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用語の定義

用語	定義・解説
ARLG	オートラジオルミノグラフィー（autoradioluminography）
AUC	血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve）
$AUC_{0\text{-}8h}$	投与後 8 時間までの血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve from time zero to 8 hours）
$AUC_{0\text{-}24h}$	投与後 24 時間までの血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve from time zero to 24 hours）
$AUC_{0\text{-}t}$	投与後最終測定可能時間までの血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve from time zero to the last measurable point）
C_{max}	最高血漿中濃度（maximum plasma concentration）
CNS	中枢神経系（central nervous system）
CSF	脳脊髄液（cerebrospinal fluid）
ECL	電気化学発光（electrochemiluminescence）
hIDS	ヒトイズロン酸-2-スルファターゼ（human iduronate-2-sulfatase）
hTfR	ヒトトランスフェリン受容体 1（human transferrin receptor 1）
hTfR KI	ヒトトランスフェリン受容体 1 遺伝子ノックイン（human transferrin receptor 1 gene knock in）
hTfR KI/Ids KO マウス	hTfR KI マウスと Ids KO マウスを交配して作出した二重遺伝子改変マウス
^{125}I	ヨウ素の放射性同位体（iodine-125）
^{125}I-JR-141	^{125}I 標識 JR-141（^{125}I-labeled JR-141）
^{125}I-RP-2703	^{125}I 標識 RP-2703（^{125}I-labeled RP-2703）
IDS	イズロン酸-2-スルファターゼ（iduronate-2-sulfatase）
Ids KO	イズロン酸-2-スルファターゼ遺伝子ノックアウト（iduronate-2-sulfatase gene knock out）
KI	ノックイン（knock in）
KO	ノックアウト（knock out）
MW	分子量（molecular weight）
PK	ファーマコキネティクス（pharmacokinetics）
RE	相対誤差（relative error）
RP-2703	JR-141 の抗体部分に変異を入れることで hTfR とカニクイザル TfR にほぼ同等の結合親和性を持たせた分子
SE-HPLC	サイズ排除高速液体クロマトグラフィー（size exclusion high performance liquid chromatography）
$t_{1/2}$	消失相の半減期（elimination half-life at terminal phase）
TCA	トリクロロ酢酸（trichloroacetic acid）
TfR	トランスフェリン受容体 1（transferrin receptor 1）
TK	トキシコキネティクス（toxicokinetics）
ULOQ	定量上限以上（upper limit of quantification）

2.6.5 薬物動態試験概要表

2.6.5.1 薬物動態試験：一覧表

被験物質：JR-141

Type of study	Species and strain	Method of administration	Duration and frequency of dose	Dose	Study site	Study number	Location in CTD
Absorption (TK)	Mature cynomolgus monkey	Intravenous infusion	4 weeks, once a week	0, 3, 10 and 30 mg/kg	[redacted] a), b)	[redacted]	4.2.3.2.2
	Juvenile cynomolgus monkey	Intravenous infusion	4 weeks, once a week	0, 3, 10 and 30 mg/kg	[redacted] a), b)	[redacted]	4.2.3.2.3
	Cynomolgus monkey	Intravenous infusion	26 weeks, once a week	0, 3, 10 and 30 mg/kg	[redacted] a), b)	[redacted]	4.2.3.2.4
Distribution	hTfR KI/Ids KO mouse	Intravenous bolus	Single	2 mg/kg	JCR c) / [redacted] b)	[redacted]	4.2.2.3.1
Distribution (CNS)	hTfR KI mouse	Intravenous bolus	Single	1 and 5 mg/kg	JCR c) / [redacted] a)	[redacted] d)	4.2.2.3.2 (参考資料)
	Cynomolgus monkey	Intravenous infusion	Single	5 mg/kg			
	Cynomolgus monkey	Intravenous infusion	Single	1 and 5 mg/kg	[redacted] a), b)	[redacted]	4.2.2.3.3
	Juvenile cynomolgus monkey	Intravenous infusion	4 weeks, once a week	0, 3, 10 and 30 mg/kg	[redacted] a), b)	[redacted]	4.2.3.2.3
	Cynomolgus monkey	Intravenous infusion	26 weeks, once a week	0, 3, 10 and 30 mg/kg	[redacted] a), b)	[redacted]	4.2.3.2.4
Distribution (ARLG)	Cynomolgus monkey	Intravenous infusion	Single	1 mg/kg	[redacted] b)	[redacted]	4.2.2.3.4
Distribution (comparative ARLG)	Cynomolgus monkey	Intravenous infusion	Single	1 mg/kg	[redacted] b)	[redacted]	4.2.2.3.5 (参考資料)
Distribution (placental transfer)	Pregnant cynomolgus monkey	Intravenous infusion	Single	10 mg/kg	[redacted] a), b)	[redacted]	4.2.2.3.6
Metabolism / excretion (comparative study)	Cynomolgus monkey	Intravenous infusion	Single	1 mg/kg	[redacted] b)	[redacted]	4.2.2.3.5 (参考資料)

a) [redacted]
b) [redacted]
c) JCR pharmaceuticals Co., Ltd.
d) [redacted]

2.6.5.2 分析方法

非臨床薬物動態試験の概要文中に記載した（2.6.4.2 参照）。

2.6.5.3 薬物動態試験：吸収

2.6.5.3.1 カニクイザル 4 週間反復静脈内投与毒性試験における TK 測定

被験物質 ：JR-141
CTD における記載箇所 ：4.2.3.2.2
試験番号 ：[redacted]

Species / strain		Mature cynomolgus monkey			
Sex / animal number		Male and female / 3 animals in 3 and 10 mg/kg groups or 5 animals in 0 and 30 mg/kg groups for each sex			
Feeding		Non fasting			
Vehicle / dose formation		Physiological saline / solution			
Method of administration		Intravenous infusion, 4 weeks, once a week			
Dose		0, 3, 10 and 30 mg/kg			
Test article		JR-141 ([redacted] and [redacted])			
Assay method		ECL			
Sampling time point		First and last doses: pre-dose, 20 min, 1, 3, 8, 24 and 48 hours after the initiation of administrations			
TK parameter		C_{max} (μg/mL)		$AUC_{0\text{-}t}$ (μg·h/mL)	
Time point for evaluation		First dose	Last dose	First dose	Last dose
3 mg/kg	Male	48.4±12.9	35.0±14.8	418±137	180±108
	Female	45.1±10.4	33.2±6.75	317±97.1	125±53.5
10 mg/kg	Male	252±66.0	161±6.43	2320±307	994±307
	Female	205±20.6	176±34.0	1980±332	1110±568
30 mg/kg [a)]	Male	784±119	662±104	9100±2130	5860±1980
	Female	699±61.3	555±97.7	6800±933	5160±1440

Means ± standard deviations, n=3
a) Means ± standard deviations, n=5

2.6.5.3.2 幼若カニクイザル４週間反復静脈内投与毒性試験における TK 測定

被験物質 : JR-141
CTD における記載箇所 : 4.2.3.2.3
試験番号 : [redacted]

Species / strain	Juvenile cynomolgus monkey			
Sex / animal number	Male / 3 animals in 3 and 10 mg/kg groups or 5 animals in 0 and 30 mg/kg groups			
Feeding	Non fasting			
Vehicle / dose formation	Physiological saline / solution			
Method of administration	Intravenous infusion, 4 weeks, once a week			
Dose	0, 3, 10 and 30 mg/kg			
Test article	JR-141 ([redacted])			
Assay method	ECL			
Sampling point	First and last doses: pre-dose, 10 min, 3, 8, 24 and 48 hours after the initiation of administrations			
TK parameter	C_{max} (μg/mL)		$AUC_{0\text{-}t}$ (μg·h/mL)	
Time point for evaluation	First dose	Last dose	First dose	Last dose
3 mg/kg	51.9±1.44	34.9±4.11	212±8.19	91.2±24.1
10 mg/kg	166±35.7	158±22.5	851±117	728±244
30 mg/kg [a)]	518±32.0	538±31.1	3550±469	3280±546

Means ± standard deviations, n=3
a) Means ± standard deviations, n=5

2.6.5.3.3 カニクイザル 26 週間反復静脈内投与毒性試験における TK 測定

被験物質 : JR-141
CTD における記載箇所 : 4.2.3.2.4
試験番号 : [redacted]

Species / strain		Cynomolgus monkey					
Sex / animal number		Male and female / 4 animals in 3 and 10 mg/kg groups or 6 animals in 0 and 30 mg/kg groups for each sex					
Feeding		Non fasting					
Vehicle / dose formation		Physiological saline / solution					
Method of administration		Intravenous infusion, 26 weeks, once a week					
Dose		0, 3, 10 and 30 mg/kg					
Test article		JR-141 ([redacted], [redacted] and [redacted])					
Assay method		ECL					
Sampling point		First, 13th and last doses: pre-dose, 20 min, 1, 3, 8, 24 and 48 hours after the initiation of administrations					
TK parameter		C_{max} (μg/mL)			AUC_{0-t} (μg·h/mL)		
Time point for evaluation		First dose	13th dose	Last dose	First dose	13th dose	Last dose
3 mg/kg	Male	44.5±4.92	27.6±13.8	20.7±14.0	316±56.3	115±89.4	113±133
	Female	42.2±5.40	24.6±9.04	9.68±3.78	256±25.6	108±100	23.5±13.0
10 mg/kg	Male	189±24.5	104±47.8	81.9±47.4	1640±350	526±420	411±454
	Female	169±16.7	130±63.8	97.1±58.3	1210±194	712±500	599±592
30 mg/kg a)	Male	540±69.1	546±77.7	432±44.9	5900±824	3710±1130	3260±985
	Female	574±79.3	442±97.2	358±71.7	5380±990	2620±1130	1870±732

Means ± standard deviations, n=4
a) Means ± standard deviations, n=6

2.6.5.4 薬物動態試験：分布

2.6.5.4.1 hTfR KI/Ids KO マウスにおける体内分布

被験物質： JR-141 及びイデュルスルファーゼ
CTD における記載箇所 : 4.2.2.3.1
試験番号 : [redacted]

Species / strain	hTfR KI/Ids KO mouse							
Sex / animal number	Male / 4 animals in each time point							
Feeding	Non fasting							
Vehicle / dose formation	Physiological saline / solution							
Method of administration	Intravenous, single bolus							
Dose	2 mg/kg							
Assay method	ECL							
Evaluation item	Drug concentrations in plasma and tissues (μg/mL or μg/g)							
Test article	JR-141 ([redacted])				Idursulfase			
Sampling time point after administration	1 hour	4 hours	8 hours	24 hours	1 hour	4 hours	8 hours	24 hours
Plasma	20.3±1.4	5.73±0.16	1.21±0.39	0.0563±0.0085	7.83±1.66	0.695±0.122	0.213±0.068	0.0262±0.0020
Brain	-	-	0.539±0.015	0.333±0.011	-	-	0.00704±0.00047	0.00591±0.01183 a)
Liver	-	-	7.88±0.67	2.85±0.33	-	-	22.7±3.0	9.44±1.00
Heart	-	-	1.02±0.08 b)	0.586±0.072	-	-	0.563±0.071	0.255±0.004
Spleen	-	-	15.2±1.5	8.03±1.75	-	-	8.40±2.62	3.29±0.32

Means ± standard deviations, n=4, -: Not applicable
a) Detected in only one animal out of 4 animals (individual value: 0.0237 μg/g)
b) Means ± standard deviations, n=3

2.6.5.4.2 hTfR KI マウス及びカニクイザルにおける脳組織移行性評価

被験物質 : JR-141 及び hIDS
CTD における記載箇所 : 4.2.2.3.2（参考資料）
試験番号 : 該当なし [1)]

Species / strain	hTfR KI mouse		Cynomolgus monkey	
Sex / animal number	Male / 3 animals in each time point		Male / 2 animals in each time point	
Feeding	Non fasting		Non fasting	
Dose formation	Solution		Solution	
Method of administration	Intravenous, single bolus		Intravenous, single infusion	
Dose	1 and 5 mg/kg		5 mg/kg	
Test article	XenoLight CF750 labeled or non-labeled JR-141 and hIDS		JR-141	
Evaluation item / assay method	Concentration in brain (ECL)	Immunohistochemical staining and *in / ex vivo* IVIS imaging	Concentration in brain (ECL)	Immunohistochemical staining
Sampling time point after administration	15 min, 1, 4, 8 and 24 hours	24 hours	8 and 24 hours	8 hours
Noteworthy Findings	JR-141 was distributed to the brain tissue and neuron cells when administered intravenously to hTfR KI mouse and cynomolgus monkey. It was thought that hIDS is mostly not delivered to hTfR KI mouse brain after intravenous administration.			

1) 文献引用

2.6.5.4.3 カニクイザルにおける単回投与時の体内分布試験（中枢神経系）

被験物質 : JR-141
CTD における記載箇所 : 4.2.2.3.3
試験番号 : [redacted]

Species / strain	Cynomolgus monkey		
Sex / animal number	Male / 2 animals in each group		
Feeding	Non fasting		
Vehicle / dose formation	Physiological saline / solution		
Method of administration	Intravenous, single infusion		
Assay method	ECL		
Test article	JR-141 ([redacted])		
Evaluation item	Concentration in plasma (μg/mL)		
Dose	1 mg/kg	5 mg/kg	
Sampling time point	Pre-dose, 20 min, 1, 3 and 8 hours after the initiation of administration	Pre-dose, 20 min, 1, 3, 8 and 24 hours after the initiation of administration	
C_{max} (μg/mL)	17.1	73.8±8.17 a)	
$AUC_{0\text{-}8h}$ (μg·h/mL)	58.1	319±18.5 a)	
$AUC_{0\text{-}24h}$ (μg·h/mL)	-	537	
$t_{1/2}$ (h)	4.42	6.41	
Evaluation item	Concentration in CSF and CNS tissues (ng/mL or μg/g)		
Sampling time point	8 hours after the initiation of administration	8 hours after the initiation of administration	24 hours after the initiation of administration
Cerebral cortex	0.0809	0.282	0.188
Hippocampus	0.0592	0.225	0.156
Cerebellum	0.0585	0.191	0.109
Medulla oblongata	0.0519	0.232	0.146
Spinal cord (cervical)	0.0296	0.132	0.0794
CSF	13.6	43.7	24.7

Mean, n=2
a) Means ± standard deviations, n=4
-: Not applicable

2.6.5.4.4 カニクイザルにおける単回投与時の体内分布試験（ARLG）

被験物質 : ^{125}I-JR-141
CTD における記載箇所 : 4.2.2.3.4
試験番号 : [redacted]

Species / strain	Cynomolgus monkey	
Sex / animal number	Male and female / each one animal in each time point	
Feeding	Non fasting	
Vehicle / dose formation	Phosphate buffer [redacted] / solution	
Method of administration	Intravenous, single infusion	
Dose	1 mg/kg	
Assay method	Radioactivity (γ-counter)	
Test article	^{125}I-JR-141	
Radiochemical purity	97.27% (label-1) and 98.69% (label-2)	
hTfR binding activity [a)]	-5.38% (label-1) and 2.48% (label-2)	
Evaluation item	Concentration in plasma (μg eq./mL)	
Sampling time point	pre-dose, 20 min, 1, 3, 8, 24, 48 and 72 hours after initiation of administration	
PK parameter [b)]	Male	Female
C_{max} (μg eq./mL)	13.8	15.1
AUC_{0-t} (μg eq.·h/mL)	101	113
$t_{1/2}$ (h)	12.0	13.3

a) RE% value compared to non-labeled JR-141
b) Calculated from mean concentrations in plasma

2.6.5.4.4 カニクイザルにおける単回投与時の体内分布試験（ARLG）（続き）

Assay method	Quantitative whole body autoradioluminography (ARLG)									
Evaluation item	Concentration in blood and tissues (μg eq./mL or μg eq./g)									
Sampling time point	2 hours		8 hours		24 hours		48 hours		72 hours	
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Blood	6.32	6.37	1.78	2.54	0.673	1.41	0.158	0.433	0.0587	0.216
Brain	0.202	0.278	0.147	0.182	0.0521	0.108	ND	ND	ND	ND
Spinal cord	0.377	0.743	0.253	0.257	0.0604	0.134	0.0256	0.0553	ND	0.0276
Pituitary gland	0.526	1.65	0.445	0.537	0.0774	0.237	0.0362	0.0726	0.0360	ND
Eyeball	0.0994	0.0802	0.202	0.148	0.0528	0.0986	ND	0.0390	ND	ND
Submandibular gland	0.496	0.827	0.514	0.834	0.158	0.247	0.0423	0.130	ND	0.0331
Thymus	1.17	1.13	1.23	0.691	0.206	1.27	0.0405	0.345	0.0606	NS
Heart	1.07	1.35	0.974	0.632	0.162	0.145	0.0467	0.195	ND	0.103
Lung	4.96	5.08	2.25	1.35	0.648	0.436	0.102	0.227	0.0301	0.0978
Liver	5.48	6.76	2.72	2.16	0.472	1.08	0.132	0.339	0.0479	0.309
Kidney	2.82	3.04	1.47	1.86	0.886	0.808	0.0722	0.145	0.0236	0.167
Adrenal gland	2.87	3.35	2.06	1.33	0.340	0.238	0.0962	0.276	0.0248	0.0681
Spleen	4.81	5.15	2.01	2.59	1.92	1.23	0.214	0.243	0.0914	0.293
Pancreas	0.874	1.22	1.27	0.540	0.612	0.384	0.0266	0.0778	ND	0.0690
Epididymis	0.843	-	0.918	-	0.255	-	0.0706	-	0.0341	-
Testis	0.554	-	0.587	-	0.177	-	0.0435	-	0.0202	-
Uterus	-	0.941	-	0.768	-	0.666	-	0.224	-	0.119
Ovary	-	0.608	-	0.637	-	0.296	-	0.0969	-	0.0637
Skin	0.768	1.53	1.05	1.34	0.740	0.650	0.0399	0.278	ND	0.130
Skeletal muscle	0.202	0.270	0.127	0.166	0.150	0.202	ND	0.0236	ND	0.0236
Bone	0.543	0.862	0.707	0.593	0.156	0.650	0.0400	0.145	0.0229	0.0718
Bone marrow	11.6	14.3	5.39	7.70	1.12	2.11	0.602	1.17	0.322	0.617

Individual values, ND: Not detected, NS: Not found on the sliced section, -: Not applicable
Thyroid gland: above the ULOQ in every time points for each sex
White fat: NS in every time points for each sex

2.6.5.4.5 幼若カニクイザルにおける週１回４週間反復投与時の体内分布（中枢神経系）

被験物質 ：JR-141
CTD における記載箇所 ：4.2.3.2.3
試験番号 ：[redacted]

Species / strain	Juvenile cynomolgus monkey					
Sex / animal number	Male / 3 animals in 3 and 10 mg/kg groups or 5 animals (2 out of 5 animals for recovery study) in 0 and 30 mg/kg groups					
Feeding	Non fasting					
Vehicle / dose formation	Physiological saline / solution					
Method of administration	Intravenous infusion, 4 weeks, once a week					
Test article	JR-141 ([redacted])					
Evaluation item	Concentration in CSF and CNS tissues (ng/mL or ng/g tissue)					
Dose	0 mg/kg		3 mg/kg	10 mg/kg	30 mg/kg	
Time point for evaluation	End of dosing period [1]	End of recovery period [2]	End of dosing period [1]	End of dosing period [1]	End of dosing period [1]	End of recovery period [2]
Cerebral cortex	ND	-	ND	10.1 [a]	28.1±25.8 [c]	ND
Hippocampus	ND	-	ND	11.5 [a]	39.3±42.4 [c]	ND
Cerebellum	ND	-	ND	ND	25.8 [b]	ND
Medulla oblongata	ND	-	ND	13.8 [a]	41.8±32.4 [c]	ND
Spinal cord (cervical)	ND	-	ND	14.0 [b]	51.3±27.3 [c]	ND
Spinal cord (lumbar)	ND	-	ND	17.9±10.3 [c]	52.4±34.7 [c]	ND
Spinal cord (thoracic)	ND	-	ND	13.2 [a]	35.3±26.5 [c]	ND
CSF	ND	ND	ND	ND	4.54 [a]	ND

ND: Not detected, -: Not applicable
1) 2 days after the last administration
2) 4 weeks after the last administration
a) Individual values, n=1 out of 3 animals
b) Means, n=2 out of 3 animals
c) Means ± standard deviations, n=3

2.6.5.4.6 カニクイザルにおける週 1 回 26 週間反復投与時の体内分布（中枢神経系）

被験物質 : JR-141
CTD における記載箇所 : 4.2.3.2.4
試験番号 : [redacted]

Species / strain	Cynomolgus monkey									
Sex / animal number	Male and female / 4 animals in 3 and 10 mg/kg groups or 6 animals (2 animals for recovery study) in 0 and 30 mg/kg groups for each sex									
Feeding	Non fasting									
Vehicle / dose formation	Physiological saline / solution									
Method of administration	Intravenous infusion, 26 weeks, once a week									
Test article	JR-141 ([redacted], [redacted] and [redacted])									
Evaluation item	Concentration in CNS tissues (ng/g tissue)									
Dose	0 mg/kg		3 mg/kg		10 mg/kg		30 mg/kg			
Time point for evaluation	End of dosing period [1]		End of dosing period [1]		End of dosing period [1]		End of dosing period [1]		End of recovery period [2]	
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Cerebral cortex	ND	ND	11.5 [a]	ND	ND	43.9 [a]	55.0±38.9 [c]	ND	ND	ND
Hippocampus	ND	ND	12.3 [a]	ND	ND	46.8 [a]	69.5 [b]	ND	ND	ND
Cerebellum	ND	ND	ND	ND	ND	52.5 [a]	60.6±50.4 [c]	11.8 [a]	ND	ND
Medulla oblongata	ND	ND	16.3 [a]	ND	ND	51.7 [a]	58.7±50.1	ND	ND	ND
Spinal cord (cervical)	ND	ND	16.1 [a]	ND	14.0 [a]	59.4 [a]	59.7±51.4	ND	ND	ND
Spinal cord (lumbar)	ND	ND	21.2 [a]	ND	19.9 [a]	98.3 [a]	98.7±60.6	13.7 [b]	ND	ND
Spinal cord (thoracic)	ND	ND	14.1 [a]	ND	18.3 [a]	41.6 [a]	52.4±33.4	ND	ND	ND

Evaluation item		Concentration in CSF (ng/mL)								
Dose		0 mg/kg		3 mg/kg		10 mg/kg		30 mg/kg		
Time point for evaluation		Last dose [3]	End of dosing period [1]	Last dose [3]	End of dosing period [1]	Last dose [3]	End of dosing period [1]	Last dose [3]	End of dosing period [1]	End of recovery period [2]
CSF	Male	ND	ND	17.5 [a]	2.26 [a]	5.34 [a]	ND	40.7±33.4 [d]	26.2 [b]	ND
	Female	ND	ND	ND	ND	21.1 [b]	14.1 [a]	12.2±14.9 [e]	ND	ND

Means ± standard deviations, n=4, ND: Not detected
1) 2 days after the last administration, 2) 8 weeks after the last administration, 3) 8 hours after the last administration
a) Individual values, n=1 out of 4 animals
b) Means, n=2 out of 4 animals
c) Means ± standard deviations, n=3 out of 4 animals
d) Means ± standard deviations, n=6
e) Means ± standard deviations, n=3 out of 6 animals

2.6.5.4.7 カニクイザルにおける ^{125}I-JR-141 と ^{125}I-RP-2703 の体内分布比較検討（ARLG）

被験物質 : ^{125}I-JR-141 及び ^{125}I-RP-2703
CTD における記載箇所 : 4.2.2.3.5（参考資料）
試験番号 : [redacted]

Species / strain	Cynomolgus monkey	
Sex / animal number	Male / 4 animals, n=1 in each time point	
Feeding	Non fasting	
Vehicle / dose formation	Phosphate buffer [redacted] / solution	
Method of administration	Intravenous infusion, single	
Dose	1 mg/kg	
Evaluation item	Concentration in plasma (μg eq./mL)	
Sampling time point	pre-dose, 20 min, 1, 3, 8 and 24 hours after initiation of administration	
Assay method	Radioactivity (γ-counter)	
Test article	^{125}I-JR-141	^{125}I-RP-2703
Radiochemical purity	98.86%	96.70%
hTfR binding activity [a)]	7.69%	20.14%
C_{max} (μg eq./mL) [b)]	9.37	9.84
AUC_{0-t} (μg eq.·h/mL) [b)]	69.4	49.2
$t_{1/2}$ (h) [b)]	12.2	9.95

a) RE% value compared to non-labeled JR-141 or non-labeled RP-2703
b) Calculated from mean concentrations in plasma until 24 hours after the initiation of administration

2.6.5.4.7 カニクイザルにおける ^{125}I-JR-141 と ^{125}I-RP-2703 の体内分布比較検討（ARLG）（続き）

Assay method	Quantitative whole body ARLG			
Evaluation item	Concentration in blood and tissue (μg eq./mL or μg eq./g)			
Test article	^{125}I-JR-141		^{125}I-RP-2703	
Sampling time point	8 hours after the initiation of administration	24 hours after the initiation of administration	8 hours after the initiation of administration	24 hours after the initiation of administration
Blood	2.99 (1.00)	1.32 (1.00)	0.923 (1.00)	0.704 (1.00)
Cerebrum	0.232 (0.0776)	0.0941 (0.0713)	0.0665 (0.0720)	0.0563 (0.0800)
Cerebellum	0.175 (0.0585)	0.0982 (0.0744)	0.0824 (0.0893)	0.0713 (0.101)
Pituitary gland	1.79 (0.599)	0.626 (0.474)	0.373 (0.404)	0.340 (0.483)
Spinal cord	0.773 (0.259)	0.129 (0.0977)	0.177 (0.192)	0.119 (0.169)
Eyeball	0.107 (0.0358)	0.0402 (0.0305)	0.0654 (0.0709)	0.0855 (0.121)
Submandibular gland	2.95 (0.987)	0.425 (0.322)	0.193 (0.209)	0.323 (0.459)
Thymus	NS (NC)	NS (NC)	0.400 (0.433)	0.442 (0.628)
Heart	1.06 (0.355)	0.877 (0.664)	0.299 (0.324)	0.255 (0.362)
Lung	1.12 (0.375)	0.607 (0.460)	0.329 (0.356)	0.604 (0.858)
Liver	1.63 (0.545)	0.849 (0.643)	1.37 (1.48)	0.541 (0.768)
Kidney	1.17 (0.391)	1.26 (0.955)	0.400 (0.433)	0.371 (0.527)
Adrenal gland	1.74 (0.582)	0.524 (0.397)	0.656 (0.711)	0.484 (0.688)
Spleen	1.29 (0.431)	2.93 (2.22)	3.29 (3.56)	1.02 (1.45)
Pancreas	0.686 (0.229)	0.642 (0.486)	0.304 (0.329)	0.376 (0.534)
White fat	NS (NC)	0.419 (0.317)	0.215 (0.233)	0.172 (0.244)
Bone	0.571 (0.191)	0.218 (0.165)	0.419 (0.454)	0.292 (0.415)
Skeletal muscle	0.192 (0.0642)	0.130 (0.0985)	0.0900 (0.0975)	0.116 (0.165)
Skin	0.862 (0.288)	0.380 (0.288)	0.522 (0.566)	0.302 (0.429)
Bone marrow	6.01 (2.01)	1.58 (1.20)	3.38 (3.66)	3.29 (4.67)
Testis	1.05 (0.351)	0.164 (0.124)	0.205 (0.222)	0.284 (0.403)
Epididymis	1.20 (0.401)	0.220 (0.167)	0.274 (0.297)	0.444 (0.631)

Individual values, figures in parentheses show tissue / blood ratio.
NS: Not found on the sliced section, NC: Not calculated
Thyroid gland: above the ULOQ in every time point

2.6.5.4.8 カニクイザルにおける胎盤通過性試験

被験物質 : JR-141
CTD における記載箇所 : 4.2.2.3.6
試験番号 : [redacted]

Species / strain	Pregnant cynomolgus monkey			
Sex / animal number	Female / 3 animals for 8 hours caesarean section group or 2 animals for 24 hours caesarean section group			
Feeding	Non fasting			
Vehicle / dose formation	Physiological saline / solution			
Method of administration	Intravenous infusion, single			
Dose	10 mg/kg			
Test article	JR-141 ([redacted])			
Assay method	ECL			
Evaluation item	Concentration in dermal plasma (μg/mL)			
Sampling time point	Pre-dose, 20 min, 1, 3, 8 and 24 hours after the initiation of administration			
PK parameter	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL) [a)]	$t_{1/2}$ (h) [a)]	
	171±24.2	892	5.44	
Evaluation item	Umbilical vein plasma		Umbilical artery plasma	
Sampling time point after the initiation of administration	8 hours	24 hours	8 hours	24 hours
Concentration	ND	ND	ND	ND

Means ± standard deviations, n=5
a) Means, n=2
ND: Not detected

2.6.5.5 薬物動態試験：代謝・排泄

2.6.5.5.1 カニクイザルにおける ^{125}I-JR-141 と ^{125}I-RP-2703 の体内分布比較検討（代謝・排泄）

被験物質 : ^{125}I-JR-141 及び ^{125}I-RP-2703
CTD における記載箇所 : 4.2.2.3.5（参考資料）
試験番号 : [redacted]

Species / strain	Cynomolgus monkey								
Sex / animal number	Male / 1 or 2 in each time point								
Evaluation item	Plasma, urine and feces								
Sampling time point	Plasma: 20 min, 8 and 24 hours after the initiation of administration Urine: from time 0 to 8 hours and 8 to 24 hours after the initiation of administration Feces: from time 0 to 8 hours and to 24 hours after the initiation of administration								
Assay method	SE-HPLC and radioactivity (γ-counter)								
Test article	^{125}I-JR-141				^{125}I-RP-2703				
Metabolite in plasma [a)]	UM-P1*	UM-P2		Total radioactivity	UM-P1*	UM-P2			Total radioactivity
20 min	4.92 (99.13)	ND (-)		4.96 (100.00)	5.49 (98.04)	0.0717 (1.28)			5.60 (100.00)
8 hours	3.39 (91.05)	0.333 (8.95)		3.72 (100.00)	1.45 (81.49)	0.325 (18.28)			1.78 (100.00)
24 hours	1.09 (82.24)	0.236 (17.76)		1.33 (100.00)	0.161 (22.60)	0.547 (75.15)			0.728 (100.00)
Estimated MW	610 - 641 kDa	1.01 - 1.12 kDa		-	592 - 622 kDa	0.92 - 1.07 kDa			-
Metabolite in urine [b)]	UM-U1	UM-U2	UM-U3	Total radioactivity	UM-U1	UM-U2	UM-U3	UM-U4	Total radioactivity
0 - 8 hours	11.94 (53.20)	9.87 (43.96)	0.43 (1.92)	25.45 (100.00)	5.29 (39.60)	7.46 (55.87)	0.25 (1.85)	0.22 (1.66)	13.36 (100.00)
8 - 24 hours	17.10 (55.95)	13.30 (43.50)	ND (-)	30.57 (100.00)	13.12 (45.36)	15.50 (53.38)	ND (-)	ND (-)	28.93 (100.00)
Estimated MW	1.51 - 1.59 kDa	0.977 - 1.03 kDa	0.127 kDa	-	1.83 - 1.92 kDa	1.02 kDa	0.277 kDa	0.121 kDa	-
Cumulative excretion [c)]	Urine	Feces		Total radioactivity	Urine	Feces			Total radioactivity
0 - 8 hours	18.63 (14.16)	0.03		18.65	11.41 (15.78)	0.01			11.42
0 - 24 hours	57.83 (16.03)	0.68		58.51	44.83 (18.29)	0.29			45.12

Study detail is described in section 2.6.5.4.7, ND: Not detected, -: Not applicable

a) μg* or μg eq./mL, figures in parentheses show % of total radioactivity.

b) % of dose, figures in parentheses show % of total radioactivity.

c) % of dose, mean of n=2 except data of 24 hours, figures in parentheses show the ratio (%) of TCA precipitate to total radioactivity.

2.6.5.6 薬物動態試験：薬物相互作用

該当資料なし。

2.6.5.7 薬物動態試験：その他の薬物動態試験

該当資料なし。