Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Swelling of foot	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Induration of the tail	NNF	NNF	NNF	NNF	NNF	NNF	+	NNF
Mass (back, neck)	NNF	NNF	NNF	NNF	NNF	+[d]	+	NNF
Shortened incisor	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Decreased activity	NNF	NNF	NNF	NNF	+[d]	+[d]	+	NNF
Bradypnea	NNF	NNF	NNF	NNF	+[d]	+[d]	+	NNF
Few feces	NNF	NNF	NNF	NNF	+[d]	+[d]	+	NNF
Hypothermia	NNF	NNF	NNF	NNF	NNF	+[d]	NNF	NNF
Emaciation	NNF	NNF	NNF	NNF	NNF	+[d]	NNF	NNF
Prostration	NNF	NNF	NNF	NNF	NNF	+[d]	NNF	NNF
Staining of nose or periocular areas	NNF	NNF	NNF	+	+[d]	+[d]	NNF	NNF
Eyes, discoloration	NNF	NNF	NNF	NNF	NNF	+[d]	NNF	NNF
Chromaturia	NNF	NNF	NNF	NNF	+[d]	NNF	NNF	NNF
Ophthalmoscopy	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Hematology[e]								
Hemoglobin concentration (g/dL)	14.7	14.0	14.8	13.8	14.4	13.5	12.8**	11.9**
MCV (fL)	54.6	54.5	54.1	53.7	53.5	52.5[#]	50.1**	51.1[##]
MCH (pg)	18.0	18.3	17.8	18.0	17.5	17.3[#]	16.2**	16.4[##]
Reticulocyte count ($\times 10^9$/L)	140.8	144.3	131.9	118.9	153.5	157.6	231.5[##]	246.7[##]
Neutrophil count ($\times 10^3$/μL)	0.79	0.55	1.09	0.53	2.29[##]	0.51	2.30[##]	0.73
Monocyte count ($\times 10^3$/μL)	0.09	0.05	0.14	0.07	0.35[#]	0.21[##]	0.56[##]	0.21[##]
Eosinophil count ($\times 10^3$/μL)	0.10	0.08	0.14	0.08	0.24[##]	0.13[#]	0.18[#]	0.16[##]
Serum Chemistry[f]								
Total bilirubin (mg/dL)	0.07	0.06	0.06	0.06	0.06	0.06	0.21	0.10**
Urinalysis								
Turbidity	NNF	NNF	NNF	NNF	+	+	+	+
Unequal-sized globules in sediment	NNF	NNF	+	+	+	+	+	+
Organ Weights								
Spleen, relative (mg/100 g BW)	147	177	155	192	190[##]	224**	210[##]	225**
Liver, relative (g/100 g BW)	2.79	2.81	2.92	2.97	3.14**	3.12**	3.58**	3.53**
Adrenals, relative (mg/100 g BW)	11	23	12	23	12	23	20[##]	26
Kidneys, relative (g/100 g BW)	0.582	0.681	0.592	0.647	0.592	0.647	0.678[##]	0.678
Ovary, relative (mg/100 g BW)	NA	33	NA	35	NA	44*	NA	32

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Gross Pathology								
Number evaluated[g]: n (n FD/MS)	14	14	14	14	14 (1)	11 (5)	14	14
Thymus								
Mass	0	0	0	0	2 (1)	1 (4)	0	0
Small	0	0	0	0	1 (0)	0 (0)	3	3
Submaxillary lymph node								
Enlarged	0	0	0	0	0 (1)	0 (2)	1	0
Mesenteric lymph node								
Enlarged	0	0	0	0	0 (1)	0 (2)	0	0
Iliac lymph node								
Enlarged	0	0	0	0	0 (0)	0 (2)	0	0
Inguinal lymph node								
Enlarged	0	0	0	0	0 (0)	0 (1)	0	0
Spleen								
Enlarged	0	0	0	0	1 (1)	0 (5)	0	0
Raised area	0	0	0	0	0 (0)	1 (0)	0	0
Ovaries								
Enlarged	NA	0	NA	0	NA	0 (2)	NA	0
Stomach								
Distention	0	0	0	0	0 (0)	0 (1)	2	0
Discolored area/focus, forestomach/ glandular stomach	1	0	0	0	0 (0)	1 (2)	3	1
Liver								
Enlarged	0	0	0	0	0 (0)	0 (1)	0	0
Incisor								
Short	0	0	0	0	0 (0)	0 (0)	2	5
Gingiva								
Swelling	0	0	0	0	0 (0)	0 (0)	2	9
Lips of mouth								
Nodule	0	0	1	0	1 (0)	0 (0)	3	0
Foot								
Nodule	0	0	0	0	0 (0)	0 (0)	1	0
Swelling	0	0	0	0	0 (0)	0 (0)	3	1

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Subcutis								
Mass	0	0	0	0	0 (0)	1 (0)	1	0
Tail								
Induration	0	0	0	0	0 (0)	0 (0)	2	0
Adrenal								
Enlarged	0	0	0	0	0 (0)	0 (0)	1	0
Histopathology								
Number evaluated: n (n FD/MS)	14	14	14	14	14(1)	11(5)	14	14
Thymus								
Lymphoma, lymphoblastic	0	0	0	0	2 (1)	2 (5)	1	0
Lymphoid depletion	0	0	0	0	2 (0)	5 (0)	13	14
Spleen								
Lymphoid depletion	0	0	0	0	5 (0)	4 (0)	13	11
Submaxillary lymph node								
Lymphoid depletion	0	0	0	0	1 (0)	0 (0)	1	3
Femur								
Trabecular formation	0	0	0	0	1 (0)	2 (0)	11	7
Sternum								
Trabecular formation	0	0	0	0	2 (0)	7 (0)	10	12
Findings in other organs								
Number evaluated: n (n FD/MS)	10	10	10	10	10 (1)	8 (4)	10	10
Incisor								
Dysplasia	0	0	0	0	0 (0)	0 (0)	6	10
Alveolar bone								
Increased bone formation	0	0	0	0	0 (0)	0 (0)	4	10
Stomach								
Erosion/ulcer	0	0	0	0	0 (0)	1 (1)	1	0
Regeneration, mucosa	0	0	0	0	4 (0)	5 (0)	8	8
Duodenum								
Hyperplasia, crypt	0	0	0	0	1 (0)	0 (0)	2	1
Kidney								
Granular material, pelvis	0	0	0	0	0 (0)	0 (1)	1	3
Noteworthy findings during the recovery period								

Daily Dose (mg/kg)	**0 (Control)**		**100**		**300**		**600**	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Number evaluated	6	6	0	0	5	4	6	6
Clinical observations								
Labial nodule with/without crust	NNF	NNF	NA	NA	+	NNF	+	+
Swelling of foot	NNF	NNF	NA	NA	NNF	NNF	+	NNF
Induration of the tail	NNF	NNF	NA	NA	NNF	NNF	+	NNF
Serum chemistry								
AST (mU/mL)	80	65	NA	NA	75	72	94	103[#,h]
Organ weights								
Spleen, relative (mg/100 g BW)	134	175	NA	NA	171**	190	189**	207
Gross pathology								
Thymus								
Enlarged	0	0	NA	NA	0	1	0	0
Incisor								
Short	0	0	NA	NA	0	0	0	5
Gingiva								
Swelling	0	0	NA	NA	0	0	3	4
Lips of mouth								
Nodule	0	0	NA	NA	2	0	2	3
Foot								
Swelling	0	0	NA	NA	0	0	1	0
Histopathology								
Number animals examined	6	6	0	0	5	4	6	6
Thymus								
Lymphoma, lymphoblastic	0	0	NA	NA	0	1	0	0
Femur								
Trabecular formation	0	0	NA	NA	1	4	6	6
Sternum								
Trabecular formation	0	0	NA	NA	1	3	6	6
Incisor								
Dysplasia	0	0	NA	NA	0	0	4	6
Alveolar bone								
Increased bone formation	0	0	NA	NA	0	0	4	6
Spleen								

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Lymphoid depletion	0	0	NA	NA	0	0	1	0

Investigative MoA studies from the 13-week rat K[redacted]009 study			
Title	**Results**	**Study Number**	**CTD Location**
The Lineage Analysis of the Cells in the Lymphoid and Hematopoietic Tissues in Rats Treated with E7438 for 13 Weeks	Increased $CD8^+$ T cell ratio and αβ T cell ratio, and decreased $CD4^+$ T cell ratio and γδ T cell ratio were observed in thymus samples from animals with T-LBL. Dose dependent decrease in αβ T cell ratio and increase in γδ T cell ratio were observed in thymus, bone marrow, and spleen samples from animals without T-LBL.	W-20[redacted]1042	4.2.3.7.3.1
Notch Target Gene Expression in Thymus Samples From a 13-Week Rat Toxicology Study with Tazemetostat	Increased expression of Notch target genes (Hes1, Hey1, and Dtx1) was not observed in neither samples from animals with or without T-LBL	EPZ-6438-PD012	4.2.3.7.3.3
Tazemetostat: Rat Leukemia Virus Reintegration Assay	No effects on retroviral reintegration of the Rat Leukemia virus were observed in neither samples from animals with or without T-LBL.	[redacted]-CR-2917	4.2.3.7.3.2

Number of animals found dead or moribund with a specific change is shown in parentheses.
+ = observed, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate transaminase, $AUC_{(0\text{-}24h)}$ = area under the concentration-time curve from 0 time to 24 hours postdose, BQL = below quantitation limit (<1 ng/mL), BW = body weight, C_{max} = maximum observed concentration, CTD = common technical document, F = female, GLP = Good Laboratory Practice, M = male, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MoA = mechanism of action, NA = not applicable, NC = not calculated, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, TK = toxicokinetics, WBC = white blood cells.

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals (main groups)	M: 16	F: 16	M: 10	F: 10	M: 16	F: 16	M: 16	F: 16

a: n=3.
b: At the end of dosing period (Day 91). For controls, group means are shown. For treated groups, percent differences from controls are shown.
c: Changes were only observed in some individual males at 600 mg/kg and animals that died or sacrificed moribund at 300 mg/kg.
d: In found dead/early sacrifice animals only.
e: Hematologic changes in moribund sacrificed animals included increases in WBC counts and related parameters particularly the lymphocyte counts, marked decreases in erythrocytic parameters, platelet counts, prolonged APTT, and atypical lymphocytes and secondary increases in erythroblasts in blood smear consistent with lymphoma.
f: Serum biochemical changes in moribund sacrificed animals included increases in AST, ALT, total bilirubin, urea nitrogen, and triglyceride, and decrease in total protein, albumin, and glucose.
g: Four animals/sex/group assigned to TK were examined macroscopically and microscopically, lymphoid organs, femur and sternum only.
h: One female exhibited high level of AST (207 mU/mL).

* $P<0.05$; ** $P<0.01$ (Dunnett's test); # $P<0.05$; ## $P<0.01$ (Dunnett's rank test) vs control.

Source: Study K[redacted]009, W-20[redacted]1042, EPZ-6438-PD012, [redacted]-CR-2917.

2.6.7.7.C **Test Article: Tazemetostat**

Report Title: E7438: A 28-Day Oral Toxicity Study in Cynomolgus Monkeys		**Study No.** 20024293
Species / Strain: Monkey/Cynomolgus	Duration of Dosing: 28 days, BID	Location in CTD: 4.2.3.2.5
Initial Age: 2.4 to 3.9 years	Duration of Postdose: NA	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral by gavage	
Vehicle / Formulation: 0.5% methylcellulose solution including 0.1% Tween 80/Suspension		
Special Features: The 1000 mg/kg/day dose was discontinued on Day 8/9 of dosing due to moribund euthanasia of 3 animals (2 males and 1 female). On Day 11/12 (females/males), dosing was re-initiated at 600 mg/kg/day for surviving animals in the high dose group, with the exception of a single female; this animal served as a recovery animal (21-day recovery period) for the 1000 mg/kg/day dose level. Central nervous system and respiratory parameters were included in the study as a part of the evaluation of Safety Pharmacology (Section 2.6.3).		
NOAEL: 100 mg/kg		

Daily Dose (mg/kg)	**0 (Control)**		**100**		**300**		**1000/600**	
Number of Animals (main groups)	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
TK: $AUC_{(0\text{-}12h)}$ (ng·h/mL)								
Day 1	NC	NC	1842.36	1532.38	6770.24	7928.34	38,373.71	42,860.66[a]
Day 28	NC	NC	471.38	537.48	1218.62	2596.57	9371.15[b]	14,892.24[b]
TK: C_{max} (ng/mL)								
Day 1	BQL	BQL	820.76	568.51	1800.75	2331.34	9149.56	8704.56[a]
Day 28	BQL	BQL	177.48	158.11	283.26	736.12	2276.74[b]	2541.41[b]
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	2	1
Body weight (kg)								
Week 1	2.4	2.4	2.6	2.1	2.5	2.3	2.5	2.2
Week 4	2.5	2.5	2.8	2.3	2.7	2.4	2.7[b]	2.4[b]
Clinical Observations								
Decreased activity	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Ophthalmoscopy	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Neurologic examinations								
Muscle tone decreased (both legs)	NNF	NNF	NNF	NNF	NNF	NNF	+	NNF
Electrocardiography								
Increased heart rate	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Hematology	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Serum Chemistry								
Number examined, Day 8/9	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2

Daily Dose (mg/kg)	0 (Control)		100		300		1000/600	
Number of Animals (main groups)	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
ALT (U/L) [c]	NA	NA	NA	NA	NA	NA	149, 279	121, 308
Triglycerides (mg/dL) [c]	NA	NA	NA	NA	NA	NA	51, 154	133, 52
Albumin (g/dL) [c]	NA	NA	NA	NA	NA	NA	3.2, 2.9	3.5, 3.2
Total protein (g/dL) [c]	NA	NA	NA	NA	NA	NA	5.9, 6.3	6.6, 6.3
Cholesterol (mg/dL) [c]	NA	NA	NA	NA	NA	NA	87, 47	124, 64
Number examined, Day 28	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 2	F: 3
ALT (U/L) [c]	58	51	62	52	90	135	652, 738	49, 55, 1344
Triglycerides (mg/dL) [c]	53	58	65	51	90	75	203, 70	55, 81, 315
Total bilirubin (mg/dL) [c]	0.3	0.2	0.1	0.1	0.1	0.1	0.1, 0.2	0.2, 0.1, 1.4
Urinalysis	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Plasma Bromide and Chloride Measurement (Ion exchange chromatography)								
Number examined, Day 28	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
Bromide (mEq/L)								
Predose Day 1	ND	ND	NA	NA	NA	NA	ND	ND
1 hour postdose Day 1 (n=4)	ND	ND	NA	NA	NA	NA	0.6	0.9
Predose Day 28 [c]	NA	NA	NA	NA	NA	NA	23, 28	29, 30
1 hour postdose Day 28 [c]	NA	NA	NA	NA	NA	NA	24, 29	28, 30
Chloride (mEq/L)								
Predose Day 1 (n=4)	ND	ND	NA	NA	NA	NA	104	101
1 hour postdose Day 1 (n=4)	107	103	NA	NA	NA	NA	107	104
Predose Day 28 [c]	NA	NA	NA	NA	NA	NA	80, 70	80, 68
1 hour postdose Day 28[c]	NA	NA	NA	NA	NA	NA	80, 69	76, 68
Organ Weights								
Number evaluated	4	4	4	4	4	4	2	3
Liver, absolute (g)	52.9	54.2	64.2	50.0	70.0	63.5	97.1	72.4
Liver, relative (g/kg BW)	21.6	22.6	23.5	22.2	26.0	26.5	34.4	31.3
Kidney, absolute (g)	10.9	10.4	13.0	9.8	12.8	10.9	15.3	10.9
Kidney, relative (g/kg BW)	4.49	4.37	4.80	4.36	4.74	4.54	5.50	4.66
Gross Pathology								
Number evaluated: n (n moribund sacrifice)	4	4	4	4	4	4	2 (2)	3 (1)
Liver								

Daily Dose (mg/kg)	0 (Control)		100		300		1000/600	
Number of Animals (main groups)	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Discoloration (pale)	0	0	0	0	0	0	0 (2)	1 (1)
Colon								
Distention	0	0	0	0	0	0	0 (2)	0 (1)
Stomach								
Distention	0	0	0	0	0	0	0 (1)	0 (0)
Histopathology								
Number evaluated: n (n moribund sacrifice)	4	4	4	4	4	4	2 (2)	3 (1)
Liver								
Hypertrophy, hepatocytes, centrilobular	0	0	0	0	0	0	1 (2)	0 (1)
Hypertrophy, Kupffer cells	0	0	0	0	0	0	2 (2)	2 (1)
Thymus								
Lymphoid depletion	0	0	0	0	1	2	2 (2)	2(1)
Spleen								
Lymphoid depletion	0	0	0	0	2	3	2 (2)	1 (1)
Submaxillary lymph depletion								
Lymphoid depletion	0	0	0	0	0	0	1 (2)	1 (1)
Mesenteric lymph node								
Lymphoid depletion	0	0	0	0	0	0	1 (2)	2 (1)
Kidneys								
Pigmentation, tubular epithelial cells	0	0	0	0	0	0	0 (2)	1 (1)
Duodenum								
Erosion/ulcer	0	0	0	0	0	0	0 (2)	0 (0)

Number of animals found dead or moribund with a specific change is shown in parentheses.
+ = observed, ALT = alanine aminotransferase, $AUC_{(0\text{-}12h)}$ = area under the concentration-time curve from 0 time to 12 hours postdose, BID = twice daily, BQL = below quantitation limit (<1 ng/mL), BW = body weight, C_{max} = maximum observed concentration, CTD = common technical document, F = female, GLP = Good Laboratory Practice, M = male, NA = not applicable, NC = not calculated, ND = not determined, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, TK = toxicokinetics.

a: n = 3.
b: n = 2.
c: For high dose group, individual data were presented.

Source: Study 20024293.

2.6.7.7.D **Test Article: Tazemetostat**

Report Title: E7438: A 13-Week Oral Toxicity Study Followed by a 28-day Recovery Period in Cynomolgus Monkeys		**Study No.** 20047690
Species / Strain: Monkey/Cynomolgus	Duration of Dosing: 13 weeks, BID	Location in CTD: 4.2.3.2.6
Initial Age: 2.5 to 6.1 years	Duration of Postdose: 4 weeks	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral by gavage[a]	
Vehicle / Formulation: 0.5% methylcellulose solution including 0.1% Tween 80/Suspension		
Special Features: Electrocardiology parameters via jacketed external telemetry. Moribundity in one 600 mg/kg/day female on Day 83 following severe clinical signs (decreased activity, cold to touch, hunched posture, shivering/tremor).		
NOAEL: 100 mg/kg		

Daily Dose (mg/kg)	**0 (Control)**		**100**		**300**		**600**	
Number of Animals	**M: 6**	**F: 6**	**M: 4**	**F: 4**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Tazemetostat[b]								
TK: $AUC_{(0\text{-}12h)}$ (ng·h/mL)								
Day 1	NC	NC	1560.43	1377.75	9707.19	7118.46	23,875.18	8070.65
Day 43	NC	NC	536.73	454.05	2487.17	3061.87	8047.91	4291.79
Day 91	NC	NC	641.17	599.05	3136.98	3574.93	8116.86	6215.10
TK: C_{max} (ng/mL)								
Day 1	BQL	BQL	483.24	500.77	2481.18	1998.49	4651.02	1611.91
Day 43	BQL	BQL	138.52	142.08	461.53	933.78	1311.80	862.51
Day 91	BQL	BQL	147.73	165.85	596.98	725.05	1297.75	1241.04
ER-897387 (EPZ-6930)[b] (metabolite)								
TK: $AUC_{(0\text{-}12h)}$ (ng·h/mL)								
Day 1	NC	NC	4815.45	4593.11	25,036.97	18,033.07	47,766.98	18,889.72
Day 43	NC	NC	3093.39	1696.51	15,553.68	15,422.40	40,679.74	17,842.27
Day 91	NC	NC	3154.20	2877.52	20,238.19	18,072.50	31,036.15	26,806.48
TK: C_{max} (ng/mL)								
Day 1	BQL	BQL	1620.32	1988.11	5835.80	4839.48	7397.79	3767.74
Day 43	BQL	BQL	1025.11	673.08	2978.53	4835.03	5472.72	3434.38
Day 91	BQL	BQL	859.69	1125.59	3427.37	3668.92	4084.09	4507.46
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	1
Body weight	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Food consumption	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals	**M: 6**	**F: 6**	**M: 4**	**F: 4**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Clinical Observations[c]								
Emesis	3 (4)	0 (0)	2 (2)	1 (1)	4 (16)	3 (7)	6 (83)	6 (22)
Fecal abnormalities (soft, mucoid, discolored)	2 (17)	0 (0)	2 (6)	1 (1)	4 (6)	2 (2)	6 (33)	3 (4)
Ophthalmoscopy	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Electrocardiography								
Qualitative analysis	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Quantitative analysis								
RR interval	NNF	NNF	NNF	NNF	decreased 38–121 msec		decreased 59–177 msec	
Hematology	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Serum Chemistry								
Number examined, Day 43	M: 6	F: 6	M: 4	F: 4	M: 6	F: 6	M: 6	F: 6
ALT (U/L)	31.5	30.3	48.3	40.5	446.2	150.0	875.3	879.0
AST (U/L)	29.5	30.8	29.3	37.3	97.5	45.0	159.5	128.3
ALP (U/L)	416.0	453.5	505.8	284.5	589.5	240.8	843.0	563.0
Triglycerides (mg/dL)	46.0	53.7	56.5	66.8	136.2	77.0	130.0	102.3
Number examined, Day 83	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 0	F: 1
ALT (U/L)	NA	NA	NA	NA	NA	NA	NA	1007
AST (U/L)	NA	NA	NA	NA	NA	NA	NA	109
ALP (U/L)	NA	NA	NA	NA	NA	NA	NA	2230
Triglycerides (mg/dL)	NA	NA	NA	NA	NA	NA	NA	61
Total bilirubin (mg/dL)	NA	NA	NA	NA	NA	NA	NA	0.91
Number examined, Day 92	M: 6	F: 6	M: 4	F: 4	M: 6	F: 6	M: 6	F: 5
ALT (U/L)	41.2	36.8	69.0	57.3	389.7	183.0	835.8	835.0
AST (U/L)	53.8	43.3	55.5	79.8	95.2	69.2	155.3	142.2
ALP (U/L)	432.8	406.7	466.3	297.8	583.3	216.5	779.7	377.4
Triglycerides (mg/dL)	45.2	55.8	64.3	61.0	62.0	86.2	93.3	106.0
Albumin (g/dL)	4.12	4.02	3.98	3.95	3.97	4.03	3.43	3.82
Urinalysis	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Moribund sacrifice								
Number examined, Day 83	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 0	F: 1
Gross Pathology								
Liver								

Daily Dose (mg/kg)	**0 (Control)**		**100**		**300**		**600**	
Number of Animals	**M: 6**	**F: 6**	**M: 4**	**F: 4**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Discoloration (dark brown)	NA	NA	NA	NA	NA	NA	NA	1
Thymus								
Small	NA	NA	NA	NA	NA	NA	NA	1
Histopathology								
Liver								
Kupffer cell hypertrophy/pigmentation	NA	NA	NA	NA	NA	NA	NA	1
Hypertrophy, hepatocytes, centrilobular	NA	NA	NA	NA	NA	NA	NA	1
Bile duct hyperplasia	NA	NA	NA	NA	NA	NA	NA	1
Thymus								
Lymphoid depletion	NA	NA	NA	NA	NA	NA	NA	1
Spleen								
Decreased germinal centers	NA	NA	NA	NA	NA	NA	NA	1
Submaxillary lymph node								
Decreased germinal centers	NA	NA	NA	NA	NA	NA	NA	1
Mesenteric lymph node								
Decreased germinal centers	NA	NA	NA	NA	NA	NA	NA	1
Kidneys								
Pigmentation, tubular epithelial cells	NA	NA	NA	NA	NA	NA	NA	1
Lung								
Inflammatory cell infiltration, focal	NA	NA	NA	NA	NA	NA	NA	1
Bone Marrow								
Atrophy, adipocytes	NA	NA	NA	NA	NA	NA	NA	1
Stomach								
Regenerative hyperplasia, glandular stomach	NA	NA	NA	NA	NA	NA	NA	1
Terminal sacrifice (Day 92)								
Number examined	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 3
Gross Pathology								
Liver								
Discoloration (dark brown)	0	0	0	0	0	2	4	2
Discoloration (white)	0	0	0	0	1	0	0	0
Prominent lobular architecture	0	0	0	0	1	1	2	1
Lymph node, mesenteric								
Large	0	0	0	0	0	0	1	0

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals	**M: 6**	**F: 6**	**M: 4**	**F: 4**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Thymus								
Small	0	0	0	0	1	1	0	0
Organ Weights								
Liver, absolute (g)	65.2	59.7	96.0	76.7	101.7	73.8	169.7	96.8
Liver, relative (g/kg BW)	19.2	20.6	23.0	25.0	23.9	25.5	39.4	30.6
Kidney, absolute (g)	13.9	12.9	16.2	13.0	17.0	13.1	23.5	15.1
Kidney, relative (g/kg BW)	4.06	4.43	3.88	4.21	3.98	4.52	5.45	4.76
Histopathology								
Liver								
Kupffer cell hypertrophy/pigmentation	0	0	0	0	4	3	4	3
Hypertrophy, hepatocytes, centrilobular	0	0	0	0	2	2	4	3
Hyperplasia, bile ducts	0	0	0	0	4	2	4	3
Thymus								
Lymphoid depletion	0	0	0	0	3	3	3	3
Spleen								
Decreased germinal centers	0	0	0	0	4	3	4	3
Submaxillary lymph node								
Decreased germinal centers	0	0	0	0	4	2	4	3
Mesenteric lymph node								
Decreased germinal centers	0	0	0	0	4	4	4	3
Kidneys								
Pigmentation, tubular epithelial cells	0	0	0	0	0	0	2	0
Glomerulopathy	0	0	0	0	0	0	2	1
Adrenal								
Cortical hypertrophy, bilateral	0	0	0	0	1	0	2	1
Lung								
Inflammatory cell infiltration	0	0	0	0	0	0	3	1
Postdose evaluation								
Number examined, Day 119	M: 2	F: 2	M: 0	F: 0	M: 2	F: 2	M: 2	F: 2
Serum chemistry (Day 119)								
ALT (U/L)	30.0	28.5	NA	NA	73.0	63.5	105.5	536.5
AST (U/L)	24.5	30.5	NA	NA	34.5	29.0	41.5	107.0
ALP (U/L)	434.0	388.5	NA	NA	639.0	122.5	675.0	432.5

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals	**M: 6**	**F: 6**	**M: 4**	**F: 4**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Recovery sacrifice								
Number examined, Day 119	M: 2	F: 2	M: 0	F: 0	M: 2	F: 2	M: 2	F: 2
Gross pathology								
Liver								
Discoloration (dark brown)	0	0	NA	NA	0	1	0	0
Organ Weights								
Liver, absolute (g)	73.714	66.107	NA	NA	68.574	70.923	93.506	88.928
Liver, relative (g/kg BW)	1.890	2.170	NA	NA	1.984	2.149	2.207	2.920
Kidney, absolute (g)	15.844	13.053	NA	NA	13.726	12.794	19.397	14.578
Kidney, relative (g/kg BW)	0.402	0.428	NA	NA	0.400	0.388	0.459	0.478
Histopathology								
Liver								
Kupffer cell hypertrophy/pigmentation	0	0	NA	NA	2	1	2	2
Hyperplasia, bile ducts	0	0	NA	NA	0	0	1	2
Thymus								
Lymphoid depletion	0	0	NA	NA	0	1	0	0
Spleen								
Decreased germinal centers	0	0	NA	NA	1	0	0	0
Submaxillary lymph node								
Decreased germinal centers	0	0	NA	NA	0	0	1	0
Mesenteric lymph node								
Decreased germinal centers	0	0	NA	NA	0	1	0	1

Number of animals found dead or moribund with a specific change is shown in parentheses.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate transaminase, $AUC_{(0\text{-}12h)}$ = area under the concentration-time curve from 0 time to 12 hours postdose, BID = twice daily, BQL = below quantitation limit (<1 ng/mL), BW = body weight, C_{max} = maximum observed concentration, CTD = common technical document, F = female, GLP = Good Laboratory Practice, M = male, NA = not applicable, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, PR = pulse rate, QD = once daily, QTc = corrected QT, TK = toxicokinetics.

a: The test and control articles were administered to the appropriate animals by BID gavage (approximately 12 hours apart) from Days 1 to 91.
b: TK samples were collected from main study animals (n=4) and analyzed.
c: Number of animals (number of incidences) for findings of emesis and fecal abnormalities are noted. Includes QD cage side observations, unscheduled observations, and postdose observations obtained 1 to 2 hours following each QD (dose 1 and dose 2) during the dosing period, Day 1 to Day 92.
Source: Study 20047690.

2.6.7.8 In vitro 遺伝毒性試験

2.6.7.8.A 重要な試験以外の試験

Test Article: Tazemetostat

Species/Strain	Method of Administration	Duration of Dosing	Dose	Gender and Number per Group	Noteworthy Findings	GLP	Study Number
Salmonella. typhimurium (TA98, TA100, and TA1535)	In vitro	NA	Up to 5000 µg/plate with and without S9	NA	Negative for bacterial mutation with and without metabolic activation	No	864270

GLP = Good Laboratory Practice, NA = not applicable.

Sources: Study 864270.

2.6.7.8.B In Vitro Genotoxicity Study: Reverse Mutation in Bacterial Cells **Test Article: Tazemetostat**

Report Title: E7438: Reverse Mutation Assay in Bacteria		Study No. 9600848
Test for Induction of: Reverse mutation in bacterial cells	No. of Independent Assays: 1	Location in CTD: 4.2.3.3.1.2
Strains: *Salmonella. typhimurium* and *Escherichia coli*	No. of Replicate Cultures: 3	GLP Compliance: Yes
Metabolizing System: Aroclor 1254-induced male rat liver S9	No. of Cells Analyzed/Cultured: ≥1000×10^6	
Vehicles: for Test Article: DMSO (tazemetostat); DMSO (9-aminoacridine, 2-nitrofluorene, NQO, 2-aminoanthracene, BaP), water (sodium azide)		
Treatment: Plate incorporation		Date of Treatment: [redacted] 20[redacted]
Cytotoxic Effects: 5000 µg/plate for strain TA1535 in the presence of S9; 5000 µg/plate for strain TA1537 in the absence and presence of S9.		
Genotoxic Effects: None		

Metabolic Activation	**Test Article**	**Dose Level (µg/plate)**	**Strain (Mean ± Standard Deviation)**				
			TA1535	**TA1537**	**TA98**	**TA100**	**WP2 *uvrA***
Without Activation	DMSO	NA	18 ± 1	15 ± 6	28 ± 6	113 ± 11	43 ± 5
	Tazemetostat	20.6	NA	17 ± 4	NA	NA	NA
		61.7	16 ± 3	15 ± 5	22 ± 3	131 ± 4	41 ± 3
		185	13 ± 6	11 ± 7	25 ± 5	115 ± 8	40 ± 8
		556	12 ± 5[p]	9 ± 5[p]	27 ± 8[p]	107 ± 8[p]	37 ± 5[p]
		1667	17 ± 2[p]	9 ± 3[p]	22 ± 5[p]	109 ± 7[p]	41 ± 7[p]
		5000	10 ± 2[p]	6 ± 3[p,t]	22 ± 9[p]	120 ± 12[p]	42 ± 6[p]
	Positive Controls						
	Sodium azide	0.5	394 ± 50	NA	NA	476 ± 34	NA
	9-Aminoacridine	50	NA	361 ± 108	NA	NA	NA
	2-Nitrofluorene	1	NA	NA	129 ± 5	NA	NA
	NQO	0.5	NA	NA	NA	NA	1310 ± 21
With Activation	DMSO	NA	14 ± 7	17 ± 3	43 ± 9	139 ± 16	57 ± 3
	Tazemetostat	20.6	16 ± 5	14 ± 4	NA	NA	NA
		61.7	12 ± 3	21 ± 8	39 ± 2	151 ± 2	34 ± 9
		185	12 ± 6	20 ± 6	40 ± 3	138 ± 12	46 ± 3
		556	11 ± 2	20 ± 3	51 ± 4	138 ± 11	48 ± 12
		1667	14 ± 4	19 ± 2	51 ± 8	105 ± 19	53 ± 4
		5000	6 ± 4[p,t]	6 ± 3[p,t]	34 ± 6[p]	116 ± 7[p]	64 ± 4[p]
	Positive Controls						
	2-Aminoanthracene	5	253 ± 24	NA	NA	NA	NA
		20	NA	NA	NA	NA	261 ± 14

	BaP	5	NA	157 ± 12	525 ± 14	1030 ± 51	NA

BaP = benzo[a]pyrene, DMSO = dimethyl sulfoxide, CTD = common technical document, GLP = Good Laboratory Practice, NA = not applicable, NQO = 4 nitroquinoline N-oxide.

p: Precipitation was observed.
t: Cytotoxicity was observed.

Source: Study 9600848.

2.6.7.8.C **Test Article: Tazemetostat**

Report Title: E7438: In Vitro Mammalian Cell Micronucleus Test in Human Peripheral Blood Lymphocytes		Study No. 9600891
Test for Induction of: Micronuclei in human peripheral blood lymphocytes	No. of Independent Assays: 2	Location in CTD: 4.2.3.3.1.3
Strains: Human peripheral blood lymphocytes	No. of Replicate Cultures: 2	GLP Compliance: Yes
Metabolizing System: Aroclor 1254-induced male rat liver S9	No. of Cells Analyzed/Cultured: 1000	
Vehicles: DMSO (tazemetostat); water (positive controls)		
Cytotoxic Effects: None		Date of Treatment: [redacted] 20[redacted] (initial);
Genotoxic Effects: None		[redacted] 20[redacted] (supplemental)

Treatment	Concentration (µg/mL)	Average CBPI	% Cytotoxicity[a]	Total Number of BC examined	% MBC
4 hours treatment in the absence of S9 (–S9)					
DMSO	NA	1.9	0.0	2000	0.35
Tazemetostat	32	1.9	–3.4	2000	0.25
	64	1.9	0.1	2000	0.25
	128	1.4	54.8	2000	0.25
MMC	0.60	1.4	51.6	2000	15.8[b]
4 hours treatment in the presence of S9 (+S9)					
Initial assay					
DMSO	NA	1.8	0.0	2000	0.30
Tazemetostat	64	1.8	3.5	2000	0.35
	128	1.8	2.7	2000	0.25
	256[c]	1.1	87.4	ND[d]	ND[d]
CP	15	1.5	35.3	2000	5.0[b]
Supplemental assay					
DMSO	NA	1.8	0.0	2000	0.30
Tazemetostat	125	1.6	27.1	2000	0.25
	145	1.5	42.1	2000	0.35
	165	1.2	76.5	ND[d]	ND[d]
CP	15	1.4	51.0	2000	4.1[b]

Treatment	Concentration (µg/mL)	Average CBPI	% Cytotoxicity[a]	Total Number of BC examined	% MBC
24 hours treatment in the absence of S9 (–S9)					
Initial assay					
DMSO	NA	1.7	0.0	2000	0.35
Tazemetostat	32	1.6	12.2	2000	0.15
	64	1.5	25.7	2000	0.30
	128	1.1	85.1	ND[d]	ND[d]
Colcemid	0.070	1.6	8.8	2000	4.1[b]
Supplemental assay					
DMSO	NA	1.7	0.0	2000	0.15
Tazemetostat	50	1.5	36.4	2000	0.25
	60	1.4	38.9	ND[e]	ND[e]
	70	1.4	47.1	ND[e]	ND[e]
	80	1.3	53.3	2000	0.45
Colcemid	0.070	1.6	14.0	2000	3.8[b]

BC = binucleated cells, CBPI = Cytokinesis-Block Proliferation Index, CP = cyclophosphamide monohydrate, DMSO = dimethyl sulfoxide, CTD = common technical document, GLP = Good Laboratory Practice, MBC = micronucleated binuclear cells, MMC = mitomycin C, NA =not applicable, ND = not determined.

a: Relative to the vehicle control.
b: Substantial increase compared to concurrent vehicle control.
c: Presence of precipitate at the end of treatment.
d: Not evaluated due to excessive cytotoxicity.
e: Concentration not selected for micronuclei evaluation.

Source: Study 9600891.

2.6.7.9 In vivo 遺伝毒性試験

Test Article: Tazemetostat

Report Title: E7438: Micronucleus Assay in Rats after Oral Administration		Study No. 9800206
Test for Induction of: Bone marrow micronuclei	Treatment Schedule: 2 doses, 24 hr apart	Location in CTD: 4.2.3.3.2.1
Species / Strain: Rat/Sprague Dawley	Sampling Time: 24 after last dose	GLP Compliance: Yes
Initial Age: 49 days old	Method of Administration: Oral by gavage	Date of Treatment: [redacted] 20[redacted];
Cells Evaluated: Polychromatic erythrocytes	No. of Cells Evaluated / Animal: 2000	[redacted] 20[redacted]
Vehicle/Formulation: 0.5% methylcellulose solution including 0.1% Tween 80 in water (tazemetostat); water (positive control)		
Special Features: None		
Toxic / Cytotoxic Effects: Clinical signs were observed at doses ≥1000 mg/kg; non-cytotoxic as no increases in micronucleated immature erythrocytes and no decrease in immature erythrocytes were observed at any dose level tested.		
Genotoxic Effects: None		
Evidence of Exposure: Clinical signs were observed at doses ≥1000 mg/kg		

Group	Number of animals	% IE/(IE+ME) Males	% IE/(IE+ME) Females	% IE/(IE+ME) Males & Females	Incidence MIE Males	Incidence MIE Females	Incidence MIE Males & Females	Incidence MME Males & Females
Vehicle controlled[a]	5M, 5F	52.5	52.9	52.7	2.0	1.4	1.7	0.0
Tazemetostat 500 mg/kg/day[a]	5M, 5F	50.3	50.9	50.6	2.0	0.6	1.3	0.0
Tazemetostat 1000 mg/kg/day[a]	5M, 5F	47.5	44.5	46.0	1.0	2.0	1.5	0.0
Tazemetostat 2000 mg/kg/day[a]	5M, 5F	52.5	44.8	48.6	0.6	2.0	1.3	0.0
Cyclophosphamide 20 mg/kg[b]	5M, 5F	43.0	NA	43.0[c]	42.0	NA	42.0[c]	0.0[c]

%IE/(IE+ME) = proportion of IE, MIE = number of micronucleated cells observed per 2000 IE examined, MME = number of MME observed (mean value expressed per 2000 ME examined).

CTD = common technical document, F = female, GLP = Good Laboratory Practice, IE = Immature erythrocytes, M = male, ME = Mature erythrocytes, MIE = Micronucleated immature erythrocytes, MME = Micronucleated mature erythrocytes, NA = not applicable.

a: Two doses were administered 24 hours apart (± 15 minutes).
b: Positive control (20 mg of the monohydrate per kg) dosed once only, 24 hours prior to sampling.
c: Values of males only.

Source: Study 9800206.

2.6.7.10 がん原性試験

タゼメトスタットは進行がんの治療を目的とした抗悪性腫瘍剤であることから，ICH S9 ガイドライン（抗悪性腫瘍の非臨床評価に関するガイドライン）にもとづき，がん原性試験は実施していない。

2.6.7.11 生殖発生毒性試験：重要な試験以外の試験

Test Article: Tazemetostat

Species / Strain	Route/Method of Administration (Vehicle/ Formulation)	Dosing Period	Dose (mg/kg)	Number per Group	Noteworthy Findings	Study Number
Study Title: A Dose Range-Finding Embryo-Fetal Development Study of Tazemetostat by Oral Gavage in Rats						
Rat/Sprague Dawley	Oral gavage 0.5% methylcellulose and 0.1% Tween 80/ suspension	DG 7 through 17	0	6	None	20097363
			100	6	Maternal body weight on DG 21 was reduced (–7.4% from controls).	
			300	6	Salivation and liquid discharge from vulva were observed in 1 rat. Maternal body weight on DG 21 was reduced (–24.7% from controls). Increased mean number resorption (9.0/litter compared with 1.2 in controls). Increased post-implantation loss (73.0% compared with 8.4% in controls). Decreased mean number of live fetuses/litter (3.8/litter compared with 13.2/litter controls). Decreased mean fetal body weight (–34% from controls).	
			600	6	Suspected dehydration, hunched posture, salivation, thin appearance, ungroomed fur, and liquid discharge from muzzle and vulva. Decreased maternal body weight gain, DG 7 to 21 (–92% from controls). Decreased maternal body weight on DG 21 (–34.7% from controls). Decreased maternal food consumption (–43.0% from controls). Increased mean number resorption (12.0/litter compared with 1.2 in controls). Increased post-implantation loss (100.0% compared with 8.4% in controls). Decreased mean number of live fetuses/litter (0.0/litter compared with 13.2/litter controls).	

DG = day of gestation, RO = reverse osmosis.

Source: Study 20097363.

Species / Strain	Route/Method of Administration (Vehicle/ Formulation)	Dosing Period	Dose (mg/kg)	Number per Group	Noteworthy Findings	Study Number
Study Title: An Acute Dose Range-Finding Study of Tazemetostat by Oral (Stomach Tube) in Rabbits						
Rabbit/New Zealand white	Oral gavage 0.5% methylcellulose and 0.1% Tween 80	DG 7 through 11	0	3	None	20097367
			250	3	None	
			500	3	Increased mean number of nonviable embryos (1.3 nonviable embryos/litter compared with 0.0/litter in controls). Increased post implantation loss (33%)	
			1000	3	Decreased fecal output was observed in 3 rabbits. Maternal body weight gain was reduced for the intervals of DG 7 to 12 (–319.93 g compared with +3.5 g in controls). Decreased mean maternal body weight on DG 12 (–7% from controls). Decreased maternal food consumption (–53% from controls). Post implantation loss was increased (100% compared with 0% in controls). Increased mean number of nonviable embryos (10.0 nonviable embryos/litter compared with 0.0/litter in controls).	

DG = day of gestation, RO = reverse osmosis.

Source: Study 20097367.

Species / Strain	Route/Method of Administration (Vehicle/ Formulation)	Dosing Period	Dose (mg/kg)	Number per Group	Noteworthy Findings	Study Number
Study Title: A Dose Range-Finding Embryo-Fetal Development Study of Tazemetostat by Oral (Stomach Tube) in Pregnant Rabbits						
Rabbit/New Zealand white	Oral gavage 0.5% methylcellulose and 0.1% Tween 80 in RO membrane-processed deionized water	DG 7 through 19	0	5	None	20097365
			150	5	None	
			250	5	Liquid feces were observed in 1 rabbit. Maternal BWG (%) was reduced for the intervals of DG 16 to 20 (–48% from controls). Mean fetal body weight was reduced (–13% from controls).	
			450	5	Liquid feces were observed in 3 rabbits. Maternal BWG (%) was reduced for the intervals of DG 16 to 20 (–40% from controls). Early resorption was increased (2.4/litter compared with none in controls). Post-implantation loss was increased (28.66% compared with 0% in controls). Mean fetal body weight was reduced (–12% from controls).	
Juvenile Rat/Sprague Dawley	Oral gavage/0.5% methylcellulose 400 solution including 0.1% Tween 80 /suspension	4 weeks	0, 50, 150, 500, 1000	5M/5F	≤150 mg/kg/day: no toxicity ≥500 or 1000 mg/kg: After 1 or 2 doses, euthanized in extremis with clinical signs of hypoactivity and cool or pale body. Gastric toxicity was considered to be the cause of moribundity.	[redacted]-779008

BWG = body weight gain, DG = day of gestation, RO = reverse osmosis.

Source: Study 20097365.

2.6.7.12 生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

タゼメトスタットは進行がんの治療を目的とした抗悪性腫瘍剤であることから，ICH S9 ガイドライン（抗悪性腫瘍の非臨床評価に関するガイドライン）にもとづき，受胎能及び着床までの初期胚発生に関する試験は実施していない。

2.6.7.13 生殖発生毒性試験：胚・胎児発生に関する試験

2.6.7.13.A **Test Article: Tazemetostat**

Report Title: An Embryo-Fetal Development Study of Tazemetostat by Oral Gavage in Rats		Study No. 20097364
Species/Strain: Rat/Sprague Dawley	Duration of Dosing: DG 7 through 17	Location in CTD: 4.2.3.5.2.2
Initial Age: 56 to 70 days	Day of Mating (vaginal plug observation): DG0	
Date of First Dose: [redacted] 20[redacted], DG 7	Day of C-Section: DG 21	GLP Compliance: Yes
Special Features: Toxicokinetics	Method of Administration: Oral by gavage	Design compliant with ICH S5(R2)? Yes
Vehicle/Formulation: 0.5% MC and 0.1% Tween 80 in RO membrane-processed deionized water		
NOAEL F_0 Females: 100 mg/kg/day	NOAEL F_1 Litters: Not established	

Daily Dose (mg/kg)	**0 (Control)**	**50**	**100**	**200**
Tazemetostat				
TK: $AUC_{(0-t)}$ (ng·h/mL)				
DG7	NC	8350	39,600	114,000
DG17	NC	14300	42,700	96,000
TK: C_{max} (ng/mL)				
DG7	BQL	2770	4680	8210
DG17	BQL	2190	3470	8850
ER-897387 (EPZ-6930, metabolite)				
TK: $AUC_{(0-t)}$ (ng·h/mL)				
DG7	NC	763	3370	15,300
DG17	NC	2400	6200	22,600
TK: C_{max} (ng/mL)				
DG7	BQL	224	431	1140
DG17	BQL	287	427	1700
Number pregnant	20	20	19	20
Number died or sacrificed moribund	0	0	0	0
Number aborted of with total resorption of litter	NNF	NNF	NNF	NNF
Number delivered	NNF	NNF	NNF	NNF
Clinical observations	NNF	NNF	NNF	NNF
Body weight (%)[a] – DG 21	388.4 g	NNF	NNF	–10.4**
Body weight gain (%)[a] DG 7 to 21	149.9 g	NNF	NNF	–23.0**
Food consumption (%) DG 7 to 21	25.5 g	NNF	NNF	NNF

Daily Dose (mg/kg)	0 (Control)	50	100	200
Mean number corpora lutea	14.00	13.25	13.05	13.70
Mean number implantations	12.95	12.55	12.74	13.30
Mean % preimplantation loss	8.4	4.3	2.2	2.9
Fetuses				
Number of fetuses evaluated	248	244	236	216
Number live fetuses				
Mean number resorptions	0.55	0.35	0.31	2.50
Mean number late resorptions	0.0	0.05	0.05	0.90**
Number litters with dead fetuses	NNF	NNF	NNF	NNF
Mean % post-implantation loss	4.0	2.7	2.5	19.7
Litters				
Mean fetal body weight (g)	6.089	6.056	5.941	4.373**
Live male fetuses (%)	49.9	53.2	50.7	53.6
Fetal anomalies:				
Gross external (F^b/L^c)				
Domed head	NNF	NNF	NNF	7/4
Short tail	NNF	NNF	NNF	4/4
Visceral anomalies (F^b/L^c)	NNF	NNF	NNF	NNF
Skeletal anomalies (F^b/L^c)				
Skull bones:				
Fused exoccipitals	NNF	NNF	NNF	89/18##
Absent supraoccipitals	NNF	NNF	NNF	1/1
Misshapen exoccipitals	NNF	NNF	1/1	7/3
Suture bone(s) present	NNF	2/1	43/13##	110/20##
Incomplete ossified supraoccipitals	NNF	NNF	NNF	35/16##
Vertebrae:				
Fused cervical arches	NNF	NNF	NNF	7/3
Absent thoracic vertebrae	NNF	NNF	16/10##	9/4
Fused centra in thoracic vertebrae	NNF	NNF	NNF	1/1
Fused lumbar	NNF	NNF	NNF	2/1
Fused sacral vertebrae	NNF	NNF	NNF	1/1
Misshapen arches in cervical	1/1	12/9##	59/17##	68/17##
Isolated ossification sites in cervical	NNF	NNF	5/3	6/4
Incompletely ossified cervical arches	NNF	NNF	NNF	36/15##

Daily Dose (mg/kg)	0 (Control)	50	100	200
Bipartite ossification centra in cervical	NNF	NNF	NNF	7/6#
Bipartite ossification centra in thoracic	3/3	6/3	11/9#	65/20##
Bipartite centra lumbar vertebrae	NNF	NNF	NNF	17/13##
Forelimbs:				
Malformed forelimbs (short digits, absent forepaw phalanges, and absent metacarpals)	NNF	NNF	NNF	3/1
Ribs:				
Malformed ribs (absent)	NNF	NNF	33/15##	12/6#
Short ribs	3/2	29/11##	88/19##	34/13##
Misshapen ribs	NNF	NNF	NNF	21/11##
Sternebrae:				
Incompletely ossified sternebrae	NNF	NNF	1/1	25/16##
Bipartite ossification in sternebrae	NNF	1/1	1/1	14/10##
Asymmetric sternebrae	NNF	2/2	1/1	4/4
Misshapen sternebrae	1/1	NNF	1/1	27/13
Supernumerary ribs:				
Supernumerary cervical ribs – full	NNF	NNF	49/16##	15/4
Supernumerary cervical ribs – short	1/1	18/12##	68/18##	7/4
Total affected fetuses (litters)				
Total affected (fetuses/litters) – malformations	NNF	NNF	33/15	24/11
Total affected (fetuses/litters) – variations	10/8	57/20	121/19	112/20

Daily Dose (mg/kg)	0 (Control)	50	100	200

$AUC_{(0-t)}$ = area under the concentration-time curve from 0 time extrapolated to the last measurable concentration, C_{max} = maximum observed concentration, DG = day of gestation, CTD = common technical document, GLP =Good Laboratory Practice, ICH = International Conference on Harmonisation, MC = methylcellulose, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, RO = reverse osmosis, TK = toxicokinetics.

a: For controls, group means are shown. For treated groups, percent differences from controls are shown.
b: Fetal incidence.
c: Litter incidence.

**$P<0.01$ (Dunn or Dunnett's test); #$P<0.05$; ##$P<0.01$ (Fisher's Exact 2-sided test). Statistical significance is based on actual data (not on the percent differences).

Source: Study 20097364.

2.6.7.13.B **Test Article: Tazemetostat**

Report Title: An Embryo-Fetal Development Study of Tazemetostat by Oral (Stomach Tube) Administration in Rabbits		Study No. 20097366
Species/Strain: Rabbit/New Zealand white	Duration of Dosing: DG 7 through 19	Location in CTD: 4.2.3.5.2.5
Initial Age: 6 months old	Day of Mating: DG 0	
Date of First Dose: [redacted] 20[redacted], DG 7	Day of C-Section: DG 29	GLP Compliance: Yes
Special Features: Toxicokinetics	Method of Administration: Oral by gavage	Design compliant with ICH S5(R2)? Yes
Vehicle/Formulation: 0.5% methylcellulose and 0.1% Tween 80 in RO membrane-processed deionized water		
NOAEL F_0 Females: 400 mg/kg/day	NOAEL F_1 Litters: Not established	

Daily Dose (mg/kg)	**0 (Control)**	**100**	**200**	**400**
Number of Animals for Toxikokinetics	2	3	3	3
Tazemetostat				
TK $AUC_{(0-t)}$ (ng·h/mL)				
DG 7	NC	3730	24,700	89,100
DG 19	NC	10,100	37,700	48,500
TK C_{max} (ng/mL)				
DG 7	BQL	1520	5960	12,000
DG 19	BQL	4390	11,100	12,200
ER-897387 (EPZ-6930, metabolite)				
TK $AUC_{(0-t)}$ (ng·h/mL)				
DG 7	NC	9400	35,200	105,000
DG 19	NC	11,300	33,300	46,300
TK C_{max} (ng/mL)				
DG 7	BQL	3130	7150	11,400
DG 19	BQL	4250	7240	8420
Number of animals (main groups)	20	20	20	20
Number pregnant	20	19	20	19
Number died or sacrificed moribund	3 (including 1 abortion)	1	NNF	1 (abortion)
Number aborted or with total resorption of litter	NNF	NNF	NNF	NNF
Number delivered	NNF	NNF	NNF	NNF
Clinical observations	NNF	NNF	NNF	NNF
Body weight (%)[a] DG 29	3609.46g	+4.2	+7.6	+3.2
Body weight gain (%)[a] DG 7 to 20	238.45g	+10.7	+43.0	–10.4

Daily Dose (mg/kg)	**0 (Control)**	**100**	**200**	**400**
Body weight gain (%)[a] DG 7 to 29	376.13g	+8.9	+40.0*	–3.3
Food consumption (%)[a] DG 7 to 29	131.1g	+5.1	+18.3*	+5.0
Mean number corpora lutea	10.1	10.0	9.8	10.2
Mean number implantations	9.9	9.3	9.3	9.8
Mean % preimplantation loss	1.81	6.93	7.50	4.07
Litters				
Number litters evaluated	17	18	20	18
Number live fetuses	166	163	174	135
Mean number resorptions	0.1	0.2	0.6	2.3**
Mean number early resorptions	0.1	0.2	0.3	1.5**
Mean number late resorptions	0.0	0.0	0.3	0.8**
Number of litters with dead fetuses	NNF	1	NNF	NNF
Mean % post-implantation loss	1.08	2.77	5.69	23.41**
Mean fetal body weight (g)	40.196	42.175	42.684	40.848
Live male fetuses (%)	47.46	48.83	35.62	43.31
Fetal anomalies:				
Gross external (F[b]/L[c])				
Ear: pinna, small	NNF	NNF	NNF	2/1
Eye: open	NNF	NNF	NNF	2/1
Face: palate, cleft	NNF	NNF	NNF	1/1
Snout, cleft	NNF	NNF	NNF	2/1
Forelimb: hyperextension	NNF	NNF	NNF	1/1
Forepaw: hyperextension	NNF	NNF	NNF	1/1
Forepaw: malrotated	NNF	NNF	NNF	2/2
Paw/digit: forepaw, absent	NNF	NNF	NNF	4/3
Paw digit: forepaw, pendulous	NNF	NNF	NNF	1/1
Trunk: distended abdomen	NNF	NNF	NNF	1/1
Tail: short	NNF	NNF	NNF	2/2
Entire body: subcutaneous edema	NNF	NNF	NNF	1/1
Visceral anomalies (F[b]/L[c])				
Adrenal gland: malpositioned	NNF	NNF	NNF	1/1
Aorta: dilated	NNF	NNF	NNF	1/1
Aortic arch: dilated	NNF	1/1	NNF	5/5[#]
Diaphragm: hernia	NNF	NNF	NNF	3/3

Daily Dose (mg/kg)	**0 (Control)**	**100**	**200**	**400**
Ductus arteriosus: patent	NNF	NNF	NNF	7/5[#]
Eye: small	2/1	NNF	NNF	3/3
Great vessels: transposition	NNF	NNF	NNF	1/1
Great vessels: truncus arteriosus, persistent	NNF	1/1	NNF	14/7[##]
Heart: ventricular septum, defect	NNF	1/1	NNF	21/10[##]
Kidney: fused	NNF	NNF	1/1	2/2
Kidney: malpositioned	NNF	NNF	2/2	7/5[#]
Kidney: absent	NNF	NNF	NNF	6/3
Liver: large	NNF	NNF	NNF	1/1
Lung: lobe, absent	NNF	1/1	NNF	3/2
Lung: absent	NNF	NNF	NNF	3/2
Lung: small	NNF	1/1	NNF	3/3
Pulmonary trunk: narrow	NNF	1/1	NNF	4/4
Stomach: malpositioned	NNF	NNF	NNF	1/1
Ureter: absent	NNF	NNF	NNF	3/1
Skeletal anomalies (F[b]/L[c])				
Forelimb				
Digits, absent	NNF	1/1	NNF	5/4
Forepaw phalanges: absent	NNF	1/1	NNF	5/4
Forepaw phalanges: misshapen	NNF	NNF	NNF	1/1
Forepaw phalanges: small	NNF	2/1	NNF	3/3
Metacarpal, absent	NNF	1/1	NNF	5/4
Ulna, absent	NNF	NNF	NNF	2/2
Rib				
Fused	NNF	NNF	1/1	1/1
Short	NNF	NNF	NNF	8/4
Supernumerary	NNF	NNF	NNF	1/1
Skull bones				
Fused exoccipitals	NNF	NNF	NNF	67/15[##]
Misshapen exoccipitals	NNF	NNF	1/1	9/6[#]
Frontal: isolated ossification	NNF	NNF	NNF	8/5[#]
Frontal: misshapen	NNF	NNF	NNF	10/5[#]
Hyoid ala: absent	NNF	NNF	NNF	14/6[#]

Daily Dose (mg/kg)	0 (Control)	100	200	400
Hyoid ala: short	NNF	NNF	NNF	21/9##
Interparietal: absent	NNF	1/1	5/4	69/15##
Interparietal: small	NNF	NNF	8/4	28/13##
Maxilla, misshapen	NNF	NNF	NNF	2/1
Nasal, misshapen	NNF	NNF	NNF	2/1
Palatine, cleft	NNF	NNF	NNF	1/1
Premaxilla, misshapen	NNF	NNF	NNF	2/1
Squamosal, misshapen	NNF	NNF	NNF	1/1
Supraoccipital, incomplete ossification	NNF	NNF	NNF	3/2
Suture: large	NNF	NNF	NNF	2/2
Suture: misshapen	NNF	NNF	NNF	7/4
Suture bone, present	NNF	NNF	1/1	7/5#
Zygomatic arch, misshapen	NNF	NNF	NNF	1/1
Sternebrae				
Bipartite ossification	NNF	1/1	2/2	5/3
Fused	1/1	8/5	13/6	43/13##
Incomplete ossification	NNF	NNF	4/4	11/8##
Isolated ossification site	8/1	19/9##	31/13##	8/6
Large	NNF	NNF	NNF	2/1
Misshapen	NNF	8/5#	34/15##	25/9##
Vertebrae				
Atlas, ventral arch: malpositioned	NNF	NNF	NNF	1/1
Atlas, ventral arch: misshapen	NNF	NNF	NNF	1/1
Caudal vertebra: absent	NNF	NNF	NNF	2/2
Caudal vertebra: fused	NNF	NNF	NNF	7/6#
Caudal vertebra: unossified	NNF	NNF	NNF	1/1
Cervical arch: fused	NNF	NNF	NNF	3/2
Cervical arch: incomplete ossification	1/1	NNF	11/6	49/15##
Cervical arch: isolated ossification	NNF	NNF	5/3	13/9##
Cervical arch: misshapen	NNF	1/1	2/1	50/16##
Cervical arch: small	NNF	NNF	NNF	8/3
Cervical arch: unossified	NNF	NNF	NNF	13/7##

Daily Dose (mg/kg)	0 (Control)	100	200	400
Cervical centrum: bipartite ossification	NNF	1/1	NNF	3/1
Cervical centrum: fused	NNF	NNF	NNF	1/1
Cervical centrum: incomplete ossification	NNF	NNF	NNF	10/7##
Cervical centrum: misshapen	NNF	NNF	NNF	2/2
Cervical centrum: unossified	NNF	NNF	NNF	81/16##
Cervical vertebra: absent	NNF	NNF	NNF	10/5#
Thoracic centrum: bipartite ossification	NNF	NNF	3/2	1/1
Thoracic centrum: fused	NNF	NNF	1/1	2/1
Thoracic centrum: unilateral ossification	NNF	NNF	NNF	1/1
Sacral arch, misshapen	NNF	NNF	NNF	1/1
Sacral centrum, fused	NNF	NNF	NNF	1/1
Thoracic vertebra, supernumerary	NNF	NNF	NNF	1/1
Total affected fetuses (litters) in skeletal examination				
Total affected (fetuses/litters) – malformations	NNF	2/2	8/6#	84/16##
Total affected (fetuses/litters) – variations	11/3	61/15##	142/19##	135/18##

$AUC_{(0\text{-}t)}$ = area under the concentration-time curve from 0 time extrapolated to the last measurable concentration, C_{max} = maximum observed concentration, DG = day of gestation, CTD = common technical document, GLP =Good Laboratory Practice, ICH = International Conference on Harmonisation, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, RO = reverse osmosis, TK = toxicokinetics.

a: For controls, group means are shown. For treated groups, percent differences from controls are shown.
b: Fetal incidence.
c: Litter incidence.

*P<0.05; **P<0.01 (Dunn or Dunnett's test); #P<0.05; ##P<0.01 (Fisher's Exact 2-sided test).

Source: Study 20097366.

2.6.7.14 生殖発生毒性試験：出生前及び出生後の発生並びに母体の機能に関する試験

タゼメトスタットは進行がんの治療を目的とした抗悪性腫瘍剤であることから，ICH S9 ガイドライン（抗悪性腫瘍の非臨床評価に関するガイドライン）にもとづき，出生前及び出生後の発生並びに母体の機能に関する試験は実施していない。

2.6.7.15 生殖発生毒性試験：幼若動物を用いた試験

Test Article: Tazemetostat

Report Title: An Oral (Gavage) Juvenile Toxicity Study of EPZ-6438 in Sprague Dawley Rats		Study No. [redacted]-154506
Species/Strain: Rat/Sprague Dawley	Duration of Dosing: PND 7 to 98	Location in CTD: 4.2.3.5.4.2
Initial Age: PND 7	Day of Mating: DG 0	
Date of First Dose: [redacted] 20[redacted]	Litters Culled: Culled on PND 4; 10 pups/litter	GLP Compliance: Yes
Special Features: Thymus and spleen immunophenotyping	Route/Method of Administration: Oral by gavage	Design compliant with ICH S5(R2)? Yes
Vehicle/Formulation: 0.5% methylcellulose and 0.1% Tween 80/Suspension		
NOAEL: M (50 mg/kg); F (not established)		

Daily Dose (mg/kg)	**0 (Control)**	**50**	**100**	**150/300[a]**	**150/600[a]**
Males TK					
Number evaluated (TK Phase)	39	39	39	39	39
Number died or euthanized in extremis (TK Phase)	0	1	0	1	2
Tazemetostat AUC_{last} (ng·h/mL)					
PND 7	NA	6850	27,700	70,100	56,900
PND 21	NA	NA	NA	35,200[b]	26,500[b]
PND 22	NA	3250[b]	11,300[b]	114,000	175,000
PND 98	NA	6340	19,200	125,000	290,000
Tazemetostat C_{max} (ng/L)					
PND 7	NA	1690	3840	9090	9690
PND 21	NA	NA	NA	8800	9000
PND 22	NA	1850	3740	13,300	15,600
PND 98	NA	1410	3800	11,500	18,200
ER-897387 (EPZ-6930) AUC_{last} (ng·h/mL)					
PND 7	NA	62,300	195,000	266,000	283,000
PND 21	NA	NA	NA	84,200	45,000
PND 22	NA	3440[b]	16,900[b]	123,000	228,000
PND 98	NA	6700	20,300	131,000	322,000
ER-897387 (EPZ-6930) C_{max} (ng/L)					
PND 7	NA	6060	12,900	19,900	19,000
PND 21	NA	NA	NA	14,000	7800
PND 22	NA	1600	3710	10,400	14,000

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
PND 98	NA	1430	3790	9370	18,600
Males					
Number evaluated – dosing period	20	20	21	20	20
Number died or euthanized in extremis	0	1	2	0	3
Clinical observations (daily examinations)					
Gasping	NNF	NNF	NNF	NNF	+[c]
Rales	NNF	NNF	NNF	NNF	+[c]
Labored respiration	NNF	NNF	NNF	NNF	+[c]
Red material around nose	NNF	NNF	NNF	+	+[c]
Red material around eyes(s)	NNF	NNF	NNF	+	+[c]
Scabbing tail	NNF	NNF	NNF	NNF	+
Scabbing forelimb(s)	NNF	NNF	NNF	NNF	+[c]
Yellow material ventral trunk	NNF	NNF	NNF	NNF	+
Scabbing hindlimb(s)	NNF	NNF	NNF	+	+
Red material around mouth	NNF	NNF	NNF	NNF	+[c]
Swollen facial area	NNF	NNF	NNF	+	+
Swollen forelimb(s)	NNF	NNF	NNF	+	+[c]
Swollen digit(s) forelimb(s)	NNF	NNF	NNF	+	+
Swollen digit(s) hindlimb(s)	NNF	NNF	NNF	+	+
Distended testicles	NNF	+	+	+	+[c]
Mass, forelimb(s)	NNF	NNF	NNF	+	+[c]
Mass, dorsal trunk	NNF	NNF	NNF	+	+[c]
Clinical observations (approximately 1 hour postdose)					
Clear material around mouth	NNF	+	+	+	+
Red material around mouth	NNF	+	+	+	+
Yellow material around mouth	NNF	NNF	+	+	+[c]
Cool body	NNF	+[c]	NNF	NNF	NNF
Pale body	NNF	+[c]	NNF	NNF	NNF
Distended testicles	NNF	+	+	+	+[c]
Gasping	NNF	NNF	+	NNF	+[d]
Rales	NNF	NNF	NNF	+	+
Unscheduled observations					
Distended testicles	NNF	+	+	+	+[c]

Daily Dose (mg/kg)	**0 (Control)**	**50**	**100**	**150/300[a]**	**150/600[a]**
Body weight[e]	549.8 g	NNF	1.1 fold	1.2 fold**	1.1 fold**
Body weight change (PND 7 to 98)	533.7 g	544.6 g	579.2 g	624.4 g**	599.6 g**
Food consumption (representative values approximately every 4 weeks)[f]					
PND 28 to 31	13.8 g/day	NNF	–0.7%	1.1 fold	1.1 fold
PND 49 to 52	28.1 g/day	1.1 fold	1.1 fold	1.2 fold**	1.1 fold**
PND 77 to 80	29.4 g/day	NNF	1.1 fold	1.1 fold*	1.1 fold*
PND 94 to 98	28.5 g/day	NNF	1.1 fold	1.1 fold	1.1 fold
Mean age at preputial separation (days)	43.3	43.6	43.4	44.1	45.9**
Body weight at preputial separation	233.6 g	1.1 fold	1.1 fold	1.2 fold**	1.2 fold**
Functional observational battery (PND 98)					
Mean hindlimb footsplay (mm)	86.0	92.5	85.6	81.0	68.9*
Body weight at physiological observations[g]	549.2 g	–0.3%	NNF	1.1 fold*	1.1 fold
Hematology (PND 99)					
White blood cell count ($\times 10^3/\mu L$)	13.10	14.26	13.73	17.49	27.04*
Mean corpuscular volume (fL)	59.8	58.7	58.9	57.7	54.5**
Mean corpuscular hemoglobin (pg)	17.9	17.7	17.6	17.2	16.4**
Mean prothrombin time (seconds)	16.5	16.5	17.0	17.5*	18.9**
Mean absolute reticulocyte count ($\times 10^3/\mu L$)	200.7	174.6	197.5	197.1	226.7
Absolute neutrophil count ($\times 10^3/\mu L$)	1.63	1.58	1.69	2.00	6.10**
Absolute lymphocyte count ($\times 10^3/\mu L$)	10.98	12.15	11.38	14.44	19.23
Absolute monocyte count ($\times 10^3/\mu L$)	0.22	0.26	0.35	0.60**	1.14**
Absolute eosinophil count ($\times 10^3/\mu L$)	0.11	0.13	0.16	0.22	0.36**
Red cell distribution width (%)	11.8	11.5	11.2*	11.0**	12.3
Hemoglobin distribution width (g/dL)	2.47	2.36	2.22**	2.25**	2.35
Serum chemistry (PND 99)					
Albumin (g/dL)	4.1	4.0	3.9	3.9	3.7**
Total protein (g/dL)	6.9	6.7	6.5**	6.3**	5.8**
Globulin (g/dL)	2.8	2.7	2.6**	2.4**	2.1**
Albumin/globulin ratio	1.45	1.50	1.54	1.68**	1.76**
Total bilirubin (mg/dL)	0.00	0.01	0.01	0.00	0.30**
Cholesterol (mg/dL)	65	61	62	66	87**
Chloride (mEq/L)	102	105	106**	112**	113**

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Necropsy observations					
Total number examined	10	11	12	10	11
Unscheduled deaths	0	1	2	0	3
Femur – thickened	NA	0	0	NA	1
Axillary lymph node – enlarged	NA	0	0	NA	1
Mediastinal lymph node – enlarged	NA	0	0	NA	1
Paws – swollen	NA	0	0	NA	1
Paws – mass	NA	0	0	NA	1
Spleen – enlarged	NA	0	0	NA	3
Spleen – swollen	NA	0	0	NA	1
Spleen – white area(s)	NA	0	0	NA	1
Thymus – enlarged	NA	0	0	NA	2
Scheduled necropsy (PND 99)	10	10	10	10	8
Femur thickened	0	0	0	0	4
Mediastinal lymph node – enlarged	0	0	0	0	1
Paws – swollen	0	0	0	0	1
Paws – scabbing	0	0	0	0	2
Skeletal muscle – mass	0	0	0	0	1
Spleen – enlarged	0	0	0	0	5
Subcutis – mass	0	0	0	0	1
Tail – scabbing	0	0	0	0	2
Tail – nodule(s)	0	0	0	0	1
Thymus – enlarged	0	0	1	1	2
Organ weights[f,h] (PND 99)					
Adrenal glands (g)	0.0761	–4.3%	1.1 fold	1.1 fold	1.3 fold*
Epididymides (g)	1.25	1.2 fold**	1.3 fold**	1.3 fold**	1.3 fold**
Liver (g)	16.37	NNF	1.1 fold	1.3 fold**	1.3 fold**
Lung (g)	1.89	NNF	NNF	1.1 fold	1.1 fold
Prostate (g)	1.06	1.1 fold	1.2 fold	1.5 fold**	1.2 fold
Seminal vesicles/coagulating glands/fluid (g)	1.88	1.2 fold	1.2 fold	1.4 fold**	NNF
Spleen (g)	0.93	1.1 fold	1.2 fold	1.7 fold**	2.3 fold**
Testes (g)	3.67	1.1 fold	1.2 fold**	1.2 fold**	1.2 fold**
Thymus (g)	0.3919	–2.1%	1.3 fold	1.9 fold	3.7 fold

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Thyroid/parathyroid (g)	0.0256	1.1 fold	NNF	1.1 fold	1.1 fold
Microscopic findings					
Unscheduled deaths	0	1	2	0	3
Malignant lymphoma – systemic tumors	NA	NA	NA	NA	3
Femur – increased trabeculae, Minimal	NA	0	0	NA	1
Spleen – increased mononuclear cells (primarily of lymphocytes), red pulp, moderate	NA	0	0	NA	1
Spleen – decreased cellularity, marginal zone	NA	0	0	NA	2
Moderate, Marked	NA, NA	0, 0	0, 0	NA, NA	1, 1
Subcutis – pyogranulomatous inflammation, Marked	NA	NA	NA	NA	1/1
Thymus – malignant lymphoma	NA	0	0	NA	3
Scheduled necropsy (PND 99)	10	10	10	10	8
Malignant lymphoma – systemic tumors	NA	NA	NA	NA	3
Femur – increased trabeculae	0	0	0	0	7
Minimal, Mild	0, 0	0, 0	0, 0	0, 0	2, 5
Paws – pyogranulomatous inflammation	NA	NA	NA	NA	2
Moderate, Marked	NA, NA	NA, NA	NA, NA	NA, NA	1, 1
Spleen – decreased cellularity, marginal zone	0	0	1	7	7
Minimal, Mild, Moderate, Marked	0, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	4, 0, 3, 0	0, 1, 3, 3
Spleen – increased cellularity, white pulp, Minimal	0	0	1	2	1
Spleen – increased mononuclear cells, red pulp	0	0	1	9	7
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	0, 1, 0	6, 1, 2	6, 0, 1
Sternebrae – increased trabeculae	0	0	0	5	8
Minimal, Mild	0, 0	0, 0	0, 0	5, 0	5, 3

Daily Dose (mg/kg)	**0 (Control)**	**50**	**100**	**150/300[a]**	**150/600[a]**
Subcutis – pyogranulomatous inflammation, Marked	NA	NA	NA	NA	1
Thymus – malignant lymphoma	0	0	0	1	3
Thymus – lymphoid hyperplasia, Minimal	0	0	1	0	0
Immunophenotyping – thymus (PND 99)					
Number evaluated	10	10	10	10	8
B cells (10^6 cells/tissue)	6.89	8.01	7.91	6.95	6.80
T cells (10^6 cells/tissue)	147.89	147.07	163.99	250.99	896.00
CD4 T cells (10^6 cells/tissue)	83.06	76.35	89.71	65.49	49.84
CD8 T cells (10^6 cells/tissue)	23.97	22.19	26.18	88.71	511.71
DN cells (10^6 cells/tissue)	13.46	13.51	16.26	59.35	32.52
DP cells (10^6 cells/tissue)	642.98	632.45	788.96	676.59	1190.40
Myeloid cells (10^6 cells/tissue)	3.97	4.18	5.66	5.75	7.26
αβ T cells (10^6 cells/tissue)	139.18	136.39	155.54	242.42	883.14
γδT cells (10^6 cells/tissue)	1.45	1.65	2.21	2.27	3.40
Immunophenotyping – spleen (PND 99)					
Number evaluated	2	2	2	2	5
B cells (10^6 cells/tissue)	22.67	37.84	19.31	143.40	82.15
T cells (10^6 cells/tissue)	10.02	14.94	10.22	46.54	57.93
CD3 T cells (10^6 cells/tissue)	9.82	15.38	10.17	46.81	55.11
CD4 T cells (10^6 cells/tissue)	4.91	7.09	4.10	17.55	25.24
CD8 T cells (10^6 cells/tissue)	3.61	5.73	4.64	22.24	22.44
DN T cells (10^6 cells/tissue)	0.15	0.27	0.22	0.87	1.70
DP T cells (10^6 cells/tissue)	1.15	2.29	1.20	6.18	5.71
Myeloid cells (10^6 cells/tissue)	6.97	19.19	11.51	70.42	44.49
αβ T cells (10^6 cells/tissue)	9.09	13.56	8.84	38.57	52.48
γδ T cells (10^6 cells/tissue)	0.50	0.58	1.02	5.17	2.84
Females TK					
Number evaluated (TK Phase)	39	39	39	39	39
Number died or euthanized in extremis (TK Phase)	0	0	1	2	1
Tazemetostat AUC_{last} (ng·h/mL)					
PND 7	NA	7300	22,800	86,100	55,100

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
PND 21	NA	NA	NA	24,000[b]	22,200[b]
PND 22	NA	3430[b]	14,200[b]	58,300[b]	169,000
PND 98	NA	18,500	67,200	229,000	425,000
Tazemetostat C_{max} (ng/L)					
PND 7	NA	1630	5190	9450	8010
PND 21	NA	NA	NA	7250	5810
PND 22	NA	1600	5410	11,100	16,800
PND 98	NA	3900	7600	17,100	26,300
ER-897387 (EPZ-6930) AUC_{last} (ng·h/mL)					
PND 7	NA	59,700	158,000	321,000	280,000
PND 21	NA	NA	NA	58,400	41,900
PND 22	NA	2850[b]	17,700[b]	128,000	191,000
PND 98	NA	2470[b]	5610[b]	54,200	134,000
ER-897387 (EPZ-6930) C_{max} (ng/L)					
PND 7	NA	5140	12,000	22,100	19,800
PND 21	NA	NA	NA	8600	7340
PND 22	NA	1390	5810	10,900	13,100
PND 98	NA	555	951	3720	7250
Females					
Number evaluated – dosing period	20	20	20	20	20
Number died or euthanized in extremis	0	1	0	0	1
Clinical observations (daily examinations)					
Labored respiration	NNF	+[d]	NNF	NNF	NNF
Pale extremities	NNF	+[d]	NNF	NNF	NNF
Decreased defecation	NNF	+[d]	NNF	NNF	NNF
Unkempt appearance	NNF	NNF	NNF	NNF	+[c]
Rales	NNF	NNF	NNF	NNF	+[d]
Red material around eye(s)	NNF	+	NNF	+	+[c]
Red material around nose	NNF	+	+	+	+[c]
Yellow material urogenital area	NNF	NNF	NNF	+	+[c]
Scabbing facial area	NNF	NNF	NNF	+	+
Scabbing tail	NNF	NNF	NNF	+	+[c]
Scabbing forelimb(s)	NNF	NNF	NNF	+	+[c]

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Scabbing hindlimb(s)	NNF	NNF	NNF	NNF	+[c]
Yellow material ventral trunk	NNF	NNF	NNF	NNF	+[c]
Red material around mouth	NNF	NNF	NNF	+	+[c]
Swollen facial area	NNF	NNF	NNF	+	+[c]
Swollen forelimb(s)	NNF	NNF	NNF	+	+
Swollen hindlimb(s)	NNF	NNF	NNF	+	+[c]
Swollen digit(s) forelimb(s)	NNF	NNF	NNF	+	+
Mass forelimb(s)	NNF	NNF	NNF	+	+
Mass, dorsal trunk	NNF	NNF	NNF	NNF	+
Mass, ventral trunk	NNF	NNF	NNF	NNF	+
Clinical observations (approximately 1 hour postdose)					
Rales	NNF	NNF	NNF	NNF	+
Yellow material urogenital area	NNF	NNF	NNF	+	+
Clear material around mouth	NNF	NNF	+	+	+
Yellow material around mouth	NNF	NNF	NNF	+	+
Red material around mouth	NNF	NNF	+	+	+
Body weight[g]	296.4 g	1.1 fold	1.2 fold**	1.3 fold**	1.4 fold**
Body weight change (PND 7 to 98)	280.9 g	301.0 g	327.3 g**	359.8 g**	404.5 g**
Food consumption (representative values approximately every 4 weeks)[f]					
PND 28 to 31	12.4 g/day	NNF	1.1 fold	1.1 fold	1.1 fold
PND 49 to 52	18.2 g/day	1.1 fold	1.1 fold*	1.2 fold**	1.2 fold**
PND 77 to 80	18.1g/day	1.1 fold	1.2 fold*	1.3 fold**	1.4 fold**
PND 94 to 98	17.3 g/day	1.1 fold	1.1 fold	1.3 fold**	1.4 fold**
Mean age at vaginal patency (days)	33.3	32.7	33.5	33.3	34.0
Body weight at vaginal patency[f]	119.6 g	NNF	1.1 fold	1.1 fold*	1.1 fold**
Functional observational battery (PND 98)					
Fur – normal; clean and groomed	10	9	10	8	5[#]
Fur – slightly soiled	0	0	0	2	5[#]
Air righting reflex – slightly uncoordinated	0	0	0	0	4
Body weight at physiological observations	292.3 g	NNF	1.1 fold*	1.3 fold**	1.4 fold**
Hematology (PND 99)					
White blood cell count ($\times 10^3/\mu L$)	10.38	12.49	13.44	19.87**	21.63**

Daily Dose (mg/kg)	**0 (Control)**	**50**	**100**	**150/300[a]**	**150/600[a]**
Red blood cell count ($\times 10^6/\mu L$)	9.46	9.12	8.91	9.08	8.18**
Hemoglobin (g/dL)	17.2	16.8	16.2	15.4*	13.4**
Hematocrit (%)	56.5	54.6	53.7	51.3*	46.5**
Mean corpuscular volume (fL)	59.8	59.9	60.3	56.5**	56.9**
Mean corpuscular hemoglobin (pg)	18.2	18.4	18.1	16.9**	16.3**
Mean corpuscular hemoglobin concentration (g/dL)	30.5	30.7	30.1	30.0	28.7**
Mean platelet count ($\times 10^3/\mu L$)	922	842	978	1083	1539**
Mean platelet volume (fL)	7.21	7.29	7.43	7.39	8.68**
Mean prothrombin time (seconds)	16.4	16.5	16.7	17.4*	19.0**
Absolute reticulocyte count ($\times 10^3/\mu L$)	195.0	188.2	203.3	198.0	331.5**
Absolute neutrophil count ($\times 10^3/\mu L$)	0.90	1.04	1.10	4.01	10.28**
Absolute lymphocyte count ($\times 10^3/\mu L$)	9.03	10.98	11.77	14.14**	9.73
Absolute monocyte count ($\times 10^3/\mu L$)	0.22	0.21	0.26	0.97**	1.09**
Absolute eosinophil count ($\times 10^3/\mu L$)	0.09	0.10	0.12	0.18	0.32**
Red cell distribution width (%)	11.1	10.9	10.8	11.6	15.7**
Hemoglobin distribution width (g/dL)	1.93	1.92	1.88	2.06	2.33**
Serum chemistry (PND 99)					
Albumin (g/dL)	4.3	4.2	4.4	4.1	3.6**
Total protein (g/dL)	7.1	6.9	7.1	6.5**	5.7**
Globulin (g/dL)	2.8	2.7	2.7	2.3**	2.1**
Albumin/globulin ratio	1.55	1.59	1.66	1.79**	1.75**
Total bilirubin (mg/dL)	0.01	0.03	0.03	0.03	0.22**
ALP (U/L)	75	69	64	74	128**
Glucose (mg/dL)	175	201	264*	263*	298**
Calcium (mg/dL)	12.0	12.0	12.5*	12.5*	12.9**
Chloride (mEq/L)	105	106	108**	110**	117**
Phosphorous (mg/dL)	11.3	11.5	11.5	11.7	14.2**
Potassium (mEq/L)	11.15	10.97	10.71	10.05	9.20**
Magnesium (mg/dL)	3.8	4.0	4.3*	4.3**	5.0**
Necropsy observations					
Total number examined	10	10	10	10	11
Unscheduled deaths	0	1	0	0	1
Axillary lymph node – enlarged	NA	1	NA	NA	0

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Generalized lymph node – enlarged	NA	1	NA	NA	0
Mandibular lymph node – enlarged	NA	1	NA	NA	0
Mesenteric lymph node – enlarged	NA	1	NA	NA	0
Paws – nodule	NA	0	NA	NA	1
Paws – scabbing	NA	0	NA	NA	1
Spleen – enlarged	NA	1	NA	NA	0
Thymus – enlarged	NA	1	NA	NA	0
Scheduled necropsy (PND 99)	10	9	10	10	10
Femur – thickened	0	0	0	1	5
Axillary lymph node – enlarged	0	0	0	0	1
Mandibular lymph node – enlarged	0	0	0	0	1
Popliteal lymph node – mass	0	0	0	0	1
Popliteal lymph node – enlarged	0	0	0	0	1
Paws – nodule(s)	0	0	0	0	2
Paws – scabbing	0	0	0	0	2
Paws – swollen	0	0	0	0	4
Paws – open sore(s)	0	0	0	0	1
Skin – mass	0	0	0	1	2
Spleen – enlarged	0	0	0	1	1
Spleen – white area(s)	0	0	0	1	4
Spleen – swollen	0	0	0	1	0
Subcutis – mass	0	0	0	1	7
Tail – nodule(s)	0	0	0	1	6
Tail – scabbing	0	0	0	1	1
Thymus – enlarged	0	0	0	4	0
Organ weights[f,h] (PND 99)					
Adrenal glands	0.0713 g	NNF	NNF	1.2 fold*	1.4 fold**
Kidneys	2.08 g	NNF	NNF	1.2 fold*	1.3 fold**
Liver	9.02 g	NNF	1.1 fold	1.4 fold**	1.9 fold**
Lungs	1.37 g	NNF	NNF	1.2 fold**	1.3 fold**
Ovaries	0.0946 g	1.1 fold	1.3 fold*	1.6 fold**	1.5 fold**
Spleen	0.62 g	1.2 fold	1.4 fold	2.2 fold**	2.4 fold**
Thymus	0.3545 g	1.3 fold	1.5 fold	4.0 fold*	–11.3%
Thyroid/parathyroid	0.0205 g	–8.3%	1.1 fold	1.2 fold	1.2 fold

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Uterus/cervix/oviducts	0.63	1.2 fold	1.4 fold	2.2 fold**	1.6 fold
Microscopic findings					
Unscheduled deaths	0	1	0	0	1
Malignant lymphoma – systemic tumors	NA	1	NA	NA	NA
Femur – increased trabeculae, Mild	NA	0	NA	NA	1
Paws – pyogranulomatous inflammation, Mild	NA	NA	NA	NA	1
Spleen – decreased cellularity, marginal zone, Mild	NA	0	NA	NA	1
Spleen – increased mononuclear cells, red pulp, Moderate	NA	0	NA	NA	1
Sternebrae – increased trabeculae, Minimal	NA	0	NA	NA	1
Subcutis – pyogranulomatous inflammation, Marked	NA	NA	NA	NA	1
Thymus – malignant lymphoma	NA	1	NA	NA	0
Scheduled necropsy (PND 99)	10	9	10	10	10
Malignant lymphoma – systemic tumors	NA	NA	NA	1	1
Femur – increased trabeculae	0	0	2	7	10
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	2, 0, 0	3, 4, 0	0, 4, 6
Paws – pyogranulomatous inflammation	NA	NA	NA	NA	6
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	1, 4, 1
Spleen – decreased cellularity, marginal zone	0	0	0	5	10
Mild, Moderate, Marked	0, 0, 0	0, 0, 0	0, 0, 0	3, 1, 1	4, 3, 3
Spleen – increased cellularity, white pulp, Minimal	0	1	4	4	1
Spleen – increased mononuclear cells, red pulp	0	0	4	8	7
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	4, 0, 0	3, 3, 2	1, 4, 2
Sternebrae – increased trabeculae	0	0	0	5	9
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	0, 0, 0	5, 0, 0	4, 3, 2

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Subcutis – pyogranulomatous inflammation	NA	NA	NA	1	6
Moderate, Marked	0, 0	0, 0	0, 0	1, 0	3, 3
Thymus – malignant lymphoma	0	0	0	5	2
Thymus – lymphoid hyperplasia	0	0	2	0	7
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	1, 0, 1	0, 0, 0	1, 5, 1
Immunophenotyping – thymus (PND 99)					
Number evaluated	10	9	10	10	10
B cells (10^6 cells/tissue)	5.20	7.75	7.59	7.46	2.06
T cells (10^6 cells/tissue)	109.30	107.91	165.36	1062.38	57.36
CD4 T cells (10^6 cells/tissue)	56.91	61.38	77.53	60.64	35.12
CD8 T cells (10^6 cells/tissue)	20.02	20.56	28.70	204.02	29.28
DN T cells (10^6 cells/tissue)	11.87	12.49	20.23	37.63	36.37
DP T cells (10^6 cells/tissue)	583.00	577.76	803.58	2189.52	243.70
Myeloid cells (10^6 cells/tissue)	3.34	4.03	4.21	11.59	2.19
αβ T cells (10^6 cells/tissue)	100.38	101.67	150.24	1045.81	49.79
γδ T cells (10^6 cells/tissue)	1.21	1.62	2.68	2.27	3.58
Immunophenotyping – spleen (PND 99)					
Number evaluated	2	2	2	2	3
B cells (10^6 cells/tissue)	18.28	48.20	71.48	81.77	41.19
T cells (10^6 cells/tissue)	13.71	22.57	38.65	41.87	48.12
CD3 T cells (10^6 cells/tissue)	12.44	20.95	34.56	36.53	47.73
CD4 T cells (10^6 cells/tissue)	6.51	10.81	18.00	19.62	24.19
CD8 T cells (10^6 cells/tissue)	4.76	7.96	11.66	10.90	16.82
DN T cells (10^6 cells/tissue)	0.15	0.33	0.64	0.85	0.83
DP cells (10^6 cells/tissue)	1.01	1.85	4.26	5.17	5.88
Myeloid cells (10^6 cells/tissue)	5.14	12.99	22.34	25.86	32.37
αβ T cells (10^6 cells/tissue)	12.80	20.49	33.77	36.97	43.12
γδ T cells (10^6 cells/tissue)	0.61	1.44	3.01	3.04	3.32
Males – recovery period					
Number evaluated	10	9	9	10	9
Number died or euthanized in extremis	0	0	0	1	2
Clinical observations (daily examinations)					

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Gasping	NNF	NNF	NNF	NNF	+[d]
Labored respiration	NNF	NNF	NNF	+[d]	NNF
Hair loss forelimb(s)	NNF	NNF	+	+	+
Hair loss facial area	NNF	NNF	NNF	+	+
Hair loss hindlimb(s)	NNF	NNF	NNF	+	+[c]
Red material around eye(s)	NNF	NNF	NNF	+[c]	+[c]
Red material around nose	NNF	NNF	NNF	NNF	+[c]
Scabbing forelimb(s)	NNF	NNF	NNF	NNF	+[c]
Scabbing tail	NNF	NNF	NNF	+[c]	+[c]
Scabbing facial area	NNF	NNF	+	NNF	NNF
Swollen facial area	NNF	NNF	NNF	+[c]	+[c]
Swollen forelimb(s)	NNF	NNF	NNF	+	+[c]
Swelling ventral neck	NNF	NNF	NNF	+[d]	NNF
Swollen digit(s) forelimb(s)	NNF	NNF	NNF	NNF	+[d]
Distended testicles	NNF	NNF	+	+[d]	+[d]
Mass, forelimb	NNF	NNF	NNF	+	NNF
Mass, ventral trunk	NNF	NNF	NNF	NNF	+
Mass, nose	NNF	NNF	+	NNF	NNF
Mass, dorsal trunk	NNF	NNF	NNF	+	+
Body weight[i]	585 g	1.1 fold	1.2 fold*	1.2 fold**	1.3 fold**
Body weight change (PND 99 to 126)	50 g	1.1 fold	1.3 fold	1.3 fold	1.9 fold**
Food consumption (representative values approximately every 2 weeks)					
PND 99 to 102	28 g/day	NNF	1.1 fold	1.2 fold	1.4 fold**
PND 108 to 112	26 g/day	1.1 fold	1.4 fold	1.2 fold	1.4 fold
PND 122 to 126	27 g/day	NNF	1.1 fold	1.2 fold*	1.2 fold**
Functional observational battery (PND 126)					
Air righting reflex – slightly uncoordinated	0	0	1	0	3
Rotarod performance (seconds)	31.9	24.0	29.2	28.0	18.8
Hematology (PND 127)					
White blood cell count ($\times 10^3/\mu L$)	14.41	13.74	14.46	15.11	54.18
Mean prothrombin time (seconds)	17.4	18.0	17.3	18.2	18.7*
Absolute reticulocyte count ($\times 10^3/\mu L$)	213.2	194.5	193.6	174.8	135.2**
Absolute neutrophil count ($\times 10^3/\mu L$)	3.42	1.37	2.03	2.36	2.67

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Absolute lymphocyte count ($\times 10^3/\mu L$)	10.27	11.72	11.78	12.10	50.48
Absolute monocyte count ($\times 10^3/\mu L$)	0.43	0.36	0.33	0.30	0.70
Absolute eosinophil count ($\times 10^3/\mu L$)	0.11	0.13	0.14	0.14	0.21
Red cell distribution width (%)	13.2	12.4	12.6	12.9	14.0
Hemoglobin distribution width (%)	2.36	2.29	2.33	2.26	2.21
Serum chemistry (PND 127)					
Albumin (g/dL)	4.1	4.0	4.0	3.9*	3.7**
Total protein (g/dL)	7.0	6.7	6.9	6.5	6.1**
Globulin (g/dL)	2.9	2.7	2.9	2.7	2.4**
Albumin/globulin ratio	1.43	1.47	1.41	1.47	1.56
Glucose (mg/dL)	327	345	314	255	218*
Necropsy observations					
Unscheduled deaths	0	0	0	1	2
Axillary lymph node – enlarged	NA	NA	NA	1	2
Generalized lymph node – enlarged	NA	NA	NA	1	0
Mandibular lymph node – enlarged	NA	NA	NA	1	0
Mediastinal lymph node – enlarged	NA	NA	NA	0	2
Mesenteric lymph node – enlarged	NA	NA	NA	1	0
Paws – nodule(s)	NA	NA	NA	0	1
Paws – scabbing	NA	NA	NA	0	1
Spleen – enlarged	NA	NA	NA	1	2
Subcutis – mass	NA	NA	NA	0	1
Thymus – enlarged	NA	NA	NA	1	2
Scheduled necropsy (PND 127)	10	9	9	9	7
Bone thickened	0	0	0	0	1
Femur – thickened	0	0	0	0	4
Axillary lymph node – enlarged	0	0	0	0	1
Generalized lymph node – enlarged	0	0	0	0	1
Mandibular lymph node – enlarged	0	0	0	0	1
Mediastinal lymph node – enlarged	0	0	0	1	0
Mesenteric lymph node – enlarged	0	0	0	0	1
Spleen – enlarged	0	0	0	1	3
Spleen – swollen	0	0	0	0	1
Subcutis – mass	0	0	1	0	1

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Tail – mass	0	0	0	1	1
Thymus – enlarged	0	0	0	1	2
Organ weights[f,h] (PND 127)					
Adrenal glands	0.0597 g	1.1 fold	1.1 fold	1.3 fold**	1.3 fold**
Epididymides	1.35 g	1.1 fold*	1.2 fold**	1.3 fold**	1.3 fold**
Liver	17.02 g	NNF	1.1 fold	1.2 fold	1.5 fold**
Lungs	1.78 g	1.1 fold	NNF	1.1 fold	1.2 fold*
Prostate	1.00 g	1.2 fold	1.3 fold	1.5 fold**	1.6 fold**
Spleen	0.97 g	1.1 fold	1.2 fold	2.0 fold	3.9 fold
Seminal vesicles/coagulating glands/fluid	2.06 g	1.2 fold	1.1 fold	1.3 fold**	1.3 fold*
Testes	3.53 g	1.1 fold	1.2 fold**	1.2 fold**	1.2 fold**
Thymus	0.2873 g	1.2 fold	1.3 fold	5.4 fold	8.9 fold
Thyroid/parathyroid	0.0211 g	1.2 fold	1.1 fold	1.3 fold*	1.3 fold*
Microscopic findings					
Unscheduled deaths	0	0	0	1	2
Malignant lymphoma – systemic tumors	NA	NA	NA	1	2
Femur – increased trabeculae, Mild	NA	NA	NA	0	1
Paws – pyogranulomatous inflammation, Moderate	NA	NA	NA	NA	1
Sternebrae – increased trabeculae, Minimal	NA	NA	NA	0	1
Subcutis – pyogranulomatous inflammation, Moderate	NA	NA	NA	NA	1
Thymus – malignant lymphoma	NA	NA	NA	1	2
Scheduled necropsy (PND 127)	10	9	9	9	7
Malignant lymphoma – systemic tumors	NA	NA	NA	1	1
Femur – increased trabeculae	0	0	0	1	5
Minimal, Moderate	0, 0	0, 0	0, 0	1, 0	2, 3
Spleen – decreased cellularity, marginal zone	0	0	0	1	4
Mild, Marked	0, 0	0, 0	0, 0	0, 1	3, 1

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Spleen – increased cellularity, white pulp, Minimal	0	1	4	1	1
Spleen – increased mononuclear cells, red pulp	0	0	4	4	5
Minimal, Mild	0, 0	0, 0	3, 1	2, 2	4, 1
Sternebrae – increased trabeculae, Minimal	0	0	0	0	4
Subcutis – pyogranulomatous inflammation	NA	NA	1	NA	1
Mild, Moderate	NA, NA	NA, NA	1, 0	NA, NA	0, 1
Thymus – malignant lymphoma	0	0	0	1	2
Thymus – lymphoid hyperplasia	0	0	1	2	0
Minimal, Moderate	0, 0	0, 0	1, 0	0, 2	0, 0
Immunophenotyping – thymus (PND 127)					
Number evaluated	10	9	9	9	7
B cells (10^6 cells/tissue)	1.27	1.28	1.17	12.27	8.26
T cells (10^6 cells/tissue)	56.21	63.59	56.14	1832.02	1662.43
CD4 T cells (10^6 cells/tissue)	30.64	34.64	31.78	61.12	78.55
CD8 T cells (10^6 cells/tissue)	12.14	13.73	11.41	1268.67	1588.26
DN T cells (10^6 cells/tissue)	4.79	4.28	4.99	510.23	235.68
DP T cells (10^6 cells/tissue)	328.16	368.02	296.99	869.04	1689.85
Myeloid cells (10^6 cells/tissue)	5.34	5.96	5.55	55.21	29.32
αβ T cells (10^6 cells/tissue)	54.12	61.16	54.14	1799.80	1644.63
γδ T cells (10^6 cells/tissue)	0.63	0.71	0.60	0.74	1.36
Immunophenotyping – spleen (PND 127)					
Number evaluated	2	2	2	2	4
B cells (10^6 cells/tissue)	57.76	62.89	68.80	49.04	89.49
T cells (10^6 cells/tissue)	31.88	48.57	48.90	33.55	69.38
CD3 T cells (10^6 cells/tissue)	28.25	44.03	43.82	27.44	61.08
CD4 T cells (10^6 cells/tissue)	14.17	22.95	22.78	12.81	35.01
CD8 T cells (10^6 cells/tissue)	10.73	16.70	17.16	11.61	18.44
DN T cells (10^6 cells/tissue)	1.14	0.78	1.14	0.72	2.07
DP T cells (10^6 cells/tissue)	2.21	3.61	2.73	2.29	5.54
Myeloid cells (10^6 cells/tissue)	35.65	22.52	19.10	20.90	41.39

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
αβ T cells (10^6 cells/tissue)	29.02	45.63	45.43	30.50	64.31
γδ T cells (10^6 cells/tissue)	1.42	1.98	2.34	2.30	3.26
Females – recovery period					
Number evaluated	10	10	10	10	9
Number died or euthanized in extremis	1	0	1	2	2
Clinical observations (daily examinations)					
Labored respiration	NNF	NNF	NNF	+[e]	NNF
Unkempt appearance	NNF	NNF	NNF	NNF	+[d]
Red material around eye(s)	NNF	NNF	NNF	+[e]	+[e]
Red material around nose	NNF	NNF	NNF	+[e]	+[e]
Hair loss trunk	NNF	NNF	NNF	+[e]	+[e]
Hair loss hindlimb(s)	NNF	NNF	+	+[e]	+[e]
Scabbing facial area	NNF	NNF	+	+	+[e]
Scabbing tail	NNF	NNF	+	+[e]	+[e]
Scabbing forelimbs(s)	NNF	NNF	NNF	NNF	+[e]
Scabbing hindlimb(s)	NNF	NNF	NNF	NNF	+[e]
Swollen facial area	NNF	NNF	NNF	+[e]	+[e]
Swollen forelimb(s)	NNF	NNF	NNF	NNF	+[e]
Swollen hindlimb(s)	NNF	NNF	NNF	NNF	+[e]
Mass, forelimb	NNF	NNF	NNF	NNF	+[e]
Mass, hindlimb	NNF	NNF	NNF	NNF	+[e]
Mass, facial area	NNF	NNF	NNF	NNF	+
Body weight[i]	311 g	1.1 fold	1.2 fold**	1.3 fold**	1.4 fold**
Body weight change (PND 99 to 126)	19 g	–5.3%	1.2 fold	1.1 fold	1.3 fold
Food consumption (representative values approximately every 4 weeks)[f]					
PND 99 to 102	17 g/day	1.1 fold	1.2 fold*	1.3 fold**	1.8 fold**
PND 108 to 112	17 g/day	1.1 fold	1.2 fold	1.2 fold	1.5 fold**
PND 122 to 126	17 g/day	NNF	1.1 fold	1.2 fold*	1.4 fold**
Functional observational battery (PND 126)					
Rotarod performance (seconds)	58.8	35.9	42.3	28.3	25.3
Hematology (PND 127)					
White blood cell count ($\times10^3$/μL)	8.71	9.74	9.19	11.23	16.45**
Red blood cell count ($\times10^6$/μL)	9.21	9.52	9.00	9.57	8.93

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Hemoglobin (g/dL)	16.4	16.9	16.2	16.6	15.8
Hematocrit (%)	55.0	56.2	53.7	55.8	53.5
Mean platelet count ($\times 10^3/\mu L$)	926	884	976	1012	1001
Mean prothrombin time (seconds)	17.3	17.5	17.9	18.6*	19.2**
Absolute reticulocyte count ($\times 10^3/\mu L$)	170.5	151.2	155.0	133.5	141.3
Absolute neutrophil count ($\times 10^3/\mu L$)	0.95	1.16	0.77	1.48	1.93*
Absolute lymphocyte count ($\times 10^3/\mu L$)	7.42	8.21	8.07	9.35	13.67**
Absolute monocyte count ($\times 10^3/\mu L$)	0.14	0.22	0.17	0.19	0.50
Absolute basophil count ($\times 10^3/\mu L$)	0.02	0.03	0.03	0.04	0.06**
Red cell distribution width (%)	11.3	11.1	11.5	12.9**	13.7**
Hemoglobin distribution width (g/dL)	1.96	1.92	1.87	1.80*	1.83
Serum chemistry (PND 127)					
Albumin (g/dL)	4.4	4.2	4.2	4.1	3.8**
Total protein (g/dL)	7.4	7.1	7.0	7.0	6.7**
Albumin/globulin ratio	1.49	1.46	1.54	1.44	1.36
Necropsy observations					
Total number examined	10	10	10	10	9
Unscheduled deaths	1	0	1	2	2
Femur – thickened	0	NA	0	0	1
Axillary lymph node – enlarged	0	NA	0	0	1
Iliac lymph node – enlarged	0	NA	0	1	0
Popliteal lymph node – mass	0	NA	0	0	1
Renal lymph node – enlarged	0	NA	0	1	0
Paws – swollen	0	NA	0	0	1
Paws – mass	0	NA	0	0	1
Skin – mass	0	NA	0	0	1
Spleen – enlarged	0	NA	1	1	0
Thymus – enlarged	0	NA	1	2	1
Scheduled necropsy (PND 127)	9	10	9	8	7
Femur – thickened	0	0	0	0	4
Mandibular lymph node – enlarged	0	0	0	1	1
Paws – scabbing	0	0	0	0	1
Skin – mass	0	0	0	0	1
Skin – scabbing	0	0	1	0	1

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Spleen – cysts	0	0	0	0	2
Spleen – swollen	0	0	0	0	2
Subcutis – mass	0	0	0	0	1
Tail – scabbing	0	0	0	1	4
Thymus – enlarged	0	0	0	1	5
Organ weights[f,h] (PND 127)					
Adrenal glands	0.0683 g	1.2 fold	NNF	1.1 fold	1.3 fold**
Kidneys	2.04 g	1.1 fold	1.1 fold	1.1 fold	1.2 fold*
Liver	8.59 g	1.1 fold	1.2 fold	1.2 fold*	1.6 fold**
Lungs	1.35 g	1.1 fold	NNF	1.1 fold	1.2 fold**
Ovaries	0.0900 g	1.1 fold	1.3 fold*	1.4 fold**	1.8 fold**
Spleen	0.60 g	1.3 fold	1.3 fold	1.8 fold**	2.6 fold**
Thymus	0.2943 g	1.1 fold	1.4 fold	1.7 fold	2.9 fold**
Thyroid/parathyroid	0.0176 g	1.2 fold	1.1 fold	1.2 fold*	1.4 fold**
Uterus/cervix/oviducts	0.77 g	1.1 fold	1.3 fold	1.8 fold**	2.2 fold**
Microscopic findings					
Unscheduled deaths	1	0	1	2	2
Malignant lymphoma – systemic tumors	NA	NA	1	2	NA
Femur – increased trabeculae	0	NA	0	2	2
Minimal, Mild, Marked	0, 0, 0	NA, NA, NA	0, 0, 0	1, 1, 0	0, 1, 1
Paws – pyogranulomatous inflammation	NA	NA	NA	NA	2
Mild, Moderate	NA, NA	NA, NA	NA, NA	NA, NA	1, 1
Spleen – decreased cellularity, marginal zone, Mild	0	NA	0	0	2
Spleen – increased cellularity, white pulp, Minimal	0	NA	1	0	0
Spleen – increased mononuclear cells, red pulp	0	NA	0	0	2
Moderate, Marked	0, 0	NA, NA	0, 0	0, 0	1, 1
Sternebrae – increased trabeculae	0	NA	0	1	1
Mild, Moderate	0, 0	NA, NA	0, 0	1, 0	0, 1
Thymus – malignant lymphoma	0	NA	1	2	0

Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
Thymus – lymphoid hyperplasia, Markd	0	NA	0	0	1
Scheduled necropsy (PND 127)	9	10	9	8	7
Femur – increased trabeculae	0	0	2	8	7
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	2, 0, 0	7, 1, 0	0, 4, 3
Paws – pyogranulomatous inflammation, Moderate	NA	NA	NA	NA	1
Spleen – decreased cellularity, marginal zone	0	0	0	2	6
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	0, 0, 0	1, 1, 0	2, 3, 1
Spleen – increased cellularity, white pulp, Minimal	0	0	1	3	3
Spleen – increased mononuclear cells, red pulp	0	1	1	3	6
Minimum, Mild	0, 0	1, 0	1, 0	3, 0	3, 3
Sternebrae – increased trabeculae	0	0	0	2	7
Minimal, Mild, Moderate	0, 0, 0	0, 0, 0	0, 0 0	2, 0, 0	1, 5, 1
Subcutis – pyogranulomatous inflammation, Marked	NA	NA	NA	NA	1
Thymus – malignant lymphoma	0	0	0	1	0
Thymus – lymphoid hyperplasia, Minimal	0	0	2	1	3
Immunophenotyping – thymus (PND 127)					
Number evaluated	9	10	9	8	7
B cells (10^6 cells/tissue)	1.52	1.31	1.15	1.32	1.99
T cells (10^6 cells/tissue)	85.27	64.91	73.42	105.01	151.24
CD4 T cells (10^6 cells/tissue)	47.34	35.93	38.61	53.18	79.07
CD8 T cells (10^6 cells/tissue)	20.81	14.30	16.65	27.74	31.72
DN T cells (10^6 cells/tissue)	6.26	5.28	5.59	7.30	7.31
DP T cells (10^6 cells/tissue)	488.32	360.87	399.85	517.89	865.54
Myeloid cells (10^6 cells/tissue)	7.82	6.41	7.18	9.16	10.18
αβ T cells (10^6 cells/tissue)	82.24	62.67	70.63	101.66	147.54
γδ T cells (10^6 cells/tissue)	1.02	0.74	1.02	1.25	1.35
Immunophenotyping – spleen (PND 127)					
Number evaluated	2	2	2	2	2