表 2.6.5.4-4　KM12-Luc 細胞皮下移植マウスモデル連日経口投与（続）

Parameter				Cmax/ Dose	AUC(0-12h)/ Dose	AUC(0-24h)/ Dose
Unit				µmol/L/ (mg/kg)	(h*µmol/L)/ (mg/kg)	(h*µmol/L)/ (mg/kg)
Analyte	Day	Group	Dose (mg/kg)			
entrectinib	2	2	1 BID	0.0644	0.372	0.744
		3	5 BID	0.106	0.618	1.24
		4	15 BID	0.107	0.780	1.56
		5	30 BID	0.0897	0.750	1.50
		6	60 BID	0.0848	0.672	1.34
M5	2	2	1 BID	0.00805	0.0549	0.110
		3	5 BID	0.0133	0.0882	0.176
		4	15 BID	0.0145	0.108	0.216
		5	30 BID	0.0141	0.115	0.229
		6	60 BID	0.0130	0.106	0.213

表 2.6.5.4-5　ラット4週間間欠経口投与

				Test Article: Entrectinib		
				Location in CTD: 4.2.3.2-3		
				Study No. 0163-[redacted] (1087346)		
Species		Rat/Crl:CD(SD)				
Gender(M/F)/Number of Animals:		3 M, 3 F for each dose group for TK, 5 M, 5 F for each dose for brain matrix				
Feeding Condition:		Non-fasted				
Vehicle/Formulation:		0.5% (w/v) methylcellulose (MC, 400 cP) in Water for Injection				
Method of Administration:		PO (daily 2-week dosing, 2week rest, 2-week dosing)				
Dose (mg/kg):		50, 100, 200				
Sample Type:		Plasma, brain				
Analyte:		Entrectinib				
Assay:		LC-MS/MS (validated)				
PK Parameters/Dose (mg/kg/day):	50		100		200	
	M	F	M	F	M	F
Day 1						
C_{max} (µmol/L)	2.52 ± 0.11	2.90 ± 0.188	3.32 ± 0.522	4.58 ± 0.963	4.61 ± 0.362	4.60 ± 1.04
$AUC_{0\text{-}24h}$ (µmol/L·h)	30.5 ± 2.72	41.2 ± 1.42	47.9 ± 9.14	70.9 ± 8.35	81.6 ± 12.4	86.7 ± 13.0
Day 42						
C_{max} (µmol/L)	2.60 ± 0.436	3.19± 0.164	3.46 ± 0.391	6.44 ± 2.30	5.82 ± 1.05	9.04 ± 1.40
$AUC_{0\text{-}24h}$ (µmol/L·h)	36.3 ± 5.26	50.8 ± 2.57	54.0 ± 9.24	111 ± 37.1	111 ± 31.8	192 ± 21.0
$AUC_{0\text{-}48h}$ (µmol/L·h)	42.0 ± 2.15	70.5 ± 6.71	72.9 ± 17.0	143 ± 46.7	168 ± 60.4	329 ± 45.4
C_{24h} plasma (µmol/L)	0.452 ± 0.272	1.54 ± 0.333	1.36 ± 0.577	2.43 ± 0.624	3.82 ± 1.52	7.37 ± 1.46
C_{24h} brain (µmol/L)	NA	NA	0.781 ± 0.709	1.44 ± 0.463	2.26 ± 1.44	8.12 ± 5.99
C_{24h} brain to plasma ratio	NA	NA	0.574	0.591	0.592	1.10

NA: Not applicable

表 2.6.5.4-6　ラット4週間連日経口投与

				Test Article: Entrectinib		
				Location in CTD: 4.2.3.2-4		
				Study No. SR-[redacted]-006 (1087348)		
Species		Rat/Crl:CD(SD)				
Gender(M/F)/Number of Animals:		9 M, 9 F for each dose group for TK				
Feeding Condition:		nonfasted for TK animals				
Vehicle/Formulation:		0.5% (w/v) methylcellulose (MC, 400 cps) in reverse osmosis water				
Method of Administration:		PO (daily for 4 weeks)				
Dose (mg/kg):		25, 50, 100				
Sample Type:		Plasma				
Analyte:		Entrectinib				
Assay:		LC-MS/MS (validated)				
PK Parameters/Dose (mg/kg/day):	25		50		100	
	M	F	M	F	M	F
Day 1						
T_{max} (h)	4	8	8	4	8	8
C_{max} (μmol/L)	1.04	1.64	2.06	2.73	4.42	5.29
$AUC_{0\text{-}24h}$ (μmol/L·h)	11.6	19.8	25.8	36.5	54.5	83.0
Day 28						
T_{max} (h)	4	8	8	2	NA	NA
C_{max} (μmol/L)	1.17	1.51	2.88	3.51	NA	NA
$AUC_{0\text{-}24h}$ (μmol/L·h)	11.3	18.4	34.7	49.3	NA	NA
Day28/Day1　$AUC_{0\text{-}24h}$ ratio	0.974	0.929	1.34	1.35	NA	NA

NA: Not applicable

表 2.6.5.4-6　ラット4週間連日経口投与（続）

Analyte:	M5					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	25		50		100	
	M	F	M	F	M	F
Day 1						
T_{max} (h)	8	4	8	4	8	8
C_{max} (μmol/L)	0.0539	0.0573	0.110	0.112	0.369	0.180
$AUC_{0\text{-}24h}$ (μmol/L·h)	NC	NC	1.51	NC	4.15	2.19
Day 28						
T_{max} (h)	4	4	4	4	NA	NA
C_{max} (μmol/L)	0.0930	0.0544	0.313	0.149	NA	NA
$AUC_{0\text{-}24h}$ (μmol/L·h)	NC	NC	4.18	1.63	NA	NA
Day28/Day1　$AUC_{0\text{-}24h}$ ratio	NC	NC	2.77	NC	NA	NA
Day 1　M5/entrectinib ratio						
C_{max}	0.0518	0.0349	0.0534	0.0410	0.0835	0.0340
$AUC_{0\text{-}24h}$	NC	NC	0.0585	NC	0.0761	0.0264
Day 28　M5/entrectinib ratio						
C_{max}	0.0795	0.0360	0.109	0.0425	NA	NA
$AUC_{0\text{-}24h}$	NC	NC	0.120	0.0331	NA	NA
Additional Information: N = 3 at each time point; Due to mortality, plasma samples were not collected on Day 28 for 100 mg/kg Group animals;						

NA: Not applicable;　NC: Not calculable

表 2.6.5.4-7　ラット13週間連日経口投与

				Test Article: Entrectinib		
				Location in CTD: 4.2.3.2-5		
				Study No. SR-[redacted]-024 (1087349)		
Species	Rat/Crl:CD(SD)					
Gender(M/F)/Number of Animals:	9 M, 9 F for each dose group for TK					
Feeding Condition:	nonfasted for TK animals					
Vehicle/Formulation:	0.5% (w/v) methylcellulose (MC, 400 cps) in reverse osmosis water					
Method of Administration:	PO (daily for 13 weeks)					
Dose (mg/kg):	7.5, 15, 30					
Sample Type:	Plasma					
Analyte:	Entrectinib					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	7.5		15		30	
	M	F	M	F	M	F
Day 1						
T_{max} (h)	4	4	4	4	4	8
C_{max} (µmol/L)	0.382	0.344	0.589	0.756	1.40	1.77
$AUC_{0\text{-}24h}$ (µmol/L·h)	3.13	4.11	6.87	8.22	15.5	22.0
Day 42						
T_{max} (h)	4	8	8	8	8	4
C_{max} (µmol/L)	0.458	0.474	0.879	1.05	1.41	1.67
$AUC_{0\text{-}24h}$ (µmol/L·h)	4.70	6.74	11.4	14.0	20.0	27.3
Day42/Day1　$AUC_{0\text{-}24h}$ ratio	1.50	1.64	1.66	1.70	1.29	1.24
Day 91						
T_{max} (h)	4	4	4	4	4	4
C_{max} (µmol/L)	0.631	0.629	0.851	1.13	1.45	2.57
$AUC_{0\text{-}24h}$ (µmol/L·h)	5.98	6.71	10.5	15.4	19.4	29.6
Day91/Day1　$AUC_{0\text{-}24h}$ ratio	1.91	1.63	1.53	1.87	1.25	1.35

表 2.6.5.4-7　ラット13週間連日経口投与（続）

Analyte:	M5					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	7.5		15		30	
	M	F	M	F	M	F
Day 1						
T_{max} (h)	NA	NA	8	4	4	8
C_{max} (μmol/L)	0	0	0.0255	0.00878	0.0802	0.0567
$AUC_{0\text{-}24h}$ (μmol/L·h)	0	0	0.177	0.0576	0.892	0.627
Day 42						
T_{max} (h)	4	NA	4	4	4	4
C_{max} (μmol/L)	0.0285	0	0.0689	0.0368	0.155	0.0914
$AUC_{0\text{-}24h}$ (μmol/L·h)	0.215	0	0.905	0.321	2.43	1.01
Day42/Day1　$AUC_{0\text{-}24h}$ ratio	NA	NA	5.11	5.57	2.72	1.61
Day 91						
T_{max} (h)	4	4	4	4	4	4
C_{max} (μmol/L)	0.0521	0.00622	0.0965	0.0465	0.193	0.112
$AUC_{0\text{-}24h}$ (μmol/L·h)	0.349	0.0218	0.950	0.459	2.54	1.10
Day91/Day1　$AUC_{0\text{-}24h}$ ratio	NA	NA	5.37	7.97	2.85	1.75
Day 1　M5/entrectinib ratio						
C_{max}	0	0	0.0433	0.0116	0.0573	0.0320
$AUC_{0\text{-}24h}$	0	0	0.0258	0.00701	0.0575	0.0285
Day 42　M5/entrectinib ratio						
C_{max}	0.0622	0	0.0784	0.0350	0.110	0.0547
$AUC_{0\text{-}24h}$	0.0457	0	0.0794	0.0229	0.122	0.0370
Day 91　M5/entrectinib ratio						
C_{max}	0.0826	0.00989	0.113	0.0412	0.133	0.0436
$AUC_{0\text{-}24h}$	0.0584	0.00325	0.0905	0.0298	0.131	0.0372

NA: Not applicable

表 2.6.5.4-8　幼若ラット13週間連日経口投与

				Test Article: Entrectinib		
				Location in CTD: 4.2.3.5.4-3		
				Study No. SR-[redacted]-001 (1087245)		
Species	Rat/Crl:CD(SD)					
Gender(M/F)/Number of Animals:	18 M, 18 F for each dose group for TK on PND 7 6 M, 6 F for each dose group for TK on PND 97					
Feeding Condition:	nonfasted for TK animals					
Vehicle/Formulation:	0.5% (w/v) methylcellulose (MC, 400 cps) in reverse osmosis water					
Method of Administration:	PO (daily for 13 weeks)					
Dose (mg/kg):	4, 8, 16					
Sample Type:	Plasma					
Analyte:	Entrectinib					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	4		8		16	
	M	F	M	F	M[a]	F
PND 7 (first dose)						
T_{max} (h)	4	4	8	12	8	8
C_{max} (μmol/L)	0.456	0.341	0.614	0.615	1.22	1.24
$AUC_{0\text{-}24h}$ (μmol/L·h)	7.48	6.05	11.0	10.8	21.6	19.8
PND 97 (last dose)						
T_{max} (h)	4	4	4	4	4	4
C_{max} (μmol/L)	0.288	0.398	0.683	0.843	0.822	1.00
$AUC_{0\text{-}24h}$ (μmol/L·h)	2.20	3.12	5.78	8.08	6.29	11.1
PND 97/ PND 7　C_{max} ratio	0.631	1.17	1.11	1.37	0.675	0.812
PND 97/ PND 7　$AUC_{0\text{-}24h}$ ratio	0.295	0.516	0.526	0.745	0.291	0.560
Additional Information: N = 3 at each time point; [a] In the 16 mg/kg/day, three males were sampled at 1-, 8-, and 24-hour timepoints on PND 7 while only one animal was sampled at 0-, 4-, and 12-hour on PND 97 as two males at 16 mg/kg/day were euthanized on PND 22 and PND 25 due to severe toxicity observed.						

PND: postnatal day

表 2.6.5.4-8　幼若ラット13週間連日経口投与（続）

Analyte:	M5					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	4		8		16	
	M	F	M	F	M[a]	F
PND 7 (first dose)						
T_{max} (h)	12	8	8	12	8	8
C_{max} (µmol/L)	0.0254	0.0242	0.0370	0.0302	0.0606	0.0535
$AUC_{0\text{-}24h}$ (µmol/L·h)	0.326	0.297	0.420	0.359	1.08	0.882
PND 97 (last dose)						
T_{max} (h)	NC	NC	4	4	4	4
C_{max} (µmol/L)	BLQ	BLQ	0.0455	0.0178	0.0686	0.0307
$AUC_{0\text{-}24h}$ (µmol/L·h)	NC	NC	0.304	0.0623	0.418	0.192
PND 97/ PND 7　C_{max} ratio	NC	NC	1.23	0.590	1.13	0.573
PND 97/ PND 7　$AUC_{0\text{-}24h}$ ratio	NC	NC	0.725	0.173	0.389	0.217
PND 7　M5/entrectinib ratio						
C_{max}	0.0558	0.0709	0.0602	0.0491	0.0498	0.0433
$AUC_{0\text{-}24h}$	0.0436	0.0491	0.0382	0.0331	0.0498	0.0445
PND 97　M5/entrectinib ratio						
C_{max}	NC	NC	0.0667	0.0211	0.0834	0.0305
$AUC_{0\text{-}24h}$	NC	NC	0.0526	0.00771	0.0664	0.0172

Additional Information:
N = 3 at each time point;
[a] In the 16 mg/kg/day, three males were sampled at 1-, 8-, and 24-hour timepoints on PND 7 while only one animal was sampled at 0-, 4-, and 12-hour on PND 97 as two males at 16 mg/kg/day were euthanized on PND 22 and PND 25 due to severe toxicity observed.

PND: postnatal day,　NC: Not calculated,　BLQ: Below the limit of quantification limit

表 2.6.5.4-9 イヌ4週間間欠経口投与

				Test Article: Entrectinib		
				Location in CTD: 4.2.3.2-7		
				Study No. 0157-[redacted] (1087335)		
Species	Dogs/Beagles					
Gender(M/F)/Number of Animals:	5 M, 5 F for each dose group (3 M, 3 F for each dose for brain matrix)					
Feeding Condition:	Non-fasted					
Vehicle/Formulation:	0.5% (w/v) methylcellulose (MC, 400 cP) in Water for Injection					
Method of Administration:	PO (daily 2-week dosing, 2week rest, 2-week dosing)					
Dose (mg/kg):	30, 60, 120					
Sample Type:	Plasma					
Analyte:	Entrectinib					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	30		60		120	
	M	F	M	F	M	F
Day 1						
T_{max} (h)	1.60 ± 0.548	1.80 ± 1.30	1.60 ± 0.548	0.900 ± 0.224	12.0 ± 11.2	10.8 ± 12.1
C_{max} (µmol/L)	0.751 ± 0.883	1.88 ± 0.524	2.96 ± 2.33	3.45 ± 1.45	4.08 ± 1.80	3.83 ± 0.914
$AUC_{0\text{-}24h}$ (µmol/L·h)	10.5 ± 8.96[a]	18.5 ± 4.88	31.1 ± 23.4	38.2 ± 25.1	50.7 ± 8.74	50.6 ± 18.4
Day 42 (Day 10 or 11 for 120 mg/kg)						
T_{max} (h)	6.20 ± 9.96	3.20 ± 1.10	3.40 ± 2.79	2.80 ± 1.10	8.80 ± 9.01	12.2 ± 11.1
C_{max} (µmol/L)	1.68 ± 0.811	1.56 ± 1.38	2.76 ± 1.43	3.19 ± 1.06	7.43 ± 2.91	7.52 ± 2.01
$AUC_{0\text{-}24h}$ (µmol/L·h)	20.8 ± 9.29	21.1 ± 15.4[b]	37.3 ± 21.2	37.8 ± 6.75	147 ± 59.0	159 ± 50.2
$AUC_{0\text{-}48h}$ (µmol/L·h)	NA	35.7[c]	NA	47.8[c]	263 ± 128	300 ± 134
Day42/Day1 $AUC_{0\text{-}24h}$ ratio	3.48 ± 1.65	1.01 ± 0.473	1.94 ± 1.53	1.58 ± 1.37	2.98 ± 1.33	3.17 ± 0.408
Additional Information: Study included 60 and 120 mg/kg/day groups initially. After the 120 mg/kg/day dose was discontinued on the Day10 or Day 11, 30 mg/kg/day dose group was added.						

[a] n=3, [b] n=4, [c] n=2

NA: Not applicable

表 2.6.5.4-9　イヌ4週間間欠経口投与（続）

Sample Type:	Brain homogenate					
Analyte:	Entrectinib					
Assay:	LC-MS/MS (non-validated)					
PK Parameters/Dose (mg/kg/day):	30		60		120	
	M	F	M	F	M	F
Day 42 C_{24} plasma (n=5)	0.370 ± 0.349	0.163 ± 0.215	0.620 ± 0.173	0.458 ± 0.204		
Day 42 C_{24} brain (n=3)						
Cerebellum (μmol/L)	0.671 ± 0.372	0.104 ± 0.103	1.14 ± 0.313	0.983 ± 0.394	NA	NA
ratio to plasma C_{24}	1.49 ± 0.773	1.74 ± 1.53	1.79 ± 0.274	1.96 ± 0.762	NA	NA
Cortex (μmol/L)	0.789 ± 0.534	0.124 ± 0.0825	1.07 ± 0.153	0.962 ± 0.367	NA	NA
ratio to plasma C_{24}	1.60 ± 0.601	1.87 ± 1.66	1.72 ± 0.364	1.88 ± 0.603	NA	NA
Stem (μmol/L)	0.668 ± 0.450	0.127 ± 0.121	1.02 ± 0.0671	0.777 ± 0.571	NA	NA
ratio to plasma C_{24}	1.36 ± 0.543	2.17 ± 1.93	1.67 ± 0.503	1.57 ± 0.992	NA	NA
Additional Information: Study included 60 and 120 mg/kg/day groups initially.　After the 120 mg/kg/day dose was discontinued, 30 mg/kg/day dose group was added.						

NA: Not applicable

表 2.6.5.4-10　イヌ4週間連日経口投与

				Test Article: Entrectinib		
				Location in CTD: 4.2.3.2-9		
				Study No. SR-[redacted]-007 (1087342)		
Species		Dogs/Beagles				
Gender(M/F)/Number of Animals:		3-5 M, 3-5 F for each dose group				
Feeding Condition:		Non-fasted unless fasted for other study procedure				
Vehicle/Formulation:		0.5% (w/v) methylcellulose (MC, 400 cps) in reverse osmosis water				
Method of Administration:		PO (daily for 4 weeks)				
Dose (mg/kg):		15, 30, 60/45				
Sample Type:		Plasma				
Analyte:		Entrectinib				
Assay:		LC-MS/MS (validated)				
PK Parameters/Dose (mg/kg/day):	15		30		60/45	
	M	F	M	F	M	F*
Day 1						
T_{max} (h)	2 ± 0.577	2 ± 0.577	2 ± 0.577	2 ± 1.53	2 ± 0.548 / 4 ± 3.03	2 ± 2.95 / 3 ± 3
C_{max} (µmol/L)	0.350 ± 0.207	0.374 ±0.125	1.14 ± 0.171	0.998 ± 0.234	1.77 ± 0.618 /1.02 ± 0.414	1.79 ± 0.341 / 1.26 ± 0.348
$AUC_{0\text{-}24h}$ (µmol/L·h)	1.97 ± 0.991	1.95 ± 0.343	9.23 ± 0.619	8.03 ± 2.49	15.8 ± 9.83 / 10.6 ± 4.54	17.6 ± 5.97 / 10.4 ± 1.81
Day 28 (Day14 for 45 mg/kg)						
T_{max} (h)	2 ± 1.15	1 ± 0.577	2 ± 0.00	2 ± 0.00	NA / 2 ± 0.00	NA / 2 ± 1.00
C_{max} (µmol/L)	0.341 ± 0.157	0.427 ± 0.0983	1.37 ± 0.32	1.38 ± 0.671	NA / 1.14 ± 0.532	NA / 1.63 ± 0.251
$AUC_{0\text{-}24h}$ (µmol/L·h)	2.63 (n=2)	2.57 ± 0.464	9.13 ± 2.81	9.49 ± 3.84	NA / 7.97 ± 3.13	NA / 10.3 ± 1.61
Day28/Day1 $AUC_{0\text{-}24h}$ ratio	1.41	1.32	0.982	1.16	NA / 0.759	NA / 1.01

*One female given 60 mg/kg/day was found dead on Day 9.

表 2.6.5.4-10 イヌ4週間連日経口投与（続）

Analyte:	M5					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	15		30		60/45	
	M	F	M	F	M	F
Day 1						
T_{max} (h)	2 ± 1.15	2 ± 0.00	2 ± 1.15	2 ± 1.15	2 ± 2.83 / 4 ± 2.19	4 ± 4.15 / 4 ± 1
C_{max} (µmol/L)	0.401 ± 0.190	0.411 ± 0.0314	0.956 ± 0.196	0.942 ± 0.286	1.26 ± 0.543 / 0.937 ± 0.388	1.29 ±0.326 / 0.942 ± 0.193
AUC_{0-24h} (µmol/L·h)	3.71 ± 1.53	3.90 ± 0.584	13.8 ± 1.14	11.2 ±3.39	17.5 ± 8.67 / 12.8 ± 4.92	20.4 ±8.43 / 10.9 ± 1.71
Day 28 (Day14 for 45 mg/kg)						
T_{max} (h)	4 ±1.15	2 ± 1.15	2 ± 0.00	2.67 ± 1.15	NA / 2 ± 0.894	NA / 2 ± 1.00
C_{max} (µmol/L)	0.384 ± 0.145	0.463 ± 0.0618	0.843 ± 0.118	0.742 ±0.302	NA / 0.791 ± 0.283	NA / 0.921 ± 0.143
AUC_{0-24h} (µmol/L·h)	4.69 ± 0.898	5.04 ± 0.796	9.13 ± 0.690	8.52 ± 2.31	NA / 8.43 ± 2.87	NA / 9.63 ± 2.18
Day28/Day1 AUC_{0-24h} ratio	1.36	1.30	0.668	0.767	NA / 0.675	NA / 0.885
Day 1 M5/entrectinib ratio						
C_{max}	1.19	1.16	0.838	0.933	0.690 / 0.933	0.724 / 0.765
AUC_{0-24h}	1.94	2.01	1.50	1.41	1.19 / 1.23	1.14 / 1.07
Day 28 M5/entrectinib ratio (Day14 for 45 mg/kg)						
C_{max}	1.16	1.11	0.647	0.552	NA / 0.755	NA / 0.567
AUC_{0-24h}	1.84	1.98	1.06	0.935	NA / 1.12	NA / 0.936
Additional Information: For 60 mg/kg group dosing was stopped on Day 9 and resumed on Day15 at the dose level of 45 mg/kg/day.						

NA: Not applicable T_{max}: median value

表 2.6.5.4-11 イヌ13週間連日経口投与

				Test Article: Entrectinib		
				Location in CTD: 4.2.3.2-10		
				Study No. SR-[redacted]-029 (1087343)		
Species	Dogs/Beagles					
Gender(M/F)/Number of Animals:	4-6 M, 4-6 F for each dose group					
Feeding Condition:	Non-fasted unless fasted for other study procedure					
Vehicle/Formulation:	0.5% (w/v) methylcellulose (MC, 400 cps) in reverse osmosis water					
Method of Administration:	PO (daily for 13 weeks)					
Dose (mg/kg):	7.5, 15, 30					
Sample Type:	Plasma					
Analyte:	Entrectinib					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	7.5		15		30	
	M (n=4)	F (n=4)	M (n=4)	F (n=4)	M (n=6)	F (n=6)
Day 1						
T_{max} (h)	2 ± 0.00	2 ± 0.00	1.5 ± 0.577	1.50 ±0.577	2 ± 0.516	2 ± 0.408
C_{max} (µmol/L)	0.195 ± 0.110	0.136 ± 0.0282	0.274 ± 0.0965	0.299 ±0.198	0.528 ± 0.271	0.564 ± 0.450
$AUC_{0\text{-}24h}$ (µmol/L·h)	1.06 ±0.699	0.773 ± 0.212	1.52 ± 0.565	1.92 ± 1.52	3.31 ± 1.84	4.17 ± 2.97
Day 42			(n=3)			
T_{max} (h)	4 ± 1.00	3 ± 1.50	2 ± 0.577	2 ± 0.500	2 ± 0.816	2 ± 0.516
C_{max} (µmol/L)	0.311 ± 0.0702	0.187 ± 0.175	0.325 ± 0.207	0.481 ± 0.175	0.830 ± 0.598	0.775 ± 0.525
$AUC_{0\text{-}24h}$ (µmol/L·h)	2.16 ± 0.517	1.49 ± 1.62	2.66 ± 1.61	3.89 ± 0.972	7.09 ± 4.94	6.81 ±4.44
Day42/Day1 $AUC_{0\text{-}24h}$ ratio	3.73	1.97	1.79	3.15	2.01	1.93
Day 91			(n=3)			
T_{max} (h)	3 ± 1.15	2 ±0.500	2 ± 1.53	2 ± 0.00	2 ± 0.816	2 ± 0.00
C_{max} (µmol/L)	0.276 ±0.0404	0.226 ± 0.148	0.476 ± 0.232	0.673 ± 0.398	0.912 ± 0.482	0.839 ± 0.672
$AUC_{0\text{-}24h}$ (µmol/L·h)	1.93 ± 0.289	1.81 ± 1.69	3.39 ± 1.42	5.04 ± 2.18	8.04 ± 4.94	7.09 ± 5.98
Day91/Day1 $AUC_{0\text{-}24h}$ ratio	4.37	2.39	2.88	5.35	2.51	1.68

表 2.6.5.4-11　イヌ13週間連日経口投与（続）

Analyte:	M5					
Assay:	LC-MS/MS (validated)					
PK Parameters/Dose (mg/kg/day):	7.5		15		30	
	M	F	M	F	M	F
Day 1						
T_{max} (h)	4 ± 0.00	4 ±1.00	3 ± 1.15	4 ± 0.00	4 ± 0.816	4 ± 1.22
C_{max} (μmol/L)	0.203 ± 0.147	0.158 ± 0.0302	0.262 ± 0.109	0.261 ± 0.157	0.403 ± 0.187	0.451 ± 0.250
$AUC_{0\text{-}24h}$ (μmol/L·h)	2.00 ± 1.46	1.52 ± 0.314	2.53 ± 1.19	3.12 ± 2.28	4.73 ± 2.88	5.77 ± 4.42
Day 42			(n=3)			
T_{max} (h)	4 ± 0.00	4 ± 0.00	4 ± 0.00	4 ± 0.00	4 ± 0.00	4 ± 1.03
C_{max} (μmol/L)	0.382 ± 0.0655	0.241 ± 0.175	0.400 ± 0.169	0.473 ± 0.0854	0.663 ± 0.359	0.663 ±0.314
$AUC_{0\text{-}24h}$ (μmol/L·h)	4.34 ± 1.45	2.93 ± 2.35	5.85 ±2.92	6.71 ±1.57	8.99 ± 5.01	9.40 ± 4.96
Day42/Day1 $AUC_{0\text{-}24h}$ ratio	2.85	1.80	2.49	3.11	1.92	2.00
Day 91			(n=3)			
T_{max} (h)	4 ± 1.00	4 ± 1.00	4 ± 1.15	4 ±1.00	4 ± 0.00	4 ± 0.00
C_{max} (μmol/L)	0.239 ± 0.0565	0.204 ± 0.130	0.350 ± 0.122	0.488 ±0.160	0.699 ± 0.419	0.605 ± 0.467
$AUC_{0\text{-}24h}$ (μmol/L·h)	2.66 ± 0.893	2.44 ± 1.67	4.46 ± 1.76	6.45 ± 1.85	9.06 ± 5.65	8.06 ± 7.45
Day91/Day1 $AUC_{0\text{-}24h}$ ratio	1.92	1.55	2.13	3.54	1.95	1.59
Day 1　M5/entrectinib ratio						
C_{max}	1.10	1.19	0.961	0.911	0.798	0.916
$AUC_{0\text{-}24h}$	2.21	2.04	1.66	1.73	1.43	1.39
Day 42　M5/entrectinib ratio						
C_{max}	1.26	1.50	1.41	1.06	0.910	1.15
$AUC_{0\text{-}24h}$	2.03	3.04	2.48	1.75	1.42	1.62
Day 91　M5/entrectinib ratio						
C_{max}	0.866	0.905	0.797	0.804	0.763	0.837
$AUC_{0\text{-}24h}$	1.39	1.54	1.34	1.35	1.17	1.27

T_{max}: median value

2.6.5.5　薬物動態試験：分布

表 2.6.5.5-1　白色ラット単回経口投与後の組織中濃度

	Test Article: [^{14}C]entrectinib
	Location in CTD: 4.2.2.3-5
	Study No. SR-[redacted]-003 (1087284)
Species: Rat (Sprague Dawley)	
Gender (M/F)/Number of Animals: 3 M per group per sampling time	
Feeding Condition:　Fed	
Vehicle/Formulation: 0.5% methylcellulose and 1% Tween®80 in reverse osmosis water	
Method of Administration: PO	
Dose (mg/kg): 20	
Radionuclide: ^{14}C	
Specific Activity: 5.49 µCi/mg in dosing formulation (ca.111 µCi/kg)	
Analyte/Assay: Radioactivity/Quantitative whole-body autoradiography (QWBA)	
Sampling Time: 1, 3, 8, 24, 72, and 168 h postdose	

表 2.6.5.5-1　白色ラット単回経口投与後の組織中濃度（続）

	Concentration (ng Equivalents [^{14}C]RXDX-101/g)											
	Sacrifice Time (Hours)											
Tissue	1	SD	3	SD	8	SD	24	SD	72	SD	168	SD
Adrenal gland(s)	6410	2820	22500	2220	16400	2920	3750	770	765	149	426	24.2
Arterial wall	ND	0.00	ND	0.00	ND	0.00	ND	0.00	ND	0.00	ND	0.00
Bile	38300	21200	129000	54800	42200	9090	4980	1790	ND	0.00	ND	0.00
Blood	1350	394	2660	314	1570	154	BLQ	119	BLQ	0.00	ND	0.00
Bone	BLQ	130	378	173	348	182	BLQ	0.00	ND	0.00	ND	0.00
Bone marrow	2020	819	11600	1290	11500	1940	1580	343	335	122	223	21.1
Brain cerebellum	BLQ	0.00	BLQ	0.00	BLQ	0.00	ND	0.00	ND	0.00	ND	0.00
Brain cerebrum	BLQ	0.00	BLQ	108	BLQ	105	ND	0.00	ND	0.00	ND	0.00
Brain choroid plexus	1890	614	5880	619	5250	1750	1510	533	437	234	ND	0.00
Brain medulla	BLQ	0.00	BLQ	0.00	BLQ	0.00	ND	0.00	ND	0.00	ND	0.00
Brain olfactory lobe	BLQ	0.00	BLQ	0.00	BLQ	0.00	ND	0.00	ND	0.00	ND	0.00
Bulbo-urethral gland	1750	670	8990	2160	9620[a]	NA	2050[a]	NA	BLQ	158	ND	0.00
Cecum	1160	460	5290	656	4140	877	842	373	BLQ	104	ND	0.00
Diaphragm	2020	702	7810	595	5730	1120	713	85.2	BLQ	109	ND	0.00
Epididymis	BLQ	126	664	145	1190	162	702	115	265	47.5	ND	0.00
Esophagus	1040	484	4290	646	4050	762	776	94.2	BLQ	0.00	ND	0.00
Exorbital lacrimal gland	1480	693	10800	804	16000	1760	5700	1510	1980	858	1140	328
Eye lens	BLQ	0.00	BLQ	0.00	BLQ	0.00	BLQ	0.00	ND	0.00	ND	0.00
Eye uveal tract	970	518	3590	949	2680	769	608	286	ND	0.00	ND	0.00
Eye(s)	BLQ	139	523	78.3	388	121	BLQ	0.00	ND	0.00	ND	0.00
Fat (abdominal)	590	611	1470	403	962	341	BLQ	0.00	ND	0.00	ND	0.00
Fat (brown)	2880	1780	10100	2160	6950	1130	1190	249	361	152	246	51.7
Harderian gland	658	339	3840	293	11200	775	10900	1130	2830	860	384	111

BLQ: Calculated value is below the limit of quantitation (<179 ng eq/g).　NA: Not applicable.
ND: Not detectable (sample shape not discernable from background or surrounding tissue).　SD: Standard deviation.
[a] Mean is the average of two values.

表 2.6.5.5-1　白色ラット単回経口投与後の組織中濃度（続）

	Concentration (ng Equivalents [^{14}C]RXDX-101/g)											
	Sacrifice Time (Hours)											
Tissue	1	SD	3	SD	8	SD	24	SD	72	SD	168	SD
Intra-orbital lacrimal gland	1110	314	10300	1110	14300	2000	5330	1670	1910	1130	1120	404
Kidney cortex	6010	2620	21800	958	13600	2620	2560	518	701	230	314	43.1
Kidney medulla	4970	2190	18800	386	15400	2780	3130	579	781	312	319	65.1
Kidney(s)	5410	2380	20300	876	14600	2730	2820	529	733	260	316	49.1
Large intestine	924	373	3330	561	4880	1930	977	420	BLQ	0.00	ND	0.00
Liver	12800	5740	38300	3910	17700	5240	3430	728	965	299	310	63.0
Lung(s)	6790	2340	33500	3310	29200	9500	2730	781	200	197	ND	0.00
Lymph node(s)	1180	594	6550	1560	8510	1720	1690	272	454	194	BLQ	137
Muscle	605	314	4010	455	3280	575	474	89.3	BLQ	0.00	ND	0.00
Myocardium	3150	1100	10500	745	6310	1480	826	240	BLQ	113	ND	0.00
Nasal turbinates	344	114	1410	217	1790	455	722	22.2	BLQ	139	ND	0.00
Pancreas	3250	1460	14000	579	10400	1800	2100	569	434	160	216	14.3
Pituitary gland	3190	1340	15100	2960	14600	2720	2760	238	552	132	BLQ	167
Preputial gland	544	365	4990	1180	8360	1690	4660	1750	1330	1170	494	149
Prostate gland	717	183	4000	991	5180	1110	849	414	BLQ	150	ND	0.00
Salivary gland(s)	2460	998	12900	882	11300	1840	1850	450	286	99.6	BLQ	0.00
Salivary gland(s), parotid	1870	832	9820	833	8390	2190	1620	319	236	60.5	BLQ	0.00
Seminal vesicle(s)	BLQ	127	953	505	1180	205	BLQ	237	BLQ	0.00	ND	0.00
Skin (nonpigmented)	412	241	1880	335	2300	496	818	337	BLQ	115	ND	0.00
Small intestine	1460	770	7730	920	6380	935	1000	231	BLQ	160	ND	0.00
Spinal cord	BLQ	0.00	BLQ	0.00	BLQ	0.00	ND	0.00	ND	0.00	ND	0.00
Spleen	5210	2270	19200	669	15800	3670	2690	765	759	276	463	36.8
Stomach	1410	677	4090	370	3460	715	787	160	BLQ	122	BLQ	0.00

BLQ: Calculated value is below the limit of quantitation (<179 ng eq/g).
ND: Not detectable (sample shape not discernable from background or surrounding tissue).　SD: Standard deviation.

表 2.6.5.5-1　白色ラット単回経口投与後の組織中濃度（続）

	Concentration (ng Equivalents [^{14}C]RXDX-101/g)											
	Sacrifice Time (Hours)											
Tissue	1	SD	3	SD	8	SD	24	SD	72	SD	168	SD
Stomach mucosa	2090	1080	5100	357	3880	561	1120	279	181	179	BLQ	143
Stomach wall	954	338	3270	235	3180	342	639	137	BLQ	144	BLQ	0.00
Testis(es)	BLQ	0.00	249	41.5	432	46.9	380	80.2	BLQ	0.00	ND	0.00
Thymus	641	284	4300	504	6530	1680	1350	297	BLQ	194	BLQ	0.00
Thyroid	4490	1690	19500	3110	15700	5890	2600	790	691	229	445	219
Urinary bladder	922	193	2520	366	2580	445	532	101	ND	0.00	ND	0.00
Urine	685	542	3700	506	5370	1330	316	198	BLQ	0.00	ND	0.00

BLQ: Calculated value is below the limit of quantitation (<179 ng eq/g).
ND: Not detectable (sample shape not discernable from background or surrounding tissue).　SD: Standard deviation.

表 2.6.5.5-1　白色ラット単回経口投与後の組織中濃度（続）

組織／血漿中濃度比

	Tissue:Plasma Concentration Ratio											
	Sacrifice Time (Hours)											
Tissue	1	SD	3	SD	8	SD	24	SD	72	SD	168	SD
Adrenal gland(s)	6.35	0.970	19.8	3.98	23.9	1.36	22.2	19.5	42.8[a]	NA	NA	NA
Arterial wall	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Blood (QWBA analysis)	1.38	0.0349	2.31	0.178	2.31	0.128	1.66[b]	NA	NA	NA	NA	NA
Bone	0.174[b]	NA	0.335	0.167	0.495	0.212	NA	NA	NA	NA	NA	NA
Bone marrow	2.02	0.231	10.1	1.11	16.7	1.24	14.6	1.07	19.4[a]	NA	NA	NA
Brain cerebellum	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Brain cerebrum	NA	NA	0.0594	0.103	0.248[b]	NA	NA	NA	NA	NA	NA	NA
Brain choroid plexus	1.91	0.259	5.11	0.467	7.58	1.76	13.8	2.96	25.5[a]	NA	NA	NA
Brain medulla	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Brain olfactory lobe	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bulbo-urethral gland	1.76	0.156	7.98	2.65	13.0[a]	NA	18.0[a]	NA	16.3[b]	NA	NA	NA
Cecum	1.16	0.109	4.66	1.05	6.02	0.600	7.63	2.30	7.69[b]	NA	NA	NA
Diaphragm	2.04	0.163	6.79	0.250	8.35	0.791	6.63	0.263	11.3[b]	NA	NA	NA
Epididymis	0.168[b]	NA	0.575	0.101	1.78	0.528	6.67	1.77	13.6[a]	NA	NA	NA
Esophagus	1.03	0.313	3.76	0.839	5.89	0.409	7.22	0.398	NA	NA	NA	NA
Exorbital lacrimal gland	1.47	0.257	9.46	1.37	23.8	4.24	52.6	9.58	103[a]	NA	NA	NA
Eye lens	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Eye uveal tract	0.945	0.232	3.09	0.606	3.94	1.03	5.54	2.20	NA	NA	NA	NA
Eye(s)	0.185[b]	NA	0.455	0.0708	0.569	0.154	NA	NA	NA	NA	NA	NA
Fat (abdominal)	0.527	0.410	1.31	0.443	1.39	0.361	NA	NA	NA	NA	NA	NA
Fat (brown)	2.75	0.971	8.93	2.70	10.2	0.949	11.0	1.13	21.3[a]	NA	NA	NA
Harderian gland	0.642	0.181	3.35	0.306	16.6	1.66	102	3.72	148[a]	NA	NA	NA
Intra-orbital lacrimal gland	1.14	0.127	8.97	0.376	21.1	3.51	50.2	18.8	97.2[a]	NA	NA	NA
Kidney cortex	5.97	0.825	19.0	1.34	19.8	1.89	23.6	1.60	39.6[a]	NA	NA	NA
Kidney medulla	4.93	0.756	16.4	1.54	22.5	2.15	29.0	1.67	44.8[a]	NA	NA	NA
Kidney(s)	5.37	0.805	17.7	1.28	21.3	2.09	26.1	1.37	41.8[a]	NA	NA	NA

NA: Not applicable. SD: Standard deviation.

[a] Mean is the average of two values.

[b] Mean is based on one value.