

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 19 Absolute and relative organ weights (males)

Day(s): 29 Relative to Start Date

Sex: Male		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Liver (g)	Mean	59.8 ¹	62.1	60.3	64.2	66.5	76.2
	S.D.	6.9	8.0	1.9	11.7	6.1	10.6
	N	4	4	4	4	4	3
Liver (%)	Mean	1.75 ¹	1.91	1.78	1.91	2.09	2.62 ^{dd2}
	S.D.	0.14	0.12	0.20	0.18	0.24	0.21
	N	4	4	4	4	4	3
Spleen (g)	Mean	2.946 ¹	4.294	4.962	4.001	3.601	2.767
	S.D.	0.521	1.546	1.891	0.995	0.932	0.680
	N	4	4	4	4	4	3
Spleen (%)	Mean	0.086 ¹	0.131	0.148	0.121	0.113	0.095
	S.D.	0.010	0.046	0.063	0.036	0.029	0.017
	N	4	4	4	4	4	3
Pancreas (g)	Mean	5.45 ¹	4.84	5.31	5.49	5.27	4.71
	S.D.	0.94	0.38	1.10	1.41	0.78	0.96
	N	4	4	4	4	4	3

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

2 [dd - Test: Dunnett 2 Sided p < 0.01]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 19 Absolute and relative organ weights (males)

Day(s): 29 Relative to Start Date

Sex: Male		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Pancreas (%)	Mean	0.159 I ¹	0.150	0.155	0.162	0.165	0.162
	S.D.	0.020	0.022	0.025	0.024	0.021	0.023
	N	4	4	4	4	4	3
Adrenal Total (mg)	Mean	447 I ¹	423	454	404	389	456
	S.D.	86	41	103	66	56	58
	N	4	4	4	4	4	3
Adrenal Total (mg%)	Mean	13.03 I ¹	13.16	13.42	12.05	12.26	15.93
	S.D.	2.04	2.44	3.39	1.46	2.05	3.61
	N	4	4	4	4	4	3
Kidney Total (g)	Mean	11.62 I ¹	11.82	12.64	12.38	11.99	11.47
	S.D.	0.87	0.52	1.48	1.45	1.13	0.74
	N	4	4	4	4	4	3
Kidney Total (%)	Mean	0.340 R ²	0.366	0.371	0.373	0.377	0.396
	S.D.	0.018	0.046	0.005	0.060	0.032	0.027
	N	4	4	4	4	4	3

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

2 [R - Automatic Transformation Selected: Rank]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 19 Absolute and relative organ weights (males)

Day(s): 29 Relative to Start Date

Sex: Male		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Testis Total (g)	Mean	3.43 ¹	2.22	2.83	3.52	1.70	2.61
	S.D.	2.27	1.63	1.34	1.37	0.51	1.70
	N	4	4	4	4	4	3
Testis Total (%)	Mean	0.0966 ¹	0.0653	0.0808	0.1060	0.0534	0.0868
	S.D.	0.0596	0.0405	0.0281	0.0438	0.0153	0.0524
	N	4	4	4	4	4	3
Epididymis Total (g)	Mean	1.27 ¹	1.07	1.24	1.20	0.87	0.89
	S.D.	0.48	0.70	0.44	0.23	0.26	0.17
	N	4	4	4	4	4	3
Epididymis Total (%)	Mean	0.0365 ¹	0.0313	0.0356	0.0365	0.0272	0.0305
	S.D.	0.0116	0.0172	0.0080	0.0112	0.0075	0.0045
	N	4	4	4	4	4	3
Prostate (g)	Mean	0.55 ¹	0.56	0.43	0.45	0.41	0.32
	S.D.	0.28	0.47	0.19	0.12	0.17	0.05
	N	4	4	4	4	4	3

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 19 Absolute and relative organ weights (males)

Day(s): 29 Relative to Start Date

Sex: Male		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Prostate (%)	Mean	0.0158 ¹	0.0164	0.0122	0.0136	0.0132	0.0112
	S.D.	0.0074	0.0119	0.0040	0.0038	0.0074	0.0026
	N	4	4	4	4	4	3
Seminal Vesicle (g)	Mean	1.64 ¹	1.44	1.48	1.36	1.02	0.97
	S.D.	0.90	1.13	1.48	0.36	0.37	0.30
	N	4	4	4	4	4	3
Seminal Vesicle (%)	Mean	0.0465 ¹	0.0417	0.0401	0.0408	0.0328	0.0328
	S.D.	0.0225	0.0288	0.0352	0.0116	0.0158	0.0080
	N	4	4	4	4	4	3

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 20 Absolute and relative organ weights (females)

Day(s): 29 Relative to Start Date

Sex: Female		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Final Bodyweight (kg)	Mean	2.93 ¹	2.93	2.86	2.83	2.88	2.72 n ^{1 2}
	S.D.	0.41	0.32	0.24	0.37	0.38	.
	N	4	4	4	4	4	1
Brain (g)	Mean	58.4 ¹	64.5	60.7	60.2	65.1	64.3 n ^{1 2}
	S.D.	8.1	3.9	6.8	5.0	4.0	.
	N	4	4	4	4	4	1
Brain (%)	Mean	1.99 ¹	2.21	2.13	2.15	2.28	2.36 n ^{1 2}
	S.D.	0.11	0.21	0.23	0.28	0.20	.
	N	4	4	4	4	4	1
Pituitary (mg)	Mean	41 ¹	48	48	46	45	40 n ^{1 2}
	S.D.	5	5	4	4	7	.
	N	4	4	4	4	4	1
Pituitary (mg%)	Mean	1.41 ¹	1.65	1.69	1.64	1.58	1.47 n ^{1 2}
	S.D.	0.09	0.26	0.10	0.18	0.36	.
	N	4	4	4	4	4	1

1 [1 - Automatic Transformation Selected: Identity (No Transformation)]

2 [n1 - This group has only one value: Data was not statistically analyzed.]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 20 Absolute and relative organ weights (females)

Day(s): 29 Relative to Start Date

Sex: Female		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Thyroid	Mean	325 I ¹	312	333	296	348	293 n ^{1 2}
Total	S.D.	123	64	144	115	179	.
(mg)	N	4	4	4	4	4	1
Thyroid	Mean	11.38 I ¹	10.86	11.59	10.62	11.96	10.77 n ^{1 2}
Total	S.D.	4.85	3.03	4.57	4.30	6.06	.
(mg%)	N	4	4	4	4	4	1
Submandibul	Mean	2.47 I ¹	2.45	2.19	2.29	2.25	1.71 n ^{1 2}
ar gland	S.D.	0.46	0.17	0.18	0.67	0.59	.
(g)	N	4	4	4	4	4	1
Submandibul	Mean	0.0847 I ¹	0.0838	0.0771	0.0813	0.0779	0.0629 n ^{1 2}
ar gland	S.D.	0.0148	0.0057	0.0124	0.0237	0.0148	.
(%)	N	4	4	4	4	4	1
Thymus	Mean	1.130 L ³	1.240	1.430	1.520	0.558	0.515 n ^{1 2}
(g)	S.D.	0.230	0.469	0.677	0.885	0.067	.
	N	4	4	4	4	4	1

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

2 [n1 - This group has only one value: Data was not statistically analyzed.]

3 [L - Automatic Transformation Selected: Log]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 20 Absolute and relative organ weights (females)

Day(s): 29 Relative to Start Date

Sex: Female		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Thymus (%)	Mean	0.0389 R ¹	0.0420	0.0493	0.0537	0.0194	0.0189 n1 ²
	S.D.	0.0088	0.0156	0.0223	0.0303	0.0007	.
	N	4	4	4	4	4	1
Lung Total (g)	Mean	12.52 I ³	12.86	13.28	14.69	13.77	13.34 n1 ²
	S.D.	2.29	1.37	1.58	2.35	2.76	.
	N	4	4	4	4	4	1
Lung Total (%)	Mean	0.426 I ³	0.439	0.464	0.519 dd ⁴	0.477	0.490 n1 ²
	S.D.	0.020	0.020	0.038	0.026	0.059	.
	N	4	4	4	4	4	1
Heart (g)	Mean	9.71 I ³	9.83	9.17	9.28	9.54	8.81 n1 ²
	S.D.	1.13	2.34	0.74	0.98	1.16	.
	N	4	4	4	4	4	1
Heart (%)	Mean	0.334 R ¹	0.333	0.321	0.330	0.333	0.324 n1 ²
	S.D.	0.043	0.051	0.003	0.029	0.026	.
	N	4	4	4	4	4	1

1 [R - Automatic Transformation Selected: Rank]

3 [I - Automatic Transformation Selected: Identity (No Transformation)]

2 [n1 - This group has only one value: Data was not statistically analyzed.]

4 [dd - Test: Dunnett 2 Sided p < 0.01]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 20 Absolute and relative organ weights (females)

Day(s): 29 Relative to Start Date

Sex: Female		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Liver (g)	Mean	59.6 ¹	57.1	60.7	63.0	71.9	69.2 ^{n1²}
	S.D.	6.5	5.8	9.8	11.4	15.2	.
	N	4	4	4	4	4	1
Liver (%)	Mean	2.04 ¹	1.95	2.12	2.23	2.48 ^{d³}	2.54 ^{n1²}
	S.D.	0.12	0.15	0.23	0.31	0.26	.
	N	4	4	4	4	4	1
Spleen (g)	Mean	2.432 ¹	2.657	3.395	3.527	2.628	3.114 ^{n1²}
	S.D.	0.560	0.361	0.953	0.394	1.085	.
	N	4	4	4	4	4	1
Spleen (%)	Mean	0.082 ¹	0.092	0.121	0.126	0.089	0.114 ^{n1²}
	S.D.	0.009	0.018	0.044	0.019	0.024	.
	N	4	4	4	4	4	1
Pancreas (g)	Mean	4.06 ¹	4.82	4.52	4.54	4.29	4.12 ^{n1²}
	S.D.	0.96	0.58	0.50	1.10	0.42	.
	N	4	4	4	4	4	1

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

2 [n1 - This group has only one value: Data was not statistically analyzed.]

3 [d - Test: Dunnett 2 Sided p < 0.05]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 20 Absolute and relative organ weights (females)

Day(s): 29 Relative to Start Date

Sex: Female		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Pancreas (%)	Mean	0.138 ¹	0.165	0.159	0.160	0.151	0.151 n ^{1 2}
	S.D.	0.021	0.018	0.027	0.027	0.023	.
	N	4	4	4	4	4	1
Adrenal Total (mg)	Mean	468 ¹	498	485	510	505	321 n ^{1 2}
	S.D.	145	72	76	137	75	.
	N	4	4	4	4	4	1
Adrenal Total (mg%)	Mean	15.71 ¹	17.18	16.93	18.18	17.54	11.80 n ^{1 2}
	S.D.	2.82	3.62	2.28	4.73	1.08	.
	N	4	4	4	4	4	1
Kidney Total (g)	Mean	10.42 ¹	10.74	10.58	10.96	10.45	9.57 n ^{1 2}
	S.D.	2.25	1.11	0.72	2.33	1.09	.
	N	4	4	4	4	4	1
Kidney Total (%)	Mean	0.354 ¹	0.367	0.371	0.389	0.365	0.352 n ^{1 2}
	S.D.	0.043	0.027	0.020	0.069	0.026	.
	N	4	4	4	4	4	1

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

2 [n1 - This group has only one value: Data was not statistically analyzed.]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 20 Absolute and relative organ weights (females)

Day(s): 29 Relative to Start Date

Sex: Female		Control 0.5%CMC-Na	Low TM5509 2 mg/kg/day	Low-Mid TM5509 6 mg/kg/day	Mid TM5509 20 mg/kg/day	Mid-High TM5509 80 mg/kg/day	High TM5509 300 mg/kg/day
Ovary	Mean	432 ¹	256	267	298	255	155 ^{n1²}
Total	S.D.	217	102	64	86	47	.
(mg)	N	4	4	4	4	4	1
Ovary	Mean	14.82 ¹	8.53	9.44	10.62	8.96	5.70 ^{n1²}
Total	S.D.	7.97	2.61	2.70	3.27	1.84	.
(mg%)	N	4	4	4	4	4	1
Uterus	Mean	8.11 ¹	6.44	6.08	7.54	5.72	7.26 ^{n1²}
(g)	S.D.	1.35	1.79	2.05	3.12	1.56	.
	N	4	4	4	4	4	1
Uterus	Mean	0.279 ¹	0.220	0.212	0.261	0.197	0.267 ^{n1²}
(%)	S.D.	0.053	0.062	0.068	0.075	0.033	.
	N	4	4	4	4	4	1

1 [I - Automatic Transformation Selected: Identity (No Transformation)]

2 [n1 - This group has only one value: Data was not statistically analyzed.]

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 21 Histopathology (males)

SEX: MALE	GROUP	1	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6		
	REMOVAL REASON	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	D	A	
	ANIMAL	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	
	NUMBER	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	
		1	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6	6	
		M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4

Duodenum; (Continued)		
erosion/ulcer, vater papilla	2
Cecum;	X
Colon;	X
Rectum;	X
Thymus;	X
Adrenal;	+
congestion, cortex	2
hypertrophy, zona fasciculata	2

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 21 Histopathology (males)

Key Page

Group Code	Description
1	Control 0.5%CMC-Na
2	2 mg/kg/day
3	6 mg/kg/day
4	20 mg/kg/day
5	80 mg/kg/day
6	300 mg/kg/day

Removal Reason Code	Description
A	End of dosing
D	Found dead

Tissue Result Code	Description
N	N.V.L
.	Not Recorded
+	Tissue Observation Present
X	Not Examined

Grade Code	Description
.	not recorded
1	slight
2	moderate
3	severe
#	duplicate
P	present - no grade or classification

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 22 Histopathology (females)

```

-----
SEX: FEMALE
GROUP 1 1 1 1 2 2 2 2 3 3 3 3 4 4 4 4 5 5 5 5 6 6 6 6
REMOVAL REASON A A A A A A A A A A A A A A A A A A A A A D A M M

ANIMAL R R R R R R R R R R R R R R R R R R R R R R R R R R R R R R
NUMBER P P P P P P P P P P P P P P P P P P P P P P P P P P P P P P
1 1 1 1 2 2 2 2 3 3 3 3 4 4 4 4 5 5 5 5 6 6 6 6
F F F F F F F F F F F F F F F F F F F F F F F F F F F F F F
O O O O O O O O O O O O O O O O O O O O O O O O O O O O O O
1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
-----

Liver; ..... N N N N N N N N N N N N N N N N N N N N N N N N N N N N N N + + + +
proliferation, bile ductule ..... 1 1 1
cell infiltration, inflammatory cell, portal
tract ..... 3 . 2
necrosis, hepatocyte, multifocal, portal tract .. 2 . 1 1
necrosis/regeneration, bile duct ..... 1 . 1

Gallbladder; ..... N N N N N N N N N N N N N N N N N N N N N N N N N N N N N N + + + +
cell infiltration, inflammatory cell ..... 2
hemorrhage, mucosa ..... 1 . .
edema, mucosa ..... 1 1 1 .
erosion/ulcer ..... 1 2
bacterial colony (gram positive/negative) ..... 1 . 1

Extrahepatic Bile Duct; ..... + . + +
cell infiltration, inflammatory cell ..... 2 . 2
hemorrhage ..... 1 . .
erosion/ulcer ..... 3 . 2 3
bacterial colony (gram positive/negative) ..... 2 . 2

Duodenum; ..... N N N N N N N N N N N N N N N N N N N N N N N N N N N N N N + N N N N N N + N + +
ectopic tissue, pancreas ..... P . . . .
bacterial colony (gram positive/negative), vater
papilla ..... 2 . 1
hemorrhage, vater papilla ..... 1 . 1 1
cell infiltration, inflammatory cell, vater
papilla ..... 1 1

```

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 22 Histopathology (females)

SEX: FEMALE	GROUP	1	1	1	2	2	2	2	3	3	3	3	4	4	4	4	5	5	5	5	6	6	6	6		
	REMOVAL REASON	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	D	A	M	M
	ANIMAL	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
	NUMBER	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
		1	1	1	2	2	2	2	3	3	3	3	4	4	4	4	5	5	5	5	6	6	6	6	6	
		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	

Duodenum; (Continued)		
erosion/ulcer, vater papilla	3 2
Ileum;	+ . . .
cell infiltration, inflammatory cell, mucosa	1 . . .
Jejunum;	N . . .
Cecum;	N . . .
Colon;	+ . . .
cell infiltration, inflammatory cell, mucosa	1 . . .
Rectum;	X . . .
Thymus;	+ . + +
atrophy	3 . 3 3
Synovial Membrane;	+ N
hemorrhage	1 .

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 22 Histopathology (females)

Key Page

Group Code	Description
1	Control 0.5%CMC-Na
2	2 mg/kg/day
3	6 mg/kg/day
4	20 mg/kg/day
5	80 mg/kg/day
6	300 mg/kg/day

Removal Reason Code	Description
A	End of dosing
D	Found dead
M	Moribund condition

Tissue Result Code	Description
N	N.V.L
.	Not Recorded
+	Tissue Observation Present
X	Not Examined

Grade Code	Description
.	not recorded
1	slight
2	moderate
3	severe
#	duplicate
P	present - no grade or classification

TK13152

Page: 1

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 23 Plasma concentrations and toxicokinetic parameters of TM5509 (males)

Sex: Male

Day: 1

Group	Animal No.	Plasma concentration (µg/mL)					C _{max} (µg/mL)	T _{max} (h)	AUC _{0-24h} ^{a)} (µg·h/mL)
		Time post-dosing							
		1h	4h	6h	8h	24h			
Control 0.5%CMC-Na	RP1M01	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	RP1M02	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	RP1M03	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	RP1M04	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	Mean	NC	NC	NC	NC	NC	-	-	-
	S.D.	NC	NC	NC	NC	NC	-	-	-
	N	4	4	4	4	4	-	-	-
Low TM5509 2 mg/kg/day	RP2M01	16.8 [6]	20.2 [6]	18.9 [6]	17.6 [6]	7.52 [2]	20.2	4	340
	RP2M02	13.1 [6]	24.5 [6]	21.7 [6]	20.8 [6]	8.34 [2]	24.5	4	385
	RP2M03	15.2 [6]	20.6 [6]	17.5 [6]	14.9 [6]	7.99 [2]	20.6	4	315
	RP2M04	13.9 [6]	16.7 [6]	14.4 [6]	12.1 [6]	5.00 [2]	16.7	4	247
	Mean	14.8	20.5	18.1	16.4	7.21	20.5	4.0	322
	S.D.	1.6	3.2	3.0	3.7	1.51	3.2	0.0	58
	N	4	4	4	4	4	4	4	4
Low-Mid TM5509 6 mg/kg/day	RP3M01	25.2 [6]	64.7 [6]	87.6 [6]	64.8 [6]	27.0 [2]	87.6	6	1190
	RP3M02	34.1 [6]	57.0 [6]	58.3 [6]	49.0 [6]	13.5 [2]	58.3	6	876
	RP3M03	54.4 [6]	78.6 [6]	77.9 [6]	64.0 [6]	19.1 [2]	78.6	4	1190
	RP3M04	36.2 [6]	73.8 [6]	69.0 [6]	56.4 [6]	16.7 [2]	73.8	4	1040
	Mean	37.5	68.5	73.2	58.6	19.1	74.6	5.0	1070
	S.D.	12.2	9.6	12.5	7.4	5.8	12.3	1.2	150
	N	4	4	4	4	4	4	4	4

General Footnote: []: Dilution factor

BLQ: Below the lower limit of quantification (0.5 µg/mL)

NC: Not calculated

^{a)} The values of 0 hours were regarded as 0 µg/mL.

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 23 Plasma concentrations and toxicokinetic parameters of TM5509 (males)

Sex: Male		Day: 1		Plasma concentration (µg/mL)						
Group	Animal No.	Time post-dosing					C _{max} (µg/mL)	T _{max} (h)	AUC _{0-24h} ^{a)} (µg·h/mL)	
		1h	4h	6h	8h	24h				
Mid TM5509 20 mg/kg/day	RP4M01	52.6 [6]	143 [6]	146 [6]	130 [6]	48.5 [2]	146	6	2310	
	RP4M02	78.3 [6]	108 [6]	97.6 [6]	89.9 [6]	32.8 [2]	108	4	1690	
	RP4M03	20.8 [6]	114 [6]	121 [6]	143 [6]	24.9 [2]	143	8	2050	
	RP4M04	53.2 [6]	171 [6]	165 [6]	183 [6]	54.1 [2]	183	8	2940	
	Mean	51.2	134	132	136	40.1	145	6.5	2250	
	S.D.	23.6	29	29	38	13.6	31	1.9	530	
	N	4	4	4	4	4	4	4	4	
Mid-High TM5509 80 mg/kg/day	RP5M01	84.6 [6]	214 [6]	179 [6]	199 [6]	60.5 [2]	214	4	3340	
	RP5M02	36.1 [6]	192 [6]	198 [6]	187 [6]	59.0 [2]	198	6	3100	
	RP5M03	55.3 [6]	209 [6]	206 [6]	228 [6]	52.4 [2]	228	8	3520	
	RP5M04	121 [6]	168 [6]	187 [6]	202 [6]	31.7 [2]	202	8	3110	
	Mean	74.3	196	193	204	50.9	211	6.5	3270	
	S.D.	37.0	21	12	17	13.3	14	1.9	200	
	N	4	4	4	4	4	4	4	4	
High TM5509 300 mg/kg/day	RP6M01	94.8 [6]	232 [6]	239 [6]	267 [6]	144 [6] ^{b)}	267	8	4800	
	RP6M02	53.0 [6]	222 [6]	241 [6]	281 [6]	99.2 [6] ^{b)}	281	8	4470	
	RP6M03	156 [6]	235 [6]	234 [6]	218 [6]	52.7 [2]	235	4	3750	
	RP6M04	162 [6]	251 [6]	271 [6]	268 [6]	87.3 [2]	271	6	4600	
	Mean	116	235	246	259	95.8	264	6.5	4410	
	S.D.	52	12	17	28	37.7	20	1.9	460	
	N	4	4	4	4	4	4	4	4	

General Footnote: []: Dilution factor

^{a)} The values of 0 hours were regarded as 0 µg/mL.^{b)} Since the measured values exceeded the upper limit of the calibration curve (50 µg/mL), the reanalysis with diluted samples was conducted and the result was employed.

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 23 Plasma concentrations and toxicokinetic parameters of TM5509 (males)

Sex: Male Day: 28

Group	Animal No.	Plasma concentration (µg/mL)						C _{max} (µg/mL)	T _{max} (h)	AUC _{0-24h} ^{a)} (µg·h/mL)
		Pre-dosing	Time post-dosing							
			1h	4h	6h	8h	24h			
Control 0.5%CMC-Na	RP1M01	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	RP1M02	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	RP1M03	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	RP1M04	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	BLQ [1]	-	-	-
	Mean	NC	NC	NC	NC	NC	NC	-	-	-
	S.D.	NC	NC	NC	NC	NC	NC	-	-	-
	N	4	4	4	4	4	4	-	-	-
Low TM5509 2 mg/kg/day	RP2M01	8.55 [1]	31.3 [1]	31.8 [1]	31.9 [1]	25.1 [1]	10.2 [1]	31.9	6	518
	RP2M02	10.2 [1]	29.6 [1]	32.1 [1]	29.6 [1]	22.9 [1]	10.9 [1]	32.1	4	497
	RP2M03	11.7 [1]	21.4 [1]	37.0 [1]	36.1 [1]	27.8 [1]	15.1 [1]	37.0	4	584
	RP2M04	4.81 [1]	19.0 [1]	22.1 [1]	20.6 [1]	15.8 [1]	5.53 [1]	22.1	4	323
	Mean	8.82	25.3	30.8	29.6	22.9	10.4	30.8	4.5	481
	S.D.	2.96	6.0	6.2	6.5	5.1	3.9	6.2	1.0	111
	N	4	4	4	4	4	4	4	4	4
Low-Mid TM5509 6 mg/kg/day	RP3M01	23.7 [1]	39.7 [3]	78.7 [3]	63.5 [3]	55.1 [3]	21.7 [1]	78.7	4	1080
	RP3M02	9.75 [1]	39.9 [3]	57.0 [3]	45.6 [3]	37.0 [3]	10.1 [1]	57.0	4	732
	RP3M03	17.4 [1]	53.6 [3]	80.2 [3]	71.8 [3]	67.5 [3]	19.5 [1]	80.2	4	1220
	RP3M04	23.8 [1]	51.0 [3]	92.9 [3]	90.6 [3]	85.4 [3]	26.6 [1]	92.9	4	1510
	Mean	18.7	46.1	77.2	67.9	61.3	19.5	77.2	4.0	1140
	S.D.	6.7	7.3	14.9	18.7	20.4	6.9	14.9	0.0	320
	N	4	4	4	4	4	4	4	4	4

General Footnote: []: Dilution factor

BLQ: Below the lower limit of quantification (0.5 µg/mL)

NC: Not calculated

^{a)} The values of 0 hours were calculated using the pretreatment value.

A 4-Week Oral Dose Toxicity Study of TM5509 in Cynomolgus Monkeys

Table 23 Plasma concentrations and toxicokinetic parameters of TM5509 (males)

Sex: Male Day: 28

Group	Animal No.	Plasma concentration (µg/mL)					C _{max} (µg/mL)	T _{max} (h)	AUC _{0-24h} ^{a)} (µg·h/mL)	
		Pre-dosing	Time post-dosing							
			1h	4h	6h	8h				24h
Mid	RP4M01	51.4 [3]	72.5 [6]	143 [6]	148 [6]	141 [6]	39.0 [3]	148	6	2410
TM5509	RP4M02	31.6 [3]	76.2 [6]	72.4 [6]	63.5 [6]	59.9 [6]	26.3 [3]	76.2	1	1230
20	RP4M03	38.9 [3]	48.1 [6]	95.9 [6]	98.9 [6]	123 [6]	33.9 [3]	123	8	1930
mg/kg/day	RP4M04	65.5 [3]	92.1 [6]	122 [6]	138 [6]	119 [6]	54.7 [3]	138	6	2310
	Mean	46.9	72.2	108	112	111	38.5	121	5.3	1970
	S.D.	14.9	18.2	31	39	35	12.0	32	3.0	530
	N	4	4	4	4	4	4	4	4	4
Mid-High	RP5M01	43.5 [3]	63.0 [6]	127 [6]	137 [6]	118 [6]	31.1 [3]	137	6	2050
TM5509	RP5M02	46.6 [3]	43.8 [6]	117 [6]	119 [6]	120 [6]	37.9 [3]	120	8	2020
80	RP5M03	39.1 [3]	61.7 [6]	138 [6]	140 [6]	126 [6]	14.5 [3]	140	6	2020
mg/kg/day	RP5M04	32.6 [3]	84.1 [6]	98.2 [6]	80.0 [6]	80.2 [6]	20.1 [3]	98.2	4	1470
	Mean	40.5	63.2	120	119	111	25.9	124	6.0	1890
	S.D.	6.1	16.5	17	28	21	10.6	19	1.6	280
	N	4	4	4	4	4	4	4	4	4
High	RP6M01	59.9 [6]	120 [6]	139 [6]	130 [10]	148 [10]	70.4 [6]	148	8	2770
TM5509	RP6M02 ^{b)}	-	-	-	-	-	-	-	-	-
300	RP6M03	78.9 [6]	93.2 [6]	124 [6]	99.6 [10]	129 [10]	86.4 [6]	129	8	2590
mg/kg/day	RP6M04	121 [6]	151 [6]	182 [6]	162 [10]	167 [10]	66.0 [6]	182	4	3170
	Mean	86.6	121	148	131	148	74.3	153	6.7	2840
	S.D.	31.3	29	30	31	19	10.7	27	2.3	300
	N	3	3	3	3	3	3	3	3	3

General Footnote: []: Dilution factor

^{a)} The values of 0 hours were calculated using the pretreatment value.^{b)} Died on Day 16 of dosing