

and hallucinations. It would be difficult to attribute any of these to busulfan specifically in the transplantation setting where patients are on multiple medications. A seizure, however, was reported in one patient on BMT Day -2. This patient was on phenytoin, and no recurrent episode was reported. Review of the adverse events reported for this patient in the ACCESS dataset reveals that there was grade 1 and 2 emesis on transplant days -4 through Day -2. It is possible that the patient did not have an adequate serum phenytoin level if they vomited their oral phenytoin. No serum dilantin level was found by the reviewer.

3.12.2 Deaths

There were no deaths during the study period that included BMT Day +28. Two patients had died as of the clinical cutoff date – both after Day +100. Forty-three percent of patients in this study had been observed beyond Day +100 at the time of the clinical cut-off date. The two patients that died are described below.

Pt. was a 19 yo female who had nodular sclerosing Hodgkin's disease and was transplanted with active disease. She relapsed on Day +184 and died on Day +214. Death was attributed to viral pneumonia with secondary hemorrhage. Her busulfan AUC_{ss} at the 9th dose was 1227 $\mu\text{Mol} \cdot \text{min}$.

Pt. had acute myelogenous leukemia and was transplanted with active disease. She is reported to have died of infection/hemorrhage secondary to recurrent refractory AML on Day +220. Her busulfan AUC_{ss} at the 9th dose was relatively low at 857 $\mu\text{Mol} \cdot \text{min}$. This patient's BMT course was complicated by pancreatitis BMT Days +4 to +62.

The six additional deaths reported in the Safety Update were all attributed to disease recurrence/progression and are summarized as follows:

Pt. died on BMT Day +124. He had NHL that had been previously treated with chemotherapy, but no radiation. His death was attributed to relapsed disease. This patient's course had been complicated by hemorrhagic cystitis and prolonged thrombocytopenia.

Pt. was a 41 yo with Hodgkin's disease and a history of mediastinal radiotherapy (complicated with radiation pneumonitis) and treatment with chemotherapy. Death on BMT Day +187 was attributed to disease progression.

Pt. was a 38 yo female with NHL who had received prior mantle radiation and chemotherapy. Her baseline chest X-ray revealed radiation fibrosis. Death on BMT Day +285 was attributed to disease progression.

Pt. was a 41 yo with acute leukemia who is reported in the Safety Update summary to have died on BMT Day +312. Death was attributed to disease progression, but this information was obtained from a social security benefits death record, and the Patient Mortality form in the CRF indicates that the actual date of death was unknown.

Pt. was a 39 yo male with AML whose death on BMT Day + 191 was attributed to disease progression.

Pt. was a 50 yo female who had AML in CR1 at study entry. She had a prior history of pericardial effusion and CHF, and 3+ edema in the extremities at study entry. Her baseline LVEF was 60%. Her death was attributed to disease progression. This information was apparently obtained from a "BMT list".

Reviewer Comment: Review of the CRF's raises concern regarding the validity of the mortality information, as it appears to have been obtained from secondary sources in some cases. Attributed cause of death may, therefore, be flawed.

3.13 Pharmacokinetics – OMC-BUS-3

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

3.14 Summary and Conclusions – OMC-BUS-3

The sponsor has concluded from this study that, in the setting of patients with advanced hematologic malignancies, the safety and efficacy of Busulfex Injection at a dose of 0.8 mg/kg x 16 doses in combination with cyclophosphamide has been demonstrated. The sponsor believes that the data have demonstrated that this regimen produced myeloablation and was supportive of subsequent engraftment.

It should be noted again that a third of the patients in this study did not have all the protocol-defined serial hematological laboratory tests through Day +28 available for review. Lab collection stopped prematurely in these patients. In addition, there was virtually no laboratory data available after Day +28 to enable the reviewer to audit for potential under-reporting of adverse events, including late graft failure.

Despite these limitations, the reviewer agrees that the data from this study demonstrated that this regimen was myeloablative, and that the patients engrafted. The reviewer did have concerns regarding the significant drops in the ANC's observed in some patients subsequent to first evidence of engraftment, and those concerns were discussed in the engraftment section of this review. The definition of engraftment provided in the protocol was not limiting in terms of defining a required duration of first elevation of ANC over 500, and only required documentation of a single ANC >500. Patients that experienced subsequent drops in their ANC did have rising platelet counts that appeared to be self-sustaining at the time of the last provided hematological data. This supports the conclusion that engraftment had indeed occurred. The primary endpoint of this study was demonstration of engraftment, and the reviewer believes this was demonstrated in all 42 patients. The date of engraftment was, however, changed by the reviewer in 4 patients, but this did not significantly impact on the median time to engraftment.

The secondary endpoints of relapse and survival are of limited value for analysis, given that this is a small, uncontrolled trial. The reviewer has pointed out what appear to have been errors in the collection of relapse data. The survival data is meaningful primarily in that the regimen did not appear to cause deaths in the first 28 days or beyond. Because some of the mortality data appears to have been collected from secondary sources, conclusions regarding cause of death in cases beyond Day +28 may not be valid. Follow-up beyond the clinical cut-off date was limited. The median follow-up beyond that date was 70 days at the time the study report was written. Seventy-four percent of patients had been followed through Day +100, and there were no deaths

Day +17	10.8	10,368	43K	↓	
Day +20	1.9	1,368	87K	↓	
Day +21	8.2	6,970	95K	↓	
Day +24	2.3	460	112K	↓	
Day +27	4.0	2,560	93K	↓	
Pt.					
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +12	0.4	160	13	Stop	Platelets
Day +17	1.5	645	18		
Day +20	5.5	1980	35		
Day +26	3.9	2262	57		
Pt.					
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +15	0.6	240	27	NO Stop Date	Platelets
Day +16	1.1	440	20	↓	Platelets
Day +17	1.9	627	25	↓	
Day +18	3.5	1500	11	↓	Platelets
Pt.					
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +15	0.3	87	16	NO Stop Date	Platelets
Day +16	0.7	308	17	↓	Platelets
Day +17	2.0	1080	16	↓	Platelets
Day +19	7.0	4270	12	↓	Platelets
Day +24	7.5	6374	29	↓	

* Patients with hematological adverse events found in the Day +29 – Day +100 Post-Study Surveillance Data Set (as discussed above).

The only patient identified by the reviewer for whom hematology laboratory values were not provided for the last week of the 28-day study period was Pt. (discussed in table above). The last hematological laboratory values found in the dataset for this patients were on Day 18, and this patient had evidence of engraftment on Day 17.

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 20 patients. The date was changed to a later point in 16, and to an earlier date in 4. These changes are summarized below. Because differential's 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's

had no laboratory or incomplete laboratory provided in the dataset for the day that the sponsor said engraftment occurred. The resulting median day to engraftment derived from the changes in individual days of engraftment is shown at the bottom of the table that follows.

Table 12 Engraftment Date Assignment Differences Between Sponsor and Reviewer

Patient No.	Sponsor Day of Engraftment	Reviewer Day of Engraftment
	12	
	13	
	9	
	11	
	18	
	13	
	11	
	11	
	10	
	12	
	10	
	11	
	12	
	14	
	12	
	12	
	12	
	13	
	11	
	18	17
	12	
	13	
	12	
	20	
	14	13
	18	
	13	
	11	11
	14	13
	12	
	12	
	13	
	16	
	12	
	11	12
	17	
	21	
	16	17
	15	16
	12	
	16	17
	12	13
	12	13
	17	19
	13	14
	15	21
	13	14

noted during that time as well. 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.

In terms of safety, the deaths that were observed in this study besides occurring beyond Day +100, appeared to be related to recurrent disease rather than toxicity of the treatment regimen (if the secondary sources of this information can be assumed to be valid). VOD was diagnosed in 1/42 patients (2.4%), which is quite low for a heavily pretreated group of patients with advanced malignancies. Review of the laboratory and physical exam data submitted did not reveal any additional patients who had obviously experienced VOD and were not reported as such, although Pt. 02-306 certainly had elevated serum bilirubin, mild edema, 10% weight gain, and abdominal pain. If that patient were counted, the percentage of VOD (4.8%) would still have been reasonably comparable to that reported elsewhere. Depending on the definition of VOD used, the percentage of VOD reported in the literature varies, but is usually higher than observed in this study. A review article in 1995 by Bearman reported busulfan conditioning regimens to be associated with an incidence of 23-32% VOD.

Other toxicities reported appeared consistent with what one would anticipate in the transplantation setting. Single cases of clinically significant capillary leak syndrome, alveolar hemorrhage, and hemorrhagic cystitis were reported. There was one patient who had a single episode of seizure activity. All of these toxicities have been reported associated with busulfan conditioning regimens in the literature.¹ The single patients with pericarditis and pancreatitis are of interest as there has been a literature report of pericardial effusions with tamponade in patients conditioned for transplantation in the setting of thalassemia, and there have been reports of pancreatitis^{2,3} in the literature in patients who received a conditioning regimen containing busulfan.

In order to facilitate crude comparisons of the safety data from OMC-BUS-3 to that reported in the literature, the table that follows summarizes the safety data available from phase 3 trials utilizing autologous transplantation that will be discussed at length later in the literature review section of this NDA review. When examining the engraftment data provided, it should be pointed out that these studies did not generally employ G-CSF.

Table 9 Summary of Safety Data from Phase 3 Autologous Studies Utilizing Busulfan Included in the Literature Review Section of the NDA Review.

Citation	Disease	Safety
Harousseau, J.L. Blood. 1997 October; 90(8): 2978. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. The Groupe Ouest Est Leucemies Aigues Myeloblastiques.	AML, CR1	ANC > 500 = 25d after AutoBMT. Platelets >30,000=109.5 days after ABMT
	Marrow, No purging	AutoBMT = 6.5% TRM. (procedure-related)

Citation	Disease	Safety
Ravindranath, Y. NEJM. 1996 May; 334:1428. Autologous Bone Marrow Transplantation VS. Intensive Consolidation Chemotherapy for AML in Childhood	AML, CR1 Pediatric Marrow, purged	ANC > 500 AND Platelets >50,000: AutoBMT = 43 d (median) 2/115 marrow failures = 1.7% TRM: Auto BMT = 15%
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 Marrow, purged	Graft failure in 1 autotransplanted patient. (1.6%) Med. Time to ANC >500= 32d VOD: 2/63 treated (3.2%) TRM (Deaths within 100d of postremission therapy): Autologous = 14%; 9/63 treated

The reviewer believes that the safety and engraftment data from this study are supportive of a conclusion that high dose intravenous busulfan therapy is comparable to high dose oral busulfan conditioning for transplantation.

4. Pivotal Study – OMC-BUS-4: A Phase 2 Study of High-Dose Busulfan and Cyclophosphamide with Allogeneic Marrow or Peripheral Blood Progenitor Cell Transplantation for Hematologic Malignancies

Trial Accrual Dates: June 25, 1996 – December 30, 1997

Data Cutoff Date: January 9, 1997

4.1 Rationale

A commonly used conditioning regimen for hematopoietic stem cell transplantation is a non-TBI based regimen that combines the chemotherapeutic agents busulfan and cyclophosphamide. This regimen was originally developed at John's Hopkins by Santos and Tutschka as busulfan 4mg/kg/d (q 6h) x 4d + cyclophosphamide 50mg/kg/d x 4d (BU/CY200 or BU/CY4). A modified regimen was subsequently developed, which reduces the dose intensity of the cyclophosphamide 60 mg/kg/d x 2d (BU/CY120 or BU/CY2). Oral busulfan is formulated in a 2 mg tablet. The high doses of busulfan required in the described conditioning regimens necessitate

that patients swallow a large number of pills with each q 6h dose, which can be particularly difficult as the BU/CY regimen can be associated with significant nausea and vomiting. The sponsor has developed the intravenous formulation of busulfan as a means of easing the administration of busulfan in this situation – eliminating the necessity to swallow multiple pills and theoretically increasing busulfan's bioavailability by eliminating losses that potentially occur through emesis. This phase 2 trial was designed to demonstrate that the intravenous formulation of busulfan can also induce myeloablation and support engraftment, while also demonstrating an acceptable safety profile, in the setting of allogeneic transplantation.

The intravenous busulfan dose selected for this study, 0.8 mg/kg, was suggested to achieve a similar AUC (plasma concentration) to that of an oral busulfan dose of 1.0 mg/kg in the phase 1 study conducted by the sponsor. A target AUC of $<1500 \mu\text{M} \times \text{min/l}$ was selected on the basis of literature reports that indicate the risk of hepatic veno-occlusive disease (VOD) increases at higher AUC's.

4.2 Objectives of the Study

- To administer multiple doses of an intravenous formulation of busulfan at a dose that has previously been shown to be equivalent to the oral busulfan formulation when it is given at a dose of 1 mg/kg, and associated with an AUC that is less than $1500 \mu\text{M} \times \text{min/L}$, and to administer this dose intravenously over 2 hours every 6 hours for 16 doses in combination with cyclophosphamide as preparation for allogeneic hematopoietic stem cell transplantation (marrow or peripheral blood derived progenitor cells) in patients with advanced hematologic malignancies in order to demonstrate that this dose and schedule is myeloablative and supportive engraftment.
- To determine the median time to engraftment of patients undergoing allogeneic transplantation after treatment with this regimen. Data regarding relapse rate, long-term (disease-free) outcome, and overall survival were also to be collected.
- To determine the toxicity of this regimen when utilized as preparation for allogeneic transplantation.
- To describe the plasma pharmacokinetics of busulfan when administered intravenously in this regimen.

4.3 Study Design

This trial was an open-label, multicenter phase 2 study. Seven centers accrued patients.

4.3.1 Treatment Plan

Busulfan (intravenous) 0.8 mg/kg q 6h x 16 doses = Day -7 through Day -4

+

Cyclophosphamide 60 mg/kg IV q d x 2 = Day -3 and Day -2

Day -1 = Rest

Day 0 = Marrow or Stem cell infusion

Busulfan is administered in D5W or normal saline as a two-hour intravenous infusion.

Cyclophosphamide is administered in 200 ml of D5W as a one hour infusion on each of two consecutive days (specifically Day -3 and Day -2 of transplantation).

Premedication specified included:

Antiemetics as per institutional guidelines prior to the first dose of busulfan, and continued on a fixed schedule through 12-24 h after the last dose of cyclophosphamide.

Dilantin was to be administered as per institutional guidelines to all patients.

Cyclophosphamide administration required **Intravenous Fluids with Bicarbonate** at a rate of 1.5-2.0 times maintenance, starting 4 hours prior to the first cyclophosphamide dose and continuing through 24 hours after the last dose. **Furosemide** 10-20 mg IV was to be given 1 and 6 hours after each cyclophosphamide dose. **Mesna** 10 mg/kg IV 30 minutes prior to the first dose of cyclophosphamide and q 4h through 24 hours after the last cyclophosphamide dose, for a total of 12 doses was required. Alternatively, Mesna could be given as a 300 mg/m² bolus, followed by an equal dose administered by continuous infusion over 24 hours through 24 hours after completing the last dose of cyclophosphamide.

4.3.2 Dose Modifications

If unexpected, irreversible Grade 4 or unexpected, irreversible Grade 3 regimen-related toxicity occurred in 3 or more patients, the total dose of busulfan was to be decreased by 10%, or as deemed necessary from analysis of pharmacokinetic data. Such a dose modification did not become necessary during the conduct of this study.

4.3.3 Concomitant Medications

Required premedication was outlined in section 3.3.1 Treatment Plan. In addition the protocol provided for:

- GVHD prophylaxis was to be given according to institutional guidelines.
- All patients were to receive prophylactic antibiotics and intermittent immunoglobulin infusion as described in institutional guidelines.

- CNS prophylaxis “at the discretion of the attending physician as deemed necessary based on the patient’s disease history”. Such prophylaxis was to start at the time ANC had recovered $\geq 1500/\mu\text{L}$ (off G-CSF) and platelet count $\geq 50,000/\mu\text{L}$.
- Supportive care (allopurinol, menstrual suppression, prophylactic antibiotics, empiric antibiotics, IV Ig, blood product transfusion, hyperalimentation, etc.) “as per institutional guidelines.”
- G-CSF 5 $\mu\text{g}/\text{kg}/\text{d}$ SC starting on Day 0 and continuing until ANC $\geq 3500/\mu\text{L}$ for three or more days, “or according to institutional guidelines”

Reviewer Comment: Seven institutions accrued patients to this study and it is not clear if and how these institutions differed in terms of supportive care “institutional guidelines”.

4.3.4 Marrow Processing and Infusion

Although Section 6.4.1 of the protocol provided recommended guidelines regarding procedures for marrow processing infusion, each participating center was allowed to follow current institutional guidelines.

Regarding marrow procurement, marrow containing $\geq 1 \times 10^8$ mononuclear cells/kg was to be obtained from HLA-matched related donors. The marrow was not to be T-cell depleted. The marrow collected had to contain at least 2×10^8 nucleated cells/kg or 1.0×10^6 CD34+ cells/kg. The protocol stated that the marrow could be processed “per routine for major or minor ABO-incompatibilities”. Instructions for marrow infusion included rapid thaw of the marrow, drawing it up into a syringe and infusing it through a line running with normal saline. Intravenous fluids without bicarbonate were to be infused through 24 hours after marrow infusion, or again, per institutional guidelines.

If the patient was to receive peripheral stem cell transplant, peripheral blood stem cells from HLA-matched related donors were to be collected in 1-4 aphereses and cryopreserved. The apheresis collections had to contain at least 1.1×10^9 nucleated cells/kg or 4×10^6 CD34+ cells/kg. Infusion of the cryopreserved peripheral blood stem cells was to be preceded by premedication with 100 mg of hydrocortisone IV and diphenhydramine HCL 25 mg IV, “or per institutional guidelines”.

Reviewer Comment: An ACCESS query of the sponsor’s ACCESS Table “Bone Marrow” found that the majority of patients (34) appear to have received peripheral blood stem cells. Twenty-seven patients received marrow.

4.3.5 Evaluation on Study

The protocol defined 4 different evaluation periods associated with this study:

- Pretreatment

- Evaluation During Study: The "enrollment (study) period" was defined as BMT Day -7 to BMT Day +28. This data was to be collected on case report forms.
- Post-Study Surveillance BMT Day +29 to BMT Day +100: The data collected during this period would be serious adverse events and survival data. Results of surveillance laboratory and imaging would not be recorded on study case report forms.
- Post-Study Surveillance BMT after Day +100: Quarterly data collection of patient status and survival.

Reviewer Comment: The study's case report form's post-study surveillance forms provide for collection of patient status and survival data. A question regarding graft failure was included, and there was a page for collection of adverse events post-study.

Pretreatment Evaluation included an history and physical, dental evaluation, bone marrow aspirate with cytogenetics for patients with leukemia, staging CT scans and/or nuclear scans for patients with NHL or Hodgkin's disease (performed within one month prior to transplant), blood work (including CBC/Diff, reticulocyte count, PT/PTT, serum chemistry and liver enzymes), urinalysis, ABO and Rh typing, serum titers for CMV, HSV, EBV (optional), hepatitis screen, HIV antibody and antigen (optional), chest X-ray, PFT's with DLCO, EKG, and MUGA or 2-D echocardiogram with LVEF assessment.

Pretreatment evaluation of the allogeneic donor was outlined in the protocol, referencing the use, again of institutional guidelines.

Study Period Evaluation included:

- Daily physical examination daily until BMT Day +28 or until discharge. If the patient was discharged prior to Day +28, physical examination would be performed weekly from the time of discharge until Day+28.
- Toxicity grading and evaluation for adverse experiences.
- Vital signs, weights, intake/output at least once a day until Day +28 or discharge. If the patient was discharged prior to Day +28, weights would be performed weekly from that time until Day 28.
- Bone marrow aspirate with cytogenetics and biopsy at approximately Day 28, or as clinically indicated for leukemia.
- Daily CBC and platelet count to Day +28 or discharge. This would be done at least weekly until Day +28 if the patient was discharged prior to Day +28.
- Serum chemistry (sodium, potassium, chloride, magnesium, phosphorous, glucose, total protein, albumin, calcium, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT) at least twice a week until Day +28 or discharge. If the patient was discharged prior to Day +28, serum chemistry would be performed at least once a week until Day +28.
- PFT's were to be performed at discharge or per institutional guidelines.

- PT and/or PTT according to institutional guidelines until Day +28.

Reviewer Comment: It is not clear whether the five institutions that accrued patients to this study had differing guidelines.

Post-Study Surveillance Evaluation Day +29 – Day +100 (Short Term) as indicated above included survival and serious adverse event data collection. Additionally, “per institutional transplant guidelines” the following was to be collected, but not recorded on study case report forms:

- Daily physical examination until discharge, and then weekly.
- Daily toxicity grading until discharge, and then weekly.
- Daily vital signs, weights and intake/output until discharge, and then weekly.
- Daily CBC and platelet count daily until discharge, and then at least weekly.
- Twice weekly electrolytes, BUN, creatinine, glucose, SMAC, and magnesium until discharge, and then at least weekly.
- Weekly PTT, fibrinogen, and FSP’s.
- Bone marrow aspirate with cytogenetics and biopsy at approximately one month and 3 months, or as clinically indicated for leukemia.
- PFT’s at discharge or per institutional guidelines if not done prior to BMT Day +28.

Post-Study Surveillance Evaluation after BMT Day +100 (Long Term) included quarterly data collection of patient status and survival. The following data were to be collected per institutional transplant guidelines (but were not to be recorded on case report forms):

- Physical examination and screening labs at least monthly through one year, then annually.
- Bone marrow biopsy at one year for leukemia.
- Bone marrow aspirate with cytogenetics and RFLP studies at 3 months, 6 months, and 12 months for all allogeneic recipients, then annually or as clinically indicated.
- Annual thyroid function tests.
- PFT’s at discharge and at one year.
- Restaging CT scans of chest and abdomen every 3 months for patients with NHL or Hodgkin’s disease, through one year and then annually or as clinically indicated.

4.3.6 Pharmacokinetic Studies

The protocol for pharmacokinetic evaluation was the same as that in OMC-BUS-3. Refer back to section 3.3.5 for further details.

4.4 Inclusion Criteria

- Acute leukemia past first remission, in first or subsequent relapse, induction failure, or high risk first remission.; or
- Chronic Myelogenous Leukemia (CML) in chronic phase, accelerated phase or blast crisis; or
- Malignant lymphoma or Hodgkin's disease that is primary, refractory or resistant relapse; or
- Myelodysplastic Syndrome (MDS).
- Not eligible for protocol of higher priority.
- No other investigational drugs within 30 days of planned intravenous busulfan administration.
- Physiological age 15 – 55 yo.
- Zubrod performance status ≤ 2 (Zubrod 2 = Symptomatic; in bed $<50\%$ of time).
- Life expectancy not severely limited by concomitant illness and expected to be >12 weeks.
- Left ventricular ejection fraction $\geq 50\%$.
- No uncontrolled arrhythmias or symptomatic cardiac disease.
- FEV1, FVC and DLCO $\geq 50\%$ of expected , corrected for hemoglobin.
- No symptomatic pulmonary disease.
- Serum creatinine within accepted laboratory standard normal limits or considered clinically non-significant.
- SGPT ≤ 3 x ULN, serum bilirubin and alkaline phosphatase (optional) within accepted laboratory standard normal limits or considered clinically non-significant.
- No evidence of chronic active hepatitis or cirrhosis. If hepatitis serology is positive, it should be discussed with the study chairman and liver biopsy should be considered.
- No effusion or ascites ≥ 1 L prior to drainage.
- HIV-negative.

- Patient is not pregnant.
- Patient or their legal representative able to sign informed consent.
- Central venous access with an indwelling catheter.
- Existence of an HLA-matched related donor, with adequate stem cell collection as described in section 4.3.4.

4.5 Protocol Amendments

The content and dates of four protocol amendments are summarized below. Enrollment on this study started June 25, 1996 and the last patient was complete December 30, 1997.

4.5.1 Amendment #1: February 28, 1997

The upper limit of enrollment was increased from 12 to 45 patients. The content of this amendment is the same as described for Amendment #1 of OMC-BUS-3 in section 3.5.1 of this review.

4.5.2 Amendment #2: July 30, 1997

The content of this amendment is the same as described for Amendment #2 of OMC-BUS-3 in section 3.5.1 of this review.

4.5.3 Amendment #3: September 25, 1997

The content of this amendment is the same as described for Amendment #2 of OMC-BUS-3 in section 3.5.1 of this review.

4.5.4 Amendment #4: October 14, 1997

The content of this amendment is the same as described for Amendment #2 of OMC-BUS-3 in section 3.5.1 of this review.

4.6 Enrollment, Protocol Violations, Removal From Study

The protocol defined three separate time periods during the conduct of the study:

Study Period = BMT Day -7 through Day +28
 Short-Term Post-Study Surveillance Period = BMT Day +29 through +100
 Long-Term Post-Study Surveillance Period = > BMT Day +100

As of January 9, 1998, the clinical data cut-off date, 59/61 (97%) patients had completed the "Study Period." There were Short-Term Post-Study Surveillance data available through January 9, 1998 on 47/61 (77%) patients and Long-Term Post-Study Surveillance data available on 20/61 (33%) patients.

The 62 patients enrolled on this study were treated in seven centers participating in this study. The majority (34) were treated at one center, Center No. 1. All but one patient received the entire course of busulfan infusions as outlined in the protocol. That patient withdrew consent before receiving study drug. The reason given was inability to have blood drawn for the pharmacokinetic evaluations included in the study design. This patient was excluded from the safety and efficacy analysis by the sponsor. Two additional patients died during the "Study Period" before BMT Day +28 – one on Day +20, and the other on Day +27.

4.6.1 Protocol Violations Based on Eligibility Criteria

There were 16 protocol violations based on eligibility criteria. These are summarized below:

- Age Violations = 4, based on chronological age >55 yo. All were considered physiologically <55 yo by the attending physician (in keeping with Amendment #1), and all entered the study after Amendment #1.
- "Cell Number for Transplant" Violations = 1 (fewer than the required number of cells).
- DLCO <50% of expected = 1 (Pt.)
- Blood Laboratory Values Outside Eligibility Criteria = 9
 - SGPT = 1 (considered clinically non-significant) (Pt.
 - Alkaline phosphatase = 7 (but Amendment #1 made this an optional entrance requirement) and all entered after Amendment #1.
 - Bilirubin level outside normal limits = 1 (considered clinically non-significant)
- Zubrod performance status <2 = 1

Reviewer Comment: An ACCESS query of the hematological diagnosis dataset revealed one patient on study whose diagnosis was germ cell tumor (testicular) with lung metastases. This patient would not have met eligibility criteria for participation on the study. However, an SAE narrative regarding this patient indicates that he had AML.

4.6.2 Protocol Violations Based on Study Medication/Transplant Deviations

- Dose Delay of Busulfan = 2 (two hour delay of dose 15 in one patient and a two hour delay of dose 9 in another patient).
- Busulfan infused over too long a period = 1 (one dose, #8, given over 4 h 25 min).

- Busulfan dose “split” = 1 (Only part of dose 16 given as scheduled, the remaining 2/3 of the dose was “completed” 10h after the initial 1/3).
- Busulfan dose prepared at incorrect concentration (0.232 mg/ml instead of 0.545 mg/ml) = 1, but prepared incorrectly in doses 1-8 in that patient.
- Cyclophosphamide infused over 9h instead of 1 hour = 1
- Cyclophosphamide Dose #2 not given = 1 (Melfalan was substituted after a 24 h delay. Dose #2 was not given because the patient, (Pt.), experienced hypotension after Dose #1.)
- Delay of infusion of hematopoietic stem cells by one day = 1 (In Pt. who had melfelan substituted for Dose #2 of cyclophosphamide).
- Transplant infused over multiple consecutive days = 1: Due to large number of cells to be infused. This patient who received multiple infusions on consecutive days had BMT Day 0 defined as the first day any stem cell infusion occurred.

4.6.3 Protocol Violations Based on Scheduled Assessments/Evaluations

These violations were all instances of errors in collection of PK blood samples. In addition there were 5 patients who did not have weights documented in the case report form on days of PK sampling, necessitating the use of the last know weight for calculation of PK parameters.

4.7 Patient demographics and baseline characteristics; tumor characteristics

The median patient age on study was 37.5 yo (range =). Sixty percent were male and 65% were Caucasian. Twenty-four percent were Hispanic and only 6% were African American. Most of the patients enrolled had acute leukemia (n=26; 42%). Most of the acute leukemias were past CR1 (14). There were 4 induction failures and 8 in first remission at high risk for failure. CML was the next most common hematological disease on study, n= 17. There were 10 patients with lymphoma - 4 with Hodgkin's disease and 6 with NHL. The lymphomas were primary refractory or resistant relapsed disease. Nine patients with MDS participated in this study.

Forty-eight percent of patients were described as having been heavily pretreated because they met at least one of 3 criteria – a history of ≥ 3 prior chemotherapy regimens, a history of at least one prior radiation regimen, or a history of prior transplantation. Eight patients (13%) had undergone a previous transplant. Twelve patients had been previously treated with both radiation and ≥ 3 chemotherapy regimens.

A table summarizing the baseline characteristics of the participants on OMC-BUS-4 is provided below.

Table 10 Baseline Characteristics of Participants on OMC-BUS-4; Derived From Sponsor Table 11.1 Summary of Patient Disease/Disease Status at Enrollment, Volume 1.42.