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	tmax	Clast[a]	tlast	AUC(0-6h)	AUC(0-12h)[b]	AUC(0-24h[b])	AR[c] AUC(0-24h)
Unit				µmol/L	h	µmol/L	h	h*µmol/L	h*µmol/L	h*µmol/L	
Analyte	Day	Group	Dose (mg/kg)								
entrectinib	8	2C	0.050 BID	0.00131	3.00	0.00131	3.00	NR	NR	NR	NA
		3C	0.10 QD	0.00329	3.00	0.00066	6.00	NR	NR	NR	NA
		4C	0.50 BID	0.0280	3.00	0.0129	6.00	NR	NR	NR	NA
		5C	1.0 QD	0.0651	3.00	0.0258	6.00	NR	NR	NR	NA
		6C	1.5 BID	0.118	3.00	0.00271	6.00	0.431	0.581	1.16	0.95
		7C	3.0 QD	0.294	3.00	0.00458	6.00	1.01	1.41	1.77	0.65
		8C	5.0 BID	0.614	3.00	0.0107	6.00	2.32	3.29	6.58	1.2
		9C	10 QD	1.39	3.00	0.00646	6.00	5.60	10.4	14.2	1.4
		10C	15 BID	2.25	3.00	0.137	6.00	9.27	14.3	28.6	1.1
		11C	30 QD	3.45	3.00	0.159	6.00	14.4	27.4	38.8	0.90

BID = twice daily; QD = once a day; NA: not applicable; NR = nor reportable (insufficient data).
AUC(0-12h) for Groups 3C, 5C, 7C, 9C and 11C (QD dosing) calculated by interpolation. AUC(0-24h) for Groups 2C, 4C, 6C, 8C and 10C (BID dosing) calculated by doubling of AUC(0-12h). [a]Where quantifiable, C0h is listed as Clast. [b]For the AUC(0-12h) and AUC(0-24h) calculations on Day 8, predose concentrations (C0h) were mirrored as C12h for the BID groups (Groups 2C, 4C, 6C, 8C and 10C) or as C24h for the QD groups (Groups 3C, 5C, 7C, 9C and 11C). [c]AR: Accumulation ratio = AUC(0-24h) on Day 8/ AUC(0-24h) on Day 1.

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	tmax	Clast	tlast	AUC(0-6h)	AUC(0-12h)	AUC(0-24h)	M/P[a] Ratio
Unit				µmol/L	h	µmol/L	h	h*µmol/L	h*µmol/L	h*µmol/L	%
Analyte	Day	Group	Dose (mg/kg)								
M5	1	4C	0.50 BID	0.00175	3.00	0.00175	3.00	NR	NR	NR	NC
		5C	1.0 QD	0.00512	3.00	0.00386	6.00	NR	NR	NR	NC
		6C	1.5 BID	0.00860	3.00	0.000871	12.0	0.0372	0.0523	0.105	8.6
		7C	3.0 QD	0.0353	3.00	0.0139	6.00	0.142	0.211	0.267	9.7
		8C	5.0 BID	0.0500	3.00	0.0114	12.0	0.203	0.303	0.606	11.3
		9C	10 QD	0.0836	3.00	0.00294	24.0	0.421	0.787	1.10	10.5
		10C	15 BID	0.174	3.00	0.0607	12.0	0.778	1.26	2.52	9.3
		11C	30 QD	0.448	3.00	0.0183	24.0	1.80	2.94	3.98	9.2

BID = twice daily; QD = once a day; NA: not applicable; NR = nor reportable (insufficient data).
No exposure to M5 for groups 2C and 3C

AUC(0-12h) for Groups 3C, 5C, 7C, 9C and 11C (QD dosing) calculated by interpolation.

AUC(0-24h) for Groups 2C, 4C, 6C, 8C and 10C (BID dosing) calculated by doubling of AUC(0-12h). For the AUC(0-12h) and [a]M/P:
Metabolite to parent ratio = AUC(0-24h) M5/ AUC(0-24h) entrectinib *100%.

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	tmax	tlast	Clast[a]	AUC(0-6h)	AUC(0-12h)[b]	AUC(0-24h)[b]	AR[c]AUC(0-24h)	M/P[d] Ratio
Unit				µmol/L	h	h	µmol/L	h*µmol/L	h*µmol/L	h*µmol/L	-	%
Analyte	Day	Group	Dose (mg/kg)									
M5	8	4C	0.50 BID	0.00274	3.00	3.00	0.00274	NR	NR	NR	NA	NA
		5C	1.0 QD	0.00514	3.00	6.00	0.00282	NR	NR	NR	NA	NA
		6C	1.5 BID	0.0111	3.00	6.00	0.00639	NR	NR	NR	NA	NA
		7C	3.0 QD	0.0360	3.00	6.00	0.000664	0.126	0.182	0.233	0.87	13.2
		8C	5.0 BID	0.0578	3.00	6.00	0.00522	0.232	0.349	0.698	1.2	10.6
		9C	10 QD	0.108	3.00	6.00	0.00437	0.464	0.911	1.30	1.2	9.2
		10C	15 BID	0.248	3.00	6.00	0.0442	1.08	1.75	3.49	1.4	12.2
		11C	30 QD	0.397	3.00	6.00	0.0349	1.67	3.12	4.54	1.1	11.7

BID = twice daily; QD = once a day; NA: not applicable; NR = nor reportable (insufficient data).
No exposure to M5 for groups 2C and 3C
AUC(0-12h) for Groups 3C, 5C, 7C, 9C and 11C (QD dosing) calculated by interpolation. AUC(0-24h) for Groups 2C, 4C, 6C, 8C and 10C (BID dosing) calculated by doubling of AUC(0-12h). [a]Where quantifiable, C0h is listed as Clast. [b]For the AUC(0-12h) and AUC(0-24h) calculations on Day 8, predose concentrations (C0h) were mirrored as C12h for the BID groups (Groups 2C, 4C, 6C, 8C and 10C) or as C24h for the QD groups (Groups 3C, 5C, 7C, 9C and 11C). cAR: Accumulation ratio = AUC(0-24h) on Day 8/ AUC(0-24h) on Day 1.
[d]M/P: Metabolite to parent ratio = AUC(0-24h) M5/ AUC(0-24h) entrectinib * 100%.

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）

Analyte	Day	Group	Dose (mg/kg)	Cmax/Dose µmol/L/(mg/kg)	AUC(0-12h)/Dose (h*µmol/L)/(mg/kg)	AUC(0-24h)/Dose (h*µmol/L)/(mg/kg)
entrectinib	1	2C	0.050 BID	0.0618	NR	NR
		3C	0.10 QD	0.0887	0.381	0.476
		4C	0.50 BID	0.0698	0.294	0.588
		5C	1.0 QD	0.0559	0.465	0.626
		6C	1.5 BID	0.0665	0.406	0.812
		7C	3.0 QD	0.119	0.737	0.913
		8C	5.0 BID	0.0910	0.534	1.07
		9C	10 QD	0.103	0.790	1.05
		10C	15 BID	0.140	0.907	1.81
		11C	30 QD	0.129	1.06	1.44
entrectinib	8	2C	0.050 BID	0.0262	NR	NR
		3C	0.10 QD	0.0329	NR	NR
		4C	0.50 BID	0.0560	NR	NR
		5C	1.0 QD	0.0651	NR	NR
		6C	1.5 BID	0.0787	0.387	0.775
		7C	3.0 QD	0.0980	0.470	0.590
		8C	5.0 BID	0.123	0.658	1.32
		9C	10 QD	0.139	1.04	1.42
		10C	15 BID	0.150	0.953	1.91
		11C	30 QD	0.115	0.913	1.29

BID = twice daily; QD = once a day; NR = nor reportable (insufficient data).
AUC(0-12h) for Groups 3C, 5C, 7C, 9C and 11C (QD dosing) calculated by interpolation.
AUC(0-24h) for Groups 2C, 4C, 6C, 8C and 10C (BID dosing) calculated by doubling of AUC(0-12h).
For the AUC(0-12h) and AUC(0-24h) calculations on Day 8, predose concentrations (C0h) were mirrored as C12h for the BID groups (Groups 2C, 4C, 6C, 8C and 10C) or as C24h for the QD groups (Groups 3C, 5C, 7C, 9C and 11C).

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）

Analyte	Day	Group	Dose (mg/kg)	Cmax/Dose µmol/L/(mg/kg)	AUC(0-12h)/Dose (h*µmol/L)/(mg/kg)	AUC(0-24h)/Dose (h*µmol/L)/(mg/kg)
M5	1	4C	0.50 BID	0.00350	NR	NR
		5C	1.0 QD	0.00512	NR	NR
		6C	1.5 BID	0.00573	0.0349	0.0697
		7C	3.0 QD	0.0118	0.0703	0.0890
		8C	5.0 BID	0.0100	0.0606	0.121
		9C	10 QD	0.00836	0.0787	0.110
		10C	15 BID	0.0116	0.0840	0.168
		11C	30 QD	0.0149	0.0980	0.133
M5	8	4C	0.50 BID	0.00547	NR	NR
		5C	1.0 QD	0.00514	NR	NR
		6C	1.5 BID	0.00737	NR	NR
		7C	3.0 QD	0.0120	0.0607	0.0777
		8C	5.0 BID	0.0116	0.0698	0.140
		9C	10 QD	0.0108	0.0911	0.130
		10C	15 BID	0.0165	0.117	0.233
		11C	30 QD	0.0132	0.104	0.151

BID = twice daily; QD = once a day; NR = nor reportable (insufficient data).
No exposure to M5 for groups 2C and 3C, therefore not tabulated.
AUC(0-12h) for Groups 3C, 5C, 7C, 9C and 11C (QD dosing) calculated by interpolation.
AUC(0-24h) for Groups 2C, 4C, 6C, 8C and 10C (BID dosing) calculated by doubling of AUC(0-12h).

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	tmax	tlast	Clast	AUC(0-12h)	AUC(0-24h)	M/P* Ratio
Unit				µmol/L	h	h	µmol/L	h*µmol/L	h*µmol/L	%
Analyte	Day	Group	Dose (mg/kg)							
entrectinib	2	2	1 BID	0.0644	3.0	12	0.0115	0.372	0.744	
		3	5 BID	0.532	3.0	12	0.0466	3.09	6.18	
		4	15 BID	1.61	3.0	12	0.585	11.7	23.4	
		5	30 BID	2.69	3.0	12	0.833	22.5	45.0	
		6	60 BID	5.09	3.0	12	1.38	40.3	80.6	
M5	2	2	1 BID	0.00805	3.0	12	0.00280	0.0549	0.110	14.8
		3	5 BID	0.0664	3.0	12	0.0131	0.441	0.882	14.3
		4	15 BID	0.218	3.0	12	0.0746	1.62	3.23	13.8
		5	30 BID	0.423	3.0	12	0.144	3.44	6.87	15.3
		6	60 BID	0.777	3.0	12	0.273	6.38	12.8	15.8

Samples were collected at predose, 3, 8 and 12h after the 3rd dose on Day 2.

AUC(0-24h) were calculated by doubling the AUC(0-12h) values.

*M/P: Metabolite to parent ratio = AUC(0-24h) M5/ AUC(0-24h) entrectinib.