

## Supplementary Data 5. Histopathological Findings in rats – Recovery Phase

| Removal Reason(s): Scheduled Euthanasia-Termination(Recovery Phase)<br>Summary: Incidence | Male                       |                             | Female                     |                             |
|-------------------------------------------------------------------------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
|                                                                                           | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day |
| Number of Animals:                                                                        | 5                          | 5                           | 5                          | 5                           |
| Number of Completed Animals:                                                              | 5                          | 5                           | 5                          | 5                           |
| <b>Adrenal Glands</b>                                                                     |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Aorta</b>                                                                              |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Bone Marrow, Sternum</b>                                                               |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Bone, Sternum</b>                                                                      |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Bone, Femur, Including Stifle Joint</b>                                                |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 4                           | 4                          | 5                           |
| Increased Thickness; Growth Plate; Segmental                                              | 0                          | 1                           | 1                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 1                          | 0                           |
| <b>Brain</b>                                                                              |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Epididymides</b>                                                                       |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | .                          | .                           |
| No Visible Lesions                                                                        | 5                          | 4                           | .                          | .                           |
| Cell Debris; Duct; Diffuse, Bilateral                                                     | 0                          | 1                           | .                          | .                           |
| .... Mild                                                                                 | 0                          | 1                           | .                          | .                           |
| Hypospermia; Luminal, Duct; Diffuse, Bilateral                                            | 0                          | 1                           | .                          | .                           |
| .... Moderate                                                                             | 0                          | 1                           | .                          | .                           |
| <b>Esophagus</b>                                                                          |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Eyes</b>                                                                               |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Nerve(S), Optic</b>                                                                    |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Fallopian Tubes</b>                                                                    |                            |                             |                            |                             |
| Examined                                                                                  | .                          | .                           | 5                          | 5                           |
| No Visible Lesions                                                                        | .                          | .                           | 5                          | 5                           |
| <b>Harderian Glands</b>                                                                   |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 3                           | 5                          | 5                           |
| Infiltration; Mononuclear Cell, Focal, Bilateral                                          | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 0                           |
| Infiltration; Mononuclear Cell, Multifocal, Unilateral                                    | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 0                           |
| <b>Heart</b>                                                                              |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 4                           | 5                          | 4                           |

## Supplementary Data 5. Histopathological Findings in rats– Recovery Phase (continued)

| Removal Reason(s): Scheduled Euthanasia-Termination(Recovery Phase)<br>Summary: Incidence | Male                       |                             | Female                     |                             |
|-------------------------------------------------------------------------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
|                                                                                           | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day |
| Number of Animals:                                                                        | 5                          | 5                           | 5                          | 5                           |
| Number of Completed Animals:                                                              | 5                          | 5                           | 5                          | 5                           |
| <b>Heart (Continued...)</b>                                                               |                            |                             |                            |                             |
| Infiltration; Mononuclear Cell, Myocardium; Focal                                         | 0                          | 1                           | 0                          | 1                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 1                           |
| <b>Kidneys</b>                                                                            |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 3                          | 3                           | 4                          | 5                           |
| Infarct; Chronic, Cortex; Medulla; Focal, Unilateral                                      | 0                          | 0                           | 1                          | 0                           |
| .... Minimal                                                                              | 0                          | 0                           | 1                          | 0                           |
| Inflammation; Lymphohistiocytic, Medulla; Focal, Unilateral                               | 1                          | 0                           | 0                          | 0                           |
| .... Minimal                                                                              | 1                          | 0                           | 0                          | 0                           |
| Mineralization; Medulla; Focal                                                            | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 0                           |
| Cyst; Medulla; Multifocal, Unilateral                                                     | 0                          | 1                           | 0                          | 0                           |
| .... Present                                                                              | 0                          | 1                           | 0                          | 0                           |
| Dilation; Tubule; Focal, Unilateral                                                       | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 0                           |
| Infiltration; Mononuclear Cell, Interstitium; Focal, Bilateral                            | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 0                           |
| Infiltration; Mononuclear Cell, Interstitium; Focal, Unilateral                           | 1                          | 0                           | 0                          | 0                           |
| .... Minimal                                                                              | 1                          | 0                           | 0                          | 0                           |
| <b>Large Intestine, Cecum</b>                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Large Intestine, Colon</b>                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Large Intestine, Rectum</b>                                                            |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Liver</b>                                                                              |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 4                          | 5                           | 4                          | 4                           |
| Infiltration; Mononuclear Cell, Portal; Perivascular; Multifocal                          | 1                          | 0                           | 1                          | 1                           |
| .... Minimal                                                                              | 1                          | 0                           | 1                          | 1                           |
| <b>Lungs With Mainstem Bronchi</b>                                                        |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 3                          | 5                           | 5                          | 4                           |
| Mineralization; Vascular Wall; Focal                                                      | 0                          | 0                           | 0                          | 1                           |
| .... Minimal                                                                              | 0                          | 0                           | 0                          | 1                           |
| Metaplasia; Osseous, Alveolus; Focal                                                      | 1                          | 0                           | 0                          | 0                           |
| .... Present                                                                              | 1                          | 0                           | 0                          | 0                           |
| Granuloma; Alveolus; Focal                                                                | 1                          | 0                           | 0                          | 0                           |
| .... Minimal                                                                              | 1                          | 0                           | 0                          | 0                           |
| <b>Lymph Node, Mandibular</b>                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |

## Supplementary Data 5. Histopathological Findings in rats– Recovery Phase (continued)

| Removal Reason(s): Scheduled Euthanasia-Termination(Recovery Phase)<br>Summary: Incidence | Male                       |                             | Female                     |                             |
|-------------------------------------------------------------------------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
|                                                                                           | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day |
| Number of Animals:                                                                        | 5                          | 5                           | 5                          | 5                           |
| Number of Completed Animals:                                                              | 5                          | 5                           | 5                          | 5                           |
| <b>Lymph Node, Mesenteric</b>                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 4                          | 5                           |
| Erythrophagocytosis; Sinusoid; Multifocal                                                 | 0                          | 0                           | 1                          | 0                           |
| .... Mild                                                                                 | 0                          | 0                           | 1                          | 0                           |
| <b>Mammary Gland, Inguinal</b>                                                            |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Nerves, Sciatic</b>                                                                    |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 4                          | 5                           |
| Infiltration; Inflammatory Cell, Peripheral; Multifocal                                   | 0                          | 0                           | 1                          | 0                           |
| .... Minimal                                                                              | 0                          | 0                           | 1                          | 0                           |
| <b>Ovaries</b>                                                                            |                            |                             |                            |                             |
| Examined                                                                                  | .                          | .                           | 5                          | 5                           |
| No Visible Lesions                                                                        | .                          | .                           | 5                          | 5                           |
| <b>Pancreas</b>                                                                           |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Pituitary Gland</b>                                                                    |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 4                          | 4                           | 5                          | 4                           |
| Atrophy; Pars Distalis; Diffuse                                                           | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 0                           |
| <b>Pituitary Gland (Continued...)</b>                                                     |                            |                             |                            |                             |
| Cyst; Pars Distalis; Focal                                                                | 1                          | 0                           | 0                          | 1                           |
| .... Present                                                                              | 1                          | 0                           | 0                          | 1                           |
| <b>Prostate Gland</b>                                                                     |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | .                          | .                           |
| No Visible Lesions                                                                        | 1                          | 1                           | .                          | .                           |
| Atrophy; Acinus; Diffuse                                                                  | 0                          | 1                           | .                          | .                           |
| .... Minimal                                                                              | 0                          | 1                           | .                          | .                           |
| Infiltration; Inflammatory Cell, Interstitium; Multifocal                                 | 4                          | 3                           | .                          | .                           |
| .... Minimal                                                                              | 3                          | 3                           | .                          | .                           |
| .... Mild                                                                                 | 1                          | 0                           | .                          | .                           |
| <b>Salivary Gland, Mandibular</b>                                                         |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Seminal Vesicles</b>                                                                   |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | .                          | .                           |
| No Visible Lesions                                                                        | 5                          | 4                           | .                          | .                           |
| Atrophy; Acinus; Diffuse, Bilateral                                                       | 0                          | 1                           | .                          | .                           |
| .... Minimal                                                                              | 0                          | 1                           | .                          | .                           |
| <b>Skeletal Muscle, Biceps Femoris</b>                                                    |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Skin, Inguinal</b>                                                                     |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |

## Supplementary Data 5. Histopathological Findings in rats– Recovery Phase (continued)

| Removal Reason(s): Scheduled Euthanasia-Termination(Recovery Phase)<br>Summary: Incidence | Male                       |                             | Female                     |                             |
|-------------------------------------------------------------------------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
|                                                                                           | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day |
| Number of Animals:                                                                        | 5                          | 5                           | 5                          | 5                           |
| Number of Completed Animals:                                                              | 5                          | 5                           | 5                          | 5                           |
| <b>Skin, Inguinal (Continued...)</b>                                                      |                            |                             |                            |                             |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Small Intestine, Duodenum</b>                                                          |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Small Intestine, Ileum</b>                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Small Intestine, Jejunum</b>                                                           |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Spinal Cord, Cervical, Thoracic, Lumbar</b>                                            |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Spleen</b>                                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 4                          | 5                           | 4                          | 4                           |
| Extramedullary Hematopoiesis; Increased, Red Pulp; Multifocal                             | 1                          | 0                           | 1                          | 1                           |
| .... Minimal                                                                              | 1                          | 0                           | 0                          | 1                           |
| .... Mild                                                                                 | 0                          | 0                           | 1                          | 0                           |
| Decreased Cellularity; Lymphocytic, Marginal Zone; White Pulp; Diffuse                    | 0                          | 0                           | 1                          | 0                           |
| .... Mild                                                                                 | 0                          | 0                           | 1                          | 0                           |
| <b>Stomach</b>                                                                            |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 3                          | 2                           | 3                          | 4                           |
| Infiltration; Inflammatory Cell, Submucosa; Focal                                         | 1                          | 0                           | 0                          | 1                           |
| .... Minimal                                                                              | 1                          | 0                           | 0                          | 1                           |
| Vacuolation; Epithelial, Non-Glandular; Mucosa; Multifocal                                | 1                          | 3                           | 2                          | 1                           |
| .... Minimal                                                                              | 1                          | 3                           | 2                          | 1                           |
| Hyperkeratosis; Mucosa; Epithelium; Segmental                                             | 1                          | 3                           | 1                          | 0                           |
| .... Minimal                                                                              | 1                          | 3                           | 1                          | 0                           |
| <b>Testes</b>                                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | .                          | .                           |
| No Visible Lesions                                                                        | 5                          | 4                           | .                          | .                           |
| Degeneration/Atrophy; Seminiferous Tubule; Multifocal, Bilateral                          | 0                          | 1                           | .                          | .                           |
| .... Mild                                                                                 | 0                          | 1                           | .                          | .                           |
| <b>Thymus</b>                                                                             |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |
| <b>Thyroid Glands</b>                                                                     |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 4                           | 4                          | 5                           |
| Lymphoid Tissue; Interstitium; Focal, Unilateral                                          | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                              | 0                          | 1                           | 0                          | 0                           |
| Ectopia-Thymus                                                                            | 0                          | 0                           | 1                          | 0                           |
| <b>Parathyroid Gland(S)</b>                                                               |                            |                             |                            |                             |
| Examined                                                                                  | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                        | 5                          | 5                           | 5                          | 5                           |

## Supplementary Data 5. Histopathological Findings in rats– Recovery Phase (continued)

| Removal Reason(s): Scheduled Euthanasia-Termination(Recovery Phase)<br>Summary: Incidence      | Male                       |                             | Female                     |                             |
|------------------------------------------------------------------------------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
|                                                                                                | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day | Group 1,<br>0<br>mg/kg/day | Group 4,<br>12<br>mg/kg/day |
| Number of Animals:                                                                             | 5                          | 5                           | 5                          | 5                           |
| Number of Completed Animals:                                                                   | 5                          | 5                           | 5                          | 5                           |
| <b>Trachea</b>                                                                                 |                            |                             |                            |                             |
| Examined                                                                                       | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                             | 5                          | 5                           | 5                          | 5                           |
| <b>Urinary Bladder</b>                                                                         |                            |                             |                            |                             |
| Examined                                                                                       | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                             | 4                          | 5                           | 5                          | 4                           |
| Infiltration; Inflammatory Cell, Serosa; Muscularis; Focal                                     | 1                          | 0                           | 0                          | 0                           |
| .... Mild                                                                                      | 1                          | 0                           | 0                          | 0                           |
| Infiltration; Mononuclear Cell, Submucosa; Muscularis; Multifocal                              | 0                          | 0                           | 0                          | 1                           |
| .... Mild                                                                                      | 0                          | 0                           | 0                          | 1                           |
| <b>Uterus</b>                                                                                  |                            |                             |                            |                             |
| Examined                                                                                       | .                          | .                           | 5                          | 5                           |
| No Visible Lesions                                                                             | .                          | .                           | 1                          | 2                           |
| Dilation; Bilateral                                                                            | .                          | .                           | 4                          | 3                           |
| .... Minimal                                                                                   | .                          | .                           | 1                          | 0                           |
| .... Mild                                                                                      | .                          | .                           | 3                          | 3                           |
| <b>Cervix</b>                                                                                  |                            |                             |                            |                             |
| Examined                                                                                       | .                          | .                           | 5                          | 5                           |
| No Visible Lesions                                                                             | .                          | .                           | 1                          | 2                           |
| Dilation                                                                                       | .                          | .                           | 4                          | 3                           |
| .... Mild                                                                                      | .                          | .                           | 4                          | 3                           |
| <b>Vagina</b>                                                                                  |                            |                             |                            |                             |
| Examined                                                                                       | .                          | .                           | 5                          | 5                           |
| No Visible Lesions                                                                             | .                          | .                           | 4                          | 5                           |
| Mucification; Mucosa; Epithelium; Diffuse                                                      | .                          | .                           | 1                          | 0                           |
| .... Minimal                                                                                   | .                          | .                           | 1                          | 0                           |
| <b>Injection Site(S)</b>                                                                       |                            |                             |                            |                             |
| Examined                                                                                       | 5                          | 5                           | 5                          | 5                           |
| No Visible Lesions                                                                             | 5                          | 4                           | 5                          | 5                           |
| Hemorrhage; Subcutaneous; Perivascular                                                         | 0                          | 1                           | 0                          | 0                           |
| .... Minimal                                                                                   | 0                          | 1                           | 0                          | 0                           |
| Inflammation; Mixed Cell And Necrotizing, Cutaneous/Subcutaneous; Cutaneous Muscle; Multifocal | 0                          | 1                           | 0                          | 0                           |
| .... Moderate                                                                                  | 0                          | 1                           | 0                          | 0                           |
| Bacterial Colonies; Epidermis; Multifocal                                                      | 0                          | 1                           | 0                          | 0                           |
| .... Present                                                                                   | 0                          | 1                           | 0                          | 0                           |