Day +20	4.0	1,646	88		
Day+23	15.6	13,416	84		
Day +26	2.2	955	86		
Day +29	1.3	390	84		
Pt.					
BMT Day	WBC	ANC	Platelets	GCSF	Transfusion
Day +8	0.1	14	10	Stop Day +10	Platelets
Day +13	4.3	3,612	53		
Day + 22	3.0	2,100	186		
Day +29	4.9	3,675	175		
Day +34	2.2	616	130		
Pt.					
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +8	0.1	10	34		Platelets
Day +12	1.2	640	52		
Day +14	3.8	2,320	41	Stop GCSF	Platelets
Day +20	1.2	370	27		
Day +27	2.0	880	28		

Hematology laboratory values were not provided for the last week of the 28-day study period in 14/41 (34%) patients on study who remained on study through that time. (One of the total 42 patients on study withdrew consent on Day 15 secondary to relapsed disease.) Those patients and the last day of laboratory provided during the study period for each patient are summarized below.

Table 5 Summary of Patients Without Hematology Data Through Day +28

Patient Number	BMT Day Last CBC Data Provided
	Day +20
	Day +21
	Day +16
	Day +21
	Day +18
	Day +18
	Day +13
	Day +20
	Day +19
	Day +19
	Day +19
	Day +18 (Gap until Day +67)
	Day +11
	Day +13

The impact of this missing data is most important with regard to the primary endpoint of engraftment, but as noted above, all these patients had had a recovery to an ANC > 500 x 10^9/L prior to the gaps in data.

Five of the above patients (with asterisks) had hematological adverse events recorded on the Post-Study Surveillance Adverse Events record (Day +29-Day +100). Those events are summarized below.

Pt.	Grade 3 **thrombocytopenia** that did not resolve until BMT Day +44
Pt.	Grade 1 **thrombocytopenia** that resolved on BMT Day +37
Pt.	Grade 3 and 4 **thrombocytopenia** ongoing, without date of resolution in the PSS database. The patients CRF was submitted with the Safety Update due to patient's death on Day + . The CRF contained a PSS form that noted that thrombocytopenia resolved on Day +112, and that the patient had been receiving ongoing platelet transfusion support.
Pt.	Grade 3 **thrombocytopenia** and grade 2 **anemia** until BMT Day +49.
Pt.	Grade 4 **thrombocytopenia** until Day +50.

Review of the Post-Study Surveillance (PSS) ACCESS data set for additional hematologic adverse events in the remaining patients on study recorded after BMT Day +28 revealed the following Hematologic adverse events.

Pt.	Grade 2 **leukopenia** on BMT Day +101
Pt.	Grade 2 **leukopenia** that was ongoing and required intervention.
Pt.	Grade 2 **granulocytopenia** and **leukopenia** until Day +35.
Pt.	Grade 3 **leukopenia** until Day +38, and grade 4 **thrombocytopenia** until Day +52.
Pt.	Grade 4 **neutropenia** until Day +31 and grade 4 **thrombocytopenia** until Day +43.
Pt.	Grade 4 **leukopenia** until Day +40, and grade 3 **thrombocytopenia** until Day +44.

A review of the serial hematology lab values provided for each patient with the purpose of confirming the sponsor's documented day of engraftment resulted in the reviewer's altering the engraftment dates in 4 patients. The date was changed to a later point in 3, and to an earlier date in one. These changes are summarized below. Because differentials were not always documented, there were a few patients who were assigned a later engraftment date than would likely have been assigned if full data had been recorded. Pt is an example of one such patient. This patient had a WBC=4,400 on Day+10, but no differential. A differential was not performed until Day +15, which definitively demonstrated an ANC >500. The sponsor used Day +15 as the engraftment date. The following table summarizes the engraftment day for each patients as assigned by the sponsor and reviewer. The resulting median day to engraftment is shown at the bottom.

Table 6 Engraftment Date Assignment Differences Between Sponsor and Reviewer

Patient No.	Sponsor Day of Engraftment	Reviewer Day of Engraftment
	9	9
	11	11
	11	11
	10	10
	10	10

Patient No.	Sponsor Day of Engraftment	Reviewer Day of Engraftment
	10	10
	11	11
	9	9
	11	11
	10	10
	12	12
	9	9
	10	10
	12	12
	9	9
	9	9
	9	9
	10	10
	9	9
	9	9
	12	12
	8	8
	10	10
	16	16
	16	16
	12	12
	16	16
	12	13
	13	13
	13	13
	19	20
	12	12
	9	9
	10	10
	10	10
	16	11
	10	10
	11	11
	11	11
	15	15
	8	8
	10	11
MEDIAN	10	10.5

* Patients who appear to have been transplanted with both marrow and peripheral blood stem cells.

The four patients highlighted above, to which the sponsor and reviewer assigned differing engraftment dates, are summarized below.

Day +12 : "Calculated Neutrophils" = 0.25 x 109/L (Time=0300)
WBC = 1.300 % Bands = 37%

	Later in the day (1610) a WBC of 1.9 was recorded with no differential
Day +13:	"Calculated Neutrophils" = 1.89 x 109/L WBC = 2.700 %Bands = 20%
Day +19:	No hematology laboratory provided on this day.
Day +20	"Calculated Neutrophils" = 2.38 x 109/L WBC = 3.5 %Neutrophils = 68%
Day +16:	Absolute Granulocyte Count = 11.3 x 109/L WBC = 12.8 %Neutrophils = 76%
Day +11:	Absolute Granulocyte Count = 0.8 x 109/L WBC = 1.1 %Neutrophils = 76%
Day +10:	"Calculated Neutrophils" = 0.41 x 109/L WBC = 1.5 %Neutrophils = 27%
Day +11:	"Calculated Neutrophils" = 1.56 x 109/L WBC = 3.0 %Neutrophils = 52%

The median number of platelet transfusions on study was 3. The range was . The red blood cell transfusion median was 3, with a range of The median days to discharge after transplantation was 12.5 (range = days).

These results for time to engraftment in a heavily pretreated population undergoing transplantation with unpurged stem cells is favorably comparable to published data in a 43 article "core dataset" literature review provided by the sponsor that will be discussed later in the literature review section.

3.11.3 Late Graft Failure

The sponsor does not report any instances of late graft failure in this study. Because hematology laboratory beyond Day +28 is not generally provided in this application, the reviewer cannot confirm this through audit. The serious adverse event reports were reviewed for any indication of late graft failure, and the reviewer detected none. January 9,1998 was the clinical data cut-off date for all patients (N=42) that had completed the "Study Period." There were Short-Term Post-Study Surveillance data (through Day +100) available through January 9, 1998 on 31/42 patients participating, and Long-Term Post-Study Surveillance data (> Day +100) available on 18/42 patients.

In the 120-Day Safety Update there were no changes regarding late engraftment failure.

3.11.4 Relapse

At the time of the clinical cut-off 74% of patients had been observed to BMT Day +100, and 43% had been observed beyond Day +100. The median follow-up of patients who were still disease free at the time of the clinical cut-off was 70 days. Thirty-five patients were disease free at that time (83% of the study population). The median time to relapse in the 7 patients whose disease relapsed in that time was 105 days. One patient relapsed in the first 28 days of the study, and withdrew consent two days after documentation of relapse. One patient relapsed between Day+28 and Day +100 (the limited surveillance period of the study) – on Day +70. The five remaining observed relapses occurred on Day +104, +105, +107, +117, +119, and +184. (See Safety Update information below regarding the bolded numbers, which the sponsor has updated as errors.) The Kaplan-Meier probability of freedom from relapse at 100 days, as calculated by the sponsor, was 0.93 (5% CI: 0.84 – 1.0). Six of the seven relapses occurred in patients with lymphoma, and the remaining patient had leukemia. The leukemia relapse was detected at Day +107. Two (one has been reclassified as a non-relapse in the Safety Update information below) of the lymphoma relapses occurred in patients who had had ≥3 prior chemotherapy regimens, and two were in patients who had received both radiation therapy and ≥3 prior chemotherapy regimens, and prior transplants.

Reviewer Comment: Because the data from follow-up beyond 28 days was generally not available for review, the reviewer cannot comment on compliance with surveillance monitoring and whether non-compliance could have impacted on time to relapse detection. Relapse was a secondary endpoint in this study. There were follow-up bone marrow aspirate data provided on 7 patients. Three of these were performed within approximately a month of transplant. The remaining four, all at one center (05-000) had the follow-up aspirate performed later (2-3 months after transplant). Bone marrow biopsy data were provided on 3 patients, and all were performed within a month of transplant. Follow-up scan data were provided on 25 patients. All were performed within approximately 6 weeks of transplantation, except for two. The latter two were performed at approximately 10 weeks and 13 weeks post-transplantation. All but 8 scans showed persistent abnormalities.

The sponsor states in the study report and in the summary Table 14.2.3 Summary of Engraftment, Relapse and Survival Data that there were 7 relapses. However, in Section 12.3.1.1, of the study report the sponsor describes the death of Patient as death from "infection/hemorrhage secondary to recurrent refractory AML". This patient is not included in the sponsor's list of patients in relapse. The death occurred before the clinical cut-off date of the study. This patient's bone marrow after transplant was not read as showing evidence of leukemia. The case report form for this patient does not include any information on recurrence or the circumstances surrounding her death. If she did die in relapse, there were 8 relapses on study.

Additionally, review of the post-transplant scan reports reveals Patient (lymphoma) had evidence of progression of disease on the CT of chest and abdomen performed 16 days post-transplant. The sponsor did not regard this patient as having a relapse, and no further data regarding this patient's disease follow-up is available to the reviewer. Patient was mentioned in the sponsor's discussion of changes in pulmonary function tests on study in Section 12.4.2.1 as having recurrence of a pre-existent pleural effusion documented 5 days after the follow-up PFT's were performed. This may also have represented a recurrence/progression of disease.

In the 120-Day Safety Update obtained by the reviewer on 12/9/98, the sponsor noted that as of the Safety Update Report clinical cut-off date of July 31, 1998, 93% (39/42) of the 42 patients had been observed through Day +100. The three patients not followed through that point included the patient who withdrew consent on Day +15, mentioned above, another patient who withdrew consent on Day +91, and a patient lost to follow-up on Day +30. Fifteen of the 39 who completed 100 day post-transplant subsequently became unavailable for follow-up, including 6 who withdrew consent, 8 who died, and one who was lost to follow-up. All patients who withdrew from the study had relapse or disease progression when they withdrew.

The sponsor reports in the Safety Update that as of July 31, 1998, 24/42 were progression free, with a median follow-up of 321 days post-transplant. The Safety Update indicates that there were errors found in the original submission. One of those errors is the relapse reported in the original submission at Day +119 (discussed above). That patient with NHL) has been followed to Day +524 without evidence of relapse. The additional error was the date of relapse of Pt. who relapsed on Day +148 instead of Day +184. The revised Kaplan-Meier probability of freedom from relapse at 1 year is 0.56 (95% CI: 0.40-0.72). In the 12 additional relapses that the sponsor has documented up to the new clinical cut-off, there was an additional patient who relapsed before Day +28 (NHL), one additional relapse between Day +29 and Day+100 Hodgkin's disease), and the remaining 10 occurred after Day +100 (7 with NHL and 3 with AML; Range = Day +20 to Day +463).

3.11.5 Survival

Again, the fact that 74% of patients on study had been followed through Day +100 and only 43% past Day +100 by the time of the clinical cut-off date (January 9, 1998) should be noted before considering the survival data. The median follow-up from transplant for the patients who were survivors at the time of the clinical cut-off date was only 77 days. There were no deaths during the first 28 days after transplantation, or through follow-up to Day +100. The two deaths that occurred by the time of the clinical cut-off date occurred on Day +214 and Day +220. One patient had leukemia and one lymphoma. The narrative for the patient with leukemia indicated that she had been diagnosed with relapsed disease at the time of her death on Day +220. The sponsor's Kaplan-Meier estimated probability of survival at 100 days was 1.0 (95% CI: 1.0-1.0). The sponsor's Kaplan-Meier probability of disease free survival at 100 days was 0.93 (95% CI: 0.84 – 1.0).

In the Safety Update, 34/42 (81%) of patients were alive through the July 31, 1998 cut-off. The median follow-up at that point was 264 days. All 8 deaths occurred after Day +100. The median time to death was 217 days. Of the 6 new deaths reported in this update, 3 had had acute leukemia in remission at the time of transplantation, and 3 active lymphoma. Disease progression was reported as the cause of death in all these patients.

3.12 Safety Analysis

3.12.1 Adverse Events

The most commonly reported adverse events were those that could be anticipated when considering that these patients had been treated with high-dose chemotherapy requiring stem cell support. They were thrombocytopenia (100%), leukopenia (98%), anemia (90%), fever (95%),

stomatitis (95%), nausea (95%), and vomiting (86%). The following table is derived from the sponsor's Adverse Event Summary Table 14.3.4 and Table 14.3.6 Summary of Grade 3 and 4 Toxicities. The Grade 3 and 4 Toxicity and SAE's columns (darkly shaded) represents the Grade 3 and 4 toxicities from Day –7 to Day +100 in Table 14.3.6. The last two columns represent those patients from the earlier unshaded columns that were described as Grade 3 or 4 or as an SAE by the investigator up to Day +100. (The unshaded adverse event columns represent adverse events reported from Day –7 to Day +28.) The following table is not a complete listing of all adverse events. The reviewer has selected out the more common and/or pertinent adverse events to a high-dose busulfan-containing regimen.

Table 7 Summary of Adverse Events, Grade 3 and 4 Toxicities, and SAE's

Body as a Whole						
COSTART term	Mild No. (%)	Moderate No. %	Severe No. %	Total Number	Grade 3&4 Toxicity	SAE's
Fever	8 (19%)	32 (76%)	1 (2%)	41 (98%)	1 (2%)	5 (12%)
Chills	13 (31%)	7 (17%)		20 (48%)	1 (2%)	
Abdominal Pain	14 (33%)	6 (14%)		20 (48%)	1 (2%)	
Abdominal Enlargement	1 (2%)	1 (2%)		2 (5%)		
Ascites		1 (2%)		1 (2%)		
Inflammation Injection Site	9 (21%)			9 (21%)		
Chest Pain	6 (14%)	1 (2%)		7 (17%)		
Edema General	11 (26%)			11 (26%)		
Allergic Reaction	10 (24%)	7 (17%)		17 (40%)		
Headache	19 (45%)	9 (21%)	1 (2%)	29 (69%)	2 (5%)	

Cardiovascular						
	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Tachycardia	21 (50%	4 (10%)		25 (60%)		
Hypotension	3 (7%)	7 (17%)		10 (24%)		
Vasodilation	9 (21%)			9 (21%)		
Thrombosis	7 (17%)		1 (2%)	8 (19%)		1 (2%)
Postural Hypotension	1 (2%)	2 (5%)		3 (7%)		
Capillary Fragility		1 (2%)		1 (2%)		
Pericarditis		1 (2%)		1 (2%)		

Digestive						
	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Nausea	23 (55%)	17 (40%)		40 (95%)	1 (2%)	
Vomiting	17 (40%)	19 (45%)		36 (86%)	1 (2%)	

Stomatitis	19 (45%)	18 (43%)	3 (7%)	40 (95%)	5 (12%)	
Diarrhea	17 (40%)	13 (31%)	2 (5%)	32 (76%)	4 (10%)	
Hepatomegaly		1 (2%)		1 (2%)		
Jaundice	1 (2%)			1 (2%)		
VOD				1 (2%)	1 (2%)	1 (2%)
Pancreatitis		1 (2%)		1 (2%)		

Metabolic and Nutritional

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Bilirubinemia	2 (5%)	5 (12%)	1 (2%)	8 (19%)	4 (10%)	
SGPT Increase	3 (7%)	4 (10%)		7 (17%)	1 (2%)	
Edema Peripheral	5 (12%)			5 (12%)	1 (2%)	
Weight Increase	3 (7%)			3 (7%)		
Hypervolemia	2 (5%)			2 (5%)		
Creatinine Increase	3 (7%)	1 (2%)		4 (10%)		

Nervous System

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Convulsions	1 (2%)			1 (2%)		

Respiratory

	Mild	Moderate	Severe	Total Number	Grade3&4 Toxicity	SAE's
Lung Disease	13 (31%)	1 (2%)		14 (33%)		
Cough Inc.	18 (43%)	2 (5%)		20 (48%)		
Dyspnea	5 (12%)	4 (10%)		9 (21%)		
Asthma	2 (5%)			2 (5%)		
Hemoptysis	1 (2)	1 (2%)		2 (5%)	1 (2%)	1 (2%)
Epistaxis	8 (19%)	1 (2%)		9 (21%)		
Pleural Effusion		1 (2%)		1 (2%)		
Pneumonia		1 (2%)		1 (2%)		

Skin

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Rash	15 (36%)	2 (5%)		17 (40%)		

Urogenital

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Dysuria	8 (19%)	1 (2%)		9 (21%)		
Hematuria	3 (7%)		1 (2%)	4 (10%)	1 (2%)	
Hemorrhagic Cystitis		1 (2%)		1 (2%)		1 (2%)
Oliguria	1 (2%)	1 (2%)		2 (5%)	1 (2%)	

- Hematologic Adverse Events: The cytopenias observed on study were anticipated considering the therapy involved marrow ablation. Thrombocytopenia was graded severe in 40/42 patients, and leukopenia was graded "life threatening" in one.

- Nausea and Vomiting: 13/42 patients vomited during the 4 day period of administration of busulfan. Twenty-five patients had new onset vomiting during the administration period for cyclophosphamide. An ACCESS query of the sponsor's Concomitant Medication dataset reveals that 30 patients were premedicated with ondansetron or granisetron in the Day –7 to Day –4 period of busulfan administration.

- Stomatitis: Ninety-five per cent of patients experienced oral pathology including stomatitis, dry mouth, pharyngitis, esophagitis, tongue disorder, oral candida, and glossitis. Five patients experienced grade 3 stomatitis.

- Veno-occlusive Liver Disease: This adverse event was diagnosed by the principal investigator based on clinical exam and laboratory findings. *An independent central reviewer retrospectively analyzed those cases diagnosed to verify that they met the criteria published by Jones in 1987.* A single case of VOD was diagnosed and was confirmed by the independent central reviewer. That case was considered life threatening, and had its onset on BMT Day +11, according to the study report, or BMT Day +21, according to the SAE Narrative in Table 14.3.12 of the application and the Adverse Event Costart ACCESS dataset. The patient , who had a history of heavily pretreated Hodgkin's disease (no history of radiotherapy), recovered from the episode of VOD. This 30 yo patient was transplanted on 8/6/96, and discharged to home on Day +14. She was readmitted on 8/27/96 with abdominal pain and fever. CT revealed increased liver size, right pleural effusion, and ascites. A transjugular biopsy of the liver reportedly was suggestive of VOD. The total bilirubin peaked at 2.9 on 9/7/96. Urine output decreased and she began dialysis on 9/4/96. The highest creatinine documented was 2.9 on 9/3/96. Her creatinine had been 0.8 at the time of admission. She had been treated with multiple antibiotics including vancomycin and amphotericin from 8/27/96 to 9/6/96. Fever resolved on 9/4/96 and she was discharged 9/12/96, apparently off dialysis. A follow-up CT on 10/6/96 (performed for RUQ pain and nausea and vomiting) revealed near resolution of ascites and a residual small pleural effusion. Bilirubin had normalized, as had creatinine. This patients AUC_{ss} at dose 9 was 1168 μMol · min. The AUC_{ss} believed to increase the risk of development of VOD as reported by Dix in 1996 is >1500 μMol · min.

There were two episodes of abdominal pain reported in patients on this study as "probably related" to busulfan (**Pt** who had VOD and **Pt** , and there were two that were considered "possibly related" to busulfan. There were two patients with abdominal enlargement secondary to ascites (**Pt** who had VOD and **Pt.** The serum bilirubin's in **Pt** are reviewed below. **Pt.** bilirubin peaked at 1.3 on BMT Day 10 and SGPT was 236 on Day 1. **Patient** had elevated SGPT from Day 0 onward that was considered related to busulfan.

*Reviewer Comment: Review of the application's Appendix 16.2.30 Listing of Grade 3 and 4 Toxicity and Other Adverse Events Rated Serious revealed 4 patients who had had hyperbilirubinemia reported in this way (**Pt's** . The sponsor reported in the study report's text that four patients on study had liver dysfunction probably related to study drug (**Pt's** Two of the patients appear in both lists. **Pt** was the patient diagnosed with VOD on study. The summary serum*

bilirubin levels and ALT's for each of the six patients in relationship to the date of transplantation is shown below. In patients
the liver dysfunction was considered probably related to busulfan. (Grade 3 elevation in bilirubin = 1.5 – 3.0 x ULN and grade 4 = >3.0 x ULN.)

Table 8 Summaries of Bilirubin and SGPT in Patients with Liver Abnormalities Reported as Adverse Events

	Pt. (Hodgkin's Dz)	
BMT Day	**Bilirubin**	**SGPT**
Day -4	0.4	24
Day 1	0.6	31
Day +8	0.8	40
Day +10	0.9	42
Day +15	0.6	52
Day +20	0.8	49
Day +24	1.3	169
Day +25	**1.8**	199
Day +27	1.5	145
Day +28	**1.8**	128
	Pt. (Hodgkin's Dz)	
BMT Day	**Bilirubin**	**SGPT**
Day -6	0.8	55
Day -4	0.7	64
Day -1	0.7	94
Day +6	1.5	48
Day +8	1.7	
Day +10	1.9	
Day +13	1.7	
Day +20	**2.5**	
Day +21	**2.5**	
	Pt. (Hodgkin's Dz)	
BMT Day	**Bilirubin**	**SGPT**
Day –7	0.3	36
Day –5	0.2	24
Day –3	0.5	25
Day 0	0.6	63
Day 1	0.6	73
Day +7	**1.0**	28
Day +9	0.6	23
Day +11	0.6	32
Day +14	0.7	29
	Pt. (Hodgkin's Dz)	
BMT Day	**Bilirubin**	**SGPT**
Day -4	0.2	14
Day 2	0.5	39
Day 6	0.9	30
Day 8	**1.5**	
Day 9	1.4	
Day 20	0.6	39

Day 27	0.5	
	Pt. (Hodgkin's Dz)	
BMT Day	**Bilirubin**	**SGPT**
Day –4	0.4	
Day +1	1.2	29
Day +2	**1.5**	49
Day +5	0.9	122
Day +9	1.4	101
Day +13	0.6	65
Day +20	0.4	38
	Pt. (NHL)	
BMT Day	**Bilirubin**	**SGPT**
Day –25	1.0	33
Day –7	0.4	
Day –2	0.5	69
Day +2	1.7	414
Day +3	2.0	231
Day +4	2.6	151
Day +5	3.4	112
Day +6	2.1	78
Day +7	3.1	50
Day +9	2.5	34
Day +14	**4.1**	50
Day +15	**4.1**	50
Day +16	**4.1**	
Day +17	2.6	119
Day +20	2.5	180
Day +25	2.0	137

Patient on review of the adverse event table submitted in the sponsor's ACCESS dataset, was found to have had grade 1 generalized edema from Day –3 to Day +8, and hypotension grade 2 from Day –1 to Day +2, and again on Day 15. This patient had splenomegaly at baseline, and review of the serial physical examination ACCESS dataset revealed that abdominal distension and abdominal tenderness were documented throughout the transplant period. Weight on Day –7 was 42.3 kg. On Day +8 it had increased to 45.3 kg and on Day +9 was higher still at 46.8 kg. After peaking at 47.4 kg on Day +16, the weight dropped to 40.6 kg on Day +23. This patient was never diagnosed as having VOD. No elevations of creatinine were noted in review of the laboratory dataset.

In an addendum to the application, received by the Agency on December 18, 1998, the sponsor provided the methodology for selection of patients for review by the independent reviewer. Any patient identified by the investigator as having VOD was reviewed by the independent reviewer, and in this study only one such patient was identified. An ACCESS query of the database was to be conducted by Lineberry Research Associates to identify patients who may have had VOD based on elevated bilirubin, abdominal pain (not including abdominal cramping), weight gain >5%, hepatomegaly, and ascites. This search apparently yielded no additional patients for review by the independent reviewer.

- Gastrointestinal: There were two patients with ileus. Both were considered unrelated to busulfan. One was considered a grade 3 toxicity. Pancreatitis was reported in one patient on BMT Day +4, and was described as moderate in intensity.

- Capillary leak syndrome was reported in one patient, , and was reported as moderate in intensity. It was not reported as a serious adverse event (SAE). Its onset was BMT Day +9 and resolution was Day +35. Twenty-nine patients (69%) had edema, peripheral edema, edema general, hypervolemia, and/or weight increase reported and were considered by the sponsor as possibly having mild forms of capillary leak syndrome.

- Cardiovascular: Tachycardia was reported in 25 patients (60%), and in 12 the event occurred during the busulfan dosing period. One additional patient developed bradycardia on Day +3. There were two patients who developed atrial fibrillation – one on Day –1 and one on Day +11. There was one episode of hypotension that was considered possibly related to busulfan. It occurred on Day –5 and was described as moderate in intensity.

  Nine patients (21%) developed thromboses, usually of a central line, but one experienced a left femoral artery thrombosis on Day +26, four days after the patient's discharge from the hospital. This patient was readmitted for thrombectomy.

  One patient, , reportedly had an episode of grade 2 pericarditis, that resolved in one day. This occurred on BMT Day +10.

- Respiratory System: Two respiratory adverse events were reported as serious. One was sinusitis in patient The other was life threatening alveolar hemorrhage in patient The latter patient was transplanted on 1/28/97. On Day –1 she had complained of chest pressure and dyspnea, and had experienced a temperature spike (the latter persisted until BMT Day +2). Hemoptysis and continued dyspnea were reported on the day of transplantation, and she was intubated in the early a.m. of Day +1. The chest X-ray was read as "white out" of bilateral lung fields, right greater than left. Interstitial edema consistent with CHF was reported. Bronchoscopy on Day +1 had findings consistent with pulmonary hemorrhage. The platelet count had been approximately 15,000 from Day –1 to Day +1. She was treated with multiple antibiotics, acyclovir, fluconazole, solumedrol, and dopamine, and was ultimately extubated on Day +7. Chest X-ray was read as complete resolution on Day +22.

  Serial pulmonary function tests were performed in 13/42 patients on study. The FEV1 and FVC were noted to decrease by approximately 5%. The greatest change in PFT's was seen in patients who both had Hodgkin's disease that had been treated with upper mantle radiation. Patient had a pleural effusion drained prior to study entry. Five days after documentation of the deterioration of PFT's this patient was found to have recurrence of effusion.

- Urogenital: Hemorrhagic cystitis was reported as an SAE in one patient Hematuria was reported as severe in the same patient and considered related to busulfan. Oliguria was reported as severe and related to busulfan in one patient – (VOD).

- Nervous System: Eighty-eight per cent of patients had some adverse event reported related to the nervous system, but none were reported as severe. These reports included anxiety, insomnia, dizziness, confusion, nightmares, depression, nervousness, thinking abnormality,