

Table 1 Clinical signs in conscious monkeys treated subcutaneously with SR-0379

Period	Test substance	Dose (mg/kg)	Animal No.	Time after start of dosing (day)						
				0*	1	2	3	4	5	6
1	Control (Saline)	0	1	-	-	-	-	-	-	-
			2	-	-	-	-	-	-	
			3	-	-	-	-	-	-	
			4	-	-	-	-	-	-	

Period	Test substance	Dose (mg/kg)	Animal No.	Time after start of dosing (day)						
				7*	8	9	10	11	12	13
2	SR-0379	1	1	-	-	-	-	-	-	-
			2	-	-	-	-	-	-	
			3	-	-	-	-	-	-	
			4	-	-	-	-	-	-	

Period	Test substance	Dose (mg/kg)	Animal No.	Time after start of dosing (day)						
				14*	15	16	17	18	19	20
3	SR-0379	3	1	-	-	-	-	-	-	-
			2	-	-	-	-	-	-	
			3	-	-	-	-	-	-	
			4	-	-	-	-	-	-	

Period	Test substance	Dose (mg/kg)	Animal No.	Time after start of dosing (day)	
				21*	22
4	SR-0379	10	1	-	-
			2	-	-
			3	-	-
			4	-	-

* Dosing day, observed before dosing.

-: No abnormalities.

Table 2 Observation of behavior in conscious monkeys treated subcutaneously with SR-0379

Period	Test substance	Dose (mg/kg)	Animal No.	End of dosing	Behavior						
					Time after dosing (min)						
					pre-1	pre-2	5	15	30	60	120
1	Control (Saline)	0	1	11:00:27	N	N	N	N	N	N	N
			2	11:00:24	N	N	N	N	N	N	N
			3	11:00:28	N	N	N	N	N	N	N
			4	11:00:21	N	N	N	N	N	N	N
2	SR-0379	1	1	11:00:27	N	N	N	N	N	N	N
			2	11:00:25	N	N	N	N	N	N	N
			3	11:00:34	N	N	N	N	N	N	N
			4	11:00:21	N	N	N	N	N	N	N
3	SR-0379	3	1	11:00:27	N	N	N	N	N	N	N
			2	11:00:25	N	N	N	N	N	N	N
			3	11:00:28	N	N	N	N	N	N	N
			4	11:00:21	N	N	N	N	N	N	N
4	SR-0379	10	1	11:00:27	N	N	N	N	N	N	N
			2	11:00:26	N	N	N	N	N	N	N
			3	11:00:27	N	N	N	N	N	N	N
			4	11:00:22	N	N	N	N	N	N	N

pre-1: More than 1 hour before dosing. pre-2: Just before dosing.

N: No abnormalities.

Behavior was observed by recorded DVD footage from more than 1 hour before dosing until 120 minutes after end of dosing.

Data show the observed behaviors.

Table 3 Body weights in conscious monkeys treated subcutaneously with SR-0379

Animal No.	1st dosing day	2nd dosing day	3rd dosing day	4th dosing day
	Control (Saline)	SR-0379 1 mg/kg	SR-0379 3 mg/kg	SR-0379 10 mg/kg
1	3.57	3.60	3.60	3.62
2	3.26	3.36	3.37	3.43
3	3.68	3.64	3.69	3.64
4	2.84	2.81	2.84	2.92
Mean	3.34	3.35	3.38	3.40
SD	0.38	0.38	0.38	0.34

Unit: kg.

**Table 4-1 Blood pressure and heart rate in conscious monkeys treated subcutaneously with SR-0379
–Actual value**

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)								
				pre-1	pre-2	pre	5	15	30	60	120	
SBP (mmHg)	Control (Saline)	0	1	106	114	110	109	110	113	116	113	
			2	101	111	106	120	114	110	113	110	
			3	109	103	106	111	107	109	103	100	
			4	100	115	108	141	120	123	135	127	
		Mean	104	111	108	120	113	114	117	113		
		SD	4	5	2	15	6	6	13	11		
		SR-0379	1	1	112	108	110	119	115	112	112	109
				2	98	100	99	124	113	105	105	104
	3			112	114	113	109	105	106	104	106	
	4			114	113	114	48	56	80	93	105	
	Mean		109	109	109	100	97	101	104	106		
	SD		7	6	7	35	28	14	8	2		
	3		1	105	108	107	134	109	101	105	104	
			2	98	111	105	132	129	125	128	126	
		3	104	114	109	112	107	107	102	104		
		4	114	119	117	116	111	110	119	114		
Mean	105	113	110	124	114	111	114	112				
SD	7	5	5	11	10	10	12	10				
10	1	105	114	110	58	95	96	111	113			
	2	88	119	104	127	120	122	119	121			
	3	109	106	108	44	46	94	101	97			
	4	98	99	99	112	118	116	115	109			
Mean	100	110	105	85	95	107	112	110				
SD	9	9	5	40	34	14	8	10				
DBP (mmHg)	Control (Saline)	0	1	67	72	70	68	69	75	77	73	
			2	72	82	77	89	85	80	84	81	
			3	71	68	70	71	72	75	68	63	
			4	64	82	73	105	86	88	99	94	
		Mean	69	76	73	83	78	80	82	78		
		SD	4	7	3	17	9	6	13	13		
		SR-0379	1	1	71	66	69	74	71	72	71	67
				2	67	72	70	90	81	73	77	76
				3	74	78	76	65	67	70	67	69
	4			81	83	82	33	38	58	70	79	
	Mean		73	75	74	66	64	68	71	73		
	SD		6	7	6	24	18	7	4	6		
	3		1	63	70	67	92	72	65	69	64	
			2	75	81	78	101	97	94	96	94	
			3	66	76	71	73	64	69	63	67	
		4	83	90	87	87	82	82	87	81		
	Mean	72	79	76	88	79	78	79	77			
	SD	9	8	9	12	14	13	15	14			
10	1	71	76	74	36	65	66	78	71			
	2	63	90	77	97	94	92	91	92			
	3	68	70	69	28	30	66	70	57			
	4	71	71	71	83	86	88	84	79			
Mean	68	77	73	61	69	78	81	75				
SD	4	9	4	34	29	14	9	15				

pre-1: More than 1 hour before dosing. pre-2: Just before dosing.

No significant difference was noted between the control and SR-0379 treated groups.

**Table 4-2 Blood pressure and heart rate in conscious monkeys treated subcutaneously with SR-0379
-Actual value (continued)**

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)									
				pre-1	pre-2	pre	5	15	30	60	120		
MBP (mmHg)	Control (Saline)	0	1	80	86	83	82	82	88	90	86		
			2	82	92	87	100	94	90	93	91		
			3	84	80	82	85	83	87	80	75		
			4	76	93	85	117	98	100	111	105		
			Mean	81	88	84	96	89	91	94	89		
			SD	3	6	2	16	8	6	13	12		
			SR-0379	1	1	85	80	83	89	85	85	85	81
					2	77	82	80	102	91	84	87	85
	3	87			90	89	79	80	82	80	81		
	4	92			93	93	38	44	66	77	88		
	Mean	85			86	86	77	75	79	82	84		
	SD	6			6	6	28	21	9	5	3		
	SR-0379	3			1	77	83	80	106	84	77	81	77
					2	82	91	87	112	108	104	106	104
			3	79	89	84	86	78	82	76	80		
			4	93	100	97	96	92	91	98	92		
Mean			83	91	87	100	91	89	90	88			
SD			7	7	7	11	13	12	14	12			
SR-0379			10	1	83	88	86	43	75	76	89	85	
				2	71	100	86	107	103	102	100	102	
	3	82		82	82	33	35	75	81	71			
	4	80		80	80	93	97	97	94	89			
	Mean	79		88	84	69	78	88	91	87			
	SD	5		9	3	36	31	14	8	13			
	HR (beats/min)	Control (Saline)		0	1	106	102	104	108	125	112	139	118
					2	123	126	125	130	118	124	127	119
3			143		115	129	145	131	137	126	117		
4			140		137	139	153	138	137	132	130		
Mean			128		120	124	134	128	128	131	121		
SD			17		15	15	20	9	12	6	6		
SR-0379			1		1	113	112	113	130	127	133	127	116
					2	127	111	119	134	127	123	112	113
		3		132	126	129	128	134	128	132	135		
		4		159	153	156	218	188	185	175	174		
		Mean		133	126	129	153	144	142	137	135		
		SD		19	20	19	44	30	29	27	28		
		SR-0379		3	1	113	118	116	134	125	129	116	117
					2	123	125	124	167	160	152	147	145
3			136		124	130	156	141	127	125	124		
4			182		184	183	194	188	190	174	180		
Mean	139		138		138	163	154	150	141	142			
SD	30		31		30	25	27	29	26	28			
SR-0379	10		1		121	116	119	210	177	168	143	138	
			2		119	141	130	202	195	195	186	173	
		3	125	129	127	162	153	144	147	148			
		4	187	188	188	198	188	202	195	190			
		Mean	138	144	141	193	178	177	168	162			
		SD	33	31	32	21	18	27	27	24			

pre-1: More than 1 hour before dosing. pre-2: Just before dosing.

No significant difference was noted between the control and SR-0379 treated groups.

Table 4-3 Blood pressure and heart rate in conscious monkeys treated subcutaneously with SR-0379
-%Change from the pre value

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)						
				pre	5	15	30	60	120	
SBP (%Change from the pre value)	Control (Saline)	0	1	100	99	100	103	105	103	
			2	100	113	108	104	107	104	
			3	100	105	101	103	97	94	
			4	100	131	111	114	125	118	
			Mean	100	112	105	106	109	105	
	SD	0	14	5	5	12	10			
	SR-0379	1	1	1	100	108	105	102	102	99
				2	100	125	114	106	106	105
				3	100	96	93	94	92	94
				4	100	42	49	70	82	92
				Mean	100	93	90	93	96	98
		SD	0	36	29	16	11	6		
		3	1	1	1	100	125	102	94	98
2					100	126	123	119	122	120
3					100	103	98	98	94	95
4					100	99	95	94	102	97
Mean					100	113	105	101	104	102
SD		0	14	13	12	12	12			
10		1	1	1	100	53	86	87	101	103
	2			100	122	115	117	114	116	
	3			100	41	43	87	94	90	
	4			100	113	119	117	116	110	
	Mean			100	82	91	102	106	105	
SD	0	41	35	17	11	11				
DBP (%Change from the pre value)	Control (Saline)	0	1	100	97	99	107	110	104	
			2	100	116	110	104	109	105	
			3	100	101	103	107	97	90	
			4	100	144	118	121	136	129	
			Mean	100	115	108	110	113	107	
	SD	0	21	8	8	16	16			
	SR-0379	1	1	1	100	107	103	104	103	97
				2	100	129	116	104	110	109
				3	100	86	88	92	88	91
				4	100	40	46	71	85	96
				Mean	100	91	88	93	97	98
		SD	0	38	30	16	12	8		
		3	1	1	1	100	137	107	97	103
2					100	129	124	121	123	121
3					100	103	90	97	89	94
4					100	100	94	94	100	93
Mean					100	117	104	102	104	101
SD		0	19	15	13	14	13			
10		1	1	1	100	49	88	89	105	96
	2			100	126	122	119	118	119	
	3			100	41	43	96	101	83	
	4			100	117	121	124	118	111	
	Mean			100	83	94	107	111	102	
SD	0	44	37	17	9	16				

No significant difference was noted between the control and SR-0379 treated groups.

**Table 4- 4 Blood pressure and heart rate in conscious monkeys treated subcutaneously with SR-0379
-%Change from the pre value (continued)**

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)						
				pre	5	15	30	60	120	
MBP (%Change from the pre value)	Control (Saline)	0	1	100	99	99	106	108	104	
			2	100	115	108	103	107	105	
			3	100	104	101	106	98	91	
			4	100	138	115	118	131	124	
			Mean	100	114	106	108	111	106	
	SD	0	17	7	7	14	14			
	SR-0379	1	1	1	100	107	102	102	102	98
				2	100	128	114	105	109	106
				3	100	89	90	92	90	91
				4	100	41	47	71	83	95
				Mean	100	91	88	93	96	98
		SD	0	37	29	15	12	6		
		3	1	1	1	100	133	105	96	101
2					100	129	124	120	122	120
3					100	102	93	98	90	95
4					100	99	95	94	101	95
Mean					100	116	104	102	104	102
SD		0	18	14	12	13	12			
10		1	1	1	100	50	87	88	103	99
	2			100	124	120	119	116	119	
	3			100	40	43	91	99	87	
	4			100	116	121	121	118	111	
	Mean			100	83	93	105	109	104	
SD	0	44	37	18	9	14				
HR (%Change from the pre value)	Control (Saline)	0	1	100	104	120	108	134	113	
			2	100	104	94	99	102	95	
			3	100	112	102	106	98	91	
			4	100	110	99	99	95	94	
			Mean	100	108	104	103	107	98	
	SD	0	4	11	5	18	10			
	SR-0379	1	1	1	100	115	112	118	112	103
				2	100	113	107	103	94	95
				3	100	99	104	99	102	105
				4	100	140	121	119	112	112
				Mean	100	117	111	110	105	104
		SD	0	17	7	10	9	7		
		3	1	1	1	100	116	108	111	100
2					100	135	129	123	119	117
3					100	120	108	98	96	95
4					100	106	103	104	95	98
Mean					100	119	112	109	103	103
SD		0	12	12	11	11	10			
10		1	1	1	100	176	149	141	120	116
	2			100	155	150	150	143	133	
	3			100	128	120	113	116	117	
	4			100	105	100	107	104	101	
	Mean			100	141	130	128	121	117	
SD	0	31	24	21	16	13				

No significant difference was noted between the control and SR-0379 treated groups.

Table 5-1 Electrocardiography in conscious monkeys treated subcutaneously with SR-0379 –Actual value

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)									
				pre-1	pre-2	pre	5	15	30	60	120		
PR (msec)	Control (Saline)	0	1	78	78	78	77	78	79	75	76		
			2	66	65	66	68	66	66	67	65		
			3	74	77	76	74	76	77	79	76		
			4	73	70	72	70	69	70	72	74		
			Mean	73	73	73	72	72	73	73	73		
			SD	5	6	5	4	6	6	5	5		
			SR-0379	1	1	79	77	78	74	74	72	76	73
					2	65	68	67	66	67	66	68	67
	3	78			81	80	73	74	76	79	75		
	4	64			69	67	54	60	60	58	63		
	Mean	72			74	73	67	69	69	70	70		
	SD	8			6	7	9	7	7	9	6		
	SR-0379	3			1	77	78	78	78	74	73	76	74
					2	65	65	65	63	64	66	65	65
			3	76	78	77	70	70	74	78	79		
			4	65	65	65	64	63	65	64	65		
Mean			71	72	71	69	68	70	71	71			
SD			7	8	7	7	5	5	7	7			
SR-0379			10	1	82	79	81	66	71	65	69	73	
				2	66	66	66	63	64	65	63	66	
	3	76		76	76	66	69	67	70	68			
	4	66		67	67	65	65	67	66	67			
	Mean	73		72	73	65	67	66	67	69			
	SD	8		6	7	1	3	1	3	3			
	QRS (msec)	Control (Saline)		0	1	36	38	37	38	36	39	35	37
					2	34	37	36	35	35	38	34	36
3			33		38	36	35	38	37	37	37		
4			30		31	31	29	30	31	32	31		
Mean		33	36	35	34	35	36	35	35				
SD		3	3	3	4	3	4	2	3				
SR-0379		1	1	37	36	37	36	36	36	37	38		
			2	33	34	34	33	34	34	34	35		
			3	36	35	36	37	37	37	36	35		
			4	28	28	28	30	28	29	29	29		
		Mean	34	33	34	34	34	34	34	34			
		SD	4	4	4	3	4	4	4	4			
	3	1	38	37	38	35	38	37	36	37			
		2	35	37	36	34	33	34	35	35			
		3	36	37	37	34	33	37	37	36			
		4	27	28	28	28	27	27	28	27			
	Mean	34	35	35	33	33	34	34	34				
	SD	5	5	5	3	5	5	4	5				
10	1	36	36	36	38	37	40	35	40				
	2	34	35	35	35	35	35	33	34				
	3	35	37	36	36	36	40	35	35				
	4	33	32	33	34	33	32	32	32				
Mean	35	35	35	36	35	37	34	35					
SD	1	2	1	2	2	4	2	3					

pre-1: More than 1 hour before dosing pre-2: Just before dosing.

No significant difference was noted between the control and SR-0379 treated groups.

Table 5-2 Electrocardiography in conscious monkeys treated subcutaneously with SR-0379 –Actual value (continued)

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)									
				pre-1	pre-2	pre	5	15	30	60	120		
QT (msec)	Control (Saline)	0	1	291	289	290	288	279	296	261	264		
			2	229	219	224	217	230	225	227	233		
			3	227	244	236	219	235	233	243	243		
			4	249	239	244	221	228	233	237	241		
			Mean	249	248	249	236	243	247	242	245		
			SD	30	30	29	35	24	33	14	13		
			SR-0379	1	1	283	270	277	247	265	252	261	259
					2	226	233	230	206	207	218	231	223
	3	236			240	238	229	230	245	250	227		
	4	206			209	208	182	203	207	197	199		
	Mean	238			238	238	216	226	231	235	227		
	SD	33			25	29	28	28	21	28	25		
	SR-0379	3			1	273	266	270	240	249	255	260	257
					2	215	212	214	191	203	210	208	201
			3	242	244	243	217	219	228	237	238		
			4	192	195	194	201	204	200	206	201		
Mean			231	229	230	212	219	223	228	224			
SD			35	32	33	21	21	24	26	28			
SR-0379			10	1	252	256	254	176	196	197	223	213	
				2	240	208	224	174	172	175	183	188	
	3	236		229	233	205	209	226	226	207			
	4	196		194	195	194	198	186	191	200			
	Mean	231		222	227	187	194	196	206	202			
	SD	24		27	24	15	16	22	22	11			
	QTc [Bazett] (msec)	Control (Saline)		0	1	386	376	381	388	403	404	396	371
					2	328	317	323	320	323	324	330	327
3			350		339	345	339	347	351	353	338		
4			380		361	371	352	345	352	352	354		
Mean			361		348	355	350	355	358	358	348		
SD			27		26	26	29	34	33	28	19		
SR-0379			1		1	388	368	378	363	385	375	380	360
					2	329	317	323	308	300	312	316	306
		3		350	348	349	334	343	357	371	340		
		4		335	334	335	347	360	363	337	339		
		Mean		351	342	346	338	347	352	351	336		
		SD		27	22	24	23	36	28	30	22		
		SR-0379		3	1	374	373	374	357	359	373	362	358
					2	307	306	307	317	332	334	325	313
3			363		351	357	349	335	331	342	342		
4			333		341	337	362	361	356	351	348		
Mean	344		343		344	346	347	349	345	340			
SD	30		28		29	20	15	20	16	19			
SR-0379	10		1		359	357	358	329	336	329	344	322	
			2		338	319	329	319	311	314	322	320	
		3	340	336	338	337	334	350	354	326			
		4	345	344	345	353	350	341	343	357			
		Mean	346	339	343	335	333	334	341	331			
		SD	9	16	12	14	16	16	13	17			

pre-1: More than 1 hour before dosing. pre-2: Just before dosing.

No significant difference was noted between the control and SR-0379 treated groups.

Table 5-3 Electrocardiography in conscious monkeys treated subcutaneously with SR-0379
 -%Change from the pre value

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)						
				pre	5	15	30	60	120	
PR (%Change from the pre value)	Control (Saline)	0	1	100	99	100	101	96	97	
			2	100	103	100	100	102	98	
			3	100	97	100	101	104	100	
			4	100	97	96	97	100	103	
			Mean	100	99	99	100	101	100	
	SD	0	3	2	2	3	3			
	SR-0379	1	1	1	100	95	95	92	97	94
				2	100	99	100	99	101	100
				3	100	91	93	95	99	94
				4	100	81	90	90	87	94
				Mean	100	92	95	94	96	96
		SD	0	8	4	4	6	3		
		3	1	1	1	100	100	95	94	97
2					100	97	98	102	100	100
3					100	91	91	96	101	103
4					100	98	97	100	98	100
Mean					100	97	95	98	99	100
SD		0	4	3	4	2	3			
10		1	1	1	100	81	88	80	85	90
	2			100	95	97	98	95	100	
	3			100	87	91	88	92	89	
	4			100	97	97	100	99	100	
	Mean			100	90	93	92	93	95	
SD	0	7	5	9	6	6				
QRS (%Change from the pre value)	Control (Saline)	0	1	100	103	97	105	95	100	
			2	100	97	97	106	94	100	
			3	100	97	106	103	103	103	
			4	100	94	97	100	103	100	
			Mean	100	98	99	104	99	101	
	SD	0	4	5	3	5	2			
	SR-0379	1	1	1	100	97	97	97	100	103
				2	100	97	100	100	100	103
				3	100	103	103	103	100	97
				4	100	107	100	104	104	104
				Mean	100	101	100	101	101	102
		SD	0	5	2	3	2	3		
		3	1	1	1	100	92	100	97	95
2					100	94	92	94	97	97
3					100	92	89	100	100	97
4					100	100	96	96	100	96
Mean					100	95	94	97	98	97
SD		0	4	5	3	2	1			
10		1	1	1	100	106	103	111	97	111
	2			100	100	100	100	94	97	
	3			100	100	100	111	97	97	
	4			100	103	100	97	97	97	
	Mean			100	102	101	105	96	101	
SD	0	3	2	7	2	7				

No significant difference was noted between the control and SR-0379 treated groups.

**Table 5- 4 Electrocardiography in conscious monkeys treated subcutaneously with SR-0379
- %Change from the pre value (continued)**

Parameter	Test substance	Dose (mg/kg)	Animal No.	Time after dosing (min)						
				pre	5	15	30	60	120	
QT (%Change from the pre value)	Control (Saline)	0	1	100	99	96	102	90	91	
			2	100	97	103	100	101	104	
			3	100	93	100	99	103	103	
			4	100	91	93	95	97	99	
			Mean	100	95	98	99	98	99	
	SD	0	4	4	3	6	6			
	SR-0379	1		1	100	89	96	91	94	94
				2	100	90	90	95	100	97
				3	100	96	97	103	105	95
				4	100	88	98	100	95	96
				Mean	100	91	95	97	99	96
		SD	0	4	4	5	5	1		
		3			1	100	89	92	94	96
2					100	89	95	98	97	94
3					100	89	90	94	98	98
4					100	104	105	103	106	104
Mean					100	93	96	97	99	98
SD		0	8	7	4	5	5			
10				1	100	69	77	78	88	84
	2			100	78	77	78	82	84	
	3			100	88	90	97	97	89	
	4			100	99	102	95	98	103	
	Mean			100	84	87	87	91	90	
SD	0	13	12	10	8	9				
QTc [Bazett] (%Change from the pre value)	Control (Saline)	0	1	100	102	106	106	104	97	
			2	100	99	100	100	102	101	
			3	100	98	101	102	102	98	
			4	100	95	93	95	95	95	
			Mean	100	99	100	101	101	98	
	SD	0	3	5	5	4	3			
	SR-0379	1		1	100	96	102	99	101	95
				2	100	95	93	97	98	95
				3	100	96	98	102	106	97
				4	100	104	107	108	101	101
				Mean	100	98	100	102	102	97
		SD	0	4	6	5	3	3		
		3			1	100	95	96	100	97
2					100	103	108	109	106	102
3					100	98	94	93	96	96
4					100	107	107	106	104	103
Mean					100	101	101	102	101	99
SD		0	5	7	7	5	4			
10				1	100	92	94	92	96	90
	2			100	97	95	95	98	97	
	3			100	100	99	104	105	96	
	4			100	102	101	99	99	103	
	Mean			100	98	97	98	100	97	
SD	0	4	3	5	4	5				

No significant difference was noted between the control and SR-0379 treated groups.

Appendix 1-1 Clinical signs during quarantine period

Individual No.	Animal ¹⁾ No.	Day 1 (Receipt day)					Quarantine day													
		Behavior	Fur	Nose, ear, eye, oral	Tail, limbs	Others	2	3	4	5	6	7	8	9	10	11	12	13	14	
1065	1	-	-	-	-	-	Rf +	Fs +	-	-	-	-	-	-	-	-	-	-	-	
3427	2	-	-	-	-	-	Rf ++	Rf + Df	Fs +	-	-	-	-	-	-	-	-	-	-	
2905	3	-	-	-	-	-	Rf +++	Rf ++ Df	Fs + Df	-	-	-	-	-	-	-	-	-	-	
7405	4	-	-	-	-	-	Rf +++	Rf +	Rf +	Rf + Df	Rf +	Rf +	Rf +	Rf +	Rf +	Rf +	Rf +	Rf +	Rf +	
1219	(Reserve)	-	-	-	-	-	Rf ++	Rf + Df	Fs +	-	-	-	-	-	-	-	-	-	-	

1) Identification numbers after grouping.

-: No abnormalities, Rf: Residual feed, Fs: Feed spilling, Df: Decrease in feces

+: Small amount, ++: Middle amount, +++: Large amount.

Appendix 1-2 Clinical signs during acclimation period

Individual No.	Animal ¹⁾ No.	Acclimation day																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1065	1	-	Nf	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	(ope)																					
3427	2	-	Nf	Rf+	Rf+	-	-	-	-	-	-	-	-	-	-	-	Fs+	Fs+	-	-	-	-
	(ope)																					
2905	3	-	Df	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	(ope)																					
7405	4	Rf+	-	-	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+	Rf+
	(ope)																					
1219	(Reserve)	-	Df	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	(ope)																					

1) Identification numbers after grouping.

-: No abnormalities, Rf: Residual feed, Fs: Feed spilling, Nf: No-feces, Df: Decrease in feces

+: Small amount.

(ope): Operation for telemetry transmitter implanting.

Appendix 1-3 Body weights during quarantine and acclimation periods

Individual No.	Animal ¹⁾ No.	Quarantine day		Acclimation day				
		1 Receipt day	14 Final day of quarantine	1 Surgery day	2 Surgery day	8	9	20 Allocation day
1065	1	3.52	3.61	3.59 *	-	3.52	-	3.55
3427	2	3.31	3.32	3.33 *	-	3.26	-	3.27
2905	3	3.71	3.63	3.63 *	-	3.64	-	3.67
7405	4	3.22	3.12	-	3.20 *	-	2.96	2.83
1219	(Reserve)	3.19	3.17	3.21 *	-	3.17	-	3.13

Unit: kg.

1) Identification numbers after grouping.

* Operation day for telemetry transmitter implanting.

Appendix 2- 1 Statistical results on blood pressure and heart rate –Actual value

Parameter: SBP

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	6.83	2.12	0.1880
Time	5	16.8	0.57	0.7189
Dose × Time	15	17.1	1.86	0.1102

Parameter: DBP

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	5.41	1.39	0.3427
Time	5	14.1	0.50	0.7737
Dose × Time	15	17.6	2.28	0.0501

Parameter: MBP

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	5.86	1.65	0.2768
Time	5	15.3	0.51	0.7612
Dose × Time	15	17.4	2.22	0.0562

Parameter: HR

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	4.51	1.20	0.4063
Time	5	9.5	14.86	0.0003
Dose × Time	15	17.5	1.38	0.2572

NDF: Numerator degrees of freedom.

DDF: Denominator degrees of freedom.

Appendix 2- 2 Statistical results on blood pressure and heart rate -%Change from the pre-dosing

Parameter: SBP

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	6.86	1.56	0.2830
Time	5	15.1	0.45	0.8078
Dose × Time	15	17.0	1.86	0.1095

Parameter: DBP

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	6.68	1.61	0.2749
Time	5	15.1	0.51	0.7655
Dose × Time	15	16.9	2.03	0.0812

Parameter: MBP

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	6.74	1.75	0.2471
Time	5	15.0	0.48	0.7883
Dose × Time	15	16.9	2.11	0.0707

Parameter: HR

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	7.37	1.88	0.2172
Time	5	15.3	16.33	<0.0001
Dose × Time	15	17.1	1.16	0.3803

NDF: Numerator degrees of freedom.

DDF: Denominator degrees of freedom.

Appendix 3- 1 Statistical results on electrocardiography –Actual value

Parameter: PR

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	5.89	1.43	0.3245
Time	5	12.3	3.34	0.0391
Dose × Time	15	17.5	1.92	0.0957

Parameter: QRS

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	3.71	0.37	0.7833
Time	5	10.0	1.45	0.2887
Dose × Time	15	17.9	2.03	0.0779

Parameter: QT

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	4.64	1.13	0.4249
Time	5	12.8	7.85	0.0014
Dose × Time	15	17.8	1.28	0.3060

Parameter: QTc [Bazett]

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	5.04	0.76	0.5620
Time	5	11.7	1.56	0.2445
Dose × Time	15	17.5	0.80	0.6688

NDF: Numerator degrees of freedom.

DDF: Denominator degrees of freedom.

Appendix 3- 2 Statistical results on electrocardiography - %Change from the pre-dosing

Parameter: PR

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	7.03	5.54	0.0288
Time	5	16.1	4.69	0.0078
Dose × Time	15	16.5	1.78	0.1296

Detection of effective dose

Dunnett's test	Time after dosing (min) / <i>p</i> value of Dunnett's test					
	pre	5	15	30	60	120
Control vs. 1 mg/kg	-	0.2279	0.1869	0.2959	0.3919	0.3078
Control vs. 3 mg/kg	-	0.8748	0.2987	0.9235	0.9321	1.0000
Control vs. 10 mg/kg	-	0.1322	0.0812	0.1028	0.0867	0.2002

Parameter: QRS

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	6.64	6.93	0.0185
Time	5	17.3	1.96	0.1358
Dose × Time	15	16.3	1.90	0.1061

Detection of effective dose

Dunnett's test	Time after dosing (min) / <i>p</i> value of Dunnett's test					
	pre	5	15	30	60	120
Control vs. 1 mg/kg	-	0.5530	0.9862	0.7548	0.3785	0.9688
Control vs. 3 mg/kg	-	0.5530	0.2416	0.1267	0.9288	0.3932
Control vs. 10 mg/kg	-	0.3202	0.9086	0.9543	0.3048	0.9995

Parameter: QT

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	7.17	3.58	0.0731
Time	5	14.0	8.02	0.0009
Dose × Time	15	16.8	1.13	0.4040

Parameter: QTc [Bazett]

Assessing the dose-effect and time-effect (Time-sequential analysis of variance)

Effect	NDF	DDF	F value	<i>p</i> value
Dose	3	7.98	0.57	0.6488
Time	5	17.7	2.91	0.0431
Dose × Time	15	16.5	0.73	0.7242

NDF: Numerator degrees of freedom.

DDF: Denominator degrees of freedom.

Bold: Statistically significant at significant level 0.05.

添付資料 1 Certificate of analysis (特性試験)

**This document is a true copy
of the original.**

Date: 01 March 2013
Study Director: Tetsuhisa Katsumi

CERTIFICATE OF ANALYSIS

Study No. : JCL12095350
Test article : SR-0379
Lot No. : Y01011C1
Date of analysis : 12, 13, 14 and 15 February 2013
Storage conditions : Store in a freezer (below -15°C).

Test item	Results
Description (Appearance)	White powder
Identification (Ultra violet absorption spectrum) (Ultraviolet-visible spectrophotometry)	The spectrum exhibited no wavelength of maximum absorption.
Impurity (Related substances) (Liquid chromatography)	1.53%
Purity (Liquid chromatography, Calculation)	98.47%
Water (Coulometric titration)	5.12%

This study was conducted in compliance with the GLP Standards for Non-clinical Safety Studies of Drugs (Japanese Ministry of Health and Welfare Ordinance No.21, 26 March 1997: Partial amendment (Ordinance No.114), Japanese Ministry of Health, Labour and Welfare, dated 13 June 2008).

Tetsuhisa Katsumi

Tetsuhisa Katsumi

Study Director

Nishiwaki Laboratory, JCL Bioassay Corporation

01 March 2013

Date

CERTIFICATE OF ANALYSIS

Study No. : JCL14065297
 Test article : SR-0379
 Lot No. : Y01011C1
 Date of analysis : 06 November 2014 to 13 November 2014
 Storage conditions : Store in a freezer (below -15°C).

Test item	Results
Description (Appearance)	White powder
Identification (Ultraviolet absorption spectrum) (Ultraviolet-visible spectrophotometry)	The spectrum exhibited no wavelength of maximum absorption.
Impurity (Related substances) (Liquid chromatography)	1.59%
Purity (Liquid chromatography, Calculation)	98.41%
Water (Coulometric titration)	5.40%

This study was conducted in compliance with the GLP Standards for Non-clinical Safety Studies of Drugs (Japanese Ministry of Health and Welfare Ordinance No.21, 26 March 1997; Partial amendment (Ordinance No.114), Japanese Ministry of Health, Labour and Welfare, dated 13 June 2008).

Koichi Fujimoto
 Koichi Fujimoto
 Study Director
 Nishiwaki Laboratory, JCL Bioassay Corporation

10 December 2014
 Date