Daily Dose (mg/kg):		0 (Control)	0.1	0.3	1.0
	Split cartilage of thoracic centrum	2 (1.5)	13 (9.6)$^{\#w}$	51 (43.5)$^{\#\#w}$	NA
	Split cartilage of lumbar centrum	0 (0.0)	0 (0.0)	1 (0.9)	NA
	Absent lumbar vertebra	0 (0.0)	0 (0.0)	1 (1.1)	NA
	Absent sacral vertebra	0 (0.0)	0 (0.0)	1 (1.1)	NA
	Fused caudal centrum	0 (0.0)	0 (0.0)	2 (1.6)	NA
	Misshapen caudal centrum	0 (0.0)	0 (0.0)	2 (1.6)	NA
	Ossification Pattern				
	No. of Fetuses Examined	132	136	117	0
	5th sternebra	94 (69.9)	88 (65.0)	71 (56.6)	NA
	6th sternebra	62 (46.2)	48 (33.9)	33 (27.1)	NA
	Supraoccipital bone	131 (99.3)	136 (100.0)	113 (95.3)	NA
	Odontoid process	49 (37.6)	35 (25.9)	12 (11.1)$^{\#\#w}$	NA
	7th cervical body	84 (61.3)	76 (55.8)	49 (40.1)$^{\#w}$	NA
	2nd sternebra	132 (100.0)	135 (99.2)	113 (95.2)	NA
	Hyoid bone	124 (94.7)	130 (95.1)	112 (95.1)	NA
	Sacral and caudal vertebrae	7.6 ± 0.4	7.5 ± 0.4	6.7 ± 0.9$^{\#\#}$	NA
	Metacarpal (L)	3.5 ± 0.4	3.3 ± 0.3	3.0 ± 0.7$^{\#\#}$	NA
	Metacarpal (R)	3.5 ± 0.3	3.4 ± 0.3	3.0 ± 0.8$^{\#\#}$	NA
	Metatarsal (L)	3.9 ± 0.2	3.8 ± 0.4	3.1 ± 1.2$^{\#}$	NA
	Metatarsal (R)	3.9 ± 0.2	3.8 ± 0.4	3.0 ± 1.2$^{\#}$	NA
	Skeletal Variations				
	No. of Fetuses Examined	132	136	117	0
	No. of Fetuses with Skeletal Variations (mean%)	19 (14.9)	38 (28.4)	67 (57.7)$^{\#\#w}$	NA
	Cervical rib	0 (0.0)	0 (0.0)	1 (0.8)	NA
	Asymmetrical sternebra	0 (0.0)	2 (1.5)	2 (1.8)	NA
	Extra lumbar vertebra	0 (0.0)	0 (0.0)	0 (0.0)	NA
	Dumbbell-shaped vertebral centrum	1 (0.9)	4 (2.9)	7 (5.8)$^{\#w}$	NA
	Short 13th rib	0 (0.0)	0(0.0)	0 (0.0)	NA
	14th rib	18 (14.0)	26 (19.5)	50 (43.0)$^{\#\#w}$	NA
	Split vertebral centrum	0 (0.0)	9 (6.6)$^{\#w}$	36 (30.9)$^{\#\#w}$	NA

– = No noteworthy finding, + = observed, CTD = Common Technical Document, GLP = Good Laboratory Practice, NA = not applicable.
a: For controls, group means are shown. For treatment groups, percent differences from controls are shown.
**$P<0.01$ (Dunnett's test), # $P<0.05$, ##$P<0.01$ (Dunnett's rank test), #w$P<0.05$, ##w $P<0.01$ (Wilcoxon's rank test).

2.6.7.13.B　　**Test Article: lenvatinib mesilate**

Report Title: An Oral Embryo-Fetal Development Study in Rabbits		**Study No. S[redacted]009**
Species / Strain: Rabbit / NZW	Duration of Dosing: Day 6 to 18 of Pregnancy	Location in CTD: 4.2.3.5.2
Initial Age (Day 0 of pregnancy): 21 to 23 weeks old	Day of Mating: Day 0 of Pregnancy	
Date of First Dose: [redacted] 20[redacted]	Day of C-Section: Day 29 of Pregnancy	GLP Compliance: Yes
Special Features: None	Method of Administration: Oral by gavage	
No Observed Adverse Effect Level	Vehicle/Formulation: Water/Solution	Design Similar to ICH 4.1.3: Yes
F_0 Females: 0.1 mg/kg		
F_1 Litters: 0.03 mg/kg		

Daily Dose (mg/kg):		**0 (Control)**	**0.03**	**0.1**	**0.5**
Dams/Dose:					
	No. of Pregnant Animals	19	20	17	18
	No. of Died or Sacrificed Moribund	0	0	0	0
	No. of Aborted Animals	0	0	0	7@@
	No. with Total Resorption of Litter	0	0	0	10
	Clinical Observations				
	Bloodstain inside / under cage	–	–	–	+
	Necropsy Observations	–	–	–	–
	Body Weight (%)[a] on Day 6 of Pregnancy	3.81 kg	+1.8	+0.5	+0.8
	Body Weight (%)[a] on Day 18 of Pregnancy	3.97 kg	+2.0	+0.5	–3.8*
	Body Weight (%)[a] on Day 21 of Pregnancy	4.04 kg	+1.2	+0.2	–5.4**
	Body Weight (%)[a] on Day 29 of Pregnancy	4.17 kg	+1.0	+0.2	–1.7
	Body Weight gain (Day 6-18)	0.16 kg	0.17 kg	0.16 kg	–0.02 kg**
	Body Weight gain (Day 18-29)	0.20 kg	0.17 kg	0.19 kg	0.25 kg
	Food Consumption (%)[a] on Day 7 of Pregnancy	174 g	+4.6	–1.7	–4.0
	Food Consumption (%)[a] on Day 19 of Pregnancy	171 g	–1.8	+2.3	–47.4##
	Food Consumption (%)[a] on Day 29 of Pregnancy	138 g	–12.3	–2.2	+15.9
	Mean No. of Corpora Lutea	8.1	8.8	8.6	7.3
	Mean No. of Implantations	6.6	7.9	7.4	6.5
	Mean % of Preimplantation Loss	20.6	10.7	15.8	12.0
	Placenta and amniotic fluid	–	–	–	–

Daily Dose (mg/kg):		0 (Control)	0.03	0.1	0.5
Litters:					
	No. of Litters Evaluated	19	20	17	11
	No. of Live Fetuses	122	146	117	5
	Mean No. of Live Fetuses / Litter	6.4	7.3	6.9	0.5**
	Mean % of Postimplantation Loss	3.6	6.8	7.1	94.3##w
	Early Resorptions (mean %)	2.3	5.1	3.8	94.3##w
	Late Resorptions (mean %)	1.3	1.1	0.7	0.0
	Deaths (mean %)	0.0	0.6	2.7	0.0
	Mean Fetal Body Weight (g)	44.99	43.68	43.56	42.70
	Fetal Sex Ratio (males ratio %)	55.5	44.1#w	47.6	20.0
Fetuses:					
	Gross External Anomalies				
	No. of Litters Evaluated	19	20	17	1
	No. of Live Fetuses Examined	122	146	117	5
	No. of External Anomalies (mean %)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)##w
	Short tail	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)##w
	Visceral Anomalies				
	No. of Live Fetuses Examined	122	146	117	4
	No. of Visceral Anomalies (mean %)	0 (0.0)	5 (4.2)	1 (0.7)	2 (50.0)##w
	Retroesophageal aortic arch	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Retroesophageal subclavian artery	0 (0.0)	4 (3.7)	1 (0.7)	2 (50.0)##w
	Skeletal Anomalies				
	No. of Live Fetuses Examined	122	146	117	4
	No. of Skeletal Anomalies (mean %)	3 (3.9)	3 (2.1)	4 (5.2)	1 (25.0)#w
	Absent carpal bone	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)
	Branched rib	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
	Discontinuous rib cartilage	2 (3.3)	1 (1.0)	1 (2.9)	0 (0.0)
	Fused rib	0 (0.0)	0 (0.0)	2 (1.7)	1 (25.0)##w
	Fused thoracic centrum cartilage	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
	Hemicentric thoracic centrum	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
	Thoracic hemivertebra	1 (0.7)	0 (0.0)	0 (0.0)	1 (25.0)##w
	Misshapen lumber arch	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)##w
	Absent lumber vertebra	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
	Misaligned caudal centrum	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)

Daily Dose (mg/kg):		0 (Control)	0.03	0.1	0.5
	Skeletal Variations	–	–	–	–
	Skeletal Ossifications	–	–	–	–

– = No noteworthy findings, + = observed, CTD = Common Technical Document, GLP = Good Laboratory Practice, NZW = New Zealand White.
a: For controls, group means are shown. For treatment groups, percent differences from controls are shown.
@@$P<0.01$ (Fisher's exact test), *$P<0.05$, **$P<0.01$ (Dunnett's test), # $P<0.01$ (Dunnett's rank test), #w $P<0.05$, ##w $P<0.01$ (Wilcoxon's rank test).

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

該当なし

2.6.7.15　新生児を用いた試験：重要な試験以外の試験

Test Article: lenvatinib mesilate

Species / Strain	Method of Administration (Vehicle / Formulation)	Dosing Period	Doses (mg/kg)	No. Per Group	Noteworthy Findings	Study Number
Rat/Sprague Dawley	Oral gavage (water for injection/solution)	2 weeks (PND7 to PND20)	0, 0.2, 0.4, 1, 5	5M, 5F	0.2 mg/kg: Slight growth suppression, slight changes in body weight and blood urea nitrogen ≥0.4 mg/kg: Growth suppression, increase in total cholesterol, histopathologic changes in kidneys, heart, and adrenals ≥1 mg/kg: Mortality, body weight loss, severe growth suppression, histopathologic changes in incisors, bone, and intestines	J[redacted]412
		2 weeks (PND21 to PND34)	0, 0.4, 1, 5, 25	5M, 5F	≤1 mg/kg: No toxicity ≥5 mg/kg: Decreases in body weight gain and food consumption, growth suppression, histopathologic changes in incisors, adrenals, and bone 25 mg/kg: Moribundity, histopathologic changes in kidneys, intestines, testes and brain	

F = female, M = male, PND = postnatal day.

2.6.7.16　新生児を用いた試験

Test Article: lenvatinib mesilate

Report Title: A 8-Week Repeated Oral Dose Toxicity Study with 4-Week Recovery Period in Juvenile Rats		**Study No. J[redacted]193**
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: 8 weeks	Location in CTD: 4.2.3.5
Initial Age: PND21 (postnatal day 21)	Duration of Postdose: 4 weeks	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral by gavage	
Vehicle / Formulation: Water for injection / Solution		
Special Features: None		
No Observed Adverse Effect Level: 0.4 mg/kg		

Daily Dose (mg/kg):	**0 (Control)**		**0.4**		**2**		**10**	
Number of Animals:	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Number of Animals for Toxicokinetics:	**M: 8**	**F: 8**	**M: 16**	**F: 16**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·hr/mL)								
Day 1	NA	NA	1806.13	1956.97	11030.94	10682.33	52475.56	60508.84
Day 56	NA	NA	1371.36	1641.99	8323.30	8827.68	45905.68	31115.09
Toxicokinetics: C_{max} (ng/mL)								
Day 1	NA	NA	259.19	272.16	1459.98	1396.81	8341.75	7535.77
Day 56	NA	NA	254.49	416.43	1556.88	2234.45	5199.33	7512.60
Noteworthy Findings								
Died or sacrificed moribund	0	0	0	0	0	0	6	7
Body Weight (%)[a]	510.0 g	276.9 g	–4	–1	–19	–7	–66	–48
Food Consumption (%)[a]	38.8g	22.6g	–3	+8	–26	–3	–75	–52
Clinical Observations:								
Broken teeth	–	–	–	–	+	+	+	+
Diarrhea	–	–	–	–	–	–	+	+
Blackish stool	–	–	–	–	–	–	–	+
Staining around mouth/nose	–	–	–	–	–	–	+	+
Ophthalmoscopy:	–	–	–	–	–	–	–	–
Hematology:								
Red blood cell count ($\times 10^6/\mu L$)	8.34	7.82	8.41	7.91	8.61	7.89	6.97**	7.19
Hemoglobin (g/dL)	15.9	15.2	16.2	15.3	17.4##	16.3##	14.8	14.9
Hematocrit (%)	44.2	40.6	44.9	41.4	47.2**	43.1##	40.3**	41.4
White blood cell count ($\times 10^3/\mu L$)	9.47	4.03	12.07	5.22	13.57*	7.65**	5.21	4.73

Daily Dose (mg/kg):	**0 (Control)**		**0.4**		**2**		**10**	
Number of Animals:	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Neutrophil count ($\times 10^3/\mu L$)	1.16	0.60	1.95$^{\#}$	0.91	2.91$^{\#}$	1.63$^{\#\#}$	2.27	2.11$^{\#}$
Serum Chemistry:								
ALT (mU/mL)	25.7	22.2	31.6$^{\#\#}$	26.4	45.1$^{\#\#}$	34.1$^{\#\#}$	78.5$^{\#\#}$	110.1$^{\#}$
AST (mU/mL)	72.1	77.7	80.2	75.6	89.6	90.3	99.7	164.9
ALP (mU/mL)	488.5	310.7	545.7	302.9	664.6**	445.6$^{\#}$	438.7	660.2$^{\#}$
Total Cholesterol (mg/dL)	69	73	84	85	78	88	165**	129**
Urea Nitrogen (mg/dL)	13.8	17.2	15.6	17.7	18.3$^{\#\#}$	18.9	42.3$^{\#\#}$	30.8**
Glucose (mg/dL)	157	133	157	138	151	121	103**	130
Total Protein (g/dL)	5.8	5.9	5.8	5.9	5.5	5.7	4.3$^{\#\#}$	4.6**
Albumin (g/dL)	2.4	2.6	2.4	2.7	2.1$^{\#\#}$	2.5	1.7$^{\#\#}$	1.8**
Globulin (g/dL)	3.4	3.3	3.4	3.2	3.3	3.3	2.6**	2.8**
Ca (mg/dL)	10.1	9.6	10.1	9.7	9.5*	9.6	8.6**	9.2
Urinalysis:								
Protein (≥150 mg/dL)	0	0	0	0	0	0	4	1
Physiological development								
Preputial separation (postnatal day)	48.3	NA	48.2	NA	49.5	NA	59.2$^{\#\#}$	NA
Vaginal opening (postnatal day)	NA	30.6	NA	30.8	NA	31.3	NA	35.9$^{\#\#}$
Functional development	–	–	–	–	–	–	–	–
Open field test								
No. of rearing	18.0	18.1	19.2	18.1	14.8**	19.6	5.6**	8.8**
Ambulation	100.6	115.7	92.8	118.8	84.8	117.9	61.4**	82.7**
Latency (sec)	5.9	6.5	4.8	4.0	6.1	7.7	15.0$^{\#\#}$	10.2
Water maze test	–	–	–	–	–	–	NT	NT
Bone measurement								
Number Examined	10	10	10	10	10	10	5	4
Femur length (mm)	36.47	32.87	35.84	32.39	33.69**	31.24**	27.20**	25.58**
Femur width (mm)	4.61	3.97	4.75	4.06	4.90	3.98	3.79**	3.61*
Tibia length (mm)	42.44	37.95	41.98	37.58	39.76**	35.93**	31.96**	30.18**
Tibia width (mm)	3.75	2.96	3.68	2.92	3.23**	2.90	2.56**	2.42**
Organ weights:								
Number Examined	10	10	10	10	10	10	5	4
Adrenals, relative (%)	0.0141	0.0309	0.0162	0.0289	0.0196$^{\#\#}$	0.0324	0.0637$^{\#\#}$	0.0732$^{\#}$

Daily Dose (mg/kg):	**0 (Control)**		**0.4**		**2**		**10**	
Number of Animals:	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Gross Pathology:								
Number Evaluated:	10	10	10	10	10	10	5 (6)	4 (7)
Adrenals								
Enlargement, bilateral	0	0	0	0	0	0	1 (2)	0 (2)
Discoloration, red/yellow, bilateral	0	0	0	0	0	0	0 (1)	0 (1)
Common bile duct								
Dilatation	0	0	0	0	0	0	0	2
Duodenum								
Dilatation	0	0	0	0	0	0	5 (4)	4 (5)
Incisors								
Discoloration, white	0	0	0	0	4	0	4 (6)	4 (7)
Stomach								
Spot/focus, red, glandular stomach	0	0	0	0	0	0	1 (1)	0 (2)
Thymus								
Small	0	0	0	0	0	0	1 (2)	2
Histopathology:								
Number Evaluated:	10	10	10	10	10	10	5 (6)	4 (7)
Incisor								
Dysplasia	0	0	0	0	10	10	5 (6)	4 (7)
Inflammation cell infiltration, pulp	0	0	0	0	2	1	5 (5)	3 (4)
Inflammation cell infiltration, gingiva	0	0	0	0	1	1	4 (2)	4 (3)
Femur								
Increased epiphysial growth plate/articular cartilage	0	0	0	0	9	2	5 (6)	4 (7)
Sternum								
Increased epiphysial cartilage	0	0	0	0	0	0	3 (6)	2 (6)
Bone marrow (Femur)								
Hypocellularity, focal	0	0	0	0	1	0	5 (6)	2 (6)
Hyperplasia, granulocytic cell	0	0	0	0	0	0	0	1
Bone marrow (Sternum)								
Hypocellularity	0	0	0	0	0	0	3 (5)	1 (4)
Hyperplasia, granulocytic cell	0	0	0	0	0	0	0	1
Kidneys								
Glomerulopathy	0	0	0	0	1	0	4 (6)	4 (6)
Glomerulonephropathy	0	0	0	0	0	0	1	0 (1)

Daily Dose (mg/kg):	0 (Control)		0.4		2		10	
Number of Animals:	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Adrenals								
Sinusoidal dilatation	0	0	0	0	0	0	3 (2)	3 (3)
Cortical necrosis	0	0	0	0	0	0	3 (5)	0 (4)
Brain								
Eosinophilic exudate, choroid plexus	0	0	0	0	0	0	1	2
Arterial fibrinoid necrosis, choroids plexus	0	0	0	0	0	0	0	1 (2)
Stomach								
Mineralization, mucosa	0	0	0	0	0	0	4 (5)	0 (5)
Mucosal hyperplasia, glandular stomach	0	0	0	0	0	0	5 (6)	4 (5)
Inflammation cell infiltration, glandular stomach	0	0	0	0	0	0	5 (5)	4 (5)
Hemorrhage, lamina propria, focal	0	0	0	0	0	0	1 (1)	1 (2)
Duodenum								
Inflammation/cystic dilatation, duodenal glands	0	0	0	0	0	0	5 (6)	4 (7)
Mucosal hyperplasia	0	0	0	0	0	0	3 (2)	3 (2)
Cecum								
Edema, submucosa	0	0	0	0	0	0	3 (3)	2 (3)
Hyperplasia, crypt	0	0	0	0	0	0	1 (1)	1
Colon								
Edema, submucosa	0	0	0	0	0	0	1	0
Liver								
Abscess	0	0	0	0	0	0	0	1
Cholangitis	0	0	0	0	0	0	0	1
Common bile duct								
Cholangitis (No. of animals with finding/No. examined)	NA	NA	NA	NA	NA	NA	NA	2/2
Heart								
Thrombosis	0	0	0	0	0	0	0	0 (1)
Myocardial hypertrophy	0	0	0	0	0	0	0	0 (1)
Lung								
Foamy cell accumulation, alveolar, focal	0	0	0	0	0	0	0	0 (1)
Thymus								
Lymphoid depletion	0	0	0	0	1	0	2 (2)	3 (5)
Spleen								
Extramedullary hematopoiesis	0	0	0	0	0	0	3	1 (1)
Lymphoid depletion	0	0	0	0	0	0	1 (2)	1 (1)

Daily Dose (mg/kg):	**0 (Control)**		**0.4**		**2**		**10**	
Number of Animals:	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Submaxillary lymph node								
Lymphoid depletion	0	0	0	0	0	0	0 (1)	2 (1)
Mesenteric lymph node								
Lymphoid depletion	0	0	0	0	0	0	2 (1)	1 (1)
Pancreas								
Decreased zymogen granules	0	0	0	0	0	0	2 (3)	0 (4)
Edema	0	0	0	0	0	0	3	2
Submaxillary glands								
Single cell necrosis/Apoptosis	0	0	0	0	0	0	0 (2)	0 (1)
Postdose Evaluation								
Number of Animals	**M: 6**	**F: 6**	**M: 0**	**F: 0**	**M: 6**	**F: 6**	**M: 5**	**F: 5**
Died or sacrificed moribund	0	0	NA	NA	0	0	0	0
Body Weight (%)[b]	622.7 g	313.7 g	NA	NA	–15	–2	–40	–24
Food Consumption (%)[b]	36.1 g	20.6 g	NA	NA	–20	–3	–28	–12
Clinical Observations:								
Broken teeth	–	–	NA	NA	+	+	–	–
Diarrhea	–	–	NA	NA	–	–	+	+
Ophthalmoscopy	–	–	NA	NA	–	–	–	–
Hematology:	–	–	NA	NA	–	–	–	–
Serum Chemistry:	–	–	NA	NA	–	–	–	–
Urinalysis								
Protein (≥150 mg/dL)	–	–	NA	NA	–	–	2	1
Functional development	–	–	NA	NA	–	–	–	–
Open field test	–	–	NA	NA	–	–	–	–
Bone measurement								
Femur length (mm)	38.25	33.71	NA	NA	35.31**	32.25*	27.89**	26.39**
Tibia length (mm)	45.20	39.12	NA	NA	42.22*	37.37*	33.46**	31.61**
Tibia width (mm)	4.08	3.15	NA	NA	3.94	3.18	3.21**	2.69*
Organ weight	–	–	NA	NA	–	–	–	–
Gross Pathology:								
Number Evaluated:	6	6	0	0	6	6	5	5
Incisors								
Discoloration, white	0	0	NA	NA	0	1	3	2

Daily Dose (mg/kg):	0 (Control)		0.4		2		10	
Number of Animals:	**M: 16**	**F: 16**	**M: 10**	**F: 10**	**M: 16**	**F: 16**	**M: 16**	**F: 16**
Liver								
Yellowish white area	0	0	NA	NA	0	0	1	1
Histopathology:								
Number Evaluated:	6	6	0	0	6	6	5	5
Incisor								
Dysplasia, distal remnant	0	0	NA	NA	4	6	4	5
Femur								
Remodeling/Regeneration, epiphysial growth plate/articular cartilage	0	0	NA	NA	3	0	5	5
Kidneys								
Glomerulopathy, focal	0	0	NA	NA	0	0	4	1
Adrenals								
Focal cortical fibrosis, residual	0	0	NA	NA	0	0	3	1
Stomach								
Mineralization, mucosa	0	0	NA	NA	0	0	2	0
Mononuclear cell infiltration, glandular stomach	0	0	NA	NA	0	0	0	3
Duodenum								
Interstitial fibrosis, residual, duodenal glands	0	0	NA	NA	0	0	5	5
Liver								
Mononuclear cell infiltration, periportal	0	0	NA	NA	0	0	1	5
Granuloma	0	0	NA	NA	0	0	1	1

–: No noteworthy findings, +: Observed. Number of animals found dead or moribund with a specific change is shown in parentheses.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, $AUC_{(0\text{-}24)}$ = area under the concentration–time curve from zero time to 24 hours, C_{max} = maximum observed concentration, CTD = Common Technical Document, F = female, GLP = Good Laboratory Practice, M = male, NA = not applicable, NT = not tested, PND = postnatal day.
a: At the end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown.
b: At the end of recovery period. For controls, group means are shown. For treated groups, percent differences from controls are shown.
*P<0.05, **P<0.01 (Dunnett's t-test), #P<0.05, ##P<0.01 (Steel's test).

2.6.7.17 局所刺激性試験

該当なし

2.6.7.18　その他の毒性試験

Test Article: lenvatinib mesilate

Species / Strain	Method of Administration	Duration of Dosing	Dose	Gender and No. per Group	Noteworthy Findings	Study Number
Studies on Impurities: In Vitro Genotoxicity Studies						
S. typhimurium and *E. coli*	In vitro	NA	Preincubation method, with and without rat S9 mix: 313 to 5000 µg/plate	NA	Negative for bacterial mutation	K[redacted]066 (GLP)
Mouse lymphoma L5178Y $tk^{+/-}$cells	In vitro	NA	Short treatment method for 3 h, with and without rat S9 mix: 15 to 200 µg/mL Continuous treatment method for 24 h without S9 mix: 10-25 µg/mL	NA	Negative for gene mutation and clastogenicity	K[redacted]067 (GLP)
Phototoxicity Studies						
BALB/c 3T3 cells	In vitro (dissolved in 1% DMSO)	Pretreatment for 60 min and subsequent treatment with or without irradiation with UV-A for 50 min (7.6 to 7.7 J/cm^2)	Range-finding test:0.172 to 180 µg/mL Main test: 1.17 to 20 µg/mL	6 wells	No phototoxic potential was observed.	T[redacted]002 (non-GLP)
BALB/c 3T3 cells	In vitro (dissolved in water for injection)	Pretreatment for 60 min and subsequent treatment with or without irradiation with UV-A for 50 min (5 J/cm^2)	1.17 to 20 µg/mL	6 wells	No phototoxic potential was observed.	[redacted]070 (GLP)

DMSO = dimethyl sulfoxide, GLP = Good Laboratory Practice, NA = not applicable, *tk* = thymidine kinase.

The results of Ames tests for process and synthetic impurities (Study Nos. K[redacted]018, K[redacted]027, K[redacted]008, K[redacted]019, [redacted]037, [redacted]038, [redacted]039, [redacted]040, K[redacted]028, [redacted]121, [redacted]034, [redacted]576, K[redacted]025, K[redacted]026) are summarized in Tables 3.2.S.3.2-7 and 3.2.S.2.6-1 in Module 3.2.S.