FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6A - Clinical chemistry - Before treatment [1] - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	Cl^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Ca^{++} mmol/l
2350001	1	-13	95.7	142.60	4.60	2.47
2350003	1	-13	95.2	143.20	4.71	2.63
2350005	1	-13	95.1	141.90	4.81	2.73
2350007	1	-13	95.3	142.80	5.13	2.70
		Mean:	95.33	142.625	4.813	2.633
		SD:	0.22	0.545	0.228	0.116
2350009	2	-13	98.3	141.40	4.28	2.62
2350011	2	-13	97.7	143.10	4.22	2.64
2350013	2	-13	104.4	143.50	4.73	2.68
2350015	2	-13	91.4	141.70	3.82	2.73
		Mean:	97.98	142.425	4.263	2.668
		SD:	5.33	1.031	0.373	0.049
2350017	3	-13	92.0	139.60	5.00	2.75
2350019	3	-13	98.9	142.00	4.43	2.81
2350021	3	-13	96.0	140.10	4.20	2.63
2350023	3	-13	98.6	142.80	4.22	2.68
		Mean:	96.38	141.125	4.463	2.718
		SD:	3.21	1.522	0.373	0.079
2350025	4	-13	92.7	142.20	4.49	2.71
2350027	4	-13	95.9	140.40	4.43	2.67
2350029	4	-13	99.3	143.80	4.78	2.79
2350031	4	-13	96.7	142.40	5.73	2.73
		Mean:	96.14	142.200	4.858	2.725
		SD:	2.76	1.394	0.601	0.050

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Roma Toxicology Centre S.p.A
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6B - Clinical chemistry - Before treatment [2] - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	AP U/l	ALT U/l	AST U/l	UREA mg/dl	GLU mg/dl	BILT mg/dl	CHOL mg/dl	CREA mg/dl
2350002	1	-5	175.0	22.0	9.1	25.8	96.4	0.110	166.6	0.63
2350004	1	-5	208.0	19.7	8.0	24.6	96.3	0.080	213.0	0.62
2350006	1	-5	172.9	12.9	10.0	21.0	90.3	0.070	174.0	0.53
2350008	1	-5	235.5	13.9	7.7	17.3	91.3	0.090	173.8	0.61
		Mean:	197.84	17.11	8.72	22.16	93.56	0.0875	181.85	0.598
		SD:	29.83	4.41	1.05	3.86	3.22	0.0171	21.03	0.046
2350010	2	-5	175.0	14.1	6.4	19.5	88.1	0.070	161.4	0.60
2350012	2	-5	176.1	19.5	9.3	18.7	103.7	0.100	169.6	0.59
2350014	2	-5	260.1	16.6	10.0	26.8	98.0	0.090	165.6	0.67
2350016	2	-5	172.9	11.5	9.1	25.4	101.1	0.100	151.5	0.61
		Mean:	195.99	15.43	8.70	22.60	97.72	0.0900	162.02	0.618
		SD:	42.74	3.42	1.59	4.06	6.85	0.0141	7.78	0.036
2350018	3	-5	238.0	15.2	9.4	20.0	101.1	0.100	132.6	0.64
2350020	3	-5	269.0	15.5	15.6	22.5	92.6	0.040	189.0	0.58
2350022	3	-5	201.8	18.9	16.7	31.1	91.4	0.130	155.9	0.71
2350024	3	-5	253.9	13.4	6.2	21.0	101.2	0.090	222.8	0.69
		Mean:	240.67	15.75	11.99	23.61	96.58	0.0900	175.09	0.655
		SD:	28.86	2.27	5.01	5.07	5.33	0.0374	39.32	0.058
2350026	4	-5	151.7	14.1	11.3	26.0	88.8	0.080	174.3	0.70
2350028	4	-5	205.9	13.3	10.1	27.5	105.2	0.080	165.2	0.66
2350030	4	-5	352.4	24.3	10.7	25.1	83.2	0.090	162.1	0.60
2350032	4	-5	457.8	23.5	9.5	23.0	102.8	0.110	142.8	0.62
		Mean:	291.96	18.79	10.43	25.41	95.01	0.0900	161.10	0.645
		SD:	139.32	5.89	0.77	1.87	10.66	0.0141	13.25	0.044

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Roma Toxicology Centre S.p.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6B - Clinical chemistry - Before treatment [2] - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	PROT g/dl	ALB %	A1G %	A2G %	BETA %	GAM %	AGR
2350002	1	-5	5.6	60.2	4.7	7.4	9.5	18.1	1.51
2350004	1	-5	5.8	61.7	4.5	6.9	9.5	17.3	1.61
2350006	1	-5	5.5	63.7	5.0	6.7	9.4	15.2	1.76
2350008	1	-5	5.5	64.5	4.4	7.8	9.4	13.9	1.82
		Mean:	5.61	62.53	4.65	7.20	9.45	16.13	1.675
		SD:	0.14	1.95	0.26	0.50	0.06	1.92	0.141
2350010	2	-5	5.1	61.0	4.8	7.9	9.6	16.8	1.56
2350012	2	-5	5.5	65.1	4.1	6.2	13.3	11.3	1.86
2350014	2	-5	5.9	60.4	4.5	6.4	13.5	15.2	1.53
2350016	2	-5	5.6	58.9	4.5	6.6	14.9	15.1	1.43
		Mean:	5.54	61.35	4.48	6.78	12.83	14.60	1.595
		SD:	0.31	2.65	0.29	0.77	2.26	2.33	0.185
2350018	3	-5	5.2	57.3	4.8	7.2	11.5	19.2	1.34
2350020	3	-5	5.6	60.8	4.8	9.1	9.7	15.5	1.55
2350022	3	-5	5.5	65.7	3.9	6.3	8.5	15.7	1.91
2350024	3	-5	6.4	57.5	4.5	7.6	11.5	18.8	1.36
		Mean:	5.67	60.33	4.50	7.55	10.30	17.30	1.540
		SD:	0.50	3.93	0.42	1.17	1.47	1.97	0.264
2350026	4	-5	5.7	63.9	4.1	7.4	8.8	15.8	1.77
2350028	4	-5	5.2	63.9	4.6	8.0	8.3	15.2	1.77
2350030	4	-5	5.6	62.8	4.4	7.6	9.3	15.8	1.69
2350032	4	-5	5.6	62.0	4.3	7.4	10.3	16.1	1.63
		Mean:	5.54	63.15	4.35	7.60	9.18	15.73	1.715
		SD:	0.23	0.93	0.21	0.28	0.85	0.38	0.068

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Rome Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6B - Clinical chemistry - Before treatment [2] - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	Cl^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Ca^{++} mmol/l
2350002	1	-5	97.0	143.90	5.22	2.86
2350004	1	-5	94.5	145.90	5.63	3.02
2350006	1	-5	102.4	146.90	5.24	2.86
2350008	1	-5	101.7	145.20	5.02	2.82
		Mean:	98.87	145.475	5.278	2.890
		SD:	3.78	1.262	0.255	0.089
2350010	2	-5	95.5	144.10	5.64	2.81
2350012	2	-5	101.2	146.70	5.30	2.91
2350014	2	-5	100.0	145.10	5.26	2.98
2350016	2	-5	101.6	145.20	5.52	2.91
		Mean:	99.58	145.275	5.430	2.903
		SD:	2.78	1.072	0.181	0.070
2350018	3	-5	98.2	144.20	5.16	2.74
2350020	3	-5	100.4	146.70	6.48	2.92
2350022	3	-5	102.4	148.60	4.48	2.80
2350024	3	-5	97.5	145.10	5.47	2.92
		Mean:	99.64	146.150	5.398	2.845
		SD:	2.24	1.932	0.832	0.090
2350026	4	-5	97.6	146.20	5.54	2.88
2350028	4	-5	98.6	144.90	5.31	2.96
2350030	4	-5	101.4	147.20	5.47	2.90
2350032	4	-5	97.3	146.30	4.70	2.86
		Mean:	98.72	146.150	5.255	2.900
		SD:	1.88	0.946	0.382	0.043

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6B - Clinical chemistry - Before treatment [2] - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	AP U/l	ALT U/l	AST U/l	UREA mg/dl	GLU mg/dl	BILT mg/dl	CHOL mg/dl	CREA mg/dl
2350001	1	-5	194.0	18.3	8.7	15.8	94.7	0.100	201.8	0.58
2350003	1	-5	227.6	14.3	9.4	42.5	90.8	0.070	184.9	0.68
2350005	1	-5	202.4	20.1	7.8	15.6	99.8	0.110	175.5	0.57
2350007	1	-5	144.0	13.8	9.5	17.8	97.0	0.100	146.9	0.57
		Mean:	192.02	16.62	8.85	22.91	95.56	0.0950	177.24	0.600
		SD:	35.04	3.07	0.78	13.07	3.84	0.0173	22.99	0.054
2350009	2	-5	161.1	16.0	9.1	21.8	95.0	0.090	134.2	0.62
2350011	2	-5	170.7	17.0	7.5	21.6	95.2	0.090	139.1	0.58
2350013	2	-5	191.6	11.5	10.7	24.5	103.9	0.100	156.6	0.61
2350015	2	-5	233.7	14.6	10.5	18.7	98.6	0.110	147.8	0.60
		Mean:	189.25	14.77	9.47	21.64	98.16	0.0975	144.45	0.603
		SD:	32.25	2.42	1.52	2.36	4.18	0.0096	9.88	0.017
2350017	3	-5	327.0	17.0	11.2	24.4	91.1	0.130	167.7	0.55
2350019	3	-5	194.1	15.1	7.9	27.5	101.4	0.090	145.0	0.75
2350021	3	-5	179.7	18.1	8.2	26.5	97.1	0.090	135.6	0.60
2350023	3	-5	111.2	14.2	10.2	27.1	95.0	0.110	150.0	0.66
		Mean:	203.01	16.11	9.38	26.39	96.13	0.1050	149.57	0.640
		SD:	90.25	1.79	1.57	1.40	4.28	0.0191	13.46	0.086
2350025	4	-5	174.7	16.7	10.8	23.9	91.9	0.110	157.3	0.60
2350027	4	-5	172.3	12.7	7.5	21.3	93.4	0.130	137.3	0.76
2350029	4	-5	204.0	17.8	12.1	25.4	99.5	0.130	157.9	0.67
2350031	4	-5	138.5	16.1	10.9	22.4	94.7	0.120	138.5	0.61
		Mean:	172.40	15.81	10.32	23.24	94.86	0.1225	147.74	0.660
		SD:	26.79	2.21	1.99	1.76	3.31	0.0096	11.40	0.073

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6B - Clinical chemistry - Before treatment [2] - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	PROT g/dl	ALB %	A1G %	A2G %	BETA %	GAM %	AGR
2350001	1	-5	5.5	64.9	4.0	7.0	9.7	14.4	1.85
2350003	1	-5	5.6	64.0	4.5	6.4	8.4	16.8	1.78
2350005	1	-5	5.6	62.7	5.0	5.5	10.5	16.4	1.68
2350007	1	-5	5.5	66.5	4.4	5.3	8.8	15.0	1.99
		Mean:	5.56	64.53	4.47	6.05	9.35	15.65	1.825
		SD:	0.07	1.60	0.41	0.79	0.94	1.14	0.130
2350009	2	-5	5.6	63.2	4.5	5.8	8.3	18.1	1.72
2350011	2	-5	5.5	64.0	4.8	6.0	8.4	16.8	1.78
2350013	2	-5	5.1	64.4	4.8	6.5	11.6	12.7	1.81
2350015	2	-5	5.4	64.6	4.5	5.4	8.9	16.6	1.83
		Mean:	5.43	64.05	4.65	5.93	9.30	16.05	1.785
		SD:	0.23	0.62	0.17	0.46	1.56	2.33	0.048
2350017	3	-5	5.5	64.5	4.7	6.1	8.9	15.8	1.82
2350019	3	-5	5.9	60.8	4.3	6.4	10.1	18.3	1.55
2350021	3	-5	5.4	61.2	4.4	6.0	10.2	18.2	1.58
2350023	3	-5	5.6	66.7	3.8	5.7	8.0	15.8	2.00
		Mean:	5.62	63.30	4.30	6.05	9.30	17.02	1.738
		SD:	0.23	2.81	0.37	0.29	1.05	1.42	0.213
2350025	4	-5	5.8	61.6	4.7	6.4	8.9	18.3	1.60
2350027	4	-5	5.8	61.2	4.4	5.1	8.9	20.3	1.58
2350029	4	-5	6.0	65.2	4.2	6.8	8.0	15.9	1.87
2350031	4	-5	5.3	66.2	4.5	5.6	8.1	15.7	1.95
		Mean:	5.71	63.55	4.45	5.98	8.48	17.55	1.750
		SD:	0.31	2.52	0.21	0.77	0.49	2.18	0.188

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6B - Clinical chemistry - Before treatment [2] - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	Cl^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Ca^{++} mmol/l
2350001	1	-5	95.9	145.40	4.97	2.89
2350003	1	-5	97.2	145.60	4.99	2.86
2350005	1	-5	97.0	144.40	4.95	2.95
2350007	1	-5	97.1	145.90	5.10	2.90
		Mean:	96.80	145.325	5.003	2.900
		SD:	0.62	0.650	0.067	0.037
2350009	2	-5	101.5	143.90	4.72	2.79
2350011	2	-5	105.0	145.20	4.50	2.63
2350013	2	-5	99.1	144.00	5.05	2.70
2350015	2	-5	102.4	144.70	4.01	2.74
		Mean:	102.00	144.450	4.570	2.715
		SD:	2.42	0.617	0.436	0.068
2350017	3	-5	97.3	142.70	4.41	2.90
2350019	3	-5	101.0	144.60	4.50	2.84
2350021	3	-5	102.0	142.60	4.68	2.70
2350023	3	-5	99.8	144.70	4.53	2.75
		Mean:	100.03	143.650	4.530	2.798
		SD:	2.02	1.156	0.112	0.090
2350025	4	-5	99.8	144.20	4.38	2.68
2350027	4	-5	101.5	145.80	4.51	2.81
2350029	4	-5	100.4	145.30	5.13	2.95
2350031	4	-5	98.0	144.40	5.11	2.85
		Mean:	99.93	144.925	4.783	2.823
		SD:	1.45	0.755	0.393	0.112

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Roma Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6C - Clinical chemistry - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	AP U/l	ALT U/l	AST U/l	UREA mg/dl	GLU mg/dl	BILT mg/dl	CHOL mg/dl	CREA mg/dl
2350002	1	42	138.5	27.1	10.6	27.4	104.4	0.100	154.4	0.81
2350004	1	42	173.9	19.7	10.2	29.4	90.8	0.090	178.3	0.73
2350006	1	42	156.1	18.3	12.4	26.2	104.3	0.080	151.4	0.64
2350008	1	42	209.6	14.3	11.1	22.6	91.0	0.070	140.4	0.71
		Mean:	169.54	19.84	11.07	26.39	97.64	0.0850	156.14	0.723
		SD:	30.37	5.34	0.97	2.87	7.77	0.0129	15.96	0.070
2350010	2	42	144.9	20.3	9.8	22.9	101.6	0.080	153.1	0.88
2350012	2	42	140.4	21.3	13.1	28.7	103.8	0.090	153.4	0.81
2350014	2	42	235.8	19.2	13.3	25.9	99.7	0.090	176.4	0.87
2350016	2	42	165.0	23.8	11.6	26.7	98.3	0.080	125.9	0.74
		Mean:	171.51	21.15	11.92	26.03	100.87	0.0850	152.20	0.825
		SD:	44.14	1.96	1.62	2.44	2.39	0.0058	20.66	0.065
2350018	3	42	181.8	20.5	12.3	27.7	92.6	0.080	147.0	0.77
2350020	3	42	221.3	35.8	24.9	27.4	93.8	0.030	169.2	0.76
2350022	3	42	176.9	19.1	13.0	28.5	96.8	0.100	169.0	0.85
2350024	3	42	218.4	26.5	10.5	28.0	93.5	0.070	196.8	0.93
		Mean:	199.58	25.49	15.18	27.88	94.16	0.0700	170.49	0.828
		SD:	23.49	7.62	6.58	0.46	1.81	0.0294	20.40	0.079
2350026	4	42	126.3	14.4	10.9	29.5	97.7	0.100	162.7	0.89
2350028	4	42	198.9	18.8	12.4	33.3	106.7	0.070	169.3	0.89
2350030	4	42	355.3	31.1	13.3	27.2	88.1	0.100	155.1	0.81
2350032	4	42	371.1	36.8	14.7	47.5	94.4	0.110	141.4	1.10
		Mean:	262.89	25.27	12.83	34.40	96.71	0.0950	157.10	0.923
		SD:	119.73	10.44	1.60	9.11	7.77	0.0173	11.97	0.124

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6C - Clinical chemistry - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	PROT g/dl	ALB %	A1G %	A2G %	BETA %	GAM %	AGR
2350002	1	42	5.7	66.1	4.3	6.3	8.0	15.3	1.95
2350004	1	42	5.9	67.1	3.7	6.1	8.0	15.1	2.04
2350006	1	42	5.8	68.3	3.9	5.6	8.0	14.3	2.15
2350008	1	42	5.5	66.1	4.4	6.8	9.3	13.4	1.95
		Mean:	5.72	66.90	4.08	6.20	8.32	14.53	2.023
		SD:	0.18	1.05	0.33	0.50	0.65	0.87	0.095
2350010	2	42	5.3	64.7	4.4	6.9	8.6	15.5	1.83
2350012	2	42	5.6	66.9	4.0	5.9	11.5	11.7	2.03
2350014	2	42	6.3	64.9	4.1	6.1	11.4	13.5	1.85
2350016	2	42	5.7	63.4	4.5	6.3	12.3	13.4	1.74
		Mean:	5.74	64.98	4.25	6.30	10.95	13.53	1.863
		SD:	0.39	1.45	0.24	0.43	1.62	1.55	0.121
2350018	3	42	5.7	61.2	4.7	6.8	11.0	16.4	1.58
2350020	3	42	6.1	65.4	4.7	8.0	7.9	14.0	1.89
2350022	3	42	5.7	67.8	4.4	5.1	8.0	14.8	2.10
2350024	3	42	6.7	60.0	4.6	5.8	11.0	18.6	1.50
		Mean:	6.05	63.60	4.60	6.43	9.48	15.95	1.768
		SD:	0.49	3.63	0.14	1.26	1.76	2.03	0.278
2350026	4	42	6.2	64.9	4.3	7.6	8.4	14.8	1.85
2350028	4	42	5.8	68.3	3.8	7.5	6.9	13.5	2.16
2350030	4	42	5.8	68.4	3.9	5.9	6.9	15.0	2.16
2350032	4	42	5.9	65.0	4.2	7.2	8.7	14.8	1.86
		Mean:	5.91	66.65	4.05	7.05	7.73	14.53	2.008
		SD:	0.17	1.96	0.24	0.79	0.96	0.69	0.176

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6C - Clinical chemistry - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	Cl^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Ca^{++} mmol/l
2350002	1	42	104.4	144.40	5.27	2.70
2350004	1	42	105.5	148.10	4.76	2.84
2350006	1	42	110.9	146.90	4.53	2.70
2350008	1	42	108.0	145.10	4.95	2.60
		Mean:	107.21	146.125	4.878	2.710
		SD:	2.92	1.686	0.313	0.099
2350010	2	42	105.1	146.50	5.08	2.68
2350012	2	42	106.4	146.40	4.80	2.70
2350014	2	42	110.6	144.30	5.16	2.73
2350016	2	42	104.5	145.60	4.86	2.68
		Mean:	106.64	145.700	4.975	2.698
		SD:	2.75	1.014	0.172	0.024
2350018	3	42	103.3	146.70	5.01	2.64
2350020	3	42	112.9	148.70	5.88	2.79
2350022	3	42	103.3	143.30	4.32	2.51
2350024	3	42	101.0	145.70	5.07	2.73
		Mean:	105.17	146.100	5.070	2.668
		SD:	5.30	2.245	0.638	0.122
2350026	4	42	105.3	146.40	4.95	2.62
2350028	4	42	102.1	146.10	4.76	2.74
2350030	4	42	98.8	148.20	5.00	2.68
2350032	4	42	107.1	148.10	4.68	2.68
		Mean:	103.33	147.200	4.847	2.680
		SD:	3.67	1.103	0.152	0.049

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
(Dr Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6C - Clinical chemistry - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	AP U/l	ALT U/l	AST U/l	UREA mg/dl	GLU mg/dl	BILT mg/dl	CHOL mg/dl	CREA mg/dl
2350001	1	42	164.7	22.4	9.4	29.1	90.9	0.120	219.7	0.83
2350003	1	42	177.9	15.3	8.2	34.5	96.8	0.090	207.3	0.86
2350005	1	42	191.7	28.5	12.3	24.2	95.8	0.070	185.1	0.68
2350007	1	42	113.3	13.1	9.7	24.2	90.8	0.120	139.1	0.79
		Mean:	161.90	19.81	9.91	28.01	93.56	0.1000	187.79	0.790
		SD:	34.23	7.01	1.71	4.93	3.18	0.0245	35.50	0.079
2350009	2	42	132.8	17.3	12.6	32.5	90.1	0.110	126.1	0.74
2350011	2	42	159.1	17.5	10.0	23.9	87.2	0.100	116.6	0.74
2350013	2	42	191.3	22.1	15.1	36.3	103.9	0.080	131.9	0.67
2350015	2	42	221.1	15.8	11.9	24.5	93.7	0.090	157.9	0.69
		Mean:	176.07	18.20	12.41	29.32	93.71	0.0950	133.12	0.710
		SD:	38.39	2.72	2.13	6.13	7.28	0.0129	17.69	0.036
2350017	3	42	240.3	26.0	15.8	30.2	90.6	0.080	157.0	0.74
2350019	3	42	185.6	17.4	12.2	44.1	90.8	0.100	134.6	0.99
2350021	3	42	182.5	19.7	13.7	35.7	98.6	0.080	136.4	0.73
2350023	3	42	93.0	17.0	14.0	37.0	95.5	0.090	136.3	0.78
		Mean:	175.36	20.00	13.94	36.76	93.86	0.0875	141.08	0.810
		SD:	60.97	4.20	1.48	5.72	3.86	0.0096	10.65	0.122
2350025	4	42	145.0	21.3	13.1	24.6	89.2	0.130	153.9	0.77
2350027	4	42	163.5	16.5	11.4	33.3	87.1	0.130	131.6	0.91
2350029	4	42	179.7	16.6	12.6	35.0	92.3	0.100	146.4	0.87
2350031	4	42	111.4	15.6	11.6	31.9	90.3	0.120	143.0	0.78
		Mean:	149.90	17.50	12.19	31.22	89.73	0.1200	143.74	0.833
		SD:	29.32	2.59	0.79	4.56	2.18	0.0141	9.26	0.068

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LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6C - Clinical chemistry - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	PROT g/dl	ALB %	A1G %	A2G %	BETA %	GAM %	AGR
2350001	1	42	6.1	69.2	3.7	5.5	8.1	13.5	2.24
2350003	1	42	5.8	66.8	3.8	5.5	7.6	16.3	2.01
2350005	1	42	5.8	65.1	4.8	9.4	5.9	14.8	1.86
2350007	1	42	5.7	68.2	4.1	5.5	7.8	14.4	2.15
		Mean:	5.87	67.33	4.10	6.47	7.35	14.75	2.065
		SD:	0.16	1.78	0.50	1.95	0.99	1.17	0.166
2350009	2	42	5.9	67.0	4.4	5.4	6.8	16.6	2.03
2350011	2	42	5.2	67.8	5.0	4.5	7.9	14.9	2.10
2350013	2	42	5.5	69.8	4.6	4.8	8.8	12.1	2.31
2350015	2	42	5.7	65.6	4.3	6.9	8.9	14.3	1.91
		Mean:	5.57	67.55	4.58	5.40	8.10	14.48	2.088
		SD:	0.31	1.75	0.31	1.07	0.98	1.86	0.168
2350017	3	42	5.7	67.6	4.3	6.3	7.2	14.5	2.08
2350019	3	42	5.9	65.7	4.4	5.3	8.3	16.4	1.92
2350021	3	42	5.9	61.9	4.7	5.9	10.0	17.5	1.62
2350023	3	42	5.8	69.8	4.2	5.2	6.2	14.6	2.32
		Mean:	5.83	66.25	4.40	5.68	7.93	15.75	1.985
		SD:	0.09	3.35	0.22	0.52	1.63	1.46	0.294
2350025	4	42	6.1	65.6	4.4	5.6	7.2	17.2	1.91
2350027	4	42	6.1	67.3	4.2	4.6	7.5	16.5	2.05
2350029	4	42	6.1	65.3	4.5	6.5	7.7	15.9	1.89
2350031	4	42	5.7	69.6	4.2	5.6	6.4	14.3	2.29
		Mean:	5.99	66.95	4.33	5.58	7.20	15.98	2.035
		SD:	0.19	1.97	0.15	0.78	0.57	1.24	0.184

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6C - Clinical chemistry - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	Cl^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Ca^{++} mmol/l
2350001	1	42	107.4	148.70	4.48	2.72
2350003	1	42	102.6	146.30	4.80	2.57
2350005	1	42	104.8	147.70	5.10	2.69
2350007	1	42	106.1	147.70	4.99	2.63
		Mean:	105.24	147.600	4.843	2.653
		SD:	2.04	0.986	0.272	0.067
2350009	2	42	102.8	146.10	4.01	2.72
2350011	2	42	107.4	144.90	4.37	2.57
2350013	2	42	104.0	143.30	4.64	2.68
2350015	2	42	101.5	144.80	3.71	2.74
		Mean:	103.93	144.775	4.183	2.678
		SD:	2.54	1.146	0.407	0.076
2350017	3	42	102.5	143.20	4.46	2.74
2350019	3	42	105.8	145.30	4.57	2.83
2350021	3	42	103.8	143.10	4.42	2.82
2350023	3	42	102.7	145.30	4.17	2.66
		Mean:	103.69	144.225	4.405	2.763
		SD:	1.52	1.243	0.169	0.079
2350025	4	42	101.8	144.10	4.29	2.66
2350027	4	42	102.7	145.70	4.34	2.74
2350029	4	42	104.4	144.80	5.34	2.78
2350031	4	42	102.7	144.70	4.77	2.67
		Mean:	102.92	144.825	4.685	2.713
		SD:	1.06	0.659	0.487	0.057

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6D - Clinical chemistry - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	AP U/l	ALT U/l	AST U/l	UREA mg/dl	GLU mg/dl	BILT mg/dl	CHOL mg/dl	CREA mg/dl
2350002	1	86	116.1	29.4	12.7	30.2	101.3	0.130	136.1	0.69
2350004	1	86	141.1	29.7	13.9	34.3	95.6	0.110	141.8	0.71
2350006	1	86	113.7	17.6	14.1	24.2	95.2	0.090	121.2	0.59
2350008	1	86	173.4	17.8	12.1	26.8	93.3	0.100	130.3	0.77
		Mean:	136.07	23.62	13.18	28.88	96.36	0.1075	132.35	0.690
		SD:	27.79	6.82	0.97	4.38	3.45	0.0171	8.77	0.075
2350010	2	86	119.8	22.3	10.1	28.7	99.9	0.100	141.4	0.82
2350012	2	86	108.3	21.6	11.5	34.3	101.3	0.140	139.6	0.77
2350014	2	86	188.5	21.6	12.9	25.3	98.8	0.120	159.9	0.77
2350016	2	86	134.0	19.5	12.2	24.3	99.4	0.110	124.3	0.60
		Mean:	137.68	21.28	11.65	28.15	99.84	0.1175	141.29	0.740
		SD:	35.48	1.22	1.22	4.52	1.10	0.0171	14.60	0.096
2350018	3	86	143.9	23.4	14.1	29.0	104.5	0.140	146.7	0.77
2350020	3	86	178.8	24.6	12.1	28.8	104.3	0.100	140.4	0.75
2350022	3	86	178.5	19.3	13.5	25.8	97.9	0.180	164.1	0.76
2350024	3	86	168.3	24.0	11.7	24.4	99.3	0.130	163.7	0.75
		Mean:	167.35	22.84	12.83	26.98	101.48	0.1375	153.71	0.758
		SD:	16.39	2.42	1.13	2.25	3.38	0.0330	12.02	0.010
2350026	4	86	90.5	13.6	12.3	36.2	88.6	0.120	132.7	0.85
2350028	4	86	147.6	19.0	11.4	35.4	108.1	0.120	152.5	0.81
2350030	4	86	267.2	33.7	15.2	27.0	90.6	0.120	145.3	0.72
2350032	4	86	294.5	35.7	15.4	29.9	103.3	0.140	118.0	0.82
		Mean:	199.96	25.52	13.59	32.10	97.65	0.1250	137.11	0.800
		SD:	96.95	10.88	2.02	4.44	9.53	0.0100	15.14	0.056

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6D - Clinical chemistry - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	PROT g/dl	ALB %	A1G %	A2G %	BETA %	GAM %	AGR
2350002	1	86	5.5	65.2	4.0	7.1	8.3	15.4	1.87
2350004	1	86	5.6	66.7	3.6	6.2	8.6	14.9	2.00
2350006	1	86	5.3	66.9	4.3	5.8	8.4	14.6	2.03
2350008	1	86	5.4	67.0	4.2	6.3	8.4	14.0	2.03
		Mean:	5.44	66.45	4.03	6.35	8.43	14.73	1.983
		SD:	0.15	0.84	0.31	0.54	0.13	0.59	0.076
2350010	2	86	5.2	65.6	4.1	7.1	8.6	14.7	1.90
2350012	2	86	5.3	67.8	4.0	5.9	11.6	10.7	2.11
2350014	2	86	5.9	63.1	4.4	6.7	13.5	12.3	1.71
2350016	2	86	5.5	63.7	4.4	6.3	12.7	12.9	1.75
		Mean:	5.50	65.05	4.23	6.50	11.60	12.65	1.868
		SD:	0.31	2.12	0.21	0.52	2.15	1.65	0.181
2350018	3	86	5.7	65.2	3.9	6.0	10.3	14.7	1.87
2350020	3	86	5.5	63.8	4.6	7.4	9.3	14.7	1.77
2350022	3	86	5.7	65.4	4.6	6.4	8.5	15.1	1.89
2350024	3	86	6.2	59.5	4.4	5.8	11.7	18.7	1.47
		Mean:	5.76	63.48	4.38	6.40	9.95	15.80	1.750
		SD:	0.32	2.74	0.33	0.71	1.38	1.94	0.194
2350026	4	86	5.7	63.6	4.6	7.6	9.2	15.1	1.74
2350028	4	86	5.4	67.6	4.0	7.4	7.6	13.4	2.09
2350030	4	86	5.5	67.7	4.1	6.3	7.4	14.5	2.10
2350032	4	86	5.6	65.9	4.2	6.6	8.8	14.5	1.93
		Mean:	5.56	66.20	4.23	6.98	8.25	14.38	1.965
		SD:	0.12	1.92	0.26	0.62	0.89	0.71	0.169

Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6D - Clinical chemistry - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	Cl^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Ca^{++} mmol/l
2350002	1	86	96.2	141.70	4.87	2.55
2350004	1	86	95.5	144.60	4.66	2.72
2350006	1	86	103.2	142.30	4.26	2.48
2350008	1	86	100.4	142.90	4.85	2.51
		Mean:	98.83	142.875	4.660	2.565
		SD:	3.67	1.248	0.283	0.107
2350010	2	86	99.8	143.00	4.52	2.65
2350012	2	86	100.3	142.30	4.84	2.62
2350014	2	86	97.9	142.90	4.81	2.68
2350016	2	86	98.8	142.90	4.86	2.61
		Mean:	99.21	142.775	4.758	2.640
		SD:	1.05	0.315	0.160	0.032
2350018	3	86	92.8	143.40	4.52	2.64
2350020	3	86	101.6	142.30	5.03	2.64
2350022	3	86	97.3	141.50	4.62	2.53
2350024	3	86	97.2	143.30	4.74	2.67
		Mean:	97.24	142.625	4.727	2.620
		SD:	3.58	0.900	0.221	0.062
2350026	4	86	98.4	143.50	4.81	2.56
2350028	4	86	98.4	141.90	4.54	2.66
2350030	4	86	96.3	143.10	4.75	2.60
2350032	4	86	98.4	144.40	4.67	2.57
		Mean:	97.89	143.225	4.693	2.598
		SD:	1.07	1.036	0.117	0.045

LIFE SCIENCE RESEARCH
Roma Toxicology Centre

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6D - Clinical chemistry - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	AP U/l	ALT U/l	AST U/l	UREA mg/dl	GLU mg/dl	BILT mg/dl	CHOL mg/dl	CREA mg/dl
2350001	1	86	123.9	19.0	10.4	27.1	96.8	0.210	191.6	0.79
2350003	1	86	141.6	15.1	12.9	36.2	102.4	0.100	165.7	0.80
2350005	1	86	132.7	24.7	11.6	21.1	92.1	0.090	140.4	0.63
2350007	1	86	89.0	13.2	10.1	25.9	93.0	0.150	132.1	0.68
		Mean:	121.79	18.00	11.24	27.58	96.09	0.1375	157.47	0.725
		SD:	23.02	5.08	1.26	6.28	4.71	0.0550	26.87	0.083
2350009	2	86	96.6	25.5	18.8	29.7	94.4	0.150	114.9	0.75
2350011	2	86	129.8	20.0	12.5	28.3	90.1	0.150	115.3	0.81
2350013	2	86	137.5	14.5	11.6	33.3	105.8	0.130	132.5	0.68
2350015	2	86	136.9	20.4	14.9	28.0	92.2	0.150	131.1	0.78
		Mean:	125.19	20.09	14.43	29.83	95.61	0.1450	123.45	0.755
		SD:	19.35	4.48	3.22	2.45	7.00	0.0100	9.66	0.056
2350017	3	86	193.5	21.9	15.5	39.8	86.7	0.160	153.8	0.89
2350019	3	86	132.7	17.8	12.8	39.2	91.3	0.190	104.6	1.00
2350021	3	86	125.4	27.1	11.5	25.6	97.3	0.130	126.0	0.81
2350023	3	86	70.1	15.1	14.1	37.3	107.4	0.170	131.4	0.77
		Mean:	130.44	20.46	13.47	35.48	95.67	0.1625	128.95	0.868
		SD:	50.51	5.22	1.71	6.64	8.95	0.0250	20.18	0.101
2350025	4	86	117.8	22.6	14.7	24.2	91.5	0.190	137.4	0.77
2350027	4	86	143.4	16.3	11.7	31.5	99.2	0.190	117.5	0.88
2350029	4	86	125.0	17.1	10.9	31.4	94.0	0.180	132.4	0.86
2350031	4	86	91.3	16.8	10.8	20.8	101.8	0.170	135.0	0.72
		Mean:	119.39	18.23	12.05	26.98	96.64	0.1825	130.57	0.808
		SD:	21.61	2.95	1.82	5.38	4.71	0.0096	8.94	0.075

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
(Dr. Alfredo Mantovani)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6D - Clinical chemistry - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	PROT g/dl	ALB %	A1G %	A2G %	BETA %	GAM %	AGR
2350001	1	86	5.6	71.1	3.7	4.8	7.1	13.4	2.45
2350003	1	86	5.5	67.7	3.7	5.2	8.7	14.6	2.10
2350005	1	86	5.1	63.6	5.2	7.2	8.8	15.1	1.75
2350007	1	86	5.7	67.8	4.1	5.7	7.9	14.5	2.11
		Mean:	5.48	67.55	4.18	5.73	8.13	14.40	2.102
		SD:	0.25	3.07	0.71	1.05	0.79	0.72	0.286
2350009	2	86	5.7	66.1	4.6	5.0	7.4	17.0	1.95
2350011	2	86	5.1	67.7	5.2	4.5	7.9	14.8	2.10
2350013	2	86	5.3	69.4	4.9	5.0	10.1	10.7	2.27
2350015	2	86	5.4	68.1	4.4	5.3	7.7	14.5	2.14
		Mean:	5.38	67.83	4.78	4.95	8.28	14.25	2.115
		SD:	0.23	1.36	0.35	0.33	1.23	2.62	0.132
2350017	3	86	5.8	66.4	4.4	6.4	7.9	15.0	1.97
2350019	3	86	5.2	67.0	4.5	5.0	8.3	15.3	2.03
2350021	3	86	5.9	60.6	4.9	5.3	10.5	18.6	1.54
2350023	3	86	5.6	69.8	4.1	5.2	6.4	14.4	2.31
		Mean:	5.61	65.95	4.48	5.48	8.28	15.83	1.963
		SD:	0.27	3.86	0.33	0.63	1.69	1.89	0.318
2350025	4	86	5.6	67.6	4.3	5.8	7.0	15.3	2.09
2350027	4	86	5.7	66.6	4.1	4.3	7.3	17.7	2.00
2350029	4	86	5.7	69.3	4.0	5.5	6.8	14.4	2.25
2350031	4	86	5.3	70.2	4.1	5.3	6.6	13.8	2.36
		Mean:	5.58	68.43	4.13	5.23	6.93	15.30	2.175
		SD:	0.18	1.63	0.13	0.65	0.30	1.71	0.161

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 6D - Clinical chemistry - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	Cl^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Ca^{++} mmol/l
2350001	1	86	91.2	142.30	4.07	2.61
2350003	1	86	97.1	142.40	4.11	2.53
2350005	1	86	100.0	143.70	4.77	2.52
2350007	1	86	98.3	143.60	4.57	2.63
		Mean:	96.66	143.000	4.380	2.572
		SD:	3.83	0.750	0.345	0.056
2350009	2	86	95.6	143.10	4.20	2.58
2350011	2	86	99.1	143.10	4.12	2.50
2350013	2	86	95.4	140.90	4.30	2.55
2350015	2	86	96.7	143.90	3.87	2.57
		Mean:	96.70	142.750	4.122	2.550
		SD:	1.67	1.290	0.184	0.036
2350017	3	86	96.9	146.00	4.16	2.74
2350019	3	86	99.0	143.00	4.37	2.70
2350021	3	86	93.4	141.80	4.40	2.59
2350023	3	86	96.9	143.50	4.07	2.58
		Mean:	96.54	143.575	4.250	2.652
		SD:	2.31	1.766	0.161	0.080
2350025	4	86	96.7	141.70	4.29	2.55
2350027	4	86	96.6	142.30	4.07	2.57
2350029	4	86	95.3	142.20	4.40	2.56
2350031	4	86	95.9	141.20	4.85	2.54
		Mean:	96.11	141.850	4.403	2.555
		SD:	0.63	0.505	0.328	0.013

LIFE SCIENCE RESEARCH

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7A - Urinalysis - Before treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	APP	VOL ml	pH	GLUC mg/dl	PRO mg/dl	HG mg/dl	KET mg/dl	BIL mg/dl	UROB EU%	SPG g/l
2350002	1	-7	1	210.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1036
2350004	1	-7	0	10.0	6.5	0.00	20.00	0.00	0.00	0.00	2.00	1045
2350006	1	-7	0	98.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1030
2350008	1	-7	0	22.0	8.0	0.00	20.00	0.00	0.00	0.20	2.00	1054
		Mean:	0.3	85.00	6.75	0.000	15.000	0.000	0.000	0.050	1.500	1041.3
		SD:	0.5	91.99	0.87	0.000	5.774	0.000	0.000	0.100	0.577	10.5
2350010	2	-7	1	158.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1045
2350012	2	-7	1	400.0	6.0	0.00	5.00	0.06	0.00	0.00	0.20	1016
2350014	2	-7	1	130.0	6.5	0.00	20.00	0.03	0.00	0.00	1.00	1051
2350016	2	-7	0	96.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1046
		Mean:	0.8	196.00	6.13	0.000	11.250	0.023	0.000	0.000	0.800	1039.5
		SD:	0.5	138.34	0.25	0.000	6.292	0.029	0.000	0.000	0.400	15.9
2350018	3	-7	0	70.0	6.5	0.00	20.00	0.00	0.00	0.20	2.00	1048
2350020	3	-7	1	158.0	6.5	0.00	20.00	0.00	0.00	0.00	2.00	1043
2350022	3	-7	1	80.0	6.0	10.00	10.00	0.50	0.00	0.00	1.00	1049
2350024	3	-7	0	150.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1048
		Mean:	0.5	114.50	6.25	2.500	15.000	0.125	0.000	0.050	1.500	1047.0
		SD:	0.6	45.91	0.29	5.000	5.774	0.250	0.000	0.100	0.577	2.7
2350026	4	-7	0	180.0	6.5	0.00	5.00	0.00	0.00	0.00	1.00	1024
2350028	4	-7	0	100.0	6.0	0.00	10.00	0.00	0.00	0.20	2.00	1058
2350030	4	-7	0	218.0	6.5	0.00	10.00	0.00	0.00	0.00	0.20	1023
2350032	4	-7	0	92.0	7.0	0.00	50.00	0.00	0.00	0.50	3.00	1060
		Mean:	0.0	147.50	6.50	0.000	18.750	0.000	0.000	0.175	1.550	1041.3
		SD:	0.0	61.54	0.41	0.000	20.966	0.000	0.000	0.236	1.215	20.5

LIFE SCIENCE RESEARCH
Rome Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7A - Urinalysis - Before treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	RED	NIT	EPI	LEU	ERY	CRY	SPE	ABN
2350002	1	-7	0	0	1	2	0	2	0	0
2350004	1	-7	0	0	2	2	0	2	0	0
2350006	1	-7	0	0	2	2	1	0	0	0
2350008	1	-7	0	0	2	1	0	1	0	0
		Mean:	0.0	0.0	1.8	1.8	0.3	1.3	0.0	0.0
		SD:	0.0	0.0	0.5	0.5	0.5	1.0	0.0	0.0
2350010	2	-7	0	0	1	1	0	2	0	0
2350012	2	-7	0	1	2	2	1	0	0	0
2350014	2	-7	0	1	0	1	1	2	0	0
2350016	2	-7	0	1	1	1	0	1	0	0
		Mean:	0.0	0.8	1.0	1.3	0.5	1.3	0.0	0.0
		SD:	0.0	0.5	0.8	0.5	0.6	1.0	0.0	0.0
2350018	3	-7	0	0	0	1	0	1	0	0
2350020	3	-7	0	1	0	1	0	3	0	0
2350022	3	-7	0	0	1	0	1	1	0	0
2350024	3	-7	0	0	0	0	0	3	0	0
		Mean:	0.0	0.3	0.3	0.5	0.3	2.0	0.0	0.0
		SD:	0.0	0.5	0.5	0.6	0.5	1.2	0.0	0.0
2350026	4	-7	0	0	1	0	0	1	0	0
2350028	4	-7	0	0	2	0	0	2	0	0
2350030	4	-7	0	0	2	0	0	0	0	0
2350032	4	-7	0	0	1	1	0	2	0	0
		Mean:	0.0	0.0	1.5	0.3	0.0	1.3	0.0	0.0
		SD:	0.0	0.0	0.6	0.5	0.0	1.0	0.0	0.0

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7A - Urinalysis - Before treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	APP	VOL ml	pH	GLUC mg/dl	PRO mg/dl	HG mg/dl	KET mg/dl	BIL mg/dl	UROB EU%	SPG g/l
2350001	1	-6	0	84.0	7.0	0.00	30.00	0.00	0.00	0.20	2.00	1047
2350003	1	-6	0	188.0	6.0	0.00	5.00	0.00	0.00	0.00	0.20	1028
2350005	1	-6	1	5.0	7.0	0.00	30.00	0.00	0.00	0.20	3.00	1047
2350007	1	-6	0	60.0	7.0	0.00	20.00	0.00	0.00	0.20	2.00	1037
		Mean:	0.3	84.25	6.75	0.000	21.250	0.000	0.000	0.150	1.800	1039.8
		SD:	0.5	76.67	0.50	0.000	11.815	0.000	0.000	0.100	1.166	9.1
2350009	2	-6	1	86.0	6.5	0.00	20.00	0.00	0.00	0.20	1.00	1044
2350011	2	-6	1	166.0	6.5	10.00	10.00	0.00	0.00	0.00	1.00	1040
2350013	2	-6	1	5.0	6.0	10.00	50.00	0.10	0.00	0.50	3.00	1060
2350015	2	-6	0	70.0	6.5	0.00	10.00	0.00	0.00	0.00	0.20	1026
		Mean:	0.8	81.75	6.38	5.000	22.500	0.025	0.000	0.175	1.300	1042.5
		SD:	0.5	66.19	0.25	5.774	18.930	0.050	0.000	0.236	1.194	14.0
2350017	3	-6	1	172.0	5.5	0.00	10.00	0.00	0.00	0.00	1.00	1033
2350019	3	-6	1	74.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1026
2350021	3	-6	0	92.0	6.0	0.00	20.00	0.00	0.00	0.20	2.00	1046
2350023	3	-6	1	124.0	7.0	0.00	30.00	1.00	0.00	0.00	0.20	1023
		Mean:	0.8	115.50	6.25	0.000	17.500	0.250	0.000	0.050	1.050	1032.0
		SD:	0.5	42.97	0.65	0.000	9.574	0.500	0.000	0.100	0.737	10.2
2350025	4	-6	0	154.0	6.0	0.00	5.00	0.00	0.00	0.00	1.00	1024
2350027	4	-6	0	210.0	6.5	0.00	5.00	0.00	0.00	0.00	1.00	1023
2350029	4	-6	0	84.0	6.5	0.00	20.00	0.00	0.00	0.20	2.00	1054
2350031	4	-6	1	192.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1024
		Mean:	0.3	160.00	6.38	0.000	10.000	0.000	0.000	0.050	1.250	1031.3
		SD:	0.5	55.79	0.25	0.000	7.071	0.000	0.000	0.100	0.500	15.2

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7A - Urinalysis - Before treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	RED	NIT	EPI	LEU	ERY	CRY	SPE	ABN
2350001	1	-6	0	0	1	2	0	0	0	0
2350003	1	-6	0	1	1	1	0	0	0	0
2350005	1	-6	0	0	0	2	0	3	0	0
2350007	1	-6	0	0	1	1	0	2	0	0
		Mean:	0.0	0.3	0.8	1.5	0.0	1.3	0.0	0.0
		SD:	0.0	0.5	0.5	0.6	0.0	1.5	0.0	0.0
2350009	2	-6	0	1	1	0	0	3	0	0
2350011	2	-6	0	0	1	1	0	2	0	0
2350013	2	-6	0	0	1	2	0	2	0	0
2350015	2	-6	0	1	1	0	0	1	0	0
		Mean:	0.0	0.5	1.0	0.8	0.0	2.0	0.0	0.0
		SD:	0.0	0.6	0.0	1.0	0.0	0.8	0.0	0.0
2350017	3	-6	0	1	1	2	0	0	0	0
2350019	3	-6	0	1	1	2	0	1	0	0
2350021	3	-6	0	0	1	2	0	1	0	0
2350023	3	-6	0	1	1	2	1	1	0	0
		Mean:	0.0	0.8	1.0	2.0	0.3	0.8	0.0	0.0
		SD:	0.0	0.5	0.0	0.0	0.5	0.5	0.0	0.0
2350025	4	-6	0	1	1	1	0	0	0	0
2350027	4	-6	0	0	2	1	0	0	0	0
2350029	4	-6	0	0	2	2	0	1	0	0
2350031	4	-6	0	0	2	0	0	2	0	0
		Mean:	0.0	0.3	1.8	1.0	0.0	0.8	0.0	0.0
		SD:	0.0	0.5	0.5	0.8	0.0	1.0	0.0	0.0

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7B - Urinalysis - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	APP	VOL ml	pH	GLUC mg/dl	PRO mg/dl	HG mg/dl	KET mg/dl	BIL mg/dl	UROB EU%	SPG g/l
2350002	1	38	0	430.0	6.0	0.00	0.00	0.06	0.00	0.00	0.20	1018
2350004	1	38	1	124.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1035
2350006	1	38	0	120.0	6.5	0.00	20.00	0.00	0.00	0.50	2.00	1046
2350008	1	38	1	214.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1039
		Mean:	0.5	222.00	6.25	0.000	10.000	0.015	0.000	0.125	1.050	1034.5
		SD:	0.6	145.30	0.29	0.000	8.165	0.030	0.000	0.250	0.737	11.9
2350010	2	38	0	146.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1045
2350012	2	38	0	360.0	6.0	0.00	5.00	0.00	0.00	0.00	0.20	1024
2350014	2	38	1	140.0	6.0	10.00	5.00	0.06	0.00	0.00	0.20	1021
2350016	2	38	0	220.0	6.0	50.00	10.00	0.06	0.00	0.00	0.20	1034
		Mean:	0.3	216.50	6.00	15.000	7.500	0.030	0.000	0.000	0.400	1031.0
		SD:	0.5	102.35	0.00	23.805	2.887	0.035	0.000	0.000	0.400	10.9
2350018	3	38	1	116.0	6.0	0.00	20.00	0.06	0.00	0.00	1.00	1047
2350020	3	38	0	360.0	7.0	0.00	5.00	0.00	0.00	0.00	0.20	1013
2350022	3	38	0	70.0	6.0	10.00	10.00	0.00	0.00	0.00	1.00	1053
2350024	3	38	0	410.0	6.0	0.00	0.00	0.00	0.00	0.00	0.20	1018
		Mean:	0.3	239.00	6.25	2.500	8.750	0.015	0.000	0.000	0.600	1032.8
		SD:	0.5	170.85	0.50	5.000	8.539	0.030	0.000	0.000	0.462	20.2
2350026	4	38	0	108.0	6.5	0.00	20.00	0.00	0.00	0.20	1.00	1049
2350028	4	38	0	180.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1048
2350030	4	38	0	244.0	6.5	0.00	10.00	0.00	0.00	0.00	0.20	1021
2350032	4	38	0	270.0	6.0	0.00	5.00	0.00	0.00	0.00	0.20	1020
		Mean:	0.0	200.50	6.25	0.000	11.250	0.000	0.000	0.050	0.600	1034.5
		SD:	0.0	72.34	0.29	0.000	6.292	0.000	0.000	0.100	0.462	16.2

LIFE SCIENCE RESEARCH
Rama Toxicology Centre S.p.A

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7B - Urinalysis - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	RED	NIT	EPI	LEU	ERY	CRY	SPE	ABN
2350002	1	38	0	0	1	2	1	2	0	0
2350004	1	38	0	0	1	1	0	1	0	0
2350006	1	38	0	0	2	2	2	2	0	0
2350008	1	38	0	0	2	0	0	3	0	0
		Mean:	0.0	0.0	1.5	1.3	0.8	2.0	0.0	0.0
		SD:	0.0	0.0	0.6	1.0	1.0	0.8	0.0	0.0
2350010	2	38	0	1	2	3	2	2	0	0
2350012	2	38	0	0	1	3	2	1	0	0
2350014	2	38	0	0	2	1	1	1	0	0
2350016	2	38	0	0	1	1	0	1	0	0
		Mean:	0.0	0.3	1.5	2.0	1.3	1.3	0.0	0.0
		SD:	0.0	0.5	0.6	1.2	1.0	0.5	0.0	0.0
2350018	3	38	0	0	1	0	0	1	0	0
2350020	3	38	0	1	1	0	0	2	0	0
2350022	3	38	0	0	1	0	0	2	0	0
2350024	3	38	0	1	2	1	0	1	0	0
		Mean:	0.0	0.5	1.3	0.3	0.0	1.5	0.0	0.0
		SD:	0.0	0.6	0.5	0.5	0.0	0.6	0.0	0.0
2350026	4	38	0	0	1	1	0	2	0	0
2350028	4	38	0	0	1	1	0	2	1	0
2350030	4	38	0	0	1	1	0	1	1	0
2350032	4	38	0	0	1	1	0	0	0	0
		Mean:	0.0	0.0	1.0	1.0	0.0	1.3	0.5	0.0
		SD:	0.0	0.0	0.0	0.0	0.0	1.0	0.6	0.0

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LIFE SCIENCE RESEARCH
Rome Toxicology Centre S.p.A
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7B - Urinalysis - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	APP	VOL ml	pH	GLUC mg/dl	PRO mg/dl	HG mg/dl	KET mg/dl	BIL mg/dl	UROB EU%	SPG g/l
2350001	1	39	0	88.0	6.0	0.00	10.00	0.00	0.00	0.20	2.00	1043
2350003	1	39	0	76.0	6.0	0.00	10.00	0.00	0.00	0.20	1.00	1041
2350005	1	39	0	350.0	6.0	0.00	0.00	0.00	0.00	0.00	0.20	1014
2350007	1	39	0	160.0	6.0	0.00	10.00	0.00	0.00	0.00	2.00	1047
		Mean:	0.0	168.50	6.00	0.000	7.500	0.000	0.000	0.100	1.300	1036.3
		SD:	0.0	126.56	0.00	0.000	5.000	0.000	0.000	0.115	0.872	15.0
2350009	2	39	0	50.0	6.5	0.00	20.00	0.00	0.00	0.20	2.00	1058
2350011	2	39	0	212.0	6.5	0.00	5.00	0.00	0.00	0.00	1.00	1033
2350013	2	39	1	130.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1052
2350015	2	39	0	74.0	6.0	0.00	10.00	0.00	0.00	0.20	2.00	1055
		Mean:	0.3	116.50	6.25	0.000	11.250	0.000	0.000	0.100	1.500	1049.5
		SD:	0.5	71.95	0.29	0.000	6.292	0.000	0.000	0.115	0.577	11.3
2350017	3	39	1	234.0	6.0	0.00	5.00	0.00	0.00	0.00	1.00	1036
2350019	3	39	0	126.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1031
2350021	3	39	0	150.0	6.5	0.00	10.00	0.00	0.00	0.20	2.00	1049
2350023	3	39	0	98.0	6.0	0.00	10.00	0.00	0.00	0.20	1.00	1046
		Mean:	0.3	152.00	6.25	0.000	8.750	0.000	0.000	0.100	1.250	1040.5
		SD:	0.5	58.65	0.29	0.000	2.500	0.000	0.000	0.115	0.500	8.4
2350025	4	39	0	60.0	6.0	0.00	20.00	0.00	0.00	0.20	2.00	1049
2350027	4	39	0	120.0	6.5	0.00	0.00	0.00	0.00	0.00	0.20	1010
2350029	4	39	0	124.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1048
2350031	4	39	0	90.0	6.0	0.00	10.00	0.00	0.00	0.50	3.00	1060
		Mean:	0.0	98.50	6.13	0.000	10.000	0.000	0.000	0.175	1.550	1041.8
		SD:	0.0	29.82	0.25	0.000	8.165	0.000	0.000	0.236	1.215	21.9

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7B - Urinalysis - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	RED	NIT	EPI	LEU	ERY	CRY	SPE	ABN
2350001	1	39	0	0	1	2	1	1	0	0
2350003	1	39	0	0	0	1	1	1	0	0
2350005	1	39	0	1	0	1	0	1	0	0
2350007	1	39	0	0	1	1	1	2	0	0
		Mean:	0.0	0.3	0.5	1.3	0.8	1.3	0.0	0.0
		SD:	0.0	0.5	0.6	0.5	0.5	0.5	0.0	0.0
2350009	2	39	0	0	1	1	0	1	0	0
2350011	2	39	0	0	1	1	0	1	0	0
2350013	2	39	0	1	2	1	0	2	0	0
2350015	2	39	0	0	1	0	0	3	0	0
		Mean:	0.0	0.3	1.3	0.8	0.0	1.8	0.0	0.0
		SD:	0.0	0.5	0.5	0.5	0.0	1.0	0.0	0.0
2350017	3	39	0	0	1	1	0	1	0	0
2350019	3	39	0	1	1	1	1	1	0	0
2350021	3	39	0	0	1	1	0	2	0	0
2350023	3	39	0	0	1	1	0	1	0	0
		Mean:	0.0	0.3	1.0	1.0	0.3	1.3	0.0	0.0
		SD:	0.0	0.5	0.0	0.0	0.5	0.5	0.0	0.0
2350025	4	39	0	0	1	1	0	1	0	0
2350027	4	39	0	1	0	0	0	1	0	0
2350029	4	39	0	0	0	0	0	1	0	0
2350031	4	39	0	0	1	1	0	1	0	0
		Mean:	0.0	0.3	0.5	0.5	0.0	1.0	0.0	0.0
		SD:	0.0	0.5	0.6	0.6	0.0	0.0	0.0	0.0

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Roma Toxicology Center S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7C - Urinalysis - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	APP	VOL ml	pH	GLUC mg/dl	PRO mg/dl	HG mg/dl	KET mg/dl	BIL mg/dl	UROB EU%	SPG g/l
2350002	1	87	0	250.0	6.5	0.00	10.00	0.00	0.00	0.00	0.20	1037
2350004	1	87	0	60.0	6.0	0.00	50.00	0.00	0.00	0.00	2.00	1058
2350006	1	87	0	108.0	7.5	0.00	30.00	0.00	0.00	0.20	2.00	1063
2350008	1	87	0	170.0	6.5	0.00	20.00	0.00	0.00	0.00	2.00	1058
		Mean:	0.0	147.00	6.63	0.000	27.500	0.000	0.000	0.050	1.550	1054.0
		SD:	0.0	82.11	0.63	0.000	17.078	0.000	0.000	0.100	0.900	11.6
2350010	2	87	0	200.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1046
2350012	2	87	0	140.0	6.0	0.00	30.00	0.00	0.00	0.00	1.00	1047
2350014	2	87	0	280.0	6.5	0.00	10.00	0.50	0.00	0.00	0.20	1022
2350016	2	87	0	290.0	6.5	10.00	10.00	0.03	0.00	0.00	0.20	1051
		Mean:	0.0	227.50	6.25	2.500	15.000	0.133	0.000	0.000	0.600	1041.5
		SD:	0.0	70.89	0.29	5.000	10.000	0.245	0.000	0.000	0.462	13.2
2350018	3	87	1	60.0	6.0	0.00	50.00	0.00	0.00	0.00	2.00	1059
2350020	3	87	0	150.0	6.0	0.00	10.00	0.00	0.00	0.00	1.00	1045
2350022	3	87	0	98.0	6.0	0.00	30.00	>1.00	0.00	0.00	1.00	1058
2350024	3	87	1	300.0	8.5	0.00	30.00	>1.00	0.00	0.00	0.20	1017
		Mean:	0.5	152.00	6.63	0.000	30.000	0.500	0.000	0.000	1.050	1044.8
		SD:	0.6	105.34	1.25	0.000	16.330	0.577	0.000	0.000	0.737	19.6
2350026	4	87	1	46.0	6.0	>1000.00	50.00	0.20	0.00	0.00	0.20	1027
2350028	4	87	1	250.0	6.0	0.00	10.00	0.00	0.00	0.00	0.20	1023
2350030	4	87	0	190.0	6.5	0.00	20.00	0.00	0.00	0.00	1.00	1029
2350032	4	87	0	140.0	6.0	0.00	20.00	0.00	0.00	0.00	1.00	1054
		Mean:	0.5	156.50	6.13	250.000	25.000	0.050	0.000	0.000	0.600	1033.3
		SD:	0.6	86.31	0.25	500.000	17.321	0.100	0.000	0.000	0.462	14.1

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LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7C - Urinalysis - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	RED	NIT	EPI	LEU	ERY	CRY	SPE	ABN
2350002	1	87	0	0	1	2	1	1	1	0
2350004	1	87	0	0	1	2	1	2	0	0
2350006	1	87	0	0	1	1	0	1	0	0
2350008	1	87	0	0	2	0	0	3	1	0
		Mean:	0.0	0.0	1.3	1.3	0.5	1.8	0.5	0.0
		SD:	0.0	0.0	0.5	1.0	0.6	1.0	0.6	0.0
2350010	2	87	0	0	1	1	1	1	1	0
2350012	2	87	0	0	1	1	1	1	1	0
2350014	2	87	0	1	1	1	0	1	0	0
2350016	2	87	0	0	2	2	2	1	0	0
		Mean:	0.0	0.3	1.3	1.3	1.0	1.0	0.5	0.0
		SD:	0.0	0.5	0.5	0.5	0.8	0.0	0.6	0.0
2350018	3	87	0	0	1	1	1	1	1	0
2350020	3	87	0	0	2	1	1	1	1	0
2350022	3	87	0	1	1	1	3	1	0	0
2350024	3	87	0	1	2	1	3	1	0	0
		Mean:	0.0	0.5	1.5	1.0	2.0	1.0	0.5	0.0
		SD:	0.0	0.6	0.6	0.0	1.2	0.0	0.6	0.0
2350026	4	87	2	1	2	2	0	2	0	0
2350028	4	87	0	0	1	1	0	1	1	0
2350030	4	87	0	0	1	1	0	1	1	0
2350032	4	87	0	0	1	0	0	1	2	0
		Mean:	0.5	0.3	1.3	1.0	0.0	1.3	1.0	0.0
		SD:	1.0	0.5	0.5	0.8	0.0	0.5	0.8	0.0

LIFE SCIENCE RESEARCH

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7C - Urinalysis - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	APP	VOL ml	pH	GLUC mg/dl	PRO mg/dl	HG mg/dl	KET mg/dl	BIL mg/dl	UROB EU%	SPG g/l
2350001	1	88	0	70.0	6.5	0.00	30.00	0.00	0.00	0.00	2.00	1049
2350003	1	88	0	74.0	6.0	0.00	30.00	0.00	0.00	0.00	2.00	1059
2350005	1	88	0	190.0	6.5	10.00	10.00	>1.00	0.00	0.00	1.00	1035
2350007	1	88	0	164.0	6.5	0.00	10.00	0.00	0.00	0.20	1.00	1029
		Mean:	0.0	124.50	6.38	2.500	20.000	0.250	0.000	0.050	1.500	1043.0
		SD:	0.0	61.57	0.25	5.000	11.547	0.500	0.000	0.100	0.577	13.6
2350009	2	88	0	72.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1046
2350011	2	88	0	148.0	7.0	0.00	10.00	0.00	0.00	0.00	1.00	1030
2350013	2	88	0	164.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1053
2350015	2	88	0	80.0	6.0	0.00	10.00	0.00	0.00	0.00	2.00	1048
		Mean:	0.0	116.00	6.50	0.000	10.000	0.000	0.000	0.000	1.250	1044.3
		SD:	0.0	46.76	0.41	0.000	0.000	0.000	0.000	0.000	0.500	9.9
2350017	3	88	0	90.0	6.5	0.00	20.00	0.00	0.00	0.00	2.00	1055
2350019	3	88	0	140.0	6.0	0.00	20.00	0.00	0.00	0.00	2.00	1038
2350021	3	88	1	220.0	6.5	0.00	10.00	1.00	0.00	0.00	0.20	1018
2350023	3	88	0	112.0	6.5	0.00	10.00	0.00	0.00	0.00	1.00	1034
		Mean:	0.3	140.50	6.38	0.000	15.000	0.250	0.000	0.000	1.300	1036.3
		SD:	0.5	56.81	0.25	0.000	5.774	0.500	0.000	0.000	0.872	15.2
2350025	4	88	0	70.0	8.0	0.00	20.00	0.00	0.00	0.00	1.00	1038
2350027	4	88	1	182.0	7.5	0.00	10.00	0.10	0.00	0.00	0.20	1014
2350029	4	88	0	130.0	6.5	0.00	20.00	0.00	0.00	0.00	1.00	1049
2350031	4	88	0	88.0	6.0	0.00	20.00	0.00	0.00	0.00	2.00	1055
		Mean:	0.3	117.50	7.00	0.000	17.500	0.025	0.000	0.000	1.050	1039.0
		SD:	0.5	49.81	0.91	0.000	5.000	0.050	0.000	0.000	0.737	18.1

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 7C - Urinalysis - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	RED	NIT	EPI	LEU	ERY	CRY	SPE	ABN
2350001	1	88	0	0	2	3	2	1	0	0
2350003	1	88	0	0	1	2	1	1	0	0
2350005	1	88	0	1	2	1	2	3	0	0
2350007	1	88	0	0	1	2	1	1	0	0
		Mean:	0.0	0.3	1.5	2.0	1.5	1.5	0.0	0.0
		SD:	0.0	0.5	0.6	0.8	0.6	1.0	0.0	0.0
2350009	2	88	0	1	1	1	0	1	0	0
2350011	2	88	0	0	1	1	0	0	0	0
2350013	2	88	0	0	2	1	1	1	0	0
2350015	2	88	0	0	1	1	0	3	0	0
		Mean:	0.0	0.3	1.3	1.0	0.3	1.3	0.0	0.0
		SD:	0.0	0.5	0.5	0.0	0.5	1.3	0.0	0.0
2350017	3	88	0	0	2	1	0	1	0	0
2350019	3	88	0	1	2	2	1	0	0	0
2350021	3	88	0	1	2	0	1	2	0	0
2350023	3	88	0	0	2	2	0	2	0	0
		Mean:	0.0	0.5	2.0	1.3	0.5	1.3	0.0	0.0
		SD:	0.0	0.6	0.0	1.0	0.6	1.0	0.0	0.0
2350025	4	88	0	1	2	2	1	2	0	0
2350027	4	88	0	0	2	0	0	1	0	0
2350029	4	88	0	0	1	1	0	1	0	0
2350031	4	88	0	0	1	1	0	1	0	0
		Mean:	0.0	0.3	1.5	1.0	0.3	1.3	0.0	0.0
		SD:	0.0	0.5	0.6	0.8	0.5	0.5	0.0	0.0

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Roma Toxicology Centre S.p.A

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 8A - Faecal occult blood - Before treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	OBF
2350002	1	-7	0
2350004	1	-7	0
2350006	1	-7	0
2350008	1	-7	0
		Mean:	0.0
		SD:	0.0
2350010	2	-7	0
2350012	2	-7	1
2350014	2	-7	1
2350016	2	-7	1
		Mean:	0.8
		SD:	0.5
2350018	3	-7	0
2350020	3	-7	1
2350022	3	-7	1
2350024	3	-7	1
		Mean:	0.8
		SD:	0.5
2350026	4	-7	1
2350028	4	-7	1
2350030	4	-7	0
2350032	4	-7	1
		Mean:	0.8
		SD:	0.5

0 = Negative 1 = Slight

080
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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 8A - Faecal occult blood - Before treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	OBF
2350001	1	-6	1
2350003	1	-6	1
2350005	1	-6	0
2350007	1	-6	0
		Mean:	0.5
		SD:	0.6
2350009	2	-6	0
2350011	2	-6	1
2350013	2	-6	1
2350015	2	-6	0
		Mean:	0.5
		SD:	0.6
2350017	3	-6	0
2350019	3	-6	0
2350021	3	-6	0
2350023	3	-6	0
		Mean:	0.0
		SD:	0.0
2350025	4	-6	0
2350027	4	-6	0
2350029	4	-6	0
2350031	4	-6	0
		Mean:	0.0
		SD:	0.0

0 = Negative 1 = Slight

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LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 8B - Faecal occult blood - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	OBF
2350002	1	38	1
2350004	1	38	0
2350006	1	38	0
2350008	1	38	1
		Mean:	0.5
		SD:	0.6
2350010	2	38	2
2350012	2	38	2
2350014	2	38	0
2350016	2	38	2
		Mean:	1.5
		SD:	1.0
2350018	3	38	1
2350020	3	38	0
2350022	3	38	1
2350024	3	38	0
		Mean:	0.5
		SD:	0.6
2350026	4	38	0
2350028	4	38	1
2350030	4	38	0
2350032	4	38	0
		Mean:	0.3
		SD:	0.5

0 = Negative 1 = Slight 2 = Moderate

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 8B - Faecal occult blood - Week 6 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	OBF
2350001	1	39	0
2350003	1	39	0
2350005	1	39	1
2350007	1	39	0
		Mean:	0.3
		SD:	0.5
2350009	2	39	1
2350011	2	39	1
2350013	2	39	2
2350015	2	39	1
		Mean:	1.3
		SD:	0.5
2350017	3	39	2
2350019	3	39	1
2350021	3	39	0
2350023	3	39	0
		Mean:	0.8
		SD:	1.0
2350025	4	39	0
2350027	4	39	0
2350029	4	39	1
2350031	4	39	0
		Mean:	0.3
		SD:	0.5

0 = Negative 1 = Slight 2 = Moderate

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.R.A

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 8C - Faecal occult blood - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Day of Study	OBF
2350002	1	87	1
2350004	1	87	0
2350006	1	87	0
2350008	1	87	0
		Mean:	0.3
		SD:	0.5
2350010	2	87	2
2350012	2	87	1
2350014	2	87	0
2350016	2	87	1
		Mean:	1.0
		SD:	0.8
2350018	3	87	0
2350020	3	87	1
2350022	3	87	0
2350024	3	87	1
		Mean:	0.5
		SD:	0.6
2350026	4	87	0
2350028	4	87	1
2350030	4	87	1
2350032	4	87	1
		Mean:	0.8
		SD:	0.5

0 = Negative 1 = Slight 2 = Moderate

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 8C - Faecal occult blood - Week 13 of treatment - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Day of Study	OBF
2350001	1	88	2
2350003	1	88	0
2350005	1	88	0
2350007	1	88	1
		Mean:	0.8
		SD:	1.0
2350009	2	88	0
2350011	2	88	1
2350013	2	88	1
2350015	2	88	0
		Mean:	0.5
		SD:	0.6
2350017	3	88	1
2350019	3	88	2
2350021	3	88	2
2350023	3	88	0
		Mean:	1.3
		SD:	1.0
2350025	4	88	0
2350027	4	88	0
2350029	4	88	0
2350031	4	88	0
		Mean:	0.0
		SD:	0.0

0 = Negative 1 = Slight 2 = Moderate

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Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9A - Absolute organ weights (g) - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Terminal body wt.(kg)	Brain	Pituitary	Heart	Liver	Spleen	L. Kidney	R. Kidney
2350002	1	11.90	84.67	0.070	88.49	324.03	26.18	22.20	22.96
2350004	1	11.54	81.42	0.070	88.64	357.90	33.03	26.65	25.36
2350006	1	12.00	81.04	0.085	91.70	298.95	35.55	28.18	27.05
2350008	1	10.86	80.65	0.068	85.06	316.52	39.58	25.38	24.72
	Mean:	11.575	81.945	0.0733	88.472	324.350	33.585	25.603	25.022
	SD:	0.516	1.844	0.0079	2.714	24.713	5.626	2.541	1.690
2350010	2	13.06	95.88	0.083	105.62	367.00	32.63	50.51	NT
2350012	2	11.80	84.09	0.057	88.15	307.55	31.53	23.00	23.40
2350014	2	12.38	78.04	0.061	101.47	348.08	34.96	22.08	24.42
2350016	2	11.44	92.43	0.081	88.38	369.19	28.17	24.05	23.00
	Mean:	12.170	87.610	0.0705	95.905	347.955	31.823	29.910	23.607
	SD:	0.709	8.075	0.0134	8.984	28.555	2.824	13.757	0.732
2350018	3	11.52	78.92	0.054	84.97	300.94	22.72	25.75	24.50
2350020	3	11.78	84.48	0.078	104.98	397.23	28.48	26.87	26.23
2350022	3	9.36	79.71	0.074	84.86	302.88	26.92	21.77	23.74
2350024	3	11.90	82.00	0.079	80.48	328.40	30.47	25.29	23.65
	Mean:	11.140	81.278	0.0713	88.823	332.363	27.147	24.920	24.530
	SD:	1.197	2.503	0.0117	10.973	45.019	3.290	2.202	1.196
2350026	4	11.24	79.43	0.070	85.47	345.98	34.35	20.31	19.69
2350028	4	11.92	88.91	0.072	99.52	344.92	36.92	52.34	NT
2350030	4	9.60	67.50	0.056	82.90	252.33	25.04	19.57	20.00
2350032	4	9.70	74.98	0.082	92.43	267.42	21.40	22.82	21.98
	Mean:	10.615	77.705	0.0700	90.080	302.663	29.427	28.760	20.557
	SD:	1.149	8.946	0.0107	7.471	49.791	7.395	15.781	1.242

NT = Not taken

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9A - Absolute organ weights (g) - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Terminal body wt.(kg)	L. Thyroid	R. Thyroid	L. Adrenal	R. Adrenal	L. Testis	R. Testis
2350002	1	11.90	0.400	0.460	0.419	0.423	8.000	10.122
2350004	1	11.54	0.487	0.552	0.449	0.506	8.902	8.711
2350006	1	12.00	0.475	0.524	0.642	0.553	9.932	10.353
2350008	1	10.86	0.445	0.444	0.602	0.537	9.180	9.331
	Mean:	11.575	0.4518	0.4950	0.5280	0.5048	9.0035	9.6293
	SD:	0.516	0.0388	0.0514	0.1104	0.0579	0.7980	0.7525
2350010	2	13.06	0.553	0.636	0.624	0.834	9.495	8.989
2350012	2	11.80	0.382	0.427	0.579	0.564	6.456	6.865
2350014	2	12.38	0.354	0.448	0.486	0.587	7.902	7.632
2350016	2	11.44	0.362	0.428	0.452	0.460	8.153	8.333
	Mean:	12.170	0.4128	0.4848	0.5353	0.6113	8.0015	7.9548
	SD:	0.709	0.0942	0.1013	0.0799	0.1584	1.2453	0.9137
2350018	3	11.52	0.355	0.317	0.436	0.480	7.577	7.623
2350020	3	11.78	0.354	0.368	0.451	0.485	9.527	8.541
2350022	3	9.36	0.243	0.240	0.510	0.602	5.438	4.851
2350024	3	11.90	0.480	0.535	0.500	0.588	9.311	9.396
	Mean:	11.140	0.3580	0.3650	0.4743	0.5388	7.9633	7.6028
	SD:	1.197	0.0968	0.1250	0.0363	0.0652	1.8963	1.9722
2350026	4	11.24	0.455	0.451	0.473	0.546	9.317	8.690
2350028	4	11.92	0.322	0.418	0.519	0.790	10.001	8.758
2350030	4	9.60	0.341	0.408	0.520	0.495	7.181	7.871
2350032	4	9.70	0.511	0.452	0.549	0.560	8.249	8.892
	Mean:	10.615	0.4073	0.4323	0.5153	0.5978	8.6870	8.5527
	SD:	1.149	0.0907	0.0226	0.0314	0.1312	1.2360	0.4622

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9A - Absolute organ weights (g) - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Terminal body wt.(kg)	Brain	Pituitary	Heart	Liver	Spleen	L. Kidney	R. Kidney
2350001	1	9.22	80.53	0.071	81.24	288.24	23.46	24.31	22.17
2350003	1	8.34	76.54	0.064	52.73	236.93	21.03	19.36	18.50
2350005	1	11.44	79.60	0.073	84.76	331.51	27.31	30.20	27.97
2350007	1	9.78	80.65	0.474	70.24	283.89	25.04	22.61	23.59
	Mean:	9.695	79.331	0.1705	72.243	285.143	24.210	24.120	23.058
	SD:	1.306	1.917	0.2024	14.404	38.668	2.644	4.544	3.915
2350009	2	7.88	77.09	0.061	65.61	214.78	21.60	18.27	17.64
2350011	2	9.94	68.94	0.074	72.43	265.24	42.69	24.30	21.95
2350013	2	9.58	84.24	0.070	81.52	273.49	39.27	20.45	19.58
2350015	2	8.90	84.41	0.058	82.40	272.57	37.06	21.19	20.11
	Mean:	9.075	78.670	0.0658	75.490	256.520	35.155	21.052	19.820
	SD:	0.906	7.329	0.0075	7.981	28.070	9.329	2.495	1.773
2350017	3	10.20	87.50	0.063	86.45	283.45	29.57	21.21	19.95
2350019	3	9.60	77.91	0.073	78.17	304.37	31.22	19.46	19.28
2350021	3	9.72	75.41	0.090	76.74	294.28	33.04	19.64	19.66
2350023	3	7.80	73.97	0.059	69.41	239.20	20.37	15.45	14.68
	Mean:	9.330	78.698	0.0713	77.692	280.325	28.550	18.940	18.392
	SD:	1.052	6.090	0.0138	6.986	28.717	5.634	2.456	2.490
2350025	4	9.20	77.13	0.075	67.32	227.47	33.13	18.34	19.23
2350027	4	9.30	74.32	0.062	68.51	249.18	28.46	21.17	21.83
2350029	4	9.14	76.10	0.077	74.84	261.73	23.14	19.41	19.20
2350031	4	9.46	79.85	0.069	79.62	267.53	29.85	21.40	24.27
	Mean:	9.275	76.850	0.0708	72.573	251.478	28.645	20.080	21.132
	SD:	0.140	2.312	0.0068	5.742	17.743	4.160	1.461	2.428

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
Dr. Alfredo Mandarino

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9A - Absolute organ weights (g) - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Terminal body wt.(kg)	L. Thyroid	R. Thyroid	L. Adrenal	R. Adrenal	Uterus	L. Ovary	R. Ovary
2350001	1	9.22	0.340	0.325	0.526	0.469	2.112	0.358	0.356
2350003	1	8.34	0.333	0.340	0.473	0.458	1.900	0.296	0.237
2350005	1	11.44	0.316	0.343	0.600	0.576	11.070	2.481	1.425
2350007	1	9.78	0.403	0.366	0.575	0.559	1.797	0.323	0.301
	Mean:	9.695	0.3480	0.3435	0.5435	0.5155	4.2197	0.8645	0.5798
	SD:	1.306	0.0380	0.0169	0.0562	0.0606	4.5687	1.0780	0.5656
2350009	2	7.88	0.358	0.276	0.392	0.428	1.887	0.358	0.304
2350011	2	9.94	0.295	0.360	0.506	0.539	1.370	0.304	0.348
2350013	2	9.58	0.394	0.409	0.684	0.672	1.583	0.419	0.366
2350015	2	8.90	0.386	0.351	0.402	0.404	2.351	0.361	0.295
	Mean:	9.075	0.3583	0.3490	0.4960	0.5108	1.7978	0.3605	0.3283
	SD:	0.906	0.0449	0.0549	0.1355	0.1225	0.4255	0.0470	0.0342
2350017	3	10.20	0.376	0.287	0.524	0.624	12.743	0.763	0.684
2350019	3	9.60	0.386	0.491	0.465	0.595	2.977	0.304	0.328
2350021	3	9.72	0.321	0.286	0.443	0.433	1.968	0.341	0.374
2350023	3	7.80	0.230	0.250	0.515	0.543	1.163	0.415	0.369
	Mean:	9.330	0.3283	0.3285	0.4868	0.5488	4.7127	0.4558	0.4388
	SD:	1.052	0.0715	0.1097	0.0390	0.0841	5.4047	0.2100	0.1649
2350025	4	9.20	0.377	0.301	0.499	0.469	1.963	0.409	0.421
2350027	4	9.30	0.395	0.465	0.518	0.554	1.413	0.246	0.228
2350029	4	9.14	0.333	0.245	0.488	0.450	1.346	0.364	0.323
2350031	4	9.46	0.365	0.368	0.597	0.624	1.649	0.475	0.417
	Mean:	9.275	0.3675	0.3448	0.5255	0.5243	1.5928	0.3735	0.3473
	SD:	0.140	0.0261	0.0946	0.0493	0.0805	0.2790	0.0965	0.0915

LIFE SCIENCE RESEARCH
Roma Toxicology Centre

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9B - Relative organ weights+ - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Terminal body wt.(kg)	Brain	Pituitary	Heart	Liver	Spleen	L. Kidney	R. Kidney
2350002	1	11.90	0.71	0.001	0.74	2.72	0.22	0.19	0.19
2350004	1	11.54	0.71	0.001	0.77	3.10	0.29	0.23	0.22
2350006	1	12.00	0.68	0.001	0.76	2.49	0.30	0.23	0.23
2350008	1	10.86	0.74	0.001	0.78	2.91	0.36	0.23	0.23
	Mean:	11.575	0.709	0.0006	0.765	2.808	0.292	0.222	0.216
	SD:	0.516	0.028	0.0001	0.016	0.261	0.059	0.023	0.016
2350010	2	13.06	0.73	0.001	0.81	2.81	0.25	0.39	NT
2350012	2	11.80	0.71	0.000	0.75	2.61	0.27	0.19	0.20
2350014	2	12.38	0.63	0.000	0.82	2.81	0.28	0.18	0.20
2350016	2	11.44	0.81	0.001	0.77	3.23	0.25	0.21	0.20
	Mean:	12.170	0.721	0.0006	0.787	2.864	0.261	0.243	0.199
	SD:	0.709	0.073	0.0001	0.033	0.261	0.017	0.097	0.002
2350018	3	11.52	0.69	0.000	0.74	2.61	0.20	0.22	0.21
2350020	3	11.78	0.72	0.001	0.89	3.37	0.24	0.23	0.22
2350022	3	9.36	0.85	0.001	0.91	3.24	0.29	0.23	0.25
2350024	3	11.90	0.69	0.001	0.68	2.76	0.26	0.21	0.20
	Mean:	11.140	0.736	0.0006	0.803	2.995	0.246	0.224	0.222
	SD:	1.197	0.079	0.0001	0.114	0.366	0.038	0.009	0.023
2350026	4	11.24	0.71	0.001	0.76	3.08	0.31	0.18	0.18
2350028	4	11.92	0.75	0.001	0.83	2.89	0.31	0.44	NT
2350030	4	9.60	0.70	0.001	0.86	2.63	0.26	0.20	0.21
2350032	4	9.70	0.77	0.001	0.95	2.76	0.22	0.24	0.23
	Mean:	10.615	0.732	0.0007	0.853	2.839	0.274	0.265	0.203
	SD:	1.149	0.033	0.0001	0.080	0.193	0.042	0.118	0.026

+ Expressed as % organ to body weight ratio
NT = Not taken

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9B - Relative organ weights+ - Individual data

STUDY NO.: 235-003-009

MALES

Animal Number	Group	Terminal body wt.(kg)	L. Thyroid	R. Thyroid	L. Adrenal	R. Adrenal	L. Testis	R. Testis
2350002	1	11.90	0.003	0.004	0.004	0.004	0.067	0.085
2350004	1	11.54	0.004	0.005	0.004	0.004	0.077	0.075
2350006	1	12.00	0.004	0.004	0.005	0.005	0.083	0.086
2350008	1	10.86	0.004	0.004	0.006	0.005	0.085	0.086
	Mean:	11.575	0.0039	0.0043	0.0046	0.0044	0.0779	0.0832
	SD:	0.516	0.0004	0.0004	0.0010	0.0006	0.0078	0.0052
2350010	2	13.06	0.004	0.005	0.005	0.006	0.073	0.069
2350012	2	11.80	0.003	0.004	0.005	0.005	0.055	0.058
2350014	2	12.38	0.003	0.004	0.004	0.005	0.064	0.062
2350016	2	11.44	0.003	0.004	0.004	0.004	0.071	0.073
	Mean:	12.170	0.0034	0.0040	0.0044	0.0050	0.0656	0.0654
	SD:	0.709	0.0006	0.0006	0.0005	0.0010	0.0083	0.0067
2350018	3	11.52	0.003	0.003	0.004	0.004	0.066	0.066
2350020	3	11.78	0.003	0.003	0.004	0.004	0.081	0.073
2350022	3	9.36	0.003	0.003	0.005	0.006	0.058	0.052
2350024	3	11.90	0.004	0.004	0.004	0.005	0.078	0.079
	Mean:	11.140	0.0032	0.0032	0.0043	0.0049	0.0707	0.0674
	SD:	1.197	0.0006	0.0009	0.0008	0.0011	0.0107	0.0116
2350026	4	11.24	0.004	0.004	0.004	0.005	0.083	0.077
2350028	4	11.92	0.003	0.004	0.004	0.007	0.084	0.073
2350030	4	9.60	0.004	0.004	0.005	0.005	0.075	0.082
2350032	4	9.70	0.005	0.005	0.006	0.006	0.085	0.092
	Mean:	10.615	0.0039	0.0041	0.0049	0.0056	0.0817	0.0811
	SD:	1.149	0.0011	0.0005	0.0007	0.0008	0.0047	0.0079

+ Expressed as % organ to body weight ratio

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9B - Relative organ weights+ - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Terminal body wt.(kg)	Brain	Pituitary	Heart	Liver	Spleen	L. Kidney	R. Kidney
2350001	1	9.22	0.87	0.001	0.88	3.13	0.25	0.26	0.24
2350003	1	8.34	0.92	0.001	0.63	2.84	0.25	0.23	0.22
2350005	1	11.44	0.70	0.001	0.74	2.90	0.24	0.26	0.24
2350007	1	9.78	0.82	0.005	0.72	2.90	0.26	0.23	0.24
	Mean:	9.695	0.828	0.0018	0.743	2.942	0.250	0.248	0.237
	SD:	1.306	0.096	0.0021	0.103	0.126	0.008	0.019	0.010
2350009	2	7.88	0.98	0.001	0.83	2.73	0.27	0.23	0.22
2350011	2	9.94	0.69	0.001	0.73	2.67	0.43	0.24	0.22
2350013	2	9.58	0.88	0.001	0.85	2.85	0.41	0.21	0.20
2350015	2	8.90	0.95	0.001	0.93	3.06	0.42	0.24	0.23
	Mean:	9.075	0.875	0.0007	0.835	2.828	0.382	0.232	0.219
	SD:	0.906	0.128	0.0001	0.081	0.175	0.073	0.013	0.010
2350017	3	10.20	0.86	0.001	0.85	2.78	0.29	0.21	0.20
2350019	3	9.60	0.81	0.001	0.81	3.17	0.33	0.20	0.20
2350021	3	9.72	0.78	0.001	0.79	3.03	0.34	0.20	0.20
2350023	3	7.80	0.95	0.001	0.89	3.07	0.26	0.20	0.19
	Mean:	9.330	0.848	0.0008	0.835	3.011	0.304	0.203	0.197
	SD:	1.052	0.075	0.0001	0.043	0.166	0.035	0.004	0.006
2350025	4	9.20	0.84	0.001	0.73	2.47	0.36	0.20	0.21
2350027	4	9.30	0.80	0.001	0.74	2.68	0.31	0.23	0.23
2350029	4	9.14	0.83	0.001	0.82	2.86	0.25	0.21	0.21
2350031	4	9.46	0.84	0.001	0.84	2.83	0.32	0.23	0.26
	Mean:	9.275	0.829	0.0008	0.782	2.711	0.309	0.216	0.228
	SD:	0.140	0.020	0.0001	0.056	0.178	0.044	0.013	0.023

+ Expressed as % organ to body weight ratio

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 9B - Relative organ weights+ - Individual data

STUDY NO.: 235-003-009

FEMALES

Animal Number	Group	Terminal body wt.(kg)	L. Thyroid	R. Thyroid	L. Adrenal	R. Adrenal	Uterus	L. Ovary	R. Ovary
2350001	1	9.22	0.004	0.004	0.006	0.005	0.023	0.004	0.004
2350003	1	8.34	0.004	0.004	0.006	0.005	0.023	0.004	0.003
2350005	1	11.44	0.003	0.003	0.005	0.005	0.097	0.022	0.012
2350007	1	9.78	0.004	0.004	0.006	0.006	0.018	0.003	0.003
	Mean:	9.695	0.0036	0.0036	0.0056	0.0053	0.0402	0.0081	0.0056
	SD:	1.306	0.0006	0.0005	0.0003	0.0003	0.0378	0.0091	0.0046
2350009	2	7.88	0.005	0.004	0.005	0.005	0.024	0.005	0.004
2350011	2	9.94	0.003	0.004	0.005	0.005	0.014	0.003	0.004
2350013	2	9.58	0.004	0.004	0.007	0.007	0.017	0.004	0.004
2350015	2	8.90	0.004	0.004	0.005	0.005	0.026	0.004	0.003
	Mean:	9.075	0.0040	0.0038	0.0054	0.0056	0.0202	0.0040	0.0036
	SD:	0.906	0.0007	0.0003	0.0012	0.0010	0.0060	0.0007	0.0003
2350017	3	10.20	0.004	0.003	0.005	0.006	0.125	0.007	0.007
2350019	3	9.60	0.004	0.005	0.005	0.006	0.031	0.003	0.003
2350021	3	9.72	0.003	0.003	0.005	0.004	0.020	0.004	0.004
2350023	3	7.80	0.003	0.003	0.007	0.007	0.015	0.005	0.005
	Mean:	9.330	0.0035	0.0035	0.0053	0.0059	0.0478	0.0049	0.0047
	SD:	1.052	0.0005	0.0011	0.0009	0.0011	0.0519	0.0020	0.0015
2350025	4	9.20	0.004	0.003	0.005	0.005	0.021	0.004	0.005
2350027	4	9.30	0.004	0.005	0.006	0.006	0.015	0.003	0.002
2350029	4	9.14	0.004	0.003	0.005	0.005	0.015	0.004	0.004
2350031	4	9.46	0.004	0.004	0.006	0.007	0.017	0.005	0.004
	Mean:	9.275	0.0040	0.0037	0.0057	0.0056	0.0172	0.0040	0.0037
	SD:	0.140	0.0003	0.0010	0.0004	0.0008	0.0030	0.0010	0.0010

+ Expressed as % organ to body weight ratio

LIFE SCIENCE RESEARCH
Rome Toxicology Centre S.p.A

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350002 Sex: Male Group: 1 Dose level: Control
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 11.90

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	SCAB/S, One site, Skin at site.
Kidneys	No abnormalities detected.	LYMPHOCYTIC INFILTRATION, Unilateral, Moderate.
Liver	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.
Whole body	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Lungs	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350004 Sex: Male Group: 1 Dose level: Control
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 11.54

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic right saphenous	HAEMORRHAGE, Two sites, Focal, Slight, Subcutis.
	No abnormalities detected/ left cephalic	ACUTE INFLAMMATION, One site, Focal, Slight, Subcutis
Pituitary	No abnormalities detected.	Tissue is missing.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Kidneys	Liver	Lungs	Mammary area	Mesenteric nodes
Nictitating gl.	Nictitating mem.	Oesophagus	Optic nerves	Pancreas
Parathyroid gl.	Peribronc.nodes	Prostate gland	Rectum	Salivary gland
Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord
Spleen	Sternum	Stomach	Testes	Thyroid gland
Thymus	Tongue	Trachea	Urinary Bladder	

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350006 Sex: Male Group: 1 Dose level: Control
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 12.00

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic right saphenous	HAEMORRHAGE, One site, Diffuse, Moderate, Subcutis.
	No abnormalities detected/ left cephalic	
Liver	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.
Lungs	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Kidneys	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350008 Sex: Male Group: 1 Dose level: Control
Day of death: 94 Status: Final sacrifice Terminal body weight (kg): 10.86

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right saphenous	HAEMORRHAGE, One site, Diffuse, Slight, Subcutis.
	Abnormal colour, Dark, Subcutis/ right cephalic	LYMPHOCYTIC INFILTRATION, One site, Multifocal, Mild Subcutis.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Kidneys	Liver	Lungs	Mammary area	Mesenteric nodes
Nictitating gl.	Nictitating mem.	Oesophagus	Optic nerves	Pancreas
Parathyroid gl.	Peribronc.nodes	Pituitary	Prostate gland	Rectum
Salivary gland	Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin
Spinal Cord	Spleen	Sternum	Stomach	Testes
Thyroid gland	Thymus	Tongue	Trachea	Urinary Bladder

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350010 Sex: Male Group: 2 Dose level: 110.0 mg/kg/day
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 13.06

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic	HAEMORRHAGE, One site, Focal, Slight, Subcutis.
	No abnormalities detected/ left cephalic right saphenous	
Kidneys	Abnormal size, Enlarged, Left	HYPERPLASIA, Mild, Left.
	Not present, Right	
Lungs	Not collapsed	BLOOD IN BRONCHI/ALVEOLI, Multifocal.
	Abnormal consistency, Firm	
	Abnormal Area(s), Multiple, Dark/ left and right caudal, right cranial up to 30x20mm.	
Peribronc.nodes . .	Abnormal size, Enlarged/ up to 29x14x7mm	NO SIGNIFICANT LESION.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Liver	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Pancreas	Parathyroid gl.	Pituitary
Prostate gland	Rectum	Salivary gland	Submandibular ln	Sciatic Nerve
Skeletal Muscle	Skin	Spinal Cord	Spleen	Sternum
Stomach	Testes	Thyroid gland	Thymus	Tongue
Trachea	Urinary Bladder			

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350012	Sex: Male	Group: 2	Dose level: 110.0 mg/kg/day
Day of death: 93	Status: Final sacrifice		Terminal body weight (kg): 11.80

Tissue	Gross observations / Comments	Microscopic observations / Comments
Caecum	No abnormalities detected.	MUCOSAL CONGESTION, Mild.
Colon	No abnormalities detected.	MUCOSAL CONGESTION, Mild.
Injection sites . .	Abnormal colour, Dark, Subcutis/ left cephalic	NO SIGNIFICANT LESION.
	No abnormalities detected/ right cephalic right saphenous	
Lungs	Not collapsed	NO SIGNIFICANT LESION.
Spleen	Abnormal Area(s), Single, Dark, Raised/ 60x9mm	HAEMORRHAGE, Moderate.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Duodenum	Epididymis	Eyes	Gall Bladder	Heart
Ileum	Inj site control	Jejunum	Kidneys	Liver
Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus
Optic nerves	Pancreas	Parathyroid gl.	Peribronc.nodes	Pituitary
Prostate gland	Rectum	Salivary gland	Submandibular ln	Sciatic Nerve
Skeletal Muscle	Skin	Spinal Cord	Sternum	Stomach
Testes	Thyroid gland	Thymus	Tongue	Trachea
Urinary Bladder				

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APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350014	Sex: Male	Group: 2	Dose level: 110.0 mg/kg/day
Day of death: 93	Status: Final sacrifice		Terminal body weight (kg): 12.38

Tissue	Gross observations / Comments	Microscopic observations / Comments
Gall Bladder . . .	Abnormal Contents, Dark, Granular	NO SIGNIFICANT LESION.
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic	HAEMORRHAGE, One site, Focal, Mild, Subcutis.
	No abnormalities detected/ left cephalic right saphenous	
Prostate gland . .	Abnormal size, Small	HYPOPLASIA, Slight.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Lungs	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350016	Sex: Male	Group: 2	Dose level: 110.0 mg/kg/day
Day of death: 94	Status: Final sacrifice		Terminal body weight (kg): 11.44

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ left cephalic right cephalic	HAEMORRHAGE, Two sites, Diffuse, Moderate, Subcutis.
	No abnormalities detected/ right saphenous	
Lungs	Abnormal Area(s), Single, Dark/ 3x2mm, left caudal	NO SIGNIFICANT LESION.
Pituitary	No abnormalities detected.	CRANIO-PHARYNGEAL CYST/S.
Lymph nodes	Abnormal colour, Dark/ thymic	HAEMORRHAGE, Mild, Thymic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Kidneys	Liver	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Pancreas	Parathyroid gl.
Peribronc.nodes	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350018 Sex: Male Group: 3 Dose level: 220.0 mg/kg/day
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 11.52

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic	NO SIGNIFICANT LESION, One site.
	No abnormalities detected/ left cephalic right saphenous	
Lungs	Abnormal Area(s), Single, Dark, Firm/ 6x5mm, left cranial.	BRONCHOPNEUMONIA, Focal, Moderate.
Parathyroid gl. . .	No abnormalities detected.	BRANCHIAL CYST/S.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Kidneys	Liver	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Pancreas	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350020 Sex: Male Group: 3 Dose level: 220.0 mg/kg/day
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 11.78

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic	NO SIGNIFICANT LESION.
	No abnormalities detected/ left cephalic right saphenous	
Liver	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.
Lungs	Abnormal Area(s), Multiple, Pale/ Up to 5x3mm	PERIVASCULAR LYMPHOCYTIC INFILTRATION, Multifocal, Slight.
Parathyroid gl. . .	No abnormalities detected.	BRANCHIAL CYST/S.
Skin	Abnormal areas, Encrusted, Two/ Neck	ULCERATION, Moderate.
		ACUTE INFLAMMATION, Moderate.
		SCAB FORMATION.
Lymph nodes	Abnormal colour, Dark/ Pancreatic	HAEMORRHAGE, Moderate, Pancreatic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Kidneys	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Pancreas	Peribronc.nodes	Pituitary
Prostate gland	Rectum	Salivary gland	Submandibular ln	Sciatic Nerve
Skeletal Muscle	Spinal Cord	Spleen	Sternum	Stomach
Testes	Thyroid gland	Thymus	Tongue	Trachea
Urinary Bladder				

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350022 Sex: Male Group: 3 Dose level: 220.0 mg/kg/day
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 9.36

Tissue	Gross observations / Comments	Microscopic observations / Comments
Inj site control	No abnormalities detected.	HAEMORRHAGE, Focal, Slight, Subcutis.
Injection sites	No abnormalities detected/ left cephalic right cephalic right saphenous	HAEMORRHAGE, One site, Focal, Slight, Subcutis.
Submandibular ln	No abnormalities detected.	BROWN PIGMENTATION, Focal, Moderate.
Whole body	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Jejunum	Kidneys
Liver	Lungs	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350024 Sex: Male Group: 3 Dose level: 220.0 mg/kg/day
Day of death: 94 Status: Final sacrifice Terminal body weight (kg): 11.90

Tissue	Gross observations / Comments	Microscopic observations / Comments
Ileum	Abnormal colour, Red, Mucosa/ part	MUCOSAL CONGESTION, Focal, Slight.
Inj site control .	No abnormalities detected.	HAEMORRHAGE, Focal, Slight, Subcutis.
Injection sites . .	No abnormalities detected/ left cephalic right cephalic	HAEMORRHAGE, One site, Diffuse, Moderate, Subcutis.
	Abnormal colour, Dark, Subcutis/ right saphenous	
Kidneys	No abnormalities detected.	CHRONIC INTERSTITIAL NEPHRITIS, Focal, Moderate.
Lungs	Abnormal Area(s), Multiple, Dark, Pale, Firm/ up to 6x5mm.	CHRONIC INFLAMMATION, Focal, Moderate.
		BLOOD IN BRONCHI/ALVEOLI, Probably agonal.
Parathyroid gl. . .	No abnormalities detected.	BRANCHIAL CYST/S.
Pituitary	No abnormalities detected.	CRANIO-PHARYNGEAL CYST/S.
		CHRONIC INFLAMMATION, Focal, Moderate, Pars intermedia.
Spleen	No abnormalities detected.	B- HAEMANGIOMA.
Thyroid gland . . .	No abnormalities detected.	GRANULOMA.

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350024	Sex: Male	Group: 3	Dose level: 220.0 mg/kg/day
Day of death: 94	Status: Final sacrifice		Terminal body weight (kg): 11.90

Tissue	Gross observations / Comments	Microscopic observations / Comments
Lymph nodes	Abnormal colour, Dark/ thymic	HAEMORRHAGE, Slight, Pancreatic.
	Abnormal size, Enlarged/ 20x7x4mm - pancreatic	NO SIGNIFICANT LESION, Thymic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Jejunum	Liver	Mammary area
Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus	Optic nerves
Pancreas	Peribronc.nodes	Prostate gland	Rectum	Salivary gland
Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord
Sternum	Stomach	Testes	Thymus	Tongue
Trachea	Urinary Bladder			

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350026 Sex: Male Group: 4 Dose level: 440.0 mg/kg/day
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 11.24

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right cephalic	HAEMORRHAGE, One site, Focal, Slight, Subcutis.
	Abnormal colour, Dark, Subcutis/ right saphenous	ACUTE INFLAMMATION, One site, Focal, Mild, Subcutis.
Lungs	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.
Skin	Abnormal Colour, Red, Cutaneous/ right hind limb	NO SIGNIFICANT LESION.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Kidneys	Liver	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Submandibular ln	Sciatic Nerve	Skeletal Muscle	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350028 Sex: Male Group: 4 Dose level: 440.0 mg/kg/day
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 11.92

Tissue	Gross observations / Comments	Microscopic observations / Comments
Colon	No abnormalities detected.	MUCOSAL CONGESTION, Mild.
Gall Bladder . . .	Abnormal Contents, Dark, Granular	MUCOSAL CONGESTION, Mild.
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic	HAEMORRHAGE, One site, Diffuse, Moderate, Subcutis.
	No abnormalities detected/ left cephalic right saphenous	
Kidneys	Abnormal size, Enlarged, Left/ 78x40x35mm	HYPERPLASIA, Moderate, Left.
	Not present, Right	
Lungs	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.
Submandibular ln .	No abnormalities detected.	BROWN PIGMENTATION, Focal, Mild.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Duodenum	Epididymis	Eyes	Heart
Ileum	Inj site control	Jejunum	Liver	Mammary area
Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus	Optic nerves
Pancreas	Parathyroid gl.	Peribronc.nodes	Pituitary	Prostate gland
Rectum	Salivary gland	Sciatic Nerve	Skeletal Muscle	Skin
Spinal Cord	Spleen	Sternum	Stomach	Testes
Thyroid gland	Thymus	Tongue	Trachea	Urinary Bladder

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350030 Sex: Male Group: 4 Dose level: 440.0 mg/kg/day
Day of death: 94 Status: Final sacrifice Terminal body weight (kg): 9.60

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ right cephalic right saphenous	HAEMORRHAGE, Two sites, Focal, Mild, Subcutis.
	No abnormalities detected/ left cephalic	ACUTE INFLAMMATION, One site, Multifocal, Moderate, Subcutis.
Kidneys	No abnormalities detected.	LYMPHOCYTIC INFILTRATION, Unilateral, Slight, Cortex.
		TUBULAR DILATATION, Unilateral, Slight, Medulla.
Lungs	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Gall Bladder	Heart	Ileum	Inj site control	Jejunum
Liver	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350032	Sex: Male	Group: 4	Dose level: 440.0 mg/kg/day
Day of death: 94	Status: Final sacrifice		Terminal body weight (kg): 9.70

Tissue	Gross observations / Comments	Microscopic observations / Comments
Gall Bladder . . .	Abnormal Contents, Dark, Granular	NO SIGNIFICANT LESION.
Injection sites . .	No abnormalities detected/ left cephalic right cephalic	HAEMORRHAGE, One site, Diffuse, Moderate.
	Abnormal colour, Dark, Subcutis/ right saphenous	
Submandibular ln .	No abnormalities detected.	BROWN PIGMENTATION, Diffuse, Moderate.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Epididymis	Eyes
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Lungs	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Testes	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350001 Sex: Female Group: 1 Dose level: Control
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 9.22

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	NO ABNORMALITIES DETECTED.
Lungs	No abnormalities detected.	PERIVASCULAR LYMPHOCYTIC INFILTRATION, Focal, Slight.
Whole body	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Ovaries	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord
Spleen	Sternum	Stomach	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder	Uterus	

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350003 Sex: Female Group: 1 Dose level: Control
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 8.34

Tissue	Gross observations / Comments	Microscopic observations / Comments
Gall Bladder . . .	Abnormal Contents, Dark, Granular	NO SIGNIFICANT LESION.
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	NO ABNORMALITIES DETECTED.
Kidneys	No abnormalities detected.	GRANULOMA/S, Unilateral.
Lungs	Abnormal Area(s), Multiple, Dark, Pale, Firm/ up to 6x6mm	CHRONIC INFLAMMATION, Focal, Slight.
Lymph nodes	Abnormal colour, Dark/ pancreatic	HAEMORRHAGE, Mild, Pancreatic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Heart
Ileum	Inj site control	Jejunum	Liver	Mammary area
Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus	Optic nerves
Ovaries	Pancreas	Parathyroid gl.	Peribronc.nodes	Pituitary
Prostate gland	Rectum	Salivary gland	Submandibular ln	Sciatic Nerve
Skeletal Muscle	Skin	Spinal Cord	Spleen	Sternum
Stomach	Thyroid gland	Thymus	Tongue	Trachea
Urinary Bladder	Uterus			

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350005 Sex: Female Group: 1 Dose level: Control
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 11.44

Tissue	Gross observations / Comments	Microscopic observations / Comments
Gall Bladder . . .	Abnormal Contents, Dark, Granular	NO SIGNIFICANT LESION.
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	HAEMORRHAGE, One site, Focal, Moderate, Subcutis.
Lungs	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.
Submandibular ln .	Abnormal colour, Dark	BROWN PIGMENTATION, Focal, Slight.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Heart
Ileum	Inj site control	Jejunum	Kidneys	Liver
Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus
Optic nerves	Ovaries	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Sciatic Nerve
Skeletal Muscle	Skin	Spinal Cord	Spleen	Sternum
Stomach	Thyroid gland	Thymus	Tongue	Trachea
Urinary Bladder	Uterus			

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350007 Sex: Female Group: 1 Dose level: Control
Day of death: 94 Status: Final sacrifice Terminal body weight (kg): 9.78

Tissue	Gross observations / Comments	Microscopic observations / Comments
Adrenals	No abnormalities detected.	GRANULOMA/S.
Injection sites . .	Abnormal colour, Dark, Subcutis/ left cephalic	HAEMORRHAGE, Two sites, Diffuse, Moderate, Subcutis.
	No abnormalities detected/ right saphenous right cephalic	LYMPHOCYTIC INFILTRATION, One site, Multifocal, Moderate, Subcutis.
Lungs	No abnormalities detected.	CHRONIC INFLAMMATION, Focal, Slight.
Urinary Bladder . .	No abnormalities detected.	Tissue is missing.

The following tissues are normal microscopically:

Aorta	Bone Marrow	Brain	Bronchi	Caecum
Colon	Duodenum	Eyes	Gall Bladder	Heart
Ileum	Inj site control	Jejunum	Kidneys	Liver
Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus
Optic nerves	Ovaries	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Thyroid gland	Thymus	Tongue
Trachea	Uterus			

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350009	Sex: Female	Group: 2	Dose level: 110.0 mg/kg/day
Day of death: 92	Status: Final sacrifice		Terminal body weight (kg): 7.88

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic	HAEMORRHAGE, Two sites, Diffuse, Mild, Subcutis.
	Abnormal colour, Dark, Subcutis/ right cephalic right saphenous	
Lymph nodes	Abnormal size, Enlarged/ up to 15x8x6mm - pancreatic	NO SIGNIFICANT LESION, Pancreatic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Lungs	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Ovaries	Pancreas
Parathyroid gl.	Peribronc.nodes	Pituitary	Prostate gland	Rectum
Salivary gland	Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin
Spinal Cord	Spleen	Sternum	Stomach	Thyroid gland
Thymus	Tongue	Trachea	Urinary Bladder	Uterus

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350011 Sex: Female Group: 2 Dose level: 110.0 mg/kg/day
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 9.94

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right saphenous	HAEMORRHAGE, Two sites, Focal, Mild, Subcutis.
	Abnormal colour, Dark, Subcutis/ right cephalic	
Liver	No abnormalities detected.	Tissue is missing.
Submandibular ln .	No abnormalities detected.	BROWN PIGMENTATION, Focal, Moderate.
Spleen	Abnormal Shape, Swollen	NO SIGNIFICANT LESION.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Lungs	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Ovaries	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Sternum
Stomach	Thyroid gland	Thymus	Tongue	Trachea
Urinary Bladder	Uterus			

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350013 Sex: Female Group: 2 Dose level: 110.0 mg/kg/day
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 9.58

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous Thymic, pancreatic	HAEMORRHAGE, One site, Focal, Slight, Wall.
Mesenteric nodes .	Abnormal Colour, Dark	NO SIGNIFICANT LESION.
Pituitary	No abnormalities detected.	CRANIO-PHARYNGEAL CYST/S.
Lymph nodes	Abnormal colour, Dark/ Thymic, pancreatic	HAEMORRHAGE, Mild, Pancreatic,thymic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Lungs	Mammary area	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Ovaries	Pancreas	Parathyroid gl.
Peribronc.nodes	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Thyroid gland	Thymus	Tongue
Trachea	Urinary Bladder	Uterus		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data-

STUDY NO.: 235-003-009

Animal: 2350015 Sex: Female Group: 2 Dose level: 110.0 mg/kg/day
Day of death: 94 Status: Final sacrifice Terminal body weight (kg): 8.90

Tissue	Gross observations / Comments	Microscopic observations / Comments
Gall Bladder . . .	Abnormal Contents, Dark, Granular	NO SIGNIFICANT LESION.
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	HAEMORRHAGE, One site, Diffuse, Moderate, Subcutis.
Liver	No abnormalities detected.	PERIVASCULAR LYMPHOCYTIC INFILTRATION, Multifocal, Slight.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Heart
Ileum	Inj site control	Jejunum	Kidneys	Lungs
Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus
Optic nerves	Ovaries	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Thyroid gland	Thymus	Tongue
Trachea	Urinary Bladder	Uterus		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350017	Sex: Female	Group: 3	Dose level: 220.0 mg/kg/day
Day of death: 92	Status: Final sacrifice		Terminal body weight (kg): 10.20

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	NO ABNORMALITIES DETECTED.
Whole body	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Lungs	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Ovaries	Pancreas
Parathyroid gl.	Peribronc.nodes	Pituitary	Prostate gland	Rectum
Salivary gland	Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin
Spinal Cord	Spleen	Sternum	Stomach	Thyroid gland
Thymus	Tongue	Trachea	Urinary Bladder	Uterus

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350019 Sex: Female Group: 3 Dose level: 220.0 mg/kg/day
Day of death: 93 Status: Final sacrifice Terminal body weight (kg): 9.60

Tissue	Gross observations / Comments	Microscopic observations / Comments
Gall Bladder . . .	Abnormal Contents, Dark, Granular	NO SIGNIFICANT LESION.
Injection sites . .	Abnormal colour, Dark, Subcutis/ left cephalic right cephalic right saphenous	HAEMORRHAGE, One site, Diffuse, Moderate, Subcutis.
		CHRONIC INFLAMMATION, One site, Focal, Mild, Subcutis
Lymph nodes	Abnormal colour, Dark/ Pancreatic	NO SIGNIFICANT LESION, Pancreatic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Heart
Ileum	Inj site control	Jejunum	Kidneys	Liver
Lungs	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Ovaries	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord
Spleen	Sternum	Stomach	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder	Uterus	

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350021 Sex: Female Group: 3 Dose level: 220.0 mg/kg/day
Day of death: 94 Status: Final sacrifice Terminal body weight (kg): 9.72

Tissue	Gross observations / Comments	Microscopic observations / Comments
Duodenum	Abnormal area(s), Multiple, Dark/ up to 8x6mm	NO SIGNIFICANT LESION.
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	HAEMORRHAGE, One site, Focal, Mild, Subcutis.
Jejunum	Abnormal Area(s), Multiple, Dark/ up to 8x6mm.	MUCOSAL CONGESTION, Focal, Mild. VILLOUS NECROSIS, Multifocal, Moderate.
Lungs	Abnormal Area(s), Single, Dark, Firm/ 2x2mm, right caudal.	NO SIGNIFICANT LESION.
Mesenteric nodes .	Abnormal Colour, Dark	HAEMORRHAGE, Moderate.
Lymph nodes	Abnormal colour, Dark/ pancreatic	HAEMORRHAGE, Moderate, Pancreatic.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Eyes	Gall Bladder	Heart
Ileum	Inj site control	Kidneys	Liver	Mammary area
Nictitating gl.	Nictitating mem.	Oesophagus	Optic nerves	Ovaries
Pancreas	Parathyroid gl.	Peribronc.nodes	Pituitary	Prostate gland
Rectum	Salivary gland	Submandibular ln	Sciatic Nerve	Skeletal Muscle
Skin	Spinal Cord	Spleen	Sternum	Stomach
Thyroid gland	Thymus	Tongue	Trachea	Urinary Bladder
Uterus				

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350023	Sex: Female	Group: 3	Dose level: 220.0 mg/kg/day
Day of death: 94	Status: Final sacrifice		Terminal body weight (kg): 7.80

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right cephalic	HAEMORRHAGE, One site, Diffuse, Mild, Subcutis.
	Abnormal colour, Dark, Subcutis/ right saphenous	
Lungs	Abnormal Area(s), Pale, Two, Firm/ up to 2x2mm, left caudal	NO SIGNIFICANT LESION.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.
Oesophagus	Optic nerves	Ovaries	Pancreas	Parathyroid gl.
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord
Spleen	Sternum	Stomach	Thyroid gland	Thymus
Tongue	Trachea	Urinary Bladder	Uterus	

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350025 Sex: Female Group: 4 Dose level: 440.0 mg/kg/day
Day of death: 92 Status: Final sacrifice Terminal body weight (kg): 9.20

Tissue	Gross observations / Comments	Microscopic observations / Comments
Inj site control .	Abnormal colour, Dark, Subcutis/ left saphenous	NO SIGNIFICANT LESION.
Injection sites . .	Abnormal colour, Dark, Subcutis/ left cephalic right cephalic	HAEMORRHAGE, Two sites, Diffuse, Mild, Subcutis.
	No abnormalities detected/ right saphenous	
Liver	No abnormalities detected.	CHRONIC INFLAMMATION, Multifocal, Slight.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Jejunum	Kidneys	Lungs
Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus
Optic nerves	Ovaries	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Thyroid gland	Thymus	Tongue
Trachea	Urinary Bladder	Uterus		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350027	Sex: Female	Group: 4	Dose level: 440.0 mg/kg/day
Day of death: 93	Status: Final sacrifice		Terminal body weight (kg): 9.30

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right saphenous	CHRONIC INFLAMMATION, One site, Focal, Slight, Subcutis.
	Abnormal colour, Dark, Subcutis/ right cephalic	
Jejunum	Abnormal Area(s), Dark, Single/ 8x8mm	MUCOSAL CONGESTION, Focal, Moderate.
Kidneys	No abnormalities detected.	CHRONIC INTERSTITIAL NEPHRITIS, Focal, Mild.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Liver	Lungs
Mammary area	Mesenteric nodes	Nictitating gl.	Nictitating mem.	Oesophagus
Optic nerves	Ovaries	Pancreas	Parathyroid gl.	Peribronc.nodes
Pituitary	Prostate gland	Rectum	Salivary gland	Submandibular ln
Sciatic Nerve	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Thyroid gland	Thymus	Tongue
Trachea	Urinary Bladder	Uterus		

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350029	Sex: Female	Group: 4	Dose level: 440.0 mg/kg/day
Day of death: 94	Status: Final sacrifice		Terminal body weight (kg): 9.14

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	No abnormalities detected/ left cephalic right cephalic right saphenous	NO ABNORMALITIES DETECTED.
Whole body	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Lungs	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Ovaries	Pancreas
Parathyroid gl.	Peribronc.nodes	Pituitary	Prostate gland	Rectum
Salivary gland	Submandibular ln	Sciatic Nerve	Skeletal Muscle	Skin
Spinal Cord	Spleen	Sternum	Stomach	Thyroid gland
Thymus	Tongue	Trachea	Urinary Bladder	Uterus

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APPENDIX 10 - Macroscopic and Microscopic pathology - Individual data

STUDY NO.: 235-003-009

Animal: 2350031	Sex: Female	Group: 4	Dose level: 440.0 mg/kg/day
Day of death: 94	Status: Final sacrifice		Terminal body weight (kg): 9.46

Tissue	Gross observations / Comments	Microscopic observations / Comments
Injection sites . .	Abnormal colour, Dark, Subcutis/ left cephalic	HAEMORRHAGE, One site, Diffuse, Moderate, Subcutis.
	No abnormalities detected/ right cephalic right saphenous	
Parathyroid gl. . .	No abnormalities detected.	BRANCHIAL CYST/S.
Sciatic Nerve . . .	No abnormalities detected.	Tissue is missing.

The following tissues are normal microscopically:

Adrenals	Aorta	Bone Marrow	Brain	Bronchi
Caecum	Colon	Duodenum	Eyes	Gall Bladder
Heart	Ileum	Inj site control	Jejunum	Kidneys
Liver	Lungs	Mammary area	Mesenteric nodes	Nictitating gl.
Nictitating mem.	Oesophagus	Optic nerves	Ovaries	Pancreas
Peribronc.nodes	Pituitary	Prostate gland	Rectum	Salivary gland
Submandibular ln	Skeletal Muscle	Skin	Spinal Cord	Spleen
Sternum	Stomach	Thyroid gland	Thymus	Tongue
Trachea	Urinary Bladder	Uterus		

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FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 235-003-009

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FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 235-003-009

Abbreviations/parameters		Units/Key
ESR	ERYTHROCYTE SEDIMENTATION RATE	mm/hour
WBC	WHITE BLOOD CELL COUNT	10'3/cmm
RBC	RED BLOOD CELL COUNT	10'6/cmm
HGB	HAEMOGLOBIN	g/dl
HCT	HAEMATOCRIT	%
MCV	MEAN RBC CELL VOLUME	fl
MCH	MEAN CORPUSCULAR HAEMOGLOBIN	pg
MCHC	MEAN CORPUSCULAR HAEMOGLOBIN CONC.	g/dl
PLT	PLATELETS	10'3/cmm
NEU	NEUTROPHILS	%
LYM	LYMPHOCYTES	%
EOS	EOSINOPHILS	%
MON	MONOCYTES	%
BAS	BASOPHILS	%
RET	RETICULOCYTES	%
PT	PROTHROMBIN TIME	sec
APTT	PARTIAL THROMBOPLASTIN TIME	sec
AP	ALKALINE PHOSPHATASE	U/l
ALT	ALANINE TRANSFERASE	U/l
AST	ASPARTATE TRANSFERASE	U/l
CREA	CREATININE	mg/dl
GLU	GLUCOSE	mg/dl
BILT	TOTAL BILIRUBIN	mg/dl
CHOL	TOTAL CHOLESTEROL	mg/dl
PROT	TOTAL PROTEIN	g/dl
Cl-	CHLORIDE	mmol/l
Na+	SODIUM	mmol/l
K+	POTASSIUM	mmol/l
Ca++	CALCIUM	mmol/l
ALB	ALBUMIN	%
A1G	ALPHA 1 GLOBULIN	%
A2G	ALPHA 2 GLOBULIN	%
BETA	BETA GLOBULIN	%
AGR	ALBUMIN/GLOBULIN RATIO	
GAM	GAMMA GLOBULIN	%
GLUC	GLUCOSE	mg/dl
PRO	PROTEIN	mg/dl
HG	HAEMOGLOBIN	mg/dl
BIL	BILIRUBIN	mg/dl
UROB	UROBILINOGEN	EU%
KET	KETONES	mg/dl
SPG	SPECIFIC GRAVITY	g/l

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FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 235-003-009

Abbreviations/parameters		Units/Key
RED	REDUCING SUBSTANCES	0=0-2.5 g/l 1=2.5-7.5 g/l
NIT	NITRITE	0=Negative 1=Positive
EPI	EPITHELIAL CELLS	0=no cells or crystals
LEU	LEUCOCYTES	1=few cells or
ERY	ERYTHROCYTES	crystals in
		some fields
CRY	CRYSTALS	2=few cells or
		crystals in all
		fields
SPE	SPERMATOZOA	3=many cells or
		crystals in all
ABN	ABNORMAL COMPONENTS	fields
APP	URINE APPEARANCE	0=Normal 1=Turbid
VOL	URINE VOLUME (OVERNIGHT)	ml
OBF	FAECAL OCCULT BLOOD	
SD	STANDARD DEVIATION	

N	Number of animals in group Number of cages in group
Body Wt.	Body weight
Mesenteric nodes	Mesenteric lymph nodes
Parathyroid gl.	Parathyroid gland
Peri-bronc. nodes	Peri-bronchial lymph nodes
Submandibular ln	Submandibular lymph nodes
Inj site	Injection site
L.	Left
R.	Right

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Roma Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

ADDENDUM II - Certificate of analysis

STUDY NO.: 235-003-009

LIFE SCIENCE RESEARCH
Roma Toxicology
(Dr. Alfredo [illegible])

ISTITUTO RICERCHE FARMACOBIOLOGICHE INTERNAZIONALE S.p.A.
CENTRO RICERCHE DEL CONSORZIO BIOMEDICA FOSCAMA - IRFI

DIVISIONE DI CHIMICA ANALITICA

FOGLIO D'ANALISI DCAE002

RICHIESTA No :
RICHIEDENTE : Direzione Ricerca
SOSTANZA : Esafosfina Lotto L 9-050 (Fruttosio 1,6 difosfato sale sodico idratato)

DATA: 17.10.89

ANALISI No: AA0305-024

DATA: 17.10.89

DETERMINAZIONE	RISULTATO
Titolo espresso in FDPH4 (vedi analisi controllo qualita'CA70313)	73,96%
Titolo espresso in FDPNa3H	88,30%

NOTE:

FIRMA

LIFE SCIENCE RESEARCH
Roma Tossicologico Centro S.p.A.
(Dr. Alfredo Bonelli)

Mod IRFI 33

DATI DI PRODUZIONE

Tipo di soluzione infusionale: ESAFOSFINA 6% SEMIL.

N° lotto interno : P9-521 B

Data di preparazione : 04-10-89

DATI DI LABORATORIO C.Q.

Controllo visuale:

Ø PARTICELLE (µm)	BIANCO	I° CAMP.	II° CAMP.	III° CAMP.	IV° CAMP.	V° CAMP.	$\bar{m}$	$\bar{m}$/g o $\bar{m}$/$\bar{m}$l
50 um-100 um	/	/	/	/	/	/	/	/
100 um-300 um	/	/	/	/	/	/	/	/
>300 um	/	/	/	/	/	/	/	/

Controllo microscopico:

Ø PARTICELLE	BIANCO	I° CAMP.	II° CAMP.	III° CAMP.	IV° CAMP.	V° CAMP.	$\bar{m}$	$\bar{m}$/g o $\bar{m}$/$\bar{m}$l
<10 µm								
10 um - 25 µm								
25 um - 50 µm								
> 50 µm								

Controllo particellare: 09-10-89

Volume campionato: 5 ML

Ø PARTICELLE (µm)	BIANCO	I° CAMP.	II° CAMP.	III° CAMP.	IV° CAMP.	V° CAMP.	$\bar{m}$	$\bar{m}$/g o $\bar{m}$/$\bar{m}$l
2	4	1090	1010	967	958	956	992,2	3968,8
5	0	217	199	187	189	182	194,8	779,2
10	0	19	15	13	15	17	15,8	63,2
20	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0

I.F.F.I. S.p.A.
SERVIZIO AGOR. QUALITÀ
LIPH SOMM.
Roma

Prodotto ESAFOSFINA SPZ STRIL. Codice N. 60-6062 Lotto N. B.5218 del 04-10-
Fornitore/Rep. POWER N. di Lotto del fornitore L9.050
Firma del richiedente A. Bottarelli

Campionato il 5/10/89 da Dottarelli
Secondo il P.S.O. N. A4046
Campionati N. 160 di contenitori su 14490 su 6 pallets
Aspetto dei contenitori VETRO

CONTROLLO CHIMICO

Analisi N. BC/075/03 P.S.O. N. BC/0710 Data 12/10/89

SAGGI	RISULTATI	SIGLA	SAGGI	RISULTATI	SIGLA
Descrizione			Sost. ossidabili		
Identità			Solidi totali		
Int. fus. o di ebol.			Fosforo inorganico		
Potere rotatorio			Disgregazione		
Peso spec. (.....°C)			Conten. in volume		
Ind. di rifrazione			Colore della sol.		
pH			Nitriti		
Acqua (K.F.)			Nitrati		
Perd. peso t =			Cromatografia		
Peso medio			Titolo		
Carat. spettrofot.					
Ceneri					
Arsenico					
Metalli pesanti					
Ferro					
Cloruri					
Solfati					
Acido ossalico					
Ammoniaca					
Calcio					

Responsabile Laboratorio

Approvato ☐ Respinto ☐

CONTROLLO BIOLOGICO Data 12/10/89

SAGGI	RISULTATI	ANALISI N.	SIGLA
Sterilità	STERILE.	BS/238/05	LC.
Apirogenicità	APIROGENO	BF2/417/07	LC.
Atossicità	ATOSSICO	BT2/042/08	LC.
Titolo microbiologico			

Responsabile Laboratorio

Approvato ☑ Respinto ☐ 12/10/89

LIFE SCIENCE RESEARCH
Roma T...

Mod. 12-04-87 (2.000 x 3)

LABORATORI DI CONTROLLO del 04-10-89 per il Laboratorio ☒ C. Chimico ☐ C. Biologico

Prodotto ESAFOSFINA Spl sterile Codice N. 60-6062 Lotto N. P9.521B del 04-10-

Fornitore/Rep. POWER N. di Lotto del fornitore 19-050

Firma del richiedente A. Bruneri

Campionato il 5/10/89 da [illegible]

Secondo il P.S.O. N. AM046

Campionati N. 160 di contenitori su 14490 su 6 PALLETS

Aspetto dei contenitori [illegible]

CONTROLLO CHIMICO

Analisi N. CAT 031 3 P.S.O. N. AF 01400 Data 9/10/89

SAGGI	RISULTATI	SIGLA	SAGGI	RISULTATI	SIGLA
Descrizione	Conforme	A.M.	Sost. ossidabili		
Identità			Solidi totali		
Int. fus. o di ebol.			Fosforo inorganico		
Potere rotatorio			Disgregazione		
Peso spec. (..... °C)			Conten. in volume		
Ind. di rifrazione			Colore della sol.		
pH	5,4	A.M.	Nitriti		
Acqua (K.F.)	7,96%	A.M.	Nitrati		
Perd. peso t =			Cromatografia		
Peso medio Grammi	5,06	A.M.	Titolo F_2PH_4	73,96%	A.M.
Carat. spettrofot.			SOLUBILITA'	BUONA	"
Ceneri			CONT. MEDIO F_2PH_4 gr./fl.	3,74	"
Arsenico			" MINIMO " "	3,56	"
Metalli pesanti			" MASSIMO " "	3,88	"
Ferro			UNIFORMITA' PESO	Conforme	"
Cloruri			R S D	2,45%	"
Solfati					
Acido ossalico			~~CONTROLLO PARTICELLE~~		
Ammoniaca			~~PARTICELLE DA 10 µ~~	63,2	P.G.
Calcio			~~" 25 µ~~	0	P.G.

Approvato ☒ Respinto ☐ Responsabile Laboratorio 12/10/89 [illegible]

CONTROLLO BIOLOGICO Data .....

SAGGI	RISULTATI	ANALISI N.	SIGLA
Sterilità			
Apirogenicità			
Atossicità			
Titolo microbiologico			

Approvato ☐ Respinto ☐ Responsabile Laboratorio LIFE SCIENCE RESEARCH Roma Tosc.

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CENTRO RICERCHE DEL CONSORZIO BIOMEDICA FOSCAMA - IRFI

DIVISIONE DI CHIMICA ANALITICA

FOGLIO D'ANALISI

RICHIESTA No : 235-003-009 DATA: 19.03.90
RICHIEDENTE : LIFE SCIENCE RESEARCH
SOSTANZA : ESAFOSFINA 521B

ANALISI No: AF 03-03-123 DATA: 03.04.90

DETERMINAZIONE	RISULTATO
TITOLO: $FDPNa_3H$	87.0 %

NOTE:

FIRMA

135

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Roma

FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

ADDENDUM III - Formulation analyses

STUDY NO.: 235-003-009

LIFE SCIENCE RESEARCH
Roma Tossicologia S.p.A.
(Dr. Alfredo ...)

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DIVISIONE DI CHIMICA ANALITICA

FOGLIO D'ANALISI

RICHIESTA No : TOX/0037/mt DATA: 28.11.1989
RICHIEDENTE : LIFE SCIENCE RESEARCH
SOSTANZA : SOLUZIONI $FDPNa_3H$

ANALISI No: AF 03 - 03 - 112 DATA: 05.12.1989

DETERMINAZIONE	RISULTATO $FDPNa_3H$ mg/ml
CAMPIONE N° 1	0
CAMPIONE N° 2	53.8
CAMPIONE N° 3	112
CAMPIONE N° 4	219

NOTE:

FIRMA

Mod. IRFI 33

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CENTRO RICERCHE DEL CONSORZIO BIOMEDICA FOSCAMA - IRFI

DIVISIONE DI CHIMICA ANALITICA

FOGLIO D'ANALISI

RICHIESTA No : 235* - 003 - 009 DATA: 20.02.90
RICHIEDENTE : LAB. LIFE SCIENCE RESEARCH
SOSTANZA : $FDPNa_3H$

ANALISI No: AF - 03 - 03 - 120 DATA: 23.02.90

DETERMINAZIONE	RISULTATO $FDPNa_3H$ mg/ml
CAMPIONE N° 1 :	0
CAMPIONE N° 2 :	51.5 mg/ml
CAMPIONE N° 3 :	101.0 mg/ml
CAMPIONE N° 4 :	209.1 mg/ml

NOTE: * Changed according to authorization by the Sponsor. 22-3-91, M. Eilertsen

FIRMA
Marina D'Orazio

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

ADDENDUM IV - Electrocardiographic evaluation

STUDY NO.: 235-003-009

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A.
(Dr. Alfredo Minieta)

STUDY No.235-003-009; FDP: 13 Week Intravenous Toxicity Study In Dogs.

CRITICAL ANALYSIS OF THE ELECTROCARDIOGRAPHIC FINDINGS.

First recording - pre-treatment
Second recording - week 1 - treatment
Third recording - week 12 - treatment

A detailed examination of the electrocardiographic traces from study 235-003-009 resulted in the following remarks and observations.

GROUP 1

In the traces obtained during pre-treatment (dated 24/11/89) there was good homogeneity of the group, characterised by fairly uniform atrial depolarization (P wave). Dogs 2350006, 2350007 and 2350008 showed a certain slowing of conduction (segment P-Q), which defined a picture very near to first degree atrio-ventricular block. This segment appeared to be uniformly under the horizontal. The QRS complex appeared to be homogeneously characterised by an overall low voltage, with inversion in dogs 2350005 and 2350007. The T wave appeared to be of almost constantly positive polarity, whilst the frequency appeared to be superior to the norm in females and fairly normal in males.

One week after the start of treatment the most relevant modifications consisted of a "normalisation" of the QRS complex, particularly evident in dogs that had a low voltage for this complex, whilst the atrio-ventricular block shown in the base traces (pre-treatment) in dogs 2350006, 2350007 and 2350008 had almost disappeared. In addition a generalised slight increase in the voltage of the P wave was seen. The T wave remained fairly constant, with the exception of dog 2350001, the traces of which suggest an inversion of low voltage. There were no differences during the first week of treatment with respect to the frequency measured during the pre-treatment period.

In the third recordings taken during week 12 of treatment there was a slight generalised increase in the voltage of the P wave. The overall voltage of the QRS complex appeared to be increased in dogs 2350005 and 2350007, whilst in almost all dogs there was a slight to moderate increase in the duration of the QRS complex. The inversion of the polarity of the T wave was particularly evident in dogs 2350002, 2350006 and 2350008.

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GROUP 2

In the traces of the first recording (pre-treatment), the P wave appeared normal in all dogs, with the exception of dog 2350009, in which there was a certain lengthening of the P wave which, with everything considered corresponds to a lengthening of the whole P-Q interval, giving a picture of first degree atrio-ventricular block.
The QRS complex showed a diffuse tendency towards inversion of the overall polarity in the second trace with the electrocardiographic picture otherwise not to be attributed to right bundle branch block, in as much as it was not associated with a prolongation of the duration of the QRS complex itself; in dogs 2350009 and 2350010 with positive polarity of the QRS complex, the overall voltage was much reduced. The T wave had positive polarity in all dogs with the exception of dogs 2350014 and 2350016, and was generally of very low voltage. The cardiac frequency was generally superior to the mean with the exception of dogs 2350010, 2350015 and 2350016: in dogs 2350011 and 2350016 the frequency was lower than the norm.
Unlevelling of the iso-electric segment was present in all dogs.

In the traces taken during the first week of treatment a general increase in the voltage of the P wave was observed, with a mean increase of 0.1mV and the highest increase in dog 2350015. The QRS complex remained, in general, of negative polarity, whilst the overall voltage tended to increase in the dogs that had presented positive polarity. The voltage of the T wave increased slightly in the dogs in which it was already positive in the basal traces, but inverted it's polarity in dogs 2350011 and 2350016. The frequency was higher than physiological values in dogs 2350009, 2350012 and 2350014, whilst in dog 2350016 it was slightly lower.

Comparing the basal traces with those taken during week 12 of dosing, there was an increase in the voltage of the P wave in dogs 2350009, 2350013, 2350015 and 2350010: in dog 2350013 there was also an increase in the duration of the P wave.
The QRS complex showed a reduction of the overall voltage in dog 2350011 and deviation from the electric axis in dog 2350013, whilst there was a considerable increase in the same voltage for dog 2350010. In this last dog there was also a net inversion of the polarity of the T wave, which was increased in voltage in dogs 2350013 and 2350015.

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(Dr. Alfredo Nunziata)

GROUP 3

In the basal traces from the dogs in this group the voltage of the P wave appeared to be increased in dogs 2350023 and 2350017, whilst the duration (mitral P wave) was increased in dog 2350020. The QRS complex appeared to be of low voltage in dogs 2350021, 2350018 and 2350022, whilst there was also an inversion of the overall polarity in dog 2350024; in dog 2350020 there was a high overall voltage with a very well developed S wave. The T wave was positive in all animals apart from dog 2350023. The frequency was generally superior to the norm.

In the traces during the first week of dosing a modest, generalized increase of the voltage of the P wave was observed, while the QRS complex tended to normalise in voltage in dogs 2350021, 2350022 and 2350024, whilst in dog 2350017 the same ventricular complex presented a large vertical development with diphasic profile. The voltage of the T wave was generally unchanged, with the exception of dog 2350020; there was inversion of the polarity of this same wave in dog 2350022. The frequency was higher than physiological values in dogs 2350018, 2350020 and 2350024.

In the traces during week 12 of treatment there was a modest but generalised increase in the voltage of the P wave, more marked in dogs 2350021 and 2350023: in dog 2350022 there was a moderate increase in the duration of the same wave. The QRS complex tended to increase in duration in this last dog, but the voltage increased only in dog 2350019 where there was a marked deviation from the electric axis of the ventricular depolarisation. In general, the T wave tended to increase with otherwise limited variations, apart from dogs 2350023 (decrease) and 2350022 (inversion). The frequency did not present any relevant modifications.

GROUP 4

In the basal traces the P wave appeared fairly normal, with the exception of dogs 2350032 and 2350029 in which the voltage appeared to be on the increase. The QRS was of overall low voltage in all dogs except 2350027 and 2350032: the overall polarity appeared to invert in dogs 2350026 and 2350030, compared to the normal. In dogs 2350025, 2350027 and 2350031 there was a picture of first degree atrio-ventricular block. The T wave appeared negative in dogs 2350027, 2350028, 2350029 and was of elevated voltage (positive) in dog 2350032. The frequency was superior to physiological values in dogs 2350028, 2350030, 2350025 and 2350027.

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In the traces during the first week of dosing there was a generalised increase in the voltage of the P wave, more marked in dogs 2350029, 2350031 and 2350032: in the latter there was also a certain "mitralisation" of the same wave. In dog 2350028 there was a considerable increase in the overall voltage of the QRS complex. The T wave manifests in almost all dogs of this group a tendency towards an increase in the voltage and in dogs 2350027 and 2350029 it inverts compared to the "basal" polarity. The frequency appeared to be elevated only in dogs 2350030 and 2350032.

In the electrocardiographic traces during week 12 of treatment the clinically relevant modifications of the P wave referred to it's increase in voltage in dogs 2350028 and 2350031, while it seems to decrease in dog 2350032. There was a consistent deviation of the QRS complex from the electric axis in dogs 2350025, 2350026 and 2350027. The T wave inverted in polarity compared to the previous traces in dogs 2350025 and 2350031, whilst it reduced in voltage in dog 2350027. The frequency increased considerably in dog 2350029.

GENERAL CONSIDERATIONS

A specific mention of the unlevelling of the P-Q and S-T iso-electric tracts has been avoided due to their generalised diffusion in all groups and almost all animals as well as in the different phases of the study such that no correlation could be found between the groups or study phases that was worthy of attention.
The "basal" trace of dog 2350029 was illegible for some of the parameters considered.

POST-TREATMENT (15 minutes)

GROUP 1

Compared to the pre-treatment recordings this group showed a modest drop in cardiac frequency, whilst the other parameters remained unchanged, apart from a slight shift in the electric axis of the QRS complex in dog 2350006 and the voltage of the T wave in dogs 2350003, 2350004 and 2350007.

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GROUP 2

There were modest modifications, either positive or negative, of cardiac frequency values and minimal modifications of the T wave voltage. However, the unlevelling of the S-T segment present in the other recordings was accentuated in dogs 2350011 and 2350014.

GROUP 3

There was a fairly uniform and generalised drop in cardiac frequency and some modifications of the T wave which reduced in voltage in dog 2350018 and inverted in polarity in dogs 2350020 and 2350021. There was a slight deviation from the electric axis of the QRS complex in dogs 2350017, 2350019 and 2350022.

GROUP 4

The only modification of any relevance was observed in dog 2350027 and consisted of an increase in frequency, a reduction in the voltage of the P wave and inversion of the T wave. In dog 2350031 there was a moderate increase in the voltage of the P wave and a small reduction in the voltage of the T wave.

CONCLUSION

A general evaluation of the electrocardiographic analysis showed no significant changes on the traces for any group or phase of the study.
Any changes observed were considered to be attributed to physiological conditions of myocardic "maturation" processes that are completely normal in animals in the final phases of somatic development.
A similar conclusion should be drawn for the modifications of the P wave and of the electric axis (QRS complex), as well as for those of the iso-electric segments (hidden by the various cases of first degree a.v. block).
The other modifications, although limited, observed in the post-treatment traces were considered perfectly normal, such as the reduction of frequency or the changes of the T wave, in as much as they refer to effects of psychosomatic conditioning and to minimal modifications to the hydroelectrolytic arrangement as a consequence of the perfusion or the handling of the animals.

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Definitive alterations of an inflammatory or degenerative type were absent as regards the myocardium as were significant alterations of the heart or haemo-pressor dynamics, at least enough to induce substantial modifications of the electric arrangement of the heart.
As a consequence, the increases and modifications of parameters characterising the P wave are not considered significant, either because of their transitory nature or because of their lack of association with other more serious alterations of myocardic function, such as arrhythmia.
Neither should any significance be attached to the more or less intense unlevellings (present also in the control group) in the absence of more clinically relevant modifications.

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Rome Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

ADDENDUM V - Protocol and amendment

STUDY NO.: 235-003-009

LIFE SCIENCE RESEARCH
Roma Toxicology Centre S.p.A
(Dr. Alfredo Nunziata)

LIFE SCIENCE RESEARCH
ROMA TOXICOLOGY CENTRE S.P.A.

FDP
13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

Final Protocol
prepared for

ISTITUTO RICERCHE FARMACOBIOLOGICHE
INTERNAZIONALE S.p.A. (IRFI)
Via Morolese, 87
03013 Ferentino (FR)
Italy

and

BIOMEDICA FOSCAMA S.p.A.
Via Tiburtina, km. 14,500
00131 Roma
Italy

by

Life Science Research
Roma Toxicology Centre
Via Tito Speri 12
Pomezia (Roma)
Italy

Date: October 1989

LSR-RTC Enquiry no. 1984

Study no. 235-003-009

147

LIFE SCIENCE RESEARCH
Roma Toxicology Centre
(Dr. Alfredo [illegible])

VIA TITO SPERI 12 14 00040 POMEZIA (ROMA) TELEFONO 06/9120351 RIC AUT TELEX 616421 LSRITY I - TELEFAX N (06) 9125387 - CAPITALE SOCIALE L 3 500 000 000
CC I.A.A. N 375376 REG SOC TRIB DI ROMA N 2828/72 AUTORIZ MIN SANITÀ N 8002/70273/2825B DEL 3 8-74 - N 8002/70273/26860 DEL 12 3-76 COD FISC 00653120584 - PART IVA 00920611001

FDP
13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS
FINAL PROTOCOL

INTRODUCTION

Objective

The purpose of this study is to evaluate the toxicity of FDP when administered by daily intravenous injection in a 13 week study in dogs.

Species

Dog: the Beagle dog is the species of choice because it is a requirement of many regulatory authorities and because there is an accumulation of experience and background data on this species.

Route of administration

Intravenous. The intravenous route is selected to accord with one of the therapeutic routes of administration of the test substance in man.

Projected human dosage

The projected human intravenous dosage is about 75 mg/kg/day.

Treatment levels

Treatment groups and dosage levels are as follows:

No. of animals	Dosage (mg/kg/day)+
4 males and 4 females	0 (Control)
4 males and 4 females	110
4 males and 4 females	220
4 males and 4 females	440

+ In terms of Fructose-1,6-diphosphate dehydrated sodium salt (FDP Na3H).

Dosages were chosen in consultation with the Client based on the information from a preliminary study carried out at LSR-RTC.

Safety precautions

The precautions necessary when handling either the test substance or prepared formulations of the test substance are based on information supplied by the Client. The minimum safety precautions necessary are detailed under the LSR-RTC hazard classification system (see SOP STU/200). The test substance FDP has been allocated to Hazard Class 1.

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(Dr. Alfredo Nunziati)