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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	ALP (U/L)					LD (U/L)				
	-1	1	2	3	4	-1	1	2	3	4
	RP6F01	662	513	512	450 E ¹	.	208	260	257	.
RP6F02	1289	1248	887	807	910	242	244	251	184	226
RP6F03	1474	1187	957	1041 E ¹	.	283	342	325	756 E ¹	.
RP6F04	657	596	455	3110 E ¹	.	226	249	241	414 E ¹	.
Mean	1021	886	703	807	910	240	274	269	184	226
S.D.	424	385	256	.	.	32	46	38	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	CK (U/L)					GGT (U/L)				
	CK (U/L)	CK (U/L)	CK (U/L)	CK (U/L)	CK (U/L)	GGT (U/L)	GGT (U/L)	GGT (U/L)	GGT (U/L)	GGT (U/L)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	98	143	151	.	.	59.4	53.1	48.6	49.2 E ¹	.
RP6F02	171	133	144	159	183	60.6	47.8	43.2	41.1	40.6
RP6F03	83	87	83	161 E ¹	.	56.4	45.4	38.8	116.3 E ¹	.
RP6F04	193	128	116	235 E ¹	.	44.9	34.9	33.1	201.7 E ¹	.
Mean	136	123	124	159	183	55.3	45.3	40.9	41.1	40.6
S.D.	54	25	31	.	.	7.2	7.6	6.6	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	GLDH (U/L)					LAP (U/L)				
	GLDH (U/L)	GLDH (U/L)	GLDH (U/L)	GLDH (U/L)	GLDH (U/L)	LAP (U/L)	LAP (U/L)	LAP (U/L)	LAP (U/L)	LAP (U/L)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	7	16	9	43 E ¹	.	32	50	42	114 E ¹	.
RP6F02	6	7	8	7	8	36	32	32	31	30
RP6F03	10	15	43	451 E ¹	.	52	54	73	291 E ¹	.
RP6F04	10	11	17	226 E ¹	.	43	38	68	1192 E ¹	.
Mean	8	12	19	7	8	41	44	54	31	30
S.D.	2	4	16	.	.	9	10	20	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	GLU (mg/dL)					BIL (mg/dL)				
	GLU (mg/dL)	GLU (mg/dL)	GLU (mg/dL)	GLU (mg/dL)	GLU (mg/dL)	BIL (mg/dL)	BIL (mg/dL)	BIL (mg/dL)	BIL (mg/dL)	BIL (mg/dL)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	89	84	124	32 E ¹	.	0.11	0.80	1.13	1.54 E ¹	.
RP6F02	81	78	73	71	75	0.33	1.34	0.57	0.48	0.34
RP6F03	93	83	91	78 E ¹	.	0.14	0.73	0.38	3.64 E ¹	.
RP6F04	79	71	74	80 E ¹	.	0.44	1.00	1.70	1.91 E ¹	.
Mean	86	79	91	71	75	0.26	0.97	0.95	0.48	0.34
S.D.	7	6	24	.	.	0.16	0.27	0.60	.	.
N	4	4	4	1	1	4	4	4	1	1

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	UN (mg/dL)					CRE (mg/dL)				
	UN (mg/dL)	UN (mg/dL)	UN (mg/dL)	UN (mg/dL)	UN (mg/dL)	CRE (mg/dL)	CRE (mg/dL)	CRE (mg/dL)	CRE (mg/dL)	CRE (mg/dL)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	16.9	21.8	25.0	85.5 E ¹	.	0.72	1.00	0.97	1.47 E ¹	.
RP6F02	17.2	20.4	21.7	20.7	18.3	0.65	0.80	0.78	0.81	0.79
RP6F03	16.0	22.7	28.1	53.8 E ¹	.	0.76	0.97	0.73	0.96 E ¹	.
RP6F04	13.9	16.6	31.2	33.7 E ¹	.	0.76	1.00	1.00	0.91 E ¹	.
Mean	16.0	20.4	26.5	20.7	18.3	0.72	0.94	0.87	0.81	0.79
S.D.	1.5	2.7	4.1	.	.	0.05	0.10	0.13	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	CHO (mg/dL)					TG (mg/dL)				
	CHO (mg/dL)	CHO (mg/dL)	CHO (mg/dL)	CHO (mg/dL)	CHO (mg/dL)	TG (mg/dL)	TG (mg/dL)	TG (mg/dL)	TG (mg/dL)	TG (mg/dL)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	158	134	149	43 E ¹	.	25	76	65	8 E ¹	.
RP6F02	131	117	81	87	87	22	52	46	47	58
RP6F03	186	192	139	138 E ¹	.	21	47	83	91 E ¹	.
RP6F04	143	135	125	142 E ¹	.	36	37	126	63 E ¹	.
Mean	155	145	124	87	87	26	53	80	47	58
S.D.	24	33	30	.	.	7	17	34	.	.
N	4	4	4	1	1	4	4	4	1	1

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	PL (mg/dL)					IP (mg/dL)				
	PL (mg/dL)	PL (mg/dL)	PL (mg/dL)	PL (mg/dL)	PL (mg/dL)	IP (mg/dL)	IP (mg/dL)	IP (mg/dL)	IP (mg/dL)	IP (mg/dL)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	182	169	175	.	.	4.09	4.28	4.62	.	.
RP6F02	179	169	138	146	141	4.86	4.60	3.02	3.42	3.47
RP6F03	215	184	148	179 E ¹	.	6.19	4.20	3.20	5.69 E ¹	.
RP6F04	181	171	163	253 E ¹	.	4.73	3.43	4.26	3.78 E ¹	.
Mean	189	173	156	146	141	4.97	4.13	3.78	3.42	3.47
S.D.	17	7	16	.	.	0.88	0.50	0.79	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	CA (mg/dL)					NA (mEq/L)				
	CA (mg/dL)	CA (mg/dL)	CA (mg/dL)	CA (mg/dL)	CA (mg/dL)	NA (mEq/L)	NA (mEq/L)	NA (mEq/L)	NA (mEq/L)	NA (mEq/L)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	9.35	9.37	9.34	.	.	151.0	148.3	145.9	.	.
RP6F02	9.63	9.46	9.38	9.38	9.36	150.4	148.8	148.3	148.3	149.1
RP6F03	10.10	9.98	9.34	8.54 E ¹	.	151.8	148.9	139.5	130.1 E ¹	.
RP6F04	9.48	9.75	9.36	9.33 E ¹	.	148.5	145.5	139.3	129.3 E ¹	.
Mean	9.64	9.64	9.36	9.38	9.36	150.4	147.9	143.3	148.3	149.1
S.D.	0.33	0.28	0.02	.	.	1.4	1.6	4.6	.	.
N	4	4	4	1	1	4	4	4	1	1

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	K (mEq/L)					CL (mEq/L)				
	K (mEq/L)	K (mEq/L)	K (mEq/L)	K (mEq/L)	K (mEq/L)	CL (mEq/L)	CL (mEq/L)	CL (mEq/L)	CL (mEq/L)	CL (mEq/L)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	4.05	3.85	3.64	.	.	114.5	102.6	102.0	.	.
RP6F02	3.35	3.73	4.27	3.78	4.10	108.0	104.9	110.8	111.1	108.6
RP6F03	4.23	3.85	4.21	2.45 E ¹	.	116.4	99.0	101.5	84.0 E ¹	.
RP6F04	3.61	3.63	3.38	3.16 E ¹	.	110.0	101.4	96.0	84.6 E ¹	.
Mean	3.81	3.77	3.88	3.78	4.10	112.2	102.0	102.6	111.1	108.6
S.D.	0.40	0.11	0.44	.	.	3.9	2.5	6.1	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	TP (g/dL)					ALB (g/dL)				
	TP (g/dL)	TP (g/dL)	TP (g/dL)	TP (g/dL)	TP (g/dL)	ALB (g/dL)	ALB (g/dL)	ALB (g/dL)	ALB (g/dL)	ALB (g/dL)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	7.86	7.51	7.30	4.28 E ¹	.	4.19	3.59	3.62	.	.
RP6F02	8.34	8.13	7.61	7.70	7.62	4.61	3.94	3.78	3.83	3.70
RP6F03	7.93	7.95	6.90	6.22 E ¹	.	4.26	3.83	3.32	2.68 E ¹	.
RP6F04	8.03	7.73	7.26	7.37 E ¹	.	4.31	3.60	3.11	2.47 E ¹	.
Mean	8.04	7.83	7.27	7.70	7.62	4.34	3.74	3.46	3.83	3.70
S.D.	0.21	0.27	0.29	.	.	0.18	0.17	0.30	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	A/G					T-BA ($\mu\text{mol/L}$)				
	A/G	A/G	A/G	A/G	A/G	T-BA ($\mu\text{mol/L}$)	T-BA ($\mu\text{mol/L}$)	T-BA ($\mu\text{mol/L}$)	T-BA ($\mu\text{mol/L}$)	T-BA ($\mu\text{mol/L}$)
	-1	1	2	3	4	-1	1	2	3	4
RP6F01	1.14	0.92	0.98	.	.	3.3	6.9	7.4	101.7 E ¹	.
RP6F02	1.24	0.94	0.99	0.99	0.94	0.5	4.6	6.7	3.0	5.6
RP6F03	1.16	0.93	0.93	0.76 E ¹	.	1.7	2.6	7.9	307.7 E ¹	.
RP6F04	1.16	0.87	0.75	0.50 E ¹	.	0.5	19.7	3.3	31.4 E ¹	.
Mean	1.17	0.91	0.91	0.99	0.94	1.5	8.5	6.3	3.0	5.6
S.D.	0.04	0.03	0.11	.	.	1.3	7.7	2.1	.	.
N	4	4	4	1	1	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

Sex: Female Week(s) Relative to Start Date

High TM5509 300 mg/kg/day	CRP (mg/dL)				
	CRP (mg/dL)	CRP (mg/dL)	CRP (mg/dL)	CRP (mg/dL)	CRP (mg/dL)
	-1	1	2	3	4
RP6F01	0.02	0.05	0.03	1.00 E ¹	.
RP6F02	0.06	0.03	0.03	0.04	0.03
RP6F03	0.11	0.07	0.08	0.07 E ¹	.
RP6F04	0.24	1.54	0.51	3.41 E ¹	.
Mean	0.11	0.42	0.16	0.04	0.03
S.D.	0.10	0.75	0.23	.	.
N	4	4	4	1	1

1 [E, Exclude]

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

Appendix 8 Clinical chemistry (females)

General Footnote: The T-BA value of 0.5 $\mu\text{mol/L}$ was half of the lower limit of quantification (1 $\mu\text{mol/L}$).

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

Appendix 9 Absolute and relative organ weights (males)

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

Control 0.5%CMC-Na	Final Bodyweight (kg)	Brain (g)	Brain (%)	Pituitary (mg)	Pituitary (mg%)	Thyroid Right (mg)	Thyroid Right (mg%)	Thyroid Left (mg)	Thyroid Left (mg%)	Thyroid Total (mg)	Thyroid Total (mg%)	Submandib ul ar gland (g)	Submandib ul ar gland (%)	Thymus (g)
RP1M01	3.56	61.5	1.73	44	1.24	182	5.11	156	4.38	338	9.49	2.37	0.0666	1.828
RP1M02	3.03	59.8	1.97	35	1.16	129	4.26	133	4.39	262	8.65	3.34	0.1102	0.882
RP1M03	3.35	65.6	1.96	39	1.16	184	5.49	228	6.81	412	12.30	3.12	0.0931	1.824
RP1M04	3.76	70.0	1.86	45	1.20	237	6.30	298	7.93	535	14.23	3.41	0.0907	2.930
Mean	3.43	64.2	1.88	41	1.19	387	11.17	3.06	0.0902	1.866
S.D.	0.31	4.6	0.11	5	0.04	116	2.57	0.48	0.0180	0.837
N	4	4	4	4	4	4	4	4	4	4

General Footnote: [Relative organ weights: Organ to final body weight ratios]

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

Appendix 9 Absolute and relative organ weights (males)

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

Control 0.5%CMC-Na	Thymus (%)	Lung Right (g)	Lung Right (%)	Lung Left (g)	Lung Left (%)	Lung Total (g)	Lung Total (%)	Heart (g)	Heart (%)	Liver (g)	Liver (%)	Spleen (g)	Spleen (%)	Pancreas (g)
	RP1M01	0.0513	8.71	0.245	7.22	0.203	15.93	0.447	12.40	0.348	61.7	1.73	3.466	0.097
RP1M02	0.0291	7.21	0.238	5.70	0.188	12.91	0.426	9.43	0.311	49.7	1.64	2.483	0.082	4.32
RP1M03	0.0544	7.07	0.211	5.83	0.174	12.90	0.385	10.61	0.317	65.3	1.95	2.511	0.075	6.07
RP1M04	0.0779	9.03	0.240	7.03	0.187	16.06	0.427	16.40	0.436	62.4	1.66	3.322	0.088	6.36
Mean	0.0532	14.45	0.421	12.21	0.353	59.8	1.75	2.946	0.086	5.45
S.D.	0.0200	1.78	0.026	3.05	0.058	6.9	0.14	0.521	0.010	0.94
N	4	4	4	4	4	4	4	4	4	4

General Footnote: [Relative organ weights: Organ to final body weight ratios]

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

Appendix 9 Absolute and relative organ weights (males)

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

Control 0.5%CMC-Na	Pancreas (%)	Adrenal Right (mg)	Adrenal Right (mg%)	Adrenal Left (mg)	Adrenal Left (mg%)	Adrenal Total (mg)	Adrenal Total (mg%)	Kidney Right (g)	Kidney Right (%)	Kidney Left (g)	Kidney Left (%)	Kidney Total (g)	Kidney Total (%)	Testis Right (g)
	RP1M01	0.142	180	5.06	222	6.24	402	11.29	5.87	0.165	5.81	0.163	11.68	0.328
RP1M02	0.143	184	6.07	251	8.28	435	14.36	5.21	0.172	5.16	0.170	10.37	0.342	0.65
RP1M03	0.181	147	4.39	231	6.90	378	11.28	5.97	0.178	6.25	0.187	12.22	0.365	0.83
RP1M04	0.169	245	6.52	326	8.67	571	15.19	6.04	0.161	6.18	0.164	12.22	0.325	2.57
Mean	0.159	447	13.03	11.62	0.340	.
S.D.	0.020	86	2.04	0.87	0.018	.
N	4	4	4	4	4	.

General Footnote: [Relative organ weights: Organ to final body weight ratios]

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

Appendix 9 Absolute and relative organ weights (males)

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

Control 0.5%CMC-Na	Testis	Testis	Testis	Testis	Testis	Epididymis	Epididymis	Epididymis	Epididymis	Epididymis	Epididymis	Prostate	Prostate	Seminal
	Right (%)	Left (g)	Left (%)	Total (g)	Total (%)	Right (g)	Right (%)	Left (g)	Left (%)	Total (g)	Total (%)	(g)	(%)	Vesicle (g)
RP1M01	0.0787	2.94	0.0826	5.74	0.1612	0.90	0.0253	0.91	0.0256	1.81	0.0508	0.93	0.0261	2.28
RP1M02	0.0215	0.59	0.0195	1.24	0.0409	0.39	0.0129	0.34	0.0112	0.73	0.0241	0.32	0.0106	0.81
RP1M03	0.0248	0.89	0.0266	1.72	0.0513	0.51	0.0152	0.52	0.0155	1.03	0.0307	0.35	0.0104	0.92
RP1M04	0.0684	2.43	0.0646	5.00	0.1330	0.73	0.0194	0.78	0.0207	1.51	0.0402	0.61	0.0162	2.55
Mean	.	.	.	3.43	0.0966	1.27	0.0365	0.55	0.0158	1.64
S.D.	.	.	.	2.27	0.0596	0.48	0.0116	0.28	0.0074	0.90
N	.	.	.	4	4	4	4	4	4	4

General Footnote: [Relative organ weights: Organ to final body weight ratios]

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

Appendix 9 Absolute and relative organ weights (males)

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

Control 0.5%CMC-Na	Seminal Vesicle (%)
RP1M01	0.0640
RP1M02	0.0267
RP1M03	0.0275
RP1M04	0.0678
Mean	0.0465
S.D.	0.0225
N	4

General Footnote: [Relative organ weights: Organ to final body weight ratios]

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

Appendix 9 Absolute and relative organ weights (males)

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

Low TM5509 2 mg/kg/day	Final Bodyweight (kg)	Brain (g)	Brain (%)	Pituitary (mg)	Pituitary (mg%)	Thyroid Right (mg)	Thyroid Right (mg%)	Thyroid Left (mg)	Thyroid Left (mg%)	Thyroid Total (mg)	Thyroid Total (mg%)	Submandib ul ar gland (g)	Submandib ul ar gland (%)	Thymus (g)
RP2M01	3.69	80.1	2.17	51	1.38	232	6.29	208	5.64	440	11.92	3.85	0.1043	2.744
RP2M02	2.94	62.6	2.13	35	1.19	130	4.42	109	3.71	239	8.13	2.11	0.0718	3.046
RP2M03	3.42	66.9	1.96	44	1.29	148	4.33	139	4.06	287	8.39	2.66	0.0778	1.641
RP2M04	2.98	76.6	2.57	31	1.04	241	8.09	284	9.53	525	17.62	2.18	0.0732	0.608
Mean	3.26	71.6	2.21	40	1.22	373	11.52	2.70	0.0818	2.010
S.D.	0.36	8.2	0.26	9	0.15	133	4.42	0.80	0.0153	1.113
N	4	4	4	4	4	4	4	4	4	4

General Footnote: [Relative organ weights: Organ to final body weight ratios]

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

Appendix 9 Absolute and relative organ weights (males)

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

Low TM5509 2 mg/kg/day	Thymus (%)	Lung Right (g)	Lung Right (%)	Lung Left (g)	Lung Left (%)	Lung Total (g)	Lung Total (%)	Heart (g)	Heart (%)	Liver (g)	Liver (%)	Spleen (g)	Spleen (%)	Pancreas (g)
	RP2M01	0.0744	9.51	0.258	7.44	0.202	16.95	0.459	12.16	0.330	71.6	1.94	4.916	0.133
RP2M02	0.1036	7.26	0.247	5.72	0.195	12.98	0.441	8.85	0.301	52.2	1.78	5.025	0.171	5.24
RP2M03	0.0480	7.79	0.228	6.08	0.178	13.87	0.406	13.55	0.396	63.3	1.85	5.250	0.154	5.07
RP2M04	0.0204	7.87	0.264	6.64	0.223	14.51	0.487	9.13	0.306	61.2	2.05	1.985	0.067	4.45
Mean	0.0616	14.58	0.448	10.92	0.333	62.1	1.91	4.294	0.131	4.84
S.D.	0.0356	1.70	0.034	2.31	0.044	8.0	0.12	1.546	0.046	0.38
N	4	4	4	4	4	4	4	4	4	4

General Footnote: [Relative organ weights: Organ to final body weight ratios]