-	-	-	-
SUBCUTANEOUS TISSUE	NO.EXAM.:	1	2	-	2	1	-	-
- Fibrosarcoma		1	-	-	2	-	-	-
- Myxoma		-	-	-	-	1	-	-
TAIL	NO.EXAM.:	2	-	1	1	-	1	-
THORAX	NO.EXAM.:	-	-	-	-	1	1	-
THYMUS	NO.EXAM.:	22	19	27	24	28	24	12
THYROID	NO.EXAM.:	23	21	28	26	28	26	14
- Adenoma: follicular cell		-	-	-	1	1	-	-
TONGUE	NO.EXAM.:	23	21	28	26	28	26	14
TRACHEA	NO.EXAM.:	23	21	27	25	28	26	14
URETER	NO.EXAM.:	-	1	2	-	1	-	-
URINARY BLADDER	NO.EXAM.:	23	21	28	26	28	26	14
- Submucosal mesenchymal tumor (M)		-	-	-	-	1	-	-
- Carcinoma: transitional cell		-	-	-	1	-	-	-
- Sarcoma: metastasis		-	-	-	-	-	1	-
- Leiomyosarcoma		-	-	1	-	-	-	-

Table 12 Incidence of Animals with Neoplastic Lesions by Organ/Group/Sex
Terminal Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		23	21	28	26	28	26	14
UTERUS	NO.EXAM.:	23	21	28	26	28	26	14
- Sarcoma: endometrial stromal		1	-	-	-	1	-	1
- Benign granular cell tumor		-	-	1	1	-	-	-
- Leiomyoma		4	2	3	3	1	1	1
- Leiomyosarcoma		1	-	1	-	2	1	-
- Hemangioma		-	-	-	-	-	1	-
- Hemangiosarcoma		-	2	-	-	-	2	-
- Adenoma: endometrial		-	-	-	1	-	-	-
- Adenocarcinoma: endometrial		-	3	7	3	1	1	-
- Polyp: endometrial stromal		5	4	3	5	6	4	1
VAGINA	NO.EXAM.:	23	20	28	26	27	26	14
ZYMBAL'S GLAND	NO.EXAM.:	23	21	28	26	28	26	14

Attachment 2: Incidence of non-neoplastic lesions by organ/group/sex for all animals (preterminal and terminal mice)

Table 16 Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
ABDOMEN	EXAMIN:	-	3	-	1	2	-	2
- Inflammation		-	1	-	1	-	-	1
ADRENAL	EXAMIN:	59	60	70	69	68	68	70
- Hypertrophy: cortical focal		10	12	8	16	10	10	9
- Hyperplasia: cortical focal		4	5	4	7	3	5	2
- Hyperplasia: medullary		-	5	1	-	1	3	1
- Amyloidosis		12	11	8	15	13	19	10
- Hyperplasia: spindle cells		23	20	29	28	26	26	22
- Deposits: lipofuscin		21	20	32	16	15	23	23
- Hemorrhage		-	-	-	-	1	-	-
- Polyarteritis		1	-	-	1	-	1	-
- Cyst		-	-	-	-	1	-	-
- Hematopoiesis: extramedullary		1	1	-	1	1	1	2
- Mineralization		-	-	-	-	1	-	-
AORTA	EXAMIN:	60	60	70	70	69	69	70
- Necrosis: vascular		-	-	-	-	1	-	-
- Polyarteritis		1	-	-	1	-	3	-
- Degeneration and/or necrosis		-	-	-	1	-	-	-
BILE DUCT	EXAMIN:	1	-	-	-	-	-	-
- Dilatation		1	-	-	-	-	-	-
BLOOD VESSEL	EXAMIN:	-	1	-	-	-	-	-
BONE-FEMUR	EXAMIN:	60	60	70	70	69	69	70
- Fibrous osteodystrophy		4	2	3	9	4	9	3
- Fibro-osseous lesion		-	-	-	1	-	-	-
- Necrosis		-	-	1	-	-	-	-
- Fracture		-	-	-	-	-	1	-
- Hyperostosis		-	-	1	-	1	-	-
- Polyarteritis		1	-	-	-	-	-	-

Table 16 Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex
All Animals

MALE

DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
BONE-FEMUR	CONT'D.	60	60	70	70	69	69	70
- Fibrosis		-	-	-	1	-	-	-
BONE MARROW	EXAMIN:	60	60	70	70	69	69	70
- Necrosis		1	-	1	-	-	-	-
- Fibrosis		1	-	-	-	-	-	-
BONE MISCELLANEOUS	EXAMIN:	-	-	-	1	-	-	-
- Hyperostosis		-	-	-	1	-	-	-
BONE-STERNUM	EXAMIN:	60	60	70	70	69	69	70
- Fibrous osteodystrophy		2	-	1	5	2	7	2
- Fibro-osseous lesion		-	-	1	-	-	-	-
- Hyperostosis		-	-	1	-	-	-	-
- Inflammation		1	-	-	-	-	-	-
BRAIN	EXAMIN:	60	60	70	70	69	69	70
- Hemorrhage		-	1	-	1	-	-	-
- Thrombosis		-	-	-	1	-	1	-
- Infiltration: mononuclear cell		-	-	-	-	-	-	1
- Inflammation		-	-	-	-	1	-	-
- Necrosis		-	-	-	1	-	-	-
- Compression		-	-	1	-	-	-	1
- Dilatation: ventricle		-	-	-	-	1	-	-
- Polyarteritis		-	-	-	-	1	-	-
BULBOPENIS	EXAMIN:	4	3	6	4	-	1	1
- Inflammation		4	3	6	4	-	1	1
CAVITY CRANIAL	EXAMIN:	-	-	-	-	-	1	-
CAVITY PELVIC	EXAMIN:	1	1	1	-	1	1	1
CECUM	EXAMIN:	60	60	70	69	69	69	70
- Erosion		-	-	-	-	1	2	-
- Amyloidosis		2	2	-	2	2	2	1
- Edema		2	-	-	2	-	1	1
- Atrophy/necrosis: lymphoid (GALT)		1	-	-	-	-	-	-
- Deposits: pigment		5	9	4	2	-	1	-

Table 16 Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex
All Animals

MALE

DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
CECUM	CONT'D.	60	60	70	69	69	69	70
- Polyarteritis		1	1	-	4	-	2	-
- Inflammation		-	2	-	-	-	-	1
- Parasite		2	-	1	2	-	1	-
- Cyst: squamous		1	-	-	-	1	-	-
COLON	EXAMIN:	60	60	70	69	69	69	70
- Amyloidosis		-	1	1	-	1	-	2
- Parasite		3	4	6	6	4	11	-
- Polyarteritis		1	-	-	3	-	3	-
DUODENUM	EXAMIN:	60	60	70	69	68	68	69
- Amyloidosis		12	11	9	12	11	15	10
- Hemorrhage		-	-	1	-	-	-	-
- Polyarteritis		3	-	1	4	2	4	1
- Erosion		2	2	2	3	1	3	1
- Ulceration		-	1	-	-	-	-	-
- Hyperplasia: villous/mucosal		-	-	1	-	1	-	-
- Inflammation		-	-	-	-	-	1	-
EPIDIDYMIS	EXAMIN:	60	60	70	70	70	70	70
- Oligo/aspermia		18	11	19	16	17	21	8
- Inflammation		2	4	3	5	1	5	2
- Granuloma: spermatic		-	2	5	1	2	3	1
- Thrombosis		-	-	-	1	-	-	-
- Amyloidosis		1	1	-	-	-	1	-
- Polyarteritis		-	-	1	-	1	-	-
ESOPHAGUS	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		2	-	1	3	2	1	-
- Inflammation		-	-	-	1	-	-	-
- Inflammation: periesophegeal		-	-	-	-	-	1	-
- Polyarteritis		1	-	-	-	-	1	-

Table 16 Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
EYE	EXAMIN:	60	60	70	70	70	70	70
- Inflammation: conjunctiva		-	-	1	-	1	-	-
- Inflammation: cornea		3	10	7	6	11	12	2
- Inflammation: uvea		3	4	4	2	4	2	-
- Inflammation: peribulbar		-	-	-	-	1	-	-
- Erosion: conjunctiva		-	-	-	-	-	1	-
- Ulceration: cornea		-	-	1	-	-	1	-
- Fold/rosette: retina		-	-	-	-	-	-	1
- Degeneration: lens		4	6	7	16	12	9	7
- Hemorrhage: vitreous cavity		-	-	-	1	-	-	-
- Mineralization: cornea		2	9	2	10	9	6	2
- Atrophy: retina		1	1	3	1	-	2	1
- Mineralization: iris		3	2	3	1	-	1	1
FAT	EXAMIN:	-	1	-	-	-	1	-
- Hemorrhage		-	-	-	-	-	1	-
GALLBLADDER	EXAMIN:	56	54	68	69	66	69	67
- Amyloidosis		-	1	1	2	1	2	3
- Inflammation		-	-	2	1	2	1	-
- Polyarteritis		-	-	-	1	-	-	-
- Dilatation		-	-	-	1	-	-	-
HARDERIAN GLAND	EXAMIN:	60	60	70	70	70	70	70
- Inflammation		-	-	-	-	1	-	1
- Infiltration: mononuclear cell		-	-	-	1	-	-	-
- Amyloidosis		1	1	1	3	2	4	-
- Hyperplasia		2	1	4	4	-	1	2
- Thrombosis		-	1	-	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
HEART	EXAMIN:	60	60	70	70	69	69	70
- Murine progressive cardiomyopathy		32	44	42	47	36	39	31
- Amyloidosis		3	4	5	8	4	3	5
- Polyarteritis		8	9	9	7	7	13	3
- Inflammation: epicardial		3	6	4	2	2	4	-
- Inflammation: myocardial		-	-	2	2	5	1	-
- Inflammation: endocardial		-	1	-	3	3	1	1
- Thrombosis		1	-	-	1	2	-	-
- Thrombosis: atrial		5	13	9	8	2	2	1
- Hemorrhage		-	-	-	-	1	-	-
- Mineralization		1	-	1	-	2	1	3
HEMOLYM. TISSUE	EXAMIN:	5	12	3	6	14	8	1
ILEUM	EXAMIN:	60	59	70	69	69	69	70
- Amyloidosis		11	12	11	11	10	9	6
- Hemorrhage		-	-	-	-	1	1	-
- Inflammation		1	-	-	-	-	-	-
- Polyarteritis		-	1	-	4	1	1	-
- Hyperplasia: lymphoid (GALT)		-	-	-	1	-	-	-
I.S. DORS.2HO. LT	EXAMIN:	60	60	70	70	69	69	70
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	-	-	8
- Crust		1	2	3	1	5	1	7
- Inflammation: dermis		3	1	2	2	7	4	8
- Inflammation: subcutis		31	23	27	28	26	29	41
- Hyperplasia: epidermis		3	1	1	2	4	1	13
- Erosion: epidermis		1	-	-	-	-	-	-
- Ulceration: epidermis		-	-	1	-	1	1	3
- Fibrosis: dermis		2	2	2	5	12	9	21

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. DORS.THO. LT	CONT'D.	60	60	70	70	69	69	70
- Fibrosis: subcutis		18	8	11	9	27	48	55
- Degeneration: panniculus muscle		2	1	-	2	7	14	33
- Edema: subcutis		2	3	2	3	3	1	1
- Hemorrhage: subcutis		6	1	2	3	5	2	3
- Inflammation/degeneration/necrosis: vascular		-	1	-	2	-	2	13
I.S. DORS.THO. RT	EXAMIN:	60	60	70	70	69	69	69
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	-	1	7
- Crust		1	4	1	3	3	3	7
- Inflammation: dermis		2	4	1	2	3	4	12
- Inflammation: subcutis		29	21	27	26	18	27	37
- Hyperplasia: epidermis		1	2	-	4	3	5	18
- Erosion: epidermis		-	-	-	-	-	2	1
- Ulceration: epidermis		-	1	-	-	3	3	5
- Fibrosis: dermis		1	5	3	4	7	9	21
I.S. DORS.THO. RT	CONT'D.	60	60	70	70	69	69	69
- Fibrosis: subcutis		12	8	17	7	17	42	57
- Degeneration: panniculus muscle		2	2	1	1	6	19	35
- Edema: subcutis		2	2	1	3	2	1	4
- Cleft		-	-	-	-	-	-	3
- Hemorrhage: subcutis		2	2	1	3	2	2	12
- Inflammation/degeneration/necrosis: vascular		-	-	-	-	1	2	8

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. LUMBAR, LEFT	EXAMIN:	60	60	70	70	69	69	69
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	-	4	8
- Crust		1	3	1	5	4	-	2
- Inflammation: dermis		2	4	2	4	3	2	5
- Inflammation: subcutis		32	26	32	34	33	34	38
- Hyperplasia: epidermis		1	2	-	1	-	5	5
- Ulceration: epidermis		-	-	-	1	1	2	5
- Fibrosis: dermis		-	5	4	3	10	15	19
- Fibrosis: subcutis		23	6	19	23	41	60	53
- Degeneration: panniculus muscle		7	-	3	2	5	31	30
- Edema: subcutis		2	4	1	2	2	1	3
- Hemorrhage: subcutis		4	3	1	4	7	10	7
- Inflammation/degeneration/necrosis: vascular		-	-	-	-	2	3	8
I.S. LUMBAR, RIGHT	EXAMIN:	60	60	70	70	69	69	69
- Intimal thickening/medial hypertrophy: vascular		-	-	1	-	-	3	4
- Crust		3	5	-	1	3	3	-
- Inflammation: dermis		2	4	-	4	4	2	5
- Inflammation: subcutis		28	31	26	35	25	38	37
- Hyperplasia: epidermis		1	1	-	-	1	3	4
- Erosion: epidermis		-	-	-	1	-	-	-
- Ulceration: epidermis		-	-	-	-	1	1	2
- Fibrosis: dermis		-	2	2	-	7	10	22
- Fibrosis: subcutis		18	12	19	25	39	59	59
- Degeneration: panniculus muscle		2	2	3	8	10	31	36
- Edema: dermis		-	1	-	1	-	-	-
- Edema: subcutis		3	4	3	5	2	-	5
- Hemorrhage: subcutis		5	2	5	4	7	12	7
- Inflammation/degeneration/necrosis: vascular		-	-	-	1	-	5	8

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**

All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. SCAPULAR, LEFT	EXAMIN:	60	60	70	70	69	69	69
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	1	4	11
- Crust		2	2	3	4	5	7	8
- Inflammation: dermis		4	3	7	9	7	8	18
- Inflammation: subcutis		24	31	25	35	29	34	40
- Hyperplasia: epidermis		3	3	3	6	3	6	31
- Erosion: epidermis		-	-	-	-	-	-	2
- Ulceration: epidermis		-	-	-	2	1	2	4
- Fibrosis: dermis		3	5	8	9	8	16	41
I.S. SCAPULAR, LEFT	CONT'D.	60	60	70	70	69	69	69
- Fibrosis: subcutis		19	17	21	18	37	58	60
- Degeneration: panniculus muscle		3	-	-	3	8	9	14
- Cleft		-	-	-	-	-	-	3
- Edema: dermis		-	1	1	-	-	-	-
- Edema: subcutis		1	2	3	1	-	1	1
- Hemorrhage: subcutis		2	3	1	4	-	4	5
- Inflammation/degeneration/necrosis: vascular		2	1	-	-	2	10	23
I.S. SCAPULAR, RIGHT	EXAMIN:	60	60	70	70	69	69	69
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	-	1	7
- Crust		3	1	-	5	6	5	11
- Inflammation: dermis		3	2	3	10	6	11	19
- Inflammation: subcutis		20	20	22	28	14	28	38
- Hyperplasia: epidermis		3	1	-	5	4	6	20
- Erosion: epidermis		-	-	-	-	-	-	1
- Ulceration: epidermis		-	-	-	-	-	5	5
- Fibrosis: dermis		1	2	4	6	13	16	42
- Fibrosis: subcutis		12	8	17	16	14	41	58

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. SCAPULAR, RIGHT	CONT'D.	60	60	70	70	69	69	69
- Degeneration: panniculus muscle		-	1	-	3	1	12	20
- Inflammation/degeneration/necrosis: vascular		-	1	-	1	3	4	10
- Cleft		-	-	-	1	-	2	3
- Edema: dermis		-	-	-	1	-	-	1
- Edema: subcutis		-	3	2	1	-	1	4
- Hemorrhage: subcutis		2	1	3	4	3	2	2
- Amyloidosis		-	1	-	-	-	-	-
JEJUNUM	EXAMIN:	60	60	70	70	69	69	70
- Amyloidosis		8	9	6	6	4	7	3
- Hemorrhage		-	-	-	1	-	-	-
- Necrosis: lymphoid (GALT)		-	-	1	-	-	-	-
- Erosion		-	-	1	1	-	1	-
- Polyarteritis		1	1	1	1	-	-	-
- Diverticulum		-	-	-	1	1	-	1
- Parasite		-	1	-	-	-	-	-
- Ulceration		-	-	-	1	-	-	-
- Inflammation		-	-	-	-	2	-	-
- Hyperplasia: lymphoid (GALT)		-	-	-	1	-	1	-
JOINT	EXAMIN:	-	-	1	1	1	-	-
- Inflammation		-	-	1	1	1	-	-
KIDNEY	EXAMIN:	60	60	70	70	70	70	70
- Polyarteritis		11	6	11	6	10	15	-
- Nephropathy		34	35	44	43	38	46	32
- Hematopoiesis: extramedullary		-	-	-	-	-	-	1
- Dilatation: tubular		3	2	5	5	3	3	2
- Degeneration: tubular		-	-	-	-	2	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
KIDNEY	CONT'D.	60	60	70	70	70	70	70
- Vacuolation: tubular		-	-	1	-	-	-	-
- Mineralization: tubular		-	1	-	-	1	1	-
- Mineralization: corticomedullary junction		-	-	-	-	1	-	-
- Mineralization: vascular		-	1	-	-	-	-	-
- Deposits pigment: tubular		1	5	4	2	3	1	1
- Cyst		7	11	5	7	10	10	7
- Infiltration: mixed cell		-	-	-	-	1	-	1
- Inflammation: interstitial		1	1	1	4	-	2	2
- Inflammation: capsule		-	-	-	-	1	-	-
- Amyloidosis		13	10	9	16	11	18	10
- Pyelitis/pyelonephritis		3	6	5	1	5	3	3
- Hyperplasia: transitional cell		-	-	-	-	1	-	-
- Hyperplasia: tubular		-	1	-	1	-	-	-
- Dilatation: pelvis		11	15	12	15	11	9	9
- Necrosis: papilla		2	1	1	1	-	1	1
- Hemorrhage		3	-	1	1	-	-	-
- Hyaline droplet: tubular		-	2	-	-	1	-	-
- Thrombosis		-	-	-	1	-	-	-
LACRIMAL GLAND	EXAMIN:	60	60	69	69	70	68	69
- Amyloidosis		4	8	4	4	4	4	-
- Inflammation		-	-	-	-	2	-	-
- Polyarteritis		-	-	-	-	-	-	1
- Alteration: harderian gland		1	-	1	1	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

	MALE						
DOSE GROUP	1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED	60	60	70	70	70	70	70
LARYNX EXAMIN:	60	60	70	70	69	69	70
- Inflammation	6	6	5	5	8	8	3
- Dilatation: submucosal glands	-	-	-	-	-	1	1
- Hyperplasia: epithelial	2	3	2	4	6	4	2
- Polyarteritis	2	-	1	1	2	3	1
- Amyloidosis	3	6	3	4	3	2	-
LIVER EXAMIN:	60	60	70	70	70	70	70
- Hypertrophy: centrilobular	2	6	10	13	15	22	23
- Basophilic cell focus	1	5	4	1	3	3	1
- Eosinophilic cell focus	3	3	-	-	2	-	-
- Amyloidosis	10	11	11	15	16	17	10
- Fibrosis	-	-	-	-	-	1	-
- Inflammation: granulomatous	-	-	1	-	-	-	-
- Inflammation: acute	-	-	-	-	-	-	1
- Inflammation	-	-	1	1	-	-	-
- Inflammation: capsular	-	-	-	1	1	-	5
- Necrosis: single cell	7	5	4	3	3	5	18
- Necrosis	7	9	12	9	6	9	6
- Increased mitotic figures	-	-	-	-	-	-	4
- Hematopoiesis: extramedullary	6	5	2	7	5	8	16
- Vacuolation: centrilobular	1	-	1	1	2	-	2
- Vacuolation: hepatocellular	1	-	-	-	-	-	-
- Angiectasis	-	1	-	-	1	-	-
- Polyarteritis	1	-	-	1	2	2	-
- Thrombosis	-	-	-	-	1	-	-
- Cyst: biliary	1	-	-	2	1	-	-
- Tension lipidosis	1	-	2	-	2	4	3

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
LUNG	EXAMIN:	60	60	70	70	70	70	70
- Hyperplasia: bronchioloalveolar		2	1	2	2	5	-	1
- Macrophage accumulation		16	21	12	15	7	11	3
- Histiocytosis		2	4	7	5	7	3	3
- Inflammation: bronchoalveolar		1	-	2	-	1	1	-
- Inflammation: interstitial		12	11	8	11	10	6	3
- Inflammation: perivascular		-	-	-	-	-	-	1
- Inflammation: pleura		1	2	4	1	3	-	2
- Hemorrhage		7	5	7	9	7	8	2
- Thrombosis		-	1	2	-	-	-	-
- Polyarteritis		-	-	1	-	-	-	-
LYMPH NODE	EXAMIN:	9	24	16	12	21	10	27
- Erythrocytosis/hemorrhage: sinusal		1	4	2	1	5	2	4
- Plasmacytosis		4	4	9	6	6	2	10
- Hematopoiesis: extramedullary		-	1	-	1	-	1	1
- Hyperplasia: lymphoid		-	1	1	2	1	-	8
- Polyarteritis		-	1	1	-	1	-	1
- Inflammation		-	1	1	1	-	-	-
L. NODE MANDIBULAR	EXAMIN:	57	50	61	60	59	64	62
- Hematopoiesis: extramedullary		-	-	-	1	-	-	1
- Hyperplasia: lymphoid		-	-	-	1	1	-	3
- Histiocytosis		-	-	-	-	-	-	1
- Plasmacytosis		4	2	5	8	8	4	5
- Amyloidosis		2	1	-	2	1	2	-
- Erythrocytosis/hemorrhage		3	3	2	4	2	2	1
- Thrombosis		-	-	-	1	-	1	-
- Polyarteritis		-	-	1	3	1	-	1

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
L.NODS MESENTERIC	EXAMIN:	59	60	69	68	68	68	69
- Hyperplasia: lymphoid		2	5	2	2	1	-	2
- Amyloidosis		4	5	4	6	7	6	9
- Plasmacytosis		1	5	1	1	-	-	1
- Erythrocytosis/hemorrhage		23	30	27	26	23	19	23
- Dilatation: sinusal with or without congestion		-	-	1	-	-	1	-
- Hematopoiesis: extramedullary		1	2	1	3	6	1	2
- Inflammation		5	1	3	-	3	4	2
- Polyarteritis		1	3	3	-	2	3	-
MENINGES	EXAMIN:	-	-	-	-	-	1	-
MUSCLE SKELETAL	EXAMIN:	60	59	69	68	68	67	69
- Degeneration/necrosis: myofiber		1	1	3	4	3	-	6
- Inflammation		-	1	1	-	-	-	-
NERVES OPTIC	EXAMIN:	58	56	68	68	67	68	69
NERVE SCIATIC	EXAMIN:	58	60	70	70	69	70	70
- Degeneration: nerve fiber		6	5	9	13	6	12	1
PANCREAS	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		4	4	5	9	5	9	7
- Inflammation		-	3	1	1	1	-	1
- Polyarteritis		-	2	-	1	3	1	-
- Mineralization: vascular		2	-	1	2	1	-	-
- Thrombosis		-	-	-	1	-	-	-
- Necrosis		-	-	-	1	-	-	-
- Dilatation: duct		-	-	-	-	1	-	1
- Atrophy: acinar cell		-	-	-	-	1	-	-
- Hyperplasia acinar cell: focal		-	-	-	-	2	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
PANCREAS	CONT'D.	60	60	70	70	70	70	70
- Infiltration: mononuclear cell		-	-	-	1	-	+	-
PARATHYROID GLAND	EXAMIN:	38	36	42	49	42	48	40
- Amyloidosis		6	4	4	10	9	11	6
- Hyperplasia		-	-	-	-	-	2	-
PENIS	EXAMIN:	-	-	-	-	1	1	-
- Inflammation		-	-	-	-	1	1	-
PITUITARY	EXAMIN:	59	60	67	68	68	68	68
- Hyperplasia: pars distalis		-	-	-	-	-	1	-
- Polyarteritis		-	-	-	-	1	-	-
- Rathke pouch remnants		-	1	-	-	-	-	-
PREPUTIAL GLAND	EXAMIN:	59	60	69	68	67	68	69
- Inflammation		6	8	10	9	8	9	9
- Hemorrhage		1	-	1	1	-	-	-
- Dilatation		51	49	61	59	59	61	60
PROSTATE	EXAMIN:	60	60	70	70	70	69	69
- Inflammation		10	15	14	14	10	10	7
- Hemorrhage		1	-	-	-	-	-	-
- Hyperplasia: acinar epithelium		-	1	-	-	-	1	-
- Edema		1	-	-	-	-	-	-
- Polyarteritis		3	3	-	1	3	1	-
RECTUM	EXAMIN:	1	-	-	-	-	1	-
- Edema		1	-	-	-	-	1	-
SALIV.GL. MANDIBULAR	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		1	1	1	5	2	6	2
- Polyarteritis		-	-	1	-	1	-	-
- Inflammation		-	-	1	1	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
SALIV. GLAND PAROTID	EXAMIN:	-	1	-	-	-	-	-
SEMINAL VESICLE	EXAMIN:	60	60	70	70	70	70	69
- Inflammation		18	21	20	16	15	15	7
- Amyloidosis		-	-	-	1	-	1	2
- Polyarteritis		2	2	3	1	4	4	-
- Dilatation		2	6	-	-	-	4	-
- Hyperplasia: epithelium		-	-	-	-	-	1	-
- Hemorrhage		-	-	-	-	-	1	-
SKIN	EXAMIN:	60	60	70	69	69	69	70
- Inflammation: dermis		5	4	4	3	1	2	7
- Inflammation: subcutis		6	13	9	8	6	8	12
- Inflammation: vascular		-	-	-	-	-	-	2
- Erosion: epidermis		1	-	-	-	-	-	-
- Ulceration		-	-	-	-	-	1	2
- Degeneration: panniculus muscle		-	-	-	1	-	-	-
- Edema: subcutis		2	5	1	5	4	3	1
SKIN MISCELLANEOUS	EXAMIN:	17	15	20	18	23	21	18
- Cyst: epidermal		1	-	1	-	2	-	-
- Inflammation		16	14	18	17	19	21	16
- Hyperplasia: epidermal		1	-	-	-	-	-	1
- Edema		-	-	-	-	1	-	-
SPINAL CORD CERVICAL	EXAMIN:	60	60	70	70	69	69	70
- Necrosis		-	1	1	-	-	-	-
- Inflammation		-	-	-	-	1	-	-
- Hemorrhage		-	1	-	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
SPLEEN	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		6	10	11	18	13	17	12
- Angiectasis		-	1	-	-	-	1	-
- Hematopoiesis/extramedullary: increased		18	24	23	15	25	22	43
- Hyperplasia: lymphoid		2	-	-	-	3	-	-
- Atrophy/necrosis: lymphoid		2	3	7	1	4	1	1
- Inflammation: capsular		2	-	1	-	1	3	6
- Inflammation		-	-	-	-	-	1	-
- Polyarteritis		1	-	-	-	-	1	-
- Thrombosis		-	1	-	-	-	-	-
STOMACH	EXAMIN:	60	60	70	70	69	69	70
- Amyloidosis		5	7	6	7	5	9	5
- Inflammation		-	1	-	-	2	-	1
- Erosion: glandular mucosa		3	9	10	4	5	9	1
- Mineralization		1	2	-	1	-	2	2
- Polyarteritis		2	3	3	2	3	6	1
- Edema		-	-	-	-	-	1	-
SUBCUTANEOUS TISSUE	EXAMIN:	5	7	5	5	3	6	2
- Inflammation		4	1	3	4	1	4	-
- Edema		4	1	2	3	-	3	-
- Hemorrhage		-	-	-	1	-	-	-
- Cyst		-	1	-	1	-	-	-
TAIL	EXAMIN:	2	-	2	-	-	1	1
- Inflammation: vascular		-	-	-	-	-	-	1

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

	MALE						
DOSE GROUP	1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED	60	60	70	70	70	70	70
TESTIS EXAMIN:	60	60	70	70	70	70	70
- Degeneration/atrophy: seminiferous epithelium	29	33	34	32	31	41	19
- Hyperplasia: interstitial cell	1	1	-	2	2	2	2
- Mineralization: vascular	8	10	10	8	8	6	-
- Dilatation: rete testis	-	-	-	1	-	-	-
- Amyloidosis	6	4	3	2	2	3	1
- Inflammation	-	1	-	2	-	1	1
- Polyarteritis	1	1	2	3	4	2	-
- Dilatation: tubular	1	2	3	-	-	2	1
- Hemorrhage	-	1	-	-	-	-	-
- Angiectasis	-	1	-	-	-	-	-
- Edema	-	1	-	1	-	-	-
- Necrosis	1	-	-	-	-	-	-
- Hyperplasia: rete testis	1	-	-	-	1	-	-
THORAX EXAMIN:	1	-	-	-	2	-	-
THYMUS EXAMIN:	50	48	58	59	61	56	62
- Atrophy/necrosis: lymphoid	42	29	43	47	38	39	30
- Hyperplasia: lymphoid	1	1	1	1	3	1	-
- Polyarteritis	1	1	1	1	3	4	-
- Amyloidosis	-	-	-	3	1	-	-
- Hemorrhage	-	-	-	1	-	-	-
- Inflammation: perithymic	-	-	-	-	-	1	-
THYROID EXAMIN:	60	60	70	69	68	69	70
- Amyloidosis	12	14	11	18	16	17	10
- Inflammation	-	-	-	-	1	-	-
- Polyarteritis	3	1	3	1	2	2	-
TONGUE EXAMIN:	60	60	70	70	70	70	70
- Inflammation	-	-	-	-	-	1	-
- Polyarteritis	4	2	3	1	4	4	1
- Hemorrhage	-	-	-	-	-	-	1
TRACHEA EXAMIN:	60	60	70	69	70	70	69
- Polyarteritis	1	-	-	-	-	-	-

Table 16 Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex
All Animals

		MALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
URETER	EXAMIN:	13	13	11	11	15	11	9
- Dilatation		10	12	10	11	12	8	3
- Hyperplasia: transitional cell		2	2	2	2	4	2	-
- Amyloidosis		-	1	-	-	-	-	-
- Polyarteritis		-	-	1	-	-	-	-
URETHRA	EXAMIN:	-	-	-	1	-	-	-
- Dilatation		-	-	-	1	-	-	-
- Hemorrhage		-	-	-	1	-	-	-
URINARY BLADDER	EXAMIN:	60	60	70	70	70	70	70
- Hyperplasia: transitional cell		12	13	16	11	9	12	12
- Inflammation		18	20	28	21	21	19	15
- Dilatation		21	13	24	21	15	10	12
- Hemorrhage		8	3	4	5	5	2	-
- Polyarteritis		1	2	-	2	-	2	1
- Amyloidosis		-	-	-	1	-	-	-
- Ulceration/erosion		1	-	1	-	1	-	-
VAS DEFERENS	EXAMIN:	-	-	-	-	-	1	-
- Inflammation		-	-	-	-	-	1	-
ZYMBAL'S GLAND	EXAMIN:	60	60	69	70	68	68	69
- Amyloidosis		8	10	5	8	5	8	5
- Hyperplasia		-	3	1	-	2	2	-
- Polyarteritis		-	1	-	2	-	-	-
- Inflammation		-	1	-	-	1	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
ABDOMEN	EXAMIN:	-	1	2	2	1	1	1
- Inflammation		-	-	2	-	-	-	-
ADRENAL	EXAMIN:	60	60	70	69	68	70	70
- Hypertrophy: cortical		-	-	-	-	-	2	1
- Hypertrophy: cortical focal		2	-	3	2	-	2	-
- Hyperplasia: cortical		1	-	-	-	-	-	-
- Hyperplasia: cortical focal		2	-	-	1	-	2	-
- Hyperplasia: medullary		6	3	6	5	2	2	5
- Amyloidosis		6	8	5	7	7	9	5
- Hyperplasia: spindle cells		52	55	63	64	62	65	60
- Deposits: lipofuscin		49	54	59	52	53	57	44
- Hemorrhage		-	-	1	-	-	-	-
- Polyarteritis		-	-	2	2	-	-	2
- Hematopoiesis: extramedullary		1	1	3	1	2	2	-
AORTA	EXAMIN:	60	60	69	70	70	70	70
BLOOD VESSEL	EXAMIN:	-	1	-	-	-	-	-
BONE-FEMUR	EXAMIN:	60	59	70	70	70	70	70
- Fibrous osteodystrophy		2	3	10	3	5	5	2
- Fibro-osseous lesion		1	2	5	3	5	1	1
- Necrosis		-	-	-	1	-	-	-
- Hyperostosis		1	-	-	-	-	-	-
- Polyarteritis		-	1	-	-	-	-	-
- Fibrosis		-	-	-	-	-	1	-
BONE MARROW	EXAMIN:	60	60	70	70	70	70	70
- Necrosis		-	-	-	-	-	-	1
- Amyloidosis		-	-	1	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		**1**	**2**	**3**	**4**	**5**	**6**	**7**
NUMBER OF ANIMALS EXAMINED		**60**	**60**	**70**	**70**	**70**	**70**	**70**
BONE MARROW	CONT'D.	60	60	70	70	70	70	70
- Thrombosis		-	-	-	1	-	-	-
BONE MISCELLANEOUS	EXAMIN:	1	2	1	-	1	-	-
- Fracture		-	1	1	-	-	-	-
BONE-STERNUM	EXAMIN:	60	60	69	70	70	69	70
- Fibrous osteodystrophy		2	5	7	9	5	3	2
- Fibro-osseous lesion		6	6	10	17	11	5	2
- Fibrosis		1	-	-	-	-	-	-
- Hyperostosis		-	1	2	-	-	-	1
- Inflammation		-	-	-	-	-	-	1
BRAIN	EXAMIN:	60	60	70	70	70	70	70
- Hemorrhage		1	-	-	-	-	-	-
- Infiltration: mononuclear cell		-	-	2	-	-	-	-
- Necrosis		-	1	-	-	-	-	1
- Compression		1	1	3	2	1	-	-
- Dilatation: ventricle		-	-	1	1	-	-	-
- Vacuolation		-	-	2	1	-	-	-
- Polyarteritis		-	1	2	-	-	-	-
CAVITY CRANIAL	EXAMIN:	-	-	-	-	-	1	-
CAVITY ORAL	EXAMIN:	-	-	-	1	-	1	-
- Inflammation: gingiva		-	-	-	-	-	1	-
- Perforation: palate		-	-	-	1	-	-	-
CECUM	EXAMIN:	60	60	70	70	70	70	70
- Erosion		-	-	1	1	-	-	1
- Amyloidosis		1	1	-	-	1	-	-
- Edema		-	1	2	2	2	2	-
- Deposits: pigment		3	2	3	2	1	2	-
- Polyarteritis		-	1	2	1	-	-	2
- Inflammation		1	-	-	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
CECUM	CONT'D.	60	60	70	70	70	70	70
- Parasite		-	1	2	-	-	-	-
CLITORAL GLAND	EXAMIN:	58	58	67	67	64	67	65
- Inflammation		7	8	9	10	2	3	3
- Dilatation		53	53	62	67	58	64	59
COLON	EXAMIN:	60	60	70	69	70	70	70
- Amyloidosis		-	1	-	-	-	-	-
- Parasite		4	2	2	4	3	1	3
- Edema		-	1	-	-	-	-	-
- Polyarteritis		1	1	2	1	1	1	1
- Dilatation		-	-	-	1	-	-	-
DUODENUM	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		9	10	5	5	8	8	4
- Hemorrhage		1	-	-	-	-	-	-
- Polyarteritis		3	5	7	1	8	1	2
- Erosion		-	4	5	3	4	1	-
- Hyperplasia: villous/mucosal		-	-	-	-	1	-	-
- Inflammation		-	-	-	-	1	2	-
- Edema		-	1	-	-	-	-	-
ESOPHAGUS	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		1	2	-	2	1	-	1
- Inflammation		-	2	-	-	-	1	-
- Inflammation: periesophageal		-	-	1	-	-	-	-
- Dilatation		-	-	1	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
EYE	EXAMIN:	60	60	70	70	70	70	70
- Inflammation: cornea		2	3	4	2	2	4	1
- Inflammation: uvea		1	2	1	2	3	1	2
- Erosion: conjunctiva		-	-	-	-	-	-	1
- Fold/rosette: retina		-	-	1	-	-	-	-
- Degeneration: lens		7	9	8	9	2	8	6
- Mineralization: cornea		5	6	9	9	11	5	8
- Atrophy: retina		1	-	2	1	1	3	-
- Mineralization: iris		-	5	5	2	1	3	1
FAT	EXAMIN:	8	3	2	-	1	3	4
- Angiectasis		1	-	-	-	-	-	-
- Inflammation		-	-	-	-	-	-	1
GALLBLADDER	EXAMIN:	59	59	68	68	70	69	69
- Amyloidosis		-	-	-	-	1	-	-
- Hemorrhage		1	-	-	-	1	-	-
- Inflammation		2	1	-	2	1	2	3
- Polyarteritis		-	-	1	-	1	-	1
- Dilatation		1	1	-	1	1	-	2
- Hyperplasia		-	-	-	-	-	-	1
HARDERIAN GLAND	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		-	1	-	-	-	-	-
- Hyperplasia		1	-	-	-	1	-	1
- Thrombosis		-	1	-	1	-	-	-
HEAD	EXAMIN:	-	-	1	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
HEART	EXAMIN:	60	60	70	70	70	70	70
- Murine progressive cardiomyopathy		30	29	32	20	32	22	24
- Amyloidosis		3	5	4	4	5	6	4
- Polyarteritis		5	7	9	8	7	6	6
- Degeneration and/or necrosis: myocardial		-	-	-	1	-	1	-
- Inflammation: epicardial		3	6	3	2	4	8	2
- Inflammation: myocardial		-	-	-	1	-	2	1
- Inflammation: endocardial		1	1	3	2	-	1	-
- Thrombosis		1	-	-	-	-	1	1
- Thrombosis: atrial		3	6	5	1	6	4	-
- Hemorrhage		-	-	1	-	-	1	1
- Mineralization		1	4	1	1	2	-	1
HEMOLYM. TISSUE	EXAMIN:	24	20	17	16	22	24	15
ILEUM	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		9	11	6	9	9	7	8
- Hemorrhage		-	-	-	-	1	-	-
- Erosion		1	-	1	-	2	-	-
- Degeneration and/or necrosis		-	-	1	-	-	-	-
- Polyarteritis		-	3	2	1	1	2	3
I.S. DORS.THO. LT	EXAMIN:	60	60	70	70	70	70	70
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	-	-	1
- Crust		1	2	2	2	5	2	7
- Inflammation: dermis		3	1	2	4	6	12	28
- Inflammation: subcutis		28	33	34	43	43	40	55
- Hyperplasia: epidermis		2	1	2	5	2	6	15
- Erosion: epidermis		-	-	-	-	-	-	1
- Ulceration: epidermis		-	1	2	2	-	3	10
- Fibrosis: dermis		2	3	2	6	4	7	30

Table 16 Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. DORS.THO. LT	CONT'D.	60	60	70	70	70	70	70
- Fibrosis: subcutis		16	8	19	27	28	50	58
- Degeneration: panniculus muscle		-	1	1	1	4	23	37
- Edema: subcutis		3	2	5	4	3	4	6
- Hemorrhage: subcutis		7	5	8	8	3	12	11
- Inflammation/degeneration/necrosis: vascular		-	-	2	1	-	-	7
I.S. DORS.THO. RT	EXAMIN:	60	60	70	70	70	70	70
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	-	-	4
- Crust		2	2	3	3	5	5	10
- Inflammation: dermis		2	4	3	5	6	8	35
- Inflammation: subcutis		24	29	39	41	47	46	58
- Hyperplasia: epidermis		-	1	2	3	2	5	20
- Ulceration: epidermis		-	1	-	-	-	2	5
- Fibrosis: dermis		1	2	3	3	4	8	29
- Fibroais: subcutis		13	6	17	30	30	44	62
- Degeneration: panniculus muscle		6	-	1	2	7	20	34
- Edema: subcutis		3	1	1	4	4	1	4
- Hemorrhage: subcutis		7	7	7	10	5	12	9
- Inflammation/degeneration/necrosis: vascular		1	-	1	-	-	2	6
- Cyst: epidermal		-	-	1	-	-	-	-
I.S. LUMBAR, LEFT	EXAMIN:	60	60	70	70	70	70	70
- Intimal thickening/medial hypertrophy: vascular		-	-	-	-	-	-	2
- Crust		3	1	3	2	6	3	3
- Inflammation: dermis		2	2	3	8	9	8	27
- Inflammation: subcutis		36	31	40	49	47	51	50
- Hyperplasia: epidermis		-	-	1	3	1	3	18
- Erosion: epidermis		2	-	-	-	-	-	-
- Ulceration: epidermis		-	-	-	2	-	1	3
- Fibrosis: dermis		3	-	2	7	5	6	29

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. LUMBAR, LEFT	CONT'D.	60	60	70	70	70	70	70
- Fibrosis: subcutis		20	11	22	44	52	62	63
- Degeneration: panniculus muscle		1	1	1	6	6	24	44
- Cleft		-	-	-	-	-	-	2
- Edema: subcutis		4	3	2	4	6	6	5
- Hemorrhage: subcutis		6	8	7	9	9	8	6
- Inflammation/degeneration/necrosis: vascular		-	-	-	-	-	-	6
I.S. LUMBAR, RIGHT	EXAMIN:	60	60	70	70	70	70	70
- Intimal thickening/medial hyperrrophy: vascular		2	-	1	-	-	-	3
- Crust		2	2	1	4	1	2	3
- Inflammation: dermis		4	4	2	4	3	5	22
- Inflammation: subcutis		26	31	39	46	43	49	56
- Hyperplasia: epidermis		3	-	-	3	2	-	9
- Erosion: epidermis		-	-	-	-	-	1	-
- Ulceration: epidermis		-	-	1	-	-	-	2
- Fibrosis: dermis		3	2	2	2	3	4	21
- Fibrosis: subcutis		19	15	25	44	46	58	65
- Degeneration: panniculus muscle		2	-	2	2	5	27	46
- Edema: subcutis		4	3	1	5	6	4	9
- Hemorrhage: subcutis		8	8	11	15	6	12	9
- Inflammation/degeneration/necrosis: vascular		-	-	-	-	-	2	4
- Cyst: epidermal		-	-	-	-	1	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

	FEMALE						
DOSE GROUP	1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED	60	60	70	70	70	70	70
I.S. SCAPULAR, LEFT EXAMIN:	60	60	70	70	70	70	70
- Intimal thickening/medial hypertrophy: vascular	-	-	-	-	-	1	5
- Crust	1	2	6	2	6	8	17
- Inflammation: dermis	6	5	9	13	15	13	36
- Inflammation: subcutis	28	25	33	37	47	43	57
- Hyperplasia: epidermis	4	1	7	3	5	10	26
- Erosion: epidermis	-	-	1	-	-	-	3
- Ulceration: epidermis	-	-	2	1	1	1	3
- Fibrosis: dermis	4	1	7	5	5	8	45
- Fibrosis: subcutis	14	8	12	14	26	41	65
- Degeneration: panniculus muscle	2	-	1	-	2	8	19
- Cleft	-	-	1	-	-	-	-
- Edema: dermis	-	1	-	1	-	-	2
- Edema: subcutis	2	2	3	7	7	4	8
- Hemorrhage: subcutis	6	5	5	10	9	11	9
- Inflammation/degeneration/necrosis: vascular	-	1	1	-	1	-	16
I.S. SCAPULAR, RIGHT EXAMIN:	60	60	70	70	70	70	70
- Intimal thickening/medial hypertrophy: vascular	-	-	-	-	-	-	4
- Crust	-	2	2	2	4	13	12
- Inflammation: dermis	8	7	6	11	10	17	35
- Inflammation: subcutis	20	24	27	35	44	28	55
- Hyperplasia: epidermis	8	1	6	3	8	13	21
- Erosion: epidermis	2	-	-	-	-	1	2
- Ulceration: epidermis	2	-	3	1	2	3	2
- Fibrosis: dermis	7	1	7	4	7	15	34
- Fibrosis: subcutis	9	5	13	16	19	25	62

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Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
I.S. SCAPULAR, RIGHT	CONT'D.	60	60	70	70	70	70	70
- Degeneration: panniculus muscle		1	-	-	1	1	2	23
- Inflammation/degeneration/necrosis: vascular		-	-	1	-	1	2	14
- Cleft		-	-	-	-	-	-	2
- Edema: dermis		-	1	-	-	-	2	-
- Edema: subcutis		4	2	4	4	8	4	6
- Hemorrhage: dermis		2	2	-	1	-	1	-
- Hemorrhage: subcutis		3	4	8	6	4	4	5
JEJUNUM	EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis		4	7	5	4	7	7	3
- Hemorrhage		-	-	1	-	-	1	-
- Necrosis: lymphoid (GALT)		-	-	1	-	-	-	-
- Erosion		-	-	-	1	-	1	1
- Edema		-	1	-	-	-	-	-
- Polyarteritis		-	1	2	-	1	3	2
- Diverticulum		-	-	-	-	-	2	1
- Angiectasis		1	-	-	-	-	-	-
- Ulceration		-	-	-	1	-	-	-
- Inflammation		-	1	-	-	-	-	-
JOINT	EXAMIN:	-	1	-	1	-	-	-
KIDNEY	EXAMIN:	60	60	70	70	70	70	70
- Polyarteritis		2	3	5	3	3	2	2
- Nephropathy		24	34	37	36	32	32	31
- Dilatation: tubular		8	8	13	12	10	4	3
- Degeneration: tubular		-	-	1	-	-	-	-
- Mineralization: tubular		-	-	1	-	-	-	-
- Deposits pigment: tubular		-	1	-	2	-	1	-
- Cyst		3	2	5	6	1	1	1
- Inflammation: interstitial		1	-	1	3	2	-	-
- Amyloidosis		8	12	16	7	16	14	10

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
KIDNEY	CONT'D.	60	60	70	70	70	70	70
- Pyelitis/pyelonephritis		-	-	-	1	-	1	-
- Dilatation: pelvis		2	8	5	5	3	4	2
- Necrosis: papilla		-	1	-	1	1	-	-
- Necrosis		-	-	-	1	-	-	-
- Hemorrhage		-	-	-	1	1	-	-
- Hyaline droplet: tubular		5	3	4	4	4	6	4
LACRIMAL GLAND	EXAMIN:	57	59	69	70	70	69	70
- Amyloidosis		4	3	2	2	2	4	1
- Inflammation		-	-	-	-	-	-	1
- Necrosis		-	-	-	-	-	1	-
- Alteration: harderian gland		1	-	7	5	1	4	1
LARYNX	EXAMIN:	60	60	70	70	70	70	70
- Inflammation		6	8	10	6	9	6	8
- Dilatation: submucosal glands		-	-	1	-	-	-	-
- Hyperplasia: epithelial		5	4	4	2	4	1	-
- Hemorrhage		-	1	-	-	-	-	-
- Polyarteritis		-	-	3	2	-	1	1
- Amyloidosis		4	1	1	3	3	1	1
LIVER	EXAMIN:	60	60	70	70	70	70	70
- Hypertrophy: centrilobular		-	-	1	2	2	2	3
- Basophilic cell focus		-	2	-	2	-	2	1
- Eosinophilic cell focus		1	-	2	-	-	2	-
- Amyloidosis		5	9	7	12	9	8	5
- Inflammation: granulomatous		-	2	-	1	-	-	2
- Inflammation		1	1	-	-	1	1	1	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

	FEMALE						
DOSE GROUP	1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED	60	60	70	70	70	70	70
LIVER CONT'D.	60	60	70	70	70	70	70
- Inflammation: capsular	-	-	1	-	-	-	1
- Necrosis: single cell	1	3	4	4	5	1	7
- Necrosis	11	13	11	12	10	12	4
- Increased mitotic figures	-	1	-	-	1	1	1
- Hematopoiesis: extramedullary	6	7	5	10	11	10	2
- Vacuolation: centrilobular	-	-	-	-	1	-	-
- Vacuolation: hepatocellular	-	-	1	-	-	-	-
- Angiectasis	-	1	-	1	3	2	-
- Cyst: biliary	1	-	1	1	-	-	-
- Tension lipidosis	3	2	8	7	2	2	1
- Hyperplasia: bile duct	-	-	-	1	-	-	-
- Hypertrophy: bile duct	1	-	-	-	-	-	-
- Reactive sinusoidal lining cells	1	-	-	-	-	-	1
LUNG EXAMIN:	60	60	70	69	70	70	70
- Hyperplasia: bronchioloalveolar	1	1	2	-	1	3	2
- Macrophage accumulation	12	10	13	12	11	10	1
- Histiocytosis	6	6	4	6	3	2	6
- Inflammation: bronchoalveolar	-	-	2	-	-	-	-
- Inflammation: interstitial	7	4	8	7	13	5	2
- Inflammation: pleura	1	2	2	1	2	1	2
- Hemorrhage	8	9	9	12	11	4	5
- Thrombosis	1	-	-	2	-	1	-
- Amyloidosis	-	-	-	-	1	-	-
- Polyarteritis	-	-	1	-	-	-	-
LYMPH NODE EXAMIN:	22	20	20	22	31	25	24
- Erythrocytosis/hemorrhage: sinusal	2	4	4	6	6	8	6
- Plasmacytosis	5	4	7	12	10	7	7
- Hematopoiesis: extramedullary	1	-	1	1	1	-	-
- Hyperplasia: lymphoid	2	3	2	-	2	3	2
- Polyarteritis	-	-	2	2	1	-	1
- Inflammation	-	-	-	-	-	1	1
- Dilatation: sinusal with or without	-	-	-	-	1	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
congestion								
L. NODE MANDIBULAR	EXAMIN:	56	54	64	62	64	63	64
- Hyperplasia: lymphoid		-	-	1	1	-	-	-
- Plasmacytosis		-	1	4	8	3	3	-
- Amyloidosis		1	-	1	-	-	1	-
- Erythrocytosis/hemorrhage		7	7	10	14	7	7	8
- Polyarteritis		-	1	-	-	-	-	-
L.NODE MESENTERIC	EXAMIN:	60	60	70	69	70	68	70
- Hyperplasia: lymphoid		-	4	1	-	1	3	1
- Amyloidosis		4	3	3	4	1	2	3
- Plasmacytosis		1	-	2	5	1	2	2
- Erythrocytosis/hemorrhage		20	23	30	28	32	21	26
- Dilatation: sinusal with or without congestion		1	-	-	1	1	-	-
- Hematopoiesis: extramedullary		3	2	5	3	3	1	-
- Inflammation		1	-	-	1	1	3	1
- Polyarteritis		-	2	3	-	1	-	3
- Thrombosis		1	-	-	-	-	-	-
MAMMARY GLAND	EXAMIN:	56	58	68	69	68	66	70
- Ectasia: ducts and/or alveoli		10	8	16	20	9	11	-
- Hyperplasia		4	-	1	1	-	-	-
- Inflammation		-	-	1	-	-	-	-
MUSCLE SKELETAL	EXAMIN:	60	58	68	69	68	70	70
- Degeneration/necrosis: myofiber		-	4	-	2	2	3	4
- Inflammation		-	1	1	3	3	-	-
MUSCLE SKELETAL MISC	EXAMIN:	-	2	-	1	-	1	1
- Hemorrhage		-	2	-	1	-	-	-
- Inflammation		-	-	-	-	-	1	-
NERVES OPTIC	EXAMIN:	59	59	70	68	66	66	68
- Inflammation		-	-	-	1	-	-	-
NERVE SCIATIC	EXAMIN:	60	59	70	69	70	70	70
- Degeneration: nerve fiber		8	15	20	11	10	9	2

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
OVARY	EXAMIN:	60	60	70	70	70	70	70
- Cyst: follicular		15	21	22	27	22	16	13
- Dilatation/cyst: bursa		30	19	37	32	37	31	33
- Hemorrhage		1	-	1	1	-	1	1
- Amyloidosis		4	5	3	4	6	5	4
- Polyarteritis		5	9	15	6	8	4	4
- Inflammation		5	3	3	5	7	3	1
- Hyperplasia: tubulostromal		-	1	1	2	3	2	-
- Necrosis		-	-	-	1	-	-	-
- Angiectasis		2	1	2	5	1	1	1
OVIDUCT	EXAMIN:	60	60	70	70	70	70	69
- Cyst		1	-	1	3	1	-	-
- Polyarteritis		-	1	3	1	1	-	-
- Inflammation		6	3	2	2	3	1	2
- Amyloidosis		1	-	3	2	2	1	-
- Hyperplasia		-	-	-	-	3	-	-
PANCREAS	EXAMIN:	60	60	70	70	70	69	69
- Amyloidosis		2	4	2	5	4	5	2
- Inflammation		1	1	4	3	2	-	1
- Polyarteritis		-	-	4	2	1	1	1
- Mineralization: vascular		2	-	2	-	1	1	-
- Vacuolation		-	-	-	-	1	1	1
- Thrombosis		-	-	1	-	-	-	-
- Necrosis		-	-	1	-	-	-	-
- Dilatation: duct		-	1	-	1	1	1	1
- Hemorrhage		-	-	-	-	1	-	-
- Atrophy: acinar cell		-	-	1	2	1	-	2
PARATHYROID GLAND	EXAMIN:	39	38	52	51	47	51	46
- Amyloidosis		3	7	4	7	5	3	2
- Necrosis		-	-	1	-	-	-	-
- Hyperplasia		-	-	2	-	1	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
PITUITARY	EXAMIN:	59	60	69	70	69	69	67
- Hyperplasia: pars distalis		2	1	4	-	-	4	-
- Hyperplasia: pars intermedia		3	-	1	-	-	-	2
- Hemorrhage		1	1	-	-	-	-	-
- Thrombosis		-	-	-	1	-	-	-
- Polyarteritis		1	-	1	-	-	-	-
RECTUM	EXAMIN:	-	-	-	1	-	-	-
- Edema		-	-	-	1	-	-	-
SALIV.GL. MANDIBULAR	EXAMIN:	59	59	70	69	70	69	70
- Amyloidosis		2	1	2	2	3	2	2
- Polyarteritis		-	1	2	-	-	-	-
- Inflammation		-	-	-	-	-	-	1
SKIN	EXAMIN:	60	60	70	70	70	70	70
- Inflammation: dermis		-	5	2	2	1	2	1
- Inflammation: subcutis		3	4	5	6	6	8	11
- Inflammation: vascular		-	-	-	-	-	1	-
- Erosion: epidermis		-	-	1	-	-	-	1
- Ulceration		-	-	-	-	-	1	-
- Edema: subcutis		4	7	4	6	9	9	6
- Amyloidosis		-	1	-	-	-	-	-
SKIN MISCELLANEOUS	EXAMIN:	9	9	16	16	10	10	16
- Cyst: epidermal		-	1	3	2	3	-	-
- Inflammation		6	7	13	12	7	10	15
- Hemorrhage: subcutis		2	-	-	-	-	-	-
SPINAL CORD CERVICAL	EXAMIN:	60	60	70	70	70	70	70
- Inflammation		-	-	1	-	-	-	-
- Dilatation		-	1	-	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

	FEMALE						
DOSE GROUP	1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED	60	60	70	70	70	70	70
SPLEEN EXAMIN:	60	60	70	70	70	70	70
- Amyloidosis	6	9	8	11	11	11	6
- Angiectasis	-	-	-	2	1	-	-
- Hematopoiesis/extramedullary: increased	30	25	31	40	46	45	43
- Hyperplasia: lymphoid	1	-	1	1	1	1	-
- Atrophy/necrosis: lymphoid	2	2	3	4	2	3	1
- Inflammation: capsular	-	1	2	-	1	-	3
- Polyarteritis	-	2	1	-	1	-	-
- Necrosis	-	2	1	-	-	-	-
- Thrombosis	-	1	-	-	-	-	-
- Amyloidosis	5	7	1	4	4	5	-
- Hemorrhage	-	-	-	-	1	-	-
- Inflammation	1	1	1	1	1	1	-
- Erosion: glandular mucosa	5	3	6	6	4	4	6
- Mineralization	-	2	-	-	-	-	-
- Polyarteritis	1	4	7	2	2	1	3
- Cyst: squamous	1	-	-	-	-	-	-
- Edema	1	-	1	-	1	1	2
SUBCUTANEOUS TISSUE EXAMIN:	5	6	5	8	5	5	3
- Inflammation	-	1	2	5	1	4	1
- Edema	1	1	1	2	1	3	2
TAIL EXAMIN:	3	-	1	1	-	1	1
- Inflammation: vascular	-	-	-	-	-	-	1
- Inflammation	-	-	-	1	-	-	-
THORAX EXAMIN:	1	1	1	-	3	3	-
THYMUS EXAMIN:	56	51	64	61	61	62	67
- Atrophy/necrosis: lymphoid	25	28	38	32	30	31	36
- Hyperplasia: lymphoid	4	3	6	2	6	5	5
- Polyarteritis	1	7	6	5	3	2	5
- Amyloidosis	-	-	1	-	2	-	-
- Hemorrhage	2	4	4	-	1	1	1
- Necrosis	-	-	1	-	-	-	-

Table 16 **Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex**
All Animals

		FEMALE						
DOSE GROUP		1	2	3	4	5	6	7
NUMBER OF ANIMALS EXAMINED		60	60	70	70	70	70	70
THYROID	EXAMIN:	60	59	70	70	70	70	70
- Amyloidosis		7	8	6	10	11	9	7
- Hyperplasia: C-cell		-	-	-	-	-	-	1
- Hyperplasia: follicular cell		-	-	-	-	-	-	1
- Inflammation		-	-	-	-	1	-	-
- Polyarteritis		-	-	2	-	-	1	3
TONGUE	EXAMIN:	60	60	70	70	70	70	70
- Inflammation		2	-	1	-	3	1	2
- Polyarteritis		1	2	8	2	1	3	2
- Edema		-	1	-	1	-	1	-
TRACHEA	EXAMIN:	60	60	69	68	70	70	70
- Inflammation: peritracheal		-	-	-	-	-	1	-
URETER	EXAMIN:	2	4	2	2	1	1	1
- Dilatation		1	3	1	1	1	-	-
- Hyperplasia: transitional cell		-	1	-	1	-	-	-
URINARY BLADDER	EXAMIN:	60	60	70	68	70	70	69
- Hyperplasia: transitional cell		1	-	1	1	-	2	1
- Inflammation		17	19	20	26	18	17	27
- Dilatation		2	1	2	2	-	1	2
- Hemorrhage		-	-	-	-	1	-	-
- Polyarteritis		1	3	2	1	3	1	3
UTERUS	EXAMIN:	60	60	70	70	70	70	70
- Hyperplasia: endometrial		1	-	-	-	-	-	-
- Hyperplasia: endometrial cystic		53	52	64	62	63	67	64
- Hyperplasia: endometrial stroma		8	6	14	16	16	21	22
- Prolapse		-	-	1	-	-	-	-
- Polyarteritis		15	21	30	25	23	16	12
- Angiectasis		10	9	7	10	16	6	12
- Inflammation		10	3	8	15	13	5	9

Table 16 Incidence of Animals with Non-Neoplastic Lesions by Organ/Group/Sex
All Animals

		FEMALE						
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 70	4 70	5 70	6 70	7 70
UTERUS	CONT'D.	60	60	70	70	70	70	70
- Amyloidosis		1	2	1	1	1	1	-
- Thrombosis		-	1	-	-	-	1	-
VAGINA	EXAMIN:	59	58	70	69	69	70	70
- Hemorrhage		-	-	-	-	-	1	-
- Polyarteritis		3	5	8	9	2	2	2
- Inflammation		-	1	-	1	-	-	-
ZYMBAL'S GLAND	EXAMIN:	59	60	70	70	70	70	70
- Amyloidosis		6	9	3	4	5	6	3
- Hyperplasia		-	1	-	-	2	2	1
- Polyarteritis		-	-	1	-	-	1	1
- Inflammation		1	-	-	1	1	-	1

2.6.6.6 Reproductive and developmental toxicology

Except a rat s.c. fertility study (23171 RSR) using lanreotide autogel formulation being reviewed in this section, all the following resubmitted reproductive tox studies with lanreotide acetate have been reviewed under

- Fertility study by the subcutaneous route in the rat (seg I) (434/184)
- Fertility study by the intramuscular and subcutaneous routes in the rat (seg I) (434/169)
- BIM 23014 – Dose range finding study by the subcutaneous route in the pregnant rat (18991)
- Teratology study by subcutaneous route in the rat (seg II) (26791 or 434/099)
- BIM 23014 – Dose range finding study by subcutaneous route in the pregnant rabbit (18891)
- BIM 23014 – Teratology study by subcutaneous route in the rabbit (seg II) (26691 or 434/098)

Fertility and early embryonic development

Study title: Study of Fertility and Early Embryonic Development to Implantation by Subcutaneous Route in Rats

Key study findings:
Lanreotide autogel formulation was s.c. dosed every 2 weeks at 4, 10 and 20 mg/animal/injection to male and female SD rats, from pre-mating through mating and until sacrifice (males) or until Day 7 post-coitum (females). 20 mg/animal/injection was poorly tolerated at the injection sites in all males. Transient soft feces were noted in all treated groups after each dosing.

At 4 and 10 mg, lower body weight gain and FC in both sexes and lower ovulation and implantation parameters in females were considered to be drug-related effects. In males, none of the fertility parameters were affected. NOAEL for female fertility was <4 mg/animal/injection.

Study no.: 23171 RSR
Volume #, and page #: Vol A3.88, and pages 1/470 to 470/470
Conducting laboratory and location:

Date of study initiation: 03/19/2002
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Lanreotide Autogel, batch # P 85776 (syringes pre-filled with a solution at 0.246 mg per mg of supersaturated solution), and purity n/s.

Methods

Doses: 0, 4, 10, and 20 mg/animal/injection for males; and 0, 4, and 10 mg/animal/injection for females

Species/strain: rat/SD

Number/sex/group: 24/s/g

Route, formulation, volume, and infusion rate: subcutaneous injection with lanreotide autogel formulation (pre-filled syringes) at dose volume as shown in the table below:

Group	Number of animals	Dose-level (mg/animal/injection) (±10%)	Volume administered/animal (µL)	Quantity of gel administered /animal (±10%) (mg)	Graduation number on the syringe	Animal numbers
1 placebo	24 males 24 females	0	73	0	-	Z26741 to Z26764 Z26891 to Z26914
2	24 males 24 females	4	15	16.6*	1	Z26765 to Z26788 Z26915 to Z26938
3	24 males 24 females	10	37	41.6	2.5	Z26789 to Z26812 Z26939 to Z26962
4**	24 males	20	73	83.1	5	Z26813 to Z26836

*: [redacted] of pure Lanreotide active ingredient corresponded to 16.6 mg (±10%) of supersaturated solution (data supplied by the Sponsor).

**: males from group 4 were prematurely killed after the second injection due to severe local intolerance. Consequently, it was decided to did not order females of the group 4.

Satellite groups used for toxicokinetics: none

Study design: each animal was given dosage form once every 2 weeks, according to the following schedule:

Males:

- 3 months before mating,
- During the mating period,
- Until sacrifice (after hysterectomy of the females).

Females:

- 2 weeks before mating,
- During the mating period,
- During pregnancy (one injection maximum) or until sacrifice in unmated females.

Parameters and endpoints evaluated: Clinical examinations included morbidity and mortality, clinical signs, body weight and FC. During mating, estrous cycle was examined daily. Terminal examinations included seminology in males, hysterectomy in mated females on day 15 post-coitum (corpora lutea, dead and live embryos, early and late resorptions, and implantation sites). For females failed to mate, they were killed 7 days after the end of mating period and the presence of possible implantation scars on the uterus was checked. Gross and microscopic histology was assessed on all animals.

Results

Mortality: All males receiving 20 mg/animal were killed prematurely due to severe local intolerance after the second dosing. No mortality was noted in C or 4 and 10 mg/animal groups.

Clinical signs: Injection site reaction (thickness of the skin, scabs and areas of hair loss) or even abscess was seen in all dosed males and females at all dose levels. Transient soft feces was noted in some of the treated males

Body weight: A dose-related, moderate lower body weight gain was seen at 4 and 10 mg/animal during the treatment period in both males and females. Mean weight gain ↓ 24 and 31% for males at 4 and 10 mg/animal, respectively.

Female pre-mating weight gain (Day 1 to 15): ↓ 54 and 79% at 4 and 10 mg/animal, respectively,
Female pregnancy period weight gain (Day 0 to 15): ↓ 24 and 29% at 4 and 10 mg/animal

Food consumption: FC was lower in treated males and females.
Male pre-mating FC: ↓ 10 and 14% at 4 and 10 mg/animal respectively,
Female pre-mating FC: ↓ 9 and 14% at 4 and 10 mg/animal respectively,
Female pregnancy period FC: ↓10 and 16% at 4 and 10 mg/animal respectively.

Toxicokinetics: not performed

Necropsy:
The following gross findings at injection sites seemed to be due to the s.c. dosing of the long-term release formulation:

Males:
Greyish/whitish nodules and/or scabs were observed at the injection sites for the great majority of treated animals, as follows:

- 16/24 animals at 4 mg had greyish/whitish nodules and 6/24 had scabs at the different sites of injection (sites 3, 4 and/or 5).
- 23/24 animals at 10 mg had greyish/whitish nodules an 9/24 had scabs, at the different sites of injection (sites 1, 2, 3, 4 and/or 5).

Females:
Whitish nodules and/or scabs were observed for most of the treated animals:

- 12/24 females at 4 mg had whitish nodules and 16/24 had scabs at the different injection sites.
- 22/24 females at 10 mg had whitish nodules and 19/24 had scabs at the different injection sites.

Other organs:
The testis were reduced in size and/or soft in 1/24 males at 4 mg and in 1/24 males at 10 mg. The epididymides were reduced in size in the same males. The seminal vesicles were reduced in size in another male at 10 mg. However, due to very low incidence of these findings, it may not be drug-related changes.

Morphological examination
No treatment-related abnormalities of the testis and epididymides were found in the treated animals.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):

The mating index (number mated/number paired) was similar in the control and treated groups (96 to 100%). The pre-coital interval was similar in the control and treated groups. The estrous cycle was not affected by dosing.

The number of corpora lutea decreased significantly in a dose-related manner at the 4 and 10 mg/animal/injection dose levels. This change was correlated with the lower number of implantation sites at these two dose-levels. The pre-implantation loss was significantly higher.

Because of fewer implantation sites, the number of conception per female was significantly lower at the 4 and 10 mg/animal/injection groups when compared to the control group. These lower hysterectomy values were outside the range of the testing lab's — , historical control data.

The post-implantation loss (dead fetuses or resorptions) was similar at all dose-levels.

Dose-level (mg/animal/injection)		0	4	10
Pairs on study	n	24	24	24
Paired males + females	n	24 + 24	24 + 24	24 + 24
Pairs able to mate	n	24	22	24
Mating index	%	100	92	100
Mean number of days of pairing before mating	n	2.75	2.95	3.50
Pregnant female partners	n	24	22	24
Fertility index	%	100	100	100
Females with five concepti	n	24	22	24
Gestation index	%	100	100	100

Hysterectomy parameters (mean per pregnant female)

Dose-levels (mg/animal/injection)	0	4	10
Females at hysterectomy	24	22	24
Corpora lutea			
. total number	413	310	312
. number per female	17.2	14.1*** (-18%)	13.0*** (24%)
Implantation sites			
. total number	381	260	268
. number per female	15.9	11.8*** (-26%)	11.2*** (-29%)
Pre-implantation loss			
. total number	32	50*** (+56%)	44** (+37%)
.%	7.7	16.1	14.1
Concepti			
. total number	372	249	260
. number per female	15.5	11.3*** (-26%)	10.8*** (30%)
Post-implantation loss			
. total number	9	11	8
. % of implantation loss	2.4	4.2	3.0

***: p<0.001

**: p<0.01

Seminology: The very slight number and/or absence of epididymal and testicular spermatozoa recorded in a male (# Z26772) given 4 mg/animal/injection and the male (# Z26805) given 10 mg/animal/injection group was probably the consequence of the markedly reduced size of testes and epidydimides recorded at autopsy macroscopic examination. Since this finding was isolated and not dose-related, it may not be a drug-related effect.

The motility and the morphology of the epididymal sperm was similar in the control and the treated groups while the number of spermatozoa was minimally (↓11%) and slightly (↓16%) lower at 4 and 10 mg/animal/injection, respectively, when compared to the control. The testicular sperm heads as well as the daily production of sperm was minimally lower at the 4 and 10 mg/animal/injection when compared to the controls.

The mean seminology parameters are summarized in the following scanned table:

Seminology parameters

Dose-levels (mg/animal/injection)	0	4	10
Epididymal sperm			
Spermatozoa (10^3/mm^3)	533	475 (495)	445 (463)
% from control		-7	-13
Motility (% motile)	90.3	85.6 (89.36)	88.3 (92)
Normal morphology (%)	96	92 (95.78)	92 (95.82)
Testicular sperm			
Sperm heads (10^6/g of testis)	150.2	137.9 (143.56)	132.4 (137.8)
% from control		-4	-8
Daily sperm production (10^6/g of testis/day)	24.6	22.5 (23.5)	21.7 (22.6)
% from control		-4	-8

In bracket: the calculation did not take into account the data of one male (Z26772) given 4 mg/animal/injection and one male (Z26805) given 10 mg/animal/injection which had dramatically lower number of epididymal and testicular spermatozoa.

2.6.6.7 Local tolerance

Study title: Lanreotide autogel – Local tolerance study following repeated subcutaneous administration in the rabbit (study # 434/270)

Methods:
Local tolerance of lanreotide autogel formulation in the NZW rabbit after repeated s.c. dosing at a dose level comparable to the human therapeutic dose (kg equivalent) was tested. 6 male rabbits received s.c. dosing of 10 mg lanreotide autogel in a volume of 35±5 µl every 4 weeks on days 1 (site 1), 29 (site 2), 57 (site 3) and 85 (site 4). Morbidity/mortality checked twice daily. Each injection site was examined once daily for the first week after injection and then once weekly. All animals were sacrificed 14 days following the last injection (i.e. day 99), and all injection sites were fixed and processed for histopath evaluation.

Results and Conclusion:

- No mortality occurred during the study period. Following each injection, a decreased food intake was noted, which led to reduced fecal output and a lower weight gain or a loss of weight (could be a pharmacologic activity of the drug).
- Grossly, induration, erythema and edema were major detectable local reaction to the treatment:
  - induration noted for in all animals (most scored 1) persisted up to the last day of the study (day 98),
  - transient erythema (grade 1 or 2) was only noted for 1 to 3 days in several animals after the 1st and 3rd injection,
  - transient edema (grade 1 or 2) was observed for 2 to 4 animals from the day of injection or 1 to 2 days after injection, and persisted for 1 to 7 days.
- Histologically, majority of these gross lesions were seen to be cystic areas containing homogeneous material where the test compound had been deposited and surrounded by granulation tissue, foreign body giant cells and minimal fibrous capsule formation. Small focal infiltrates of monocytes and lymphocytes were observed surrounding the homogeneous material.

In conclusion, once every 4-week subcutaneous dosing of lanreotide autogel formulation to the rabbit at a dose level comparable to the human therapeutic dose (kg equivalent) in 4 injection sites during a 98-day period (each site only receive one injection of the 4 dosing) induced irreversible induration, transient erythema and edema at injection sites. The induration was resulted from drug component deposition and its consequent tissue reaction including granuloma formation and chronic inflammatory infiltration of macrophages and lymphocytes. The lesions persisted up to 98 days following the very first dosing. Longer term reversibility was not assessed in this study.

Study title: Lanreotide autogel – Local tolerance study following repeated intramuscular administration in the rabbit (study # 434/269)

Methods:
The study design is similar to the local tolerance test as reviewed above (434/270) except the dosing route (i.m.). 6 male rabbits received i.m. dosing of 10 mg lanreotide autogel in a volume of 35±5 µl every 4 weeks on days 1 (site 1), 29 (site 2), 57 (site 3) and 85

(site 4). Morbidity/mortality checked twice daily. Each injection site was examined once daily for the first week after injection and then once weekly. All animals were sacrificed 14 days following the last injection (i.e. on day 99), and all injection sites were fixed and processed for histopath evaluation.

Results and Conclusion:

- No mortality occurred during the study period. Following each injection, a decreased FC was noted, which led to reduced fecal output and a lower weight gain or a loss of weight.
- Grossly, slight induration was observed for one (after the 1st and 3rd injections) to four rabbits (after the 2nd injection) for 1 to 7 days. Neither erythema nor edema was observed.
- Histologically, the gross lesions were seen to be cystic areas containing homogeneous material where the test formulation had been deposited and surrounded by focal granulation tissue, few foreign body giant cells and minimal fibrous capsule formation. Muscle cell necrosis was noticed around the cystic material in some animals. Focal infiltrates of monocytes and lymphocytes (moderate to severe chronic inflammation) were observed surrounding the homogeneous material.

In conclusion, once every 4-week i.m. injection of lanreotide autogel formulation to the rabbit at a dose level comparable to the human therapeutic dose in 4 injection sites during a 98-day period (each site only receive one injection of the 4 dosing) induced foreign body granulomatous inflammation, which was resulted from the drug formulation deposition and tissue reaction intramuscularly.

2.6.6.8 Special toxicology studies None

2.6.6.9 Discussion and Conclusions

Lanreotide AUTOGEL is a synthetic analogue of somatostatin and is provided in three strengths (60, 90 or 120 mg) as sterile, ready to use, pre-filled syringes containing supersaturated bulk solution of 24.6% (w/w) lanreotide base.

Extensive pharmacology/toxicology studies in nonclinical species have been performed with the IRF, MPF, and Autogel® formulations. The results of the toxicological studies suggest that:

- The single-dose toxicity of lanreotide was assessed in mice and rats with IRF via i.v. and s.c. routes as have been reviewed under —— . The i.v. LD_{50} was 120 - 135 mg/kg in mice and of > 48 mg/kg in rats; the s.c. LD_{50} was >1200 mg/kg in mice and of >1500 mg/kg in rats. Commonly seen clinical signs in both mice and rats included reduced body weight gain, decreased activity, prostration, abnormal gait, decreased muscle tone, edema and scab formation at injection sites, etc. No histopathology has been performed on these single dose studies. The single-dose toxicity of the therapeutic formulation (autogel) has not been investigated.

- The repeated bi-weekly subcutaneous injection of lanreotide (the therapeutic formulation) in rats and dogs up to 26 weeks demonstrated that the new formulation of lanreotide did not induce systemic target organ toxicity. The chronic administration of lanreotide induced a reduction of growth rate (decreased body weight, decrease in weight of some organs) related to the pharmacological activity of the drug. The subcutaneous chronic inflammatory reaction at the injection sites was the primary finding in both species at all dose levels tested. The reversibility was not assessed. There were no additional target organ toxicities observed compared to previously conducted repeated dose tox studies in the same duration.

- In standard battery tests of genotoxicity, lanreotide does not show any genotoxic potential.

- In 2-year carcinogenicity studies in mice and rats administered daily by the subcutaneous route, lanreotide did not induce or increase the incidence of systemic neoplastic changes. Significant increase in neoplastic changes with lanreotide compared to controls was limited to the injection sites, including fibrosarcoma and/or malignant fibrous histiocytoma. These neoplastic changes appeared to be attributed to local irritation of the supersaturated acetate salt of the drug in addition to the highly frequent injection thereby leading to subcutaneous inflammation and local tissue hyperplasia. The dose selection in the rat study was not appropriate (HD equals to 1/10 maximum human exposure) and the dosing regimen was not relevant to that used in humans (daily vs. monthly).

  The mouse study was considered adequate although the daily dosing regimen likely limited systemic exposure. Fibrosarcomas in both genders and malignant fibrous histiocytoma in males were increased at the high dose which produces 3 times the maximum clinical exposure. Based on the frequency of dosing in mice relative to therapeutic use, the local tumors observed may not be clinically relevant.

- Fertility studies performed with lanreotide administered by different routes revealed that lanreotide reduced female fecundity at doses less than the maximum human exposure. The reduction in female fertility likely to be an expected side effect in light of the pharmacological activity of the drug (inhibition of GH secretion). The fertility of males was unaffected by the treatment, though seminiferous tubule atrophy/degeneration was observed, but the significance to humans is unclear. In the female rats at dose levels less than that of clinical exposure, decreased implantation sites, decreased fetal survival and increased incidence in skeletal variations (numbers of ribs) were observed. Gestation length was significantly increased at dose level less than maximum human exposure.

- Specific local tolerance studies with the lanreotide Autogel formulation have been

conducted with repeated dosing in NZW rabbits, once every 4-week subcutaneously or intramuscularly at 10 mg/animal in 4 injection sites during a 98-day period. The irreversible indurations were resulted from drug component deposition and its consequent tissue reaction, including granuloma formation and chronic inflammatory infiltration of macrophages and lymphocytes. Both s.c. and i.m. routes showed similar tissue reactions.

2.6.6.10 Tables and Figures (see individual study review)

2.6.7 TOXICOLOGY TABULATED SUMMARY

Two pivotal repeat dose chronic toxicity studies in rats and dogs with the therapeutic formulation (lanreotide autogel) are summarized in the scanned tables below. Other tox studies with IRF and MPF have been reviewed under

Report Title: 26-week toxicity study by repeated s.c. injection every 14 days in rats **Test Article:** LANREOTIDE AUTOGEL

Species/Strain: Rat/Sprague-Dawley **Duration of Dosing:** 26 weeks **Study No.** 28223 TCR

Initial Age: 6 weeks **Duration of Postdose:** - **Location in CTD:** Section 4.2.3.2

Date of First Dose: 30th Nov. 2004 **Method of Administration:** s.c.

Vehicle/Formulation: 0.9% saline/19-56 µL/injection site **GLP Compliance:** Yes

Special Features: Total of 13 administrations every 14 days; 7 injection sites/animal. Each injection site administered twice (except site 7, injected once). Toxicokinetics

No Observed Adverse Effect Level: Systemic NOAEL: 15 mg/animal/administration

Daily Dose (mg/animal)	0 (Control)		5 mg/animal		10 mg/animal		15 mg/animal	
Number of Animals	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12
Toxicokinetics								
1st administration								
Cmax (ng/ml)	NA	NA	106	169	150	140	165	169
AUC_t (ng/ml).day	NA	NA	284	245	598	558	809	814
7th administration								
Cmax (ng/ml)	NA	NA	279	1278	1635	2482	2256	2572
AUC_t (ng/ml).day	NA	NA	1460	5744	9412	19637	11881	17338
13th administration								
Cmax (ng/ml)	NA	NA	755	1620	1373	4294	2055	3699
AUC_t (ng/ml).day	NA	NA	4713	9460	9853	32918	14230	32917
Number of Animals	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	1	0	0	0	0	0
Body weight [1]	622 g	332 g	-21.9**	-16.0**	-19.8**	-14.2**	-25.7**	-15.4**
Food consumption [1]	26.4 (g/animal/day)	18.1 (g/animal/day)	-10.6**	-5.0	-7.2	-0.6	-14.4**	+2.8

NA = not applicable

1 = at the end of dosing period. Group mean for controls and percent difference from controls for treated rats. Statistical differences are based on the absolute numbers not based on percent differences

Statistical significance: **significant = p<0.01

Daily Dose (mg/animal	0 (Control)		5 mg/animal		10 mg/animal		15 mg/animal	
Number of Animals	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20
Clinical signs								
At injection sites[2]								
Scabs	8	5	111	136	133	139	139	140
Abscess	0	0	1	1	2	4	1	14
Nodules	0	0	131	137	140	140	140	140
Increase in size	0	0	132	135	140	140	140	140
Blood Biochemistry								
Calcium (mmol/l)	2.72	2.70	2.58**	2.56**	2.57**	2.55**	2.55**	2.54**
I Phosphorus (mmol/l)	1.83	1.28	1.76	1.45	1.62**	1.31	1.60**	1.44
Glucose (mmol/l)	6.94	7.86	6.73	6.92**	6.68	6.75**	7.35	6.86**
Protein (g/l)	73	76	68**	68**	69**	69**	67**	70**
Albumin (g/l)	37	43	34	36**	36	35**	34*	36**
Albumin/Globulin	1.05	1.28	1.04	1.13*	1.08	1.06**	1.03	1.09**
Triglycerides (mmol/l)	0.73	0.41	0.40*	0.27	0.39*	0.28	0.39**	0.28
ALP (IU/l)	199	80	216	117*	195	121**	179	137**
Organ weights: Liver absolute (g) / relative (% body weight)	16.35/2.73	9.03/2.92	11.55**/ 2.47**	7.22**/2.73	11.67**/ 2.47**	6.66**/ 2.51**	10.52**/ 2.40**	6.21**/ 2.32**
Macroscopic findings								
At injection sites (incidence)								
Days 1 and 99: site 1								
Nodules	0	0	1	3	15	10	16	14
Thickened subcutaneous tissue	0	0	0	0	0	1	2	0
Days 15 and 113: site 2								
Nodules	0	0	4	3	19	13	19	18
Thickened subcutaneous tissue	0	0	1	0	1	0	1	0
Scabs	0	0	0	1	0	0	0	0
Days 29 and127: Site 3								
Nodules	0	0	6	9	17	12	17	11
Scabs	0	0	0	3	0	2	0	0

2 = total incidence for all animals/group (total = 20x7=140 injection sites)
Statistical significance compared with controls: * slightly significant = p<0.05, **significant = p<0.01
ALP = alkaline phosphatase
Site 1 = thoracic left; Site 2 = dorsal left; Site 3 = flank left; Site 4 = thoracic right; Site 5 = dorsal right; Site 6 = flank right; Site 7 = scapular

Daily Dose (mg/animal	0 (Control)		5 mg/animal		10 mg/animal		15 mg/animal	
Number of Animals	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20
Days 43 and 141: site 4								
Nodules	0	0	8	11	20	19	19	19
Thickened subcutaneous tissue	0	0	0	0	0	1	0	0
Scabs	0	0	0	0	1	0	0	0
Days 57 and 155: site 5								
Nodules	0	0	14	17	20	16	19	17
Thickened subcutaneous tissue	0	0	1	0	0	0	0	0
Scabs	0	0	0	0	1	0	0	5
Days 71 and 169: site 6								
Nodules	0	0	14	17	18	20	18	18
Scasb	0	0	6	10	7	9	14	14
Day 85: site 7								
Nodules	0	0	3	0	8	1	10	1
Scabs	0	0	0	0	0	1	0	1
Microscopic findings								
At injection sites (all sites)								
acanthosis/hyperkeratosis	P	P	P	P	P	P	P	P
Days 1 and 99: site 1								
Subcutaneous granuloma (incidence)	0/20	0/20	2/2	3/3	15/16	10/11	15/20	13/20
Vasculitis (incidence)	-	-	-	-	-	-	-	-
Intimal thickening (incidence)	2/20	1/20	2/3	1/3	11/16	8/11	13/20	15/20
Days 15 and 113: site 2								
Subcutaneous granuloma (incidence)	0/20	0/20	2/5	2/5	16/19	13/13	18/20	18/20
Vasculitis (incidence)	-	-	-	-	-	-	-	-
Intimal thickening (incidence)	1/20	-	1/6	3/4	17/19	13/13	18/20	19/20
Days 29 and127: Site 3								
Subcutaneous granuloma (incidence)	0/20	0/20	5/6	9/11	16/17	13/14	13/20	9/20
Vasculitis (incidence)	-	-	-	-	-	-	-	-
Intimal thickening (incidence)	4/20	1/20	7/7	10/11	15/17	11/14	16/20	19/20

Site 1 = thoracic left; Site 2 = dorsal left; Site 3 = flank left; Site 4 = thoracic right; Site 5 = dorsal right; Site 6 = flank right; Site 7 = scapular
- = no noteworthy findings
P = present

Daily Dose (mg/animal	0 (Control)		5 mg/animal		10 mg/animal		15 mg/animal	
Number of Animals	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20
Days 43 and 141: site 4								
Subcutaneous granuloma (incidence)	0/20	1/20	5/7	8/11	18/20	19/19	19/20	19/20
Vasculitis (incidence)	-	-	1/8	-	-	1/19	-	-
Intimal thickening (incidence)	5/20	2/20	5/8	6/11	16/20	12/19	16/20	20/20
Days 57 and 155: site 5								
Subcutaneous granuloma (incidence)	0/20	0/20	12/15	17/17	20/20	16/16	19/20	16/20
Vasculitis (incidence)	-	-	3/16	1/17	2/20	1/16	-	-
Intimal thickening (incidence)	2/20	-	13/16	10/17	19/20	14/16	19/20	20/20
Days 71 and 169: site 6								
Subcutaneous granuloma (incidence)	0/20	0/20	12/16	0/17	18/19	0/20	19/20	1/20
Vasculitis (incidence)	-	-	11/17	9/17	12/19	3/20	4/20	-
Intimal thickening (incidence)	3/20	1/20	14/17	15/17	19/19	19/20	17/20	20/20
Day 85: site 7								
Subcutaneous granuloma (incidence)	0/20	0/20	2/3	0/0	8/8	0/1	7/20	1/20
Vasculitis (incidence)	-	-	-	-	-	-	-	-
Intimal thickening (incidence)	1/20	2/20	3/4	-	5/8	1/1	13/20	13/20
Presence of antibodies (incidence)	0	0-	6	9	10	12	8	11

Site 1 = thoracic left; Site 2 = dorsal left; Site 3 = flank left; Site 4 = thoracic right; Site 5 = dorsal right; Site 6 = flank right; Site 7 = scapular
- = no noteworthy findings

Report Title: 26-week toxicity study by repeated subcutaneous injection every 14 days in Beagle dogs

Test Article: LANREOTIDE AUTOGEL

Species/Strain: Dog/Beagle
Initial Age: 6 months
Date of First Dose: 26th Oct. 2004

Duration of Dosing: 26 weeks
Duration of Postdose: -
Method of Administration: s.c.
Vehicle/Formulation: 0.9% saline/111 µL-668 µL/injection site

Study No. 28224 TCC
Location in CTD: Section 4.2.3.2
GLP Compliance: Yes

Special Features: Total of 13 administrations every 14 days; 2 sites injected/administration. 26 injection sites/animal. Each injection site administered once. Toxicokinetics

No Observed Adverse Effect Level: Systemic NOAEL: 120 mg/animal/administration

Daily Dose (mg/animal)	0 (Control)		60 mg/animal		120 mg/animal		360 mg/animal	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Toxicokinetics:								
1st administration (Day 1)								
Cmax (ng/ml)	NA	NA	41.6	56.3	55.3	73.4	107	149
AUC_t (ng/ml).day	NA	NA	178	155	220	293	564	773
7th administration (Day 85)								
Cmax (ng/ml)	NA	NA	52.4	38.3	72.0	89.6	262	288
AUC_t (ng/ml).day	NA	NA	226	238	517	620	1391	1338
13th administration (Day 169)								
Cmax (ng/ml)	NA	NA	63.2	79.4	142	139	316	210
AUC_t (ng/ml).day	NA	NA	313	389	694	748	1711	1236
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight[1]	9.7 kg	7.3 kg	-3.1	+15.1	-12.4	+12.3	-4.1	-1.4
Food Consumption	-	-	-	-	-	-	-	-

NA = not applicable; - =no noteworthy findings
1 = at the end of dosing period. Group mean for controls and percent difference from controls for treated dogs.

Daily Dose (mg/animal)	0 (Control)		60 mg/animal		120 mg/animal		360 mg/animal	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Clinical signs								
At injection sites[2]								
Nodules	0	0	78	78	78	78	78	78
Abscesses	0	0	9	10	25	20	5	32
Scabs	0	0	11	12	21	17	4	23
Organ weights: Liver								
absolute (g) / relative (% body weight)	252.2/2.65	242.1/3.27	256.9/2.78	218.5/2.62	249.9/2.96	256.6/3.14	293.1/3.14	281.6/3.91
Macroscopic findings								
Gall bladder dilated (incidence)	0	0	1	0	2	2	1	2
Injection sites (incidence)								
Day 1: sites1 and 2								
Nodules	0	0	0	6	2	4	3	2
Thickened subcutaneous tissue	0	0	1	0	1	0	3	1
Yellowish contents	0	0	0	4	0	2	1	0
Day 15: sites 3 and 4								
Nodules	0	0	0	0	0	0	1	0
Thickened subcutaneous tissue	0	0	1	3	0	2	3	1
Yellowish contents	0	0	0	0	0	0	1	0
Day 29: sites 5 and 6								
Nodules	0	0	1	2	2	3	3	2
Thickened subcutaneous tissue	0	0	1	3	1	2	0	1
Yellowish contents	0	0	1	2	1	1	2	0
Day 43: sites 7 and 8								
Nodules	0	0	0	1	1	3	4	3
Thickened subcutaneous tissue	0	0	1	4	4	3	1	2
Yellowish contents	0	0	0	1	0	1	2	1
Day 57: sites 9 and 10								
Nodules	0	0	1	2	0	3	5	4
Thickened subcutaneous tissue	0	0	1	2	1	2	1	0
Yellowish contents	0	0	1	2	0	2	3	2

2 = total incidence for all animals/group (total = 26x3=78 injection sites)

Daily Dose (mg/animal)	0 (Control)		60 mg/animal		120 mg/animal		360 mg/animal	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Day 71: sites 11 and 12								
Nodules	0	0	0	1	2	6	5	4
Thickened subcutaneous tissue	0	0	2	4	1	0	1	0
Yellowish contents	0	0	0	1	2	3	2	2
Day 85: sites 13 and 14								
Nodules	0	0	1	0	1	6	4	4
Thickened subcutaneous tissue	0	0	1	5	1	0	2	1
Yellowish contents	0	0	0	0	0	4	2	3
Day 99: sites 15 and 16								
Nodules	0	0	2	1	0	2	5	4
Thickened subcutaneous tissue	0	0	1	1	2	4	1	0
Yellowish contents	0	0	1	1	0	0	3	2
Day 113: sites 17 and 18								
Nodules	0	0	2	2	3	4	5	3
Thickened subcutaneous tissue	0	0	2	0	0	2	1	0
Yellowish contents	0	0	1	2	2	1	3	2
Day 127: sites 19 and 20								
Nodules	0	0	5	2	2	4	5	5
Thickened subcutaneous tissue	0	0	0	1	2	2	1	1
Yellowish contents	0	0	2	1	1	2	2	2
Day 141: sites 21 and 22								
Nodules	0	0	2	3	2	4	6	5
Thickened subcutaneous tissue	0	0	2	2	4	2	0	0
Yellowish contents	0	0	1	1	0	2	4	3
Day 155: sites 23 and 24								
Nodules	0	0	3	5	6	5	6	6
Thickened subcutaneous tissue	0	0	2	1	0	1	0	0
Yellowish contents	0	0	2	5	3	2	4	2
Day 169: sites 25 and 26								
Nodules	0	0	6	5	6	6	6	6
Thickened subcutaneous tissue	0	0	0	0	0	0	0	0
Yellowish contents	0	0	2	4	4	4	2	2

Daily Dose (mg/animal)	0 (Control)		60 mg/animal		120 mg/animal		360 mg/animal	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Microscopic findings (incidence)								
Prostate not fully developed	-	-	-	-	1	-	2	-
Kidney – cortical vacuolated tubular cells	-	-	-	-	-	-	3	-
Gall bladder – adhesion of intraluminal substance to the epithelium	-	-	-	-	-	-	-	1
Lungs - bronchitis/(peri-)bronchiolitis	-	-	-	-	1	-	1	3
Injection site (incidence)								
Day 1: sites1 and 2								
Subcutaneous macrophage infiltration	0	0	1	0	2	0	1	0
Subcutaneous granulomatous inflammation	0	0	2	1	4	2	3	2
Prominent mononuclear cell infiltration	0	0	0	2	3	3	2	1
Granulation tissue	0	0	0	0	0	0	1	0
Subcutaneous fibrosis	0	0	0	0	1	1	1	1
Day 15: sites 3 and 4								
Subcutaneous macrophage infiltration	0	0	6	1	1	2	3	1
Subcutaneous granulomatous inflammation	0	0	0	4	2	1	1	1
Prominent mononuclear cell infiltration	0	0	0	1	1	1	3	0
Granulation tissue	0	0	0	0	0	0	0	0
Subcutaneous fibrosis	0	0	1	0	0	0	0	0
Day 29: sites 5 and 6								
Subcutaneous macrophage infiltration	0	0	2	0	1	1	1	1
Subcutaneous granulomatous inflammation	0	0	3	3	3	4	6	2
Prominent mononuclear cell infiltration	0	0	3	2	2	2	6	0
Granulation tissue	0	0	1	0	0	0	0	1
Subcutaneous fibrosis	0	0	0	2	0	0	1	1
Day43: sites 7 and 8								
Subcutaneous macrophage infiltration	0	0	0	0	3	0	0	0
Subcutaneous granulomatous inflammation	0	0	3	1	2	3	6	3
Prominent mononuclear cell infiltration	0	0	2	1	3	3	4	1
Granulation tissue	0	0	0	0	0	0	0	0
Subcutaneous fibrosis	0	0	1	1	0	0	1	1

- =no noteworthy findings

Daily Dose (mg/animal)	0 (Control)		60 mg/animal		120 mg/animal		360 mg/animal	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Day 57: sites 9 and 10								
Subcutaneous macrophage infiltration	0	0	3	2	2	0	2	0
Subcutaneous granulomatous inflammation	0	0	4	2	0	4	5	4
Prominent mononuclear cell infiltration	0	0	2	0	0	5	4	2
Granulation tissue	0	0	0	0	0	0	0	0
Subcutaneous fibrosis	0	0	2	3	1	0	1	1
Day 71: sites 11 and 12								
Subcutaneous macrophage infiltration	0	0	2	0	2	1	0	0
Subcutaneous granulomatous inflammation	0	0	2	2	4	5	6	4
Prominent mononuclear cell infiltration	0	0	2	2	4	3	4	2
Granulation tissue	0	0	0	0	0	0	2	2
Subcutaneous fibrosis	0	0	1	1	4	1	2	2
Day 85: sites13 and 14								
Subcutaneous macrophage infiltration	0	0	1	3	1	0	0	0
Subcutaneous granulomatous inflammation	0	0	2	1	1	6	6	4
Prominent mononuclear cell infiltration	0	0	1	1	0	3	6	3
Granulation tissue	0	0	0	0	0	1	0	1
Subcutaneous fibrosis	0	0	1	3	0	0	2	2
Day 99: sites 15 and 16								
Subcutaneous macrophage infiltration	0	0	2	4	1	0	0	2
Subcutaneous granulomatous inflammation	0	0	3	1	0	3	6	4
Prominent mononuclear cell infiltration	0	0	1	0	0	1	6	4
Granulation tissue	0	0	0	2	0	0	0	0
Subcutaneous fibrosis	0	0	0	4	1	0	3	3

Daily Dose (mg/animal)	0 (Control)		60 mg/animal		120 mg/animal		360 mg/animal	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Day 113: sites 17 and 18								
Subcutaneous macrophage infiltration	0	0	1	3	0	1	1	1
Subcutaneous granulomatous inflammation	0	0	3	4	2	4	6	4
Prominent mononuclear cell infiltration	0	0	1	3	2	1	6	2
Granulation tissue	0	0	0	0	0	0	0	1
Subcutaneous fibrosis	0	0	1	4	2	3	4	3
Day 127: sites 19 and 20								
Subcutaneous macrophage infiltration	0	0	0	0	0	0	0	1
Subcutaneous granulomatous inflammation	0	0	5	2	1	4	6	3
Prominent mononuclear cell infiltration	0	0	5	3	2	3	6	2
Granulation tissue	0	0	3	0	1	0	1	1
Subcutaneous fibrosis	0	0	3	1	0	2	3	3
Day 141: sites21 and 22								
Subcutaneous macrophage infiltration	0	0	0	3	1	1	0	0
Subcutaneous granulomatous inflammation	0	0	4	3	4	5	6	5
Prominent mononuclear cell infiltration	0	0	3	3	4	2	6	4
Granulation tissue	0	0	2	0	1	3	0	2
Subcutaneous fibrosis	0	0	3	2	1	3	6	4
Day 155: sites 23 and 24								
Subcutaneous macrophage infiltration	0	0	1	0	0	0	0	0
Subcutaneous granulomatous inflammation	0	0	4	5	5	5	6	6
Prominent mononuclear cell infiltration	0	0	3	4	1	5	4	2
Granulation tissue	0	0	1	2	6	2	0	4
Subcutaneous fibrosis	0	0	3	4	3	3	5	2
Day 169: sites 25 and 26								
Subcutaneous macrophage infiltration	0	0	0	0	0	0	0	0
Subcutaneous granulomatous inflammation	0	0	6	4	3	6	6	2
Prominent mononuclear cell infiltration	0	0	6	3	0	0	2	0
Granulation tissue	0	0	2	5	6	6	5	3
Subcutaneous fibrosis	0	0	4	1	2	0	2	0
Presence of antibodies (incidence)	0	0	2	2	0	1	0	2

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Pharmcology/toxicology recommends approval (AP) for Somatuline ®Autogel® injection based on all available pharm/tox data submitted and upon acceptance of the recommended labeling changes.

Unresolved toxicology issues: None

Recommendations: None

Suggested labeling:

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Appendix/attachments:

Appendix I: Historical Carcinogenicity Data: CD-1 mouse (provided by sponsor)
Appendix II: Recommended labeling changes

Appendix I:

Historical Carcinogenicity Data: CD-1 mouse (provided by sponsor)

Species: MOUSE
Strain: Swiss CD-1 (ICR)BR
Age: Approximately 2 years old
Study Finalized: From 6/22/1999 to 6/22/2004

Males:

	Total No. of animals				Study ID	A	B	C	D	E	F	G	H	I
	805				Study Start:	1998	1999	2000	1997	1998	1999	2000	1998	1998
					Total no. of animal examined:	120	100	120	100	130	65	60	50	60
Organ Lesion	Total No of Lesions	%	%Min	%Max										
SUBCUTANEOUS TISSUE *														
Fibrosarcoma	2	0.25	0.00	1.67		0	1	0	0	0	0	1	0	0
Hemangiosarcoma	4	0.50	0.00	1.67		1	1	0	0	1	0	1	0	0
Sarcoma (not otherwise specified)	1	0.12	0.00	1.00		0	0	0	1	0	0	0	0	0

Females:

	Total No. of animals				Study ID	A	B	C	D	E	F	G	H	I
	805				Study Start:	1998	1999	2000	1997	1998	1999	2000	1998	1998
					Total no. of animal examined:	120	100	120	100	130	65	60	50	60
Organ Lesion	Total No of Lesions	%	%Min	%Max										
SUBCUTANEOUS TISSUE *														
Fibrosarcoma	15	1.86	0.00	4.17		4	1	5	3	1	0	0	0	1
Hemangiosarcoma	2	0.25	0.00	3.08		0	0	0	0	0	2	0	0	0
Liposarcoma	2	0.25	0.00	1.54		0	0	0	0	2	0	0	0	0
Myxosarcoma	1	0.12	0.00	0.83		0	0	1	0	0	0	0	0	0
Osteosarcoma	1	0.12	0.00	0.83		1	0	0	0	0	0	0	0	0

3 Page(s) Withheld

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