**Study title: Lanreotide acetate: induction of chromosome aberration in cultured human peripheral blood lymphocytes**

**Key findings**: Lanreotide acetate did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, when tested to its limit of solubility (3+17 hr treatment - S9) or its limit of cytotoxicity (3+17 hr treatment + S9, 20+0 hr treatment - S9) in the absence and presence of S9 metabolic activation system.

**Study no.**: — 434/86

**Volume #, and page #**: Vol A3.53, and pages 1 to 52
**Conducting laboratory and location**: —

**Date of study initiation**: 01/25/2002
**GLP compliance**: yes
**QA reports**: yes ( X ) no ( )
**Drug, lot #, and % purity**: Lanreotide acetate, batch # K012 (Ispen Pharma), M11344 and M11349 (Dreux), and purity —

**Methods**

Strains/species/cell line: Human peripheral blood lymphocytes

Doses used in definitive study: Based on the results of three cytotoxicity trials, the following doses were used in the definitive studies (MI: mitotic inhibition at the highest dose):

3+17 hrs, -S9: 655.4, 1280, 2000 μg/ml (MI 54%)
3+17 hrs, +S9: 419.4, 524.3, 655.4 μg/mL (MI 50%)

20+0 hrs, -S9: 393.7. 545.0, 641.1 μg/ml (MI 32%)
3+17 hrs, +S9: 463.2, 641.1, 887.4 μg/ml (MI 52%)

20+0 hours. -S-9: 545.0, 641.1, 754.3 μg/ml (MI 57%)

Basis of dose selection: At least 50% mitotic inhibition should be observed for the highest dose to be tested. Results for three trials of mitotic index determination are shown in the scanned tables below:

Trial 1:

| Treatment (µg/mL) | Mitotic index (%) 3+17, -S-9 | | | 3+17, +S-9 | | |
|---|---|---|---|---|---|---|
| | A/C | B/D | MIH* | A/C | B/D | MIH* |
| Solvent | 11.0/8.4 | 13.2/7.9 | - | 9.8/7.3 | 10.8/8.0 | - |
| 45.04 | NS | NS | - | NS | NS | - |
| 56.29 | NS | NS | - | NS | NS | - |
| 70.37 | NS | NS | - | NS | NS | - |
| 87.96 | NS | NS | - | NS | NS | - |
| 110.0 | NS | NS | - | NS | NS | - |
| 137.4 | NS | NS | - | NS | NS | - |
| 171.8 | NS | NS | - | NS | NS | - |
| 214.7 | NS | NS | - | NS | NS | - |
| 268.4 | NS | NS | - | NS | NS | - |
| 335.5 | NS | NS | - | NS | NS | - |
| 419.4 | NS | NS | - | 9.3 | 7.0 | 9 |
| 524.3 | 11.0 | 11.2 | 0 | 7.3 | 8.4 | 13 |
| 655.4 | 9.2 | 8.6 | 12 | 3.9 | 5.0 | 50 |
| 819.2 | 6.5 | 5.4 | 41 | 3.3 | 4.1 | 59 |
| 1024 | 5.7 | 8.9 | 28 | 3.1 | 3.8 | 62 |
| 1280 | 7.0 | 5.7 | 37 | 3.0 | 2.1 | 72 |
| 1600 | 5.6 | 5.0 | 48 | 3.1 | 1.5 | 74 |
| 2000 | 4.5 | 4.9 | 54 | 2.2 | 1.7 | 78 |

NS = not scored
*Mitotic inhibition (%) = [1 - (mean MI$_T$/mean MI$_C$)] x 100%
(where T = treatment and C = negative control)
(Slides from solvent control cultures C and D scored for mitotic index only)

Trial 2:

| Treatment (µg/mL) | Mitotic index (%) 2010, -S-9 | | | 3+17, +S-9 | | |
|---|---|---|---|---|---|---|
| | A/C | B/D | MIH* | A/C | B/D | MIH* |
| Solvent | 7.6/7.9 | 7.0/9.5 | - | 9.8/8.5 | 8.8/10.5 | - |
| 126.2 | NS | NS | - | NT | NT | - |
| 148.5 | NS | NS | - | NT | NT | - |
| 174.7 | NS | NS | - | NT | NT | - |
| 205.5 | NS | NS | - | NT | NT | - |
| 241.8 | NS | NS | - | NT | NT | - |
| 284.5 | NS | NS | - | NT | NT | - |
| 334.7 | NS | NS | - | NS | NS | - |
| 393.7 | 6.4 | 8.8 | 5 | NS | NS | - |
| 463.2 | 6.9 | 7.5 | 10 | 9.6 | 8.9 | 2 |
| 545.0 | 6.6 | 5.1 | 27 | 7.0 | 7.3 | 24 |
| 641.1 | 6.8 | 4.1 | 32 | 6.7 | 6.0 | 32 |
| 754.3 | 3.0 | 4.6 | 53 | 5.3 | 5.2 | 44 |
| 887.4 | 3.4 | 3.8 | 55 | 5.5 | 3.6 | 52 |
| 1044 | 3.2 | 2.6 | 64 | 4.9 | 3.0 | 58 |
| 1228 | 1.7 | 3.1 | 70 | 4.1 | 2.5 | 65 |
| 1445 | 1.6 | 2.2 | 76 | 4.4 | 3.5 | 58 |
| 1700 | 1.2 | 1.8 | 81 | NT | NT | - |
| 2000 | 1.4 | 0.8 | 86 | NT | NT | - |

NT = not tested NS = not scored
*Mitotic inhibition (%) = [1 - (mean MIT/mean MIC)] x 100%
(where T = treatment and C = negative control)
(Slides from solvent control cultures C and D scored for mitotic index only).

Trial 3:

| Treatment (µg/ml.) | Mitotic index (%) 20+0, -S-9 A/C | B/D | MIH* |
|---|---|---|---|
| Solvent | 6.9/4.7 | 5.4/6.4 | - |
| 126.2 | NS | NS | - |
| 148.5 | NS | NS | - |
| 174.7 | NS | NS | - |
| 205.5 | NS | NS | - |
| 241.8 | NS | NS | - |
| 284.5 | NS | NS | - |
| 334.7 | NS | NS | - |
| 393.7 | 6.7 | 5.7 | 0 |
| 463.2 | 6.3 | 4.6 | 7 |
| 545.0 | 5.2 | 6.3 | 2 |
| 641.1 | 4.5 | 3.8 | 29 |
| 754.3 | 2.1 | 2.9 | 57 |
| 887.4 | 3.0 | 1.7 | 60 |
| 1044 | 1.0 | 0.7 | 85 |
| 1228 | 0.7 | 0.5 | 90 |
| 1445 | 0.3 | 0.5 | 93 |
| 1700 | 0.3 | 0.4 | 94 |
| 2000 | 0.0 | 0.0 | 100 |

NS – not scored
*Mitotic inhibition (%) = [1 - (mean MIT/mean MIC)] x 100%
(where T = treatment and C = negative control)
(Slides from solvent control cultures C and D scored for mitotic index only).

Negative controls: The solvent DMSO

Positive controls:

| Chemical | Supplier | Concentration of treatment solution (mg/mL) | Final concentration (µg/mL) | S-9 |
|---|---|---|---|---|
| 4-Nitroquinoline 1-oxide (NQO) | / / | 0.125 | 1.25 | - |
| | | 0.250 | 2.50 | - |
| | | 0.500 | 5.00 | - |
| Cyclophosphamide (CPA) | / / | 0.3125 | 3.125 | + |
| | | 0.625 | 6.25 | + |
| | | 1.25 | 12.5 | + |

Incubation and sampling times:

**Summary of Treatment Conditions**

| Treatment | | S-9 | Duration of treatment (hours) | Harvest time (hours after start of treatment) |
|---|---|---|---|---|
| Continuous | 20+0 | - | 20 | 20 |
| Pulse | 3+17 | + | 3 | 20 |
| | 3+17 | - | 3 | 20 |

**Results**

Study validity:
The assay is considered valid if the following criteria are met:

1. the binomial dispersion test demonstrates acceptable heterogeneity between replicate cultures, and
2. the proportion of cells with structural aberrations (excluding gaps) in negative controls falls within the normal range, and
3. at least 160 cells out of an intended 200 are analyzable at each dose level, and
4. the positive controls induce statistically significant increases in the number of cells with structural aberrations.

The test drug would be considered positive in this sassy if:

1. the proportions of cells with structural aberrations at one or more concentrations exceeds the normal range in both replicate cultures, and
2. a statistically significant increase in the proportion of cells with structural aberrations (excluding gaps) occurs at these doses.

Study outcome:
Based on the validity and evaluation criteria and study results, the assay is considered valid.

Treatment of cultures with lanreotide acetate in the absence and presence of S9 resulted in frequencies of cells with structural aberrations similar to those in concurrent negative controls as shown in the scanned data tables 1 to 5 below. Numbers of aberrant cells in all treated cultures fell within historical control ranges (scanned historical range data table). No increases in the frequencies of cells with numerical aberrations that exceeded the historical negative control range were observed in treated groups.

**Table 1**
**3 hour treatment -S-9, 17 hour recovery (3+17), Experiment 1**

**Donor sex: female**

| Treatment (µg/mL) | Replicate | Cells Scored | Cells with Aberrations Including Gaps | Cells with Aberrations Excluding Gaps | Mitotic Index (mean) |
|---|---|---|---|---|---|
| Solvent | A | 100 | 1 | 1 | 11.0 |
| | B | 100 | 0 | 0 | 13.2 |
| | C | ND | ND | ND | 8.4 |
| | D | ND | ND | ND | 7.9 |
| | Totals | 200 | 1 | 1 | (10.1) |
| 655.4 | A | 100 | 2 | 1 | 9.2 |
| | B | 100 | 1 | 1 | 8.6 |
| | Totals | 200 | 3 | 2 | (8.9) |
| 1280 | A | 100 | 1 | 1 | 7.0 |
| | B | 100 | 1 | 0 | 5.7 |
| | Totals | 200 | 2 | 1 | (6.4) |
| 2000 | A | 100 | 5 | 2 | 4.5 |
| | B | 100 | 2 | 1 | 4.9 |
| | Totals | 200 | 7 | 3 | (4.7) |
| NQO, 2.50 | A | 100 | **22** | **21** | |
| | B | 100 | **13** | **13** | |
| | Totals | 200 | 35 | 34[a] | |

Binomial Dispersion Test $\chi^2$= 2.35, not significant
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

**Table 2**
**3 hour treatment +S-9, 17 hour recovery (3+17), Experiment 1**

**Donor sex: female**

| Treatment (μg/mL) | Replicate | Cells Scored | Cells with Aberrations Including Gaps | Cells with Aberrations Excluding Gaps | Mitotic Index (mean) |
|---|---|---|---|---|---|
| Solvent | A | 100 | 0 | 0 | 9.8 |
| | B | 100 | 2 | 1 | 10.8 |
| | C | ND | ND | ND | 7.3 |
| | D | ND | ND | ND | 8.0 |
| | Totals | 200 | 2 | 1 | (9.0) |
| 419.4 | A | 100 | 2 | 1 | 9.3 |
| | B | 100 | 4 | 1 | 7.0 |
| | Totals | 200 | 6 | 2 | (8.2) |
| 524.3 | A | 100 | 0 | 0 | 7.3 |
| | B | 100 | 1 | 1 | 8.4 |
| | Totals | 200 | 1 | 1 | (7.9) |
| 655.4 | A | 100 | 3 | 1 | 3.9 |
| | B | 100 | 3 | 2 | 5.0 |
| | Totals | 200 | 6 | 3 | (4.5) |
| CPA, 6.25 | A | 100 | **43** | **42** | |
| | B | 100 | **41** | **39** | |
| | Totals | 200 | 84 | 81[a] | |

Binomial Dispersion Test $\chi^2 = 2.35$, not significant
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

**Table 3**
**20 hour treatment -S-9, 0 hour recovery (20+0), Experiment 2, Trial 1**

**Donor sex: female**

| Treatment (µg/mL) | Replicate | Cells Scored | Cells with Aberrations Including Gaps | Cells with Aberrations Excluding Gaps | Mitotic Index (mean) |
|---|---|---|---|---|---|
| Solvent | A | 100 | 0 | 0 | 7.6 |
| | B | 100 | 2 | 0 | 7.0 |
| | C | ND | ND | ND | 7.9 |
| | D | ND | ND | ND | 9.5 |
| | Totals | 200 | 2 | 0 | (8.0) |
| 393.7 | A | 100 | 3 | 1 | 6.4 |
| | B | 100 | 2 | 1 | 8.8 |
| | Totals | 200 | 5 | 2 | (7.6) |
| 545 | A | 100 | 0 | 0 | 6.6 |
| | B | 100 | 3 | 1 | 5.1 |
| | Totals | 200 | 3 | 1 | (5.9) |
| 641.1 | A | 100 | 0 | 0 | 6.8 |
| | B | 100 | 0 | 0 | 4.1 |
| | Totals | 200 | 0 | 0 | (5.5) |
| NQO, 2.50 | A | 100 | **20** | **19** | |
| | B | 100 | **22** | **21** | |
| | Totals | 200 | 42 | 40[a] | |

Binomial Dispersion Test $\chi^2$ = 1.01, not significant
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

**Table 4**
**20 hour treatment -S-9, 0 hour recovery (20+0), Experiment 2, Trial 2**

**Donor sex: female**

| Treatment (µg/mL) | Replicate | Cells Scored | Cells with Aberrations Including Gaps | Cells with Aberrations Excluding Gaps | Mitotic Index (mean) |
|---|---|---|---|---|---|
| Solvent | A | 100 | 1 | 1 | 6.9 |
| | B | 100 | 3 | 2 | 5.4 |
| | C | ND | ND | ND | 4.7 |
| | D | ND | ND | ND | 6.4 |
| | Totals | 200 | 4 | 3 | (5.9) |
| 545.0 | A | 100 | 2 | 1 | 5.2 |
| | B | 100 | 3 | 1 | 6.3 |
| | Totals | 200 | 5 | 2 | (5.8) |
| 641.1 | A | 100 | 3 | 2 | 4.5 |
| | B | 100 | 4 | 3 | 3.8 |
| | Totals | 200 | 7 | 5 | (4.2) |
| 754.3 | A | 100 | 3 | 3 | 2.1 |
| | B | 100 | 3 | 1 | 2.9 |
| | Totals | 200 | 6 | 4 | (2.5) |
| NQO, 5.00 | A | 100 | **29** | **28** | |
| | B | 100 | **18** | **16** | |
| | Totals | 200 | 47 | 44[a] | |

Binomial Dispersion Test $\chi^2 = 1.56$, not significant
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

**Table 5**
**3 hour treatment +S-9, 17 hour recovery (3+17), Experiment 2**

**Donor sex: female**

| Treatment (μg/mL) | Replicate | Cells Scored | Cells with Aberrations Including Gaps | Cells with Aberrations Excluding Gaps | Mitotic Index (mean) |
|---|---|---|---|---|---|
| Solvent | A | 100 | 0 | 0 | 9.8 |
| | B | 100 | 0 | 0 | 8.8 |
| | C | ND | ND | ND | 8.5 |
| | D | ND | ND | ND | 10.5 |
| | Totals | 200 | 0 | 0 | (9.4) |
| 463.2 | A | 100 | 0 | 0 | 9.6 |
| | B | 100 | 1 | 0 | 8.9 |
| | Totals | 200 | 1 | 0 | (9.3) |
| 641.1 | A | 100 | 1 | 1 | 6.7 |
| | B | 100 | 1 | 1 | 6.0 |
| | Totals | 200 | 2 | 2 | (6.4) |
| 887.4 | A | 100 | 1 | 0 | 5.5 |
| | B | 78 | 1 | 1 | 3.6 |
| | Totals | 178 | 2 | 1 | (4.6) |
| CPA, 6.25 | A | 100 | **34** | **31** | |
| | B | 100 | **28** | **25** | |
| | Totals | 200 | 62 | 56[a] | |

Binomial Dispersion Test $\chi^2$= 1.29, not significant
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

**Historical ranges for solvent controls**

| Sex and S-9 treatment | Category | Total number of cells scored | Aberrant cells scored per 100 cells | |
|---|---|---|---|---|
| | | | Mean | Calculated normal range |
| Female -S-9 | Structural aberrations including gaps | 10399 | 2.04 | 0-6 |
| | Structural aberrations excluding gaps | 10399 | 1.13 | 0-5 |
| | Numerical aberrations | 10436 | 0.35 | 0-3 |
| Female +S-9 (Aroclor 1254) | Structural aberrations including gaps | 9800 | 1.62 | 0-6 |
| | Structural aberrations excluding gaps | 9800 | 0.84 | 0-4 |
| | Numerical aberrations | 9833 | 0.33 | 0-2 |

**Study title: Lanreotide acetate: induction of lacZ mutations in tissues of treated MutaMice**

**Key findings**: Lanreotide acetate did not induce mutation in the liver or bone marrow of Muta™Mice, following subcutaneous dosing for a total of 18 out of 21 days at dose levels of 120 and 180 mg/kg/day.

**Study no.**: 434/88

**Volume #, and page #**: Vol A3.54, and pages 1/42 to 42/42
**Conducting laboratory and location**:

**Date of study initiation**: 03/14/2002
**GLP compliance**: yes
**QA reports**: yes ( X ) no ( )
**Drug, lot #, and % purity**: Lanreotide acetate, lot # K012 (Ipsen Pharma Biotech) with three sub-batches M11286, M11344 and M11349; purity

**Methods**

Strains/species/cell line: Young adult Muta™Mouse designated CD2-lacZ80/HazfBR

Doses used in definitive study: MTD (180 mg/kg/d) and the lower treatment dose being 2/3 of the MTD (120 mg/kg/d) were used in the main study. The treatment regimen is shown in the scanned table below:

| Target Treatment (mg kg day) | Group | Stock Conc. (mg mL) | Number | Dosing Volume (mL kg) | Number | Dates Dosed (2002) |
|---|---|---|---|---|---|---|
| 0 | 1 | 0 | 6 | 20 | 11+7 | 27 8-6 9, 10 9-16 9 |
| 120 | 2 | 6 | 6 | 20 | 11+7 | 27 8-6 9, 10 9-16 9 |
| 180 | 3 | 9 | 6 | 20 | 11+7 | 27 8-6 9, 10 9-16 9 |
| 0 | 4 | 0 | 6 | 20 | 11+7 | 27 8-6 9, 10 9-16 9 |
| 120 | 5 | 6 | 6 | 20 | 11+7 | 27 8-6 9, 10 9-16 9 |
| 180 | 6 | 9 | 6 | 20 | 11+7 | 27 8-6 9, 10 9-16 9 |

Due to a lack of available test article, all animals had an off dose period of 3 days following the initial 11 consecutive days of dosing. The off-dose period was followed by a further 7 consecutive days dosing period for all animals. This treatment regimen was taken in order to compensate for the off-dose period of the animals, as 4 additional dosing days were added to the treatment period from that initially intended (total dosing days amended from 14 to 18). In this way, any reductions in lac Z transgene mutations that may have occurred during the off-dose period were considered to have been more than counteracted by an increased total treatment period and sufficient doses subsequent to the off-dose period. By this means, the off-dose period was not considered to have adversely affected the sensitivity of this assay system.

Basis of dose selection: Based on MTD which was determined in a range finding study using groups of 3 male mice for the treatment regimen shown in the following table:

| Target Treatment (mg kg day) | Stock Concentration (mg/mL) | Number of Males | Dosing Volume (mL/kg) | Number Days Dosed | Dates Dosed |
|---|---|---|---|---|---|
| 70 | 7 | 3 | 10 | 7 | 15.3.02-21.3.02 |
| 210 | 21 | 3 | 10 | 7 | 21.3.02-27.3.02 |
| 440 | 22 | 3 | 20 | 2 | 3.4.02-4.4.02 |
| 320 | 16 | 3 | 20 | 4.2* | 8.4.02-11.4.02 |
| 240 | 12 | 3 | 20 | 9 | 12.4.02-20.4.02 |
| 280 | 14 | 3 | 20 | 9 | 12.4.02-20.4.02 |
| 180 | 9 | 3 | 20 | 14 | 24.6.02-7.7.02 |
| 210 | 10.5 | 3 | 20 | 14.7# | 24.6.02-7.7.02 |

* 1 of 3 animals dosed for only 2 days, due to poor condition.
\# 1 of 3 animals dosed for only 7 days, after which time it was killed *in extremis*.

Negative controls: water for injection, 20 ml/kg

Positive controls: none

Incubation and sampling times:
24 days after the initial dosing, mice allocated for bone marrow sampling were sacrificed. 42 days after the initial dosing, mice allocated for liver sampling were sacrificed. Bone marrow and liver tissues were processed and analyzed using a 'block' design, where DNA samples from the negative controls and each treatment group were processed together. A further sample of DNA isolated from an animal previously treated with a positive control chemical, was processed in parallel with these samples. This DNA acted as an internal positive control, to confirm the success of each packaging and plating occasion. The positive control DNA samples were obtained from the liver of male Muta$^{TM}$Mice treated once with 200 mg/kg of Ethylnitrosourea (ENU) by i.p. injection and sacrificed 21 days after this dosing. This treatment regimen has previously been demonstrated to provide clear increases in mutation frequency.

Data were generated for at least 200,000 plaque forming units (pfu) per tissue for each animal, to give a total yield in excess of 1 million pfu for each group. Mutation data were subject to statistical analysis (ANOVA).

**Results**

Study validity:
Sufficient data were generated and provided to permit a thorough and valid assessment of mutation in these tested tissues, as greater than 1 million pfu per group were analyzed.

Study outcome:
Lanreotide acetate treatments at 120 and 180 mg/kg/day resulted in mean group

mutation frequencies in bone marrow samples of 62.9 x $10^{-6}$ and 25.8 x $10^{-6}$ respectively, neither of which are significantly above the concurrent vehicle mean group mutation frequency of 51.9 x $10^{-6}$, and all vehicle and drug treated mean group mutation frequencies were comparable with the testing lab's historical control data for bone marrow of 42.7 ± 29.8 x $10^{-6}$.

Similarly, mean group mutation frequencies of 60.3 x $10^{-6}$ and 58.0 x $10^{-5}$ were obtained from liver samples of lanreotide treated animals at 120 and 180 mg/kg/d respectively, which were comparable to both the concurrent vehicle control mutation frequency of 54.1 x $10^{-6}$, and to the lab's historical negative control mutation frequency data for liver of 64.3 ± 26.4 x $10^{-6}$.

This study was therefore considered to have provided no indication of lanreotide acetate mutation induction in the bone marrow or liver of treated Muta™Mice.

**Summary of results, individual animal and group mean mutation frequency (MF)**

**Summary of bone marrow samples**

| Treatment (mg/kg/day) | Group | Animal No | pfu | MF (x$10^{-6}$) | Group MF (x$10^{-6}$) | Group SD |
|---|---|---|---|---|---|---|
| 0 mg/kg | 1 | 647 | 204,102 | 79.22 | **51.90** | 26.17 |
| | | 648 | 575,621 | 17.56 | | |
| | | 649 | 419,543 | 48.18 | | |
| | | 650 | 258,129 | 62.64 | | |
| 120 mg/kg | 2 | 651 | 1,470,735 | 10.31 | **62.86** | 32.94 |
| | | 652 | 300,817 | 83.99 | | |
| | | 653 | 206,770 | 68.43 | | |
| | | 654 | 231,449 | 100.43 | | |
| | | 655 | 290,812 | 38.23 | | |
| | | 656 | 200,100 | 75.76 | | |
| 180 mg/kg | 3 | 660 | 434,884 | 30.21 | **25.79** | 12.63 |
| | | 661 | 679,673 | 38.66 | | |
| | | 662 | 1,281,974 | 8.67 | | |
| | | 679 | 236,785 | 25.61 | | |

pfu Plaque forming units
MF Mutation frequency

**Summary of liver samples**

| Treatment (mg/kg/day) | Group | Animal No | pfu | MF ($x10^{-6}$) | up MF ($x10^{-6}$) | Group SD |
|---|---|---|---|---|---|---|
| 0 mg/kg | 4 | 663 | 2,942,137 | 14.08 | **54.14** | 26.68 |
| | | 664 | 617,642 | 45.81 | | |
| | | 665 | 206,770 | 92.86 | | |
| | | 666 | 406,203 | 54.73 | | |
| | | 667 | 443,555 | 45.57 | | |
| | | 668 | 633,650 | 71.77 | | |
| 120 mg/kg | 5 | 669 | 312,823 | 77.53 | **60.27** | 26.40 |
| | | 670 | 420,877 | 40.82 | | |
| | | 671 | 705,019 | 58.77 | | |
| | | 672 | 965,816 | 103.59 | | |
| | | 673 | 442,221 | 31.99 | | |
| | | 674 | 660,997 | 48.93 | | |
| 180 mg/kg | 6 | 675 | 306,153 | 59.42 | **58.04** | 14.25 |
| | | 676 | 1,498,749 | 64.73 | | |
| | | 678 | 848,424 | 70.28 | | |
| | | 680 | 616,308 | 37.71 | | |

pfu Plaque forming units
MF Mutation frequency

**Historical negative control mutation frequency data**

| Tissue | Number of data sets | Mean | SD | Median |
|---|---|---|---|---|
| Bone marrow | 48 | 42.69 | 29.79 | 39.41 |
| Liver | 58 | 64.25 | 26.37 | 59.33 |

**Study title**: **Bone marrow micronucleus test by intravenous route in mice**

**Key findings**: The test article BIM 23014C does not induce damage to the chromosomes or the mitotic apparatus of mice bone marrow cells after two intravenous administrations, at a 24-hour interval, at the dose-levels of 6.25, 12.5 and 25 mg/kg/day, under the experiment conditions performed.

**Study no.**: 20563 MAS

**Volume #, and page #**: Vol A3.54, and pages 1/96 to 96/96
**Conducting laboratory and location**:

**Date of study initiation**: 09/05/2000
**GLP compliance**: yes
**QA reports**: yes ( X ) no ( )
**Drug, lot #, and % purity**: BIM23014C (lanreotide acetate), batch # M10799, and purity

**Methods**

Strains/species/cell line: Mosue/OF1

Doses used in definitive study: 0, 6.25, 12.5, 25 or 50 mg/kg/d

Basis of dose selection: Range finding was conducted at 25, 30, 50 and 100 mg/kg/d with i.v. bolus injection. 100 mg/kg induced mortality, 50 mg/kg showed partial mortality (1/3 M and 2/3 F) with clinical signs (↓ activity and tremors), therefore 25 mg/kg/d was chosen as the HD.

Negative controls: 0.9% saline solution for injection

Positive controls: CPA at 50 mg/kg

Study design: Two i.v. injections were given to mice at dose levels show in the scanned table below at 24 hr interval at a dosing volume of 10 ml/kg with injection rate of 1 ml/min. Animals were sacrificed by CO2, bone marrow smears from femurs were prepared and the slides stained with Giemsa were coded for scoring under microscope for MPE in 2000 polychromatic erythrocytes each animal.

| Treatment | Animals per group | | Target dose-level mg/kg/day | Sampling time after the last treatment |
|---|---|---|---|---|
| Vehicle | Principal | 5 males<br>5 females | 0 | 24 h |
| Test substance (Low) | Principal | 5 males<br>5 females | 6.25 | 24 h |
| Test substance (intermediate) | Principal | 5 males<br>5 females | 12.5 | 24 h |
| Test substance (high) | Principal | 8 males (1)<br>8 females (1) | 25 | 24 h |
| | Satellite | 3 males (2)<br>3 females (2) | | |
| Positive control CPA | Principal | 5 males<br>5 females | 50 | 24 h |

(1) Only the five surviving animals of each sex were subjected to bone marrow analysis.
(2) Satellite animals allocated for determination of serum level of the test substance

**Results**

Study validity:
For the result to be considered positive, a statistically significant increase in the frequency of MPE must be demonstrated when compared to the concurrent vehicle control as well as referenced to historical control data.

Study outcome:
The study is considered valid based on dose selection, study design and the results of negative and positive controls.

For both males and females, the mean values of MPE as well as the PE/NE ratio in the groups treated with BIM23014C, were equivalent to those of the vehicle control group (see the scanned data table below).

Cyclophosphamide induced a highly significant increase ($p < 0.001$) in the frequency of MPE, indicating the sensitivity of the test system under our experimental conditions.

Table 3: Results of the cytogenetic test: data summary

| Group | Doses [1] (mg/kg/day) [2] | MPE/1000PE mean | (sd) | | PE/NE ratio mean | (sd) | Time of sacrifice after the last administration |
|---|---|---|---|---|---|---|---|
| Males | | | | | | | |
| Vehicle | - | 1,9 | (1,0) | | 0,5 | (0,1) | |
| Test substance | 6,25 | 1,5 | (0,7) | | 0,5 | (0,1) | 24 h |
| | 12,5 | 1,1 | (0,2) | | 0,6 | (0,2) | |
| | 25 | 1,4 | (0,8) | | 0,4 | (0,1) | |
| Cyclophosphamide | 50 mg/kg | 39,5 | (12,0) | *** | 0,5 | (0,1) | |
| Females | | | | | | | |
| Vehicle | - | 1,4 | (0,7) | | 0,7 | (0,1) | |
| Test substance | 6,25 | 1,2 | (0,6) | | 0,8 | (0,1) | |
| | 12,5 | 0,6 | (0,7) | | 0,8 | (0,3) | 24 h |
| | 25 | 1,0 | (0,5) | | 0,7 | (0,2) | |
| Cyclophosphamide | 50 mg/kg | 27,3 | (10,0) | *** | 0,7 | (0,1) | |

### 2.6.6.5 Carcinogenicity

**Study title: Lanreotide (BIM23014): A 104-Week Subcutaneous Injection Carcinogenicity Study in the Albino Rat**

**Key study findings**: BIM23014 was administered in rats by daily s.c. injection for 104 weeks at dose levels of 0, 0.1, 0.2 or 0.5 mg/kg/d. Each predetermined injection site was scheduled by dosing approximately 104 times during the 104 weeks of treatment.

- The agency's statistic review suggests that male rats at HD groups has the highest mortality over all groups with statistically significant decrease in survival ($p<0.0300$); in females, mortality was lower in all treated groups (0.1, 0.2 and 0.5 mg/kg/day) compared to controls.
- In males, statistically significant and dose-related decrease in mean body weight (-5 to -25% compared to controls) were noted from Week 5 onwards. In females at similar doses, a statistically significant and dose-related decrease in mean body weight (-9 to -21 % compared to controls) was observed from Week 8 onwards. These body weight effects are likely to be attributed to the pharmacological activity of lanreotide, and were not associated with an alteration in FC.

- Neoplastic findings in animals given BIM23014 were mainly limited to the injection sites. Statistically significant increase in the incidence of cutaneous/subcutaneous fibrous connective tissue tumors, including subcutaneous fibrosarcoma and malignant fibrous histiocytoma, were observed in animals treated at HD 0.5 mg/kg/d, malignant tumors were recorded in 16/70 males corresponding to 16/490 potential injection sites and in 11/70 females corresponding to 11/490 potential injection sites, with 1 benign fibroma in 70 males. These tumors were occasionally seen at 0.2 mg/kg/d (2/70 fibroma and 2/70 malignant fibrous histiocytoma in males, and 1/70 fibroma in females only). At 0.1 mg/kg/d, the incidence of neoplastic changes was comparable to or less than that of the controls. In addition, a statistically significant increase in the incidence of malignant lymphoma was observed in the high dose treated males (3/70 or 4.28%); however, the incidence of this tumor fell within the range of historical data (0.91 to 6%), hence it is not considered a drug-related finding. No drug effect on malignant lymphoma was seen in female rats. Non-neoplastic changes consisting of epidermal hyperplasia, epidermal/dermal erosion or ulceration, vascular intimal hyperplasia and dermal fibrosis were observed at 0.1, 0.2 and 0.5 mg/kg/d with increased incidence following increasing doses, especially epidermal hyperplasia and fibrosis, which were parallel to the incidence of neoplastic lesions at injection sites, indicating a possible relevance.
- No systemic exposure-induced tumors were observed.
- The exposure level at 0.5 mg/kg/d with significant local tumorigenicity was only a fraction (1/10) of the proposed human maximum dose.
- Injection site tumorigenicity is likely to be attributed to the irritation of local injection with supersaturated acetate salt of the drug.

Adequacy of the carcinogenicity study and appropriateness of the test model:
The doses selected for the assay were apparently too low compared to anticipated human doses (AUC = 1877, 2887, and 3619 ng/ml.h corresponding to doses of 60, 90, and 120 mg with monthly dosing). Based on AUC value at 0.5 mg/kg/d in rats (337 ng/ml.h, daily dosing, sex combined), the HD tested is only a fraction (~1/10) of the max human exposure level (sponsor stated that *"the dose levels were selected according to the potential human exposure, existing toxicity data and any limitations imposed by the test article"*, but without specification). Dosing with daily injection is not relevant to that used in humans (monthly). The study protocol was not prior assessed by the ECAC. In general, the study design is considered suboptimal.

Evaluation of tumor findings:
Tumor findings in animals given BIM23014 were mainly limited to the injection sites. Statistically significant increase in the incidence of cutaneous/subcutaneous fibrous connective tissue tumors, including subcutaneous fibrosarcoma and malignant fibrous histiocytoma, were observed in animals treated at HD 0.5 mg/kg/d, malignant tumors were recorded in 16/70 males corresponding to 16/490 potential injection sites and in 11/70 females corresponding to 11/490 potential injection sites, with 1 benign fibroma in 70 males. These tumors were occasionally seen at 0.2 mg/kg/d (2/70 fibroma and 2/70 malignant fibrous histiocytoma in males, and 1/70 fibroma in females only) without

statistically significance compared to that of controls. At 0.1 mg/kg/d, the incidence of neoplastic changes was comparable to or less than that of the controls. No drug-related, systemic exposure-induced tumors were observed at any dose level compared to Charles River Lab's historical data (the testing lab's historical control data were not provided), except increased incidence of malignant lymphomas found in "hemolymphoid tissue" (as a total) in the HD treated males, which fell within the historical range and was not observed in HD treated females, hence it is not considered to be drug-related, though the incidence of malignant lymphomas in male rats was statistically significant according to the statistics review of CDER.

According to the statistics review, potentially statistically significant tumorigenicity was concluded in injection site tumors between the HD group and pooled controls, including fibrosarcoma (p=0.0010) and malignant fibrous histiocytoma (p=0.0000) in male rats and fibrosarcoma (p=0.0008) and malignant fibrous histiocytoma (p=0.0023) in female rats.

The sponsor proposed that "it is known that prolonged and repetitive administration of many substances by injection in this manner may occasionally induce local tumor formation at the injection sites. Therefore, it is not unexpected to observe such changes in this study since each of the seven injection sites was scheduled for use more than 100 times over 104 weeks". However, pharm/tox review would consider that chronic irritation to local tissues by supersaturated salt of the drug with highly frequent injection might be the cause of the tumor findings, which exceeds the irritation/inflammation caused by mechanical injury of the injection alone as the tumor incidence with drug exceeds that of controls as the similar findings seen in marketed drug Sandostatin.

Sandostatin, a same class of lanreotide, has shown similar tumorigenesis at the injection site. *"In a 116-week subcutaneous study in rats, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1.25 mg/kg/d. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. There have been no reports of injection site tumors in patients treated with Sandostatin*", according to the labeling.

In conclusion, drug-related, statistically significant increase in the incidence of cutaneous/subcutaneous fibrous connective tissue tumors, including subcutaneous fibrosarcoma and malignant fibrous histiocytoma, were limited to the injection sites at 0.5 mg/kg/d. The doses of 0.2 and 0.1 mg/kg/d did not induce a significant increase in incidence of neoplastic lesions at the injection sites. At the HD dose 0.5 mg/kg/d there was no evidence of an increase in neoplastic changes due to systemic exposure, the corresponding AUC at 0.5 mg/kg/d was 337.4 ng/ml.h (sex combined) on Week 104, a fraction of the maximum human exposure (1/10).

**Study no.:** 77005
**Volume #, and page #:** Vol A3.76, and page 1 to 3425
**Conducting laboratory and location:** / / /

**Date of study initiation:** 11/7/2002
**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 # P85943.001, P85943.002, 85943.003, P60016, P60024, P60027, P60054, P60055
**CAC concurrence:** N/A (protocol was not assessed by ECAC )

**Methods**

Doses: 0, 0, 0.1, 0.2, 0.5 mg/kg/d

**Study Design**

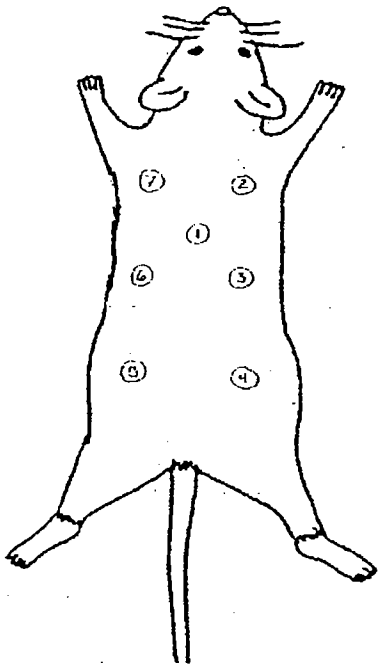
| Group No. Identification | Dose Level (mg/kg/day) | Number of Animals | | | |
|---|---|---|---|---|---|
| | | Main Study | | Toxicokinetic | |
| | | Males | Females | Males | Females |
| 1. Vehicle Control | 0 | 60 | 60 | — | — |
| 2. Vehicle Control | 0 | 60 | 60 | — | - |
| 3. BIM23014 | 0.1 | 70 | 70 | 15 | 15 |
| 4. BIM23014 | 0.2 | 70 | 70 | 15 | 15 |
| 5. BIM23014 | 0.5 | 70 | 70 | 15 | 15 |
| 7. Health Screen | — | 10 | 10 | — | |

Basis of dose selection (MTD, MFD, AUC etc.): Not specified. According to the sponsor, "the dose levels were selected based on the potential human exposure, existing toxicity data and any limitations imposed by the test article".

Species/strain: Rat/SD

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

Route, formulation, volume: Daily s.c. injection of vehicle or test article (bulk drug acetate salt dissolved in 0.9% saline) into 7 predefined dosing sites in the dorsal region at a dosing volume of 1 ml/kg/d. The 7 injection sites as illustrated below were used alternatively (rotated).




Site #1: Dorsal Thoracic
Site #2: Right Scapular
Site #3: Right Dorsal Thoracic
Site #4: Right Lumbar
Site #5: Left Lumbar
Site #6: Left Dorsal Thoracic
Site #7: Left Scapular

Frequency of dosing: Once daily for a minimum of 104 weeks
Satellite groups used for toxicokinetics or special groups: 16 rat/s/g for TK
Age: 6 weeks old
Animal housing: Housed individually in stainless steel wire mesh-bottomed cages equipped with an automatic watering valve and/or water bottle.
Restriction paradigm for dietary restriction studies: n/a
Drug stability/homogeneity: Stability was determined for 1 day at room temperature and 2 days refrigerated. Homogenecity samples were collected from Weeks 1, 13, 26, 39, 65, 78, 91 and 104 and analyzed.
Dual controls employed: Yes
Interim sacrifices: None
Deviations from original study protocol: Occasional minor deviations from the protocol and/or procedures occurred, and were documented in raw data as reported. These deviations seem no impact on the outcome of the study or upon the interpretation of the results.

**Observation times**

Mortality: twice daily throughout the study
Clinical signs: twice daily throughout the study
Body weights: weekly through the first 13 weeks, thereafter performed once every 4 weeks
Food consumption: daily through the first 13 weeks, thereafter performed daily for one week every 4 weeks (recorded the number of uneaten pellets if $\geq$ 1 pellet remained)

Histopathology: all tissues from all main study animals (and premature deaths) were evaluated histopathologically with paraffin sectioning and H & E staining; histopath findings were peer reviewed by a pathologist designated by the sponsor.
Toxicokinetics: samples were collected on Day 1 and during Weeks 26, 52 and 104 from satellite groups of 3 rats/sex/group/time point at 0, 0.5, 2, 4, 10 and 24 hrs after dosing.

**Results**

Mortality: In males, mortality rate in treated groups seems comparable to controls, according to the sponsor; while the CDER statistics review indicates that male rats at HD groups has the highest mortality over all groups with statistically significant decrease in survival ($p<0.0300$); in females, mortality rate was lower in the treated groups compared to controls, and statistics review suggests that survival trend in treated female mice was statistically nonsignificant, and control females seem to have highest mortality (as shown in the table below):

Mortality:

| Group | | Dose (mg/kg/d) | MALE | FEMALE |
|---|---|---|---|---|
| | | | Death Number per 60 or 70 (%) | Death Number per 60 or 70 (%) |
| 1 | Control 1 | 0 | 17/60 (28%) | 26/60 (43%) |
| 2 | Control 2 | 0 | 22/60 (37%) | 35/60 (58%) |
| 3 | Lanreotide | 0.1 | 17/70 (24%) | 25/70 (36%) |
| 4 | Lanreotide | 0.2 | 13/70 (19%) | 21/70 (30%) |
| 5 | Lanreotide | 0.5 | 28/70 (40%) | 21/70 (30%) |

Clinical signs: Clinically observed masses at injection sites were noted in a similar proportion of animals from control and treated groups as shown in the scanned table below:

**Text Table 5 Incidence of Animals with Clinically Recorded Masses**

| Group No. Identification | Dose Level (mg/kg/day) | Masses | | | |
|---|---|---|---|---|---|
| | | Males | % | Females | % |
| 1 Vehicle | 0 | 5/60 | 8 | 54/60 | 90 |
| 2 Vehicle | 0 | 12/60 | 20 | 51/60 | 85 |
| 3 BIM23014 | 0.1 | 15/70 | 21 | 63/70 | 90 |
| 4 BIM23014 | 0.2 | 12/70 | 17 | 32/70 | 46 |
| 5 BIM23014 | 0.5 | 18/70 | 26 | 27/70 | 39 |

An increased incidence of thin fur cover at the dosing site (and some adjacent areas) was noted in all treated groups when compared to controls. A dose-related increase in incidence of blue skin, red skin, scabs at the injection sites was noted in animals at all dose levels.

Body weights: Dose-related statistically significant decreases in mean body weight were noted throughout the treatment period in both sexes. These decreases are likely to be attributed to the pharmacological activity of lanreotide, and were not associated with an

alteration in FC. The mean and differences in body weight change between control and treated groups are presented in the scanned table below:

**Text Table 6 Mean Body Weight and Differences on 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 | 532.5 | - | 333.6 | - |
| 3 BIM23014 | 0.1 | 506.5 | -5 | 302.9 | -9 |
| 4 BIM23014 | 0.2 | 461.7 | -13 | 287.6 | -14 |
| 5 BIM23014 | 0.5 | 398.8 | -25 | 265.1 | -21 |

Food consumption: Unaffected

Gross pathology: Cutaneous scabs, ulceration, swelling and/or thickening were observed at one or more injection sites in all groups with minimal incidence in some vehicle control animals (2/120 males and 3/120 females), while similar lesions showed a dose-related increases in incidence at 0.1 mg/kg/d (6/70 M and 4/70 F), 0.2 mg/kg/d (25/70 M and 11/70 F) and 0.5 mg/kg/d (57/70 M and 41/70 F).

The injection site masses/nodules were noted with a lower incidence in control animals (8/120 M and 11/120 F), and the incidence was similar in animals at 0.1 and 0.2 mg/kg/d compared to controls. A slightly higher incidence was observed at 0.5 mg/kg/d (17/70 M and 14/70 F). Selected injection site gross findings are shown in the scanned Table 8 below.

Other findings include a dose-related increase in incidence and extent of pale and/or raised areas in the lungs in treated animals (scanned Table 9 below).

**Text Table 8** **Incidence of Treatment-related Macroscopic Finding at Injections Sites**

| Tissue/Finding Sex | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 0 | 0 | 0.1 | 0.2 | 0.5 | 0 | 0 | 0.1 | 0.2 | 0.5 |
| No. of animals examined | 60 | 60 | 70 | 70 | 70 | 60 | 60 | 70 | 70 | 70 |
| **I.S. Dorsal thoracic** | | | | | | | | | | |
| Mass or nodule | 0 | 1 | 0 | 2 | 2 | 0 | 0 | 0 | 3 | 1 |
| Scab | 1 | 0 | 1 | 21 | 37 | 0 | 1 | 1 | 6 | 21 |
| Swelling/thickening/ raised | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 1 |
| Ulceration | 0 | 0 | 1 | 3 | 7 | 0 | 0 | 0 | 0 | 0 |
| Area dark or clot | 1 | 3 | 1 | 6 | 7 | 1 | 10 | 3 | 7 | 13 |
| **I.S. Dorsal thoracic right** | | | | | | | | | | |
| Mass or nodule | 0 | 0 | 0 | 1 | 0 | 1 | 4 | 2 | 0 | 2 |
| Scab | 0 | 0 | 3 | 0 | 16 | 0 | 0 | 1 | 1 | 16 |
| Swelling/thickening/ raised | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Ulceration | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 |
| Area dark or clot | 1 | 2 | 2 | 3 | 6 | 1 | 3 | 4 | 4 | 7 |
| **I.S. Dorsal thoracic left** | | | | | | | | | | |
| Mass or nodule | 0 | 2 | 3 | 1 | 6 | 2 | 3 | 2 | 0 | 4 |
| Scab | 0 | 0 | 1 | 5 | 23 | 0 | 0 | 1 | 4 | 16 |
| Swelling/thickening/ raised | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Ulceration | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 0 |
| Area dark or clot | 4 | 3 | 4 | 6 | 6 | 4 | 5 | 4 | 4 | 2 |
| **I.S. Lumbar right** | | | | | | | | | | |
| Mass or nodule | 1 | 0 | 0 | 0 | 3 | 0 | 1 | 1 | 1 | 0 |
| Scab | 0 | 0 | 0 | 3 | 14 | 0 | 0 | 0 | 1 | 4 |
| Swelling/thickening/ raised | 0 | 0 | 1 | 0 | 4 | 0 | 0 | 0 | 0 | 2 |
| Ulceration | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 1 | 0 |
| Area dark or clot | 4 | 5 | 9 | 16 | 12 | 4 | 11 | 9 | 7 | 11 |

| Tissue/Finding Sex | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 0 | 0 | 0.1 | 0.2 | 0.5 | 0 | 0 | 0.1 | 0.2 | 0.5 |
| No. of animals examined | 60 | 60 | 70 | 70 | 70 | 60 | 60 | 70 | 70 | 70 |
| **I.S. Lumbar left** | | | | | | | | | | |
| *Mass or nodule* | *0* | *2* | *2* | *2* | *7* | 0 | 0 | 5 | 1 | 4 |
| Scab | 0 | 1 | 0 | 2 | 17 | 0 | 0 | 0 | 1 | 5 |
| Swelling/thickening/ raised | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 6 |
| Ulceration | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Area dark or clot | 1 | 4 | 3 | 3 | 2 | 6 | 6 | 2 | 2 | 6 |
| **I.S. Scapular right** | | | | | | | | | | |
| Mass or nodule | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 |
| Scab | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 4 |
| Swelling/thickening/ raised | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0. |
| Ulceration | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Area dark or clot | 1 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 0 | 0 |
| **I.S. Scapular left** | | | | | | | | | | |
| Mass or nodule | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Scab | 1 | 0 | 0 | 2 | 5 | 0 | 0 | 1 | 1 | 2 |
| Swelling/thickening/ raised | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 0 | 0 |
| Ulceration | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Area dark or clot | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 2 | 0 | 1 |
| **I.S. Interscapular** | | | | | | | | | | |
| Mass or nodule | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Scab | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 1 | 0 | 2 |
| Swelling/thickening/ raised | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Ulceration | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Area dark or clot | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 3 |
| ***Total number of animals affected*** | | | | | | | | | | |
| Mass or nodule | 2 | 6 | 6 | 7 | 17 | 3 | 8 | 9 | 4 | 14 |
| Scab/swelling/ thickening/area raised/ulceration | 1 | 1 | 6 | 29 | 58 | 1 | 2 | 4 | 11 | 41 |

**Text Table 9 Incidence of Treatment-related Macroscopic Finding in the Lungs**

| Tissue/Finding Sex | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 0 | 0 | 0.1 | 0.2 | 0.5 | 0 | 0 | 0.1 | 0.2 | 0.5 |
| No. of animals examined | 60 | 60 | 70 | 70 | 70 | 60 | 60 | 70 | 70 | 70 |
| **Lungs** | | | | | | | | | | |
| Area pale | 7 | 3 | 9 | 9 | 13 | 4 | 6 | 12 | 17 | 18 |
| Area raised | 2 | 6 | 2 | 11 | 18 | 5 | 6 | 11 | 9 | 13 |

Histopathology:

Non-neoplastic: Drug-related non-neoplastic changes were observed at the injection sites, other areas of skin and the lungs. The incidence and severity of these lesions increased with increasing dose of lanreotide. These changes were restricted to the epidermis/dermis and consisted of epidermal hyperplasia, epidermal erosion or ulceration, dermal fibrosis, reduced numbers of hair follicles and hyperplasia of vascular intima in subcutaneous blood vessels, often accompanied by secondary inflammatory infiltrations of the dermis and the subcutis. These dermal/epidermal lesions were seen at

all three dose levels but were particularly frequent and severe in animals dosed at 0.2 and the 0.5 mg/kg/d as shown in the scanned Table 11 below.

At the skin sites without injection, a higher incidence of scab formation was noted at 0.5 mg/kg/d as 12/70 (M) and 23/70 (F) vs. controls' 5/60 (M) and 8/60 (F).

In the lung, grossly pale and occasionally raised areas were noted and were associated with the presence of alveolar macrophage aggregation predominantly at 0.5 mg/kg/d. The macrophages were typically large with pale featureless cytoplasm and did not attract other inflammatory infiltrates.

No other remarkably drug-related non-neoplastic lesions in systemic organs were observed. Summary data tables for incidence of non-neoplastic findings in all animals are attached to this rat study review as Attachment 2: Incidence of animals with non-neoplastic lesions by organ/group/sex for all animals (preterminal and terminal rats).

**Text Table 11 Incidence of Treatment-related Histopathological Changes at Injection Sites**

| Tissue/Finding Se: | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 0 | 0 | 0.1 | 0.2 | 0.5 | 0 | 0 | 0.1 | 0.2 | 0.5 |
| No. of animals examined | 60 | 60 | 70 | 70 | 70 | 60 | 60 | 70 | 70 | 70 |
| **I.S. Dorsal thoracic** | | | | | | | | | | |
| Reduced hair follicles | 0 | 1 | 1 | 4 | 9 | 0 | 0 | 1 | 4 | 15 |
| Hyperplasia: epidermis | 0 | 0 | 5 | 30 | 47 | 0 | 0 | 3 | 22 | 46 |
| Erosion/ulceration | 0 | 0 | 1 | 11 | 17 | 0 | 0 | 0 | 1 | 6 |
| Fibrosis: dermis | 0 | 3 | 18 | 49 | 45 | 0 | 0 | 18 | 34 | 45 |
| Fibrosis: subcutis | 0 | 0 | 1 | 0 | 3 | 1 | 0 | 1 | 3 | 2 |
| Degeneration: panniculus muscle | 0 | 0 | 3 | 3 | 8 | 0 | 0 | 0 | 3 | 4 |
| Hemorrhage: subcutis | 0 | 2 | 1 | 2 | 3 | 1 | 5 | 1 | 4 | 4 |
| Hyperplasia: vascular intima | 0 | 0 | 4 | 12 | 34 | 0 | 0 | 0 | 8 | 31 |
| **I.S. Dorsal thoracic right** | | | | | | | | | | |
| Reduced hair follicles | 0 | 0 | 0 | 3 | 9 | 0 | 0 | 1 | 8 | 15 |
| Hyperplasia: epidermis | 0 | 0 | 3 | 8 | 26 | 0 | 0 | 4 | 7 | 41 |
| Erosion/ulceration | 0 | 0 | 1 | 0 | 9 | 0 | 0 | 1 | 0 | 7 |
| Fibrosis: dermis | 0 | 0 | 13 | 31 | 30 | 0 | 0 | 12 | 22 | 45 |
| Fibrosis: subcutis | 0 | 0 | 2 | 2 | 2 | 0 | 1 | 3 | 2 | 1 |
| Degeneration: panniculus muscle | 0 | 1 | 1 | 3 | 4 | 0 | 0 | 0 | 9 | 2 |

| Tissue/Finding Se | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 0 | 0 | 0.1 | 0.2 | 0.5 | 0 | 0 | 0.1 | 0.2 | 0.5 |
| No. of animals examined | 60 | 60 | 70 | 70 | 70 | 60 | 60 | 70 | 70 | 70 |
| *Hemorrhage: subcutis* | *0* | *2* | *1* | *1* | *2* | *0* | *3* | *2* | *3* | *3* |
| Hyperplasia: vascular intima | 0 | 0 | 10 | 9 | 20 | 0 | 0 | 2 | 20 | 34 |
| **I.S. Dorsal thoracic left** | | | | | | | | | | |
| Reduced hair follicles | 0 | 0 | 0 | 8 | 5 | 0 | 0 | 1 | 4 | 13 |
| Hyperplasia: epidermis | 0 | 0 | 4 | 16 | 32 | 0 | 0 | 6 | 14 | 38 |
| Erosion/ulceration | 0 | 0 | 1 | 2 | 9 | 0 | 0 | 0 | 2 | 9 |
| Fibrosis: dermis | 0 | 1 | 24 | 25 | 31 | 0 | 0 | 18 | 24 | 35 |
| Fibrosis: subcutis | 0 | 0 | 10 | 2 | 4 | 1 | 1 | 3 | 2 | 2 |
| *Degeneration:* panniculus muscle | 0 | 1 | 3 | 6 | 4 | 0 | 0 | 0 | 5 | 15 |
| Hemorrhage: subcutis | 3 | 0 | 3 | 6 | 4 | 1 | 4 | 2 | 2 | 0 |
| Hyperplasia: vascular intima | 0 | 0 | 13 | 15 | 19 | 0 | 0 | 3 | 10 | 30 |
| **I.S. Lumbar right** | | | | | | | | | | |
| Reduced hair follicles | 1 | 0 | 0 | 22 | 23 | 0 | 0 | 2 | 14 | 29 |
| Hyperplasia: epidermis | 1 | 0 | 9 | 32 | 40 | 0 | 0 | 4 | 14 | 46 |
| *Erosion/ulceration* | 0 | 0 | 1 | 1 | 9 | 1 | 0 | 2 | 1 | 5 |
| Fibrosis: dermis | 2 | 7 | 40 | 58 | 50 | 0 | 1 | 18 | 40 | 56 |
| Fibrosis: subcutis | 0 | 0 | 2 | 1 | 3 | 0 | 0 | 3 | 5 | 4 |
| Degeneration: panniculus muscle | 0 | 0 | 3 | 10 | 3 | 0 | 0 | 2 | 4 | 0 |
| Hemorrhage: subcutis | 2 | 4 | 8 | 12 | 7 | 0 | 7 | 5 | 7 | 7 |
| Hyperplasia: vascular intima | 0 | 0 | 16 | 30 | 34 | 0 | 0 | 2 | 30 | 29 |
| **I.S. Lumbar left** | | | | | | | | | | |
| Reduced hair follicles | 0 | 0 | 2 | 18 | 25 | 0 | 0 | 3 | 5 | 30 |
| *Hyperplasia:* epidermis | *0* | *0* | *2* | *27* | *39* | *0* | *0* | *2* | *14* | *45* |
| Erosion/ulceration | 0 | 0 | 0 | 1 | 7 | 0 | 0 | 0 | 2 | 6 |
| Fibrosis: dermis | 0 | 5 | 32 | 57 | 43 | 0 | 1 | 15 | 43 | 49 |
| Fibrosis: subcutis | 0 | 0 | 3 | 1 | 2 | 0 | 0 | 5 | 4 | 3 |
| Degeneration: panniculus muscle | 0 | 0 | 1 | 6 | 0 | 0 | 0 | 1 | 3 | 0 |
| Hemorrhage: subcutis | 1 | 0 | 2 | 2 | 4 | 3 | 4 | 1 | 2 | 3 |
| Hyperplasia: vascular intima | 0 | 0 | 7 | 20 | 28 | 0 | 0 | 2 | 27 | 33 |
| **I.S. Scapular right** | | | | | | | | | | |
| Reduced hair follicles | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Hyperplasia: epidermis | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 | 5 |
| Erosion/ulceration | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 3 |
| Fibrosis: dermis | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 7 |
| Fibrosis: subcutis | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Degeneration: panniculus muscle | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 0 |

| Tissue/Finding Sc | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 0 | 0 | 0.1 | 0.2 | 0.5 | 0 | 0 | 0.1 | 0.2 | 0.5 |
| No. of animals examined | 60 | 60 | 70 | 70 | 70 | 60 | 60 | 70 | 70 | 70 |
| Hemorrhage: subcutis | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 |
| Hyperplasia: vascular intima | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 0 |
| **I.S. Scapular left** | | | | | | | | | | |
| Reduced hair follicles | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia: epidermis | 1 | 0 | 0 | 3 | 5 | 0 | 0 | 1 | 1 | 6 |
| Erosion/ulceration | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 2 |
| Fibrosis: dermis | 0 | 0 | 0 | 2 | 4 | 0 | 0 | 0 | 2 | 10 |
| Fibrosis: subcutis | 1 | 2 | 0 | 1 | 2 | 1 | 1 | 0 | 0 | 0 |
| Degeneration: panniculus muscle | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 1 | 2 |
| Hemorrhage: subcutis | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| Hyperplasia: vascular intima | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **Total number of animals affected** | 10 | 20 | 65 | 70 | 70 | 7 | 20 | 50 | 70 | 70 |

Neoplastic: The major finding was a drug-related significant increase in the incidences of cutaneous/ subcutaneous tumors at the injection sites, including subcutaneous fibrosarcoma and/or malignant fibrous histiocytoma, which were limited to the injection sites in some animals treated at 0.5 mg/kg/d in 16/70 animals corresponding to 16/490 potential injection sites in males and in 11/70 animals corresponding to 11/490 potential injection sites in females, with 1 benign fibroma in 70 males. These tumors were occasionally seen at 0.2 mg/kg/d (2/70 fibroma and 2/70 malignant fibrous histiocytoma in males, and 1/70 fibroma only in females) without statistically significance compared to that of controls. At 0.1 mg/kg/d, the incidence of neoplastic changes was comparable to or less than that of the controls. The incidence of neoplastic changes was higher in the dorsal thoracic and lumbar injections sites than in the scapular injection sites. Time points of palpability of the tumors were not identifiable due to formation of subcutaneous nodules at injection sites.

There were three classes of the injection site tumors at the HD 0.5 mg/kg/d:

- Benign fibroma: 1/70 in males and 0/70 in females (background level and ignorable)
- Malignant fibrosarcoma with local invasion or metastasis: 6/70 (8.57%) in male rats and 5/70 (7.14%) in female rats (statistically significant and out of historical range as well)
- Malignant fibrous histiocytoma with extensive local invasion and metastases: 10/70 (14.29%) in males and 6/70 (8.57%) in females (statistically significant and out of historical range as well)

In addition, a statistically significant increase in the incidence of malignant lymphoma was observed in the high dose treated males (3/70 or 4.28%); however, the incidence of this tumor fell within the range of historical data (0.91 to 6%), hence it is not considered a drug-related finding. No drug effect on malignant lymphoma was seen in female rats.

Based on these findings, the tumor development is considered to be resulted from local exposure to the drug at 0.5 mg/kg/d and chronic irritation (evidenced by the highest incidence in epidermal hyperplasia and fibrosis at this dose level) while an effect may possibly be present at the 0.2 mg/kg/d dose level.

The incidence of neoplastic lesions at the injection sites is summarized in the following scanned Table 10:

**Text Table 10 Incidence of Principal Injection Site Neoplasms**

| Tissue/Finding | Sex | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | | 0 | 0 | 0.1 | 0.2 | 0.5 | 0 | 0 | 0.1 | 0.2 | 0.5 |
| No. of animals examined | | 60 | 60 | 70 | 70 | 70 | 60 | 60 | 70 | 70 | 70 |
| **I.S. Dorsal thoracic** | | | | | | | | | | | |
| Fibroma | | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Fibrous histiocytoma - malignant | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| **I.S. Dorsal thoracic right** | | | | | | | | | | | |
| Fibroma | | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Fibrosarcoma | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **I.S. Dorsal thoracic left** | | | | | | | | | | | |
| Fibroma | | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fibrosarcoma | | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 2 |
| Fibrous histiocytoma - malignant | | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 2 |
| **I.S. Lumbar right** | | | | | | | | | | | |
| Fibrosarcoma | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Fibrous histiocytoma - malignant | | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| **I.S. Lumbar left** | | | | | | | | | | | |
| Fibroma/myxoma | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Fibrosarcoma | | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| Fibrous histiocytoma - malignant | | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 1 |
| **I.S. Scapular right** | | | | | | | | | | | |
| Fibrous histiocytoma - malignant | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **I.S. Scapular left** | | | | | | | | | | | |
| Fibrosarcoma | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Fibrous histiocytoma - malignant | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***Total no. of tumors*** | | *0* | *3* | *1* | *4* | *17* | *0* | *1* | *0* | *1* | *11* |
| **Total number of animals affected** | | 0 | 3 | 1 | 4 | 15 | 0 | 1 | 0 | 1 | 9 |

In addition to the above, fibrohistiocytic sarcoma was seen in the lymph nodes of 4/60 male animals and in a single spleen of male animals at 0.5 mg/kg/d, which is considered

to be drug-related and likely to be a consequence of metastasis from the original subcutaneous tumors. No statistically significance for this tumor incidence in lymph nodes.

The incidence of all neoplastic lesions seen in all animals (preterminal and terminal) by organ/group/sex are illustrated in the following scanned Table 13, including pituitary adenoma/adenocarcinoma, pheochromocytoma, lymphoma, astrocytoma and glioma, mammary tumors and thyroid C-cell adenoma with similar incidence among all groups including controls. Since the testing lab's historical data are not available, they are only compared to concurrent controls. In addition, statistics review did not find potential significance for these neoplastic lesions relative to controls.

Separate data sets for incidence of neoplastic findings in preterminal and terminal animals, respectively, are attached to this rat study review (Attachment 1: sponsor's Tables 11 and 12).

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| ABDOMEN | NO.EXAM.: | - | 1 | 1 | 1 | 2 |
| - Mesothelioma | | - | - | - | 1 | - |
| - Lymphangioma | | - | - | 1 | - | - |
| ADRENAL | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Benign pheochromocytoma | | 3 | 4 | - | 2 | 2 |
| - Malignant pheochromocytoma | | - | 1 | - | - | - |
| - Malignant pheochromocytoma: complex | | - | 1 | - | 1 | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| AORTA | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Leiomyosarcoma | | - | 1 | - | - | - |
| BILE DUCT | NO.EXAM.: | 3 | 3 | 2 | 4 | 2 |
| BLOOD VESSEL | NO.EXAM.: | 1 | - | - | - | - |
| BONE-FEMUR | NO.EXAM.: | 59 | 60 | 70 | 70 | 70 |
| BONE MARROW | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: lymphoid | | - | - | - | 1 | - |
| BONE MISCELLANEOUS | NO.EXAM.: | - | 1 | - | - | 1 |
| BONE-STERNUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| BRAIN | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Malignant astrocytoma | | - | - | 1 | 1 | 1 |
| - Malignant mixed glioma | | - | 2 | - | 1 | - |
| - Malignant meningioma | | 1 | - | - | - | - |
| - Carcinoma: metastasis | | - | - | 1 | - | - |
| CAVITY CRANIAL | NO.EXAM.: | 2 | - | - | - | 2 |
| - Sarcoma: metastasis | | 1 | - | - | - | - |
| CAVITY ORAL | NO.EXAM.: | 1 | - | 1 | - | - |
| - Osteosarcoma | | 1 | - | - | - | - |
| - Papilloma: squamous cell | | - | - | 1 | - | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| CECUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| COLON | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| DIAPHRAGM | NO.EXAM.: | - | - | - | 1 | 1 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| DUODENUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| EPIDIDYMIS | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| ESOPHAGUS | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| EYE | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| FAT | NO.EXAM.: | - | 3 | - | 1 | 3 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| HARDERIAN GLAND | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| HEAD | NO.EXAM.: | - | - | 1 | - | - |
| - Sarcoma: squamous cell | | - | - | 1 | - | - |
| HEART | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Sarcoma: metastasis | | - | 1 | - | - | - |
| HEMOLYM. TISSUE | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Malignant lymphoma | | - | - | 1 | 1 | 3 |
| - Histiocytic sarcoma | | 1 | 2 | 1 | 2 | 3 |
| ILEUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| I.S. DORSAL THORACIC | NO.EXAM.: | 59 | 59 | 69 | 70 | 69 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Fibroma | | - | 1 | - | - | - |
| - Keratoacanthoma | | - | - | - | 1 | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| I.S. DORS.THO. LT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Papilloma: epidermal | | - | - | - | 1 | - |
| - Fibrosarcoma | | - | - | - | - | 3 |
| - Fibrous histiocytoma: malignant | | - | 1 | - | - | 3 |
| - Fibroma | | - | - | 1 | 1 | - |
| - Lipoma | | - | 1 | 1 | - | - |
| I.S. DORS.THO. RT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Fibroma | | - | - | - | 1 | - |
| I.S. INTERSCAPULAR | NO.EXAM.: | - | - | 1 | 1 | 6 |
| I.S. LUMBAR, LEFT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Fibrosarcoma | | - | 1 | - | - | 2 |
| - Fibrous histiocytoma: malignant | | - | - | - | 2 | 3 |
| - Myxoma | | - | - | - | - | 1 |
| - Hemangiosarcoma | | - | - | - | - | 1 |
| I.S. LUMBAR, RIGHT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: sebaceous gland | | 1 | - | - | - | - |
| - Fibrosarcoma | | - | - | - | - | 1 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 3 |
| I.S. SCAPULAR, LEFT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| I.S. SCAPULAR, RIGHT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| JEJUNUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| JOINT | NO.EXAM.: | 1 | - | - | - | 1 |
| KIDNEY | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: tubular cell | | - | - | 1 | - | - |
| LACRIMAL GLAND | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| LARYNX | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| LIVER | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: hepatocellular | | - | 1 | 2 | - | - |
| - Carcinoma: hepatocellular | | 1 | 2 | - | 2 | - |
| - Sarcoma: metastasis | | - | 1 | - | - | 1 |
| - Carcinoma: metastasis | | - | - | - | 1 | - |
| LUNG | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: alveolar/bronchiolar | | 1 | - | 1 | - | - |
| - Fibrous histiocytoma: malignant | | - | 1 | - | - | 2 |
| - Carcinoma: metastasis | | 1 | - | - | 1 | - |
| - Sarcoma: metastasis | | - | 1 | 1 | - | - |
| LYMPH NODE | NO.EXAM.: | 13 | 13 | 19 | 18 | 22 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 4 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| L. NODE MANDIBULAR | NO.EXAM.: | 60 | 59 | 69 | 70 | 69 |
| - Sarcoma: metastasis | | - | 1 | - | - | - |
| L.NODE MESENTERIC | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Hemangioma | | - | - | 1 | 1 | - |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| MAMMARY GLAND | NO.EXAM.: | 6 | 9 | 6 | 2 | - |
| MUSCLE SKELETAL | NO.EXAM.: | 60 | 60 | 69 | 70 | 68 |
| MUSCLE SKELETAL MISC | NO.EXAM.: | - | 1 | - | 1 | - |
| NERVE OPTIC | NO.EXAM.: | 60 | 60 | 70 | 69 | 70 |
| NERVE SCIATIC | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| PANCREAS | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: islet cell | | 2 | 3 | 2 | 2 | - |
| - Carcinoma: islet cell | | 1 | 2 | 1 | 2 | 1 |
| - Fibrous histiocytoma | | - | - | - | - | 1 |
| PARATHYROID GLAND | NO.EXAM.: | 48 | 47 | 56 | 55 | 66 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| PERICARDIUM | NO.EXAM.: | - | 1 | - | - | - |
| PITUITARY | NO.EXAM.: | 60 | 60 | 70 | 70 | 69 |
| - Adenoma: pars distalis | | 35 | 37 | 34 | 32 | 34 |
| - Carcinoma: pars distalis | | - | 1 | 1 | - | - |
| - Sarcoma: metastasis | | 1 | - | 1 | - | - |
| PREPUTIAL GLAND | NO.EXAM.: | 60 | 59 | 70 | 70 | 70 |
| PROSTATE | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenocarcinoma | | - | - | - | 1 | - |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| RECTUM | NO.EXAM.: | - | 1 | - | - | - |
| SALIV.GL. MANDIBULAR | NO.EXAM.: | 60 | 59 | 70 | 70 | 70 |
| SEMINAL VESICLE | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| SKIN | NO.EXAM.: | 60 | 60 | 69 | 69 | 69 |
| SKIN MISCELLANEOUS | NO.EXAM.: | 29 | 26 | 35 | 38 | 44 |
| - Papilloma: squamous cell | | 1 | - | - | - | 1 |
| - Carcinoma: basal cell | | - | - | - | 1 | - |
| SPINAL CORD CERVICAL | NO.EXAM.: | 60 | 60 | 70 | 69 | 70 |
| - Malignant astrocytoma | | - | - | 2 | - | - |
| - Malignant mixed glioma | | 1 | - | - | - | - |
| SPLEEN | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Hemangioma | | - | 1 | - | - | - |
| - Hemangiosarcoma | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| STOMACH | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| SUBCUTANEOUS TISSUE | NO.EXAM.: | 2 | 5 | 5 | 4 | 2 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Benign schwannoma | | - | 1 | - | - | - |
| - Lipoma | | - | - | - | 2 | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | 1 | 2 | 3 | 4 | 5 |
| **NUMBER OF ANIMALS EXAMINED** | | 60 | 60 | 70 | 70 | 70 |
| SUBCUTANEOUS TISSUE | CONT'D. | 2 | 5 | 5 | 4 | 2 |
| - Fibroma | | - | 1 | - | - | - |
| - Fibrosarcoma | | 1 | 1 | 2 | - | - |
| TAIL | NO.EXAM.: | 2 | 3 | 3 | - | - |
| TESTIS | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: interstitial cell | | 1 | 2 | 1 | 5 | 1 |
| THORAX | NO.EXAM.: | - | - | - | - | 1 |
| THYMUS | NO.EXAM.: | 57 | 56 | 67 | 62 | 65 |
| THYROID | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: follicular cell | | 2 | - | 1 | 1 | - |
| - Carcinoma: follicular cell | | 1 | 1 | - | - | - |
| - Adenoma: C-cell | | 2 | 5 | 8 | 1 | 1 |
| - Carcinoma: C-cell | | - | - | - | - | 1 |
| - Sarcoma: metastasis | | - | 1 | - | - | - |
| TONGUE | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Hemangiosarcoma | | - | - | 1 | - | - |
| TRACHEA | NO.EXAM.: | 60 | 59 | 70 | 70 | 70 |
| URETER | NO.EXAM.: | 1 | - | 1 | 1 | 1 |
| URINARY BLADDER | NO.EXAM.: | 60 | 59 | 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** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| ABDOMEN | NO.EXAM.: | 1 | 2 | - | - | - |
| - Carcinoma: metastasis | | - | 1 | - | - | - |
| ADRENAL | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Benign pheochromocytoma | | 1 | 1 | 1 | - | 1 |
| - Malignant pheochromocytoma | | - | - | 1 | 1 | - |
| - Adenoma: cortical | | 1 | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| AORTA | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| BILE DUCT | NO.EXAM.: | 1 | 3 | 3 | 10 | 3 |
| BONE-FEMUR | NO.EXAM.: | 60 | 60 | 69 | 70 | 70 |
| BONE MARROW | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| BONE MISCELLANEOUS | NO.EXAM.: | - | - | - | - | 1 |
| BONE-STERNUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| BRAIN | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Malignant astrocytoma | | - | 2 | - | - | - |
| - Malignant meningioma | | - | - | - | - | 1 |
| - Carcinoma: metastasis | | - | 3 | 3 | 3 | - |
| CAVITY CRANIAL | NO.EXAM.: | - | 1 | - | - | - |
| CECUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| CLITORAL GLAND | NO.EXAM.: | 59 | 57 | 70 | 67 | 70 |
| COLON | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| DIAPHRAGM | NO.EXAM.: | - | 1 | - | - | 1 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| DUODENUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| ESOPHAGUS | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| EYE | NO.EXAM.: | 60 | 60 | 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 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| FAT | NO.EXAM.: | - | 4 | - | - | 1 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| HARDERIAN GLAND | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| HEART | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| HEMOLYM. TISSUE | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Malignant lymphoma | | - | 1 | - | 1 | - |
| - Histiocytic sarcoma | | 3 | 4 | 2 | - | - |
| ILEUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| I.S. DORSAL THORACIC | NO.EXAM.: | 60 | 59 | 70 | 70 | 70 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Fibroma | | - | - | - | 1 | - |
| I.S. DORS.THO. LT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Fibrosarcoma | | - | - | - | - | 2 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 2 |
| I.S. DORS.THO. RT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Squamous cell carcinoma | | - | 1 | - | - | - |
| - Fibroma | | - | 1 | - | - | - |
| - Fibrosarcoma | | - | - | - | - | 1 |
| I.S. INTERSCAPULAR | NO.EXAM.: | - | 1 | 2 | 1 | 4 |
| I.S. LUMBAR, LEFT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| I.S. LUMBAR, RIGHT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| I.S. SCAPULAR, LEFT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| I.S. SCAPULAR, RIGHT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| JEJUNUM | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenocarcinoma | | - | 1 | - | - | - |
| - Fibroma | | - | - | - | 1 | - |
| - Hemangiosarcoma | | - | - | 1 | - | 1 |
| JOINT | NO.EXAM.: | 1 | - | 1 | 1 | - |
| KIDNEY | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Renal mesenchymal tumor | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| LACRIMAL GLAND | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| LARYNX | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| LIVER | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: hepatocellular | | 1 | 1 | 1 | 4 | 1 |
| - Carcinoma: hepatocellular | | - | 1 | - | - | - |
| - Cholangioma | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| - Carcinoma: metastasis | | - | 1 | 1 | - | - |
| LUNG | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Carcinoma: metastasis | | 1 | 3 | 1 | 1 | - |
| - Renal mesenchymal tumour: metastasis | | - | 1 | - | - | - |
| LUNG | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Sarcoma: metastasis | | - | - | 1 | - | 3 |
| LYMPH NODE | NO.EXAM.: | 30 | 28 | 33 | 22 | 19 |
| - Sarcoma: metastasis | | - | - | 1 | 1 | 2 |
| - Carcinoma: metastasis | | - | 1 | - | 1 | - |
| - Renal mesenchymal tumour: metastasis | | - | 1 | - | - | - |
| L. NODE MANDIBULAR | NO.EXAM.: | 58 | 59 | 70 | 70 | 67 |
| L.NODE MESENTERIC | NO.EXAM.: | 60 | 60 | 68 | 70 | 69 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| MAMMARY GLAND | NO.EXAM.: | 60 | 60 | 70 | 69 | 69 |
| - Fibroadenoma | | 13 | 11 | 13 | 12 | 10 |
| - Adenoma | | 10 | 10 | 15 | 5 | 2 |
| - Adenocarcinoma | | 10 | 16 | 13 | 5 | 2 |
| - Carcinosarcoma | | 1 | - | 1 | 2 | - |
| - Fibroma | | 1 | - | 2 | - | - |
| MUSCLE SKELETAL | NO.EXAM.: | 59 | 59 | 70 | 70 | 70 |
| MUSCLE SKELETAL MISC | NO.EXAM.: | - | 1 | 1 | 2 | 1 |
| NERVE OPTIC | NO.EXAM.: | 60 | 60 | 69 | 70 | 70 |
| NERVE SCIATIC | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| OVARY | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: tubulostromal | | - | - | - | 1 | - |
| - Adenoma: sertoliform tubular | | 1 | - | - | - | - |
| - Carcinoma: sertoliform | | - | - | - | - | 1 |
| - Cystadenoma | | 2 | - | - | - | - |
| - Malignant granulosa-theca cell tumor | | - | 1 | 1 | 1 | - |
| OVIDUCT | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| PANCREAS | NO.EXAM.: | 60 | 59 | 69 | 70 | 70 |
| - Adenoma: islet cell | | 1 | 1 | - | 1 | - |
| - Carcinoma: islet cell | | 1 | - | - | 1 | 1 |
| - Carcinoma: metastasis | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| PARATHYROID GLAND | NO.EXAM.: | 47 | 49 | 53 | 50 | 65 |
| - Adenoma | | - | 1 | - | - | - |
| - Adenocarcinoma | | - | - | - | - | 1 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| PITUITARY | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenoma: pars distalis | | 53 | 48 | 51 | 50 | 34 |
| - Carcinoma: pars distalis | | 1 | 4 | 3 | 3 | - |
| RECTUM | NO.EXAM.: | 1 | 1 | - | - | - |
| SALIV.GL. MANDIBULAR | NO.EXAM.: | 60 | 59 | 70 | 70 | 70 |
| SKIN | NO.EXAM.: | 60 | 60 | 70 | 69 | 69 |
| SKIN MISCELLANEOUS | NO.EXAM.: | 27 | 28 | 36 | 43 | 51 |
| - Keratoacanthoma | | - | - | - | 1 | - |
| - Sarcoma: squamous cell | | 1 | - | - | - | - |
| SPINAL CORD CERVICAL | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Malignant astrocytoma | | - | - | - | - | 1 |
| SPLEEN | NO.EXAM.: | 60 | 60 | 69 | 70 | 70 |
| - Hemangioma | | - | 1 | - | - | - |
| STOMACH | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - ECL cell tumour | | 1 | - | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| SUBCUTANEOUS TISSUE | NO.EXAM.: | 5 | 3 | 6 | 6 | 4 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Fibroma | | 1 | - | 1 | 3 | - |
| SUBCUTANEOUS TISSUE | CONT'D. | 5 | 3 | 6 | 6 | 4 |
| - Fibrosarcoma | | 1 | - | 1 | 1 | 1 |
| TAIL | NO.EXAM.: | 2 | 2 | 3 | 2 | 2 |
| - Fibrosarcoma | | - | - | 1 | 1 | - |
| THORAX | NO.EXAM.: | 1 | 2 | 1 | - | 1 |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| THYMUS | NO.EXAM.: | 54 | 57 | 66 | 69 | 63 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| THYROID | NO.EXAM.: | 60 | 59 | 70 | 70 | 70 |
| - Adenoma: follicular cell | | - | 2 | - | 1 | - |
| - Carcinoma: follicular cell | | - | - | - | 1 | - |
| - Adenoma: C-cell | | 2 | 4 | 3 | 7 | 2 |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| TONGUE | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Papilloma: squamous cell | | - | - | - | - | 1 |
| TRACHEA | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| URETER | NO.EXAM.: | 2 | 3 | 4 | 1 | 2 |
| URETHRA | NO.EXAM.: | - | - | 1 | - | - |
| URINARY BLADDER | NO.EXAM.: | 59 | 60 | 70 | 70 | 70 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| UTERUS | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |
| - Adenosarcinoma: endometrial | | - | 1 | 1 | - | - |
| - Adenoma: endometrial | | - | - | - | 2 | - |
| - Polyp: endometrial stromal | | 6 | 3 | 14 | 4 | 7 |
| - Fibroma | | - | - | 1 | - | - |
| - Fibrosarcoma | | - | - | - | - | 1 |
| - Sarcoma: endometrial stromal | | 1 | - | 1 | 1 | - |
| UTERUS | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Leiomyoma | | 2 | - | - | - | - |
| - Benign granular cell tumor | | - | - | - | 1 | - |
| - Hemangioma | | - | - | - | 1 | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| VAGINA | NO.EXAM.: | 60 | 60 | 70 | 70 | 70 |

Toxicokinetics: TK data are summarized in Table 7 below. Some gender difference in exposure were noted in Cmax values on the different dosing days at each dose level, particularly at 0.1 and 0.5 mg/kg/d. The overall increase in Cmax values was lower than proportional with the increase in dose in both genders. The increase $AUC_{0-t}$ values was proportional with the increase in dose, particularly in females.

**Text Table 7** **Exposure ($C_{max}$ ng/ml, AUC ng/ml.h-1) Values after *Daily Treatment in Both Genders***

| | | | DOSES (mg/kg/day) | | |
|---|---|---|---|---|---|
| | | | 0.1 | 0.2 | 0.5 |
| Day 1 | Males | $C_{max}$ | 48.5 | 45.3 | 95.6 |
| | | $AUC_t$ | 69.5 | 91.8 | 328.8 |
| | Females | $C_{max}$ | 45.5 | 43.4 | 130.3 |
| | | $AUC_t$ | 51.3 | 102.3 | 266.5 |
| Week 26 | Males | $C_{max}$ | 26.4 | 40.8 | 85.1 |
| | | $AUC_\tau$ | 69.8 | 153.9 | 508.3 |
| | Females | $C_{max}$ | 22.1 | 53.5 | 126.9 |
| | | $AUC_\tau$ | 57.6 | 137.5 | 397.0 |
| Week 52 | Males | $C_{max}$ | 42.6 | 39.9 | 96.6 |
| | | $AUC_\tau$ | 129.7 | 173.6 | 426.3 |
| | Females | $C_{max}$ | 52.3 | 75.4 | 85.1 |
| | | $AUC_\tau$ | 103.7 | 177.9 | 315.2 |
| Week 104 | Males | $C_{max}$ | 24.2 | 34.2 | 60.8 |
| | | $AUC_\tau$ | 94.3 | 152.5 | 323.1 |
| | Females | $C_{max}$ | 16.9 | 34.3 | 63.2 |
| | | $AUC_\tau$ | 54.0 | 129.6 | 351.7 |

Putative lanreotide antibodies: The specific antibody response to lanreotide was evaluated on 3 TK animals/sex/group treated from 0.5 to 30 mg/kg/d at Week 26 and on all surviving main study animals at terminal euthanasia. A total of 3 mice (2 F at 5 mg/kg/d and 1 M at 30 mg/kg/d) showed a specific antibody response with a titer of 16, 2 and 4, respectively. No putative lanreotide antibodies were demonstrated at terminal euthanasia. Concerning samples with a non-specific binding greater than 30%, one male at 10 mg/kg/d, one male and female at 5 mg/kg/d and one female at 10 mg/kg/d showed a specific antibody response.

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

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **17** | **23** | **17** | **13** | **28** |
| ABDOMEN | NO.EXAM.: | - | - | - | 1 | 2 |
| - Mesothelioma | | - | - | - | 1 | - |
| ADRENAL | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Benign pheochromocytoma | | - | 1 | - | - | - |
| - Malignant pheochromocytoma | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| AORTA | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Leiomyosarcoma | | - | 1 | - | - | - |
| BILE DUCT | NO.EXAM.: | - | - | - | 1 | - |
| BONE-FEMUR | NO.EXAM.: | 16 | 23 | 17 | 13 | 28 |
| BONE MARROW | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| BONE MISCELLANEOUS | NO.EXAM.: | - | 1 | - | - | 1 |
| BONE-STERNUM | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| BRAIN | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Malignant astrocytoma | | - | - | 1 | 1 | 1 |
| - Malignant mixed glioma | | - | 2 | - | 1 | - |
| - Malignant meningioma | | 1 | - | - | - | - |
| - Carcinoma: metastasis | | - | - | 1 | - | - |
| CAVITY CRANIAL | NO.EXAM.: | 2 | - | - | - | 2 |
| - Sarcoma: metastasis | | 1 | - | - | - | - |
| CAVITY ORAL | NO.EXAM.: | 1 | - | - | - | - |
| - Osteosarcoma | | 1 | - | - | - | - |
| CECUM | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| COLON | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| DIAPHRAGM | NO.EXAM.: | - | - | - | 1 | 1 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **17** | **23** | **17** | **13** | **28** |
| DUODENUM | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| EPIDIDYMIS | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| ESOPHAGUS | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| EYE | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| FAT | NO.EXAM.: | - | 2 | - | 1 | 3 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| HARDERIAN GLAND | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| HEAD | NO.EXAM.: | - | - | 1 | - | - |
| - Sarcoma: squamous cell | | - | - | 1 | - | - |
| HEART | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Sarcoma: metastasis | | - | 1 | - | - | - |
| HEMOLYM. TISSUE | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Malignant lymphoma | | - | - | - | - | 3 |
| - Histiocytic sarcoma | | - | 1 | 1 | 2 | 1 |
| ILEUM | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| I.S. DORSAL THORACIC | NO.EXAM.: | 16 | 22 | 16 | 13 | 27 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| I.S. DORS.THO. LT | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Fibrosarcoma | | - | - | - | - | 3 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 3 |
| I.S. DORS.THO. RT | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Fibroma | | - | - | - | 1 | - |
| I.S. INTERSCAPULAR | NO.EXAM.: | - | - | - | 1 | 3 |
| I.S. LUMBAR, LEFT | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Fibrosarcoma | | - | 1 | - | - | 1 |
| - Fibrous histiocytoma: malignant | | - | - | - | 1 | 3 |
| - Myxoma | | - | - | - | - | 1 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **17** | **23** | **17** | **13** | **28** |
| I.S. LUMBAR, RIGHT | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| I.S. SCAPULAR, LEFT | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| I.S. SCAPULAR, RIGHT | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| JEJUNUM | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| JOINT | NO.EXAM.: | - | - | - | - | 1 |
| KIDNEY | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| LACRIMAL GLAND | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| LARYNX | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| LIVER | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Carcinoma: hepatocellular | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| LUNG | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Carcinoma: metastasis | | 1 | - | - | - | - |
| - Sarcoma: metastasis | | - | 1 | 1 | - | - |
| LYMPH NODE | NO.EXAM.: | 3 | 4 | 5 | 9 | 16 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 3 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| L. NODE MANDIBULAR | NO.EXAM.: | 17 | 22 | 16 | 13 | 27 |
| - Sarcoma: metastasis | | - | 1 | - | - | - |
| L.NODE MESENTERIC | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Hemangioma | | - | - | - | 1 | - |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| MAMMARY GLAND | NO.EXAM.: | 4 | 5 | 4 | - | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 17 | 23 | 17 | 13 | 28 |
| MUSCLE SKELETAL | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| MUSCLE SKELETAL MISC | NO.EXAM.: | - | - | - | 1 | - |
| NERVE OPTIC | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| NERVE SCIATIC | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| PANCREAS | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Adenoma: islet cell | | - | 1 | - | - | - |
| - Carcinoma: islet cell | | - | 1 | - | - | - |
| - Fibrous histiocytoma | | - | - | - | - | 1 |
| PARATHYROID GLAND | NO.EXAM.: | 14 | 18 | 16 | 11 | 26 |
| PERICARDIUM | NO.EXAM.: | - | 1 | - | - | - |
| PITUITARY | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Adenoma: pars distalis | | 10 | 14 | 6 | 6 | 3 |
| - Carcinoma: pars distalis | | - | 1 | 1 | - | - |
| - Sarcoma: metastasis | | 1 | - | 1 | - | - |
| PREPUTIAL GLAND | NO.EXAM.: | 17 | 22 | 17 | 13 | 28 |
| PROSTATE | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Mesothelioma: metastasis | | - | - | - | 1 | - |
| SALIV.GL. MANDIBULAR | NO.EXAM.: | 17 | 22 | 17 | 13 | 28 |
| SEMINAL VESICLE | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| SKIN | NO.EXAM.: | 17 | 23 | 17 | 12 | 27 |
| SKIN MISCELLANEOUS | NO.EXAM.: | 11 | 9 | 6 | 5 | 13 |
| SPINAL CORD CERVICAL | NO.EXAM.: | 17 | 23 | 17 | 12 | 28 |
| - Malignant astrocytoma | | - | - | 1 | - | - |
| SPLEEN | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Hemangiosarcoma | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **17** | **23** | **17** | **13** | **28** |
| STOMACH | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| SUBCUTANEOUS TISSUE | NO.EXAM.: | - | 3 | 3 | 3 | 1 |
| - Benign schwannoma | | - | 1 | - | - | - |
| - Lipoma | | - | - | - | 1 | - |
| - Fibrosarcoma | | - | 1 | 2 | - | - |
| TAIL | NO.EXAM.: | - | 1 | - | - | - |
| TESTIS | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Adenoma: interstitial cell | | - | - | - | 1 | - |
| THORAX | NO.EXAM.: | - | - | - | - | 1 |
| THYMUS | NO.EXAM.: | 17 | 21 | 16 | 9 | 25 |
| THYROID | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Adenoma: follicular cell | | - | - | 1 | - | - |
| - Carcinoma: follicular cell | | 1 | - | - | - | - |
| - Adenoma: C-cell | | - | 3 | 1 | - | - |
| - Sarcoma: metastasis | | - | 1 | - | - | - |
| TONGUE | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |
| - Hemangiosarcoma | | - | - | 1 | - | - |
| TRACHEA | NO.EXAM.: | 17 | 22 | 17 | 13 | 28 |
| URETER | NO.EXAM.: | - | - | - | 1 | 1 |
| URINARY BLADDER | NO.EXAM.: | 17 | 23 | 17 | 13 | 28 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | 1 | 2 | 3 | 4 | 5 |
| **NUMBER OF ANIMALS EXAMINED** | | 27 | 36 | 26 | 21 | 21 |
| ABDOMEN | NO.EXAM.: | 1 | 2 | - | - | - |
| - Carcinoma: metastasis | | - | 1 | - | - | - |
| ADRENAL | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Benign pheochromocytoma | | 1 | 1 | - | - | 3 |
| - Adenoma: cortical | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| AORTA | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| BILE DUCT | NO.EXAM.: | - | - | - | 2 | - |
| BONE-FEMUR | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| BONE MARROW | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| BONE MISCELLANEOUS | NO.EXAM.: | - | - | - | - | 1 |
| BONE-STERNUM | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| BRAIN | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Malignant astrocytoma | | - | 2 | - | - | - |
| - Carcinoma: metastasis | | - | 2 | 1 | 2 | - |
| CAVITY CRANIAL | NO.EXAM.: | - | 1 | - | - | - |
| CECUM | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| CLITORAL GLAND | NO.EXAM.: | 26 | 34 | 26 | 20 | 21 |
| COLON | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| DIAPHRAGM | NO.EXAM.: | - | 1 | - | - | 1 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| DUODENUM | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| ESOPHAGUS | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| EYE | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| FAT | NO.EXAM.: | - | 4 | - | - | 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** |
| **NUMBER OF ANIMALS EXAMINED** | | **27** | **36** | **26** | **21** | **21** |
| HARDERIAN GLAND | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| HEART | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| HEMOLYM. TISSUE | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Malignant lymphoma | | - | 1 | - | 1 | - |
| - Histiocytic sarcoma | | 2 | 4 | - | - | - |
| ILEUM | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| I.S. DORSAL THORACIC | NO.EXAM.: | 27 | 35 | 26 | 21 | 21 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| I.S. DORS.THO. LT | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 2 |
| I.S. DORS.THO. RT | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Squamous cell carcinoma | | - | 1 | - | - | - |
| - Fibroma | | - | 1 | - | - | - |
| - Fibrosarcoma | | - | - | - | - | 1 |
| I.S. INTERSCAPULAR | NO.EXAM.: | - | 1 | 1 | - | 2 |
| I.S. LUMBAR, LEFT | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| I.S. LUMBAR, RIGHT | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| I.S. SCAPULAR, LEFT | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| I.S. SCAPULAR, RIGHT | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| JEJUNUM | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Adenocarcinoma | | - | 1 | - | - | - |
| - Hemangiosarcoma | | - | - | 1 | - | - |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **27** | **36** | **26** | **21** | **21** |
| JOINT | NO.EXAM.: | - | - | 1 | - | - |
| KIDNEY | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Renal mesenchymal tumor | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | 1 | - | 1 |
| LACRIMAL GLAND | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| LARYNX | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| LIVER | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Cholangioma | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| - Carcinoma: metastasis | | - | 1 | - | - | - |
| LUNG | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Carcinoma: metastasis | | 1 | 3 | 1 | 1 | - |
| - Renal mesenchymal tumour: metastasis | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | 1 | - | 2 |
| LYMPH NODE | NO.EXAM.: | 13 | 17 | 12 | 4 | 7 |
| - Sarcoma: metastasis | | - | - | 1 | 1 | 1 |
| - Carcinoma: metastasis | | - | 1 | - | 1 | - |
| - Renal mesenchymal tumour: metastasis | | - | 1 | - | - | - |
| L. NODE MANDIBULAR | NO.EXAM.: | 25 | 35 | 26 | 21 | 19 |
| L.NODE MESENTERIC | NO.EXAM.: | 27 | 36 | 25 | 21 | 20 |
| MAMMARY GLAND | NO.EXAM.: | 27 | 36 | 26 | 20 | 20 |
| - Fibroadenoma | | 5 | 6 | 3 | 1 | 1 |
| - Adenoma | | 4 | 2 | 3 | 1 | - |
| - Adenocarcinoma | | 6 | 11 | 6 | - | - |
| MUSCLE SKELETAL | NO.EXAM.: | 26 | 35 | 26 | 21 | 21 |
| MUSCLE SKELETAL MISC | NO.EXAM.: | - | 1 | - | 2 | 1 |
| NERVE OPTIC | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| NERVE SCIATIC | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 27 | 36 | 26 | 21 | 21 |
| OVARY | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Adenoma: sertoliform tubular | | 1 | - | - | - | - |
| OVIDUCT | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| PANCREAS | NO.EXAM.: | 27 | 35 | 25 | 21 | 21 |
| - Adenoma: islet cell | | - | 1 | - | - | - |
| - Carcinoma: islet cell | | - | - | - | 1 | - |
| - Carcinoma: metastasis | | - | 1 | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| PARATHYROID GLAND | NO.EXAM.: | 21 | 29 | 21 | 13 | 21 |
| PITUITARY | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Adenoma: pars distalis | | 24 | 29 | 18 | 13 | 8 |
| - Carcinoma: pars distalis | | 1 | 3 | 1 | 2 | - |
| RECTUM | NO.EXAM.: | 1 | 1 | - | - | - |
| SALIV.GL. MANDIBULAR | NO.EXAM.: | 27 | 35 | 26 | 21 | 21 |
| SKIN | NO.EXAM.: | 27 | 36 | 26 | 20 | 20 |
| SKIN MISCELLANEOUS | NO.EXAM.: | 8 | 18 | 9 | 11 | 12 |
| - Sarcoma: squamous cell | | 1 | - | - | - | - |
| SPINAL CORD CERVICAL | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| SPLEEN | NO.EXAM.: | 27 | 36 | 25 | 21 | 21 |
| STOMACH | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| SUBCUTANEOUS TISSUE | NO.EXAM.: | 3 | 3 | 2 | 2 | 4 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Fibroma | | - | - | - | 1 | - |
| - Fibrosarcoma | | - | - | 1 | 1 | 1 |
| TAIL | NO.EXAM.: | - | 2 | - | 1 | 1 |
| - Fibrosarcoma | | - | - | - | 1 | - |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **27** | **36** | **26** | **21** | **21** |
| THORAX | NO.EXAM.: | 1 | 2 | 1 | - | 1 |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| THYMUS | NO.EXAM.: | 23 | 33 | 25 | 21 | 17 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| THYROID | NO.EXAM.: | 27 | 35 | 26 | 21 | 21 |
| - Carcinoma: follicular cell | | - | - | - | 1 | - |
| - Adenoma: C-cell | | - | 1 | 1 | 1 | - |
| - Sarcoma: metastasis | | - | - | 1 | - | - |
| TONGUE | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| TRACHEA | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| URETER | NO.EXAM.: | 2 | 1 | 2 | 1 | 1 |
| URETHRA | NO.EXAM.: | - | - | 1 | - | - |
| URINARY BLADDER | NO.EXAM.: | 26 | 36 | 26 | 21 | 21 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| UTERUS | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |
| - Polyp: endometrial stromal | | 1 | - | 2 | 1 | 1 |
| - Fibroma | | - | - | 1 | - | - |
| - Fibrosarcoma | | - | - | - | - | 1 |
| - Sarcoma: endometrial stromal | | 1 | - | 1 | 1 | - |
| UTERUS | CONT'D. | 27 | 36 | 26 | 21 | 21 |
| - Leiomyoma | | 1 | - | - | - | - |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| VAGINA | NO.EXAM.: | 27 | 36 | 26 | 21 | 21 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 43 | 37 | 53 | 57 | 42 |
| ABDOMEN | NO.EXAM.: | - | 1 | 1 | - | - |
| - Lymphangioma | | - | - | 1 | - | - |
| ADRENAL | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Benign pheochromocytoma | | 3 | 3 | - | 2 | 2 |
| - Malignant pheochromocytoma: complex | | - | 1 | - | 1 | - |
| AORTA | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| BILE DUCT | NO.EXAM.: | 3 | 3 | 2 | 3 | 2 |
| BLOOD VESSEL | NO.EXAM.: | 1 | - | - | - | - |
| BONE-FEMUR | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| BONE MARROW | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Hyperplasia: lymphoid | | - | - | - | 1 | - |
| BONE-STERNUM | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| BRAIN | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| CAVITY ORAL | NO.EXAM.: | - | - | 1 | - | - |
| - Papilloma: squamous cell | | - | - | 1 | - | - |
| CECUM | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| COLON | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| DUODENUM | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| EPIDIDYMIS | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| ESOPHAGUS | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| EYE | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| FAT | NO.EXAM.: | - | 1 | - | - | - |
| HARDERIAN GLAND | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| HEART | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| HEMOLYM. TISSUE | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Malignant lymphoma | | - | - | 1 | 1 | - |
| - Histiocytic sarcoma | | 1 | 1 | - | - | 2 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 43 | 37 | 53 | 57 | 42 |
| ILEUM | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| I.S. DORSAL THORACIC | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Fibroma | | - | - | - | - | - |
| - Keratoacanthoma | | - | - | - | - | - |
| I.S. DORS.THO. LT | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Papilloma: epidermal | | - | - | - | 1 | - |
| - Fibrous histiocytoma: malignant | | - | 1 | - | - | - |
| - Fibroma | | - | - | 1 | 1 | - |
| - Lipoma | | - | - | - | - | - |
| I.S. DORS.THO. RT | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| I.S. INTERSCAPULAR | NO.EXAM.: | - | - | 1 | - | 3 |
| I.S. LUMBAR, LEFT | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| - Fibrous histiocytoma: malignant | | - | - | - | 1 | - |
| - Hemangiosarcoma | | - | - | - | - | 1 |
| I.S. LUMBAR, RIGHT | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenoma: sebacecus gland | | 1 | - | - | - | - |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 2 |
| I.S. SCAPULAR, LEFT | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| I.S. SCAPULAR, RIGHT | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| JEJUNUM | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| JOINT | NO.EXAM.: | 1 | - | - | - | - |
| KIDNEY | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenoma: tubular cell | | - | - | - | - | - |
| LACRIMAL GLAND | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| LARYNX | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **43** | **37** | **53** | **57** | **42** |
| LIVER | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenoma: hepatocellular | | - | 1 | 2 | - | - |
| - Carcinoma: hepatocellular | | 1 | 1 | - | 2 | - |
| - Sarcoma: metastasis | | - | 1 | - | - | - |
| - Carcinoma: metastasis | | - | - | - | 1 | - |
| LUNG | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenoma: alveolar/bronchiolar | | 1 | - | 1 | - | - |
| - Fibrous histiocytoma: malignant | | - | 1 | - | - | 1 |
| - Carcinoma: metastasis | | - | - | - | 1 | - |
| LYMPH NODE | NO.EXAM.: | 10 | 9 | 14 | 9 | 6 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| L. NODE MANDIBULAR | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| L.NODE MESENTERIC | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Hemangioma | | - | - | 1 | - | - |
| MAMMARY GLAND | NO.EXAM.: | 2 | 4 | 2 | 2 | - |
| MUSCLE SKELETAL | NO.EXAM.: | 43 | 37 | 52 | 57 | 42 |
| MUSCLE SKELETAL MISC | NO.EXAM.: | - | 1 | - | - | - |
| NERVE OPTIC | NO.EXAM.: | 43 | 37 | 53 | 56 | 42 |
| NERVE SCIATIC | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| PANCREAS | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenoma: islet cell | | 2 | 2 | 2 | 2 | - |
| - Carcinoma: islet cell | | 1 | 1 | 1 | 2 | 1 |
| PARATHYROID GLAND | NO.EXAM.: | 34 | 29 | 40 | 44 | 40 |
| PITUITARY | NO.EXAM.: | 43 | 37 | 53 | 57 | 41 |
| - Adenoma: pars distalis | | 25 | 23 | 28 | 26 | 11 |
| PREPUTIAL GLAND | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| PROSTATE | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenocarcinoma | | - | - | - | 1 | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **43** | **37** | **53** | **57** | **42** |
| RECTUM | NO.EXAM.: | - | 1 | - | - | - |
| SALIV.GL. MANDIBULAR | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| SEMINAL VESICLE | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| SKIN | NO.EXAM.: | 43 | 37 | 52 | 57 | 42 |
| SKIN MISCELLANEOUS | NO.EXAM.: | 18 | 17 | 29 | 33 | 31 |
| - Papilloma: squamous cell | | 1 | - | - | - | 1 |
| - Carcinoma: basal cell | | - | - | - | 1 | - |
| SPINAL CORD CERVICAL | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Malignant astrocytoma | | - | - | 1 | - | - |
| - Malignant mixed glioma | | 1 | - | - | - | - |
| SPLEEN | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Hemangioma | | - | 1 | - | - | - |
| STOMACH | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| SUBCUTANEOUS TISSUE | NO.EXAM.: | 2 | 2 | 2 | 1 | 1 |
| - Fibrous histiocytoma: malignant | | - | - | - | - | 1 |
| - Lipoma | | - | - | - | 1 | - |
| - Fibroma | | - | 1 | - | - | - |
| - Fibrosarcoma | | 1 | - | - | - | - |
| TAIL | NO.EXAM.: | 2 | 2 | 3 | - | - |
| TESTIS | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenoma: interstitial cell | | 1 | 2 | 1 | 4 | 1 |
| THYMUS | NO.EXAM.: | 40 | 35 | 51 | 53 | 40 |
| THYROID | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| - Adenoma: follicular cell | | 2 | - | - | 1 | - |
| - Carcinoma: follicular cell | | - | 1 | - | - | - |
| - Adenoma: C-cell | | 2 | 2 | 7 | 1 | 1 |
| - Carcinoma: C-cell | | - | - | - | - | 1 |
| TONGUE | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |

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

MALE

| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS EXAMINED | | 43 | 37 | 53 | 57 | 42 |
| TRACHEA | NO.EXAM.: | 43 | 37 | 53 | 57 | 42 |
| URETER | NO.EXAM.: | 1 | - | 1 | - | - |
| URINARY BLADDER | NO.EXAM.: | 43 | 36 | 53 | 57 | 42 |

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

FEMALE

| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS EXAMINED | | 33 | 24 | 44 | 49 | 49 |
| ADRENAL | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Benign pheochromocytoma | | - | - | 1 | - | 1 |
| - Malignant pheochromocytoma | | - | - | 1 | 1 | - |
| - Adenoma: cortical | | 1 | - | - | - | - |
| AORTA | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| BILE DUCT | NO.EXAM.: | 1 | 3 | 3 | 8 | 3 |
| BONE-FEMUR | NO.EXAM.: | 33 | 24 | 43 | 49 | 49 |
| BONE MARROW | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| BONE-STERNUM | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| BRAIN | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Malignant meningioma | | - | - | - | - | 1 |
| - Carcinoma: metastasis | | - | 1 | 2 | 1 | - |
| CECUM | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| CLITORAL GLAND | NO.EXAM.: | 33 | 23 | 44 | 47 | 49 |
| COLON | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| DUODENUM | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| ESOPHAGUS | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| EYE | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **33** | **24** | **44** | **49** | **49** |
| HARDERIAN GLAND | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| HEART | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| HEMOLYX. TISSUE | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Histiocytic sarcoma | | 1 | - | 2 | - | 1 |
| ILEUM | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| I.S. DORSAL THORACIC | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Fibroma | | - | - | - | 1 | - |
| I.S. DORS.THO. LT | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| I.S. DORS.THO. RT | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| I.S. INTERSCAPULAR | NO.EXAM.: | - | - | 1 | 1 | 2 |
| I.S. LUMBAR, LEFT | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Fibrosarcoma | | - | - | - | - | 1 |
| I.S. LUMBAR, RIGHT | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| I.S. SCAPULAR, LEFT | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| I.S. SCAPULAR, RIGHT | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| JEJUNUM | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Fibroma | | - | - | - | 1 | - |
| JOINT | NO.EXAM.: | 1 | - | - | 1 | - |
| KIDNEY | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| LACRIMAL GLAND | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| LARYNX | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| LIVER | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Adenoma: hepatocellular | | 1 | 1 | 1 | 4 | 1 |
| - Carcinoma: hepatocellular | | - | 1 | - | - | - |
| - Carcinoma: metastasis | | - | - | 1 | - | - |
| LUNG | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **33** | **24** | **44** | **49** | **49** |
| LYMPH NODE | NO.EXAM.: | 17 | 11 | 21 | 18 | 12 |
| - Sarcoma: metastasis | | - | - | - | - | 1 |
| L. NODE MANDIBULAR | NO.EXAM.: | 33 | 24 | 44 | 49 | 48 |
| L.NODE MESENTERIC | NO.EXAM.: | 33 | 24 | 43 | 49 | 49 |
| MAMMARY GLAND | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Fibroadenoma | | 8 | 5 | 10 | 11 | 9 |
| - Adenoma | | 6 | 8 | 12 | 4 | 2 |
| - Adenocarcinoma | | 4 | 5 | 7 | 5 | 2 |
| - Carcinosarcoma | | 1 | - | 1 | 2 | - |
| - Fibroma | | 1 | - | 2 | - | - |
| MUSCLE SKELETAL | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| MUSCLE SKELETAL MISC | NO.EXAM.: | - | - | 1 | - | - |
| NERVE OPTIC | NO.EXAM.: | 33 | 24 | 43 | 49 | 49 |
| NERVE SCIATIC | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| OVARY | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Adenoma: tubulostromal | | - | - | - | 1 | - |
| - Carcinoma: sertoliform | | - | - | - | - | 1 |
| - Cystadenoma | | 2 | - | - | - | - |
| - Malignant granulosa-theca cell tumor | | - | 1 | 1 | 1 | - |
| OVIDUCT | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| PANCREAS | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Adenoma: islet cell | | 1 | - | - | 1 | - |
| - Carcinoma: islet cell | | 1 | - | - | - | 1 |
| PARATHYROID GLAND | NO.EXAM.: | 26 | 20 | 32 | 37 | 44 |
| - Adenoma | | - | 1 | - | - | - |
| - Adenocarcinoma | | - | - | - | - | 1 |
| PITUITARY | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Adenoma: pars distalis | | 29 | 20 | 38 | 37 | 26 |
| - Carcinoma: pars distalis | | - | 1 | 2 | 1 | - |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 33 | 24 | 44 | 49 | 49 |
| SALIV.GL. MANDIBULAR | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| SKIN | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| SKIN MISCELLANEOUS | NO.EXAM.: | 13 | 10 | 27 | 32 | 39 |
| - Keratoacanthoma | | - | - | - | 1 | - |
| SPINAL CORD CERVICAL | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Malignant astrocytoma | | - | - | - | - | 1 |
| SPLEEN | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Hemangioma | | - | 1 | - | - | - |
| STOMACH | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - ECL cell tumor | | 1 | - | - | - | - |
| SUBCUTANEOUS TISSUE | NO.EXAM.: | 2 | - | 4 | 4 | - |
| - Fibroma | | 1 | - | 1 | 2 | - |
| - Fibrosarcoma | | 1 | - | - | - | - |
| TAIL | NO.EXAM.: | 2 | - | 3 | - | 1 |
| - Fibrosarcoma | | - | - | 1 | - | - |
| THYMUS | NO.EXAM.: | 31 | 24 | 41 | 48 | 46 |
| THYROID | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Adenoma: follicular cell | | - | 2 | - | 1 | - |
| - Adenoma: C-cell | | 2 | 3 | 2 | 6 | 2 |
| TONGUE | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Papilloma: squamous cell | | - | - | - | - | 1 |
| TRACHEA | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| URETER | NO.EXAM.: | - | 2 | 2 | - | 1 |
| URINARY BLADDER | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| UTERUS | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |
| - Adenocarcinoma: endometrial | | - | 1 | 1 | - | - |
| - Adenoma: endometrial | | - | - | - | 2 | - |
| - Polyp: endometrial stromal | | 5 | 3 | 12 | 3 | 6 |
| - Leiomyoma | | 1 | - | - | - | - |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **33** | **24** | **44** | **49** | **49** |
| UTERUS | CONT'D. | 33 | 24 | 44 | 49 | 49 |
| - Benign granular cell tumor | | - | - | - | 1 | - |
| - Hemangioma | | - | - | - | 1 | - |
| VAGINA | NO.EXAM.: | 33 | 24 | 44 | 49 | 49 |

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

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| ABDOMEN | EXAMIN: | - | 1 | 1 | 1 | 2 |
| - Inflammation: vascular | | - | 1 | - | - | - |
| ADRENAL | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: cortical focal zona glomerulosa | | 34 | 27 | 26 | 13 | 24 |
| - Hyperplasia: cortical focal | | 13 | 11 | 13 | 5 | 4 |
| - Hyperplasia: cortical | | 1 | - | 1 | - | - |
| - Angiectasis | | - | 1 | - | - | - |
| - Degeneration: cystic | | 5 | 15 | 4 | 5 | 1 |
| - Hyperplasia: medullary | | 5 | 3 | 8 | 7 | 4 |
| ADRENAL | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Vacuolation: cortical | | 1 | - | 1 | 1 | 2 |
| - Hematopoiesis: extramedullary | | - | - | 1 | - | 2 |
| - Cyst | | - | - | - | - | 1 |
| - Congestion | | 7 | 9 | 4 | 2 | 6 |
| - Hemorrhage | | 1 | 3 | 2 | - | - |
| - Deposits: pigment | | - | - | - | - | 1 |
| AORTA | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Mineralization: vascular | | 2 | - | - | 1 | - |
| BILE DUCT | EXAMIN: | 3 | 3 | 2 | 4 | 2 |
| - Dilatation | | 3 | 3 | 2 | 4 | 2 |
| - Inflammation | | 1 | - | - | - | 2 |
| BLOOD VESSEL | EXAMIN: | 1 | - | - | - | - |
| BONE-FEMUR | EXAMIN: | 59 | 60 | 70 | 70 | 70 |
| BONE MARROW | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: lymphoid | | - | - | - | - | 1 |
| - Atrophy | | 1 | - | - | - | - |
| - Necrosis | | - | - | - | 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** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| BONE MISCELLANEOUS | EXAMIN: | - | 1 | - | - | 1 |
| - Hemorrhage | | - | 1 | - | - | - |
| BONE-STERNUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| BRAIN | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Compression | | 9 | 12 | 13 | 4 | 2 |
| - Dilatation: ventricle | | 5 | 5 | 7 | 1 | - |
| - Hemorrhage | | 1 | - | - | 1 | - |
| - Mineralization | | - | - | - | - | 1 |
| CAVITY CRANIAL | EXAMIN: | 2 | - | - | - | 2 |
| - Hemorrhage | | 1 | - | - | - | - |
| CAVITY ORAL | EXAMIN: | 1 | - | 1 | - | - |
| CECUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | - | 1 | - | 2 | - |
| - Inflammation: vascular | | - | 1 | - | - | - |
| - Necrosis | | - | - | - | 1 | - |
| - Ulceration | | - | 1 | - | - | - |
| COLON | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Parasite | | 5 | 4 | 9 | 4 | 3 |
| DIAPHRAGM | EXAMIN: | - | - | - | 1 | 1 |
| DUODENUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation: granulomatous | | - | - | - | 1 | - |
| - Erosion | | - | 2 | 1 | - | - |
| EPIDIDYMIS | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Oligo/aspermia | | 8 | 8 | 10 | 15 | 8 |
| - Inflammation | | - | - | 1 | - | - |
| ESOPHAGUS | EXAMIN: | 60 | 60 | 70 | 70 | 70 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| EYE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Degeneration: retina | | 4 | 3 | 7 | 8 | 10 |
| - Degeneration: lens | | 1 | 1 | 1 | 1 | - |
| - Exudate: anterior compartment | | - | 2 | 1 | - | - |
| - Ulceration: cornea | | - | - | 1 | - | - |
| - Congestion | | - | - | - | 1 | - |
| FAT | EXAMIN: | - | 3 | - | 1 | 3 |
| - Necrosis | | - | 2 | - | - | - |
| HARDERIAN GLAND | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | - | - | - | 1 | - |
| HEAD | EXAMIN: | - | - | 1 | - | - |
| HEART | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Degeneration and/or necrosis: myocardial | | 1 | - | - | - | - |
| - Fibrosis | | 9 | 4 | 4 | 4 | 2 |
| - Inflammation | | 5 | 1 | 2 | 2 | 1 |
| - Endocardiosis | | - | 1 | 1 | - | - |
| - Dilatation | | - | - | 1 | - | - |
| - Hemorrhage | | - | - | - | 1 | 1 |
| - Congestion | | 1 | - | - | - | - |
| HEMOLYM. TISSUE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| ILEUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - 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 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| I.S. DORSAL THORACIC | EXAMIN: | 59 | 59 | 69 | 70 | 69 |
| - Reduced hair follicles | | - | 1 | 1 | 4 | 9 |
| - Hyperplasia: epidermis | | - | - | 9 | 30 | 47 |
| - Scab | | - | - | 4 | 18 | 38 |
| - Fibrosis: dermis | | - | 3 | 18 | 49 | 45 |
| - Fibrosis: subcutis | | - | - | 1 | - | 3 |
| - Inflammation: dermis | | - | - | - | 12 | 6 |
| - Inflammation: subcutis | | - | 2 | 1 | 1 | 3 |
| - Anscess: subcutis | | - | - | - | 1 | - |
| - Degeneration/inflammation: muscle | | - | - | 3 | 3 | 8 |
| I.S. DORSAL THORACIC | CONT'D. | 59 | 59 | 69 | 70 | 69 |
| - Hyperplasia: vascular intima | | - | - | 4 | 12 | 34 |
| - Erosion: epidermis | | - | - | - | 6 | 6 |
| - Ulceration | | - | - | 1 | 5 | 11 |
| - Hemorrhage: subcutis | | - | 2 | 1 | 2 | 3 |
| - Deposit: pigment | | - | - | - | - | 1 |
| - Edema: subcutis | | - | - | - | - | 2 |
| I.S. DORS.THO. LT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | - | 8 | 5 |
| - Hyperplasia: epidermis | | - | - | 4 | 16 | 32 |
| - Scab | | - | - | 2 | 3 | 19 |
| - Fibrosis: dermis | | - | 1 | 24 | 25 | 31 |
| - Fibrosis: subcutis | | - | - | 10 | 2 | 4 |
| - Inflammation: dermis | | - | 2 | - | 2 | 2 |
| - Inflammation: subcutis | | 1 | 1 | 4 | 3 | 14 |
| - Degeneration/inflammation: muscle | | - | 1 | 3 | 6 | 4 |
| - Dilatation: follicles | | 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** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| I.S. DORS.THO. LT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: follicular epithelium | | 1 | - | - | - | - |
| - Epidermoid cyst | | - | - | 1 | 1 | - |
| - Erosion: epidermis | | - | - | - | 1 | 2 |
| - Ulceration | | - | - | 1 | 1 | 2 |
| - Hemorrhage: subcutis | | 3 | - | 3 | 6 | 4 |
| - Hyperplasia: vascular intima subcutis | | - | - | 13 | 15 | 19 |
| I.S. DORS.THO. RT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | - | 3 | 9 |
| - Hyperplasia: epidermis | | - | - | 3 | 8 | 26 |
| - Scab | | - | - | 4 | 1 | 17 |
| - Fibrosis: dermis | | - | - | 13 | 31 | 30 |
| - Fibrosis: subcutis | | - | - | 2 | 2 | 2 |
| - Inflammation: subcutis | | - | 1 | 3 | - | 3 |
| - Degeneration/Inflammation: muscle | | - | 1 | 1 | 3 | 4 |
| - Epidermoid cyst | | - | - | - | 1 | - |
| - Erosion: epidermis | | - | - | - | - | 1 |
| I.S. DORS.THO. RT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Ulceration | | - | - | 1 | - | 3 |
| - Hemorrhage: dermis | | - | - | - | 1 | 1 |
| - Hemorrhage: subcutis | | - | 2 | 1 | 1 | 2 |
| - Deposit: pigment subcutis | | - | - | 1 | - | - |
| - Hyperplasia: vascular intima subcutis | | - | - | 10 | 9 | 20 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| I.S. INTERSCAPULAR | EXAMIN: | - | - | 1 | 1 | 6 |
| - Scab | | - | - | - | - | 4 |
| - Hyperplasia: epidermis | | - | - | - | - | 2 |
| - Fibrosis: dermis | | - | - | - | - | 2 |
| - Fibrosis: subcutis | | - | - | 1 | - | - |
| - Cyst: epidermoid | | - | - | - | - | 1 |
| - Ulceration | | - | - | - | - | 1 |
| I.S. LUMBAR, LEFT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | 2 | 18 | 25 |
| - Hyperplasia: epidermis | | - | - | 2 | 27 | 39 |
| - Scab | | - | - | - | 3 | 17 |
| - Fibrosis: dermis | | - | 5 | 32 | 57 | 43 |
| - Fibrosis: subcutis | | - | - | 3 | 1 | 2 |
| - Inflammation: dermis | | - | - | 1 | 1 | 4 |
| - Inflammation: subcutis | | - | 1 | 1 | - | 5 |
| - Degeneration/inflammation: muscle | | - | - | 1 | 6 | - |
| - Erosion: epidermis | | - | - | - | - | 1 |
| I.S. LUMBAR, LEFT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Ulceration | | - | - | - | 1 | 6 |
| - Hyperplasia: vascular intima subcutis | | - | - | 7 | 20 | 28 |
| - Hemorrhage: subcutis | | 1 | - | 2 | 2 | 4 |
| - Epidermoid cyst | | - | 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 |
| **NUMBER OF ANIMALS EXAMINED** | | 60 | 60 | 70 | 70 | 70 |
| L.S. LUMBAR, RIGHT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | 1 | - | - | 22 | 23 |
| - Hyperplasia: epidermis | | 1 | - | 9 | 32 | 40 |
| - Hyperplasia: basal cells | | 1 | - | - | - | - |
| - Scab | | - | 1 | 1 | 2 | 15 |
| - Fibrosis: dermis | | 2 | 7 | 40 | 58 | 50 |
| - Inflammation: dermis | | - | - | 1 | 1 | 6 |
| - Fibrosis: subcutis | | - | - | 2 | 1 | 3 |
| - Inflammation: subcutis | | - | 2 | 2 | 2 | 5 |
| - Degeneration/inflammation: muscle | | - | - | 3 | 10 | 3 |
| L.S. LUMBAR, RIGHT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Necrosis: subcutis | | - | - | 1 | - | - |
| - Erosion: epidermis | | - | - | 1 | 1 | - |
| - Ulceration | | - | - | - | - | 9 |
| - Hemorrhage: subcutis | | 2 | 4 | 8 | 12 | 7 |
| - Hyperplasia: vascular intima | | - | - | 16 | 30 | 34 |
| L.S. SCAPULAR, LEFT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | - | - | 1 |
| - Hyperplasia: epidermis | | 1 | - | - | 3 | 5 |
| - Scab | | - | - | - | 2 | 4 |
| - Fibrosis: dermis | | - | - | - | 2 | 4 |
| - Inflammation: dermis | | - | - | - | 1 | 1 |
| - Fibrosis: subcutis | | 1 | 2 | - | 1 | 2 |
| - Inflammation: subcutis | | 1 | 1 | 2 | - | 4 |
| - Hyperplasia: vascular intima | | - | - | - | - | 1 |
| - Degeneration/inflammation: muscle | | - | - | 1 | - | 2 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| I.S. SCAPULAR, LEFT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: follicular epithelium | | 1 | - | - | - | - |
| - Erosion: epidermis | | - | - | - | 1 | 3 |
| - Hemorrhage: subcutis | | - | - | - | 1 | - |
| - Hyperplasia:vascular intima | | - | - | - | - | 1 |
| - Epidermoid cyst | | 1 | - | - | - | - |
| I.S. SCAPULAR, RIGHT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: epidermis | | 1 | - | - | - | 2 |
| - Scab | | - | - | - | - | 4 |
| - Fibrosis: dermis | | - | - | - | 1 | 2 |
| - Fibrosis: subcutis | | - | 1 | - | - | 1 |
| - Inflammation: subcutis | | - | - | - | - | 5 |
| - Degeneration/inflammation: muscle | | - | - | - | - | 4 |
| - Hyperplasia: vascular intima | | - | - | - | - | 4 |
| - Ulceration | | - | - | - | - | 2 |
| - Hemorrhage: subcutis | | 1 | - | - | - | 1 |
| I.S. SCAPULAR, RIGHT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Epidermoid cyst | | - | 1 | - | - | - |
| JEJUNUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | 1 | - | 1 | 1 | - |
| - Diverticulum | | - | - | - | 1 | - |
| JOINT | EXAMIN: | 1 | - | - | - | 1 |
| - Inflammation | | 1 | - | - | - | 1 |
| KIDNEY | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Glomerulonephritis/glomerulopathy | | 17 | 13 | 1 | 3 | - |
| - Nephropathy | | 2 | - | - | - | - |

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

**All Animals**

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| KIDNEY | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Pyelitis/pyelonephritis | | 2 | - | 4 | 2 | - |
| - Inflammation | | 2 | 2 | - | 1 | - |
| - Inflammation: interstitial | | 5 | 3 | 3 | 2 | 3 |
| - Adipose nodule | | - | - | 1 | - | - |
| - Dilatation: pelvis | | 2 | 1 | - | 2 | 2 |
| - Hyperplasia: transitional cell | | 5 | 3 | 4 | 4 | 2 |
| - Mineralization: pelvis epithelium | | 3 | 2 | 2 | - | 1 |
| - Necrosis: papilla | | 1 | - | - | - | - |
| - Dilatation: tubular | | 1 | - | - | 2 | - |
| KIDNEY | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Basophilia: tubular | | 2 | 1 | 2 | - | 3 |
| - Hyperplasia: tubular | | 1 | - | - | - | - |
| - Cyst | | 4 | - | 4 | - | 2 |
| - Hyaline droplet: tubular | | 1 | 2 | 2 | 2 | 4 |
| - Deposits: pigment | | - | 2 | - | - | - |
| - Hemorrhage | | 1 | 1 | - | - | - |
| - Congestion | | 1 | - | - | - | 1 |
| LACRIMAL GLAND | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Harderianisation | | 8 | 4 | 5 | 6 | 4 |
| - Atrophy | | - | 1 | - | - | - |
| - Fibrosis | | - | - | - | 1 | - |
| LARYNX | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation: ventral pouch | | - | 1 | 3 | 3 | 8 |
| - Inflammation | | - | - | 1 | 1 | 1 |
| - Hyperplasia: epithelial | | - | - | - | - | 1 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| LIVER | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Basophilic cell focus | | 1 | - | - | - | 1 |
| - Eosinophilic cell focus | | 9 | 15 | 5 | 4 | 1 |
| - Hyperplasia: bile duct | | 8 | 8 | 4 | 10 | 3 |
| - Tension lipidosis | | 7 | 6 | 9 | 9 | 2 |
| - Vacuolation: periportal | | 1 | 1 | 1 | - | - |
| - Cytoplasmic rarefaction | | 1 | 1 | - | - | - |
| - Hematopoiesis: extramedullary | | - | 1 | 1 | 2 | 5 |
| - Inflammation | | 1 | 1 | - | 1 | - |
| - Inflammation: biliary | | 3 | 3 | 4 | 2 | 1 |
| LIVER | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Necrosis | | - | 1 | 1 | - | 3 |
| - Necrosis: single cell | | - | - | - | 1 | - |
| - Cyst: biliary | | 1 | - | 2 | - | - |
| - Degeneration: cystic | | 1 | - | - | - | - |
| - Dilatation: sinusoidal with congestion | | 4 | 3 | 3 | 6 | 1 |
| - Atrophy | | - | - | - | - | 3 |
| - Congestion | | 3 | 4 | 1 | 2 | - |
| LUNG | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: alveolar epithelium | | - | - | 1 | - | - |
| - Macrophage accumulation | | 3 | 6 | 8 | 12 | 19 |
| - Inflammation | | 3 | 1 | - | - | 8 |
| - Fibrosis: pleura | | - | 1 | 1 | - | - |
| - Congestion | | 2 | 1 | 1 | 1 | - |
| - Hemorrhage | | 3 | 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** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| LYMPH NODE | EXAMIN: | 13 | 13 | 19 | 18 | 22 |
| - Hyperplasia: lymphoid | | - | 2 | 2 | 1 | 1 |
| - Plasmacytosis | | 1 | 2 | 3 | 1 | 2 |
| - Histiocytosis | | - | 2 | - | 1 | 1 |
| - Cyst | | 3 | 3 | 7 | 3 | 5 |
| - Inflammation | | - | - | 1 | - | - |
| - Erythrocytosis/hemorrhage: sinusal | | 4 | 2 | 4 | 8 | 5 |
| - Deposits: pigment | | 1 | - | 1 | 2 | - |
| L. NODE MANDIBULAR | EXAMIN: | 60 | 59 | 69 | 70 | 69 |
| - Erythrocytosis/hemorrhage | | 10 | 4 | 5 | 9 | 6 |
| - Hyperplasia: lymphoid | | 9 | 9 | 6 | 5 | 6 |
| - Plasmacytosis | | 2 | 5 | - | 2 | 2 |
| - Histiocytosis | | - | - | - | - | 1 |
| - Cyst | | 2 | 4 | 4 | 7 | 4 |
| - Deposits: pigment | | 1 | 1 | - | - | - |
| L.NODE MESENTERIC | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: lymphoid | | - | 2 | - | - | - |
| - Erythrocytosis/hemorrhage | | 2 | 2 | - | 7 | 5 |
| - Histiocytosis | | - | 1 | - | - | 1 |
| - Inflammation | | - | - | 1 | 1 | - |
| - Deposits: pigment | | - | - | 1 | 1 | - |
| - Cyst | | - | 1 | - | - | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| MAMMARY GLAND | EXAMIN: | 6 | 9 | 6 | 2 | - |
| - Ectasia: ducts and/or alveoli | | 4 | 8 | 5 | - | - |
| - Hyperplasia | | 2 | - | 1 | 1 | - |
| - Inflammation | | - | - | - | 1 | - |
| - Deposits: pigment | | - | 1 | - | - | - |
| MUSCLE SKELETAL | EXAMIN: | 60 | 60 | 69 | 70 | 68 |
| - Atrophy: myofiber | | - | 1 | - | 1 | - |
| - Infiltration: mixed cell | | - | 1 | - | - | - |
| MUSCLE SKELETAL MISC | EXAMIN: | - | 1 | - | 1 | - |
| NERVE OPTIC | EXAMIN: | 60 | 60 | 70 | 69 | 70 |
| NERVE SCIATIC | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | - | 1 | - | - | 1 |
| - Degeneration: nerve fiber | | - | 4 | 1 | 3 | - |
| PANCREAS | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: islet cell | | - | 1 | 1 | 1 | 2 |
| - Atrophy: acinar cell | | 7 | 1 | 4 | 1 | 1 |
| - Dilatation: duct | | - | 2 | - | - | - |
| - Cyst: islets | | 1 | - | - | - | - |
| - Inflammation | | - | 1 | - | - | - |
| PANCREAS | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Inflammation: vascular | | - | 1 | 1 | - | - |
| - Polyarteritis | | - | 2 | - | - | - |
| - Deposits: pigment | | 1 | - | - | - | - |
| PARATHYROID GLAND | EXAMIN: | 48 | 47 | 56 | 55 | 66 |
| - Hyperplasia | | 2 | - | 1 | - | 5 |
| PERICARDIUM | EXAMIN: | - | 1 | - | - | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| PITUITARY | EXAMIN: | 60 | 60 | 70 | 70 | 69 |
| - Hyperplasia: pars distalis | | 10 | 3 | 8 | 15 | 9 |
| - Cyst | | 9 | 2 | 4 | 11 | 6 |
| - Hemorrhage | | 1 | - | - | - | - |
| - Deposits: pigment | | - | - | 1 | - | - |
| PREPUTIAL GLAND | EXAMIN: | 60 | 59 | 70 | 70 | 70 |
| - Dilatation | | - | - | 1 | 1 | 2 |
| - Inflammation | | 10 | 7 | 3 | 5 | 2 |
| - Cyst | | - | 1 | - | - | - |
| PROSTATE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | 22 | 20 | 22 | 21 | 14 |
| RECTUM | EXAMIN: | - | 1 | 1 | - | - |
| - Parasite | | - | 1 | - | - | - |
| SALIV.GL. MANDIBULAR | EXAMIN: | 60 | 59 | 70 | 70 | 70 |
| SEMINAL VESICLE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | 2 | 1 | 2 | 2 | - |
| - Edema | | - | - | - | 1 | - |
| SKIN | EXAMIN: | 60 | 60 | 69 | 69 | 69 |
| - Hyperplasia: epidermal | | - | - | 1 | - | - |
| SKIN MISCELLANEOUS | EXAMIN: | 29 | 26 | 35 | 38 | 44 |
| - Scab | | 7 | 8 | 7 | 7 | 12 |
| - Erosion | | 2 | - | - | - | - |
| - Ulceration | | 13 | 13 | 19 | 18 | 20 |
| - Hyperplasia: epidermal | | 2 | 3 | 7 | 5 | 7 |
| - Inflammation | | 5 | 6 | 3 | 3 | 3 |
| - Pustule | | 10 | 9 | 3 | 12 | 14 |
| - Necrosis | | - | - | - | - | 3 |
| - Cyst: squamous | | - | - | 3 | 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 |
| **NUMBER OF ANIMALS EXAMINED** | | 60 | 60 | 70 | 70 | 70 |
| SPINAL CORD CERVICAL | EXAMIN: | 60 | 60 | 70 | 69 | 70 |
| - Degeneration: nerve fiber | | - | - | 1 | 3 | - |
| - Hemorrhage | | 1 | - | - | - | - |
| SPLEEN | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hematopoiesis: extramedullary | | 5 | 6 | 7 | 13 | 18 |
| - Hyperplasia: lymphoid | | 4 | 3 | 3 | 7 | 4 |
| - Atrophy: lymphoid | | 3 | 4 | 4 | 4 | 2 |
| - Cyst: capsular | | - | 1 | 1 | 1 | 1 |
| - Deposits: pigment | | 3 | 13 | 11 | 12 | 4 |
| - Congestion | | - | - | 1 | - | - |
| STOMACH | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | - | 1 | 1 | - | - |
| - Ulceration | | 2 | 1 | - | - | - |
| - Erosion | | 2 | 1 | 3 | 3 | - |
| - Edema | | 1 | - | - | 1 | - |
| - Dilatation: glandular | | - | 1 | - | 1 | - |
| - Hyperplasia: squamous mucosa | | 1 | - | - | - | - |
| - Cyst | | - | - | - | 1 | - |
| - Mineralization | | 1 | - | - | - | - |
| - Polyarteritis | | - | 1 | - | - | - |
| STOMACH | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Congestion | | 2 | 3 | - | 1 | 1 |
| SUBCUTANEOUS TISSUE | EXAMIN: | 2 | 5 | 5 | 4 | 2 |
| - Inflammation | | - | 1 | - | - | - |
| - Abscess | | - | 1 | - | - | - |
| - Fibrosis | | - | - | 2 | - | - |
| - Edema | | - | - | - | - | 2 |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| TAIL | EXAMIN: | 2 | 3 | 3 | - | - |
| - Inflammation | | 1 | 2 | - | - | - |
| - Abscess | | - | - | 1 | - | - |
| - Ulceration | | 1 | - | - | - | - |
| - Hemorrhage | | - | - | 1 | - | - |
| TESTIS | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Atrophy: seminiferous epithelium | | 8 | 8 | 11 | 18 | 7 |
| - Dilatation: tubular | | - | - | - | 3 | 2 |
| - Inflammation: vascular | | - | 2 | - | - | - |
| - Mineralization: tubular | | - | - | 1 | - | - |
| TESTIS | CONTD. | 60 | 60 | 70 | 70 | 70 |
| - Hemorrhage | | 2 | 1 | - | 1 | - |
| - Congestion | | 1 | - | - | - | - |
| - Exudate: subcapsular | | - | - | - | - | 1 |
| THORAX | EXAMIN: | - | - | - | - | 1 |
| THYMUS | EXAMIN: | 57 | 56 | 67 | 62 | 65 |
| - Atrophy/necrosis: lymphoid | | 54 | 53 | 65 | 61 | 62 |
| - Hemorrhage | | 1 | 1 | 1 | - | 2 |
| THYROID | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Cyst | | - | 1 | 2 | - | - |
| - Hyperplasia: C-cell | | 4 | 2 | 4 | 2 | 3 |
| TONGUE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | 1 | - | - | - | - |
| - Inflammation: vascular | | - | - | 1 | - | - |
| TRACHEA | EXAMIN: | 60 | 58 | 70 | 70 | 70 |
| - Inflammation | | - | 1 | - | - | - |

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

| | | MALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| URETER | EXAMIN: | 1 | - | 1 | 1 | 1 |
| - Dilatation | | 1 | - | 1 | 1 | 1 |
| - Inflammation | | - | - | 1 | 1 | - |
| URINARY BLADDER | EXAMIN: | 60 | 59 | 70 | 70 | 70 |
| - Dilatation | | 2 | - | - | 2 | - |
| - Hyperplasia: transitional cell | | 2 | 2 | 3 | 1 | - |
| - Inflammation | | 3 | 2 | 3 | 2 | - |
| - Hemorrhage | | 2 | - | - | 2 | - |
| - Adhesion | | - | - | - | 1 | - |
| ABDOMEN | EXAMIN: | 1 | 2 | - | - | - |
| ADRENAL | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: cortical focal zona glomerulosa | | 37 | 36 | 29 | 37 | 40 |
| - Hyperplasia: cortical focal | | 8 | 10 | 3 | 7 | 3 |
| - Hyperplasia: cortical | | 3 | 2 | 1 | 1 | - |
| - Degeneration: cystic | | 46 | 48 | 27 | 22 | 16 |
| - Necrosis | | - | - | 1 | - | - |
| - Hyperplasia: medullary | | 1 | 2 | 5 | 2 | 2 |
| - Vacuolation: cortical | | - | - | 1 | 1 | 1 |
| ADRENAL | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Hematopoiesis: extramedullary | | 2 | 2 | - | - | - |
| - Cyst | | - | - | 2 | 1 | 1 |
| - Congestion | | 3 | 5 | 7 | 6 | 8 |
| - Hemorrhage | | 31 | 18 | 14 | 15 | 6 |
| - Thrombosis | | 1 | - | - | - | - |
| - Deposits: pigment | | 1 | - | - | - | - |
| AORTA | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - 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 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| BILE DUCT | EXAMIN: | 1 | 3 | 3 | 10 | 3 |
| - Dilatation | | - | 3 | 3 | 9 | 3 |
| - Inflammation | | - | - | - | - | 1 |
| BONE-FEMUR | EXAMIN: | 60 | 60 | 69 | 70 | 70 |
| BONE MARROW | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Infiltration: adipose tissue | | 1 | - | - | - | - |
| - Atrophy | | 1 | - | - | - | 1 |
| - Necrosis | | - | - | - | 1 | - |
| BONE MISCELLANEOUS | EXAMIN: | - | - | - | - | 1 |
| - Fracture | | - | - | - | - | 1 |
| - Hemorrhage | | - | - | - | - | 1 |
| BONE-STERNUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| BRAIN | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Compression | | 21 | 31 | 15 | 12 | 6 |
| - Dilatation: ventricle | | 7 | 6 | 6 | 5 | 2 |
| - Aneurysm | | - | - | 1 | - | - |
| - Hemorrhage | | 2 | - | 3 | 2 | 1 |
| CAVITY CRANIAL | EXAMIN: | - | 1 | - | - | - |
| - Hemorrhage | | - | 1 | - | - | - |
| CECUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | - | 1 | 1 | - | - |
| - Ulceration | | - | - | - | 1 | - |
| - Edema | | 1 | 1 | 1 | - | 1 |
| CLITORAL GLAND | EXAMIN: | 59 | 57 | 70 | 67 | 70 |
| - Inflammation | | 3 | 2 | 2 | 5 | 3 |
| - Colloid retention | | 3 | - | - | 2 | 1 |
| - Cyst | | 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 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| COLON | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Edema | | 1 | - | - | - | - |
| - Parasite | | 3 | 4 | 3 | 13 | 1 |
| DIAPHRAGM | EXAMIN: | - | 1 | - | - | 1 |
| DUODENUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Infiltration: mononuclear cell | | - | - | - | 1 | - |
| - Erosion | | 2 | - | - | - | - |
| - Fibrosis | | - | 1 | - | - | - |
| ESOPHAGUS | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| EYE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Degeneration: retina | | 7 | 11 | 5 | 12 | 14 |
| - Degeneration: lens | | - | 1 | - | - | 1 |
| - Exudate: anterior compartment | | - | 1 | - | 1 | - |
| - Inflammation | | 1 | - | - | - | 1 |
| - Hemorrhage | | - | - | - | - | 1 |
| FAT | EXAMIN: | - | 4 | - | - | 1 |
| - Necrosis | | - | 2 | - | - | - |
| HARDERIAN GLAND | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hemorrhage | | - | - | - | - | 1 |
| HEART | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Fibrosis | | 2 | 1 | 2 | 1 | 3 |
| - Inflammation | | - | 1 | 3 | 1 | 1 |
| - Mineralization | | - | - | 1 | - | - |
| - Thrombosis | | - | - | - | 1 | - |
| - Endocardiosis: valvular | | - | - | - | - | 1 |
| - Hemorrhage | | - | - | - | - | 1 |
| HEMOLYM. TISSUE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| ILEUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: lymphoid (GALT) | | - | - | 1 | - | - |
| - Erosion | | - | - | - | - | 1 |
| - Hemorrhage | | - | - | - | - | 1 |
| I.S. DORSAL THORACIC | EXAMIN: | 60 | 59 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | 1 | 4 | 15 |
| - Hyperplasia: epidermis | | - | - | 3 | 22 | 46 |
| - Scab | | - | 2 | 4 | 9 | 24 |
| - Fibrosis: dermis | | - | - | 18 | 34 | 45 |
| - Fibrosis: subcutis | | 1 | - | 1 | 3 | 2 |
| - Inflammation: dermis | | - | - | - | 2 | 1 |
| - Inflammation: subcutis | | - | - | - | 2 | 5 |
| - Degeneration/inflammation: muscle | | - | - | - | 3 | 4 |
| - Hyperplasia: vascular intima | | - | - | - | 8 | 31 |
| I.S. DORSAL THORACIC | CONT'D. | 60 | 59 | 70 | 70 | 70 |
| - Erosion: epidermis | | - | - | - | - | 2 |
| - Ulceration | | - | - | - | 1 | 4 |
| - Hemorrhage: subcutis | | 1 | 5 | 1 | 4 | 4 |
| - Deposits: pigment | | - | - | - | 1 | 3 |
| - Edema: subcutis | | - | 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** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| I.S. DORS.THO. LT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | 1 | 4 | 13 |
| - Hyperplasia: epidermis | | - | - | 6 | 14 | 38 |
| - Scab | | - | - | 1 | 5 | 18 |
| - Fibrosis: dermis | | - | - | 18 | 24 | 35 |
| - Fibrosis: subcutis | | 1 | 1 | 3 | 2 | 2 |
| - Inflammation: dermis | | - | - | - | - | 1 |
| - Inflammation: subcutis | | - | 2 | - | 3 | 8 |
| - Degeneration/inflammation: muscle | | - | - | - | 5 | 15 |
| - Dilatation: follicles | | - | - | - | - | 2 |
| I.S. DORS.THO. LT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Epidermoid cyst | | - | 1 | - | - | - |
| - Erosion: epidermis | | - | - | - | 1 | 2 |
| - Ulceration | | - | - | - | 1 | 7 |
| - Hemorrhage: subcutis | | 1 | 4 | 2 | 2 | - |
| - Hyperplasia: vascular intima subcutis | | - | - | 3 | 10 | 30 |
| I.S. DORS.THO. RT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | 1 | 8 | 15 |
| - Hyperplasia: epidermis | | - | - | 4 | 7 | 41 |
| - Scab | | - | 1 | 2 | 2 | 15 |
| - Fibrosis: dermis | | - | - | 12 | 22 | 45 |
| - Fibrosis: subcutis | | - | 1 | 3 | 2 | 1 |
| - Inflammation: dermis | | - | - | - | - | 1 |
| - Inflammation: subcutis | | - | 1 | 1 | 1 | 4 |
| - Degeneration/inflammation: muscle | | - | - | - | 3 | 2 |
| - Erosion: epidermis | | - | - | 1 | - | 4 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| I.S. DORS.THO. RT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Ulceration | | - | - | - | - | 3 |
| - Hemorrhage: dermis | | - | - | 1 | - | 1 |
| - Hemorrhage: subcutis | | - | 3 | 2 | 3 | 5 |
| - Deposit: pigment subcutis | | - | - | - | - | 1 |
| - Edema: subcutis | | - | 2 | - | - | - |
| - Hyperplasia: vascular intima subcutis | | - | - | 2 | 20 | 34 |
| I.S. INTERSCAPULAR | EXAMIN: | - | 1 | 2 | 1 | 4 |
| - Scab | | - | - | - | - | 1 |
| - Hemorrhage: subcutis | | - | - | - | - | 2 |
| I.S. LUMBAR, LEFT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | 3 | 5 | 30 |
| - Hyperplasia: epidermis | | - | - | 2 | 24 | 45 |
| - Scab | | 1 | 1 | 1 | 1 | 14 |
| - Fibrosis: dermis | | - | 1 | 15 | 43 | 49 |
| - Fibrosis: subcutis | | - | - | 5 | 4 | 3 |
| - Inflammation: dermis | | - | 1 | 2 | - | 3 |
| - Inflammation: subcutis | | - | 1 | 2 | - | 5 |
| - Degeneration/inflammation: muscle | | - | - | 1 | 3 | - |
| - Erosion: epidermis | | - | - | - | - | 5 |
| I.S. LUMBAR, LEFT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Ulceration | | - | - | - | 2 | 1 |
| - Hyperplasia: vascular intima subcutis | | - | - | 2 | 27 | 33 |
| - Hemorrhage: subcutis | | 3 | 4 | 1 | 2 | 3 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| **DOSE GROUP** | | **1** | **2** | **3** | **4** | **5** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| I.S. LUMBAR, RIGHT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | 2 | 14 | 29 |
| - Hyperplasia: epidermis | | - | - | 4 | 14 | 46 |
| - Scab | | 2 | - | - | 3 | 7 |
| - Fibrosis: dermis | | - | 1 | 18 | 40 | 56 |
| - Inflammation: dermis | | - | - | 1 | - | - |
| - Fibrosis: subcutis | | - | - | 3 | 5 | 4 |
| - Inflammation: subcutis | | - | 1 | 1 | 3 | 1 |
| - Degeneration/inflammation: muscle | | - | - | 2 | 4 | - |
| - Erosion: epidermis | | - | - | 2 | - | 3 |
| I.S. LUMBAR, RIGHT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Ulceration | | 1 | - | - | 1 | 2 |
| - Hemorrhage: subcutis | | - | 7 | 5 | 7 | 7 |
| - Edema: subcutis | | - | - | - | - | 1 |
| - Hyperplasia: vascular intima | | - | - | 2 | 30 | 29 |
| I.S. SCAPULAR, LEFT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: epidermis | | - | - | 1 | 1 | 6 |
| - Scab | | - | - | 1 | 2 | 2 |
| - Fibrosis: dermis | | - | - | - | 2 | 10 |
| - Inflammation: dermis | | - | - | - | 1 | - |
| - Fibrosis: subcutis | | 1 | 1 | - | - | - |
| - Inflammation: subcutis | | 1 | - | - | - | - |
| - Degeneration/inflammation: muscle | | 1 | - | - | 1 | 2 |
| - Ulceration | | - | - | - | - | 2 |
| - Hemorrhage: subcutis | | - | 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 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| I.S. SCAPULAR, RIGHT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Reduced hair follicles | | - | - | - | - | 2 |
| - Hyperplasia: epidermis | | - | - | - | 1 | 5 |
| - Scab | | - | - | - | - | 2 |
| - Fibrosis: dermis | | - | - | - | - | 7 |
| - Inflammation: dermis | | - | - | - | - | 1 |
| - Inflammation: subcutis | | - | 1 | 1 | - | - |
| - Degeneration/inflammation: muscle | | - | - | - | 1 | - |
| - Hyperplasia: vascular intima | | - | - | - | 1 | - |
| - Ulceration | | - | 1 | - | - | 3 |
| I.S. SCAPULAR, RIGHT | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Hemorrhage: subcutis | | - | 2 | - | - | - |
| - Edema: subcutis | | - | 1 | 1 | - | - |
| JEJUNUM | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | 1 | - | - | 1 | - |
| - Hyperplasia: muscularis | | - | - | - | 1 | - |
| JOINT | EXAMIN: | 1 | - | 1 | 1 | - |
| - Inflammation | | 1 | - | 1 | - | - |
| - Hyperostosis | | - | - | - | 1 | - |
| KIDNEY | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Glomerulonephritis/glomerulopathy | | 9 | 7 | 2 | 2 | - |
| - Nephropathy | | 1 | - | - | - | - |
| - Pyelitis/pyelonephritis | | 1 | 4 | 5 | - | 2 |
| - Inflammation | | 2 | 1 | 3 | 1 | - |
| - Inflammation: interstitial | | 1 | - | 3 | 3 | 2 |
| - E.coli: bacterial | | - | - | - | 1 | - |
| - Dilatation: pelvis | | 3 | 6 | 8 | 3 | 5 |
| - Hyperplasia: transitional cell | | 10 | 15 | 10 | 3 | 6 |
| - Mineralization: pelvis epithelium | | 13 | 11 | 7 | 1 | - |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| KIDNEY | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Dilatation: tubular | | 2 | - | - | - | - |
| - Basophilia: tubular | | - | - | - | 1 | - |
| - Cyst | | 1 | 1 | 1 | 1 | 2 |
| - Hyaline droplet: tubular | | 3 | 4 | 1 | - | 3 |
| - Hemorrhage | | - | 2 | - | - | - |
| - Congestion | | 4 | 4 | 3 | 4 | 6 |
| LACRIMAL GLAND | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hardertanisation | | - | - | 1 | 1 | - |
| - Infiltration: mononuclear cell | | - | - | - | - | 1 |
| LACRIMAL GLAND | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Amyloidosis | | - | - | 1 | - | - |
| LARYNX | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation: ventral pouch | | 4 | 2 | 2 | 1 | 4 |
| - Inflammation | | - | 3 | - | 2 | 1 |
| - Hyperplasia: epithelial | | - | 2 | - | - | - |
| - Dilated | | - | - | - | - | 1 |
| - Hemorrhage | | - | - | - | | - |
| LIVER | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Basophilic cell focus | | 3 | 8 | 1 | 3 | 3 |
| - Eosinophilic cell focus | | 10 | 7 | 6 | 5 | 3 |
| - Hyperplasia: bile duct | | 3 | 6 | 9 | 7 | 4 |
| - Tension lipidosis | | 6 | 5 | 6 | 3 | 2 |
| - Vacuolation: perinatal | | - | 1 | - | - | - |
| - Hematopoiesis: extramedullary | | 4 | 2 | 4 | 4 | 3 |
| - Inflammation | | - | 1 | - | - | - |
| - Inflammation: biliary | | 1 | 5 | 2 | 4 | 2 |
| - Necrosis | | 5 | 4 | 1 | 4 | 2 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| LIVER | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Necrosis: single cell | | 1 | - | 1 | - | - |
| - Fibrosis | | 1 | - | 2 | - | 1 |
| - Cyst: biliary | | - | 3 | - | 3 | 1 |
| - Adhesion | | 1 | - | - | - | 2 |
| - Dilatation: sinusoidal with congestion | | 9 | 6 | 4 | 6 | - |
| - Atrophy | | - | - | 1 | 2 | 1 |
| - Congestion | | 2 | - | 3 | 3 | - |
| - Deposits: pigment | | 1 | - | - | 3 | - |
| LUNG | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: alveolar epithelium | | - | 1 | 1 | 1 | - |
| - Macrophage accumulation | | 3 | 5 | 17 | 12 | 19 |
| - Inflammation | | 1 | 1 | - | - | - |
| - Infiltration: mononuclear cell | | - | - | - | - | 1 |
| - Granuloma | | - | - | 1 | - | - |
| - Mineralization: vascular | | - | - | - | 1 | 2 |
| - Fibrosis: pleura | | - | - | 1 | 1 | 3 |
| - Deposits: pigment | | - | 1 | - | - | - |
| - Congestion | | - | - | 1 | - | - |
| LUNG | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Hemorrhage | | - | - | 2 | 3 | 2 |
| LYMPH NODE | EXAMIN: | 30 | 28 | 33 | 22 | 19 |
| - Hyperplasia: lymphoid | | 3 | 1 | 5 | - | 1 |
| - Plasmacytosis | | 3 | 2 | 2 | 2 | 3 |
| - Histiocytosis | | 3 | 2 | 1 | - | 3 |
| - Cyst | | - | 1 | 1 | - | 1 |
| - Erythrocytosis/hemorrhage: sinusal | | 7 | 7 | 7 | 3 | 2 |
| - Deposits: pigment | | 2 | 6 | 4 | 4 | 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** |
| **NUMBER OF ANIMALS EXAMINED** | | **60** | **60** | **70** | **70** | **70** |
| LYMPH NODE | CONT'D. | 30 | 28 | 33 | 22 | 19 |
| - Congestion | | - | - | 1 | - | - |
| L. NODE MANDIBULAR | EXAMIN: | 58 | 59 | 70 | 70 | 67 |
| - Erythrocytosis/hemorrhage | | 6 | 11 | 7 | 6 | 11 |
| - Hyperplasia: lymphoid | | 5 | 1 | 4 | 1 | - |
| - Plasmacytosis | | 10 | 3 | 3 | 11 | 6 |
| - Histiocytosis | | - | 1 | 1 | - | 3 |
| - Cyst | | 1 | 1 | 1 | 1 | 3 |
| - Deposits: pigment | | - | 1 | 2 | 5 | 1 |
| L.NODE MESENTERIC | EXAMIN: | 60 | 60 | 68 | 70 | 69 |
| - Hyperplasia: lymphoid | | 2 | 1 | - | - | 2 |
| - Erythrocytosis/hemorrhage | | 3 | 5 | 2 | 4 | 8 |
| - Histiocytosis | | 1 | - | - | 2 | 1 |
| - Deposits: pigment | | 6 | - | 1 | 4 | 3 |
| - Cyst | | - | - | 2 | 1 | 1 |
| MAMMARY GLAND | EXAMIN: | 60 | 60 | 70 | 69 | 69 |
| - Fibrosis | | - | - | 1 | - | - |
| - Ectasia: ducts and/or alveoli | | 4 | 4 | 3 | 4 | 1 |
| - Hyperplasia | | 11 | 20 | 16 | 16 | 9 |
| - Hyperplasia: nodular | | 1 | 5 | 3 | 2 | 1 |
| - Cyst | | 2 | - | - | - | 2 |
| - Inflammation | | - | - | - | 1 | - |
| MUSCLE SKELETAL | EXAMIN: | 59 | 59 | 70 | 70 | 70 |
| - Atrophy: myofiber | | - | - | - | - | 1 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| MUSCLE SKELETAL MISC | EXAMIN: | - | 1 | 1 | 2 | 1 |
| - Hemorrhage | | - | 1 | - | 2 | 1 |
| NERVE OPTIC | EXAMIN: | 60 | 60 | 69 | 70 | 70 |
| NERVE SCIATIC | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | - | - | - | 1 | - |
| - Degeneration: nerve fiber | | 1 | 1 | 2 | 2 | 1 |
| OVARY | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: tubular | | 1 | 3 | 1 | 1 | 1 |
| - Hyperplasia: tubulostromal | | 5 | 1 | 1 | - | 3 |
| - Mesothelial proliferation | | 1 | - | - | - | - |
| - Cyst: follicular | | 11 | 9 | 12 | 18 | 15 |
| - Cyst: bursal | | 1 | 3 | 8 | 6 | 2 |
| - Hemorrhage | | - | 1 | - | - | 1 |
| OVIDUCT | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Dilatation | | - | - | - | - | 1 |
| PANCREAS | EXAMIN: | 60 | 59 | 69 | 70 | 70 |
| - Hyperplasia: islet cell | | 1 | - | - | - | - |
| - Atrophy: acinar cell | | 2 | - | - | 1 | 1 |
| - Degranulation | | - | - | - | 1 | - |
| - Inflammation | | - | 1 | 1 | - | 1 |
| - Inflammation: vascular | | 1 | - | - | - | - |
| - Polyarteritis | | - | - | 1 | - | - |
| - Thrombosis | | - | - | - | 1 | - |
| PARATHYROID GLAND | EXAMIN: | 47 | 49 | 53 | 50 | 65 |
| - Hyperplasia | | 2 | - | 2 | 2 | - |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| PITUITARY | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: pars distalis | | 4 | 3 | 1 | 3 | 5 |
| - Cyst | | 2 | 3 | 1 | 6 | 4 |
| - Hemorrhage | | - | 1 | 2 | - | - |
| - Deposits: pigment | | - | - | - | - | 1 |
| RECTUM | EXAMIN: | 1 | 1 | - | - | - |
| SALIV.GL. MANDIBULAR | EXAMIN: | 60 | 59 | 70 | 70 | 70 |
| SKIN | EXAMIN: | 60 | 60 | 70 | 69 | 69 |
| - Scab | | - | - | - | 1 | - |
| SKIN MISCELLANEOUS | EXAMIN: | 21 | 28 | 36 | 43 | 51 |
| - Scab | | 5 | 6 | 9 | 7 | 23 |
| - Erosion | | - | - | - | 1 | - |
| - Ulceration | | 8 | 10 | 5 | 11 | 13 |
| - Hyperplasia: epidermal | | 1 | 4 | 5 | 2 | 6 |
| - Inflammation | | 2 | 4 | 7 | 2 | 9 |
| - Pustule | | 8 | 15 | 13 | 24 | 13 |
| - Necrosis | | - | - | 2 | 1 | - |
| - Abnormal mitotic figures | | - | - | 1 | - | - |
| - Hyperplasia: chondroid | | 1 | - | - | - | - |
| SKIN MISCELLANEOUS | CONT'D. | 21 | 28 | 36 | 43 | 51 |
| - Cyst: squamous | | - | - | 2 | - | - |
| SPINAL CORD CERVICAL | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Degeneration: nerve fiber | | - | 1 | - | - | - |
| SPLEEN | EXAMIN: | 60 | 60 | 69 | 70 | 70 |
| - Hematopoiesis: extramedullary | | 13 | 22 | 17 | 9 | 9 |
| - Hyperplasia: lymphoid | | 4 | 7 | 2 | 4 | 4 |
| - Atrophy: lymphoid | | 1 | 4 | 7 | 5 | 7 |
| - Cyst: capsular | | - | 1 | 1 | 1 | 1 |
| - Deposits: pigment | | 37 | 37 | 39 | 45 | 39 |

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

**All Animals**

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| SPLEEN | CONT'D. | 60 | 60 | 69 | 70 | 70 |
| - Fibrosis: capsular | | - | - | 1 | 1 | - |
| STOMACH | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | - | - | - | - | 1 |
| - Ulceration | | - | - | 1 | 1 | - |
| - Erosion | | 4 | 4 | 4 | 1 | 3 |
| - Edema | | - | - | 1 | 1 | 1 |
| - Dilatation: glandular | | - | 2 | 3 | 2 | - |
| - Hyperplasia: squamous mucosa | | 1 | 2 | - | - | - |
| - Cyst | | 1 | - | - | - | - |
| STOMACH | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Congestion | | 1 | 1 | - | - | - |
| SUBCUTANEOUS TISSUE | EXAMIN: | 5 | 3 | 6 | 6 | 4 |
| - Fibrosis | | - | - | 1 | - | - |
| - Edema | | - | 2 | 1 | - | - |
| - Hemorrhage | | 1 | 1 | - | - | 2 |
| TAIL | EXAMIN: | 2 | 2 | 3 | 1 | 2 |
| - Inflammation | | - | 1 | 1 | - | - |
| - Ulceration | | 1 | 1 | - | - | 1 |
| - Hyperplasia: epidermal | | - | - | 1 | - | - |
| THORAX | EXAMIN: | 1 | 2 | 1 | - | 1 |
| - Hemorrhage | | - | - | - | - | 1 |
| THYMUS | EXAMIN: | 54 | 57 | 66 | 69 | 63 |
| - Atrophy/necrosis: lymphoid | | 49 | 52 | 62 | 66 | 60 |
| - Hyperplasia: lymphoid | | - | - | - | 1 | 1 |
| - Cyst | | 4 | 1 | 5 | 5 | 3 |
| - Hemorrhage | | 1 | 3 | 4 | 1 | 2 |
| - Deposits: pigment | | 1 | - | - | - | - |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| THYROID | EXAMIN: | 60 | 59 | 70 | 70 | 70 |
| - Cyst | | 2 | - | 1 | - | - |
| - Hyperplasia: C-cell | | 3 | 2 | 5 | 5 | - |
| TONGUE | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Hyperplasia: epithelial | | - | 1 | - | - | - |
| - Inflammation: vascular | | - | - | - | 1 | - |
| - Congestion | | - | 1 | - | - | - |
| TRACHEA | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Inflammation | | 1 | - | - | - | - |
| URETER | EXAMIN: | 2 | 3 | 4 | 1 | 2 |
| - Dilatation | | 1 | 3 | 4 | 1 | 2 |
| - Inflammation | | - | 3 | 1 | - | 1 |
| - Hyperplasia: transitional cell | | - | - | 1 | - | - |
| URETHRA | EXAMIN: | - | - | 1 | - | - |
| - Dilatation | | - | - | 1 | - | - |
| - Inflammation | | - | - | 1 | - | - |
| URINARY BLADDER | EXAMIN: | 59 | 60 | 70 | 70 | 70 |
| - Polyp | | - | - | - | - | 1 |
| - Dilatation | | 1 | 1 | - | - | - |
| - Hyperplasia: transitional cell | | 2 | 5 | 3 | - | 3 |
| - Infiltration: mononuclear cell | | 1 | - | 2 | - | - |
| - Inflammation | | 2 | 5 | 5 | - | 1 |
| - Edema | | - | - | - | - | 1 |
| - Adhesion | | - | - | - | - | 1 |

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

| | | FEMALE | | | | |
|---|---|---|---|---|---|---|
| DOSE GROUP | | 1 | 2 | 3 | 4 | 5 |
| NUMBER OF ANIMALS EXAMINED | | 60 | 60 | 70 | 70 | 70 |
| UTERUS | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Prolapse | | 1 | - | - | - | - |
| - Hyperplasia: glandular focal | | 3 | 1 | 1 | - | 1 |
| - Hyperplasia: endometrial cystic | | - | - | - | 3 | - |
| - Hyperplasia: squamous cell | | - | - | 1 | 1 | - |
| - Dilatation | | 1 | 3 | 9 | 9 | 6 |
| - Cyst | | 10 | 11 | 15 | 16 | 10 |
| - Hyperplasia: smooth muscle | | 1 | 2 | 3 | 5 | 2 |
| - Hyperplasia: endometrial stroma | | 2 | - | - | - | - |
| - Inflamration | | - | 1 | 2 | 1 | 1 |
| UTERUS | CONT'D. | 60 | 60 | 70 | 70 | 70 |
| - Deposits: pigment | | - | - | - | 2 | - |
| VAGINA | EXAMIN: | 60 | 60 | 70 | 70 | 70 |
| - Prolapsed polyp | | - | - | 1 | - | - |
| - Fibrosis | | - | 1 | - | - | - |
| - Cyst | | - | - | - | 1 | - |
| - Inflammation | | - | - | 1 | - | - |
| - Edema | | - | 1 | - | - | - |

**Study title: Lanreotide (BIM23014): A 104-Week Subcutaneous Injection Carcinogenicity Study in the Albino Mouse**

**Key study findings**: BIM23014 was administered by daily s.c. injection for 104 weeks at dose levels of 0, 0.5, 1.5, 5, 10 and 30mg/kg/d to male and female mice. Each predetermined injection site was scheduled for dosing 120 times during the 104 weeks of treatment.

- Reduced survival was observed in both male and female mice at 30 mg/kg/d, mainly due to compound-related dermal changes at the injection sites leading to premature euthanasia for humane reason from Week 87.
- Statistically significant decreases in mean body weight were 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 concurrent controls.
- Drug-related changes in treated animals were mainly limited to clinical and histopathological changes at the injections sites. A range of non-neoplastic lesions were observed at the injection sites, including subcutaneous and/or dermal fibrosis, panniculus muscle degeneration, epidermal hyperplasia, epidermal ulceration, subcutaneous vascular inflammation/degeneration/necrosis or vascular intimal thickening/medial hypertrophy that were considered to be due to the prolonged and repetitive injection of either vehicle or test article.
- Drug-related neoplastic changes were observed at injection sites and consisted of subcutaneous fibrosarcoma and malignant fibrous histiocytoma, primarily observed in animals treated at 30mg/kg/d, while the incidence was very low in males at 10 mg/kg/d and in females at 0.5, 5, and 10 mg/kg/d. Though the tumor incidence at lower doses was higher than that in concurrent controls, they fell within the historical incidence range and mean value.
- Metastasis of fibrosarcoma were seen in the draining lymph nodes of 2/70 males at 30 mg/kg/d.
- All other systemic neoplastic lesions seen in mice were commonly encountered in animals of this strain and age compared to the NTP historical control data.
- AUC at 30 mg/kg/d with local tumorigenicity was 10993.5 ng/ml.h (sex combined), which would achieve 3X exposures the human highest dose. However, since no other drug-related tumors were found with systemic exposure, local effect of supersaturated salt of the drug at injections sites might be the major cause of these fibrous connective tissue tumors.

Adequacy of the carcinogenicity study and appropriateness of the test model:
According to the sponsor, *"dose selection was based on the results of two preliminary 13-week dose ranging studies"*, which demonstrated that *"30 mg/kg/day was the MTD indicated by a body weight decrease of 12% in males and 29% in females and by increased incidence of slight skin lesions at the injection sites"*. However, the protocol and dose selection were not prior assessed by the ECAC.

Upon review of the two dose ranging studies, dose levels tested in the first 13-week study (77004) at 0.5, 1, and 5 mg/kg/d were too low to define a MTD or any other parameters. In the second dose ranging study (800036), 10, 30, and 60 mg/kg/d of lanreotide were

tested with daily s.c. injection, 1/15 mice died at 60 mg/kg/d; at 30 mg/kg/d, body weight decreased 8% in M and 12% in F, and slight miscellaneous changes in hematology and serum chemistry as well as higher incidences in injection site inflammation and muscle degeneration compared to controls were observed. Although the effect of body weight at $\geq$ 30 mg/kg/d is likely related to pharmacological activity of the drug and the weight effect is a less sensitive indicator in the mouse of a MTD, the upper dose 60 mg/kg/d has induced mortality, therefore 30 mg/kg/d as a HD for the 2-year assay appeared acceptable based on clinical pathology changes and injection site skin lesions (in the 2-year study, animals at this dose level had higher mortality and were premature euthanized in Weeks 87 for males and 97 for females due to drug-related dermal lesions for humane reason, so 30 mg/kg/d may have exceeded the MTD). AUC at 30 mg/kg/d with local tumorigenicity was 10993.5 ng/ml.h (sex combined), which achieved 3X exposures that at the human highest dose.

It is also noted that the dosing regimen in animals with daily injection was not relevant to that in clinic use as once every 4 weeks. In this case, it is assumed that the animal cutaneous/ subcutaneous tissue reactions should be surpassing the severity in humans; therefore it is acceptable for extrapolating the mouse local toxicity to humans though it was not an ideal design. In general, the study design appears relatively acceptable and the assay is considered valid.

Evaluation of tumor findings:
Reduced survival was observed in animals treated at 30mg/kg/d mainly due to compound-related dermal changes at the injection sites leading to premature euthanasia of the animals in Weeks 87 (males) and 97 (females). The survival rate of the animals treated at 0.5, 1.5, 5 arid 10 mg/kg/day was comparable to that of the two control groups.

Neoplastic changes were only observed at injection sites and consisted of subcutaneous fibrosarcoma and malignant fibrous histiocytoma observed in animals treated at 30mg/kg/d with statistically significance (please see the agency's statistics review in DFS), while the incidence was very low in males at 10 mg/kg/d and in females at 0.5, 5, and 10 mg/kg/d without statistically significance when compared to controls. Metastasis of fibrosarcoma were seen in the draining lymph nodes of 2/70 males at 30 mg/kg/d. The incidence of neoplastic changes tended to be higher when BIM23014 was dosed in the dorsal and lumbar injection sites than in the scapular injection sites. These tumors seen at lower doses did not show any dose relationship. No neoplastic changes were observed in males treated at 0.5 and 5 mg/kg/d. Though the tumor incidence at lower doses was higher than that in concurrent controls, they fell within the historical incidence range and the mean value (please see the Appendix for the testing lab's historical control data at the end of this review), suggesting that the effect is not treatment-related. Incidence of all other systemic neoplastic lesions seen in treated mice was comparable with that of concurrent controls.

Since no other drug-related and remarkably increased tumors were found due to systemic drug exposure, local effect of supersaturated salt of the drug at injections sites in association with highly frequent injections appears to be the major cause of these fibrous