

10. Effect of body size on busulfan clearance. The sponsor stated in the labeling that if a patient's body size was normalized to body surface area or adjusted ideal body weight, there were no differences in BUSULFEX clearance. However, the sponsor determined that normalization with other factors, such as actual body weight, did lead to a significant difference in BUSULFEX clearance between obese and non-obese patients (vol. 1.22). Similar findings have been reported by Gibbs et al, 1998 (Appendix Xb). Consequently, the sponsor must clarify the labeling to explain that BUSULFEX adjusted by these other factors does produce differences in BUSULFEX disposition that may be clinically relevant.

VIII. Labeling Comments

1. Sponsor labeling, page 2

FDA Recommendation:

2. Sponsor labeling, page 2

FDA Recommendation:

3. Sponsor labeling, page 3:

FDA Recommendation: The pharmacokinetic parameters of BUSULFEX and busulfan were inappropriately determined during dose 1. Therefore, replace the proposed table with the revised table below using steady state BUSULFEX data.

4. Sponsor labeling, page 3.

FDA Recommendation: DELETE SENTENCE.

5. Sponsor labeling, page 3

FDA Recommendation: Delete this sentence.

6. Sponsor labeling, page 3.

FDA Recommendation:

7. Sponsor labeling, page 3.

FDA Recommendation:

8. Sponsor labeling, page 16.

FDA Recommendation:

9. Sponsor labeling, page 18: Renal Insufficiency:

FDA Recommendation:

Comments for the Medical Officer:

The following comments require the consideration of the FDA medical officer.

1. Sponsor labeling, page 11; Indications and Usage

BUSULFEX pharmacokinetics have NOT been determined with other chemotherapeutic agents (except cyclophosphamide) or radiotherapy. Therefore, CPB makes the following labeling recommendation:

FDA Recommendation:

2. Sponsor labeling, page 16. Drug Interactions:

The sponsor makes very sweeping generalizations in this sentence. BUSULFEX, (or busulfan) has not been tested with ALL antifungal agents or 5-HT₃ antiemetics. Furthermore, some of the Orphan Medical Inc. data suggested that there might be a drug interaction between BUSULFEX and 5-HT₃ antiemetics. Itraconazole clearly alters the kinetics of busulfan, by up to 25%. The following changes are recommended by CPB.

FDA Recommendation:

**3. Sponsor labeling, page 17. Special Populations
Pediatric:**

The sponsor proposes that 0.8 mg/kg BUSULFEX can be administered to children. The pharmacokinetics of busulfan in children are different than adults. CPB recommends the following change.

FDA Recommendation:

Comment for the Medical Officer and the Chemistry Reviewer:

The following addition is suggested by CPB based on information supplied by the chemistry reviewer. The consideration of the medical officer and the chemistry reviewer is required.

1. Sponsor labeling, page 29. Preparation for Intravenous Administration:

FDA ADDITION:

Redacted

19

pages of trade

secret and/or

confidential

commercial

information

Formulation and use in clinical medicine in bone marrow transplantation and other conditions covered by United States Patent numbers 5,430,057 and 5,559,148.

Rev. 7/98

Part No. 4040290

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Table 9
 Summary of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (μMol·min)	CL (mL/min)	V _Z (L)	CL/ABW (mL/min/kg)	V _Z /ABW (L/kg)
39.00	39	39.00	39.00	39	39.00	39.00	39.00	39.00
Mean	1284	2.10	3.47	1225	180.26	54.97	2.25	0.68
Median	1303	2.00	3.09	1199	170.33	47.50	2.23	0.62
SD	290	0.25	1.36	216	42.33	28.14	0.46	0.34
CV	23	11.71	39.10	18	23.48	51.20	20.40	49.89
Maximum								
Minimum								

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Table 7
 Summary of Intravenous Busulfan Pharmacokinetic Parameters from Dose 1 (BMT Day -7)

Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{last} (uMol-min)	AUC _{inf} (uMol-min)	AUC _{ext} (%)	CL (mL/min)	V _z (L)	CL/ABW (mL/min/kg)	V _z /ABW (L/kg)
N	59	59.00	59.00	59	59	59	59.00	59.00	59.00	59.00
Mean	947	2.16	2.83	751	1106	30	210.29	49.13	2.74	0.64
Median	937	1.97	2.71	762	1084	30	208.82	46.77	2.63	0.63
SD	239	0.50	0.76	149	318	9	65.64	11.73	0.82	0.10
CV	25	22.98	26.69	20	29	29	31.21	23.88	29.90	16.24
Maximum										
Minimum										

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Table 8
 Summary of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (μMol·min)	CL (mL/min)	V _z (L)	CL/ABW (mL/min/kg)	V _z /ABW (L/kg)
59.00	59	59.00	59.00	59	59.00	59.00	59.00	59.00
53.53	1222	2.07	2.99	1167	193.05	49.51	2.52	0.64
53.00	1249	1.95	2.98	1180	185.85	46.57	2.40	0.61
9.79	216	0.25	0.56	228	51.10	14.91	0.62	0.20
18.30	18	11.95	18.82	20	26.47	30.12	24.50	30.51
N								
Mean								
Median								
SD								
CV								
Maximum								
Minimum								

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Appendix 6

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 1 (BMT Day -7)

Patient ID	Dose (mg)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUClast (uMol-min)	AUCinf (uMol-min)	AUCext (%)	CL (mL/min)	Vz (L)	CL/ABW (mL/min/kg)	Vz/ABW (L/kg)
	50.00	867	2.25	2.98	762	1156	34	175.63	45.31	2.51	0.65
	55.00	828	2.25	3.21	687	1065	35	209.71	58.23	2.68	0.74
	47.00	823	2.25	2.65	702	957	27	199.42	45.71	3.44	0.79
	51.00	1054	2.48	2.59	866	1256	31	184.89	36.91	2.56	0.57
	51.00	415	2.73	1.97	287	413	30	501.72	85.52	6.00	1.02
	39.00	663	2.25	1.78	459	620	26	255.39	39.35	5.23	0.81
	58.00	739	2.17	2.71	537	777	31	302.92	70.98	2.85	0.67
	44.00	747	2.48	3.06	567	896	37	199.46	52.87	2.12	0.56
	36.00	661	2.33	2.73	448	769	42	190.14	44.93	2.81	0.66
	73.00	843	2.25	3.23	717	1240	42	239.01	66.85	2.28	0.64
	52.00	726	1.80	2.59	633	832	24	253.64	56.88	2.99	0.67
	45.00	959	2.75	2.76	802	1248	36	146.34	34.98	2.65	0.63
	62.00	1413	0.25	2.30	835	1026	19	245.43	48.87	3.15	0.63
	53.00	806	1.92	2.00	648	771	16	279.00	48.35	3.42	0.59
	61.00	948	1.90	2.57	801	1176	32	210.52	46.77	2.84	0.63
	55.00	941	1.97	2.61	814	1106	26	201.84	45.61	2.97	0.67
	62.00	932	2.00	2.51	744	1084	31	232.26	50.44	2.80	0.61
	43.00	910	1.92	3.19	788	1177	33	148.27	40.89	2.02	0.56
	46.00	1282	4.20	6.81	1063	2511	58	74.37	43.85	1.28	0.75
	36.00	872	1.92	2.10	711	870	18	167.94	30.50	3.25	0.59
	64.00	666	1.92	2.53	602	794	24	327.42	71.81	2.90	0.64
	47.00	888	2.00	3.10	837	1235	32	154.45	41.45	2.59	0.70
	64.00	1768	3.00	2.47	914	1132	19	229.55	49.07	2.39	0.51
	60.00	1041	1.88	2.52	830	1088	24	223.90	48.86	2.65	0.58
	51.00	969	1.97	2.36	767	992	23	208.82	42.70	3.22	0.66
	60.00	1080	1.92	2.71	908	1244	27	195.84	45.87	2.49	0.58
	53.00	1092	1.92	2.56	932	1267	26	169.86	37.70	2.58	0.57
	44.00	986	1.92	2.55	857	1150	25	155.28	34.27	2.32	0.51

* Patient Not Included in Summary

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Appendix 6

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 1 (BMT Day -7)

Patient ID	Dose (mg)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUClast (uMol-min)	AUCinf (uMol-min)	AUCext (%)	CL (mL/min)	Vz (L)	CL/ABW (mL/min/kg)	Vz/ABW (L/kg)
	41.00	965	1.83	2.45	881	1179	25	141.13	29.98	2.76	0.59
	62.00	752	1.92	2.81	686	968	29	260.08	63.30	2.45	0.60
	55.00	1003	1.92	2.51	856	1120	24	199.39	43.35	2.40	0.52
	46.00	956	1.92	2.66	845	1145	26	163.15	37.50	2.29	0.53
	60.00	725	1.92	2.40	546	795	31	306.25	63.67	3.14	0.65
	58.00	687	2.25	2.79	660	937	30	251.18	60.65	2.30	0.55
	44.00	918	2.33	3.53	863	1379	37	129.56	39.55	2.02	0.62
	59.00	1029	1.87	2.82	782	1209	35	198.12	48.28	2.63	0.64
	52.00	958	1.92	3.28	727	1225	41	172.32	48.97	1.80	0.51
	43.40	767	1.95	2.32	664	824	19	213.78	42.94	2.12	0.43
	52.00	882	2.03	3.41	868	1342	35	157.36	46.51	1.96	0.58
	64.00	1026	1.92	2.10	861	1085	21	239.56	43.60	2.91	0.53
	59.00	1057	2.25	4.21	985	1718	43	139.44	50.83	1.93	0.70
	64.00	919	1.92	2.66	758	1019	26	254.96	58.67	2.41	0.56
	36.00	1705	2.50	3.42	912	1341	32	109.03	32.26	1.30	0.38
	62.00	1100	0.82	3.78	956	1455	34	172.95	56.54	1.84	0.60
	58.00	927	1.92	2.77	722	986	27	238.83	57.19	3.28	0.78
	70.00	962	3.33	2.94	809	1298	38	218.96	55.64	2.52	0.64
	33.00	1504	2.25	3.45	806	1600	50	83.74	25.00	2.04	0.61
	76.00	1211	2.25	3.49	762	1202	37	256.62	77.45	2.27	0.69
	46.00	1127	2.47	2.07	781	963	19	193.87	34.69	3.52	0.63
	50.00	1096	2.52	4.18	920	1644	44	123.50	44.66	1.96	0.71
	46.00	986	1.72	2.07	739	895	17	208.56	37.34	3.36	0.60
	41.00	668	1.92	2.39	614	784	22	212.42	43.99	4.15	0.86
	51.00	1001	1.80	2.15	782	966	19	214.29	39.88	3.30	0.61
	64.00	1046	1.92	3.76	960	1567	39	165.79	54.03	1.87	0.61
	45.00	748	1.92	1.69	567	645	12	283.04	41.33	4.53	0.66
	64.00	822	2.97	2.41	596	900	34	288.86	60.32	3.03	0.63

* Patient Not Included in Summary

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Appendix 6

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 1 (BMT Day -7)

Patient ID	Dose (mg)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUClast (uMol-min)	AUCInf (uMol-min)	AUCext (%)	CL (mL/min)	Vz (L)	CL/ABW (mL/min/kg)	Vz/ABW (L/kg)
	68.00	1116	1.92	3.51	1076	1665	35	165.82	50.44	1.72	0.52
	57.00	937	1.92	2.85	629	1055	40	219.28	54.08	2.90	0.71
	63.00	776	2.25	2.89	741	1066	30	240.04	60.10	3.00	0.75
	45.00	650	2.67	3.54	535	1004	47	181.99	55.73	2.34	0.72
	65.00	981	2.25	2.79	731	1038	30	254.27	61.40	3.13	0.76

* Patient Not Included in Summary

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Appendix 7
 Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

Patient ID	Dose (mg)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUCss (uMol-min)	CL (mL/min)	Vz (L)	CL/ABW (mL/min/kg)	Vz/ABW (L/kg)
	50.00	1328	2.42	3.08	1265	160.45	42.75	2.28	0.61
	55.00	1166	1.92	3.77	1201	185.85	60.72	2.42	0.79
	47.00	1185	2.25	2.66	1028	185.58	42.79	3.13	0.72
	51.00	1395	1.92	2.37	1170	176.97	36.29	2.73	0.56
	51.00	496	2.75	2.97	556	372.47	95.90	4.31	1.11
	39.00	797	2.67	5.05	794	199.32	87.09	3.89	1.70
	58.00	1083	2.25	3.33	962	244.79	70.48	2.34	0.67
	44.00	1574	2.22	3.21	1222	146.18	40.58	1.60	0.44
	36.00	825	3.00	3.13	900	162.45	44.03	2.40	0.65
	73.00	1246	1.97	2.12	1324	223.79	41.00	2.13	0.39
	52.00	1148	1.87	2.56	1029	205.09	45.38	2.38	0.53
	45.00	1284	2.42	2.82	1322	138.24	33.74	2.50	0.61
	62.00	1096	1.93	2.39	1028	244.95	50.75	3.10	0.64
	53.00	883	1.92	3.52	741	290.22	88.42	3.57	1.09
	61.00	1484	1.92	2.75	1351	183.29	43.66	2.53	0.60
	55.00	1163	2.25	2.88	1194	186.97	46.57	2.75	0.68
	62.00	1262	1.92	2.60	1179	213.52	47.97	2.57	0.58
	43.00	1233	2.00	3.23	1207	144.62	40.45	2.00	0.56
	46.00	1318	1.92	2.88	1300	143.64	35.79	2.47	0.62
	36.00	1024	1.92	2.11	878	166.54	30.43	3.20	0.59
	64.00	1053	1.92	2.99	1011	256.93	66.41	2.31	0.60
	47.00	1300	1.92	3.00	1294	147.50	38.25	2.47	0.64
	64.00	1078	1.92	2.46	934	278.23	59.35	2.88	0.61
	60.00	1386	1.92	2.75	1239	196.62	46.84	2.27	0.54
	51.00	925	2.00	2.54	826	250.52	55.12	3.95	0.87
	60.00	1359	1.92	2.76	1394	174.78	41.82	2.26	0.54
	53.00	1373	1.87	2.60	1283	167.68	37.74	2.60	0.59
	44.00	1419	2.00	2.98	1491	119.80	30.91	1.85	0.48

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Appendix 7

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

Patient ID	Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (uMol·min)	CL (mL/min)	Vz (L)	CL/ABW (mL/mIn/kg)	Vz/ABW (L/kg)
	62.00	1156	1.92	2.99	1106	227.68	58.89	2.08	0.54
	55.00	1189	1.95	2.47	1143	195.34	41.78	2.37	0.51
	46.00	1102	2.25	3.59	1122	166.44	51.75	2.32	0.72
	60.00	1116	1.92	3.29	1120	217.55	61.96	2.20	0.63
	58.00	1100	1.92	3.18	1180	199.61	54.98	1.81	0.50
	44.00	1315	1.92	3.23	1294	138.00	38.55	2.15	0.60
	59.00	1475	1.83	2.94	1369	175.00	44.54	2.37	0.60
	52.00	971	1.98	3.27	978	215.77	61.15	2.20	0.62
	43.40	1029	1.95	2.23	924	190.73	36.81	1.91	0.37
	52.00	1359	1.92	4.01	1395	151.36	52.53	1.88	0.65
	64.00	1386	2.25	2.96	1253	207.35	53.12	2.52	0.65
	59.00	1633	2.25	3.27	1673	143.16	40.55	1.99	0.56
	64.00	1168	2.25	3.46	1197	217.04	64.99	2.09	0.63
	36.00	1249	1.92	3.01	1174	124.51	32.42	1.49	0.39
	58.00	1240	2.15	2.89	1164	202.33	50.68	2.75	0.69
	70.00	1422	2.33	3.12	1334	213.09	57.62	2.44	0.66
	33.00	1395	1.93	3.19	1325	101.08	27.91	2.30	0.63
	76.00	1322	2.25	3.26	1368	225.56	63.73	1.94	0.55
	46.00	1336	2.53	2.24	1078	173.21	33.66	3.09	0.60
	50.00	1435	2.32	4.33	1617	125.54	47.03	2.01	0.75
	46.00	1371	1.85	2.39	1108	168.60	34.89	2.75	0.57
	41.00	1321	1.75	2.46	1228	135.53	28.87	2.75	0.59
	51.00	1311	1.95	2.37	1118	185.13	38.03	2.86	0.59
	64.00	1377	2.05	4.22	1604	161.99	59.16	1.81	0.66
	45.00	957	2.23	2.19	771	236.95	44.83	3.90	0.74
	64.00	1030	1.87	2.34	923	281.48	56.90	3.00	0.61
	68.00	1684	1.97	3.66	1586	174.08	55.22	1.81	0.57
	57.00	1063	1.92	2.98	1047	221.06	57.10	2.89	0.75

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Appendix 7

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

Patient ID	Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (uMol-min)	CL (mL/min)	V _Z (L)	CL/ABW (mL/min/kg)	V _Z /ABW (L/kg)
	63.00	1344	1.92	3.09	1338	191.20	51.08	2.40	0.64
	45.00	1431	1.93	3.07	1346	135.69	36.02	1.77	0.47
	65.00	913	2.25	3.00	822	321.11	83.35	3.90	1.01

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Appendix 6

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 1 (BMT Day -7)

Patient ID	Dose (mg)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUClast (uMol·min)	AUCinf (uMol·min)	AUCext (%)	CL (mL/min)	Vz (L)	CL/ABW (mL/min/kg)	Vz/ABW (L/kg)
	41.00	896	2.25	2.93	677	1172	42	142.08	36.07	2.84	0.72
	49.00	1007	2.25	2.59	756	1032	27	192.82	43.30	2.82	0.63
	36.00	773	2.25	2.49	649	903	28	161.94	34.85	3.18	0.68
	57.00	1021	2.25	2.70	871	1232	29	187.88	43.99	2.47	0.58
	62.00	910	1.92	3.13	823	1214	32	207.28	56.08	2.35	0.64
	59.00	696	2.25	4.34	706	1320	47	181.44	68.10	2.19	0.82
	47.00	984	2.25	2.91	936	1386	32	137.71	34.65	2.33	0.59
	46.00	681	2.33	2.71	586	860	32	217.05	50.93	2.54	0.60
	51.00	845	2.42	2.85	770	1132	32	182.88	45.12	2.36	0.58
	52.00	637	1.92	3.31	477	770	38	274.12	78.55	3.42	0.98
	39.00	587	2.62	2.15	393	607	35	260.73	48.53	3.34	0.62
	47.00	656	1.92	2.96	549	928	41	205.53	52.64	2.82	0.72
	56.00	969	1.92	3.60	842	1339	37	169.75	52.83	2.17	0.67
	45.00	714	1.78	2.65	590	810	27	225.60	51.79	2.00	0.46
	53.00	679	1.83	2.96	630	916	31	234.91	60.21	2.06	0.53
	56.00	832	1.92	3.48	756	1178	36	192.94	58.05	1.85	0.56
	40.00	831	1.92	2.71	701	965	27	168.33	39.55	1.83	0.43
	49.00	880	1.88	2.54	728	964	24	206.47	45.46	3.04	0.67
	61.00	936	1.88	2.60	823	1107	26	223.64	50.36	2.60	0.58
	57.00	1082	1.87	2.85	913	1268	28	182.55	45.01	2.57	0.63
	67.00	945	1.92	3.30	759	1306	42	208.27	59.41	2.36	0.67
	44.00	846	2.25	3.08	807	1188	32	150.39	40.09	1.99	0.53
	62.00	1007	1.92	2.81	889	1240	28	202.95	49.33	2.00	0.49
	60.00	889	1.92	3.06	763	1101	31	221.24	58.61	1.85	0.49
	44.00	839	1.92		196						
	57.00	959	2.23	3.30	909	1402	35	165.05	47.15	2.28	0.65
	44.00	662	1.92	3.49	632	982	36	181.91	54.91	1.46	0.44
	57.00	1039	2.00	3.85	840	1392	40	166.29	55.47	1.90	0.64

* Patient Not Included in Summary

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Appendix 6

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 1 (BMT Day -7)

Patient ID	Dose (mg)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUClast (uMol-min)	AUCinf (uMol-min)	AUCext (%)	CL (mL/min)	Vz (L)	CL/ABW (mL/min/kg)	Vz/ABW (L/kg)
	53.00	1002	2.00	3.76	957	1541	38	139.63	45.45	1.79	0.58
	51.00	1406	0.75	2.87	937	1247	25	165.99	41.90	2.26	0.56
	33.00	928	2.52	3.04	779	1188	34	112.79	29.67	2.67	0.70
	63.00	1059	2.28	3.23	957	1448	34	176.67	49.35	2.04	0.57
	49.00	1019	2.42	2.30	877	1140	23	174.50	34.79	2.89	0.58
	54.00	938	1.92	2.67	811	1246	35	175.93	40.63	2.61	0.60
	44.00	948	1.78	2.30	739	1067	31	167.36	33.32	3.10	0.62
	48.00	1209	1.78	2.45	937	1242	25	156.91	33.34	2.62	0.56
	70.00	945	2.28	7.03	792	2190	64	129.78	78.96	1.22	0.74
	73.00	855	1.92	7.33	729	2148	66	137.96	87.54	1.20	0.76
	66.00	826	1.58	2.79	702	1070	34	250.39	60.47	2.10	0.51
	48.00	441	4.25	1.93	399	608	34	320.39	53.56	4.31	0.72
	66.00	1216	2.17	3.16	985	1595	38	168.02	45.90	2.03	0.55
	70.00	847	2.25	3.69	765	1301	41	218.46	69.70	2.44	0.78

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Appendix 7

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

Patient ID	Dose (mg)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUCss (uMol·min)	CL (mL/min)	Vz (L)	CL/ABW (mL/min/kg)	Vz/ABW (L/kg)
	41.00	1344	2.25	2.74	1227	135.71	32.15	2.71	0.64
	49.00	1353	2.25	2.07	1168	170.33	30.56	2.46	0.44
	36.00	953	2.50	2.08	973	150.20	27.09	2.90	0.52
	62.00	1050	2.50	7.90	1112	226.45	154.77	2.57	1.75
	59.00	1380	2.53	4.33	1569	152.68	57.19	1.83	0.68
	47.00	1518	2.25	3.09	1413	135.06	36.17	2.35	0.63
	46.00	1016	2.00	3.06	1037	180.17	47.75	2.14	0.57
	51.00	1331	2.35	3.04	1293	160.17	42.11	2.09	0.55
	52.00	1026	2.25	4.46	975	216.44	83.57	2.75	1.06
	39.00	942	2.53	4.34	857	184.86	69.39	2.37	0.89
	47.00	988	1.58	9.42	968	197.16	160.68	2.68	2.18
	56.00	1362	2.25	3.44	1425	159.52	47.50	2.07	0.62
	45.00	957	1.92	3.60	1055	173.19	54.02	1.58	0.49
	53.00	2265	1.83	2.75	1330	161.81	38.47	1.44	0.34
	56.00	943	1.92	4.04	1007	225.76	79.04	2.20	0.77
	40.00	1162	1.92	2.88	1134	143.25	35.71	1.54	0.38
	61.00	1347	1.88	2.98	1254	197.49	50.87	2.28	0.59
	57.00	1365	1.92	3.18	1300	178.07	49.04	2.47	0.68
	67.00	1129	1.92	2.97	1135	239.75	61.63	2.66	0.68
	44.00	1303	2.25	2.90	1292	138.27	34.68	1.87	0.47
	62.00	1487	1.92	3.03	1428	176.22	46.15	1.76	0.46
	60.00	944	1.92	3.50	926	262.93	79.72	2.17	0.66
	57.00	1625	2.25	3.32	1562	148.14	42.54	2.03	0.58
	44.00	979	1.92	3.62	1031	173.20	54.34	1.40	0.44
	57.00	1414	2.50	3.05	1374	168.42	44.50	1.92	0.51
	53.00	1585	1.92	3.97	1591	135.26	46.45	1.76	0.60
	51.00	1433	1.92	2.80	1341	154.43	37.39	2.17	0.52
	33.00	1200	1.90	2.62	1127	118.90	27.00	2.87	0.65
	63.00	1588	1.92	3.46	1619	157.98	47.28	1.82	0.54
	49.00	1452	1.92	2.72	1200	165.84	38.99	2.74	0.64

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Appendix 7

Listing of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

Patient ID	Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-∞} (uMol·min)	CL (mL/min)	V _z (L)	CL/ABW (mL/mIn/kg)	V _z /ABW (L/kg)
	54.00	1134	2.07	3.13	1132	193.70	52.50	2.99	0.81
	44.00	1108	1.98	3.11	1080	165.43	44.55	3.13	0.84
	48.00	1871	2.33	3.29	1430	136.25	38.80	2.31	0.66
	70.00	1168	2.00	2.78	1184	240.01	57.74	2.23	0.54
	73.00	939	2.25	2.57	893	331.99	73.91	2.89	0.64
	66.00	1409	1.83	3.09	1353	197.98	52.91	1.66	0.44
	48.00	1159	2.50	2.47	1062	183.51	39.24	2.49	0.53
	66.00	1706	2.25	4.18	1711	156.65	56.69	1.92	0.70
	70.00	1153	1.92	3.45	1199	237.03	70.84	2.63	0.79