アキャルックス点滴静注 250 mg

第 2 部（モジュール 2）CTD の概要（サマリー）

2.6 非臨床試験の概要文及び概要表

2.6.5 薬物動態試験概要表

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2.6.5 薬物動態試験の概要表

1. 薬物動態試験：一覧表（1／2）

					Test Article: RM-1929		
Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dosing**	**Doses (mg/kg)**	**GLP Compliance**	**Testing Facility**	**Study Number**
Single dose TK	Sprague Dawley Rat	Intravenous Infusion	NA	2.6, 7.8, 26	No	Explora, San Diego, CA/ MicroConstants, San Diego, CA	EB10-039-016C/ MC13B-0228
	Sprague Dawley Rat	Intravenous Infusion	NA	10, 30, 100	Yes	Charles River Laboratories, Reno, NV/ MicroConstants, San Diego, CA	20065734
	Cynomolgus Monkey	Intravenous Infusion	NA	32 mg/kg cetuximab, 35 mg/kg RM-1929	No	Xenometrics, Stillwell, KS/ Celerion, Lincoln, NE	11108
	Cynomolgus Monkey	Intravenous Infusion	NA	40, 80 mg/kg RM-1929, 16 mg/kg for cetuximab	Yes	Xenometrics, Stillwell, KS/ Celerion, Lincoln, NE	11286
Tissue Distribution	Cynomolgus Monkey	Intravenous Infusion	NA	40, 80 mg/kg RM-1929, 16 mg/kg for cetuximab	No[1]	Xenometrics, Stillwell, KS/ Celerion, Lincoln, NE	11286
Metabolism: Studies not conducted							

2.6.5 薬物動態試験の概要表

1. 薬物動態試験：一覧表（2／2）

					Test Article: RM-1929		
Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dosing**	**Doses (mg/kg)**	**GLP Compliance**	**Testing Facility**	**Study Number**
Excretion:	Sprague Dawley Rat	Intravenous Infusion	NA	2.6, 7.8, 26	No	Explora, San Diego, CA/ MicroConstants, San Diego, CA	EB10-039-016C/ MC13B-0228
Other Pharmacokinetic Studies: No studies were conducted							

1 Biodistribution portion of Study 11286 was not conducted under GLPs.

2. 分析方法及びバリデーション試験

Module 2.6.4.2 参照

3. 薬物動態試験：吸収、単回投与

3.1 ラットにおける単回投与（非 GLP 試験）（試験番号 EB10-039-016C/MC13B-0228）

	Test Article: IRDye 700DX Carboxylate
Study/Report Number:	**Explora Study No. EB10-039-016C/Report No. MC13B-0228**
Species:	Sprague Dawley Rats
Gender (M/F)/Number of animals:	2 M for the vehicle control group; 6 M for each IRDye 700DX Carboxylate dose groups.
Vehicle/Formulation:	Phosphate Buffered Saline
Test Article Lot Numbers:	IR 700-CO_2-Na+ in PBS, Lot # [redacted]
Method of Administration:	Administered intravenously into the lateral tail vein.
Dose (mg/kg):	2.6, 7.8, 26 (once on Day 0 at t=0 at dose volume of 4 ml/kg)
Analyte:	IRDye 700DX Carboxylate
Samples (e.g., whole blood, plasma, serum):	Serum
Assay Method:	HPLC/FLUD

Analysis:	**Serum Concentrations of IRDye 700DX Carboxylate (µg/mL) at Each Sample Time Point†**								
Dose (mg/kg)	**1 min**	**8 min**	**10 min**	**15 min**	**30 min**	**1 h**	**3 h**	**24 h**	**72 h**
2.6	27.4	12.9	8.82	7.25	4.85	3.61	1.18	0.00*	0.00*
7.8	72.7	37.8	26.2	21.3	15.6	11.3	4.04	0.00*	0.00*
26	239	123	92.0	72.7	51.3	35.2	10.8	0.00*	0.00*

†Serum measurements presented as means, where N=6 for dose group at each time point; all animals were male.
* Below Limit of Quantification < 0.100 µg/mL

	Non-compartmental Analysis		
TK Parameters:	**2.6 mg/kg**	**7.8 mg/kg**	**26 mg/kg**
C_0(µg/mL)	33.1	85.7	282
AUC(µg·h/mL)	11.8	36.4	115
$T_{1/2}$(h)	1.23	1.30	1.13
V_{ss}(L/kg)	0.260	0.273	0.253
CL(mL/h/kg)	0.187	0.178	0.196

3.2 ラットにおける単回投与（GLP 試験）（試験番号 20065734）（1／2）

	Test Article: IRDye 700DX Carboxylate								
Study/Report Number:	**Charles River Laboratories Study No. 20065734**								
Species:	Sprague Dawley Rats								
Gender (M/F)/Number of animals:	3 M and 3 F for the vehicle control group; 8 M and 8 F for each IRDye 700DX Carboxylate dose groups.								
Vehicle/Formulation:	HyClone™ Phosphate Buffered Saline								
Test Article Lot Number:	[redacted] for the 1 mg/mL and 3 mg/mL groups; [redacted] for the 10 mg/mL group								
Method of Administration:	Administered intravenously into the lateral tail vein.								
Dose (mg/kg):	10, 30, 100 (once on Day 0 at t=0 at dose volume of 4 mL/kg)								
Analytes:	IR 700 Carboxylate								
Samples (e.g., whole blood, plasma, serum):	Serum								
Assay Methods:	HPLC-UV								
Analysis:	**Serum Concentrations of IR 700 Carboxylate (µg/mL)† at Each Sample Time Point**								
Sex	**Dose (mg/kg)**	**0.0167 h**	**0.250 h**	**1.00 h**	**3.00 h**	**6.00 h**	**24.0 h**	**72.0 h**	**360 h**
Females	10	127 (24.7)	31.8 (6.27)	13.6 (3.36)	4.60 (0.966)	0.935 (0.627)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	30	316 (14.2)	109 (8.87)	48.5 (9.28)	12.9 (1.60)	3.89 (1.56)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	100	1010 (72.1)	281 (32.7)	128 (20.1)	41.2 (13.8)	10.9 (3.74)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Males	10	129 (18.6)	28.2 (1.31)	14.8 (1.12)	6.08 (0.958)	1.79 (0.278)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	30	345 (35.5)	96.0 (17.9)	62.2 (10.5)	22.0 (6.38)	6.10 (0.683)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	100	911 (76.7)	274 (37.3)	140 (11.8)	66.0 (9.60)	18.3 (3.49)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
†Serum measurements presented as means (standard deviation), where N=4 for each sex in each dose group at each time point.									

3.2　　ラットにおける単回投与（GLP 試験）（試験番号 20065734）（2／2）

Analysis:	Toxicokinetic Measures of IRDye 700DX Carboxylate†										
Sex	Dose (mg/kg)	T_{max} (h)	C_{max} (µg/mL)	C_{max}/D [(µg/mL)/(mg/kg)]	AUC_{0-t} (µg·h/mL)	AUC_{0-t}/D [(µg·h/mL)/(mg/kg)]	AUC_{inf} (µg·h/mL)	AUC_{inf}/D [(µg·h/mL)/(mg/kg)]	$T_{1/2}$ (h)	CL (mL/h/kg)	Vd (mL/kg)
Females	10	0.0167	127 (12.3)	12.7	64.3 (5.47)	6.43	66.0	6.60	1.30	151	283
	30	0.0167	316 (7.11)	10.5	201 (7.36)	6.69	208	6.95	1.40	144	290
	100	0.0167	1010 (36.1)	10.1	568 (27.1)	5.68	590	5.90	1.42	169	348
Males	10	0.0167	129 (9.31)	12.9	69.3 (1.20)	6.93	73.5	7.35	1.64	136	322
	30	0.0167	345 (17.8)	11.5	243 (12.7)	8.10	256	8.53	1.45	117	246
	100	0.0167	911 (38.3)	9.11	642 (23.6)	6.42	687	6.87	1.70	146	356

† Serum measurements presented as means (standard errors where applicable).

3.3 サルにおける単回投与（非 GLP 試験）（試験番号 11108）（1／2）

		Test Article: RM-1929 (cetuximab-IRDye 700DX conjugate)							
Study/Report Number:		**Xenometrics Study No. 11108**							
Species:		Cynomolgus Monkey							
Gender (M/F)/Number of animals:		2 M for the vehicle control group; 2 M for cetuximab group; 2 M for cetuximab-IRDye 700DX group.							
Vehicle/Formulation:		HyClone™ Phosphate Buffered Saline							
Test Article Lot Number:		[redacted] for cetuximab, [redacted] for cetuximab-IRDye 700DX							
Method of Administration:		Administered as a single intravenous dose via a 1.8-h intravenous infusion							
Dose (mg/kg):		32 mg/kg for cetuximab, 35 mg/kg for cetuximab-IRDye 700DX							
Analytes:		cetuximab for cetuximab group, cetuximab-IR700 for cetuximab-IRDye 700DX group							
Samples (e.g., whole blood, plasma, serum):		Serum							
Assay Methods:		ELISA and HPLC-SEC							
Analysis:	**Toxicokinetic Measures of Cetuximab and RM-1929 from ELISA Data Using Non-Compartmental Analysis**								
Test Article	**Animal**	**$T_{1/2}$ (h)**	**T_{max} (h)**	**C_{max} (µg/mL)**	**AUC_{0-24} (µg·h/mL)**	**AUC_{last} (µg·h/mL)**	**AUC_{inf} (µg·h/mL)**	**V_{ss} (mL/kg)**	**CL (mL/h/kg)**
Cetuximab (32 mg/kg)	131798	138.52	0.25	845.00	15365.41	60119.00	98289.48	64.04	0.33
	131831	87.64	1.00	944.00	14455.16	60081.04	77024.03	51.73	0.42
	Mean	**113.08**	**0.63**	**894.50**	**14910.28**	**60100.02**	**87656.75**	**57.89**	**0.37**
	SD	**35.98**	**0.53**	**70.00**	**643.64**	**26.84**	**15036.94**	**8.71**	**0.06**
RM-1929 (35 mg/kg)	131720	26.96	0.25	506.00	5588.22	10319.05	10356.24	106.14	3.09
	131822	23.16	0.25	431.00	4725.98	9023.67	9057.76	116.59	3.53
	Mean	**25.06**	**0.25**	**468.50**	**5157.10**	**9671.36**	**9707.00**	**111.37**	**3.31**
	SD	**2.69**	**0.00**	**53.03**	**609.70**	**915.97**	**918.17**	**7.39**	**0.31**

3.3 サルにおける単回投与（非 GLP 試験）（試験番号 11108）（2／2）

Analysis:	**Toxicokinetic Measures of RM-1929 from HPLC-SEC Data Using Non-Compartmental Analysis**								
Test Article	**Animal**	**$T_{1/2}$ (h)**	**T_{max} (h)**	**C_{max} (µg/mL)**	**AUC_{0-24} (µg·h/mL)**	**AUC_{last} (µg·h/mL)**	**AUC_{inf} (µg·h/mL)**	**V_{ss} (mL/kg)**	**CL (mL/h/kg)**
RM-1929 (35 mg/kg)	131720	29.52	0.25	486.00	4431.18	7760.07	7977.27	135.46	4.01
	131822	27.50	0.25	348.00	3802.32	6712.02	7001.26	152.59	4.57
	Mean	**28.51**	**0.25**	**417.00**	**4116.75**	**7236.05**	**7489.27**	**144.02**	**4.29**
	SD	**1.43**	**0.00**	**97.58**	**444.67**	**741.08**	**690.14**	**12.11**	**0.40**

Analysis:	**Serum Concentrations of IRDye 700DX Carboxylate (µg/mL)† from HPLC-SEC Data at Each Time Point**										
Test Article	**Animal**	**0.25 h**	**1 h**	**8 h**	**24 h**	**48 h**	**72 h**	**120 h**	**144 h**	**168 h**	**192 h**
RM-1929 (35 mg/kg)	131720	0.108	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	131822	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

†BLQ = Below Limit of Quantification (<0.1 µg/mL)

3.4 サルにおける単回投与（GLP 試験）（試験番号 11286）（1／6）

	Test Article: RM-1929 (cetuximab-IRDye 700DX conjugate)
Study/Report Number:	**Xenometrics Study No. 11286**
Species:	Cynomolgus Monkey
Gender (M/F)/Number of animals:	5 M and 5 F for the vehicle control group; 3 M and 3 F for 40 mg/kg certuximab-IRDye 700DX dose group; 5 M and 5 F for 80 mg/kg certuximab-IRDye 700DX dose group; 3 M and 3 F for cetuximab.
Vehicle/Formulation:	HyClone™ Phosphate Buffered Saline
Test Article Lot Number:	[redacted] for cetuximab, [redacted] for cetuximab-IRDye 700DX
Method of Administration:	Administered as a single dose via a 2-h intravenous infusion
Dose (mg/kg):	40 mg/kg and 80 mg/kg for cetuximab-IRDye 700DX, 16 mg/kg for cetuximab
Analytes:	Cetuximab-IRDye 700DX and IRDye 700DX
Samples (e.g., whole blood, plasma, serum):	Serum
Assay Methods:	ELISA and HPLC-SEC

Analysis: **Serum Concentrations of Cetuximab and RM-1929 (µg/mL)† from ELISA Data at Each Time Point**

Time (h)	Cetuximab (16 mg/kg)				RM-1929 (40 mg/kg)				RM-1929 (80 mg/kg)			
	Males		Females		Males		Females		Males		Females	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.67	154.33	32.39	147.67	32.01	317	99.32	239.8	68.1	585	59.3	603.2	113.7
1.33	303.33	30.62	300.67	55.61	577.8	56.51	558.6	89.46	1015.2	206.48	1048	262.51
2	482	46.77	433	43.84	934.8	138.16	892.6	250.41	1807.5	309.45	1269	269.06
2.5	456.33	42.71	418	57.94	763.75	88.27	756	189.58	1546.75	557.68	960.8	211.69
4	427.33	58.4	376.33	50.64	666	53.02	539.6	81.24	1297.75	271.94	947	118.1
8	365.67	21.94	343.67	21.22	454	40.39	354.4	37.17	844	83.25	817.6	132.5
24	232	4	243.33	26.1	193.8	33.8	148.2	22.52	418	130.09	356.2	41.49
32	205	5.66	197	1.41	96.05	19.73	207	14.14	295.2	64.15	350.6	111.26
48	167	22.61	164.67	13.43	87.5	15	99.4	26.81	224.6	29.35	234.4	64.76
72	132.67	27.68	113	2.65	81.3	25.2	60.07	11.3	191.8	53.2	156	41.65
120	120.67	28.01	94.6	9.18	36.3	14.4	24.43	6.36	116.74	56.36	94.64	14.08

3.4 サルにおける単回投与（GLP 試験）（試験番号 11286）（2／6）

Time (h)	Cetuximab (16 mg/kg)				RM-1929 (40 mg/kg)				RM-1929 (80 mg/kg)			
	Males		Females		Males		Females		Males		Females	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
144	102.93	27.03	84.27	9.17	30.5	10.1	17.83	6.07	95.22	39.01	71.76	21.3
168	87.1	27.74	75.33	17.71	20.5	6.28	9.83	4.49	36.02	17.48	25.39	15.65
288	31.07	22	16.83	18.86	1.19	1.35	BLQ*	-	21.03	10.96	10.84	8.62
360	5.74	3.06	4.55	4.1	BLQ*	-	BLQ*	-	3.91	4.21	1.93	2.55
480†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	BLQ*	-	BLQ*	-
672†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	BLQ*	-	BLQ*	-

†Samples for these time points only collected from Recovery Animals in high dose group.
N/A: Not Applicable; BLQ: Below Limit of Quantification.
*RM-1929 BLQ = 0.5 µg/mL

3.4 サルにおける単回投与（GLP 試験）（試験番号 11286）（3／6）

Analysis:	Serum Concentrations of RM-1929 (µg/mL)† from HPLC-SEC Data at Each Time Point							
Time (h)	RM-1929 (40 mg/kg)				RM-1929 (80 mg/kg)			
	Males		Females		Males		Females	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.67	320	51.42	199.33	70.27	652.2	65.19	537.4	69.62
1.33	594	89.01	456.67	83.86	1214	186.9	997.2	196.33
2	887.67	92.68	732	35.79	1627.5	174.62	1455	167.63
2.5	672.5	9.19	668	27.71	1667.5	179.7	1335.4	453.97
4	520	8.49	468.67	9.61	1282.5	126.85	872	148.93
8	378.67	50.65	289.67	25.01	740.6	97.42	564.6	89.81
24	161.67	18.5	124.33	7.23	345.4	34.45	265	36.18
32†	N/A	N/A	N/A	N/A	275	43.28	218.4	43.24
48	83.27	15.35	61.97	4.03	188.2	27.36	142.6	29.36
72	57.2	14.1	38.97	0.55	134.6	24.39	100.44	23.39
120	29.87	9.25	16.97	1.02	79.64	23.42	56.36	16.25
144	21.93	8.56	11.56	2.02	62	18.98	41.38	12.15
168	14.25	6.37	6.45	1.47	49.9	19.27	32.22	10.43
288	BLQ*	1.27	BLQ*	-	12.37	11.19	7.79	4.86
360	BLQ*	-	BLQ*	-	3.66	5.3	BLQ*	1.54
480††	N/A	N/A	N/A	N/A	BLQ*	-	BLQ*	-
672††	N/A	N/A	N/A	N/A	BLQ*	-	BLQ*	-

†Samples not collected at this time point for RM-1929 low dose group
††Samples for these time points only collected from Recovery Animals in RM-1929 high dose group.
N/A: Not Applicable; BLQ: Below Limit of Quantification.
*RM-1929 BLQ = 2.0 µg/mL

3.4 サルにおける単回投与（GLP 試験）（試験番号 11286）（4／6）

Analysis:	Serum Concentrations of IRDye 700DX (µg/mL)† from HPLC-SEC Data at Each Time Point							
Time (h)	RM-1929 (40 mg/kg)				RM-1929 (80 mg/kg)			
	Males		Females		Males		Females	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.67	0.0389	0.00121	0.0356	0.00624	0.0795	0.00872	0.0704	0.0082
1.33	0.0567	0.00302	0.05	0.0067	0.117	0.0137	0.091	0.0278
2	0.0608	0.00474	0.064	0.007	0.145	0.0144	0.107	0.0255
2.5	0.036	0.00156	0.0461	0.00929	0.0808	0.01459	0.064	0.0102
4	BLQ	BLQ	0.018	0.0153	0.0505	0.00674	0.036	0.002
8	BLQ	BLQ	BLQ	BLQ	0.00992	0.0136	BLQ	BLQ
24	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
32†	N/A	N/A	N/A	N/A	BLQ	BLQ	BLQ	BLQ
48	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
72	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
120	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
144	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
168	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
288	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
360	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
480††	N/A	N/A	N/A	N/A	BLQ	BLQ	BLQ	BLQ
672	N/A	N/A	N/A	N/A	BLQ	BLQ	BLQ	BLQ

†Samples not collected at this time point for RM-1929 low dose group
††Samples for these time points only collected from Recovery Animals in RM-1929 high dose group.
N/A: Not Applicable; BLQ: Below Limit of Quantification.
*IRDye700 DX BLQ = 0.02 µg/mL

3.4 サルにおける単回投与（GLP 試験）（試験番号 11286）（5／6）

Analysis:	**Toxicokinetic Measures† of Cetuximab and RM-1929 from ELISA Data Using Non-Compartmental Analysis**								
Test Article and Dose	**Sex**	**T_{max} (h)**	**C_{max} (µg/mL)**	**$T_{1/2}$ (h)**	**Vd (mL/kg)**	**CL (mL/h/kg)**	**AUC_{0-24} (µg·h/mL)**	**AUC_{last} (µg·h/mL)**	**AUC_{inf} (µg·h/mL)**
Cetuximab (16 mg/kg)	Male	2 (0)	482.00 (46.77)	66.2 (20.48)	46.35 (6.28)	0.47 (0.12)	7644.67 (444.51)	34327.02 (5897.47)	35359.13 (8850.43)
	Female	2.33 (0.29)	429.67 (44.50)	64.68 (12.56)	49.39 (2.95)	0.54 (0.08)	7316.99 (403.65)	29508.22 (4489.64)	30138.36 (4726.81)
RM-1929 (40 mg/kg)	Male	2 (0)	934.8 (138.16)	30.22 (14.29)	95.45 (32.81)	2.4 (0.62)	9550.27 (583.36)	16694.01 (5239.42)	17575.02 (4490.95)
	Female	2.2 (0.27)	894.8 (249.91)	35.04 (10.20)	130.72 (35.00)	2.61 (0.25)	7737.28 (677.37)	13595.03 (1930.13)	15428.99 (1403.08)
RM-1929 (80 mg/kg)	Male	2.4 (0.89)	1624.2 (489.71)	51.7 (13.11)	128.94 (23.35)	1.89 (0.29)	18282.81 (2674.49)	45241.1 (7628.50)	43098.3 (6453.48)
	Female	2.4 (0.89)	1173.8 (315.61)	47.88 (7.50)	138.7 (27.35)	2.02 (0.46)	15784.69 (2061.32)	39061.76 (8137.59)	41092.44 (8239.68)
†values presented as means (standard deviation)									
Analysis:	**Toxicokinetic Measures† of RM-1929 from HPLC-SEC Data Using Non-Compartmental Analysis**								
Test Article and Dose	**Sex**	**T_{max} (h)**	**C_{max} (µg/mL)**	**$T_{1/2}$ (h)**	**Vd (mL/kg)**	**CL (mL/h/kg)**	**AUC_{0-24} (µg·h/mL)**	**AUC_{last} (µg·h/mL)**	**AUC_{inf} (µg·h/mL)**
RM-1929 (40 mg/kg)	Male	2 (0)	887.67 (92.68)	41.67 (5.28)	145.58 (18.19)	2.45 (0.48)	8326.39 (6265.94)	16210.78 (3402.98)	16724.82 (3235.44)
	Female	2 (0)	732 (35.79)	35.68 (3.49)	172.21 (20.75)	3.34 (0.08)	6488.36 (371.94)	11644.6 (394.49)	11981.17 (297.08)
RM-1929 (80 mg/kg)	Male	2.2 (0.27)	1704 (173.58)	57 (16.32)	169.39 (47.73)	2.07 (0.27)	16934.4 (1760.66)	38249.45 (5386.14)	39164.34 (5073.52)
	Female	2.2 (0.27)	1453.4 (427.86)	50.93 (6.85)	205.67 (20.40)	2.86 (0.63)	13082.95 (2185.36)	28593.35 (6128.70)	29039.94 (6347.19)
†values presented as means (standard deviation)									

3.4 サルにおける単回投与（GLP 試験）（試験番号 11286）（6／6）

Analysis:	Toxicokinetic Measures† of IRDye 700DX from HPLC-SEC Data Using Non-Compartmental Analysis							
Test Article and Dose	Sex	T_{max} (h)	C_{max} (µg/mL)	$T_{1/2}$ (h)	Vd (mL/kg)	CL (mL/h/kg)	AUC_{last} (µg·h/mL)	AUC_{inf} (µg·h/mL)
RM-1929 (40 mg/kg)	Male	2 (0)	0.06 (0)	-	-	-	0.1 (0)	-
	Female	2 (0)	0.06 (0)	-	-	-	0.14 (0)	-
RM-1929 (80 mg/kg)	Male	1.87 (0)	0.14 (0)	3.06 (0)	584889.42 (124694.00)	131943.99 (8046.00)	0.36 (0)	0.61 (0)
	Female	1.87 (0)	0.1 (0)	-	-	-	0.24 (0)	-
†Serum measurements presented as means (standard deviation), where N=3 or N=5 for 40 mg/kg or 80 mg/kg dose group, respectively								

4. 薬物動態試験：吸収、反復投与

RM-1929 の反復投与試験は実施していない。

5. 薬物動態試験：分布

Study Number: 11286				**Test Article:** RM-1929	
Species/ Strain	**Route of Admin.**	**Dose (mg/kg)**	**Sex/No. per Group**	**Noteworthy Findings**	**GLP**
Cynomolgus Monkeys[†]	Intravenous infusion over 2 h	16 of cetuximab (Day 15) 40 of RM-1929 (Day 2) 80 of RM-1929 (Day 15)	40 mg/kg RM-1929: 2M/2F Terminated on Day 3 80 mg/kg RM-1929: 2M/2F Terminated on Day 15 16 mg/kg cetuximab: 2M/2F Terminated on Day 15	INTACT TISSUES: The highest levels of fluorescent RM-1929 measured in Group 2 (40 mg/kg RM-1929, terminated on Day 3) were in the liver, gall bladder, and axillary lymph node; the lowest levels were in the brain and spinal cord. The highest levels of fluorescent in Group 3 (80 mg/kg RM-1929, terminated on Day 15) group were measured in the lymph nodes (inguinal, mesenteric, axillary) and prostate and the lowest levels were in the brain and spinal cord. The total fluorescent RM-1929 in all tissues collected from animals in Groups 2 and 3 averaged 38.4 ± 1.6% and 2.84 ± 0.75% of the total dose. TISSUE HOMOGENATES: Using gel electrophoresis, the highest levels of fluorescent RM-1929 in Group 2 animals were in the blood, lung, liver, gall bladder, and skin (inner forearm). The lowest levels were in the brain tissues and femur marrow. In Group 3 animals (terminated on Day 15), ≤ 10% of the total dose was detected indicating that RM-1929 does not accumulate in the tissues and cleared from the tissues within two weeks after administration. TISSUE SECTIONS: The highest levels of fluorescent RM-1929 in Group 2 were measured in the axillary lymph node, gall bladder, vagina, skin (inner forearm), and liver. The lowest levels were found in the brain, spinal cord, and bone. For Group 3, the highest levels of fluorescent RM-1929 were in the gall bladder, urinary bladder, duodenum, skin (outer forearm). The lowest levels were the spinal cord, pituitary gland, uterus, and lung. There were no apparent differences in the distribution of the fluorescent RM-1929 in tissues collected from animals terminated on Day 3 (Group 2) vs. animals terminated on Day 15. When present, fluorescent RM-1929 in the skin was detected predominantly in the dermis, and was multifocal to diffuse in distribution. In general, fluorescent RM-1929 detected in other organs was predominantly located in connective tissue; in the liver, fluorescent RM-1929 was detected in portal areas, with	No[††]

2.6.5 薬物動態試験の概要表

Study Number: 11286				**Test Article:** RM-1929	
Species/ Strain	**Route of Admin.**	**Dose (mg/kg)**	**Sex/No. per Group**	**Noteworthy Findings**	**GLP**
				moderate diffuse distribution in the hepatic parenchyma. Fluorescent RM-1929 was detected in other tissues, including the retina, the pigment epithelium of the eye, cornea, trabecular bone of the sternum and femur, red pulp of the spleen, and renal tubules.	
†Biodistribution study was a component of single-dose GLP toxicology study (described above in 3.4). ††The biodistribution component was performed non-GLP.					

6. 薬物動態試験：代謝

RM-1929 の代謝試験は実施していない。

7. 薬物動態試験：排泄

	Test Article: IR 700 Carboxylate		
Study/Report Number:	**Explora Study No. EB10-039-016C/Report No. MC13B-0228**		
Species:	Sprague Dawley Rats		
Gender (M/F)/Number of animals:	2 M for the vehicle control group; 6 M for each IRDye 700DX Carboxylate dose groups.		
Vehicle/Formulation:	Phosphate Buffered Saline		
Test Article Lot Numbers:	IR700-CO_2-Na+ in PBS, Lot # [redacted]		
Method of Administration:	Administered intravenously into the lateral tail vein.		
Dose (mg/kg):	2.6, 7.8, 26 (once on Day 0 at t=0 at dose volume of 4 ml/kg)		
Analyte:	IR 700 Carboxylate		
Samples:	Urine		
Assay Method:	HPLC/FLUD		
	Individual Urine Concentrations of IRDye 700DX Carboxylate in Rats		
Dose (mg/kg)	**Urine Concentration (µg/mL)**	**Measured Urine Volume(µL)**	**Amount in Urine (µg)**
2.6	240	250	60.0
	NSR	NSR	NC
	512	335	172
	186	14	2.60
	287	480	138
	392	270	106
	337	380	128

7.8	727	240	174
	739	250	185
	717	35	25.1
	775	510	395
	660	37	24.4
2.6	NSR	NSR	NC
	632	385	240
	2390	550	1310
	2610	530	1380
	2220	490	1090
	2050	115	236
NC = Not Calculated; NSR = No sample received.			

8. 薬物動態試験：その他

RM-1929 のその他の薬物動態試験は実施していない。