Daily Dose (mg/kg)	0 (Control)	50	100	150/300[a]	150/600[a]
B cells (10^6 cells/tissue)	13.47	13.28	67.27	30.29	124.11
T cells (10^6 cells/tissue)	12.72	14.18	57.23	27.93	77.44
CD3 T cells (10^6 cells/tissue)	10.70	11.80	50.45	26.44	71.14
CD4 T cells (10^6 cells/tissue)	4.92	5.80	28.58	12.28	39.62
CD8 T cells (10^6 cells/tissue)	4.73	5.02	18.17	10.98	20.86
DN T cells (10^6 cells/tissue)	0.27	0.26	0.77	0.87	3.86
DP T cells (10^6 cells/tissue)	0.78	0.72	2.92	2.32	6.84
Myeloid cells (10^6 cells/tissue)	4.98	4.25	14.70	14.71	38.06
αβ T cells (10^6 cells/tissue)	11.70	13.24	52.96	25.65	67.70
γδ T cells (10^6 cells/tissue)	0.77	0.71	3.42	1.51	7.55

+ = observed, AUC_{last} = area under the concentration-time curve from 0 time to the last 24 hours postdose, CD = cluster of differentiation, C_{max} = maximum observed concentration, CTD = common technical document, DG = day of gestation, DN = double negative, DP = double positive, F = female, GLP =Good Laboratory Practice, ICH = International Conference on Harmonisation, M = males, NA = not applicable, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, PND = postnatal day, TK = toxicokinetics.

a: Groups 4 and 5 dosed at 150 mg/kg/day during PND 7 to 21. Dosages increased to 300 and 600 mg/kg/day, respectively, on PND 22 for the remainder of the treatment period.
b: AUC_{last} of 8 hours.
c: Observed in at least 1 animal that was found dead or euthanized in extremis.
d: Noted only in animal(s) found dead or euthanized in extremis.
e: At end of dosing period. For control group, means are shown. For test article-treated groups, percent lower or fold higher than controls are shown.
f: For control group, means are shown. For test article-treated groups, percent lower or fold higher than control are shown. Statistical significance is based on actual data.
g: At end of dosing period. For control group, means are shown. For test article-related groups, percent lower or fold higher than controls are shown. Statistical significance is based on actual data.
h: Both absolute and relative weights generally differed from controls in the direction indicated. Number indicates difference for the absolute organ weights.
i: At end of recovery period. For control group, means are shown. For test article-treated groups, percent lower or fold higher than control are shown.

*P<0.05; **P<0.01 (Dunnett's test); $^{\#}P$<0.05 (Fisher's Exact Test) vs control.

Source: Study [redacted]-154506.

2.6.7.16 局所刺激性試験

ICH M3(R2)ガイドラインにもとづき，タゼメトスタットでの独立した局所刺激性試験は実施していない。

2.6.7.17 その他の毒性試験

Test Article: Tazemetostat

Species/Strain	Method/Duration of Administration	Doses (µg/mL)	Gender and No. per Group	Noteworthy Findings	GLP[a]	Study Number
Phototoxicity						
Mouse BALB/c 3T3 fibroblasts	Cells treated for 90 minutes before irradiation, and irradiated for approximately 30 minutes	1.78, 3.16, 5.62, 10.0, 17.8, 31.6, 56.2, and 100.0	NA	Viability of fibroblasts exposed to tazemetostat was measured in the presence and absence of ultraviolet radiation. Promethazine was used as the positive control. Tazemetostat showed phototoxic potential (phototoxic IC_{50} of 19-24 µg/mL) in the definitive assay.	Yes	20079676

GLP = Good Laboratory Practice, IC_{50} = half-maximal inhibitory concentration, NA = not applicable.

a: Indicates study report includes a GLP compliance statement.

Source: Study 20079676.

2.6.7.17A　　**Test Article: Tazemetostat**

Report Title: E7438: A 4-Week Oral Toxicity Study in Rats (additional study)		**Study No.** K[redacted]025
Species / Strain: Rat/Sprague Dawley	Duration of Dosing: 4 weeks	Location in CTD: 4.2.3.7.6.1
Initial Age: 8 weeks old	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: Since half of the males at 1000 mg/kg were dead or euthanized, the surviving males at that dose were terminated and euthanized on Day 15.		
NOAEL: 300 mg/kg		

Daily Dose (mg/kg)	**0 (Control)**		**100**		**300**		**1000**	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Number of Animals for TK:	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
TK: $AUC_{(0\text{-}24h)}$ (ng·h/mL)								
Day 1	NC	NC	2589	16,609	11,137	56,499	75,969	257,850
Day 28	NC	NC	8386	29,829	30,007	56,147	208,649[a]	425,426[a]
TK: C_{max} (ng/mL)								
Day 1	BQL	BQL	1014	5066	2634	9587	5731	17,653
Day 28	BQL	BQL	2984	9119	6708	10,948	10,918[a]	24,607[a]
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	5	5
Bodyweight[b]	344.9 g	205.8 g	+1	0	–2	–2	295.2 g	–8
Food consumption[b]	21 g	14 g	0	0	0	0	15 g	0
Clinical Observations								
Decreased activity	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Staining	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Abdominal distension	NNF	NNF	NNF	NNF	NNF	NNF	NNF	+
Soft stool	NNF	NNF	NNF	NNF	NNF	NNF	NNF	+
Few feces	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Hypothermia	NNF	NNF	NNF	NNF	NNF	NNF	+	+
Lateral position	NNF	NNF	NNF	NNF	NNF	NNF	NNF	+
Hematology[c]								
Red blood cell count ($\times 10^6/\mu L$)	7.83	7.54	7.72	7.39	7.93	7.49	7.59	5.61**
Hemoglobin concentration (g/dL)	14.6	14.1	14.7	14.0	14.8	13.7	14.4	9.8**
Hematocrit (%)	42.9	40.6	43.0	40.1	43.2	39.6	41.1	28.8

Daily Dose (mg/kg)	0 (Control)		100		300		1000	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Mean corpuscular volume (fL)	54.8	53.9	55.7	54.3	54.5	52.9	54.4	51.4**
Mean corpuscular hemoglobin (pg)	18.7	18.7	19.1	18.9	18.7	18.3	19.1	17.6**
Reticulocyte count ($\times10^9$/L)	181.5	138.0	145.3*	128.2	157.7	140.8	126.2**	423.6**
White blood cells ($\times10^3$/µL)	9.12	4.31	8.91	5.74	10.09	4.54	7.39	12.19##
Neutrophil count ($\times10^3$/µL)	1.00	0.54	0.91	0.55	0.81	0.68	1.83	5.73##
Lymphocyte count ($\times10^3$/µL)	7.86	3.64	7.67	4.98	8.76	3.57	5.03	5.77
Monocyte count ($\times10^3$/µL)	0.11	0.05	0.16	0.09	0.29##	0.17##	0.30##	0.38##
Eosinophil count ($\times10^3$/µL)	0.10	0.06	0.11	0.09	0.16*	0.10#	0.19**	0.31##
Serum Chemistry[d]								
Total bilirubin (mg/dL)	0.06	0.06	0.05	0.06	0.05	0.07	0.10	0.36##
Total protein (g/dL)	5.1	5.4	5.1	5.3	4.9**	5.0*	4.6**	4.5**
Albumin (g/dL)	2.4	2.6	2.3	2.7	2.3	2.6	2.0**	1.9**
Glucose (mg/dL)	234	204	230	205	216	197	210	167##
Total cholesterol (mg/dL)	56	59	59	66	60	62	90#	113##
Calcium (mg/dL)	9.5	9.4	9.5	9.4	9.4	9.2	9.7	11.5#
Urinalysis								
Turbidity	NNF	NNF	NNF	NNF	+	+	NA	NNF
Unequal-sized globules in sediment	NNF	NNF	NNF	+	+	+	NA	+
Ophthalmology	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Organ Weights								
Adrenals, relative (mg/100g BW)	15	28	17	27	17	31	NA	37**
Liver, relative (g/100gBW)	3.19	2.87	3.26	3.02	3.39*	3.29##	NA	5.21##
Kidneys, relative (g/100gBW)	0.682	0.735	0.682	0.721	0.642*	0.760	NA	0.938**
Spleen, relative (mg/100gBW)	174	195	183	224*	192	228**	NA	267**
Gross Pathology								
Number evaluated: n (n found dead)	10	10	10	10	10	10	5[a] (5)	5 (5)
Stomach								
Distention	0	0	0	0	0	0	4 (5)	5 (5)
Raised focus, forestomach	0	0	0	0	0	0	2 (1)	4 (3)
Watery contents	0	0	0	0	0	0	0 (5)	0 (5)
Duodenum								
Watery contents	0	0	0	0	0	0	0 (3)	0 (4)
Jejunum								

Daily Dose (mg/kg)	**0 (Control)**		**100**		**300**		**1000**	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Watery contents	0	0	0	0	0	0	0 (3)	0 (4)
Ileum								
Watery contents	0	0	0	0	0	0	0 (3)	0 (4)
Colon								
Small feces	0	0	0	0	0	0	1 (5)	0 (3)
Rectum								
Small feces	0	0	0	0	0	0	1 (5)	0 (3)
Liver								
Discoloration	0	0	0	0	0	0	0 (0)	3 (0)
Thymus								
Small	0	0	0	0	0	0	5 (5)	5 (4)
Adrenals								
Enlarged	0	0	0	0	0	0	3 (5)	0 (4)
General								
Emaciation	0	0	0	0	0	0	0 (0)	0 (1)
Histopathology								
Number evaluated: n (n found dead)	10	10	10	10	10	10	5[a] (5)	5 (5)
Stomach								
Erosion/ulcer	0	0	0	0	0	0	2 (2/4[e])	4 (4)
Degeneration/necrosis, glandular stomach	0	0	0	0	0	0	0 (4/4[e])	0 (3)
Duodenum								
Degeneration/necrosis, epithelial cells	0	0	0	0	0	0	4 (4/4[e])	0 (2/2[e])
Hyperplasia, crypt	0	0	0	0	0	0	0 (0/4[e])	4 (0/2[e])
Jejunum								
Degeneration/necrosis, epithelial cells	0	0	0	0	0	0	4 (4/4[e])	1 (1/1[e])
Hyperplasia, crypt	0	0	0	0	0	0	0 (0/4[e])	2 (0/1[e])
Ileum								
Degeneration/necrosis, epithelial cells	0	0	0	0	0	0	2 (3/4[e])	1 (3/4[e])
Lymphoid depletion/necrosis (Peyer's Patch)	0	0	0	0	0	0	0 (0/4[e])	0 (3/4[e])
Cecum								
Degeneration/necrosis, epithelial cells	0	0	0	0	0	0	0 (1/4[e])	0 (3/4[e])
Colon								

Daily Dose (mg/kg)	0 (Control)		100		300		1000	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Degeneration/necrosis, epithelial cells	0	0	0	0	0	0	0 (1)	0 (1)
Rectum								
Degeneration/necrosis, epithelial cells	0	0	0	0	0	0	0 (3)	0 (4)
Hyperplasia, crypt	0	0	0	0	0	0	0 (0)	2 (0)
Bone marrow								
Hypocellularity	0	0	0	0	0	0	0 (4)	0 (3)
Increased hematopoiesis	0	0	0	0	0	0	0 (0)	2 (0)
Femur								
Trabecular formation	0	0	0	0	0	0	3 (0)	2 (3)
Thymus								
Lymphoid depletion/necrosis	0	0	0	0	0	0	5 (5)	5 (5)
Spleen								
Lymphoid depletion/necrosis	0	0	0	0	0	0	0 (5)	2 (5)
Increased extramedullary hematopoiesis	0	0	0	0	0	0	0 (0)	3 (0)
Submaxillary lymph node								
Lymphoid depletion/necrosis	0	0	0	0	0	0	0 (5)	1 (5)
Mesenteric lymph node								
Lymphoid depletion/necrosis	0	0	0	0	0	0	0 (5)	1 (5)
Increased histiocytes	0	0	0	0	0	0	1 (2)	0 (0)
Kidneys								
Eosinophilic droplet, tubular epithelial cells	0	0	0	0	0	0	0 (0)	0 (3)
Degeneration/necrosis, tubular epithelium	0	0	0	0	0	0	2 (5)	1 (4)
Lung								
Inflammatory cell infiltration, peribronchiolar	0	0	0	0	0	0	2 (4)	5 (4)
Liver								
Hypertrophy, hepatocytes, centrilobular	0	0	0	0	0	0	0 (0)	3 (0)
Mononuclear cell infiltration, multifocal	0	0	0	0	0	0	0 (1)	0 (0)
Vacuolation, hepatocytes, diffuse	0	0	0	0	0	0	0 (4)	0 (5)
Submaxillary glands								
Acinar atrophy	0	0	0	0	0	0	0 (1)	0 (3)
Pancreas								

Daily Dose (mg/kg)	0 (Control)		100		300		1000	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Decreased zymogen granules	0	0	0	0	0	0	0 (4)	0 (4)
Adrenals								
Cortical hypertrophy	0	0	0	0	0	0	1 (2)	0 (4)
Seminal vesicles/coagulating glands								
Atrophy	0	NA	0	NA	0	NA	0 (5)	NA
Prostate								
Atrophy	0	NA	0	NA	0	NA	0 (5)	NA
Ovaries								
Atrophy	NA	0	NA	0	NA	0	NA	2 (4)
Uterus								
Atrophy	NA	0	NA	0	NA	0	NA	0 (2)
Vagina								
Atrophy, epithelium	NA	0	NA	0	NA	0	NA	3 (4)

+ = observed, $AUC_{(0\text{-}24h)}$ = area under the concentration-time curve from 0 time to 24 hours postdose, BQL = below quantitation limit (<1 ng/mL), C_{max} = maximum observed concentration, CTD = common technical document, F = female, GLP = Good Laboratory Practice, M = male, NA = not applicable, NC = not calculated, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, PT = prothrombin time, TK = toxicokinetics.

a: Data from Day 15.

b: At the end of the dosing period (Day 28). For controls, group means are shown. For treated groups, percent differences from controls are shown. For 1000 mg/kg male group, group means on Day 15 (body weights) or Day 13 (food consumption) are shown.

c: For 1000 mg/kg male group, group means on Day 15 are shown. In moribund sacrificed animals at 1000 mg/kg, increases in red blood cell counts, hemoglobin, hematocrit, or neutrophil and monocyte counts, prolongation of PT, and decreases in reticulocyte and lymphocyte counts were observed.

d: For 1000 mg/kg male group, group means on Day 15 are shown. In moribund sacrificed animals at 1000 mg/kg, increases in total bilirubin, urea, nitrogen, creatinine, glucose, and total cholesterol, and decreases in total protein were observed.

e: Number of animals with lesion/number of animals examined (marked autolysis was excluded).

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

Source: Study K[redacted]025.

2.6.7.17B **Test Article: EPZ-10961 (E7961)**

Report Title: E7961 tartrate: A 13-Week Oral Toxicity Study with 8-Week Recovery Period in Rats		**Study No.** K[redacted]040
Species / Strain: Rat/Sprague Dawley	Duration of Dosing: 13 weeks	Location in CTD: 4.2.3.7.3.4
Initial Age: 8 weeks old	Duration of Postdose: 8 weeks	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral by gavage	
Vehicle / Formulation: 0.5% methylcellulose solution/ Suspension		
Special Features: A number of animals shown with findings of enlarged thymus and/or lymphoblastic lymphoma. At scheduled necropsy thymus tissue was collected and used for immunophenotyping and genomic investigations.		
NOAEL: <50 mg/kg		

Daily Dose (mg/kg)	**0 (Control)**		**50**		**100**		**300**	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Number of Animals for TK[a]	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
TK: AUC $_{(0\text{-}24h)}$ (ng·h/mL)								
Day 1	NC	NC	1881.42	1499.86	1753.40	2709.27	5783.84	9301.89
Day 91	NC	NC	2758.40	3825.67	4254.74	5740.96	29,523.14	33,086.57
TK: C_{max} (ng/mL)								
Day 1	BQL	BQL	408.31	417.40	403.71	534.79	963.45	1538.65
Day 91	BQL	BQL	585.28	862.07	696.07	1248.70	3318.86	3971.51
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	2 (SM: Days 80 and 85)	1 (FD: Day 78)	5 (SM: Days 56, 69,and 85 FD: Days 46 and 69)	0	0	0
Organ Weights (Days 92-93)								
Number Evaluated	M: 10	F: 10	M: 8	F: 9	M: 6	F: 10	M: 10	F: 10
Body weight (g)	457.1	256.4	455.1	251.3	453.4	242.8*	429.2*	241.4*
Thymus (mg)	431	288	568[b]	238[b]	551	223	206[##]	122**
Thymus (mg/100gBW)	94	112	122[b]	95[b]	125	91	48[##]	50**
Organ Weights (Days 148)								
Number Evaluated	M: 6	F: 6	M: 0	F: 0	M: 5	F: 6	M: 6	F: 6
Body weight (g)	535.6	269.9	ND	ND	515.4	259.1	494.5**	261.2
Thymus (mg)	400	240	ND	ND	328	221	319*	274

Daily Dose (mg/kg)	**0 (Control)**		**50**		**100**		**300**	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Thymus (mg %)	75	89	ND	ND	63	85	65	105
Gross Pathology (Days 92-93)								
Number Evaluated[e]	M: 14	F: 14	M: 12 (2)	F: 11 (3)	M: 10 (5)	F: 14	M: 14	F: 14
Mesenteric lymph node								
Enlarged	0	0	1 (1)	0 (0)	0 (1)	0	0	0
Spleen								
Discolored focus	0	0	0 (0)	0 (0)	0 (0)	0	0	1
Enlarged	0	0	1 (2)	1 (2)	0 (5)	0	0	0
Submaxillary lymph node								
Enlarged	0	0	0(1)	0 (0)	0 (0)	0	0	0
Thymus								
Mass	0	0	3 (2)	2 (3)	2 (5)	0	0	0
Small	0	0	1 (0)	0 (0)	2 (0)	5	8	13
Hepatic lymph node								
Enlarged	0	0	0 (1)	0 (2)	0 (1)	0	0	0
Kidney								
Enlarged	0	0	0 (0)	0 (0)	0 (1)	0	0	0
Liver								
Enlarged	0	0	0 (1)	0 (0)	0 (2)	0	0	0
Incisor								
Short	0	0	0 (0)	0 (0)	0 (0)	0	1	3
Gross Pathology (Day 148)								
Number Evaluated	M: 6	F: 6	M: 0	F: 0	M: 5	F: 6	M: 6	F: 6
Thymus	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF
Histopathology (Days 92-93)								
Number Evaluated[e]	M: 14	F: 14	M: 12 (2)	F: 11 (3)	M: 10 (5)	F: 14	M: 14	F: 14
Thymus								
Lymphoblastic lymphoma	0	0	4 (2)	2 (3)	2 (5)	2	0	0
Lymphoid depletion 1+	0	0	0 (0)	0 (0)	4 (0)	2	4	6
Lymphoid depletion 2+	0	0	0 (0)	0 (0)	0 (0)	0	8	7
Lymphoid depletion 3+	0	0	0 (0)	0 (0)	0 (0)	0	1	1
Femur								
Trabecular formation 1+	0	0	0 (0)	1 (0)	1 (0)	5	7	7

Daily Dose (mg/kg)	0 (Control)		50		100		300	
Number of Animals (main groups)	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Trabecular formation 2+	0	0	0 (0)	0 (0)	0 (0)	0	4	4
Sternum								
Trabecular formation 1+	0	0	2 (0)	5 (0)	6 (0)	9	7	5
Trabecular formation 2+	0	0	0 (0)	0 (0)	0 (0)	0	7	9
Histopathology (Day 148)								
Number Evaluated	M: 6	F: 6	M: 0	F: 0	M: 5	F: 6	M: 6	F: 6
Thymus	NNF	NNF	NNF	NNF	NNF	NNF	NNF	NNF

Investigative mechanism of action studies from the 13-week rat Study K[redacted]040

Title	Results	Study Number	CTD Location
The lineage analysis of thymic lymphoid cells from lymphomatous rats treated with E7961 tartrate—Interim assessment	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.	M[redacted]002	4.2.3.7.3.5
The lineage analysis of thymic lymphoid cells in rats treated with E7961 tartrate for 13 weeks	Dose dependent decreases in $CD4^+$ T cell ratio and αβ T cell ratio, and increases in $CD8^+$ T cell ratio and γδ T cell ratio were observed in thymus samples from animals without T-LBL.	M[redacted]006	4.2.3.7.3.7
Thymus sample collection from rats treated with E7961 tartrate for 13 weeks		M[redacted]004	4.2.3.7.3.6

E7961 (EPZ-10961) is a related EZH2 inhibitor.

$AUC_{(0\text{-}24h)}$ = area under the concentration-time curve from 0 time to 24 hours postdose, BQL = below quantitation limit (<1 ng/mL), C_{max} = maximum observed concentration, CTD = common technical document, EZH2 = enhancer of zeste homolog 2, F = female, FD = found dead, GLP = Good Laboratory Practice, M = male, NC = not calculated, ND = not determined, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, SM = sacrificed moribund, TK = toxicokinetics.

a: 4 animals for TK groups, but 2 females on Day 91 at 50 mg/kg.

b: n=7.

c: Number in parentheses shows the number of animals found moribund or dead.

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

Source: Study K[redacted]040, M[redacted]002, M[redacted]004, and M[redacted]006.

2.6.7.17C **Test Article: EPZ011989**

Report Title: A 3-Month Oral (Gavage) Toxicity and Toxicokinetic Study of EPZ011989 in Sprague Dawley Rats		**Study No.** [redacted]-154502
Species / Strain: Rat/Sprague Dawley	Duration of Dosing: 13 weeks	Location in CTD: 4.2.3.7.3.8
Initial Age: 7 to 8 weeks old	Duration of Postdose: NA	GLP Compliance: No
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: A number of animals shown with findings of enlarged thymus and/or lymphoblastic lymphoma, and those sacrificed moribund or found dead, includes animals from the TK subgroup. Thymus tissue was collected for immunophenotyping analyses and genomic analyses.		
NOAEL: None		

Daily Dose (mg/kg)	**0 (Control)**		**100**		**300**		**600**	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Number of Animals for TK	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
TK: $AUC_{(0\text{-}24h)}$ (ng·h/mL)								
Day 1	NC	NC	4301	5578	11,318	19,261	42,525	31,923
Day 88	NC	NC	3243	4030	15,992	13,045	41,787	31,529
TK: C_{max} (ng/mL)								
Day 1	BQL	BQL	861	1230	2358	5282	8618	6098
Day 88	BQL	BQL	1003	777	3918	4080	9964	6396
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	Main: 1, TK: 1	Main: 1, TK: 1	0	Main: 1, TK: 1	0	0
Organ Weights								
Final body weight (g)	420	261	429	256	413	253	395	246
Spleen (g/100g BW)[a]	0.157	0.193	+1.3	+51.8	–5.1	+30.6	+28.0	–1.0
Thymus (g/100g BW)[a]	0.060	0.107	+60.0	+1168.2	–38.3	+626.2	–41.7	–45.8
Gross Pathology								
Number Evaluated[b]	10	10	9 (1)	9 (1)	10	9 (1)	10	10
Thymus								
Enlarged	NNF	NNF	2 (1)	5 (1)	NNF	3 (1)	NNF	NNF
Firm	NNF	NNF	NNF	3 (0)	NNF	3 (0)	NNF	NNF
Spleen								
Enlarged	NNF	NNF	NNF	0 (1)	NNF	1 (1)	1	NNF
Axillary lymph nodes								

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Enlarged	NNF	NNF	NNF	NNF	NNF	0 (1)	NNF	NNF
Discoloration, dark red	NNF	NNF	NNF	NNF	1	1 (0)	NNF	NNF
Mandibular lymph nodes								
Discoloration, dark red	NNF	1	NNF	1 (0)	NNF	1 (1)	NNF	NNF
Mesenteric lymph nodes								
Enlarged	NNF	NNF	NNF	0 (1)	NNF	1 (1)	NNF	NNF
Renal lymph nodes								
Enlarged	NNF	NNF	NNF	0 (1)	NNF	0 (1)	NNF	NNF
Histopathology								
Number examined: (FD/SM)[b]	10	10	9 (1)	9 (1)	10	9 (1)	10	10
Axillary lymph nodes								
Erythrocytosis, sinus	1	NNF	0 (1)	0 (1)	NNF	1 (0)	NNF	NNF
Lymphoma, malignant	NNF	NNF	0 (1)	NNF	NNF	1 (1)	NNF	NNF
Mandibular lymph nodes								
Erythrocytosi, sinus	2	2	1 (0)	2 (0)	2	2 (1)	1	NNF
Lymphoma, malignant	NNF	NNF	NNF	0 (1)	NNF	0 (1)	NNF	NNF
Mesenteric lymph nodes								
Erythrocytosis, sinus	NNF	NNF	0 (1)	NNF	NNF	NNF	NNF	NNF
Lymphoma, malignant	NNF	NNF	0 (1)	0 (1)	NNF	1 (1)	NNF	NNF
Renal lymph nodes								
Lymphoma, malignant	NNF	NNF	NNF	0 (1)	NNF	0 (1)	NNF	NNF
Marrow, femur								
Lymphoma, malignant	NNF	NNF	0 (1)	3 (1)	NNF	1 (1)	NNF	NNF
Marrow, sternum								
Lymphoma, malignant	NNF	NNF	0 (1)	3 (1)	NNF	1 (1)	NNF	NNF
Prostrate								
Lymphoma, malignant	NNF	NA	0 (1)	NA	NNF	NA	NNF	NA
Spleen								
Lymphoid depletion	NNF	NNF	NNF	NNF	NNF	NNF	1	NNF
Necrosis	NNF	NNF	NNF	NNF	NNF	NNF	1	NNF
Lymphoma	NNF	NNF	0 (1)	NNF	NNF	NNF	NNF	NNF
Lymphoma, malignant	NNF	NNF	NNF	3 (1)	NNF	1 (1)	NNF	NNF
Thymus								

Daily Dose (mg/kg)	0 (Control)		100		300		600	
Number of Animals (main groups)	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Decreased lymphocytes	NNF	NNF	3 (0)	2 (0)	2	3 (0)	4	2
Hemorrhage	2	NNF	2 (0)	3 (0)	5	3 (0)	7	2
Lymphoma, malignant	NNF	NNF	2 (1)	4 (1)	NNF	3 (1)	NNF	NNF

Investigative mechanism of action studies from the 13-week rat Study [redacted]-154502			
Title	**Results**	**Study Number**	**CTD Location**
Notch target gene expression analysis from EPZ011989 13-week study	Expression level of Notch target genes (Hes1 and Dtx1) were lower in thymus samples from animals with T-LBL than those from animals without T-LBL.	EPZ-6438-PD014	4.2.3.7.3.9
Myc gene expression analysis from EPZ011989 13-week study	Increased level of Myc gene expression was observed in thymus samples from animals with T-LBL.	EPZ-6438-PD015	4.2.3.7.3.10
RNAseq data analysis from EPZ011989 13-week study	No significant increased expression of common molecular determinants of human T-ALL was observed in thymus samples from animals with T-LBL. Expression pattern did not resemble that observed in human T-ALL associated with genetic PRC2 loss.	EPZ-6438-PD016	4.2.3.7.3.11

EPZ011989 is a related EZH2 inhibitor.

$AUC_{(0\text{-}24h)}$ = area under the concentration-time curve from 0 time to 24 hours postdose, BQL = below quantitation limit, BW = body weight, C_{max} = maximum observed concentration, CTD = common technical document, EZH2 = enhancer of zeste homolog 2, F = female, FD = found dead, GLP = Good Laboratory Practice, M = male, NA = not applicable, NC = not calculated, NNF = no noteworthy findings, NOAEL = no observed adverse effect level, SM = sacrificed moribund, TK = toxicokinetics.

a: Percentage difference group mean to control group are shown for treated groups.
b: Number in parenthesis shows the number of animals found moribund or dead.
Source: Study [redacted]-154502, EPZ-6438-PD014, EPZ-6438-PD015, and EPZ-6438-PD016.