

Table 11

Histopathology

B130235

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SEX: MALE
      GROUP 1 1 2 2 3 3 4 4
REMOVAL REASON F F F F F F F F

      ANIMAL 1 1 1 1 1 1 1 1
NUMBER 0 0 0 0 0 0 0 0
      1 1 2 2 3 3 4 4
      0 0 0 0 0 0 0 0
      1 2 1 2 1 2 1 2
-----

Lacrimal Gland; ..... N N N N N N + N
  Cell infiltration; lymphocyte; focal ..... . 1 .

Femoral Muscle; ..... N N N N N N N N

Femur; ..... N N N N N N N N

Sternum; ..... N N N N N N N N

Skin; ..... N N N N N N N N

Administered Site, Right Forelimb; ..... N N N N N + + +
  Proliferation; intima; vascular wall ..... . 4 .
  Cell infiltration; inflammatory; perivascular ... . . . . 2 . 2

Administered Site, Right Hindlimb; ..... N N N N N + N +
  Hemorrhage ..... . . . . . 2
  Proliferation; intima; vascular wall ..... . . . . 3 . 3
  Cell infiltration; inflammatory; perivascular ... . . . . 1

Administered Site, Left Forelimb; ..... N N N N N + + +
  Necrosis ..... . . . . 2 . 4
  Ulcer ..... . . . . 3 .
  Hemorrhage ..... . . . . 2 2 2
  Proliferation; intima; vascular wall ..... . . . . 3 .
  Cell infiltration; inflammatory; perivascular ... . . . . 4 1 4
  
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SEX: MALE
          GROUP 1 1 2 2 3 3 4 4
REMOVAL REASON F F F F F F F F

          ANIMAL 1 1 1 1 1 1 1 1
NUMBER    0 0 0 0 0 0 0 0
          1 1 2 2 3 3 4 4
          0 0 0 0 0 0 0 0
          1 2 1 2 1 2 1 2
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Administered Site, Left Hindlimb; ..... N N N N + + + +
Necrosis ..... . . . . 1 .
Hemorrhage ..... . . . 1 2 1 .
Thrombus ..... . . . 3 . . .
Proliferation; intima; vascular wall ..... . . . 3 . 3
Cell infiltration; inflammatory; perivascular ... . . . 2 . . 1
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Table 11

## Histopathology

B130235

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SEX: FEMALE	GROUP	1	1	2	2	3	3	4	4
	REMOVAL REASON	F	F	F	F	F	F	F	F
	ANIMAL	5	5	5	5	5	5	5	5
	NUMBER	0	0	0	0	0	0	0	0
		1	1	2	2	3	3	4	4
		0	0	0	0	0	0	0	0
		1	2	1	2	1	2	1	2

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Tongue; .....	N	N	N	N	N	N	N	N	N
Esophagus; .....	N	N	N	N	N	N	N	+	N
Cell infiltration; lymphocyte; focal .....	.	.	.	.	.	.	.	1	.
Stomach; .....	+	+	N	+	+	+	+	N	+
Cell infiltration; inflammatory; lamina propria;									
diffuse .....	1	1	.	1	1	1	.	1	
Duodenum; .....	N	N	N	N	N	N	N	N	N
Jejunum; .....	N	N	N	N	N	N	N	N	N
Ileum; .....	N	N	N	N	N	N	N	N	N
Cecum; .....	N	N	N	N	N	N	N	N	N
Colon; .....	N	N	N	N	N	N	N	N	N
Rectum; .....	N	N	N	N	N	N	N	N	N
Liver; .....	N	N	N	N	N	N	N	N	+
Pigment deposition; kupffer cell .....	.	.	.	.	.	.	.	.	1
Gallbladder; .....	N	N	N	N	N	N	N	N	N

---

SEX: FEMALE	GROUP	1	1	2	2	3	3	4	4
	REMOVAL REASON	F	F	F	F	F	F	F	F
	ANIMAL	5	5	5	5	5	5	5	5
	NUMBER	0	0	0	0	0	0	0	0
		1	1	2	2	3	3	4	4
		0	0	0	0	0	0	0	0
		1	2	1	2	1	2	1	2

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Pancreas; .....	N	N	N	N	N	N	N	N	N
Submandibular Gland; .....	N	N	N	N	N	N	N	N	N
Sublingual Gland; .....	N	N	N	N	N	N	N	N	N
Parotid Gland; .....	+	N	N	+	N	N	N	N	N
Cell infiltration; lymphocyte; focal .....	1	.	.	1	.	.	.	.	.
Trachea; .....	N	N	N	N	N	N	N	N	N
Lungs (And Bronchus); .....	N	N	N	N	N	N	N	N	+
Granuloma .....	.	.	.	.	.	.	.	.	1
Thymus; .....	N	N	N	N	N	N	N	N	N
Spleen; .....	N	N	N	N	+	N	N	+	
Pigment deposition; brown; red pulp .....	.	.	.	.	1	.	.	.	1
Bone Marrow (Femur); .....	N	N	N	+	N	N	N	N	
Pigment deposition; brown .....	.	.	.	1	.	.	.	.	.
Bone Marrow (Sternum); .....	N	N	N	N	N	N	N	+	+
Increase; hematopoietic cell .....	.	.	.	.	.	.	.	1	1
Mandibular Lymph Node; .....	N	N	N	N	+	N	N	N	
Extramedullary hematopoiesis .....	.	.	.	.	1	.	.	.	.

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SEX: FEMALE

GROUP	1	1	2	2	3	3	4	4
REMOVAL REASON	F	F	F	F	F	F	F	F
ANIMAL	5	5	5	5	5	5	5	5
NUMBER	0	0	0	0	0	0	0	0
	1	1	2	2	3	3	4	4
	0	0	0	0	0	0	0	0
	1	2	1	2	1	2	1	2

Mesenteric Lymph Node; .....	N	+	N	N	N	+	N	N
Increase; pigmentophage .....	.	1	.	.	.	1	.	.
Heart; .....	N	+	N	+	+	N	N	N
Cell infiltration; inflammatory; focal .....	.	1	.	1	1	.	.	.
Aorta; .....	N	N	N	N	N	N	N	N
Kidney; .....	N	N	N	+	+	+	+	N
Cell infiltration; lymphocyte; focal .....	.	.	.	.	1	.	.	.
Arteritis .....	.	.	.	.	.	1	.	.
Cyst .....	.	.	.	.	.	.	.	P
Hyaline cast .....	.	.	.	1	.	.	.	.
Urinary Bladder; .....	N	N	N	N	N	N	N	N
Ovary; .....	N	N	N	N	N	+	N	N
Mineralization .....	.	.	.	.	.	1	.	.
Uterus; .....	N	N	N	N	N	N	N	N
Vagina; .....	N	N	N	N	N	N	N	N
Mammary Gland; .....	N	N	N	N	N	N	+	N
Cell infiltration; lymphocyte; focal .....	.	.	.	.	.	.	1	.
Pituitary; .....	N	N	N	N	N	N	+	N
Cyst .....	.	.	.	.	.	.	.	P

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SEX: FEMALE	GROUP	1	1	2	2	3	3	4	4
	REMOVAL REASON	F	F	F	F	F	F	F	F
	ANIMAL	5	5	5	5	5	5	5	5
	NUMBER	0	0	0	0	0	0	0	0
		1	1	2	2	3	3	4	4
		0	0	0	0	0	0	0	0
		1	2	1	2	1	2	1	2

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Thyroid; .....	N	N	+	N	N	N	N	N	N
Cell infiltration; lymphocyte; focal .....	.	.	1	.	.	.	.	.	.
Cell infiltration; macrophage; follicle .....	.	.	1	.	.	.	.	.	.
Cyst .....	.	.	P	.	.	.	.	.	.
Parathyroid; .....	N	N	N	N	N	N	N	N	+
Congestion .....	.	.	.	.	.	.	.	.	1
Adrenal; .....	N	N	N	N	N	N	N	N	N
Brain; .....	N	N	N	N	+	N	N	+	N
Pigment deposition; brown; perivascular; focal ..	.	.	.	.	1	.	.	.	.
Cell infiltration; inflammatory; choroid plexus; focal .....	.	.	.	.	.	.	.	.	1
Spinal Cord; .....	N	N	N	N	N	N	N	N	N
Optic Nerve; .....	N	N	N	N	N	N	N	N	N
Sciatic Nerve; .....	N	N	N	N	N	N	N	N	N
Eyeball; .....	N	N	+	N	+	N	+	N	N
Cell infiltration; mononuclear cell; focal .....	.	.	1	.	1	.	.	.	.
Lacrimal Gland; .....	+	N	N	N	N	N	N	N	N
Cell infiltration; lymphocyte; focal .....	1	.	.	.	.	.	.	.	.

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Table 11

Histopathology

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SEX: FEMALE
      GROUP 1 1 2 2 3 3 4 4
REMOVAL REASON F F F F F F F F

      ANIMAL 5 5 5 5 5 5 5 5
NUMBER 0 0 0 0 0 0 0 0
      1 1 2 2 3 3 4 4
      0 0 0 0 0 0 0 0
      1 2 1 2 1 2 1 2
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Femoral Muscle; ..... N N N N N + N N
  Degeneration; muscle fiber; focal ..... . . . . 1 . .

Femur; ..... N N N N N N N N

Sternum; ..... N N N N N N N N

Skin; ..... N N N N N N N N

Administered Site, Right Forelimb; ..... N N N N N + N +
  Hemorrhage ..... . . . . . 2
  Proliferation; intima; vascular wall ..... . . . . 3 . 4

Administered Site, Right Hindlimb; ..... N N N N + N N +
  Hemorrhage ..... . . . . 3 . . 2
  Proliferation; intima; vascular wall ..... . . . . . 2

Administered Site, Left Forelimb; ..... N N N N + + + +
  Hemorrhage ..... . . . . 1 2 . .
  Thrombus ..... . . . . 3 . . .
  Proliferation; intima; vascular wall ..... . . . . 3 3 3
  Cell infiltration; inflammatory; perivascular ... . . . . 1 1 1 .

Administered Site, Left Hindlimb; ..... N N N N N + + +
  Necrosis ..... . . . . . 2 .
  Hemorrhage ..... . . . . . 2 1
  Thrombus ..... . . . . . 3
  Proliferation; intima; vascular wall ..... . . . . 1 . .
  
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SEX: FEMALE

GROUP	1	1	2	2	3	3	4	4
REMOVAL REASON	F	F	F	F	F	F	F	F
ANIMAL	5	5	5	5	5	5	5	5
NUMBER	0	0	0	0	0	0	0	0
	1	1	2	2	3	3	4	4
	0	0	0	0	0	0	0	0
	1	2	1	2	1	2	1	2

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Administered Site, Left Hindlimb; (Continued)

Cell infiltration; inflammatory; perivascular ... . . . . 1 2 1



Table 12 Blood Concentration of P092

B130235

&lt;Day 1, Male&gt;

Dose (mg/kg)	Animal No.	Blood concentration of P092 (ng/mL)						C <sub>0</sub> (ng/mL)	t <sub>1/2</sub> (h)	AUC <sub>0-24h</sub> (ng·h/mL)
		0.083 h	1 h	2 h	4 h	8 h	24 h			
1	10201	168.3	61.21	43.43	40.77	41.34	21.70	184.4	21.5	924.9
	10202	171.0	39.16	49.79	43.16	41.70	14.51	195.4	12.3	868.4
	Mean	169.7	50.19	46.61	41.97	41.52	18.11	189.9	16.9	896.7
10	10301	1109 *	549.8	364.5	424.1	244.0	141.0	1182	14.8	6518
	10302	918.4	548.8	440.3	317.7	243.0	155.7	962.2	20.7	6314
	Mean	1014	549.3	402.4	370.9	243.5	148.4	1072	17.8	6416
30	10401	2924 *	1170 *	1571 *	850.6 *	697.0	207.9	3177	9.6	16260
	10402	1855 *	1392 *	1400 *	1389 *	627.9	258.6	1904	8.7	16960
	Mean	2390	1281	1486	1120	662.5	233.3	2541	9.2	16610

\*: The sample was reanalyzed because the measured value exceeded the upper limit of quantification.

Table 12 Blood Concentration of P092

B130235

&lt;Day 1, Female&gt;

Dose (mg/kg)	Animal No.	Blood concentration of P092 (ng/mL)						C <sub>0</sub> (ng/mL)	t <sub>1/2</sub> (h)	AUC <sub>0-24h</sub> (ng·h/mL)
		0.083 h	1 h	2 h	4 h	8 h	24 h			
1	50201	190.2	84.77	33.18	24.58	65.32	18.68	204.6	11.4	1111
	50202	145.1	49.80	39.60	41.49	48.92	23.33	159.8	24.1	986.6
	Mean	167.7	67.29	36.39	33.04	57.12	21.01	182.2	17.8	1049
10	50301	934.3 *	397.0	476.5	291.9	182.9	117.0	1010	12.5	5245
	50302	982.4	471.4	261.5	270.9	179.0	116.4	1050	18.2	4913
	Mean	958.4	434.2	369.0	281.4	181.0	116.7	1030	15.4	5079
30	50401	1542 *	1409 *	564.0 *	567.4	474.8	195.3	1555	12.8	11040
	50402	1436 *	835.8	738.3	503.4	301.8	125.4	1508	10.6	8221
	Mean	1489	1122	651.2	535.4	388.3	160.4	1532	11.7	9631

\*: The sample was reanalyzed because the measured value exceeded the upper limit of quantification.

Table 12 Blood Concentration of P092

B130235

## &lt;Day 8, Male&gt;

Dose (mg/kg)	Animal No.	Blood concentration of P092 (ng/mL)
		pre
1	10201	7.139
	10202	5.720
	Mean	6.430
10	10301	107.0
	10302	164.3
	Mean	135.7
30	10401	304.4
	10402	230.2
	Mean	267.3

## &lt;Day 8, Female&gt;

Dose (mg/kg)	Animal No.	Blood concentration of P092 (ng/mL)
		pre
1	50201	8.626
	50202	8.602
	Mean	8.614
10	50301	119.6
	50302	127.7
	Mean	123.7
30	50401	321.1
	50402	275.4
	Mean	298.3

Table 12 Blood Concentration of P092

B130235

&lt;Day 22, Male&gt;

Dose (mg/kg)	Animal No.	Blood concentration of P092 (ng/mL)							C <sub>0</sub> (ng/mL)	t <sub>1/2</sub> (h)	AUC <sub>0-24h</sub> (ng·h/mL)
		pre	0.083 h	1 h	2 h	4 h	8 h	24 h			
1	10201	14.76	186.1	91.03	86.58	68.63	72.39	38.54	198.5	19.6	1557
	10202	13.66	189.7	73.89	67.57	69.74	60.09	27.98	206.6	15.0	1310
	Mean	14.21	187.9	82.46	77.08	69.19	66.24	33.26	202.6	17.3	1434
10	10301	576.7	2406	1128 *	942.2	753.2	606.9	382.7	2577	21.4	15190
	10302	371.6	2694	1468 *	1159 *	968.2	758.2	513.1	2846	23.4	19200
	Mean	474.2	2550	1298	1051	860.7	682.6	447.9	2712	22.4	17200
30	10401	662.3	6232	3746	3371	2455	1273 *	940.4 *	6526	12.1	39650
	10402	567.0	4890	2652	2192	1603	958.0 *	780.6	5168	14.5	29120
	Mean	614.7	5561	3199	2782	2029	1116	860.5	5847	13.3	34390

\*: The sample was reanalyzed because the measured value exceeded the upper limit of quantification.

Table 12 Blood Concentration of P092

B130235

&lt;Day 22, Female&gt;

Dose (mg/kg)	Animal No.	Blood concentration of P092 (ng/mL)							C <sub>0</sub> (ng/mL)	t <sub>1/2</sub> (h)	AUC <sub>0-24h</sub> (ng·h/mL)
		pre	0.083 h	1 h	2 h	4 h	8 h	24 h			
1	50201	16.88	407.6	150.4	114.9	93.87	86.91	46.54	446.1	19.1	2062
	50202	19.42	203.1	76.54	62.07	60.07	54.21	36.87	221.9	28.5	1294
	Mean	18.15	305.4	113.5	88.49	76.97	70.56	41.71	334.0	23.8	1678
10	50301	257.1	1575	883.8 *	730.6	469.1	382.4	297.5	1660	33.4	10410
	50302	332.7	2591	1091 *	913.0	673.6	522.4	335.1	2802	21.1	13750
	Mean	294.9	2083	987.4	821.8	571.4	452.4	316.3	2231	27.3	12080
30	50401	652.4	4829	2652	2212	1728	1427 *	1202 *	5098	43.2	37560
	50402	477.4	3311	2076	1816	1409	1220 *	500.8	3454	13.1	26950
	Mean	564.9	4070	2364	2014	1569	1324	851.4	4276	28.2	32260

\*: The sample was reanalyzed because the measured value exceeded the upper limit of quantification.

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Key Page

Code	Description
BD	Before dosing
T10	After dosing

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Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date																
					1 BD	1 T10	2 Day	3 Day	4 Day	5 Day	6 Day	7 Day	8 BD	8 T10	9 Day	10 Day	11 Day	12 Day	13 Day	14 Day	15 BD
1	m	10101	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		10102	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

---

Severity Codes: X = Present

Group 1 - 0 mg/kg    Group 2 - 1 mg/kg    Group 3 - 10 mg/kg    Group 4 - 30 mg/kg

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Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date														
					16 Day	17 Day	18 Day	19 Day	20 Day	21 Day	22 BD	22 T10	23 Day	24 Day	25 Day	26 Day	27 Day	28 Day	29 Day
1	m	10101	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		10102	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

---

Severity Codes: X = Present

Group 1 - 0 mg/kg    Group 2 - 1 mg/kg    Group 3 - 10 mg/kg    Group 4 - 30 mg/kg



---

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date																	
					1 BD	1 T10	2 Day	3 Day	4 Day	5 Day	6 Day	7 Day	8 BD	8 T10	9 Day	10 Day	11 Day	12 Day	13 Day	14 Day	15 BD	15 T10
2	m	10201	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		10202	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

---

Severity Codes: X = Present

Group 1 - 0 mg/kg    Group 2 - 1 mg/kg    Group 3 - 10 mg/kg    Group 4 - 30 mg/kg

---

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date													
					16 Day	17 Day	18 Day	19 Day	20 Day	21 Day	22 BD	22 T10	23 Day	24 Day	25 Day	26 Day	27 Day	28 Day
2	m	10201	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X
		10202	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Severity Codes: X = Present

Group 1 - 0 mg/kg    Group 2 - 1 mg/kg    Group 3 - 10 mg/kg    Group 4 - 30 mg/kg

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date																	
					1 BD	1 T10	2 Day	3 Day	4 Day	5 Day	6 Day	7 Day	8 BD	8 T10	9 Day	10 Day	11 Day	12 Day	13 Day	14 Day	15 BD	15 T10
3	m	10301	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		10302	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	-	-	-	-	-	-	-
			Erythema	Right Forelimb	-	-	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X
			Erythema	Left Forelimb	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
			Swelling	Right Forelimb	-	-	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X
			Swelling	Left Forelimb	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X

Severity Codes: X = Present

Group 1 - 0 mg/kg    Group 2 - 1 mg/kg    Group 3 - 10 mg/kg    Group 4 - 30 mg/kg

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	16 Day	17 Day	18 Day	19 Day	20 Day	21 Day	22 BD	22 T10	23 Day	24 Day	25 Day	26 Day	27 Day	28 Day	29 Day
3	m	10301	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		10302	No Abnormalities Detected		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Erythema	Right Forelimb	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Erythema	Left Forelimb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Swelling	Right Forelimb	X	X	X	X	-	-	-	-	-	-	-	-	-	-	-
			Swelling	Left Forelimb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present

Group 1 - 0 mg/kg    Group 2 - 1 mg/kg    Group 3 - 10 mg/kg    Group 4 - 30 mg/kg