

Appendix 1: Individual and Mean Concentration vs Time Data and Toxicokinetic Values

Plasma [REDACTED] - Day 1 0 mg/kg/day of [REDACTED], Oral Group 1						
Sex	Animal Number	Concentrations (µg/mL)				
		Hours After Dosing				
		1	2	4	8	24
Male	1001	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1002	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1003	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1004	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1005	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1006	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
Female	1501	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1502	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1503	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1504	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1505	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1606	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
<LLOQ = Less than the lower limit of quantification (0.00500 µg/mL).						

Plasma [REDACTED] - Week 13
0 mg/kg/day of [REDACTED] Oral
Group 1

Sex	Animal Number	Concentrations (µg/mL)				
		Hours After Dosing				
		1	2	4	8	24
Male	1001	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1002	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1003	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1004	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1005	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1006	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
Female	1501	<LLOQ	<LLOQ	0.00887	<LLOQ	<LLOQ
	1502	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1503	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1504	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1505	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1606	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
<LLOQ = Less than the lower limit of quantification (0.00500 µg/mL).						

Plasma [REDACTED] - Week 39
0 mg/kg/day of [REDACTED] Oral
Group 1

Sex	Animal Number	Concentrations (µg/mL)				
		Hours After Dosing				
		1	2	4	8	24
Male	1001	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1002	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1003	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1004	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1005	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1006	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
Female	1501	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1502	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1503	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1504	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1505	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	1606	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
<LLOQ = Less than the lower limit of quantification (0.00500 µg/mL).						

Plasma [REDACTED] - Day 1 1 mg/kg/day of [REDACTED] Oral Group 2									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	2001	0.612	0.703	0.716	0.499	0.521	13.0	0.716	4.0
	2002	0.966	1.19	1.14	0.854	1.37	25.7	1.37	24
	2003	0.627	0.680	0.683	0.585	0.331	12.2	0.683	4.0
	2004	0.724	1.46	1.39	1.04	1.39	28.6	1.46	2.0
	Mean	0.732	1.01	0.982	0.745	0.903	19.9	1.06	8.5
	SD	0.164	0.382	0.342	0.248	0.556	8.49	0.415	10
Female	2501	0.430	0.875	0.742	0.671	0.683	16.1	0.875	2.0
	2502	0.554	0.759	0.692	0.587	0.824	16.2	0.824	24
	2503	0.651	0.902	0.745	0.590	0.638	15.2	0.902	2.0
	2504	0.449	0.634	0.574	0.680	0.458	13.6	0.680	8.0
	Mean	0.521	0.792	0.688	0.632	0.651	15.3	0.820	9.0
	SD	0.102	0.123	0.0800	0.0504	0.151	1.20	0.0989	10

Plasma [REDACTED] - Day 1 3 mg/kg/day of [REDACTED] Oral Group 3									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	3001	1.07	1.50	1.62	1.31	2.54	41.6	2.54	24
	3002	0.745	1.49	2.32	2.13	1.31	41.7	2.32	4.0
	3003	0.847	1.82	1.72	1.47	1.23	33.3	1.82	2.0
	3004	0.605	1.51	1.40	1.86	2.81	48.1	2.81	24
	3005	1.23	2.03	2.18	1.67	1.18	36.9	2.18	4.0
	3006	0.821	1.26	1.43	1.86	1.93	41.0	1.93	24
	Mean	0.886	1.60	1.78	1.72	1.83	40.4	2.27	14
	SD	0.227	0.275	0.387	0.297	0.711	5.01	0.372	11
Female	3501	0.600	1.47	2.40	2.33	1.89	48.4	2.40	4.0
	3502	0.565	1.39	1.96	1.81	1.44	38.2	1.96	4.0
	3503	0.589	1.02	1.11	0.921	0.470	18.4	1.11	4.0
	3504	0.809	1.89	1.56	1.42	2.57	43.1	2.57	24
	3505	0.649	0.877	0.797	0.682	0.532	15.4	0.877	2.0
	3506	0.796	1.36	1.57	1.29	1.20	30.1	1.57	4.0
	Mean	0.668	1.33	1.57	1.41	1.35	32.3	1.75	7.0
	SD	0.108	0.357	0.574	0.598	0.807	13.4	0.685	8.4

Plasma [REDACTED] - Day 1 10 mg/kg/day of [REDACTED], Oral Group 4									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	4001	0.638	1.64	3.21	6.04	6.87	128	6.87	24
	4002	0.944	2.00	2.35	3.46	4.21	79.2	4.21	24
	4004	0.900	1.59	1.45	1.11	0.758	24.8	1.59	2.0
	4005	0.957	2.16	2.35	3.58	4.19	80.6	4.19	24
	4006	0.680	0.946	1.14	0.918	2.01	30.8	2.01	24
	4103	0.822	1.52	2.03	5.26	5.60	107	5.60	24
	Mean	0.824	1.64	2.09	3.39	3.94	75.1	4.08	20
	SD	0.137	0.424	0.736	2.09	2.25	40.9	2.03	9.0
Female	4501	0.744	3.35	8.24	11.1	10.1	222	11.1	8.0
	4502	0.958	3.03	5.32	4.42	6.86	121	6.86	24
	4503	1.56	1.88	2.04	1.84	2.42	48.3	2.42	24
	4504	0.933	3.40	5.52	10.0	10.1	204	10.1	24
	4506	0.956	1.68	2.53	2.49	1.92	51.4	2.53	4.0
	4605	0.598	1.05	1.23	1.26	1.85	33.2	1.85	24
	Mean	0.958	2.40	4.15	5.18	5.54	113	5.81	18
	SD	0.328	0.991	2.67	4.30	3.99	83.2	4.13	9.4

Plasma [REDACTED] - Week 13 1 mg/kg/day of [REDACTED] Oral Group 2									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	2001	2.36	3.05	3.02	2.26	1.41	50.6	3.05	2.0
	2002	3.25	3.91	3.63	2.98	3.10	76.1	3.91	2.0
	2003	3.74	3.93	4.26	3.75	3.91	93.1	4.26	4.0
	2004	2.97	3.44	3.16	2.47	1.79	57.5	3.44	2.0
	Mean	3.08	3.58	3.52	2.87	2.55	69.3	3.67	2.5
	SD	0.576	0.421	0.560	0.663	1.16	19.2	0.530	1.0
Female	2501	2.01	2.51	2.26	1.67	1.42	41.3	2.51	2.0
	2502	3.60	4.44	3.61	3.63	3.60	87.9	4.44	2.0
	2503	3.01	3.44	3.18	2.45	2.03	59.4	3.44	2.0
	2504	2.97	3.45	2.94	2.25	1.81	54.8	3.45	2.0
	Mean	2.90	3.46	3.00	2.50	2.21	60.9	3.46	2.0
	SD	0.658	0.788	0.564	0.823	0.957	19.6	0.788	0.0

Plasma [REDACTED] - Week 13 3 mg/kg/day of [REDACTED] Oral Group 3									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	3001	6.43	5.50	7.40	4.06	7.35	140	7.40	4.0
	3002	4.77	7.33	5.38	3.34	2.37	85.4	7.33	2.0
	3003	3.61	4.60	4.26	5.84	2.43	102	5.84	8.0
	3004	6.38	7.65	7.42	7.08	4.71	151	7.65	2.0
	3005	6.13	8.24	8.11	5.98	5.67	151	8.24	2.0
	3006	7.69	9.02	7.71	5.95	6.70	161	9.02	2.0
	Mean	5.83	7.06	6.71	5.38	4.87	132	7.58	3.3
	SD	1.43	1.68	1.53	1.39	2.12	30.7	1.06	2.4
Female	3501	9.54	11.5	11.7	10.8	8.03	238	11.7	4.0
	3502	10.0	12.8	12.1	9.58	9.83	245	12.8	2.0
	3503	3.65	4.84	4.24	3.16	1.91	71.5	4.84	2.0
	3504	5.96	5.84	5.77	5.41	4.68	126	5.96	1.0
	3505	8.35	7.71	7.23	6.68	5.60	156	8.35	1.0
	3506	3.54	3.72	3.62	4.74	5.72	116	5.72	0.0
	Mean	6.84	7.74	7.44	6.73	5.96	159	8.23	1.7
	SD	2.88	3.69	3.68	2.94	2.74	69.6	3.34	1.4

Plasma [REDACTED] - Week 13 10 mg/kg/day of [REDACTED], Oral Group 4									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	4001	19.1	21.6	19.9	18.7	17.0	443	21.6	2.0
	4002	17.3	21.4	30.0	27.2	19.8	580	30.0	4.0
	4004	11.6	12.5	12.0	10.4	7.94	238	12.5	2.0
	4005	13.7	15.8	17.8	15.2	11.6	341	17.8	4.0
	4006	14.6	16.3	20.5	19.2	12.0	395	20.5	4.0
	4103	14.0	16.6	17.8	15.5	12.1	350	17.8	4.0
	Mean	15.1	17.4	19.7	17.7	13.4	391	20.0	3.3
	SD	2.70	3.52	5.89	5.62	4.26	115	5.81	1.0
Female	4501	12.5	15.9	20.8	19.2	14.0	410	20.8	4.0
	4502	11.1	13.1	17.3	15.0	12.0	334	17.3	4.0
	4503	18.2	19.6	23.3	20.5	15.9	458	23.3	4.0
	4504	17.3	20.7	21.5	22.4	17.8	488	22.4	8.0
	4506	16.1	16.8	15.6	13.0	10.3	305	16.8	2.0
	4605	19.0	19.5	19.2	16.0	12.6	373	19.5	2.0
	Mean	15.7	17.6	19.6	17.7	13.8	395	20.0	4.0
	SD	3.20	2.86	2.84	3.59	2.73	70.9	2.65	2.2

Plasma [REDACTED] - Week 39 1 mg/kg/day of [REDACTED] Oral Group 2									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	2001	2.16	2.59	2.35	1.87	1.24	42.3	2.59	2.0
	2002	2.87	2.86	2.60	2.05	1.98	52.3	2.87	1.0
	2003	2.87	3.10	3.13	2.97	3.22	73.9	3.22	0.0
	2004	3.04	3.49	3.08	2.88	2.32	66.1	3.49	2.0
	Mean	2.73	3.01	2.79	2.44	2.19	58.6	3.04	1.2
	SD	0.392	0.382	0.378	0.563	0.821	14.1	0.394	0.96
Female	2501	2.47	3.25	2.77	2.39	2.01	56.6	3.25	2.0
	2502	3.19	3.63	3.12	2.47	1.71	57.2	3.63	2.0
	2503	4.42	5.16	4.27	3.24	2.75	80.7	5.16	2.0
	2504	4.04	4.77	4.77	4.21	2.65	90.1	4.77	2.0
	Mean	3.53	4.20	3.73	3.08	2.28	71.2	4.20	2.0
	SD	0.874	0.908	0.943	0.847	0.502	16.9	0.908	0.0

Plasma [REDACTED] - Week 39 3 mg/kg/day of [REDACTED], Oral Group 3									
Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	3001	6.09	7.60	7.05	6.45	6.11	155	7.60	2.0
	3002	4.68	5.09	4.55	3.43	2.13	78.4	5.09	2.0
	3003	3.51	4.60	4.47	4.00	2.95	88.9	4.60	2.0
	3004	8.61	8.43	8.26	7.05	6.41	171	8.61	1.0
	3005	7.37	7.70	7.38	5.33	3.92	128	7.70	2.0
	3006	8.67	7.73	7.84	6.38	5.57	155	8.67	1.0
	Mean	6.49	6.86	6.59	5.44	4.51	129	7.04	1.7
	SD	2.11	1.59	1.66	1.46	1.77	38.2	1.77	0.52
Female	3501	9.29	11.4	10.6	9.40	8.46	224	11.4	2.0
	3502	7.53	9.37	8.42	6.93	7.16	177	9.37	2.0
	3503	2.96	5.07	4.63	3.17	2.48	77.2	5.07	2.0
	3504	5.52	5.95	5.29	5.66	4.98	129	5.95	2.0
	3505	4.94	5.19	4.20	4.14	4.51	105	5.19	2.0
	3506	6.32	6.67	6.15	4.92	5.05	127	6.67	2.0
	Mean	6.09	7.28	6.55	5.70	5.44	140	7.28	2.0
	SD	2.18	2.56	2.48	2.22	2.10	52.7	2.56	0.0

Plasma [REDACTED] - Week 39
 10 mg/kg/day of [REDACTED], Oral
 Group 4

Sex	Animal Number	Concentrations (µg/mL)					AUC(0-24h) (µg·h/mL)	Cmax (µg/mL)	Tmax (h)
		Hours After Dosing							
		1	2	4	8	24			
Male	4001	23.7	24.9	23.4	20.2	16.1	470	24.9	2.0
	4002	23.7	25.0	24.7	24.1	18.9	538	25.0	2.0
	4004	17.5	15.6	19.6	20.8	14.8	433	20.8	8.0
	4005	14.3	17.9	18.5	13.5	10.7	323	18.5	4.0
	4006	11.0	12.3	13.6	10.6	7.72	242	13.6	4.0
	4103	14.4	17.8	18.6	14.1	11.0	332	18.6	4.0
	Mean	17.4	18.9	19.7	17.2	13.2	390	20.2	4.0
	SD	5.27	5.10	3.96	5.22	4.11	109	4.35	2.2
Female	4501	8.49	10.0	12.6	12.1	9.14	260	12.6	4.0
	4502	18.8	19.9	21.1	19.0	13.1	414	21.1	4.0
	4503	10.1	13.9	16.2	19.7	14.5	400	19.7	8.0
	4504	14.2	15.1	15.4	12.0	8.34	274	15.4	4.0
	4506	14.8	17.0	12.3	16.2	12.1	341	17.0	2.0
	4605	14.9	16.5	14.1	17.5	9.70	339	17.5	8.0
	Mean	13.5	15.4	15.3	16.1	11.1	338	17.2	5.0
	SD	3.71	3.33	3.23	3.35	2.45	62.9	3.03	2.4