

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

Table 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
CA (mg/dL)	-1	Mean	9.93 ¹	9.72	9.97	10.09	9.69	9.64
		S.D.	0.35	0.27	0.37	0.47	0.42	0.33
		N	4	4	4	4	4	4
	1	Mean	10.11 ^{R2}	9.79	9.72	9.49	9.51	9.64
		S.D.	0.34	0.72	0.54	0.30	0.06	0.28
		N	4	4	4	4	4	4
	2	Mean	9.63 ^{R2}	9.69	9.75	9.63	9.55	9.36
		S.D.	0.49	0.27	0.36	0.17	0.16	0.02
		N	4	4	4	4	4	4
	3	Mean	9.63 ¹	9.37	9.54	9.28	9.22	9.38 ^{n1³}
		S.D.	0.37	0.16	0.44	0.18	0.21	.
		N	4	4	4	4	4	1
	4	Mean	9.51 ¹	9.38	9.61	9.88	9.66	9.36 ^{n1³}
		S.D.	0.31	0.19	0.32	0.56	0.55	.
		N	4	4	4	4	4	1

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

2 [R - Automatic Transformation Selected: Rank]

3 [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 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
NA (mEq/L)	-1	Mean	151.8 R ¹	151.6	154.3	154.2	152.6	150.4
		S.D.	0.5	1.7	3.9	6.4	3.9	1.4
		N	4	4	4	4	4	4
	1	Mean	150.5 I ²	149.2	148.7	149.1	149.4	147.9
		S.D.	2.4	5.7	1.8	2.3	1.2	1.6
		N	4	4	4	4	4	4
	2	Mean	145.6 I ²	148.9	149.0	147.0	148.4	143.3
		S.D.	2.9	3.3	0.9	1.9	1.3	4.6
		N	4	4	4	4	4	4
	3	Mean	150.8 I ²	149.3	149.3	149.1	149.4	148.3 n1 ³
		S.D.	3.2	3.5	2.0	2.1	3.3	.
		N	4	4	4	4	4	1
	4	Mean	147.6 R ¹	148.7	147.2	148.9	151.5	149.1 n1 ³
		S.D.	2.3	1.4	0.6	3.2	5.0	.
		N	4	4	4	4	4	1

1 [R - Automatic Transformation Selected: Rank]

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

3 [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 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
K (mEq/L)	-1	Mean	4.04 ¹	3.99	4.01	4.04	4.10	3.81
		S.D.	0.31	0.41	0.38	0.36	0.50	0.40
		N	4	4	4	4	4	4
	1	Mean	4.52 ¹	4.36	4.01	3.86 ^{d4}	3.96	3.77 ^{d4}
		S.D.	0.29	0.57	0.32	0.14	0.31	0.11
		N	4	4	4	4	4	4
	2	Mean	4.46 ¹	4.95	4.53	4.06	4.23	3.88
		S.D.	0.25	0.69	0.49	0.08	0.57	0.44
		N	4	4	4	4	4	4
	3	Mean	4.11 ^{L2}	4.21	3.97	3.71	3.88	3.78 ⁿ¹⁵
		S.D.	0.30	0.52	0.20	0.07	0.58	.
		N	4	4	4	4	4	1
	4	Mean	4.01 ^{R3}	4.13	4.10	4.06	4.40	4.10 ⁿ¹⁵
		S.D.	0.05	0.42	0.48	0.23	1.00	.
		N	4	4	4	4	4	1

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

3 [R - Automatic Transformation Selected: Rank]

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

2 [L - Automatic Transformation Selected: Log]

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

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

Table 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
CL (mEq/L)	-1	Mean	112.7 I ¹	109.9	114.3	112.4	113.8	112.2
		S.D.	3.5	1.7	2.8	4.7	2.2	3.9
		N	4	4	4	4	4	4
	1	Mean	106.6 I ¹	108.2	108.3	109.2	110.0	102.0 d ²
		S.D.	1.4	2.8	2.3	2.2	1.5	2.5
		N	4	4	4	4	4	4
	2	Mean	108.7 I ¹	112.2	112.4	110.2	112.0	102.6
		S.D.	1.6	1.5	2.2	2.3	2.5	6.1
		N	4	4	4	4	4	4
	3	Mean	112.9 I ¹	113.5	114.1	114.1	114.6	111.1 n1 ³
		S.D.	1.5	1.4	2.6	1.9	2.9	.
		N	4	4	4	4	4	1
	4	Mean	108.3 I ¹	111.2	110.3	110.1	111.3	108.6 n1 ³
		S.D.	1.7	0.6	1.7	3.9	2.3	.
		N	4	4	4	4	4	1

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

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

3 [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 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
TP (g/dL)	-1	Mean	7.68 1 ¹	7.62	7.93	7.84	7.85	8.04
		S.D.	0.42	0.29	0.20	0.50	0.24	0.21
		N	4	4	4	4	4	4
	1	Mean	7.59 1 ¹	7.53	7.59	7.42	7.65	7.83
		S.D.	0.38	0.58	0.32	0.22	0.10	0.27
		N	4	4	4	4	4	4
	2	Mean	7.18 1 ¹	7.20	7.19	7.04	7.21	7.27
		S.D.	0.33	0.38	0.18	0.19	0.15	0.29
		N	4	4	4	4	4	4
	3	Mean	7.20 1 ¹	7.18	7.12	7.18	7.16	7.70 n1 ²
		S.D.	0.33	0.25	0.27	0.25	0.25	.
		N	4	4	4	4	4	1
	4	Mean	7.18 1 ¹	7.10	7.22	7.36	7.50	7.62 n1 ²
		S.D.	0.33	0.30	0.18	0.29	0.24	.
		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 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
ALB (g/dL)	-1	Mean	4.22 ¹	3.98	4.29	4.35	4.29	4.34
		S.D.	0.24	0.11	0.20	0.31	0.11	0.18
		N	4	4	4	4	4	4
	1	Mean	4.13 ¹	3.88	4.07	3.93	3.88	3.74 ^{d2}
		S.D.	0.16	0.30	0.21	0.17	0.05	0.17
		N	4	4	4	4	4	4
	2	Mean	3.99 ¹	3.74	3.94	3.80	3.77	3.46 ^{dd3}
		S.D.	0.19	0.28	0.14	0.16	0.12	0.30
		N	4	4	4	4	4	4
	3	Mean	4.09 ¹	3.81	3.96	3.88	3.88	3.83 ⁿ¹⁴
		S.D.	0.25	0.20	0.21	0.20	0.19	.
		N	4	4	4	4	4	1
	4	Mean	3.95 ¹	3.63	3.89	3.80	3.88	3.70 ⁿ¹⁴
		S.D.	0.18	0.19	0.17	0.28	0.18	.
		N	4	4	4	4	4	1

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

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

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

4 [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 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
A/G	-1	Mean	1.22 ¹	1.10	1.18	1.25	1.21	1.17
		S.D.	0.09	0.09	0.07	0.14	0.05	0.04
		N	4	4	4	4	4	4
	1	Mean	1.20 ¹	1.06	1.16	1.13	1.03 ^{d2}	0.91 ^{dd3}
		S.D.	0.08	0.09	0.02	0.11	0.03	0.03
		N	4	4	4	4	4	4
	2	Mean	1.26 ¹	1.09	1.21	1.18	1.10	0.91 ^{dd3}
		S.D.	0.08	0.11	0.04	0.14	0.03	0.11
		N	4	4	4	4	4	4
	3	Mean	1.32 ¹	1.14	1.25	1.18	1.18	0.99 ⁿ¹⁴
		S.D.	0.14	0.14	0.05	0.15	0.04	.
		N	4	4	4	4	4	1
	4	Mean	1.23 ¹	1.06	1.16	1.08	1.07	0.94 ⁿ¹⁴
		S.D.	0.12	0.14	0.06	0.13	0.04	.
		N	4	4	4	4	4	1

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

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

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

4 [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 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
T-BA ($\mu\text{mol/L}$)	-1	Mean	2.0 ¹	2.6	2.4	1.8	0.8	1.5
		S.D.	1.3	2.4	1.2	1.4	0.5	1.3
		N	4	4	4	4	4	4
	1	Mean	1.9 ^{R2}	2.8	2.6	2.1	1.7	8.5
		S.D.	1.5	1.7	2.2	0.1	0.8	7.7
		N	4	4	4	4	4	4
	2	Mean	13.0 ^{L3}	10.8	12.3	14.8	4.2	6.3
		S.D.	18.8	8.4	9.9	21.3	2.6	2.1
		N	4	4	4	4	4	4
	3	Mean	2.2 ¹	2.6	6.1 ^{d4}	2.3	1.2	3.0 ⁿ¹⁵
		S.D.	0.9	1.5	3.7	1.3	0.9	.
		N	4	4	4	4	4	1
	4	Mean	12.7 ^{L3}	7.3	6.3	21.2	8.4	5.6 ⁿ¹⁵
		S.D.	20.8	8.2	4.4	32.8	10.7	.
		N	4	4	4	4	4	1

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

3 [L - Automatic Transformation Selected: Log]

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

2 [R - Automatic Transformation Selected: Rank]

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

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

Table 14 Clinical chemistry (females)

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
Week(s) Relative to Start Date								
CRP (mg/dL)	-1	Mean	0.08 I ¹	0.11	0.13	0.13	0.09	0.11
		S.D.	0.05	0.13	0.06	0.06	0.08	0.10
		N	4	4	4	4	4	4
	1	Mean	0.11 L ²	0.12	0.09	0.11	0.09	0.42
		S.D.	0.09	0.17	0.06	0.08	0.06	0.75
		N	4	4	4	4	4	4
	2	Mean	0.13 I ¹	0.13	0.11	0.18	0.10	0.16
		S.D.	0.07	0.15	0.07	0.09	0.06	0.23
		N	4	4	4	4	4	4
	3	Mean	0.14 I ¹	0.15	0.12	0.16	0.09	0.04 n1 ³
		S.D.	0.11	0.16	0.07	0.10	0.08	.
		N	4	4	4	4	4	1
	4	Mean	0.12 L ²	0.16	0.13	0.90	0.16	0.03 n1 ³
		S.D.	0.07	0.19	0.04	1.48	0.19	.
		N	4	4	4	4	4	1

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

2 [L - Automatic Transformation Selected: Log]

3 [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 15 Cytokine (males)

Group	Animal No.	Interleukin 6 (pg/mL)				
		Pre_1W	Week of dosing (prior to dosing)			
			1	2	3	4
Control 0.5%CMC-Na	RP1M01	3.036	<2	<2	<2	<2
	RP1M02	<2	<2	<2	<2	<2
	RP1M03	2.265	2.416	2.329	<2	<2
	RP1M04	<2	<2	2.221	<2	<2
	Mean	1.325 ¹	0.604 ¹	1.138 ²	0.000 ¹	0.000 ¹
	S.D.	1.562	1.208	1.314	0.000	0.000
	N	4	4	4	4	4
Low TM5509 2 mg/kg/day	RP2M01	2.681	<2	<2	<2	<2
	RP2M02	3.209	2.583	4.813	<2	<2
	RP2M03	2.128	<2	2.503	<2	<2
	RP2M04	2.223	2.555	4.856	<2	<2
	Mean	2.560	1.285	3.043	0.000	0.000
	S.D.	0.495	1.483	2.307	0.000	0.000
	N	4	4	4	4	4
Low-Mid TM5509 6 mg/kg/day	RP3M01	3.530	2.780	4.346	<2	3.145
	RP3M02	<2	3.544	<2	<2	<2
	RP3M03	2.388	2.223	<2	<2	<2
	RP3M04	<2	2.416	<2	<2	<2
	Mean	1.480	2.741	1.087	0.000	0.786
	S.D.	1.771	0.583	2.173	0.000	1.573
	N	4	4	4	4	4

General Footnote: Pre_1W: 1 week prior to the start of dosing

<2: Values less than the lower limit of quantification (2 pg/mL) and regarded as zero in the calculation of mean and S.D. values.

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

2 [L - Automatic Transformation Selected: Log]

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

Table 15 Cytokine (males)

Group	Animal No.	Interleukin 6 (pg/mL)				
		Pre_1W	Week of dosing (prior to dosing)			
			1	2	3	4
Mid TM5509 20 mg/kg/day	RP4M01	9.320	2.758	8.485	2.217	9.046
	RP4M02	5.198	4.765	6.214	<2	3.591
	RP4M03	4.980	3.162	8.081	6.286	9.973
	RP4M04	<2	<2	3.085	<2	2.285
	Mean	4.875	2.671	6.466	2.126	6.224 ^{dd1}
	S.D.	3.814	1.981	2.462	2.964	3.850
	N	4	4	4	4	4
Mid-High TM5509 80 mg/kg/day	RP5M01	4.825	<2	2.308	2.073	4.404
	RP5M02	<2	2.252	3.106	2.760	2.642
	RP5M03	3.427	<2	6.150	<2	2.734
	RP5M04	<2	<2	<2	<2	<2
	Mean	2.063	0.563	2.891	1.208	2.445
	S.D.	2.450	1.126	2.541	1.423	1.820
	N	4	4	4	4	4
High TM5509 300 mg/kg/day	RP6M01	<2	<2	<2	<2	2.112
	RP6M02	<2	6.103	45.609	. ^{a)}	.
	RP6M03	<2	4.902	11.500	<2	3.028
	RP6M04	<2	<2	2.676	<2	3.282
	Mean	0.000	2.751	14.946	0.000	2.807
	S.D.	0.000	3.214	21.024	0.000	0.615
	N	4	4	4	3	3

General Footnote: Pre_1W: 1 week prior to the start of dosing

<2: Values less than the lower limit of quantification (2 pg/mL) and regarded as zero in the calculation of mean and S.D. values.

^{a)} Died on Day 16 of dosing

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

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

Table 16 Cytokine (females)

Group	Animal No.	Interleukin 6 (pg/mL)				
		Pre_1W	Week of dosing (prior to dosing)			
			1	2	3	4
Control 0.5%CMC-Na	RP1F01	<2	<2	<2	<2	<2
	RP1F02	<2	<2	<2	<2	<2
	RP1F03	<2	<2	<2	<2	<2
	RP1F04	<2	<2	<2	<2	<2
	Mean	0.000 L ¹	0.000 L ¹	0.000 L ¹	0.000 L ¹	0.000 L ¹
	S.D.	0.000	0.000	0.000	0.000	0.000
	N	4	4	4	4	4
Low TM5509 2 mg/kg/day	RP2F01	2.550	<2	<2	2.537	<2
	RP2F02	<2	3.235	<2	10.502	<2
	RP2F03	<2	<2	<2	<2	<2
	RP2F04	22.400	16.533	8.856	8.269	4.341
	Mean	6.238	4.942	2.214	5.327	1.085
	S.D.	10.842	7.876	4.428	4.885	2.171
	N	4	4	4	4	4
Low-Mid TM5509 6 mg/kg/day	RP3F01	<2	5.111	2.044	4.527	<2
	RP3F02	3.192	<2	<2	<2	<2
	RP3F03	2.267	2.221	2.881	3.412	<2
	RP3F04	<2	2.068	<2	<2	<2
	Mean	1.365	2.350	1.231	1.985	0.000
	S.D.	1.620	2.101	1.462	2.337	0.000
	N	4	4	4	4	4

General Footnote: Pre_1W: 1 week prior to the start of dosing

<2: Values less than the lower limit of quantification (2 pg/mL) and regarded as zero in the calculation of mean and S.D. values.

1 [L - Automatic Transformation Selected: Log]

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

Table 16 Cytokine (females)

Group	Animal No.	Interleukin 6 (pg/mL)				
		Pre_1W	Week of dosing (prior to dosing)			
			1	2	3	4
Mid TM5509 20 mg/kg/day	RP4F01	4.005	3.922	<2	4.249	<2
	RP4F02	<2	<2	<2	2.673	<2
	RP4F03	<2	<2	<2	<2	<2
	RP4F04	<2	<2	<2	<2	<2
	Mean	1.001	0.981	0.000	1.731	0.000
	S.D.	2.003	1.961	0.000	2.099	0.000
	N	4	4	4	4	4
Mid-High TM5509 80 mg/kg/day	RP5F01	58.270	82.990	62.639	71.887	57.597
	RP5F02	<2	<2	<2	<2	<2
	RP5F03	<2	<2	<2	<2	<2
	RP5F04	3.042	3.434	<2	<2	<2
	Mean	15.328	21.606	15.660	17.972	14.399
	S.D.	28.664	40.955	31.320	35.944	28.799
	N	4	4	4	4	4
High TM5509 300 mg/kg/day	RP6F01	<2	3.321	<2	. ^{a)}	.
	RP6F02	<2	<2	<2	2.227	<2
	RP6F03	<2	9.881	<2	15.567 ^{b)}	.
	RP6F04	<2	6.143	27.162	29.073 ^{b)}	.
	Mean	0.000	4.836	6.791	2.227	0.000
	S.D.	0.000	4.197	13.581	.	.
	N	4	4	4	1	1

General Footnote: Pre_1W: 1 week prior to the start of dosing

<2: Values less than the lower limit of quantification (2 pg/mL) and regarded as zero in the calculation of mean and S.D. values.

^{a)} Died on Day 20 of dosing^{b)} Necropsied on Day 19 of dosing due to a moribund condition. Excluded from the statistical calculation since the data were obtained in the additional examination.

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

Table 17 Gross pathology (males)

Sex: Male Day(s): 29 Relative to Start Date/Dead

Organ and tissue	Findings	Group Animal No.	Control 0.5%CMC-Na				Low TM5509 2 mg/kg/day				Low-Mid TM5509 6 mg/kg/day			
			RP1M01	RP1M02	RP1M03	RP1M04	RP2M01	RP2M02	RP2M03	RP2M04	RP3M01	RP3M02	RP3M03	RP3M04
Thymus	Small		-	P	-	-	-	-	-	P	-	-	-	-
Stomach	Focus, dark reddish, mucosa, body, scattered, ø 1-2 mm		-	-	-	-	-	-	-	-	P	-	-	-
Small intestine	Abnormal contents, dark reddish		-	-	-	-	-	-	-	-	-	-	-	-
Large intestine	Abnormal contents, reddish brown		-	-	-	-	-	-	-	-	-	-	-	-
Rectum	Focus, dark reddish, mucosa, scattered, 1×1 to 5×2 mm		-	-	-	-	-	-	-	-	-	-	-	-
Liver	Nodule, light brownish, left lateral lobe, ø 5 mm		-	-	-	-	-	-	-	-	-	-	-	-
Gallbladder	Dilatation		-	-	-	-	-	-	-	-	-	-	-	-
	Increase, bile, 9 mL		-	-	-	-	-	-	-	-	-	-	-	-
	Increase, bile, 15 mL		-	-	-	-	-	-	-	-	-	-	-	-
	Increase, bile, dark reddish, 10 mL		-	-	-	-	-	-	-	-	-	-	-	-
	Retention, substance, dark reddish		-	-	-	-	-	-	-	-	-	-	-	-
Extrahepatic bile duct	Dilatation		-	-	-	-	-	-	-	-	-	-	-	-
Adrenal	Discoloration, dark brownish, bilateral		-	-	-	-	-	-	-	-	-	-	-	-
	Large, bilateral		-	-	-	-	-	-	-	-	-	-	-	-
Synovial membrane	Focus, dark reddish, knee joint, left, 5×2 mm		-	-	-	-	-	-	-	-	-	-	-	-
	Focus, dark reddish, scattered, knee joint, right, ø 1-2 mm		-	-	-	-	-	-	-	-	-	-	-	-

General Footnote: -: None/Negative P: Present

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

Table 17 Gross pathology (males)

Sex: Male Day(s): 29 Relative to Start Date/Dead

Organ and tissue	Findings	Group Animal No.	Mid TM5509 20 mg/kg/day				Mid-High TM5509 80 mg/kg/day				High TM5509 300 mg/kg/day			
			RP4M01	RP4M02	RP4M03	RP4M04	RP5M01	RP5M02	RP5M03	RP5M04	RP6M01	RP6M02 ^{a)}	RP6M03	RP6M04
Thymus	Small		-	-	P	-	-	P	P	-	P	P	P	
Stomach	Focus, dark reddish, mucosa, body, scattered, ø 1-2 mm		-	-	-	-	-	-	-	-	-	-	-	
Small intestine	Abnormal contents, dark reddish		-	-	-	-	-	-	-	-	-	-	-	
Large intestine	Abnormal contents, reddish brown		-	-	-	-	-	-	-	-	P	-	-	
Rectum	Focus, dark reddish, mucosa, scattered, 1×1 to 5×2 mm		-	-	-	-	-	-	-	-	-	-	-	
Liver	Nodule, light brownish, left lateral lobe, ø 5 mm		-	-	-	-	-	-	-	-	-	P	-	
Gallbladder	Dilatation		-	-	-	-	-	-	-	-	P	-	-	
	Increase, bile, 9 mL		-	-	-	-	-	-	-	-	-	-	-	
	Increase, bile, 15 mL		-	-	-	-	-	-	-	-	P	-	-	
	Increase, bile, dark reddish, 10 mL		-	-	-	-	-	-	-	-	-	-	-	
Extrahepatic bile duct	Retention, substance, dark reddish		-	-	-	-	-	-	-	-	-	-	-	
	Dilatation		-	-	-	-	-	-	-	-	P	P	-	
Adrenal	Discoloration, dark brownish, bilateral		-	-	-	-	-	-	-	-	P	-	-	
	Large, bilateral		-	-	-	-	-	-	-	-	P	-	-	
Synovial membrane	Focus, dark reddish, knee joint, left, 5×2 mm		-	-	-	-	-	-	-	-	-	-	-	
	Focus, dark reddish, scattered, knee joint, right, ø 1-2 mm		-	-	-	-	-	-	-	-	-	-	-	

General Footnote: -: None/Negative P: Present

^{a)} Died on Day 16 of dosing

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

Table 18 Gross pathology (females)

Sex: Female Day(s): 29 Relative to Start Date/Dead or moribund

Organ and tissue	Findings	Group Animal No.	Control 0.5%CMC-Na				Low TM5509 2 mg/kg/day				Low-Mid TM5509 6 mg/kg/day			
			RP1F01	RP1F02	RP1F03	RP1F04	RP2F01	RP2F02	RP2F03	RP2F04	RP3F01	RP3F02	RP3F03	RP3F04
Thymus	Small		-	-	P	-	P	-	-	-	-	-	P	-
Stomach	Focus, dark reddish, mucosa, body, scattered, ø 1-2 mm		-	-	-	-	-	-	-	-	-	-	-	-
Small intestine	Abnormal contents, dark reddish		-	-	-	-	-	-	-	-	-	-	-	-
Large intestine	Abnormal contents, reddish brown		-	-	-	-	-	-	-	-	-	-	-	-
Rectum	Focus, dark reddish, mucosa, scattered, 1×1 to 5×2 mm		-	-	-	-	-	-	-	-	-	-	-	-
Liver	Nodule, light brownish, left lateral lobe, ø 5 mm		-	-	-	-	-	-	-	-	-	-	-	-
Gallbladder	Dilatation		-	-	-	-	-	-	-	-	-	-	-	-
	Increase, bile, 9 mL		-	-	-	-	-	-	-	-	-	-	-	-
	Increase, bile, 15 mL		-	-	-	-	-	-	-	-	-	-	-	-
	Increase, bile, dark reddish, 10 mL		-	-	-	-	-	-	-	-	-	-	-	-
Extrahepatic bile duct	Retention, substance, dark reddish		-	-	-	-	-	-	-	-	-	-	-	-
	Dilatation		-	-	-	-	-	-	-	-	-	-	-	-
Adrenal	Discoloration, dark brownish, bilateral		-	-	-	-	-	-	-	-	-	-	-	-
	Large, bilateral		-	-	-	-	-	-	-	-	-	-	-	-
Ovary	Cyst, right, ø 5 mm		P	-	-	-	-	-	-	-	-	-	-	-
Synovial membrane	Focus, dark reddish, knee joint, left, 5×2 mm		-	-	-	-	-	-	-	-	-	-	-	-
	Focus, dark reddish, scattered, knee joint, right, ø 1-2 mm		-	-	-	-	-	-	-	-	-	-	-	-

General Footnote: -: None/Negative P: Present

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

Table 18 Gross pathology (females)

Sex: Female Day(s): 29 Relative to Start Date/Dead or moribund

Organ and tissue	Findings	Group Animal No.	Mid TM5509 20 mg/kg/day				Mid-High TM5509 80 mg/kg/day				High TM5509 300 mg/kg/day			
			RP4F01	RP4F02	RP4F03	RP4F04	RP5F01	RP5F02	RP5F03	RP5F04	RP6F01 ^{a)}	RP6F02	RP6F03 ^{b)}	RP6F04 ^{b)}
Thymus	Small		-	P	P	-	P	P	P	P	P	P	P	
Stomach	Focus, dark reddish, mucosa, body, scattered, ø 1-2 mm		-	-	-	-	-	-	-	-	-	-	-	
Small intestine	Abnormal contents, dark reddish		-	-	-	-	-	-	-	P	-	-	-	
Large intestine	Abnormal contents, reddish brown		-	-	-	-	-	-	-	P	-	-	-	
Rectum	Focus, dark reddish, mucosa, scattered, 1×1 to 5×2 mm		-	-	-	-	-	-	-	P	-	-	-	
Liver	Nodule, light brownish, left lateral lobe, ø 5 mm		-	-	-	-	-	-	-	-	-	-	-	
Gallbladder	Dilatation		-	-	-	-	-	-	-	P	-	P	-	
	Increase, bile, 9 mL		-	-	-	-	-	-	-	-	-	P	-	
	Increase, bile, 15 mL		-	-	-	-	-	-	-	-	-	-	-	
	Increase, bile, dark reddish, 10 mL		-	-	-	-	-	-	-	P	-	-	-	
Extrahepatic bile duct	Retention, substance, dark reddish		-	-	-	-	-	-	-	P	-	P	P	
	Dilatation		-	-	-	-	-	-	-	P	-	P	P	
Adrenal	Discoloration, dark brownish, bilateral		-	-	-	-	-	-	-	-	-	-	-	
	Large, bilateral		-	-	-	-	-	-	-	-	-	-	-	
Ovary	Cyst, right, ø 5 mm		-	-	-	-	-	-	-	-	-	-	-	
Synovial membrane	Focus, dark reddish, knee joint, left, 5×2 mm		-	-	-	-	-	-	-	-	-	-	P	
	Focus, dark reddish, scattered, knee joint, right, ø 1-2 mm		-	-	-	-	-	-	-	-	-	P	-	

General Footnote: - : None/Negative P: Present

^{a)} Died on Day 20 of dosing^{b)} Necropsied on Day 19 of dosing due to a moribund condition

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
Final Bodyweight (kg)	Mean	3.43 I ¹	3.26	3.41	3.36	3.20	2.90
	S.D.	0.31	0.36	0.42	0.47	0.44	0.27
	N	4	4	4	4	4	3
Brain (g)	Mean	64.2 I ¹	71.6	70.6	63.0	62.6	66.9
	S.D.	4.6	8.2	5.1	4.0	7.2	6.8
	N	4	4	4	4	4	3
Brain (%)	Mean	1.88 I ¹	2.21	2.08	1.91	1.99	2.31
	S.D.	0.11	0.26	0.18	0.31	0.38	0.21
	N	4	4	4	4	4	3
Pituitary (mg)	Mean	41 R ²	40	40	46	45	39
	S.D.	5	9	7	1	6	6
	N	4	4	4	4	4	3
Pituitary (mg%)	Mean	1.19 I ¹	1.22	1.17	1.40	1.41	1.35
	S.D.	0.04	0.15	0.11	0.21	0.16	0.09
	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
Thyroid Total (mg)	Mean	387 I ¹	373	400	491	359	305
	S.D.	116	133	97	164	24	111
	N	4	4	4	4	4	3
Thyroid Total (mg%)	Mean	11.17 I ¹	11.52	12.01	14.49	11.44	10.64
	S.D.	2.57	4.42	4.06	4.30	2.27	4.28
	N	4	4	4	4	4	3
Submandibul ar gland (g)	Mean	3.06 I ¹	2.70	2.38	2.35	3.61	2.70
	S.D.	0.48	0.80	0.63	0.36	0.95	0.37
	N	4	4	4	4	4	3
Submandibul ar gland (%)	Mean	0.0902 I ¹	0.0818	0.0710	0.0708	0.1112	0.0927
	S.D.	0.0180	0.0153	0.0224	0.0130	0.0176	0.0050
	N	4	4	4	4	4	3
Thymus (g)	Mean	1.866 I ¹	2.010	1.890	1.591	1.686	0.479
	S.D.	0.837	1.113	0.612	0.614	1.256	0.176
	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
Thymus (%)	Mean	0.0532 ¹	0.0616	0.0558	0.0489	0.0503	0.0163
	S.D.	0.0200	0.0356	0.0195	0.0243	0.0328	0.0051
	N	4	4	4	4	4	3
Lung Total (g)	Mean	14.45 ¹	14.58	14.06	13.71	17.28	12.67
	S.D.	1.78	1.70	2.76	2.01	4.11	0.76
	N	4	4	4	4	4	3
Lung Total (%)	Mean	0.421 ¹	0.448	0.410	0.412	0.535 ^{dd2}	0.437
	S.D.	0.026	0.034	0.029	0.063	0.065	0.015
	N	4	4	4	4	4	3
Heart (g)	Mean	12.21 ¹	10.92	11.52	11.57	10.05	9.03
	S.D.	3.05	2.31	1.13	0.99	1.52	0.94
	N	4	4	4	4	4	3
Heart (%)	Mean	0.353 ¹	0.333	0.339	0.347	0.314	0.311
	S.D.	0.058	0.044	0.028	0.021	0.028	0.009
	N	4	4	4	4	4	3

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

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