- **Nausea and Vomiting:** 26/61 patients vomited during the 4 day period of administration of busulfan. Forty patients were reported to have "new onset" vomiting during the administration period for cyclophosphamide. An ACCESS query of the sponsor's Concomitant Medication dataset revealed that 46 patients were premedicated with ondansetron or granisetron in the Day –7 to Day –4 period of busulfan administration.

- **Stomatitis:** All patients experienced oral pathology including stomatitis, dry mouth, pharyngitis, esophagitis, tongue disorder, oral candida, and glossitis. Sixteen 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.* The independent reviewer confirmed 5 cases of VOD (Pt.'s), although he considered one case (**Pt.** "probably correct, based upon minimal criteria", one case "possibly early VOD"(**Pt.**), and one "possible very low grade VOD (**Pt.** Two cases were fatal and one was considered life threatening. Four of five were reported as serious. (Pt. VOD was not reported as an SAE.) The sponsor's Table 12.1 – Summary Data for Patients with VOD is reproduced here.

Table 13 Summary of Patient Characteristics and Busulfan AUC's for Patients with VOD; Derived from Sponsor Table 12.1 – Summary Data for Patients with VOD, Vol. 1.42.

Pt. No.	Disease	Prior Therapy	Day of Onset/ Max. Bilirubin	Outcome	Dose #1 AUC (μMol-min)	Dose #9 AUC (μMol-min)
	Hodgkin's Dz	C, R, T	Day +25 3.9	Resolution	1256	1170
	AML	C	Day +12 58.6	**Death**	1106	1194
	HD/MDS	R	Day +8 3.8	Resolution	1225	978
	MDS	C, R, T	Day +26 18.8	**Death**	**1644**	**1617**
	CML	R	Day +9 6.3	Resolution	**1567**	**1604**

Eight per cent of patients in this study developed VOD and 3% of patients in this study died with VOD. Forty percent of patients that developed VOD died. Two of the patients that developed VOD in this study had AUC's at both Dose #1 and #9 that were greater than the target upper limit AUC for busulfan in this study – 1500 μMol · min. Death occurred in one of these patients. The other patient who died with VOD met the goal AUC at both doses. Depending on the definition of VOD used, the percentage of VOD reported in the literature varies. A review article in 1995 by Bearman reported busulfan conditioning regimens to be associated with an incidence of 23-32% VOD. Bearman also reported that approximately 50% of cases of VOD are fatal. The results of this study are not out of line with what has been reported in the literature, including articles within the sponsor's 43 article literature review to be discussed in a later section. The fact that

the deaths on this study occurred in patients with the highest bilirubin levels is in keeping with observations that the fatality from VOD increases with increasing levels of serum bilirubin.

Reviewer Comment: An ACCESS query of the Adverse Event Data Set for reports of hyperbilirubinemia of Toxicity Grade 3 or 4 yielded a list of 7 patients not included in the sponsor's list of VOD (. An additional query of the ACCESS Chemistry Laboratory dataset for patient's with bilirubin's greater than 1.8 yielded 4 more patients with hyperbilirubinemia who were not reported as VOD (Pt's . The summary serum bilirubin levels and ALT's for each of the nine patients whose bilirubin elevations were sustained in relationship to the date of transplantation are shown below. The three patients listed in bold were evaluated by the independent reviewer, but were not judged to have VOD. Pt. was felt to have atypical timing and more likely causes of events. A CT was considered necessary by the reviewer to make a diagnosis of VOD in this case, and was not available. Pt. did not meet the criteria of diagnosing VOD, according to the independent reviewer.

Table 14 Summaries of Bilirubin and SGPT in Patients with Liver Abnormalities Reported as Adverse Events

Pt. (AML)		
BMT Day	**Bilirubin**	**SGPT**
Day 0	0.6	21
Day 3	0.8	
Day 4	2.0	42
Day 5	**3.8**	
Day 7	1.3	
Day 11	1.4	33
Day 14	0.9	
Day 23	0.7	16
Day 28	2.1	21
"engraftment failure" and disease relapse Day +34		

Pt. (AML)		
BMT Day	**Bilirubin**	**SGPT**
Day –8	0.5	17
Day -2	1.2	19
Day +2	2.7	54
Day +3	**5.0**	115
Day +4	3.8	164
Day +5	2.0	92
Day +6	1.9	64
Day +13	2.2	18
Day +26	0.6	16
SAE reported for delirium (see neurological adverse events). Death on Day +275.		

Pt. (AML)		
BMT Day	**Bilirubin**	**SGPT**
Day -4	0.3	9
Day +9	1.0	11
Day +12	**2.9**	6
Day +13	2.0	6
Day +17	1.3	6

Pt. (Transformed MDS)

BMT Day	Bilirubin	SGPT
Day –6	<0.2	38
Day +2	0.5	38
Day +4	1.1	36
Day +9	2.1	21
Day +10	4.0	15
Day +11	**7.0**	17
Day +14	5.7	16
Day +18	3.4	16
Day +24	4.3	

Pt. (Hodgkin's Disease)

BMT Day	Bilirubin	SGPT
Day -7	1.2	205
Day 1	2.6	246
Day 2	4.1	234
Day 3	6.3	152
Day 4	**8.3**	116
Day 5	4.7	55
Day +7	5.7	44
Day +9	4.7	27
Day +13	4.2	40
Day +16	2.7	31
Day +20	2.2	20
Day +27	2.6	23

Pt. (MDS)

BMT Day	Bilirubin	SGPT
Day –7	0.5	35
Day -3	0.7	32
Day 0	1.6	19
Day +1	4.0	16
Day +2	6.5	40
Day +3	8.2	40
Day +4	9.5	35
Day +5	**10.1**	33
Day +9	4.8	24
Day +15	4.2	20
Day +22	2.0	21
Day +30	1.4	37
Day +33	1.2	34

Pt. (AML)

BMT Day	Bilirubin	SGPT
Day +1	0.5	42
Day +4	1.0	98
Day +10	2.2	9
Day +15	5.7	8
Day +16	4.7	
Day +17	**5.8**	
Day +22	2.2	12
Day +25	2.8	28
Day +26	1.7	

Day +27	1.6	28

Pt. (NHL)		
BMT Day	**Bilirubin**	**SGPT**
Day +1	0.9	22
Day +3	3.0	41
Day +5	2.6	60
Day +11	2.9	20
Day +13	3.1	10
Day +15	5.8	9
Day +17	**9.5**	16
Day +18	7.2	26
Day +20	5.1	29

See narrative for death on Day +20. Multi-organ failure but sponsor states no other signs of VOD

Pt. (Transformed MDS)		
BMT Day	**Bilirubin**	**SGPT**
Day 0	0.4	
Day 2	0.7	
Day +4	1.2	
Day +5	2.1	70
Day +7	2.4	36
Day +9	2.8	27
Day +11	**2.9**	29
Day +14	2.4	22
Day +23	0.8	
Day +28	0.8	

Pt. in the table above died on Day +20 with multi-organ failure. VOD was considered but not diagnosed. This patient was not reviewed by the independent reviewer. There are other recognized etiologies of elevated serum bilirubin in the allogeneic transplantation setting beyond VOD. Although the patients listed above had significant elevations of bilirubin reported on study, the reviewer cannot argue that these cases were secondary to VOD. In addition, **Pt** (who does not appear in the table above because pertinent lab occurred after discharge) had a course complicated by HUS/TTP on Day +85.

Reviewer Comment: The applicant submitted a summary of the methodology used to determine which patients would undergo independent review for VOD in an addendum received by the Agency on December 18, 1998. Patients identified by the investigator as having VOD were reviewed by the independent reviewer. In addition, a query of the ACCESS database was performed by Lineberry Research Associates to identify patients "who may have met the Jones' criteria for VOD but did not have an AE of VOD reported", using bilirubin, ascites, hepatomegaly, abdominal pain (excluding cramping), and weight gain >5% to conduct the search. This ACCESS query yielded the 3 additional patients discussed above for review by the central reviewer.

- **Gastrointestinal:** There were five patients with ileus, and 50 patients with diarrhea (82%). Diarrhea was grade 3 in 3 (5%). Pancreatitis was reported in one patient on BMT Day +26, and was described as grade 2. There was one severe gastrointestinal bleed that occurred on Day +20 in one of the patients with VOD

- Capillary leak syndrome was not reported in any patient participating in this study. Forty-four (72%) had edema, peripheral edema, edema general, hypervolemia, and/or weight increase reported.

- Cardiovascular: Tachycardia was reported in 27 patients (44%), and in 7 the event occurred during the busulfan dosing period. There were four patients who developed arrhythmias considered mild or moderate, except in one patient who developed a "severe dysrhythmia" during a terminal episode of alveolar hemorrhage. The latter patient developed atrial fibrillation on BMT Day +47 that required cardioversion. Subsequently on BMT Day +50 the patient developed third degree heart bock that necessitated placement of a transvenous pacemaker. This all occurred while he was intubated. He was subsequently extubated on Day +52, but deteriorated and required re-intubation on Day +54. He then developed a junctional rhythm followed by a wide-complex tachycardia that resolved with lidocaine.

  There were seven patients with reports of hypotension. Two were considered grade 3 and one was reported as an SAE. The latter case occurred on BMT Day –3 in a 35 yo woman with MDS secondary to treatment for breast cancer. This patient was noted to be hypotensive just prior to starting her first dose of cyclophosphamide (90/54). The next day her blood pressure was noted to be 84/54 prior to starting the second infusion of cyclophosphamide, which was held. She was transferred to an ICU and started on dopamine. Melphalan was substituted for the second dose of cyclophosphamide on the following day. The hypotension was considered possibly related to the study drug, intravenous busulfan. Blood cultures were negative and she was transferred out of the ICU on the day of transplant.

  Nineteen patients (31%) developed thromboses, all of a central line. Mild cardiomegaly, noted in two patients on Day +1 and Day +12, was considered possibly related to busulfan. There was one case of grade 3 severe CHF on BMT +31. This episode was reported in association with diffuse alveolar hemorrhage in the patient with "severe dysrhythmia" described above. There was one patient who had **pericarditis**, not considered related to busulfan.

- Respiratory System: Respiratory adverse events were reported in 52 patients (85%) in the early study period that ended on Day +28. Twelve of those events were reported as SAE's. There were two diffuse alveolar hemorrhages (Pt. on Day +31 and Pt. on Day +30). In addition, Pt. SAE narrative for interstitial pneumonitis indicates that bronchoscopy on Day +21 revealed diffuse alveolar hemorrhage that was considered to be secondary to complications from interstitial pneumonitis. Because pulmonary complications have been associated with busulfan, the pulmonary SAE's reported in this study will be listed here.

Pt. Interstitial Pneumonitis: 44 yo female with AML in first relapse who developed dyspnea and mild chest discomfort on BMT Day +9 after a transfusion of RBC's. Bibasilar rales were noted on examination, and O_2 saturation on 2L was 95%. The following day the chest X-ray revealed bibasilar infiltrates, small pleural effusions, and interstitial pneumonitis. The patient began complaining of pleuritic chest pain, and physical examination revealed +1 edema in the extremities. A RLL pneumonia was suspected on Day +14 after a rise in temperature. A bronchoscopy on Day +16 was viewed as compatible with bilateral pneumonia. She was intubated on Day +20, and repeat bronchoscopy on Day +21 revealed diffuse alveolar hemorrhage. She expired on Day+27 with deterioration of her "ARDS and/or possible cytokine syndrome vs. worsening interstitial pneumonitis".

Pt. **Bibasilar Pneumonia**: 36 yo male with AML. On Day +12 the patient complained of increased abdominal discomfort and a chest X-ray revealed fluid or pneumonia in bilateral lower lobes. A follow-up X-ray on Day +15 confirmed pneumonia, and the patient required transfer to an ICU setting on Day +18, when the chest X-ray showed right sided pleural effusion and consolidation of the left lung. On Day +20 a shunt was placed to relieve hepatic congestion related to VOD and the patient had to be intubated secondary to aspiration. The Day +22 chest X-ray was read as bilateral pneumonia and pulmonary edema. The patient expired after an intracranial hemorrhage that occurred on Day +25.

Pt. **Progression of Pneumonia, LLL Pneumonia and Bilateral Effusion**: 41 yo female with AML was discharged from hospital on BMT Day +23. She had had "reoccurrence of LLL pneumonia and MRSA infection" on BMT Day +2. She was readmitted to the hospital on Day +30 for progression of MRSA infection and LLL pneumonia. Chest X-ray revealed LLL pneumonia with moderate bilateral pleural effusions. On Day +34 the ANC had dropped to 300 and she was diagnosed as having had engraftment failure. Bone marrow revealed relapsed disease. The Day +38 chest X-ray was read as showing RUL nodular opacity, LLL consolidation, and probable fungal pneumonia, and on the following day the left pleural effusion and LLL consolidation were noted to be worsening. The respiratory status worsened and the patient elected not to be intubated. She expired on Day +42.

Pt. **Diffuse Alveolar Hemorrhage**: This 44 yo male had refractory Hodgkin's disease and MDS with aplastic anemia. He developed hemoptysis and progressive dyspnea on Day +31. CT on Day +33 showed right pleural effusion and glossy infiltrate consistent with pneumocystis pneumonia. Thoracentesis cultures revealed Klebsiella, CMV, candida, and MRSA ongoing since baseline. Bronchoscopy on Day +37 revealed fresh blood consistent with pulmonary hemorrhage. Intubation became necessary on Day +39 and the chest X-ray on Day +41 demonstrated worsening bilateral and diffuse alveolar infiltrates. The patient improved and was extubated on Day +52, but on day +54 had to be reintubated. He expired on Day +62.

Pt. **Pneumonia**: 49 yo male with AML was discharged on BMT Day +19, but had to be readmitted on Day +24 for dyspnea and substernal chest pain. CT of the chest revealed LLL pneumonia. Cultures were negative and the symptoms resolved.

Pt. **Respiratory Failure/ARDS**: 35 yo male with secondary AML was discharged on Day +13. On Day +70 he presented with increased dyspnea, right sided chest pain, and yellow sputum production. Video assisted thoracoscopy with wedge biopsies showed non-specific interstitial fibrosis. The patient was intubated on Day +72. He became hypotensive and required pressor support on Day +72, and he began plasma exchange on Day +85 for HUS/TTP. Bronchoalveolar lavage on Day +91 revealed no interval change in the lungs, and sputum cultures were negative. The patient did not improve and supported measures were discontinued. He expired on BMT Day +98.

Pt. **Diffuse Alveolar Hemorrhage**: 41 yo female who was transplanted for MDS. She was diagnosed with VOD on Day +30, and was moved to the ICU on that day for worsening respiratory failure. She was intubated and started on dopamine and epinephrine for pressor support. Emergent bronchoscopy revealed diffuse alveolar hemorrhage. She died on Day +31.

Pt. **Interstitial Infiltrates**: 51 yo male who developed dyspnea on Day +38, associated with a fever. Chest X-ray reveal worsening of previously noted infiltrates, and bronchoscopy on Day +41 demonstrated hemosiderin laden macrophages, coag-negative staphylococcus, and

adenovirus. The infiltrates responded to antibiotics and steroids, and the patient was discharged from the hospital on Day +51.

Pt. **Respiratory Failure Secondary to Aspergillus Pneumonia**: 51 yo male with recurrent low grade NHL and therapy-induced myelodysplasia. He had a history of previous bone marrow transplant seven years prior. On Day +17 this patient developed respiratory distress and inability to handle secretions secondary to oral mucositis. He was emergently intubated on that day, and a chest X-ray revealed LLL infiltrate and left medial lung patchy infiltrates. Bronchoscopy and BAL on Day +18 revealed upper airway obstruction due to mucositis, progressive left lung infiltrate and atelectasis with dense mucus plugs obstructing the left main stem bronchus. Bronchial washing showed Aspergillus. Follow-up bronchoscopy on Day +20 revealed a necrotic lesion from the left main stem and left upper lobe bronchus that had associated black, necrotic fibrous tissue sloughing from the left lower lobe. The patient became unresponsive, which was attributed to probable CNS Aspergillus. The patient was extubated and died on Day +21.

Reviewer Comment: The reviewer considered the respiratory SAE's related to diffuse alveolar hemorrhage in Pt's. and the non-specific interstitial fibrosis with ARDS in as respiratory events that should be considered related to busulfan in this complex transplantation setting.

Serial pulmonary function tests were performed in 13/61 patients on study. The FEV1 and FVC decreases were small, except in one patient (Pt. whose FVC deteriorated form 2.93 (80% of predicted) to 2.51L (65% of predicted). A tabular summary of the changes in PFT's observed in this study follows.

Table 15 Summary of Pulmonary Function Test Changes on Study; Derived from Sponsor Table 14.3.7 Summary of Pre-treatment and Post-Transplant Pulmonary Function Tests, Vol. 1.42.

	Pretreatment (n=61) Median	Post Transplant (n=13) Median	Post Transplant Change from Pretreatment Median
FEV1 (liters)	3.4	3.7	-0.1
FEV (%Predicted)	97%	94%	-1.0
FVC (liters)	4.2	4.8	-0.1
FVC (% Predicted)	97%	96%	-3.0
DLCO (%)	83.5%	77%	-1.0

- **Urogenital**: Hemorrhagic cystitis was reported as serious in four patients. In one patient , it occurred during the early study period (before Day +28). Hematuria was reported as an SAE in one patient and was considered in the study report to be related to CMV. Oliguria was reported as mild or moderate in 9 patients. In six of these patients it developed between Day –2 and Day +1 and was considered probably related to busulfan. There were 3 patients who had polyuria reported on study and one case was considered as probably related to busulfan. The GU SAE's are summarized briefly below:

Pt. **Right Ureteral Obstruction with Hydronephrosis:** 44 yo female with CML. She was discharged on Day +16. She presented with RLQ pain on Day +90 and IVP revealed right ureteral dilatation and right hydronephrosis. A ureteral stent was placed on Day +104 and the patient was discharged on Day +116. The event was considered unrelated to busulfan.

Pt. **Hemorrhagic Cystitis**: 23 yo female with CML was discharged from the hospital on Day +14. She was readmitted on Day +37 with diarrhea and elevated bilirubin and was diagnosed with VOD. On **Day +62** she developed hemorrhagic cystitis. Urine viral cultures were negative for CMV, but urine cytology was read as dysplastic cells suggestive of viral effect. The catheter was discontinued on Day +76, but had to be reinserted the following day for hematuria. Cystoscopy on Day +86 revealed diffuse mucosal hemorrhage covering the entire mucosa. Resolution of hemorrhagic cystitis was reported n Day +141, but she was able to be discharged on Day +92.

Pt. **Hemorrhagic Cystitis**: 29 yo female with AML was discharged for the hospital on Day +18. She was readmitted on **Day +44** with dysuria and hematuria with clots. The catheter was removed on Day +47, and she was discharged on Day +49 with IV fluid hydration ongoing. Complete resolution was noted on Day +65.

Pt. **Hemorrhagic Cystitis**: 20 yo male with AML. Hematuria with clots developed on **Day +20**. Continuous bladder irrigation with hydrocortisone was started on Day +23. Cystoscopy on Day +59 involved cauterization of 30-40% of the bladder surface area. Bladder irrigation stopped on Day +61, and at the time of discharge on Day +66 hematuria was described as minimal. It resolved on Day +73.

Pt. **Hemorrhagic Cystitis:** 38 yo female with MDS who was discharged from the hospital on Day +25. She was readmitted on **Day +62** for dysuria and hematuria, and required transfusion with 4 units of PRBC's. A cystoscopy and biopsy on Day +69 demonstrated human polyoma virus. She was discharged on Day +87. The event was considered probably related to study medication.

Pt. **Hematuria**: 35 yo male with AML was discharged from the hospital on Day +29. He was readmitted on **Day +31** for right flank pain and hematuria. Cystoscopy, bilateral retrograde pyelography and right ureteral stent placement was performed on Day +34. A narrowed segment of ureter at the pelvic inlet was stent in the hopes of relieving symptoms. The patient was discharged on Day +41. The urine culture was positive for CMV. The investigator felt the event was possibly related to study medication.

Reviewer Comment: The delayed onset of hemorrhagic GU events is consistent with the temporal pattern for this adverse event in the transplant setting reported in the literature.

- **Nervous System:** Ninety-eight per cent of patients had some adverse event reported related to the nervous system. These reports included anxiety, insomnia, dizziness, confusion, nightmares, depression, nervousness, thinking abnormality, and hallucinations. It would be difficult to attribute any of these to busulfan specifically in the transplantation setting where patients are on multiple medications. No seizures, however, were reported. The CNS events that were reported as severe included one case of insomnia, one patient with grade 3 disorientation, grade 4 coma, and grade 3 hepatic encephalopathy, one patient with grade 3 delirium, one with grade 3 confusion, one patient with grade 1 hallucinations, and one patient with grade 3 agitation. The patient with disorientation, hepatic encephalopathy and coma was Pt. who died secondary to VOD and an intracerebral hemorrhage. The case of grade

3 delirium was reported in a safety report regarding **Pt.** who, the night of BMT Day – 4 (busulfan dosing period), became agitated and combative. Delirium did not resolve until BMT Day +5. This patient was 55 yo and had AML. The patient with grade 3 confusion was **Pt.** who developed VOD, alveolar hemorrhage, and multi-organ failure. The remaining patient, **Pt.** . who had grade 3 agitation reported, had multi-organ failure and died on Day +20 of the study. CNS involvement with aspergillosis was suspected.

- Graft versus Host Disease: There were 11 patients with GVHD (18%). It was reported as serious in 4. None was fatal, although two patients did die on study. Their deaths on Day +164 and Day +62 were attributed to infection and hemorrhage (Pt. respectively). In 5/11patients GVHD was said to primarily involve the skin. In 2 it involved the gastrointestinal tract, and in one it involved both skin and gut. One patient, **Pt.** had grade 4 GVHD, and 2 patients had grade 3 GVHD (Pt. 01-418 and Pt.). The remaining cases were described as grade 1 or 2.

Pt. GVHD This 34 yo male with CML had GVHD grade 4 reported as an SAE. He had been discharged on BMT Day +19, only to be readmitted on Day +26 with diarrhea and abdominal pain. A flexible sigmoidoscopy biopsy confirmed GVHD . A rash biopsied on Day +15 had been negative for GVHD. This persisted on Day +28 and was thought to be suggestive of GVHD. The patient's diarrhea finally responded to a 4 day course of ATG started on Day +44. He was discharged on Day +63.

The Safety Update stated that there were 3 deaths that occurred subsequent to the original application study report that were attributed to GVHD. Those deaths occurred on Days +105, +199, and +212.

4.11.2 Deaths

There were **2 deaths** during the study period that included BMT Day +28. Six patients died in the short-term follow-up interval between Day +29 to Day +100. There were **two** additional deaths that occurred beyond Day +100. These deaths occurred before the clinical cutoff date of January 9, 1998. Thirty-three percent of patients in this study had been observed beyond Day +100 at the time of the clinical cut-off date. The patients that died are described below.

Pt. Pt with active AML at the time of transplantation, relapse on Day +106 and died on Day +164. Her death was attributed to infection.

Pt. 44 yo female with AML in first relapse was described in the respiratory adverse event section above for Interstitial Pneumonitis. She died on Day +27 with gradually worsening respiratory insufficiency, despite mechanical ventilation. She had ARDS, Diffuse Alveolar Hemorrhage vs. Interstitial pneumonitis.

Pt. 36 yo male with AML, described above in the respiratory adverse event section for Bibasilar Pneumonia. The patient had VOD, renal insufficiency, bilateral pneumonia and pulmonary edema, and developed a right temporal intracranial hemorrhage. He expired on Day +30. The cause of death was VOD concurrent with intracerebral bleed.

Pt. 41 yo female with AML described above in the respiratory adverse event section for LLL Pneumonia and Bilateral Effusion. She died on BMT Day +42 after she had had engraftment failure noted on Day +34 and relapsed leukemia noted on a bone marrow biopsy on Day +36 (18% blasts). On the day prior to death she had persistent pancytopenia, a bilirubin of 6.9, 4+pedal edema, and sinusitis. Her left pleural effusion had increased and she had consolidation of the right lung.

Pt. 55 yo male with AML (in remission at transplantation) who died on Day +275 after relapse was documented on Day +255. His transplantation course had been complicated by an SAE of acute delirium reported on Day –4 that was considered to be possibly related to busulfan (described in the nervous system adverse events section).

Pt. 44 yo male with refractory Hodgkin's disease and MDS with aplastic anemia who died on Day +62. He was described earlier in the respiratory adverse events section with Diffuse Alveolar Hemorrhage. In addition, his course was complicated by arrhythmia, which was described in the cardiovascular adverse events section (atrial fibrillation, third degree heart block, and wide-complex tachycardia). His death with diffuse, bilateral and interstitial airspace disease was not considered by the investigator to be related to study medication.

Pt. 35 yo male with secondary AML died on Day +98. His course is described in the respiratory adverse events section with Respiratory failure/ARDS. His course was complicated by **HUS/TTP** that necessitated plasma exchange starting on Day +85. His death was considered probably related to study medication.

Pt. 55 yo male with relapsed AML who was discharged from the hospital on BMT Day +26. Relapse of AML was diagnosed on Day +67, and he was readmitted on Day +75 with fever, cough, hypotension, and increasing thrombocytopenia. He was placed on multiple antibiotics and required dopamine support. He developed dyspnea the following day that was considered possibly due to leukemic infiltrates. He began to show evidence of tumor lysis syndrome and he died on Day +80. Death was not considered related to study medication.

Pt. 41 yo female with MDS who was discussed above in the respiratory adverse events section for Diffuse Alveolar Hemorrhage. Her course was also complicated by the development of VOD diagnosed on Day +30. She developed multi-organ failure with diffuse alveolar hemorrhage, renal failure, and septic shock and died on Day +31.

Pt. 53 yo male with low-grade NHL and therapy induced myelodysplasia who died on Day +20 with Aspergillus pneumonia and multi-system organ failure. His course had been complicated by acute development of hyperbilirubinemia on Day +3 (bilirubin=3.0), but no other signs of VOD were apparently noted, and VOD was not reported in this patient. His death was considered probably related to study drug.

The Safety Update added **8** patients who died beyond Day +100. Three of these deaths were attributed to disease progression, two to infection (Day +113 and Day +226), and three to GVHD (Day +164, +199, and +212). One of the three patients whose deaths were attributed to GVHD had experienced disease relapse prior to death. One of the patients who died from an infection had documentation of disease relapse prior to death.

4.12 Pharmacokinetics – OMC-BUS-4

The reviewer refers the reader to the detailed Biopharm review of this application.

4.13 Summary and Conclusions – OMC-BUS-4

The sponsor has concluded from this study that the safety and efficacy of Busulfex Injection at a dose of 0.8 mg/kg for 16 doses in combination with cyclophosphamide has been demonstrated in the setting of patients with advanced hematologic malignancies treated with allogeneic transplantation. The sponsor believes that the data have demonstrated that this regimen produced myeloablation and was supportive of subsequent engraftment, noting that all patients engrafted except for one patient who died on Day +20 before engraftment occurred. The median time to engraftment on this study was 13 days, and the one case of graft failure on Day +34 reported in the initial study report has been rescinded and attributed to relapsed disease in the Safety Update, because a mixed chimera was noted on the bone marrow performed when the ANC dropped below 500.

The reviewer concurs that this study, conducted in the setting of allogeneic transplantation, demonstrated that intravenous busulfan produces similar myeloablation and engraftment as oral busulfan when given in combination with cyclophosphamide. If the patient who died prior to demonstration of engraftment (total WBC <0.2 on the day of death) and the graft failure on Day +34 are counted as lack of engraftment, then 2/61 (3%) of patients treated on this study did not have successful engraftment. If the patient whose drop in ANC has been attributed to disease relapse rather than graft failure is dropped from this analysis, the one case of non-engraftment prior to death in the first 28 days yields a 1.6% graft failure in this study. This is not out of line with the literature reports reviewed in the literature review section of this NDA. As mentioned earlier, patients who die prior to engraftment in BMT studies are variably reported in articles as failure to engraftment.

A historical comparison of toxicity associated with this BU/CY regimen that employed intravenous busulfan to BU/CY regimens utilizing oral busulfan reveals similarities. The percentage of interstitial pneumonitis/diffuse alveolar hemorrhage reported as SAE's in this study (4/61; 6.6%) and the percentage of VOD reported as an SAE (8%) appears comparable to what has been reported in the literature with oral high dose busulfan conditioning regimens that combine it with cyclophosphamide. Forty per cent of the cases of VOD in this study were fatal, which is in keeping with review articles that report that approximately 50% of cases of VOD are fatal. There were 5 cases of hemorrhagic cystitis and hematuria reported as SAE's (8.2%). GVHD was reported in 18% of patients in the original study report. There were 3 deaths attributed to GVHD (4.9%) in the Safety Update.

Two (3.3%) of the deaths in this study occurred within the first 28 days. If the death that occurred on Day +30 from VOD and intracranial hemorrhage, and the death on Day +31 from diffuse alveolar hemorrhage are counted as well, the acute treatment related mortality increases to 6.6%. Inclusion of the death of Pt. (Day +85 from HUS/TTP, considered treatment related by the investigator) and the death of Pt. (Day +62 from interstitial airspace disease) are counted, treatment related mortality increases to 9.8%. If all eight deaths in the first 100 days are considered, there was a 13.1% mortality in the first 100 days. These percentages can be compared to those reported in the randomized controlled trials in allogeneic transplantation that will be discussed in greater depth in the literature review section of this NDA.

To facilitate a comparison of the safety data from OMC-BUS-4 an abbreviated table of those phase 3 studies is shown below. When making these crude comparisons, one should keep in mind that the patients in the studies listed in the following table were generally less heavily pretreated than those that participated in OMC-BUS-4. In addition, when making comparisons to times of engraftment, it should be noted that G-CSF was not commonly used in the studies included in this table.

Table 16 Safety Summary of Allogeneic Transplantation Randomized Trials Presented in the NDA's Literature Review

Citation	Disease	Safety
Blaise, D. Blood. 1992 May; 79(10):2578. Allogeneic BMT for AML in first remission: a randomized trial of busulfan-cytoxan vs. Cytoxan-TBI as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse.	AML, CR1	1/51 BU/CY not evaluable for engraftment for death within 1 month of BMT ANC = 500: Med.=19d BU/CY = 27%±7% TRM (K-M – probability of non-leukemic mortality) 3/6 VOD died 6 VOD=5.9% IPS = 2/51=3.9% Acute GVHD ≥ Gr. 2 = 31%±4% (K-M probability)
Blume, K. Blood. 1993 April; 81(8): 2187. A Prospective Randomized Comparison of Total Body Irradiation-Etoposide VS. Busulfan-Cyclophosphamide as Preparatory Regimens for Bone Marrow Transplantation in Patients With Leukemia Who Were No in First Remission: A SWOG Study	Leukemia failing prior therapy	BU/CY = 3/61 death from VOD (4.9%) Acute GVHD = 2/59 death from Chronic GVHD = 1/59 death from

Citation	Disease	Safety
Ringden, O. Blood. 1994 May; 83(9):2723. Randomized Trial Comparing Busulfan with TBI as Conditioning in Allogeneic Marrow Transplant Recipients with Leukemia: A Report from the Nordic BMT Group.	Hematological malignancy	86/88 BU/CY Engrafted (2.3% non-engraftment) ANC > 500 = 20d BU/CY (11-44) TRM = 28% BU/CY (non-relapse death) VOD : BU/CY=12% IPS = 14% Hemorrhagic Cystitis: BU/CY= 24% Acute GVHD (4 mo) ≥ GR. 2 = 26% Chronic GVHD = 45% %'s = cumulative incidence
Cassileth, P. NEJM. 1998 December; 339(23):1649-1656. Chemotherapy Compared with Autologous or Allogeneic BMT in the Management of AML in First Remission	AML CR1	Median to ANC > 500:Allo = 19 d No graft failure Death from VOD: Allo = 6/92 treated (6.5%) Death from Acute GVHD= 5/92 TRM = Deaths within 100d of postremission therapy: Allo = 21%; 19/92 treated
Clift, RA. Blood. 1994 September; 84(6): 2036-2043. Marrow Transplantation for CML: A Randomized Study Comparing Cyclophosphamide and TBI with Busulfan and Cyclophosphamide	CML, Chronic Phase	One patient on CY/TBI died before engraftment (on D18) ANC ≥ 500: BU/CY = 22.26 d (mean) 3/73 died in first 100d= 4.1% TRM K-M probability of ≥ Gr. 2 Acute GVHD = 35%

Citation	Disease	Safety
Devergie, A. Blood. 1995 April; 85(8): 2263-2268. Allogeneic BMT for CML in First Chronic Phase: A Randomized Trial of Busulfan-Cytoxan Versus Cytoxan-TBI as Preparative Regimen: A Report from the French Society of Bone Marrow Graft (SFGM). (1988-1991 accrual)	CML, Chronic Phase	4/65 (6.1%) BU/CY failed to engraft (1) or rejected graft (3) TRM: BU/CY = 38% VOD: BU/CY = 5 (7.7%) 3/5 result in death IPS = 11/65 = 16.9% Hemorrhagic Cystitis = 7/65 = 10.8% Acute GVHD ≥ Gr. 2 = 41%

In summary, the reviewer believes that the safety and efficacy data from OMC-BUS-4 support the conclusion that high dose intravenous busulfan therapy is comparable to high dose oral busulfan conditioning for transplantation.

5. Pharmacokinetic Studies OMC-BUS-2 and Amendment #4 to OMC-BUS-3 and OMC-BUS-4

OMC-BUS-2 was the original phase 1 study conducted by the sponsor to identify the appropriate dose of intravenous busulfan that was comparable to oral busulfan in achieving a target level of AUC_{ss}. Six patients were treated at that dose, 0.8 mg/kg, in this study, in which the first in a series of 16 busulfan doses in a BU/CY120 conditioning regimen was delivered as the intravenous formulation. All subsequent doses were the standard oral formulation.

The goal of Amendment #4 to both phase 2 studies (OMC-BUS-3 and OMC-BUS-4) was to obtain more complete pharmacokinetic characterization of intravenous busulfan as it compared to the oral formulation. In this amendment, 12 additional patients in each study were treated with an initial dose of oral busulfan, 1.0 mg/kg, followed then by the remaining series of 15 intravenous doses at 0.8 mg/kg.

The clinical cut-off date for the report submitted on the patients treated in this Amendment was July 31, 1998. It was received by the Agency on October 1, 1998. Twelve patients treated under this amendment were the subject of the report – 3 treated on the autologous transplantation study (OMC-BUS-3) and 9 on the allogeneic study (OMC-BUS-4). The pharmacokinetic data can be found discussed in depth in the Biopharm review of this application. The medical reviewer will merely briefly summarize the engraftment and safety reports of this small number of patients in this section.