Table 2.6.7.7-3: Taletrectinib: 28-Day Oral Repeat-Dose Toxicity Study in Cynomolgus Monkey with a 28-Day Treatment-free Period

Test Article: Taletrectinib

Species/Strain:	Monkey/Cynomolgus	**Report Number:**	VPT1578/2013
Initial Age:	~ 2.5 years	**Testing Facility:**	[redacted] Italy
Date of First Dose:	[redacted]20[redacted]		
Lot Number:	RS101		
Duration of Dosing:	28 days	**GLP Compliance:**	Yes
Duration of Post dose:	28 days		
Method of Administration:	Oral (gavage)		
Vehicle/Formulation:	0.5% (w/v) MC (400 cps) in sterile water for injections/suspension		
Special Features:	Electrocardiography		
HNSTD	100 mg/kg/day		

Repeat-Dose Toxicity									
Daily Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main study + Recovery)		**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Toxicokinetics									
$AUC_{0\text{-}24}$ (ng•h/mL)	Day 1	NA[a]	NA[a]	1930 ± 570	1560 ± 726	3560 ± 1260	6670 ± 1200	6560 ± 3290	4260 ± 1240
	Day 28	NA[a]	NA[a]	2130 ± 352	1880 ± 1200	4220 ± 1200	6600 ± 2250	6590 ± 3300	10000 ± 2010
C_{max} (ng/mL)	Day 1	NA[a]	NA[a]	171 ± 84.8	123 ± 53.5	249 ± 92.1	455 ± 47.0	485 ± 239	324 ± 122
	Day 28	NA[a]	NA[a]	151 ± 32.4	138 ± 70.8	304 ± 125	463 ± 153	427 ± 247	601 ± 86.1

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Noteworthy Findings								
Died or Sacrificed Moribund	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Clinical Observations	Beginning on Day 1, vomit/emesis was observed almost daily in the cage of animals administered 100 mg/kg/day; the same observation was sporadically recorded in animals administered 10 or 30 mg/kg/day. A few occasions of loose/watery feces were also observed in animals administered 100 mg/kg/day. Dose reflux was sporadically recorded for one animal administered 30 mg/kg/day. Dehydration was recorded on single/few occasions for some animals administered 100 mg/kg/day; animals were hydrated with appropriate subcutaneous fluids for injection. Up to moderate hair loss was recorded in one female monkey given 100 mg/kg/day on head and both shoulders, starting from Day 19 until necropsy (Day 29).							
Body Weight[b] (kg)								
Day -1	3.052	3.064	3.028	2.812	3.074	2.940	3.030	2.830
Day 29	-3%	-3%	+12%	+2%	-3%	-4%	-11%	-6%
Ophthalmoscopy								
Week 2	-	-	-	-	-	-	-	-
Week 4	-	-	-	-	-	-	-	-
Electrocardiography								
Week 4	-	-	-	-	-	-	-	-
Hematology[c]								
Week 2 (n=5)								
Lymphocytes ($\times 10^9$/L)	3.998	4.748	4.480	4.490	5.052	5.250	4.602	4.032
Monocytes ($\times 10^9$/L)	0.330	0.540	0.406	0.472	0.426	0.474	0.376	0.562
Eosinophils ($\times 10^9$/L)	0.108	0.488	0.298**	0.320	0.118	0.204	0.118	0.124
Large Unstained Cells ($\times 10^9$/L)	0.096	0.116	0.312**	0.316	0.186	0.278	0.190	0.420*

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Week 4 (n=5)								
Hematocrit (L/L)	0.432	0.434	0.446	0.400*	0.420	0.412	0.418	0.372**
Hemoglobin (g/L)	136.8	135.8	136.6	124.6*	132.4	125.4*	132.6	117.6**
Red Blood Cells ($\times 10^{12}$/L)	6.794	6.800	7.054	6.452	6.514	6.496	6.632	5.956*
Eosinophils ($\times 10^{9}$/L)	0.126	0.268	0.366**	0.288	0.170	0.204	0.148	0.180
Large Unstained Cells ($\times 10^{9}$/L)	0.124	0.104	0.158	0.168	0.108	0.190	0.092	0.108
Coagulation								
Week 2	-	-	-	-	-	-	-	-
Week 4	-	-	-	-	-	-	-	-
Serum Chemistry[c]								
Week 2 (n=5)								
Alanine aminotransferase (U/L)	47.8	54.4	57.0	50.6	105.2**	91.4**	135.4*	153.8**
Aspartate aminotransferase (U/L)	55.6	38.4	55.8	44.0	44.0*	41.8	86.8	105.2**
Creatine kinase (U/L)	178.6	317.6	280.4	332.0	347.0	413.8	659.0*	832.2*
Cholesterol (mmol/L)	2.988	3.518	2.462	2.998	2.454	2.764*	2.124*	1.700**
Sodium (mmol/L)	149.8	151.2	149.6	151.0	150.8	153.0	147.6	145.2*
Chloride (mmol/L)	110.6	110.0	108.6	109.6	110.0	112.0	99.6**	100.8**
Week 4 (n=5)								
Alanine aminotransferase (U/L)	47.2	54.2	68.2*	50.6	94.0**	94.8**	168.8	192.8**
Aspartate aminotransferase (U/L)	53.0	39.0	58.0	40.8	49.0	48.2	105.4**	93.2**
Creatine kinase (U/L)	205.6	309.8	447.6	258.0	815.6	370.4	828.4*	988.2**

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Glutamate dehydrogenase (U/L)	13.92	13.66	23.70	15.32	16.50	24.08**	34.42	22.04**
Cholesterol (mmol/L)	3.416	3.538	2.400*	3.344	2.478*	3.088	2.254*	2.070**
Sodium (mmol/L)	150.6	141.8	149.4	148.2	150.4	152.2	142.0	148.6
Chloride (mmol/L)	108.6	110.6	108.4	108.6	110.2	112.0	91.8	107.2
Urinalysis[c]								
Week 2 (n=5)[d]								
Creatinine (µmol/L)	4148.4	2138.6	4696.8	3479.8	4048.4	1615.0[e]	1847.8	8978.7[f]
Total protein (ratio with creatinine; mg/mmol)	10.854	30.284	17.004	50.474	15.166	158.935*[e]	14332.620*	21.243[f]
Week 4 (n=5)								
Creatinine (µmol/L)	7155.2	6642.2	3325.6	9311.8	8175.6	4196.8	2300.5[e]	3281.0
Total protein (ratio with creatinine; mg/mmol)	11.368	18.394	15.560	19.574	21.806	143.024	9469.863[e]	126.494*
Organ Weights[g]								
Week 5 (n=3)								
Kidneys (absolute) (g)	13.9533	14.4333	+24%*	-3%	+14%	-5%	+14%	+12%
Kidneys (relative to BW)	0.477	0.487	+6%	+1%	+13%	0%	+26%	+25%
Adrenal Gland (absolute) (g)	0.6533	0.9000	+26%*	+11%	+63%**	-15%	+15%	-14%
Adrenal Gland (relative to BW)	0.0233	0.0307	+8%	+12%	+58%**	-11%	+27%*	-5%
Testes (absolute) (g)	1.3233	NA	+62%*	NA	+57%	NA	+19%	NA
Testes (relative to BrW)	1.87	NA	+66%*	NA	+57%*	NA	+21%	NA

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Gross Pathology								
Week 5	-	-	-	-	-	-	-	-
Histopathology								
Duodenum								
Inflammatory cell infiltrate; foamy macrophage; lamina propria; multifocal								
Minimal	0	0	0	0	0	0	1	1
Mild	0	0	0	0	0	0	0	1
Ileum								
Inflammatory cell infiltrate; foamy macrophage; lamina propria; multifocal								
Minimal	0	0	0	0	0	1	1	0
Mild	0	0	0	0	0	0	0	1
Jejunum								
Inflammatory cell infiltrate; foamy macrophage; lamina propria; multifocal								
Minimal	0	0	0	0	0	1	0	1
Mild	0	0	0	0	0	0	1	2
Kidneys								
Dilation; distal tubule; cortex; multifocal								

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Minimal	0	0	0	0	0	0	1	0
Vacuolation; proximal tubule; cortex; multifocal								
Minimal	0	0	0	0	0	0	1	0
Lymph Node - Mesenteric								
Histiocytosis; foamy macrophage; sinus; multifocal								
Minimal	0	0	0	0	0	1	1	2
Stomach								
Erosion; epithelium; body; focal								
Minimal	0	0	0	0	0	1	0	0
Basophilia; luminal; epithelium; body; focal								
Minimal	0	0	0	0	1	0	0	0
Basophilia; luminal; epithelium; body; multifocal								
Minimal	0	0	0	0	0	1	1	0
Mild	0	0	0	0	0	0	1	0
Hyperplasia; foveolar cell; body; focal								
Minimal	0	0	0	0	1	0	0	0
Hyperplasia; foveolar cell; body; multifocal								
Minimal	0	0	0	0	0	1	2	0

Repeat-Dose Toxicity																	
Daily Dose (mg/kg/day)		**0 (Control)**				**10**				**30**				**100**			
Number of Animals (Main study + Recovery)		**M: 5 (3 + 2)**		**F: 5 (3 + 2)**		**M: 5 (3 + 2)**		**F: 5 (3 + 2)**		**M: 5 (3 + 2)**		**F: 5 (3 + 2)**		**M: 5 (3 + 2)**		**F: 5 (3 + 2)**	
Additional Examinations:																	
Post dose Evaluation:																	
Number Evaluated		**M: 2**		**F: 2**		**M: 2**		**F: 2**		**M: 2**		**F: 2**		**M: 2**		**F: 2**	
Animal IDs		4	5	9	10	14	15	19	20	24	25	29	30	34	35	39	40
Clinical Observations		Alopecia noted from Day 26 through Day 57 recovery necropsy in one male monkey administered 100 mg/kg/day															
Body Weight	**Day 57**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology[h]	**Week 8**																
Lymphocytes ($\times 10^9$/L)		11.75	9.27	4.22	5.16	5.95	5.30	6.88	4.04	6.35	6.98	6.62	6.04	6.30	8.35	4.25	4.01
Monocytes ($\times 10^9$/L)		0.42	0.28	1.11	0.73	0.37	0.42	0.70	0.57	0.43	0.54	0.71	0.46	0.32	0.66	0.42	0.61
Eosinophils ($\times 10^9$/L)		0.74	0.19	1.63	0.14	0.81	0.41	2.60	0.27	0.54	0.54	0.18	0.05	0.16	0.34	0.23	0.16
Coagulation	**Week 8**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum Chemistry	**Week 8**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis[h]	**Week 8**																
Creatinine (µmol/L)		4214	5640	8116	7742	3690	670	5626	8891	14150	1821	1698	6357	1179	15234	3205	8746
Organ Weight[g]	**Week 9**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gross Pathology	**Week 9**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Histopathology	**Week 9**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- = no noteworthy findings; $AUC_{0\text{-}24}$ = area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; BLQ = below the lower limit of quantification; BrW = brain weight; BW = body weight; C_{max} = maximum plasma concentration; F = female; GLP = Good Laboratory Practice; HNSTD = highest non-severely toxic dose; MC = methyl cellulose; M = male; NA = not applicable.

* $P < 0.05$. **$P < 0.01$. Significantly different from the control value. Statistical methods are detailed in Report Number VPT1578, Section 11.

[a] Quantifiable levels of taletrectinib were observed in 8 of the 90 vehicle control samples. In these samples levels of taletrectinib were lower than the C_{max} range observed at all taletrectinib doses administered on Day 1 and Day 28 in both males and females. Combined with the lack of a toxicokinetics profile in any of these animals, accidental dosing of control animals can be excluded and the detectable levels in these samples were likely due to ex vivo contamination of samples from taletrectinib, and therefore the impact on the overall toxicokinetics evaluation was considered minimal.

[b] Group means (n = 5) are shown for Day -1; % of means vs Day -1 are shown for Day 29 (n = 3)
[c] Values are reported as group means. During the treatment period, single animals showed high levels of urine creatinine at all doses tested (up to 9.2-fold pretreatment) and urine total protein/creatinine ratio at 100 mg/kg/day (up to 3631-fold pretreatment).
[d] Data collected during weeks 2 & 3 are reported as Week 2 group mean values
[e] n = 4
[f] n = 3
[g] Absolute organ weight values are reported as group means (animals administered vehicle) or % of means (test item treated vs vehicle); relative organ weight values are reported as % with respect to body weight (BW) or brain weight (BrW) (animals administered vehicle) or % of relative means (test item treated vs vehicle)
[h] Individual values are reported

Table 2.6.7.7-4: 85-Day Repeated-Dose Toxicity Study of Taletrectinib by Oral Gavage in Cynomolgus Monkeys with a 57-Day			
			Test Article: Taletrectinib
Species/Strain:	Monkey/Cynomolgus	**Report Number:**	2021010
Initial Age:	3.4-4.9 years (M); 3.4-4.7 years (F)	**Testing Facility:**	[redacted]
Date of First Dose:	[redacted]20[redacted] (M-F, respectively)		
Lot Number:	CPo124073-01-04-01-26-01		
Duration of Dosing:	85 days	**GLP Compliance:**	Yes
Duration of Post dose:	57 days		
Method of Administration:	Oral (gavage)		
Vehicle:	0.5% MC		
Special Features:	Electrocardiography, Body Temperature, Blood Pressure, and Bone Marrow Smears		
HNSTD	30 mg/kg/day		

Repeat-Dose Toxicity									
Daily Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)		**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Toxicokinetics[b]									
$AUC_{0\text{-}24}$ (ng•h/mL)	Day 1	NA		2081.18 ± 1357.48		8905.66 ± 4293.54		14998.00 ± 6368.60	
	Day 85	NA		3424.25 ± 687.30		13941.54 ± 5539.35		20383.30 ± 5624.45	
C_{max} (ng/mL)	Day 1	NA		174.95 ± 146.97		649.19 ± 469.17		935.75 ± 555.40	
	Day 85	NA		245.97 ± 71.09		813.04 ± 454.36		1023.19 ± 229.00	
Noteworthy Findings									
Died or Sacrificed Moribund		0	0	0	0	1[c]	0	2[d]	1[e]

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Clinical Observations	Intermittent diarrhea observed in 2 females administered 30 mg/kg, from Days 9 to 69 of treatment phase. Intermittent diarrhea was also observed in 1 male administered 60/48 mg/kg from Days 13 to 31 in the treatment phase.							
Body Weight	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-
Hematology								
Red blood cell (10^{12}/L)								
Day 22-21 (M-F, respectively)	6.01		5.56		5.28**		5.03**	
Day 43	5.84		5.64		5.27*		5.09**	
Day 64	5.84		5.54		5.27**		5.08*	
Day 86	5.90		5.24*		4.88**		4.79**	
Hemoglobin (g/L)								
Day 22-21 (M-F, respectively)	135		128		121		112**	
Day 43	132		131		119		111*	
Day 64	133		129		120*		114**	
Day 86	134		122		110**		104**	
Hematocrit (%)								
Day 22-21 (M-F, respectively)	48.0		44.4		43.6		40.7**	
Day 43	47.7		45.9		43.6		41.1	
Day 64	48.4		45.4		44.2		41.2*	
Day 86	47.9		41.9*		39.8**		38.2**	

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Serum Chemistry								
ALT (U/L)								
Day 22-21 (M-F, respectively)	41		47		86*		124**	
Day 43	43		46		82		126*	
Day 64	52		46		74		125**	
Day 86	68		56		95		145**	
AST (U/L)								
Day 22-21 (M-F, respectively)	42		47		67		66*	
Day 43	46		44		64		84	
Day 64	45		44		53		85*	
Day 86	70		72		93		126	
CK (U/L)								
Day 22-21 (M-F, respectively)	196		296		516*		679*	
Day 64	198		258		425		916**	
Day 86	292		430		1009		1296*	
Cl^- (mmol/L)								
Day 22-21 (M-F, respectively)	105.9		107.3		107.6		110.0*	
Day 86	106.8		110.6		109.5		111.5*	
P (mg/dl)								
Day 22-21 (M-F, respectively)	2.06		1.98		1.83		1.85	
Day 86	1.77		1.63		1.46		1.29*	

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
CRE (µmol/L)								
Day 22-21 (M-F, respectively)	55		66*		68		68	
C3 (g/L)								
Day 64	1.33		1.15		1.18		0.99*	
Day 86	1.25		1.07		1.05		0.93**	
C4 (g/L)								
Day 64	0.25		0.19		0.20		0.15*	
Day 86	0.25		0.18		0.18		0.15*	
Urinalysis								
Color								
Day 28								
Colorless	2/10		2/10		1/9		2/7*	
Light Yellow	2/10		1/10		1/9		3/7	
Yellow	6/10		7/10		7/9		2/7	
Day 80								
Colorless	3/10		3/10		1/9		1/7	
Light Yellow	2/10		5/10		6/9		2/7	
Yellow	5/10		2/10		2/9		4/7	

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Protein (g/L)								
Day 28								
- (Normal)	4/10		6/10		4/9		4/7	
± (Minimal change)	6/10		3/10		4/9		3/7	
1+ (Mild change)	0/10		1/10		1/9		0/7	
Day 80								
- (Normal)	7/10		8/10		8/9		3/7*	
± (Minimal change)	3/10		2/10		1/9		4/7	
Bone Marrow	-		-		-		-	
Organ Weights	-		-		-		-	
Gross Pathology	-		-		-		-	
Histopathology (n = 3 or 2/ group)	**3**	**3**	**3**	**3**	**3**	**3**	**2**	**2**
Stomach: regeneration of glandular epithelium of the fundic glands in lamina propria.								
Minimal change	0	0	1	0	0	0	1	0
Mild change	0	0	0	0	1	0	0	0
Small intestine: infiltration of foamy macrophages in lamina propria								
Duodenum								
Minimal change	0	0	0	0	0	0	1	0

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Jejunum								
Minimal change	0	0	0	0	0	1	0	0
Mild change	0	0	0	0	1	1	1	1
Moderate change	0	0	0	0	1	0	1	1
Ileum								
Minimal change	0	0	0	0	1	0	0	0
Mesenteric lymph nodes: histiocytosis in the medullary sinus								
Minimal change	0	0	0	0	2	2	1	2
Mild change	0	0	0	0	0	0	1	0
Lung: accumulation of foamy macrophages, alveolus								
Minimal change	0	0	0	0	0	0	0	1
mild change	0	0	0	0	0	0	0	1
Granulomatous inflammation with or without necrosis								
Minimal change	0	0	0	0	0	0	0	1
Mild change	1	0	0	0	2	0	0	1
Moderate change	0	1	0	0	0	0	0	0
Infiltration, inflammatory cells, capsule								
Minimal change	0	0	1	0	0	1	1	0

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Additional Examinations:								
Post dose Evaluation:								
Number Evaluated	**2**	**2**	**2**	**2**	**1**	**2**	**1**	**2**
Hematology								
Reticulocyte (%)								
Day 142	1.02±0.12		0.86±0.40		0.89±0.25		0.70±0.04*	
Reticulocyte (10^9/L)								
Day 142	61.6±4.5		51.6±21.2		48.4±13.4		39.1±4.5**	
Serum Chemistry								
C3 (g/L)								
Day 142	1.16±0.06		1.33±0.05*		1.50±0.34		1.31±0.13	
Urinalysis								
Leukocyte (number/μL)								
Day 112								
-	4/4		4/4		1/3		1/3*	
25	0/4		0/4		1/3		0/3	
75	0/4		0/4		1/3		1/3	
250	0/4		0/4		0/3		1/3	
Day 140								
-	4/4		4/4		1/3*		1/3*	
25	0/4		0/4		0/3		1/3	

Repeat-Dose Toxicity								
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**	
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
250	0		0		2/3		1/3	
Histopathology (n= 2 or 1/group)	2	2	2	2	1	2	1	2
Mesenteric lymph nodes: histiocytosis, medullary sinus								
Minimal change	0	0	0	0	0	0	0	1
Mild change	0	0	0	0	0	0	1	1
Lung: accumulation of foamy macrophages, alveolus								
Minimal change	0	0	1	1	0	0	0	0

- = no noteworthy findings; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC_{0-24} = area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; C3 = Complement C3; C4 = complement C4; CK= creatinine kinase; Cl^- = chlorine; C_{max} = maximum plasma concentration; CRE = creatinine; GLP = Good Laboratory Practice; HNSTD = highest non-severely toxic dose; P = inorganic phosphorus; F = female; MC = methyl cellulose; M = male; NA = not applicable; TK = toxicokinetics.

* $P < 0.05$. ** $P < 0.01$. Significantly different from the control value. Statistical methods are detailed in Report Number 2021010, Section 7.5.

[a] The high dose was 60 mg/kg/day administered from Day 1 to 10 in males and from Day 1 to 9 in females, and was then decreased to 48 mg/kg/day until necropsy due to intolerance seen in these high dose animals.

[b] n = 9 in the last-dose TK middle dose group, 1 animal death; n=7 in the last-dose TK high-dose group, 3 animal deaths.

[c] Cause of death was not test article related.

[d] Cause of death was test article related.

[e] Cause of death was not determined.

2.6.7.8 In Vitro 遺伝毒性試験

Table 2.6.7.8-1: Bacterial Reverse Mutation Study of Taletrectinib

			Test Article: Taletrectinib
Test for Induction of:	Reverse mutation in bacterial cells	**Report Number:**	[redacted]160646
Strains:	*S. typhimurium* (TA98, TA100, TA1535, TA1537), *E. coli* (WP2 *uvr*A)	**Testing Facility:**	[redacted] Japan
Lot No.:	RS-102		
Metabolizing System:	S9 mix		
Number of Independent Assays:	2		
Number of Replicate Cultures:	3	**GLP Compliance:**	Yes
Number of Cells Analyzed/Culture:	≥1×10^9/mL	**Date of Treatment:**	Assay 1: [redacted] 20[redacted] Assay 2: [redacted] 20[redacted]
Vehicles for Test Article:	DMSO	**Vehicles for Positive Controls:**	Water (sodium azide); DMSO (2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, 9-aminoacridine hydrochloride monohydrate, 2-aminoanthracene)
Treatment:	Pre-incubation method: 48 hours ± S9 at 37°C		
Cytotoxic Effects:	Cytotoxicity was observed ≥ 78.1 µg/plate (± S9) in tester strains		
Genotoxic Effects:	Dose-dependent increase in the number of revertant colonies for TA98 +S9		

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Assay 1 Revertant Colony Counts (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without Activation	DMSO	0.1 mL	18 ± 2	89 ± 2	8 ± 5	8 ± 7	26 ± 1
	Taletrectinib	2.44	14 ± 5	89 ± 13	10 ± 1	6 ± 1	24 ± 3
		4.88	12 ± 3	88 ± 4	11 ± 2	5 ± 2	29 ± 5
		9.77	15 ± 7	88 ± 11	11 ± 0	9 ± 3	27 ± 3
		19.5	10 ± 2	89 ± 2	12 ± 3	6 ± 2	29 ± 4
		39.1	13 ± 4	81 ± 11	6 ± 2	6 ± 2	27 ± 10
		78.1	11 ± 4[a]	80 ± 5[a]	10 ± 2[a]	2 ± 1[a]	20 ± 2[a]
		156	3 ± 3[a]	0 ± 0[a]	0 ± 0[a]	0 ± 0[a]	13 ± 4[a]
	2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide	0.1	559 ± 30	526 ± 28 (0.01 µg/plate)	NT	NT	134 ± 8 (0.01 µg/plate)
	sodium azide	0.5	NT	NT	494 ± 34	NT	NT
	9-aminoacridine hydrochloride monohydrate	80	NT	NT	NT	164 ± 32	NT
With Activation	DMSO	0.1 mL	23 ± 2	98 ± 14	8 ± 2	16 ± 3	36 ± 2
	Taletrectinib	2.44	NT	95 ± 5	9 ± 4	13 ± 4	NT
		4.88	20 ± 5	95 ± 11	8 ± 1	16 ± 5	34 ± 5
		9.77	35 ± 9	125 ± 20	8 ± 1	12 ± 7	36 ± 10
		19.5	158 ± 18	113 ± 13	11 ± 9	12 ± 4	43 ± 8
		39.1	409 ± 25	122 ± 4	10 ± 2	9 ± 2	33 ± 5
		78.1	574 ± 60	106 ± 9[a]	7 ± 4[a]	11 ± 4[a]	27 ± 1
		156	726 ± 63[a]	103 ± 5[a]	7 ± 1[a]	11 ± 3[a]	27 ± 5[a]
		313	159 ± 17[a]	NT	NT	NT	0 ± 0[a]
	2-aminoanthracene	0.5	248 ± 13	NT	NT	NT	NT
		1	NT	805 ± 74	NT	NT	NT
		2	NT	NT	187 ± 22	158 ± 16	NT
		10	NT	NT	NT	NT	776 ± 46

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Assay 2 Revertant Colony Counts (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvrA*
Without Activation	DMSO	0.1 mL	15 ± 2	100 ± 6	9 ± 0	7 ± 4	24 ± 2
	Taletrectinib	2.44	14 ± 3	93 ± 16	6 ± 2	7 ± 4	23 ± 4
		4.88	14 ± 3	105 ± 10	7 ± 2	8 ± 5	23 ± 5
		9.77	14 ± 3	89 ± 13	5 ± 1	7 ± 5	23 ± 6
		19.5	14 ± 2	103 ± 15	3 ± 1	5 ± 3	23 ± 6
		39.1	14 ± 4	97 ± 7	7 ± 3	7 ± 1	25 ± 3
		78.1	12 ± 6[a]	73 ± 3[a]	3 ± 1[a]	3 ± 0[a]	21 ± 1[a]
		156	2 ± 2[a]	0 ± 0[a]	0 ± 0[a]	0 ± 0[a]	16 ± 5[a]
	2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide	0.1	612 ± 46	451 ± 3 (0.01 µg/plate)	NT	NT	127 ± 24 (0.01 µg/plate)
	sodium azide	0.5	NT	NT	429 ± 21	NT	NT
	9-aminoacridine hydrochloride monohydrate	80	NT	NT	NT	138 ± 47	NT
With Activation	DMSO	0.1 mL	24 ± 2	110 ± 6	9 ± 2	15 ± 4	30 ± 5
	Taletrectinib	2.44	NT	110 ± 6	8 ± 3	19 ± 3	NT
		4.88	28 ± 9	116 ± 4	7 ± 1	18 ± 2	29 ± 7
		9.77	47 ± 7	118 ± 7	8 ± 1	16 ± 1	32 ± 4
		19.5	160 ± 27	128 ± 19	5 ± 2	14 ± 3	31 ± 10
		39.1	357 ± 76	129 ± 2	9 ± 2	14 ± 2	29 ± 6
		78.1	656 ± 102	123 ± 12[a]	6 ± 2[a]	12 ± 3[a]	26 ± 2
		156	662 ± 131[a]	108 ± 8[a]	5 ± 4[a]	11 ± 4[a]	16 ± 1[a]
		313	172 ± 24[a]	NT	NT	NT	0 ± 0[a]
	2-aminoanthracene	0.5	255 ± 8	NT	NT	NT	NT
		1	NT	763 ± 59	NT	NT	NT
		2	NT	NT	187 ± 19	160 ± 12	NT
		10	NT	NT	NT	NT	835 ± 65

DMSO = dimethyl sulfoxide; GLP = Good Laboratory Practice; NT = not tested; SD = standard deviation.

[a] Toxicity was observed.

Table 2.6.7.8-2: Taletrectinib: Bacterial Reverse Mutation Assay in *Salmonella Typhimurium* and *Escherichia Coli*				
				Test Article: Taletrectinib
Test for Induction of:	Reverse mutation in bacterial cells		**Report Number:**	95206-19-1043
Strains:	*S. typhimurium* (TA98, TA100, TA1535, TA1537), *E. coli* (WP2 uvrA)		**Testing Facility:**	[redacted] China
Lot No.:	CPo124073-01-04-01-26-01			
Metabolizing System:	S9 mix			
Number of Independent Assays:	1			
Number of Replicate Cultures:	3		**GLP Compliance:**	Yes
Number of Cells Analyzed/Culture:	-		**Date of Treatment:**	[redacted]20[redacted]
Vehicles for Test Article:	DMSO	**Vehicles for Positive Controls:**	Water (sodium azide); DMSO (2-nitrofluorene, ICR191, N-methyl-N-nitro-N-nitrosoguanidine, 2-aminoanthracene)	
Treatment:	Plate incorporation method:48 to 72 hours ± S9 at 37 ± 2°C			
Cytotoxic Effects:	Obvious cytotoxicity was exhibited at higher concentrations tested in each tester strain			
Genotoxic Effects:	None			

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Assay 1 Revertant Colony Counts (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without Activation	DMSO	0.1 mL	49.67 ± 3.06	115.67 ± 5.51	5.00 ± 2.00	20.33 ± 1.15	20.33 ± 1.53
	Taletrectinib	5	NT	98.33 ± 0.58	8.33 ± 5.03	16.00 ± 4.36	NT
		10	48.33 ± 11.59	112.00 ± 2.00	8.33 ± 1.53	17.67 ± 2.89	24.33 ± 4.73
		20	56.33 ± 3.79	113.67 ± 4.04	6.00 ± 2.00	16.67 ± 3.21	21.33 ± 4.04
		50	55.67 ± 1.53	82.33 ± 8.96	5.67 ± 1.15	6.67 ± 3.06	17.33 ± 1.53
		75	NT	54.67 ± 7.77	3.67 ± 0.58	9.33 ± 0.58	NT
		100	47.33 ± 8.39	43.67 ± 1.53	3.33 ± 2.52	[a]	22.33 ± 2.08
		200	32.00 ± 5.57	NT	NT	NT	15.67 ± 5.69
		250	[a]	NT	NT	NT	NT
		300	NT	NT	NT	NT	13.00 ± 4.36
	2-nitrofluorene	10	987.33 ± 36.02	NT	NT	NT	NT
	sodium azide	1.2	NT	848.00 ± 330.45	418.67 ± 226.46	NT	NT
	ICR-191	1	NT	NT	NT	182.67 ± 45.45	NT
	N-methyl-N-nitro-N-nitrosoguanidine	5	NT	NT	NT	NT	441.33 ± 82.59

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Assay 1 Revertant Colony Counts (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
With Activation	DMSO	0.1 mL	43.67 ± 8.08	71.67 ± 6.03	5.67 ± 3.79	11.67 ± 1.53	23.33 ± 7.02
	Taletrectinib	5	NT	NT	8.67 ± 1.15	10.33 ± 2.89	NT
		10	47.00 ± 2.65	62.00 ± 2.65	3.67 ± 2.52	10.00 ± 2.00	21.00 ± 4.36
		20	50.33 ± 0.58	67.00 ± 4.36	7.67 ± 1.53	14.00 ± 5.20	25.00 ± 2.65
		50	54.33 ± 1.53	55.67 ± 9.81	6.67 ± 2.08	13.00 ± 5.20	28.67 ± 7.57
		75	NT	NT	6.67 ± 0.58	6.00 ± 1.00	NT
		100	52.67 ± 2.52	55.33 ± 6.43	7.67 ± 2.08	7.00 ± 3.00	19.33 ± 0.58
		150	NT	36.33 ± 3.21	NT	NT	NT
		200	37.67 ± 10.02	[a]	NT	NT	17.67 ± 2.08
		250	22.67 ± 4.04	NT	NT	NT	NT
		300	NT	NT	NT	NT	10.00 ± 4.00
	2-aminoanthracene	3	2182.67 ± 685.04	2552.00 ± 124.00	139.33 ± 39.00	106.33 ± 12.74	NT
		20	NT	NT	NT	NT	347.33 ± 56.32

DMSO = dimethyl sulfoxide; GLP = Good Laboratory Practice; NT = not tested; SD = standard deviation.

[a] Not counted due to pinpoint colonies.

Table 2.6.7.8-3: Taletrectinib: Bacterial Reverse Mutation Assay

Test Article: Taletrectinib

Test for Induction of:	Reverse mutation in bacterial cells	**Report Number:**	946-0003-GT
Strains:	*S. typhimurium* (TA98, TA100, TA1535, TA1537), *E. coli* (WP2 *uvr*A)	**Testing Facility:**	[redacted] China
Lot No.:	CPo124073-01-04-01-26-01		
Metabolizing System:	S9 mix		
Number of Independent Assays:	1		
Number of Replicate Cultures:	3	**GLP Compliance:**	Yes
Number of Cells Analyzed/Culture:	-	**Date of Treatment:**	[redacted]20[redacted]
Vehicles for Test Article:	DMSO	**Vehicles for Positive Controls:**	Water (sodium azide); DMSO (2-nitrofluorene, acridine mutagen ICR191, 2-aminoanthracene); None for methyl methane sulfonate
Treatment:	Pre-incubation method: 48 hours ± S9 at 37 ± 2°C		
Cytotoxic Effects:	-S9 ≥ 80 µg/plate for TA98; -S9 ≥ 50 µg/plate for TA100, TA1535, TA1537; -S9 ≥ 150 µg/plate for WP2 *uvr*A. +S9 ≥ 200 µg/plate for TA98 and WP2 *uvr*A; +S9 ≥ 150 µg/plate for TA100, TA1535, and TA1537.		
Genotoxic Effects:	None		

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Assay 1 Revertant Colony Counts (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without Activation	DMSO	0.1 mL/plate	22.67 ± 2.08	128.00 ± 5.29	13.00 ± 6.56	17.00 ± 7.94	22.33 ± 12.10
	Taletrectinib	5	22.67 ± 0.58	122.00 ± 18.08	7.33 ± 3.21	13.33 ± 4.04	21.33 ± 4.16
		10	23.33 ± 4.16	132.67 ± 9.45	11.33 ± 6.66	12.33 ± 3.51	17.67 ± 2.31
		25	20.67 ± 4.51	122.33 ± 3.79	11.33 ± 6.66	9.33 ± 2.89	20.33 ± 5.03
		50	17.67 ± 5.86	102.00 ± 17.52	9.67 ± 3.79	7.67 ± 1.53	17.00 ± 4.58
		80	16.33 ± 3.21	104.33 ± 13.65	8.00 ± 1.73	7.33 ± 3.21	20.00 ± 2.65
		100	20.33 ± 6.11	95.33 ± 8.02	8.00 ± 3.00	5.00 ± 1.73	19.33 ± 2.31
		150	13.33 ± 3.79	0.00 ± 0.00[a]	0.00 ± 0.00[a]	0.00 ± 0.00[a]	17.00 ± 2.65
		250	0.00 ± 0.00[a]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	10.67 ± 2.52
	2-nitrofluorene	10	1371.67 ± 148.54	NT	NT	NT	NT
	sodium azide	1.0	NT	840.67 ± 19.86	572.00 ± 14.42	NT	NT
	acridine mutagen ICR-191	1.0	NT	NT	NT	695.33 ± 36.02	NT
	methyl methane sulfonate	2.5 µL/plate	NT	NT	NT	NT	801.67 ± 53.41
With Activation	DMSO	0.1 mL/plate	25.00 ± 6.08	168.00 ± 11.53	11.67 ± 1.15	11.67 ± 3.06	24.33 ± 4.73
	Taletrectinib	5	35.67 ± 10.97	149.00 ± 15.13	5.67 ± 3.21	15.00 ± 3.61	26.00 ± 3.61
		10	27.33 ± 8.02	148.00 ± 20.30	12.67 ± 6.35	17.33 ± 4.73	29.33 ± 6.03
		25	27.67 ± 4.04	149.67 ± 7.51	13.33 ± 2.08	17.33 ± 2.31	24.67 ± 4.62
		50	30.33 ± 4.73	144.33 ± 20.26	12.00 ± 1.00	15.67 ± 0.58	22.00 ± 7.55
		100	33.67 ± 1.53	159.00 ± 9.00	11.00 ± 2.65	11.00 ± 1.73	24.00 ± 11.36
		150	26.67 ± 6.51	134.33 ± 4.73	8.67 ± 3.06	8.33 ± 4.16	23.00 ± 4.36
		200	35.33 ± 6.35	112.33 ± 29.19	8.00 ± 3.61	0.00 ± 0.00[a]	14.67 ± 1.53
		250	20.67 ± 8.08	87.67 ± 11.15	9.67 ± 4.16	0.00 ± 0.00[a]	11.33 ± 2.52
	2-aminoanthracene	2.0	3696.67 ± 149.00	3965.67 ± 546.53	138.67 ± 9.24	253.67 ± 38.73	NT
		20.0	NT	NT	NT	NT	104.67 ± 10.50

DMSO = dimethyl sulfoxide; GLP = Good Laboratory Practice; NT = not tested; SD = standard deviation.

[a] Pinpoint colonies were observed.

Table 2.6.7.8-4: Taletrectinib: Bacterial Reverse Mutation Assay

Test Article: Taletrectinib

Test for Induction of:	Reverse mutation in bacterial cells	**Report Number:**	[redacted]2315501[redacted]211
Strains:	*S. typhimurium* (TA97a, TA98, TA100, TA102, TA1535)	**Testing Facility:**	[redacted] China
Lot No.:	RS-102		
Metabolizing System:	S9 mix		
Number of Independent Assays:	1		
Number of Replicate Cultures:	3	**GLP Compliance:**	Yes
Number of Cells Analyzed/Culture:	-	**Date of Treatment:**	[redacted]20[redacted]
Vehicles for Test Article:	DMSO	**Vehicles for Positive Controls:**	Water (sodium azide); DMSO (Dexon, 2-Aminofluorene)
Treatment:	Plate incorporation method:48 to 72 hours ± S9 at 37°C		
Cytotoxic Effects:	Discernable cytotoxicity was exhibited at higher concentrations tested in each tester strain		
Genotoxic Effects:	None		

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)[a]	Assay 1 Revertant Colony Counts (Mean ± SD)				
			TA97a	TA98	TA100	TA102	TA1535
Without Activation	DMSO	0.1 mL	107.3±6.7	37.0±4.6	133.0±3.6	320.3±7.6	10.3±1.5
	Taletrectinib	3.277	-	-	126.7±4.2	-	-
		6.144	106.3±5.1	35.7±4.2	-	-	-
		8.192	-	-	133.7±4.5	327.0±7.2	10.7±2.5
		15.36	107.7±3.2	39.0±2.6	-	-	-
		20.48	-	-	137.0±4.6	314.3±12.9	10.0±1.0
		38.4	105.0±7.0	39.7±2.1	-	-	-
		51.2	-	-	139.3±6.5	329.7±3.1	10.0±2.6
		96	103.3±7.5	37.0±3.6	-	-	-
		128	-	-	76.0±3.6	228.3±7.6	10.0±2.0
		240	42.0±3.6	15.0±2.0	-	-	-
		320	-	-	-	176.3±6.5	3.0±1.0
	Dexon	50	1048.0±66.1	968.0±43.3	-	1489.3±54.6	-
	NaN3	1.5	-	-	1098.7±30.3	-	408.0±21.2

Metabolic Activation	Test Article	Concentration or Dose Level (μg/plate)[a]	Assay 1 Revertant Colony Counts (Mean ± SD)				
			TA97a	TA98	TA100	TA102	TA1535
With Activation	DMSO	0.1 mL	100.7±3.1	39.0±3.0	139.7±3.1	320.0±3.6	9.7±1.5
	Taletrectinib	8.192	109.0±3.6	36.7±5.7	137.0±4.6	-	-
		15.36	-	-	-	326.3±4.7	-
		20.48	105.3±4.7	38.0±2.0	136.0±3.6	-	10.3±2.1
		38.4	-	-	-	313.3±11.6	-
		51.2	105.3±7.5	37.3±6.0	137.0±5.0	-	10.0±1.0
		96	-	-	-	320.7±11.9	-
		128	106.0±4.0	34.3±3.2	138.3±7.6	-	10.7±2.1
		240	-	-	-	323.0±9.6	-
		320	41.0±3.5	14.3±1.2	50.3±5.5	-	7.3±0.6
		600	-	-	-	107.3±7.5	-
		800	-	-	-	-	2.7±0.6
	2-Aminofluorene	10	925.3±52.2	1114.7±225.4	978.7±42.4	1529.3±23.4	140.0±17.4

−: not tested; Mean = total number of revertant colonies per plate/number of replicates; SD = standard deviation; number of revertant colonies per plate in the vehicle control group and each concentration group of the test article = counting result; number of revertant colonies per plate in the positive control group = counting result × 4.

[a] In this study, the salt form of taletrectinib was employed.

Table 2.6.7.8-5: Chromosome Aberration Study of Taletrectinib with Mammalian Cultured Cells

Test Article: Taletrectinib

Test for Induction of:	Forward mutation in mammalian cells	**Report Number:**	[redacted]160647
Cells:	CHL/IU	**Testing Facility:**	[redacted] Japan
Lot No.:	RS-102		
Metabolizing System:	S9 mix		
Number of Independent Assays:	1		
Number of Replicate Cultures:	2	**GLP Compliance:**	Yes
Number of Cells Analyzed/Culture:	150 cells/plate; 300 cells/concentration	**Date of Treatment:**	[redacted]20[redacted]
Vehicles for Test Article:	DMSO	**Vehicles for Positive Controls:**	Water (mitomycin C [-S9]); DMSO (benzo[a]pyrene [+S9])
Treatment:	6-hour treatment + 18-hour recovery -S9 6-hour treatment + 18-hour recovery +S9 24-hour treatment -S9		
Cytotoxic Effects:	IC_{50} was 27.8, 44.5, and 9.56 µmol/L for 6-hour -S9, +S9, and 24-hour assay.		
Genotoxic Effects:	A significant increase in structural aberrations with +S9 mix for 6 hours and in numerical aberrations with ± S9 mix for 6 hours.		

Metabolic Activation	Test Article	Assay 1			
		Concentration (µmol/L)	Total Structural Aberrant Cells (%)	Cell Growth Index x10^5/mL (%)	Total Numerical Aberrant Cells (%)
6-hour treatment + 18-hour recovery without activation	DMSO	0	3 (1.0)	1.70 (100.0)	0 (0.0)
	Taletrectinib	6	ND	1.51 (88.5)	ND
		8	3 (1.0)	1.47 (86.6)	2 (0.7)
		10	2 (0.7)	1.47 (86.2)	7 (2.3*)[a]
		20	3 (1.0)	0.92 (53.9)	9 (3.0*)[a]
		25	ND	0.71 (41.4)	ND
		30	ND	0.71 (41.3)	ND
		40	ND	0.32 (18.8)	ND
		50	ND	0.12 (7.0)	ND
	mitomycin C	0.1 µg/mL	128 (42.7*)		0 (0.0)
6-hour treatment + 18-hour recovery with activation	DMSO	0	1 (0.3)	1.90 (100.0)	0 (0.0)
	Taletrectinib	10	ND	1.78 (93.9)	ND
		20	ND	1.86 (98.1)	ND
		30	4 (1.3)	1.54 (81.0)	1 (0.3)
		40	4 (1.3)	1.20 (63.5)	9 (3.0*)[a]
		45	8 (2.7*)[a]	0.97 (51.1)	9 (3.0*)[a]
		50	ND	0.86 (45.4)	ND
		60	ND	0.57 (30.0)	ND
		70	ND	0.45 (23.6)	ND
	benzo[a]pyrene	15 µg/mL	198 (66.0*)		0 (0.0)

Metabolic Activation	Test Article	Assay 1			
		Concentration (µmol/L)	Total Structural Aberrant Cells (%)	Cell Growth Index x10^5/mL (%)	Total Numerical Aberrant Cells (%)
24-hour treatment + without activation	DMSO	0	4 (1.3)	1.89 (100.0)	0 (0.0)
	Taletrectinib	1	ND	2.04 (108.0)	ND
		2	6 (2.0)	1.87 (98.8)	1 (0.3)
		4	3 (1.0)	1.56 (82.5)	0 (0.0)
		6	3 (1.0)	1.10 (57.9)	1 (0.3)
		8	ND	1.08 (57.0)	ND
		9	ND	1.00 (53.1)	ND
		10	ND	0.92 (48.6)	ND
		20	ND	0.15 (7.8)	ND
	mitomycin C	0.05 µg/mL	123 (41.0*)		0 (0.0)

CHL = Chinese hamster lung cell line; DMSO = dimethyl sulfoxide; GLP = Good Laboratory Practice; IC_{50} = concentration resulting in 50% inhibition; ND = not determined.
* $P < 0.05$. Significantly different from the control value. Statistical methods are detailed in Report Number [redacted]160647.
[a] Dose-dependent increase was recognized in Cochran-Armitage test ($p<0.05$).

2.6.7.9 In Vivo 遺伝毒性試験

Table 2.6.7.9-1: Micronucleus Study in Bone Marrow of Rats Treated Orally with Taletrectinib			
			Test Article: Taletrectinib (Lot No.:RS-102)
Test for Induction of:	Bone marrow micronuclei	**Report Number:**	[redacted]160648
Species/Strain:	Rat/Sprague Dawley	**Testing Facility:**	[redacted] Japan
Age:	7 weeks		
Cells Evaluated:	Erythrocytes		
Number of Cells Analyzed/Animal:	4000	**GLP Compliance:**	Yes
Special Features:	None	**Date of Dosing:**	[redacted]20[redacted]
Treatment Schedule:	Once	**Sampling Time:**	24 and 48 hours after dosing
Method of Administration	Oral (gavage)	**Vehicle:**	0.5% Methyl cellulose
Toxic/Cytotoxic Effects:	Body weight reduced at 300 mg/kg, 48h group		
Genotoxic Effects:	None		
Evidence of Exposure:	Positive control showed a significant increase in the incidence of micronucleated immature erythrocytes.		

Time After Dosing	Test Article	Dose (mg/kg)	Number of Animals	Incidence of Micronucleated Immature Erythrocytes (%) Mean ± SD	Immature Erythrocytes Ratio Among Total Erythrocytes (%) Mean ± SD
24 hours	Methyl cellulose	0	6	0.113 ± 0.034	66.1 ± 3.2
	Taletrectinib	30	6	0.108 ± 0.020	60.2 ± 2.3*
		100	6	0.096 ± 0.019	58.4 ± 1.5*
		300	6	0.117 ± 0.026	55.8 ± 2.6*
	Cyclophosphamide monohydrate	20	6	3.175 ± 0.547 **	50.7 ± 3.2**
48 hours	Methyl cellulose	0	6	0.108 ± 0.013	62.1 ± 2.3
	Taletrectinib	30	6	0.100 ± 0.027	59.7 ± 6.1
		100	6	0.100 ± 0.022	54.8 ± 4.3*
		300	6	0.104 ± 0.019	54.1 ± 5.5*

GLP = Good Laboratory Practice; SD = standard deviation.
*$P < 0.05$. **$P < 0.01$. Significantly different from the control value. Statistical methods are detailed in Report Number [redacted]160648

Table 2.6.7.9-2: Micronucleus Study of Taletrectinib in Rat Liver			
			Test Article: Taletrectinib (Lot No.:RS-102)
Test for Induction of:	micronuclei in rat hepatocytes	**Report Number:**	[redacted]160649
Species/Strain:	Rat/Sprague Dawley	**Testing Facility:**	[redacted] Japan
Age:	7 weeks old		
Cells Evaluated:	Hepatocytes		
Number of Cells Analyzed/Animal:	4000	**GLP Compliance:**	Yes
Special Features:	Liver weights	**Date of Dosing:**	[redacted](Day 1) and [redacted]20[redacted]
Treatment Schedule:	Twice	**Sampling Time:**	5 days after first dose
Method of Administration	Oral (gavage)	**Vehicle:**	0.5% Methyl cellulose
Toxic/Cytotoxic Effects:	Body weight at 300 mg/kg was lower, day6		
Genotoxic Effects:	None		
Evidence of Exposure:	Positive control showed a significant increase in the incidence of micronucleated hepatocytes.		

Test Article	Dose (mg/kg)	Number of Animals	Number of Micronucleated Hepatocytes	Incidence of Micronucleated Hepatocytes (%) Mean ± SD	Mitotic Index[a] (%) Mean ± SD
Methyl cellulose	0	5	74	0.370 ± 0.041	0.339 ± 0.108
Taletrectinib	30	5	84	0.420 ± 0.108	0.443 ± 0.164
	100	5	75	0.375 ± 0.098	0.502 ± 0.233
	300	5	69	0.345 ± 0.129	0.309 ± 0.120
Diethylnitrosamine	25	3	356	2.967 ± 0.469**	0.794 ± 0.113

GLP = Good Laboratory Practice; SD = standard deviation.
**$P < 0.01$. Significantly different from the control value. Statistical methods are detailed in Report Number [redacted]160649
[a] [(Number of M-phase cells) / (4000 Hepatocytes + Number of Mphase cells)] × 100 (%)

2.6.7.10 がん原生試験

該当する試験なし。

2.6.7.11 生殖発生毒性試験：重要な試験以外の試験

該当する試験なし。

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

Table 2.6.7.12-1: Toxicity Study on Fertility and Early Embryonic Development Reproductive after Repeated Oral Gavage Administration of Taletrectinib in Sprague Dawley Rats (Seg I)					
				Test Article: Taletrectinib (Lot No.: CPo124073-01-04-01-26-01)	
Design Similar to 4.1.1 of ICH S5(R2):	Yes	**Duration of Dosing:**	M: 83 days[a] F: 21-34 days[b]	**Report Number:**	02049-20003
Species/Strain:	Rat/Sprague Dawley	**Mating period:**	Days 71 to 83	**Testing Facility:**	[redacted] China
Initial Age[c]:	M: 8-9 weeks old F: 10-11 weeks old	**Day of C-Section:**	GD 15		
Date of First Dose:	M: [redacted]20[redacted](Day 1) F: GD (-)14 (Day 57)	**Method of Administration:**	Oral (gavage)		
Special Features:	None	**Vehicle:**	0.5% MC		
No Observed Adverse-Effect Level:				**GLP Compliance:**	Yes
F_0 Males:	60 mg/kg/day				
F_0 Females:	100 mg/kg/day				
F_1 Litters:	NA				

Daily Dose (mg/kg/day)		**0 (Control)**	**4**	**25**	**60**
Males					
Number of Males		25	25	25	25
Number of TK Animals + Spare[d]		8 + 1	8 + 1	8 + 1	8 + 1
Toxicokinetics					
AUC_{0-24} (ng•h/mL)	Day 1	NA	78.848	3019.603	6489.630
	Day 83	NA	239.099	3758.667	9599.867
C_{max} (ng/mL)	Day 1	NA	14.816	317.743	512.501
	Day 83	NA	24.814	289.328	584.198

Daily Dose (mg/kg/day)	0 (Control)	4	25	60
Males				
Number Evaluated	25	25	25	25
Number Died or Sacrificed Moribund	0	0	0	0
Clinical Observations (Premating)	-	-	-	-
Clinical Observations (Mating to Sacrifice)	-	-	-	-
Necropsy Observations	-	-	-	-
Body Weight (g)				
Day 32	399.1	399.3	389.2	383.9*
Food Consumption	-	-	-	-
Mean Number Days Prior to Mating[c]	70	70	70	70
Number of Males that Mated	25	25	25	25
Number of Fertile Males	24/25	21/25	22/25	24/25
Sperm Number	301.0	307.6	315.9	310.9
Sperm Motility (%)	77.7	74.8	76.2	76.6
Sperm Abnormality Rate (‰)	1.47	3.40**	2.52	4.00**
Testis Weight (g)	3.04	2.98	3.08	3.08
Histopathology	-	-	-	-

Daily Dose (mg/kg/day)		0 (Control)	4	25	100
Females					
Number of Females		25	25	25	25
Number of TK Animals + Spare[d]		8 + 1	8 + 1	8 + 1	8 + 1
Toxicokinetics					
AUC_{0-24} (ng•h/mL)	Day 1 (GD -14)	NA	143.468	4506.170	10314.446
	Day 21-34 (GD 6)	NA	107.089	2745.008	12784.837
C_{max} (ng/mL)	Day 1 (GD -14)	NA	14.806	343.155	659.189
	Day 21-34 (GD 6)	NA	16.746	247.450	823.517

Daily Dose (mg/kg/day)	0 (Control)	4	25	100
Females				
Number Evaluated	25	25	25	25
Number Died or Sacrificed Moribund	0	0	0	0
Clinical Observations (Premating)	-	-	-	-
Clinical Observations (Mating)	-	-	-	-
Clinical Observations (Gestation)	-	-	-	-
Necropsy Observations	-	-	-	-
Body Weight (Premating) (g)	256.4	256.4	256.4	256.4
Body Weight (Gestation-GD15) (g)	323.2	326.0	327.5	312.6
Mean Food Consumption (Premating-Day 67) (g)	13.3	13.2	14.2	14.3
Mean Food Consumption (Gestation-GD 13) (g)	21.6	20.5	21.7	21.6
Mean Estrous Cycle (day)	4	4	4	4
Mean Number Days Prior to Mating[r]	14	14	14	14
Number of Females Sperm-Positive	25	25	25	25
Number of Pregnant Females	24/25	21/25	22/25	24/25
Mean Number Corpora Lutea	14.08	14.52	13.64	13.83
Mean Number Implantations	13.67	13.76	12.86	12.96
Mean Number Resorption	1.13	0.76	1.14	1.04
Mean Number Dead Conceptuses	0	0	0	0
Mean Number Live Conceptuses	12.54	13.00	11.73	11.92
Mean % Preimplantation Loss	-	-	-	-
Mean % Post-implantation Loss	-	-	-	-
Organ Weight	-	-	-	-
Histopathology	-	-	-	-

- = no noteworthy findings; $AUC_{0\text{-}24}$ = area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; C_{max} = maximum plasma concentration; F = female; GD = gestational day; GLP = Good Laboratory Practice; MC = methyl cellulose; M = male; NA = not applicable; TK = toxicokinetic.
Additional Information:

Additional Information:
The date when a vaginal plug or sperm were observed was counted as GD 0.
Compared with the vehicle control group, the sperm abnormality rate in the low and high dose groups increased significantly ($p<0.01$). The sperm abnormality rates in the 4, 25, and 100 mg/kg/day dose groups were 3.4%, 2.5%, and 4.0%, respectively, which were 2.31, 1.71 and 2.72 times higher than those in the vehicle control group without correlation to dose. Combined with the histopathological results and the absence of changes in sperm motility or number, the above changes were considered unrelated to the test article.
* $P < 0.05$, **$P < 0.01$. Significantly different from the control value. Statistical methods are detailed in Report Number 02049-20003.
[a] Dosing began 10 weeks prior to mating (Day 1) until the end of the mating period (Day 83).
[b] Dosing began 2 weeks prior to mating (Day 57) until GD 6.
[c] Age at first dosing.
[d] Spare animals were treated the same as the test animals during the study.
[e] Data presented is number of days males were dosed prior to mating. Mean number of days for successful matings by group are 2, 2, 3, 2 for 0, 4, 25, and 100 mg/kg/day, respectively.
[f] Data presented is number of days females were dosed prior to mating. Mean number of days for successful matings by group are 2, 2, 3, 2 for 0, 4, 25, and 100 mg/kg/day, respectively.

2.6.7.13 生殖発生毒性試験：胚及び胎児発生に関する試験

Table 2.6.7.13-1: Effects on Embryo-Fetal Development Reproductive Study with Taletrectinib via Oral Administration in Sprague Dawley Rats (Seg II)

Test Article: Taletrectinib (Lot No.: CPo124073-01-04-01-26-01)

Design Similar to 4.1.3 of ICH S5(R2):	Yes	**Duration of Dosing:**	12 days (GD 6 to 17)	**Report Number:**	02049-20004
Species/Strain:	Rat/Sprague Dawley	**Day of Mating:**	28 April 2021	**Testing Facility:**	[redacted] China
Mating Age:	11 to 13 weeks	**Method of Administration:**	Oral (gavage)		
Date of First Dose:	[redacted]20[redacted]	**Vehicle:**	0.5% MC		
Special Features:	Organ Weights				
No Observed Adverse-Effect Level:				**GLP Compliance:**	Yes
F_0 Females:	73.5 mg/kg/day				
F_1 Litters:	22.1 mg/kg/day				

Daily Dose (mg/kg/day)		**0 (Control)**	**7.35**	**22.1**	**73.5**
Dams/Dose					
Number of Females + Spare[a]		20 + 5	20 + 5	20 + 5	20 + 5
Number of TK Animals + Spare[a]		5 + 3	5 + 3	5 + 3	5 + 3
Toxicokinetics					
$AUC_{0\text{-}24}$ (ng•h/mL)	First (GD 6)	NA	230.377	2848.627	7241.032
	Last (GD 17)	NA	568.310	3906.008	12339.190
C_{max} (ng/mL)	First (GD 6)	NA	27.168	243.338	546.312
	Last (GD 17)	NA	96.290	325.596	982.200
Number Pregnant		24/25	21/25	22/25	24/25
Number Died or Sacrificed Moribund		0	0	0	0

Daily Dose (mg/kg/day)	0 (Control)	7.35	22.1	73.5
Dams/Dose				
Number Aborted or with Total Resorption of Litter	0	0	0	0
Clinical Observations	-	-	-	-
Necropsy Observations	-	-	-	-
Gestation Body Weight	-	-	-	-
Gestation Food Consumption	-	-	-	-
Mean Number Corpora Lutea	15.9	16.4	16.9	17.6
Mean Number Implantations	14.4	15.0	16.0	16.2*[b]
Mean % Preimplantation Loss	0	0	0	0
Organ Weights	-	-	-	-

Daily Dose (mg/kg/day)	0 (Control)	7.35	22.1	73.5
Number of Litters Evaluated	20	20	20	20
Mean Number Live Fetuses	13.0	14.0	14.4	15.3*[b]
Total Number Live Fetuses	260	280	287	305
Males	131	132	139	159
Females	129	148	148	146
Mean Number Resorptions				
Early	0.0	0.0	0.0	0.0
Late	1.4	1.0	0.9	1.0
Total	27	19	17	19
Mean Fetal Body Weight (g)	3.82	3.78	3.75	3.44*
Males	-	-	-	-
Females	-	-	-	-
Fetal Sex Ratios (% males)	-	-	-	-

Daily Dose (mg/kg/day)	0 (Control)	7.35	22.1	73.5
Fetal Anomalies				
Gross External				
Total Affected	10	9	9	5
Number Fetuses (%)	3.85	3.21	3.14	1.64
Number Litters (%)	25.00	25.00	26.32	20.00
Visceral Anomalies				
Total Affected (%)	0	0	0	0
Number Fetuses (%)	-	-	-	-
Number Litters (%)	-	-	-	-
Skeletal Variation				
Total Affected	121/134	138/145	107/147	134/157
Number Fetuses (%)	90.30	95.17	72.79*	85.35
Number Litters (%)	100.00	100.00	94.74	100.00
Skeletal Anomalies				
Total Affected	7/133	23/145	7/147	10/157
Number Fetuses (%)	5.26	15.86*	4.76	6.37
Number Litters (%)	30.00	45.00	15.79	40.00

- = no noteworthy findings; $AUC_{0\text{-}24}$ = area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; C_{max} = maximum plasma concentration; concentration; GD = gestation day; GLP = Good Laboratory Practice; MC = methyl cellulose; NA = not applicable; TK = toxicokinetic.

Additional Information:

The first day of mating was defined as Day 1.

The date when a vaginal plug was observed was counted as GD 0.

* $P < 0.05$. Significantly different from the control value. Statistical methods are detailed in Report Number 02049-20004.

[a] Spare animals were treated the same as the test animals during the study.

[b] Effect has no toxicological significance.

[c] The doses of 10, 30, 100 mg/kg were calculated as taletrectinib salt form, corresponding to 7.35, 22.1, 73.5 mg/kg taletrectinib free base form.

Table 2.6.7.13-2: Embryo-fetal Development Toxicity and Toxicokinetics Study of Taletrectinib by Oral Gavage in New Zealand Rabbits					
					Test Article: Taletrectinib (Lot No.: CPo124073-01-04-01-26-01)
Design Similar to 4.1.3 of ICH S5(R2):	Yes	**Duration of Dosing:**	14 days (GD 6 to 19)	**Report Number:**	T2102034
Species/Strain:	Rabbits/New Zealand	**Day of Mating:**	[redacted]20[redacted]	**Testing Facility:**	[redacted] China
Initial Age (on arrival):	~5 months	**Method of Administration:**	Oral (gavage)		
Date of First Dose:	[redacted]20[redacted]	**Vehicle:**	0.5% MC		
Special Features:	None				
No Observed Adverse-Effect Level:				**GLP Compliance:**	Yes
F_0 Females:	< 15 mg/kg/day				
F_1 Litters:	90 mg/kg/day				

Daily Dose (mg/kg/day)		**0 (Control)**	**15**	**30**	**90**
Dams/Dose					
Number of Females		24	24	32	34
Number of TK Females (pregnant)		6 (3)	7 (3)	6 (4)	6 (3)
Toxicokinetics					
$AUC_{0\text{-}24}$ (ng•h/mL)	First (GD 6)	NA	214.80	507.50	2333.00
	Last (GD 19)	NA	374.67	915.75	4649.33
C_{max} (ng/mL)	First (GD 6)	NA	31.53	59.25	248.43
	Last (GD 19)	NA	66.37	163.98	445.67

Daily Dose (mg/kg/day)	0 (Control)	15	30	90
Dams/Dose				
Number Pregnant	16	19	16	19
Number Died or Sacrificed Moribund	2	1	2	11[a]
Number Aborted or with Total Resorption of Litter	0	1	4	5
Clinical Observations	-	-	-	-
Necropsy Observations	-	-	-	-
Gestation Body Weight	-	-	-	-
Gestation Food Consumption				
GD 6	246.7	249.7	231.8	205.8*
GD 14	244.0	244.6	213.7	155.2*
Mean Number Corpora Lutea	10	9	9	12
Mean Number Implantations	9	8	8	9

Daily Dose (mg/kg/day)	0 (Control)	15	30	90
Number of Litters Evaluated	16	19	13	10
Number Live Fetuses (mean)	8	7	7	8
Mean Number Resorptions				
Early	0	0	1	0
Late	0	0	0	0
Total	0	0	1	0
Mean Fetal Body Weight (g)	41.16	43.27	41.90	42.72
Males (g)	40.73	43.06	41.78	43.05
Females (g)	41.60	42.74	42.06	42.75
Fetal Sex Ratios (% males)	49.77	43.43	42.59	42.63

Daily Dose (mg/kg/day)	0 (Control)	15	30	90
Fetal Anomalies				
Gross External				
Total Affected	-	-	-	-
Number Fetuses (%)	0.0	0.0	3.8	0.0
Number Litters (%)	0.0	0.0	7.7	0.0
Fixed Visceral Variation				
Total Affected	-	NA	-	-
Number Fetuses (%)	0.6	NA	0.9	0.0
Number Litters (%)	6.3	NA	7.7	0.0
Fixed Visceral Anomalies				
Total Affected	-	NA	-	-
Number Fetuses (%)	0.0	NA	3.8	0.0
Number Litters (%)	0.0	NA	7.7	0.0
Fresh Visceral Variation				
Total Affected	-	NA	-	-
Number Fetuses (%)	0.0	NA	0.0	0.0
Number Litters (%)	0.0	NA	0.0	0.0
Fresh Visceral Anomalies				
Total Affected	-	NA	-	-
Number Fetuses (%)	0.0	NA	0.0	1.7
Number Litters (%)	0.0	NA	0.0	10.0

Daily Dose (mg/kg/day)	0 (Control)	15	30	90
Skeletal Anomalies				
Total Affected	-	NA	-	-
Number Fetuses (%)	0.8	NA	5.6	0.0
Number Litters (%)	6.3	NA	23.1	0.0
Skeletal Variation				
Total Affected	-	NA	-	-
Number Fetuses (%)	44.7	NA	63.0*	28.0
Number Litters (%)	100.0	NA	100.0	80.0

- = no noteworthy findings; AUC_{0-24} = area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; C_{max} = maximum plasma concentration; concentration; GD = gestation day; GLP = Good Laboratory Practice; MC = methyl cellulose; NA = not applicable; TK = toxicokinetic.

* $P \leq 0.05$. Significantly different from the control value. Statistical methods are detailed in Report Number T2102034.

[a] Nine of 11 high dose animals found dead/moribund from GD 11 to 19. The main target organs were liver and kidneys, with the highest score for lesions being severe.

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

該当する試験なし。

2.6.7.15 新生児を用いた試験

該当する試験なし。

2.6.7.16 局所刺激性試験

該当する試験なし。

2.6.7.17 その他の毒性試験

Table 2.6.7.17-1: Other Toxicity Studies

Test Article: Taletrectinib

Species/Strain	Method of Administration	Duration of Dosing	Doses (µg/mL)	Sex and Number per Group	Noteworthy Findings	Report Number
BALB/c 3T3 cells	In vitro	1 hour	+UVA; 0.00671, 0.0134, 0.0269, 0.0537, 0.107, 0.215, 0.430 and 0.859 µg/mL -UVA; 0.859, 1.72, 3.44, 6.88, 13.8, 27.5, 55.0 and 110 µg/mL	NA	The PIF was 26.6 and the MPE was 0.278. Since MPE > 0.15 predicts phototoxicity, on the basis of the results obtained, it is concluded that taletrectinib is potentially phototoxic under these experimental conditions.	95860

MPE = mean photo effect; NA = not applicable; PIF = photo irritation factor; UVA = ultraviolet A.