

Supplementary Data 4. Histopathology Findings in rats – Dosing Phase

Removal Reason(s): Scheduled Euthanasia-Termination(Dosing Phase) Summary: Incidence	Male				Female			
	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
Adrenal Glands								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Aorta								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Bone Marrow, Sternum								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Bone, Sternum								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Bone, Femur, Including Stifle Joint								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Brain								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Epididymides								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	9	.	.	.	.
Infiltrate; Mononuclear Cell, Interstitium; Multifocal	0	.	.	1	.	.	.	.
.... Minimal	0	.	.	1	.	.	.	.
Esophagus								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Eyes								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Nerve(S), Optic								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Fallopian Tubes								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
Harderian Glands								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Infiltration; Mononuclear Cell, Multifocal, Unilateral	0	.	.	0	1	.	.	0
.... Mild	0	.	.	0	1	.	.	0
Heart								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Infiltration; Mononuclear Cell, Myocardium; Focal	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0
Kidneys								
Examined	10	0	0	10	10	0	0	10

Supplementary Data 4. Histopathology Findings in rats – Dosing Phase (continued)

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	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
Kidneys (Continued...)								
No Visible Lesions	7	.	.	5	7	.	.	6
Nephroblastematosi; Benign, Cortex; Incidental	0	.	.	0	0	.	.	1
Infaret; Chronic, Cortex; Medulla; Focal, Unilateral	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0
Mineralization; Medulla; Multifocal, Bilateral	0	.	.	0	1	.	.	0
.... Minimal	0	.	.	0	1	.	.	0
Mineralization; Medulla; Focal	0	.	.	3	0	.	.	1
.... Minimal	0	.	.	3	0	.	.	1
Basophilia; Tubule; Focal, Unilateral	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0
Basophilia; Tubule; Multifocal, Unilateral	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0
Cyst; Medulla; Focal, Unilateral	0	.	.	0	1	.	.	1
.... Present	0	.	.	0	1	.	.	1
Infiltration; Mononuclear Cell, Interstitium; Focal, Bilateral	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0
Infiltration; Mononuclear Cell, Interstitium; Focal, Unilateral	1	.	.	3	2	.	.	2
.... Minimal	1	.	.	3	2	.	.	2
Infiltration; Mononuclear Cell, Interstitium; Multifocal, Unilateral	0	.	.	1	0	.	.	1
.... Minimal	0	.	.	1	0	.	.	1
Large Intestine, Cecum								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Large Intestine, Colon								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Large Intestine, Rectum								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Liver								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	8	9	.	.	9
Infiltration; Inflammatory Cell, Portal; Parenchyma; Multifocal	0	.	.	1	0	.	.	0
.... Minimal	0	.	.	1	0	.	.	0
Infiltration; Mononuclear Cell, Portal; Parenchyma; Multifocal	0	.	.	0	0	.	.	1
.... Minimal	0	.	.	0	0	.	.	1
Infiltration; Mononuclear Cell, Portal; Perivascular; Multifocal	1	.	.	1	1	.	.	0
.... Minimal	1	.	.	1	1	.	.	0

Supplementary Data 4. Histopathology Findings in rats – Dosing Phase (continued)

Removal Reason(s): Scheduled Euthanasia-Termination(Dosing Phase) Summary: Incidence	Male				Female			
	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
Liver (Continued...)								
Necrosis/Infiltration; Hepatocyte; Subcapsular; Multifocal	0	.	.	1	0	.	.	0
.... Minimal	0	.	.	1	0	.	.	0
Lungs With Mainstem Bronchi								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	9	7	.	.	5
Increased; Alveolus; Macrophage; Focal	0	.	.	1	0	.	.	0
.... Minimal	0	.	.	1	0	.	.	0
Increased; Alveolus; Macrophage; Multifocal	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0
Hemorrhage; Alveolus; Subcapsular; Focal	0	.	.	1	0	.	.	0
.... Minimal	0	.	.	1	0	.	.	0
Mineralization; Vascular Wall; Focal	0	.	.	1	0	.	.	0
.... Minimal	0	.	.	1	0	.	.	0
Inflammation; Mixed Cell, Bronchiolo-Alveolar; Focal	0	.	.	0	2	.	.	1
.... Minimal	0	.	.	0	1	.	.	1
.... Mild	0	.	.	0	1	.	.	0
Thrombus; Intravenous; Focal	0	.	.	0	1	.	.	0
.... Minimal	0	.	.	0	1	.	.	0
Metaplasia; Osseous, Alveolus; Focal	0	.	.	0	1	.	.	1
.... Present	0	.	.	0	1	.	.	1
Lungs With Mainstem Bronchi (Continued...)								
Degeneration/Regeneration; Bronchiole; Epithelium; Focal	0	.	.	0	0	.	.	1
.... Minimal	0	.	.	0	0	.	.	1
Granuloma; Alveolus; Focal	0	.	.	0	0	.	.	1
.... Minimal	0	.	.	0	0	.	.	1
Granuloma; Alveolus; Multifocal	0	.	.	0	0	.	.	1
.... Minimal	0	.	.	0	0	.	.	1
Lymph Node, Mandibular								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	8	.	.	10
Erythrocyte; Sinusoid; Multifocal	0	.	.	0	2	.	.	0
.... Minimal	0	.	.	0	2	.	.	0
Lymph Node, Mesenteric								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	10	.	.	10
Erythrophagocytosis; Sinusoid; Multifocal	0	.	.	1	0	.	.	0
.... Minimal	0	.	.	1	0	.	.	0
Mammary Gland, Inguinal								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Nerves, Sciatic								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10

Supplementary Data 4. Histopathology Findings in rats – Dosing Phase (continued)

Removal Reason(s): Scheduled Euthanasia-Termination(Dosing Phase) Summary: Incidence	Male				Female			
	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
Ovaries								
Examined	.	.	.	.	10	0	1	10
No Visible Lesions	.	.	.	.	10	.	0	10
Cyst; Follicle; Single, Unilateral	.	.	.	.	0	.	1	0
.... Present	.	.	.	.	0	.	1	0
Pancreas								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Pituitary Gland								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Cyst; Pars Distalis; Multifocal	1	.	.	0	0	.	.	0
.... Present	1	.	.	0	0	.	.	0
Prostate Gland								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	8	.	.	10	.	.	.	.
Infiltration; Inflammatory Cell, Interstitium; Multifocal	2	.	.	0	.	.	.	.
.... Minimal	2	.	.	0	.	.	.	.
Salivary Gland, Mandibular								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Seminal Vesicles								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
Skeletal Muscle, Biceps Femoris								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Skin, Inguinal								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Small Intestine, Duodenum								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Small Intestine, Ileum								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Small Intestine, Jejunum								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Spinal Cord, Cervical, Thoracic, Lumbar								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Spleen								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	9	10	.	.	10
Extramedullary Hematopoiesis; Increased, Red Pulp; Multifocal	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0

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Removal Reason(s): Scheduled Euthanasia-Termination(Dosing Phase) Summary: Incidence	Male				Female			
	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
Spleen (Continued...)								
Decreased Cellularity; Lymphocytic, Marginal Zone; White Pulp; Diffuse	0	.	.	1	0	.	.	0
.... Minimal	0	.	.	1	0	.	.	0
Stomach								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Vacuolation; Cytoplasmic, Epithelium; Multifocal	1	.	.	0	0	.	.	0
.... Minimal	1	.	.	0	0	.	.	0
Testes								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	9	.	.	10	.	.	.	.
Degeneration/Atrophy; Seminiferous Tubule; Multifocal, Bilateral	1	.	.	0	.	.	.	.
.... Mild	1	.	.	0	.	.	.	.
Thymus								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Thyroid Glands								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Lymphoid Tissue; Interstitium; Focal, Unilateral	0	.	.	0	1	.	.	0
.... Minimal	0	.	.	0	1	.	.	0
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Trachea								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Urinary Bladder								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Uterus								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	8	.	.	7
Dilation; Bilateral	.	.	.	.	1	.	.	3
.... Mild	.	.	.	.	1	.	.	3
Dilation; Unilateral	.	.	.	.	1	.	.	0
.... Mild	.	.	.	.	1	.	.	0
Cervix								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	8	.	.	7
Dilation	.	.	.	.	2	.	.	3
.... Mild	.	.	.	.	2	.	.	3
Vagina								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	9

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Removal Reason(s): Scheduled Euthanasia-Termination(Dosing Phase) Summary: Incidence	Male				Female			
	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12	Group 1, 0	Group 2, 3	Group 3, 6	Group 4, 12
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
Vagina (Continued...)								
Mucification; Mucosa; Epithelium; Diffuse	.	.	.	.	0	.	.	1
.... Minimal	.	.	.	.	0	.	.	1
Injection Site(S)								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	6	5	0	6	6	5	3
Edema; Subcutaneous; Perivascular	0	0	0	1	0	0	0	0
.... Minimal	0	0	0	1	0	0	0	0
Hemorrhage; Subcutaneous; Perivascular	0	0	1	2	0	0	0	3
.... Minimal	0	0	1	1	0	0	0	3
.... Mild	0	0	0	1	0	0	0	0
Inflammation; Mixed Cell, Subcutaneous; Perivascular	0	4	5	5	4	4	5	6
.... Minimal	0	4	4	1	4	4	4	3
.... Mild	0	0	1	3	0	0	1	3
.... Moderate	0	0	0	1	0	0	0	0
Inflammation; Mixed Cell And Necrotizing, Cutaneous/Subcutaneous; Cutaneous Muscle	0	0	0	2	0	0	0	1
.... Moderate	0	0	0	1	0	0	0	1
.... Marked	0	0	0	1	0	0	0	0
Necrosis; Cutaneous/Subcutaneous; Cutaneous Muscle	0	0	0	2	0	0	0	0
.... Mild	0	0	0	2	0	0	0	0
Necrosis; Cutaneous/Subcutaneous; Vein	0	0	0	1	0	0	0	0
.... Mild	0	0	0	1	0	0	0	0
Injection Site(S) (Continued...)								
Thrombosis; Intravenous; Focal	0	0	0	0	0	0	0	2
.... Mild	0	0	0	0	0	0	0	2
Congestion; Cutaneous/Subcutaneous; Multifocal	0	0	0	1	0	0	0	0
.... Mild	0	0	0	1	0	0	0	0
Bacterial Colonies; Epidermis; Multifocal	0	0	0	1	0	0	0	0
.... Present	0	0	0	1	0	0	0	0