Treatment evaluation (BMT day –10 through +28) included daily physical examination until discharge then weekly if before day +28, daily vital signs until discharge then weekly if before day +28, daily CBC with differential and reticulocyte count until discharge then weekly if before day +28, weekly coagulation profile, chemistry and electrolytes twice weekly or as clinically indicated, and urinalysis weekly.

Evaluation and recording of adverse experiences and toxicities, as well as concomitant medications, was undertaken daily until discharge or through day +28, then once a week through day +28 during patient checkup.

Information on serious adverse event experiences, grade 3 or 4 toxicities, relapse, survival, and disease-free survival was collected through BMT day +100.

The protocol consisted of the following transplant regimen :

Table 6 : OMC-BUS-5 Transplant Regimen

Day	Treatment
-9	Intravenous busulfan (Dose 1-4)
-8	Intravenous busulfan (Dose 5-8)
-7	Intravenous busulfan (Dose 9-12)
-6	Intravenous busulfan (Dose 13-16)
-5	Cyclophosphamide
-4	Cyclophosphamide
-3	Cyclophosphamide
-2	Cyclophosphamide
-1	Rest
0	Stem cell infusion

Patients > 4 years of age were to receive an initial dose of 0.8 mg/kg of busulfan over 2 hours. Patients > 2 weeks through 4 years old were to receive an initial dose of 1.0 mg/kg over 2 hours. All subsequent dosing was to be administered over 2 hours every 6 hours for 4 consecutive days (total 16 doses BMT days –9 through -6). Patients were to be dosed to achieve a desired plasma area under the curve (AUC) of 900-1350 umol/min/L +/- 5%. Doses were to be adjusted as necessary pending the results of first dose pharmacokinetics. For patients whose AUC values were greater than 5% outside of the acceptable AUC range, the patient's dose was to be adjusted to achieve a target AUC of 1125 umol/min/L (midpoint of acceptable range) not to exceed a maximum dose of 1.6 mg/kg/dose of busulfan.

Cyclophosphamide 50 mg/kg/day was to be administered intravenously daily over 1 hour for 4 days (BMT days –5 through –2). On day 0, stem cells were to be infused intravenously.

Reviewer Comment : The initial protocol provided for an interim analysis of PK data that was completed in 1998 using data from 7 patients who received 0.8 mg/kg as their initial dose of busulfan. The results of this analysis suggested that children < 4 years old exhibited lower busulfan AUC's compared to both adults and older children administered the same dose (0.8 mg/kg). These data were consistent with literature that suggested that oral clearance of high dose busulfan is greater relative to body size in children less than 4 years old. For these reasons, amendment #2 included the following changes:

1. To stratify enrollment into 2 age groups only : ≤ 4 and > 4 years of age.
2. To modify the initial busulfan dosing regimen so that children ≤ 4 years old received 1.0 mg/kg busulfan. Children > 4 years continued to receive an initial dose of 0.8 mg/kg busulfan. All patients would continue to have pharmacokinetic evaluation to allow for targeted dose adjustment, if required.

Pharmacokinetic Sampling

All patients had blood samples obtained for analysis of busulfan concentrations and eventual pharmacokinetic analysis of concentration-time profiles. For each time point, 2-3 ml of blood were to be collected in heparanized 3 ml green top vacutainers.

Blood sample collections were designated for doses 1, 9 and 13 of busulfan. The number of blood samples drawn depended on whether a peripheral IV line or a central catheter line was used to draw the blood samples. It was stated in the protocol that peripheral samples are preferred since a greater number of samples are obtainable for busulfan concentration and AUC calculation. A total of 8 samples were to be collected around doses 1 and 9 if a central line was used and 11 if a peripheral line was used. Only two samples (peak and trough) were to be collected around dose 13.

Supportive Care

Each center was allowed to follow institutional guidelines for supportive care after approval from Orphan Medical for the following : antiemetics, preparation of patients for marrow or PBPC infusion, menstrual suppression, prophylactic antibiotics, transfusions, hyperalimentation, immunoglobulins, GCSF, graft versus host disease prophylaxis/treatment, and hemorrhagic cystitis prophylaxis/treatment.

All sites were required to utilize a standard seizure prophylaxis regimen using phenytoin and to adjust dosage to keep total plasma phenytoin concentrations in the therapeutic range of 10-20 mg/L.

The stem cell product to be infused on day 0 was specified to include $\geq 1.0 \times 10^8$ marrow nucleated cells/kg or $\geq 1.0 \times 10^8$ nucleated cells/kg for a PBPC product.

Definition of Endpoints

Toxicity : Investigators were required to report all adverse signs and symptoms that occurred during the course of the trial (day –10 through +28) and all serious adverse experiences and Grade 3 and 4 toxicities through BMT day +100. A grading system (1-4) was utilized for defining toxicity (Appendix D of the protocol).

Reviewer Comment : The grading system used for grading toxicity was adapted from the National Cancer Institute (NCI) toxicity grading scale.

Acute Graft Versus Host Disease : A staging system based on skin findings, bilirubin, and gut changes (diarrhea) was utilized as described in Table 7 :

Table 7 : Staging of GVHD

Stage	Skin	Liver (Bilirubin)	Gastrointestinal (Diarrhea)
0	No Rash	< 2 mg/dl	No Changes
1	Maculopapular rash < 25% BSA	2-3 mg/dl	> 10 ml/kg/24 hrs
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dl	> 16 ml/kg/24 hrs
3	Generalized erythroderma	6.1-15 mg/dl	> 21 ml/kg/24 hrs
4	Generalized erythroderma with bullous formation and desquamation	> 15 mg/dl	Severe abdominal pain with or without ileus

BSA = Body Surface Area

Grading of GVHD was as described in Table 8 :

Table 8 : Overall Grading of GVHD

GRADE	SKIN	LIVER	AND/OR	GI
I	+1 to +2	0		0
II	+1 to +3	+1	and/or	+1
III	+2 to +3	+2 to +3	and/or	+2 to +3
IV	+2 to +4	+2 to +4	and/or	+2 to +4

Reviewer Comment : In the initial protocol, guidelines for staging individual organs for GVHD only were provided. In amendment #1, guidelines for overall grading of GVHD were

incorporated into the assessment. This system of evaluating stage and overall grade was originally described at the Fred Hutchinson Cancer Research Center, Seattle and is widely utilized. The staging for diarrhea has been modified to be more relevant to the pediatric population, in that volume of stool/kg/24 hr is used as opposed to number of stools.

Veno-Occlusive Disease : Clinical criteria included hyperbilirubinemia (> 2.0 mg/dL) and two of the following within 21 days of transplant: hepatomegaly, ascites, weight gain > 5% from BMT day –10 baseline. Ultrasonographic criteria were outlined as arrest of portal blood flow by pulsed Doppler sonography, in a patient with two of the following, within 30 days of transplant: hyperbilirubinemia (> 1.6 mg/dL), hepatomegaly, ascites and/or weight gain > 5% from BMT day –10 baseline.

Engraftment : This was defined as the day the absolute neutrophil count (ANC) exceeded 0.5 x 10^9/L.

Reviewer comment : In amendment #3, the collection of chimerism data was added not as a requirement but as data to be collected when available.

Nonengraftment : This was defined as failure to engraft by day 100 after transplantation.

Myeloablation : This was defined as any one or combination of the following ;
Neutropenia (absolute neutrophil count < 0.5 x 10^9/L, lymphopenia (absolute lymphocyte count < 0.1 x 10^9/L), or thrombocytopenia (platelet transfusion or platelet count < 20,000/mm^3.

Reviewer Comment : A more conservative definition would entail meeting all 3 of the criteria described above for myeloablation.

Relapse : This was recorded as the day of detection of recurrent disease.

Survival : This was measured from the day of study entry to the day of death. Cause of death was to be noted.

2. Trial Results

Randomization

Not applicable.

Blinding

Not applicable

Protocol Violations

Eligibility Criteria : Patient 09-502 was enrolled with a 6/6 HLA-matched first cousin bone marrow donor instead of a related sibling donor. This patient also had a bilirubin > 1.5 X normal at enrollment. Patient 02501 had a GGT > 4 X the upper limit of normal. Patient 08502 had a chronically elevated bilirubin associated with hemolysis. Patient 10504 had a bilirubin = 1.5 X normal at enrollment. Patient 23503 had a normal echocardiogram by report, but the percentage shortening fraction or ejection fraction were not provided.

Busulfan Dosing : Twenty-two patients had at least one of their 16 infusions deviate from an exact 2 hours duration. Six patients did not have stop times recorded for the end of busulfex infusion for one or more of their doses.

Cyclophosphamide Dosing : All 24 patients received the prescribed 4 doses of cylophosphamide. Twelve of 96 doses deviated from the protocol-specified 1 hour duration by greater than 15 minutes.

Transplant Deviations : Patient 04-502 received donor marrow that had been T-cell depleted.

Enrollment, Demographics, Baseline Characteristics

Enrollment by Study Center

Twenty-four patients were enrolled at 10 centers in the study as outlined in Table 9.

Table 9: Enrollment by Center

Center	Number of Patients
01 Cardinal Glennon	1
02 St. Louis Children's	1
03 St. Petersburg	1
04 Univ. of Connecticut	3
08 Children's San Diego	2
09 Children's Memorial Chicago	5
10 M.D. Anderson Cancer Center	4
14 Rainbow Children's Cleveland	3
15 Emory University	1
23 Baylor College of Medicine	3
Total	*24*

Baseline Demographics

There were 12 males and 12 females. Patients' age range was from 5 months to 16 years. Fourteen patients were less than 5 years old, three were between 5 – 9 years of age, and seven were 10 years of age or older.

Diagnoses included malignant and non-malignant diseases. Patient diagnoses at the time of enrollment are listed in Table 10.

Table 10 : Patient Diagnoses

Diagnosis	**N**
acute myelogenous leukemia (AML)	7
progression to AML from a diagnosis of myelodysplastic syndrome	1
acute lymphoblastic leukemia (ALL)	2
juvenile chronic myelogenous leukemia (JCML)	2
beta-thalassemia	3
chronic myelogenous leukemia (CML)	1
Myelodysplastic syndrome (MDS) after treatment for ALL	1
MDS after treatment for Wilms tumor	1
congenital thrombocytopenia	1
osteopetrosis	1
congenital erythropoietic porphyria	1
alpha-mannosidosis	1
Krabbe's disease*	1
fucosidosis	1
Total	*24*

*deficiency of lysosomal galactocerebroside B-galactosidase

Prior therapy included chemotherapy in 16 patients, radiation in 5 patients, and prior bone marrow transplantation in one patient. Patient 09504, a 7 month old with Krabbe's disease, had four prior preparative regimens for transplantation. His prior preparative regimens included, cyclophosphamide, methotrexate, hydroxyurea, and total body irradiation. Six patients had prior surgery such as splenectomy and other procedures.

Reviewer comment : The heterogeneity of the population with regard to diagnosis and prior therapy makes extrapolation of efficacy data to any specific disease population impossible.

Efficacy

a. Myeloablation

All 24 patients achieved at least one of the three criteria for myeloablation. The median time to neutropenia was 2 days post-transplant. The median duration of neutropenia was 10 days.

Reviewer comment : When all three criteria are used (neutropenia, thrombocytopenia or platelet transfusion, and lymphopenia), all 24 patients met the criteria for myeloablation. Although 3 patients did not have platelet counts <20,000/mm^3 recorded, these patients received platelet transfusions and hence met the criterion for thrombocytopenia .In this setting, myeloablation should be regarded as safety information, and cannot be considered evidence of efficacy.

b. Engraftment

Engraftment was documented in 23 patients (96%) as defined by an ANC exceeding 0.5 x 10^9/L. One patient died on day +28 without reaching an ANC > 0.5 x 10^9/L . Median time to engraftment was BMT day +13 with a range of BMT day +9 to day +22.

Reviewer comment : Patient 09504 died on BMT day +28 due to pneumonia and veno-occlusive disease with an ANC of 0.1. For the 23 patients who had documented engraftment, mean ANC on day of engraftment was 1.02 x 10^9/L.As with myleoablation, engraftment data in this setting should be regarded as safety information and does not constitute evidence of benefit. The median time to engraftment of 13 days is comparable to that reported in the literature, with median time to engraftment for children undergoing allogeneic stem cell transplantation for malignant hematologic and non-malignant conditions reported between day +10 and day +13. (14, 15)

To support clinical evidence of engraftment, chimerism data were collected to document evidence of stable donor derived hematopoiesis. Interpretable data were available for 21 patients (88%) and all had positive evidence of engraftment by donor cells (18 donor only ; 3 mixed chimera at initial assessment).

Reviewer comment : No chimerism data were provided for patients 09504 and 08501. Patient 09504 died of pneumonia on BMT day +28 with concomitant VOD. Patient 08501 was the first patient enrolled into the study, with a BMT date of December 11, 1997. Amendment #3, calling for collection of chimerism data when available, was introduced in 1999. For patient 10503, only blood typing data were provided, with conversion to blood type B+ (blood type of donor sibling). Techniques used in evaluating chimerism included —— *The source of samples for analysis was peripheral blood in 10 patients, marrow in 7 patients, and both peripheral blood and marrow in 4 patients.*

c. Survival

Four (17%) patients died during the study : two patients died during the Study Period (BMT days –9 through +28), and two died during the Short-Term Post-Study Surveillance Period (BMT days +29 through +100). As of the last day of follow-up for the last patient enrolled in the study (March 16, 2000), 20 (83%) patients were still alive. The median follow-up time for these patients was 305 days post-transplant. The Kaplan-Meier estimated probability for survival at the time of median follow-up (305 days) was 0.82 (95% CI: 0.67 to 0.98)

Reviewer comment :

Survival data in the setting of an uncontrolled trial that includes patients with a variety of malignant and non-malignant diseases is not useful in evaluating the efficacy of the preparative regimen.

The reviewer has summarized his findings on review of CRF's for the four patients who died below :

Patient 04-502, an 18 month old with AML and trisomy 21, was intubated on BMT day +6 due to pneumonia and capillary leak syndrome. On day +16, a bone marrow biopsy showed persistent leukemia and support was withdrawn as requested by the family. The patient died of respiratory arrest.

Patient 09-504, a 7 month old with Krabbe's disease, had a post BMT course complicated by veno-occlusive disease and pneumonia. He died on day +28 due to respiratory arrest. This patient had 3 prior failed allogeneic transplant attempts.

Patient 01-501, a 3 year old with AML in partial remission, had a documented relapse on BMT day +48. He died of disease progression on day +70.

Patient 09-502, a 9 year old with beta-thalassemia major, had multiple complications in the post transplant setting including Klebsiella pneumonia. She died of multi-organ failure on day +97.

D. Efficacy Conclusions

The data submitted do not provide adequate evidence of effectiveness. Survival data is uninterpretable due to the wide range of patient diagnoses, the small number of patients entered on the study, and the lack of a control arm. Data on myeloablation and engraftment should be regarded in the context of safety and do not constitute evidence of benefit. Since no new indication is being sought, there is general agreement on this issue between the sponsor and FDA. However, the sponsor is proposing [redacted] of the special populations section, and the reviewer does not agree with this proposal for the reasons discussed here.

Chimerism data should not be included in the label, as it is limited by the variability of techniques used and unavailability of chimerism data for some patients.

VII. Integrated Review of Safety

A. Conclusions

Preparative regimens for allogeneic hematopoietic stem cell transplantation, including those with busulfan as a component, are associated with a number of serious adverse events which are mostly related to the cytotoxic effect of alkylators and the vulnerability of proliferating cells of the marrow and gastrointestinal tract. Stomatitis, cytopenias, vomiting, and diarrhea are examples of such toxicity. GVHD and VOD are toxicities somewhat unique to the transplant setting, and these were observed in the children treated on OMC-BUS-5 as they have been observed in children and adults undergoing allogeneic hematopoietic cell transplantation in a number of settings.

a. Nausea and Vomiting

Nausea occurred in all patients and vomiting occurred in 83% of patients. However, grade 3 nausea or vomiting occurred in 8% and 13% of patients, respectively.

b. Stomatitis

Nineteen patients (79%) experienced stomatitis. Grade 3 or 4 stomatitis was reported in 17% of patients.

c. HVOD

HVOD occurred in 21% of patients. One patient who died of pneumonia on BMT day +20 had a concomitant diagnosis of HVOD at the time of death. Although the incidence of HVOD appears

to be increased in OMC-BUS-5 over that observed in the adult phase 2 trial of busulfan injection (8% in OMC-BUS-4), the two populations differ in age, diagnosis, and dosing of preparative regimen.

d. Infection

Infections were reported in more than half the patients. Pneumonia was diagnosed in 21% of patients. One patient died of pneumonia on BMT day +20 with a concomitant diagnosis of VOD and another patient died of pneumonia/capillary leak syndrome on BMT day +16.

e. Nervous System

The most common nervous system adverse events reported were agitation (29%) and nervousness (25%). Serious nervous system AE's were uncommon (total 8%). Specifically, one patient had a convulsive episode on BMT day +3 associated with acidosis. Another patient had an episode of hypertensive encephalopathy on BMT day +70.

B. Description of Patient Exposure

1. Busulfan

All 24 patients enrolled in the study received all of the scheduled intravenous busulfan doses (16/16). Busulfan treatment was initiated on day –9 and continued through day –6 for all 24 patients. The average dose per administration for dose 1 was 0.89 mg/kg (N=24). All patients were dosed based on actual body weight.

Following first dose pharmacokinetics, individual dose adjustments were performed if the target AUC (within 5% of 900-1350 μMol-min) was not achieved. Nine (38%) patients underwent dosage adjustments : five because of AUC's below the target range, two because of AUC's above the target range, and two who were within the target range but received dose adjustments based on the clinical judgement of the treating physician. Specifically, patient 04503 had an AUC at the lower end of the target range, the investigator preferred to adjust the dose to achieve a higher AUC. Patient 23503's dose 1 AUC calculation was based on an end-of-doseinterval plasma value that was unexpectedly high; follow-up plasma levels from dose 6 suggested that the original AUC estimate was high and that the patient's actual AUC was slightly below the target range. For that reason, the patient's busulfan dose was adjusted for doses 11-16. Eight of the nine patients receiving a dose adjustment had repeat pharmacokinetic samples obtained. All had a dose 9 AUC within the target range. Table 11 outlines dose 1 and dose 9 AUC's for patients who underwent a dose adjustment.

Table 11 : Dose 1 and 9 AUC's in Patients with Busulfan Dose Adjustment

Relationship to Target	Patient ID	Age (years)	Dose 1 AUC (μMol-min)	Dose 9 AUC (μMol-min)
Below	02501	1.1	644	1204
	08502	4.5	450	896
	09501	7.19	831	885
	09502	9.42	740	1374
	10502	2.25	630	1074
Above	09504	0.59	1591	1359*
	14501	16.7	1634	1128
Within	04503	1.97	883	1285
	23503	0.73	1168	Not done

*Dose 13 AUC

The final average per patient busulfan dose per administration was 1.01 mg/kg. The average total dose of busulfan for the entire regimen was 15.47 mg/kg with a range of 10.23 to 22.54 mg/kg.

Patients were initially given 0.8 mg/kg busulfan per dose prior to amendment #2. Per amendment #2, 11 patients ≤ 4 years of age were given initial doses of 1.0 mg/kg. Two patients ≤ 4 years of age were enrolled prior to amendment #2 and received initial doses of 0.8 mg/kg. The average per patient dose per administration for dose 1 was 0.97 mg/kg (N=13) for patients ≤ 4 years of age and 0.8 mg/kg for patients > 4 years of age.

Five patients ≤ 4 years old and four patients > 4 years old were dose adjusted. The mean final busulfan dose per administration for patients ≤ 4 years old and > 4 years old was 1.1 mg/kg and 0.89 mg/kg respectively.

Reviewer comment : In general, busulfan dosing was given over 2 hours as described in the protocol. For 6 patients, the stopping time was not provided for one or more doses. Therefore, infusion time could not be ascertained.

2. Cyclophosphamide

All patients received 4/4 doses of cyclophosphamide. Patients received doses of 50 mg/kg/day days –5 to –2 as per protocol (total of 0.2 grams/kg).

Reviewer comment : In general, cyclophosphamide was given over an hour as per protocol. In 11 patients, the stopping time for the cyclophosphamide infusion was not recorded for one or more doses. Therefore, the infusion time could not be ascertained. In 4 patients, at least one dose was given over a 2-hour period (total of 5 doses)

3. Stem Cell Infusion

All patients received a stem cell infusion on day 0. Five patients received stem cells from a peripheral blood stem cell source —— and 19 patients received stem cells from a marrow source. Cellular content of the stem cell product ranged from — nucleated cells/kg to — nucleated cells/kg with a median of 5.0 x 10^8 nucleated cells/kg.

Reviewer comment : Twenty-three patients received > 1 X 10^8 nucleated cells/kg. Patient 04502 received only — nucleated cells/kg. This patient's original donor product contained — nucleated cells/kg in 560 ml, a volume considered too large for infusion into a 9- kg , 1.5 year-old. The specimen was concentrated and enriched for CD34+ cells by passage through an — specific for the CD34 marker. The result was a 78 ml suspension containing 1.2 X 10^7 nucleated cells. This process is considered a form of T-cell depletion, which is a protocol deviation.

C. Methods and Specific Findings of Safety Review

All adverse events (AEs) that occurred during the study (BMT day –10 through day +28, inclusive) were recorded in the CRF. BMT day –10 was the day prior to the first busulfan dose and represents baseline for each patient. Adverse events first reported on BMT day –10 were followed through the study period to day +28. New AEs or a change in any parameter of an AE existing at baseline (i.e., pattern, severity, drug relationship, toxicity grade, change to serious) were recorded as a new entry on the CRF during the period following initial busulfan dosing (BMT day –9 through +10). Only serious adverse events (SAEs) and toxicity grade 3 or 4 AE's were reported after BMT day +28.

The most frequently reported adverse events from BMT day –9 through +28, occurring in at least 75% of patients, were fever (100%), vomiting (100%), leukopenia (100%), anorexia (96%), anemia (92%), thrombocytopenia (88%), nausea (83%) and stomatitis (79%). These events are expected consequences of myelosuppressive therapy used to prepare patients for hematopoietic progenitor cell transplant. Table 12 lists adverse events occurring in ≥ 15% of patients in OMC-BUS-5.

Reviewer comment : FDA analysis of COSTART listings in dataset AEALL revealed some discrepancies with sponsor's listing of AE's by COSTART. Total numbers of patients per FDA analysis for terms where a discrepancy exists are listed in column 4 of table 12.

Table 12 Adverse Events Occurring in ≥ 15% of Patients: Sponsor vs FDA*

Body System	COSTART Adverse Event	N (%) Sponsor	N (%) FDA
Body As a Whole	Fever	24 (100%)	
	Pain (Abdominal)	13 (54%)	
	Edema (face)	11 (46%)	
	Pain	11 (46%)	
	Chills	9 (38%)	
	Asthenia	8 (33%)	
	Abdominal Enlargement	7 (29%)	
	Injection Site Reaction	7 (29%)	
	Allergic Reaction	5 (21%)	
	Headache	5 (21%)	
	Infection (bacterial)	5 (21%)	
	Ascites	4 (17%)	
	Hem Injection Site	4 (17%)	
	Lab Test Abnormality	4 (17%)	
Cardiovascular System	Hypertension	14 (58%)	
	Tachycardia	13 (54%)	14 (58%)
	Thrombosis	10 (42%)	
	Vasodilation	5 (21%)	
	Hem	4 (17%)	
	Hypotension	4 (17%)	
Digestive System	Vomiting	24 (100%)	
	Anorexia	23 (96%)	24 (100%)
	Nausea	20 (83%)	
	Stomatitis	19 (79%)	
	Diarrhea	16 (67%)	
	Rectal disease	10 (42%)	11 (46%)
	Hepatomegaly	7 (29%)	
	Constipation	6 (25%)	
	Venoocclusive Liver Syndr.	4 (17%)	see below
Hemic and Lymphatic System	Leukopenia	24 (100%)	
	Anemia	22 (92%)	23 (96%)
	Thrombocytopenia	21 (88%)	
	Prothrombin decreased	8 (33%)	
	Thromboplastin decreased	8 (33%)	
	Graft vs Host disease	6 (25%)	see below
	Ecchymosis	4 (17%)	
	Petechia	4 (17%)	
Metabolic and Nutritional	Hyperglycemia	21 (88%)	

	Hypocalcemia	16 (67%)	
	Hypokalemia	15 (63%)	16 (67%)
	SGPT increased	15 (63%)	
	SGOT increased	14 (58%)	
	Hypomagnesemia	13 (54%)	
	Bilirubinemia	11 (46%)	
	Hypoproteinemia	9 (38%)	
	Enzyme Abnormality	8 (33%)	
	Hyponatremia	8 (33%)	
	Hyperkalemia	7 (29%)	
	Weight increased	7 (29%)	
	BUN increased	6 (25%)	
	Hypophosphatemia	6 (25%)	
	Hyperchloremia	4 (17%)	
	Hyperphosphatemia	4 (17%)	
	Hypoglycemia	4 (17%)	
	Phosphatase Alk increased	4 (17%)	
Nervous System	Agitation	8 (29%)	
	Nervousness	6 (25%)	
	Dizziness	5 (21%)	
Respiratory System	Cough increased	12 (50%)	
	Rhinitis	11 (46%)	
	Hyperventilation	9 (38%)	
	Dyspnea	7 (29%)	
	Epistaxis	7 (29%)	
	Lung disease	6 (25%)	7 (29%)
	Pneumonia	4 (17%)	5 (21%)
Skin and Appendages	Rash	15 (63%)	
	Alopecia	11 (46%)	
	Pruritis	8 (33%)	
Urogenital	Oliguria	11 (46%)	
	Hematuria	9 (38%)	
	Albuminuria	5 (21%)	
	Dysuria	5 (21%)	

*partially derived from sponsor table 12.2

For tachycardia, anorexia, hypokalemia, lung disease, and rectal disease, individual patients each reported the event on day –10 (prior to busulfan administration), which is captured in the FDA analysis but not in the sponsor's table. This explains the difference in number of AE's between the sponsor and FDA for these adverse events For anemia, patient 09-502 reported the event after Day +28 and therefore was considered an event occurring in the post-study surveillance period by the sponsor. However, this was a grade 3 toxicity which was recorded and is included in the FDA analysis. Similarly, for pneumonia, patient 09502 reported the event after day +28 and therefore this was excluded from the sponsor's presentation of the AE listing for the study.

Adverse events of significant clinical relevance are discussed below on an individual basis. Note that some of the reviewer's tables listing AE's by grade (Tables 10, 14, 17, 18, and 19) are based on reporting for individual events not patients, therefore an individual patient may have an AE listed under more than one grade, and hence the total # of events may be greater than the number of patients on the trial in some instances.

Nausea and Vomiting : Vomiting was reported in all 24 patients (100%). Nausea was reported in 20 patients (83%). Three patients had toxicity grade 3 vomiting, and 2 patients had toxicity grade 3 nausea. One of these patients (14-501) had severe vomiting and one patient had severe nausea. The one day episode of severe vomiting in patient 14501 occurred on BMT day –4 during cyclophosphamide administration. The severe nausea in patient 08-501 initiated on BMT day –3 and continued through BMT day +27. Since both busulfan and cyclophosphamide were delivered intravenously, nausea and vomiting did not interfere with the conditioning regimen or dose administered.

Reviewer comment : The number of patients with nausea or vomiting reported are listed by grade in Table 13.

Table 13 : Nausea or Vomiting by Grade

Grade	Nausea N (%)	Vomiting N (%)
1	15 (63%)	21 (88%)
2	10 (42%)	17 (71%)
3	2 (8%)	3 (13%)
4	0	0

Stomatitis (Mucositis) : Oral pathology was defined to include adverse events in the COSTART categories of stomatitis, dry mouth, oral candida, discolored tongue, edema of the tongue, gingivitis, and gum hemorrhage. Nineteen patients (79%) experienced stomatitis; some of whom also had one or more episodes of other oral pathologies. Three patients were reported with toxicity grade 3 stomatitis.

Reviewer comment : The number of patients with stomatitis reported are listed by grade in Table 14.

Table 14 Stomatitis by Grade

Grade	Stomatitis N (%)
1	16 (67%)
2	9 (38%)
3	3 (13%)
4	1 (4%)

Hepatic Veno-Occlusive Disease : Clinical criteria for defining VOD included hyperbilirubinemia (> 2.0 mg/dL) and two of the following within 21 days of transplant: hepatomegaly, ascites, weight gain > 5% from BMT day –10 baseline. Ultrasonographic criteria were outlined as arrest of portal blood flow by pulsed Doppler sonography, in a patient with two of the following, within 30 days of transplant: hyperbilirubinemia (> 1.6 mg/dL), hepatomegaly, ascites and/or weight gain > 5% from BMT day –10 baseline.

According to the sponsor, VOD was diagnosed in four patients (17%) ; 01501, 09504, 10501, and 10503. All four met the clinical diagnostic criteria of hyperbilirubinemia, ascites and/or weight gain. Patients 01501 and 09504 also had hepatomegaly. In addition, patient 10501 had arrest/reversal of portal blood flow by ultrasonography. Patient 23-501 met the clinical criteria for VOD on BMT day +21. Doppler ultrasound studies and a transjugular liver biopsy were performed to evaluate the child's liver disease; these studies were not consistent with VOD according to the investigator and sponsor.

Reviewer comment : As described by the sponsor, patient 23501 did meet the clinical criteria for VOD as outlined in the protocol, with physical examination and laboratory findings as follows: bilirubin = 2.1 mg/dl, ascites, hepatomegaly, and weight gain > 10% of baseline. Furthermore, although the patient's liver biopsy report does not indicate the presence of characteristic histologic changes associated with VOD, it is known that the pathologic lesions of VOD can be patchy in nature. Finally, the protocol specified definition clearly distinguishes a set of exclusively clinical criteria for the diagnosis of VOD, which the patient has clearly met. Therefore, the reviewer's analysis indicates that VOD was observed in 5 patients (21%). Table 15 provides summary data for patients with VOD.

Table 15: VOD Summary Data

Pt #	Age (yrs)	Wt (kg)	Outcome (Duration)	Disease Status	Prior* Therapy	Dose 1 AUC ( )	Dose 9 AUC	Total Bu given (mg/kg)	Max. Bili. mg/dL (day)
01501	3.77	17.1	Resolved (10 days)	AML active	C (≥ 3)	909	921	12.82	2.7 (+13)
09504	0.59	7.1	Not resolved at death	Krabbe's disease	C, R, T	1591	1359	14.52	15.6 (+20)
10501	14.77	49.0	Resolved (9 days)	AML in remission	C	1306	1460	12.80	2.4 (+23)
10503	1.60	9.1	Resolved (3 days)	Osteo-petrosis	none	1219	1337	16.02	2.6 (+18)
23501	0.44	8.5	Resolved	JCML active	C	1324	1274	16.0	2.1 (+21, +27)

* R=prior radiation ; C=prior chemotherapy ; T=prior transplants

Potential risk factors for the development of VOD in the setting of allogeneic transplantation include prior therapy (chemotherapy or radiation) and underlying liver toxicity/injury. This is reflected in this small group of patients, where 4/5 patients with VOD had prior chemotherapy. Although patient 10503 did not have prior chemotherapy or radiation, it should be noted that patients with osteopetrosis often have altered hepatic morphology secondary to extramedullary hematopoiesis. This patient had a relatively short duration of VOD with resolution. Patient 09504, in addition to having been heavily pretreated (three prior attempts at allogeneic transplantation), also had a dose 1 target AUC for busulfan above the therapeutic range, and this is the only 1 of 5 patients with VOD who did not have resolution of VOD, but actually died with pneumonia and concomitant VOD. These findings are consistent with the multifactorial nature of processes involved in the development of VOD. Any potential correlation between busulfan AUC and VOD development is difficult to ascertain in this small number of patients. For further information on the relationship between busulfan AUC and VOD, see the state of armamentarium and the biopharmaceutics review.

The overall incidence of VOD observed (21%) appears to be consistent with what is described in the literature. For patients undergoing stem cell transplantation for non-malignant hematologic disorders such as thalassemia, the incidence of VOD has been reported in some centers to be as low as 2%. For patients undergoing allogeneic transplantation for malignant conditions such as AML, the incidence of VOD is reported as up to 50% in some studies. Overall, the incidence of VOD reported in the allogeneic matched related donor setting is reportedly between 20% and 40% in most studies.

Graft Versus Host Disease (GVHD) : By definition, GVHD occurring prior to BMT Day +100 is considered acute and GVHD occurring after day +100 is considered chronic. Since this study only followed AE's through BMT day +28 and SAE's through BMT day +100, all reported cases of GVHD represent acute GVHD. The occurrence of chronic GVHD was not documented in this study.

GVHD was diagnosed by each site's principle investigator based on clinical examination and laboratory findings. In the protocol, a staging system for GVHD based on skin findings, SGOT, bilirubin, and gut changes (diarrhea) was outlined (see Table 7). According to the sponsor, six patients (25%) had acute GVHD. All episodes of GVHD occurring prior to BMT day +28 were reported as either mild or moderate in intensity. No episode of GVHD was fatal; however, two patients with GVHD ultimately died of other causes (01-501, of disease progression on BMT day +71 and 09502, of multisystem organ failure on BMT day +100). In all six patients, GVHD involved the skin. In three patients, GVHD also involved the GI tract.

Reviewer comment : Table 16 provides summary data for patients with acute GVHD.

Table 16 : Acute GVHD

Patient ID#	Donor Source/ HLA	Skin (stage)	Bilirubin (stage)	Gut changes (stage)	Skin Biopsy	Overall Grade	Prophylaxis (MTX, CSP)
01501	6/6 sib	Yes (1)	Yes (1)	Yes (1)	No	2	MTX, CSP
03501	6/6 sib	Yes (1)	No	No	Yes	1	CSP
04501	6/6 sib	Yes (2)	No	No	No	1	MTX, CSP
04503	6/6 sib	Yes (3)	No	No	No	1	CSP
09502	6/6 cous	Yes (3)	Yes (3)	Yes (2)	Yes	3	MTX
10502	6/6 sib	Yes (3)	No	Yes (2)	Yes	3	MTX

In addition to staging GVHD for each organ, investigators provided an assessment of overall GVHD grade.

The two main predictors of GVHD risk are age and donor-host factors related to incompatibility. With respect to age, risk clearly increases with advancing age, but a significant increase in risk is not seen until age 40 and in patients over 50 years of age. Since all patients in this trial were less than 18 years of age, this was not likely to be a factor in GVHD development.

Human leukocyte antigen disparity between marrow donor and recipient is an important factor governing the severity and kinetics of GVHD. Of the six patients who developed GVHD, all had a 6/6 HLA matched donor, one of whom was a cousin and not a sibling. In these cases, mismatch in minor antigens may have played a role in the development of GVHD.

The duration and severity of GVHD may be modulated by approaches used as prophylaxis as well as treatment. No uniform approach was used in this trial, with discretion given to investigators within each institution. However, an examination of the database for concomitant medications indicates that 11 patients (46%) received methotrexate and cyclosporine for GVHD prophylaxis, 8 received methotrexate alone (33%), and 5 received cyclosporine alone (21%). Of the 6 patients who developed GVHD, 2 had received cyclosporine, 2 methotrexate, and 2 had received both for GVHD prophylaxis.

Taking into account the heterogeneity of the population with respect to diagnosis and approach used for GVHD prophylaxis/therapy, the occurrence of acute GVHD in 6 patients (25%) appears to be consistent with the incidence described in the literature. In the setting of HLA-matched allogeneic sibling stem cell transplantation for hematologic disorders, the incidence of acute GVHD has been reported between 16% and 64%. Higher incidence appears related to treatment in the setting of leukemias. The inclusion of a significant number of patients with non-malignant conditions in this trial and the requirement for a 6/6 sibling match may have contributed to the observation of an incidence in the lower range of what has been described in the pediatric population. Of note, the incidence of GVHD in the trial of adults with hematologic malignancies undergoing allogeneic transplant with a cyclophosphamide/busulfan preparative regimen reviewed with the initial busulfan injenction application was 18%, similar to that noted here.

Infection : The sponsor considered the following categories of adverse events together ; infection (COSTART term "infect"), bacterial infection ("infect bact"), fungal infection ("infect fung"), viral infection ("infect viral"), urinary tract infection, abscess, sepsis, and pneumonia or interstitial pneumonia.

Excluding vaginitis, cellulitis and rhinitis, 15 patients (63%) were reported to have infections according to the sponsor.

Pneumonia was reported in four patients (17%) from BMT Days –9 through +28. Patient 09502 had interstitial pneumonia during the study period and developed pneumonia (Klebsiella pneumoniae bacteremia) after BMT day +28. Therefore a total of five patients (21%) had a diagnosis of pneumonia. Three of these cases were of toxicity grade 3 or 4. Pneumonia was fatal in patient 09504, resulting in death on day +20. Patient 04502 had pneumonia in conjunction with capillary leak syndrome leading to death on BMT day +16.

Reviewer comment : Although localized processes such as cellulitis may not be considered a disseminated infection, these can have profound sequelae in severely immuno-compromised hosts, such as the patients treated in this study. Therefore, the medical reviewer has listed the individual infectious processes and their incidence by grade in Table 17.

Table 17: Infections - Events by Grade

Infection	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Total N (%)
Cellulitis	1	0	0	0	1 (4%)
Infection	1	4	1	0	6 (25%)
Fungal	1	2	0	0	3 (13%)
Urinary tract	2	2	0	0	4 (17%)
Viral	1	2	0	0	3 (13%)
Monilia oral	1	0	0	0	1 (4%)
Vaginitis	1	0	0	0	1 (4%)
Bacterial	0	5	0	0	5 (21%)
Pneumonia	0	2	2	1	5 (21%)
Sepsis	0	0	0	1	1 (4%)

Nervous System : Most nervous system events involved non-specific, global disturbances of the central nervous system. The most common events included agitation (29%), nervousness (25%), and dizziness (21%). Most events were of mild or moderate intensity.

Patient 23501 had severe agitation starting on BMT day +21, which was accompanied by anorexia, hyperglycemia, and respiratory distress.

Patient 09504 had a SAE of convulsions on BMT day +3. His initial dose of busulfan was 1.0 mg/kg and his dose 9 was reduced to 0.79 mg/kg. The event was judged by the investigator to be related to fever, acidosis, and hypotension resulting from RSV.

Patient 09502 had an episode of hypertensive encephalopathy reported as serious on BMT day +70.

No convulsions were reported during the conditioning regimen.

Reviewer comment : The lack of any seizure episode during the preparative regimen may be related to two factors; the prophylactic use of phenytoin and the therapeutic monitoring of busulfan levels. Of note as well is the lack of somnolence as a significant AE in this study. Table 18 describes the incidence by grade of nervous system adverse events using COSTART term.

Table 18 : Nervous System AE's

COSTART Term	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Total N (%)
Agitation	2 (8%)	5 (21%)	0	0	7 (29%)
Nervousness	N/A	N/A	N/A	N/A	6 (25%)
Dizziness	N/A	N/A	N/A	N/A	5 (21%)
Anxiety	2 (8%)	0	0	0	2 (8%)
Depression	2 (8%)	0	0	0	2 (8%)
Somnolence	1 (4%)	0	0	0	1 (4%)
Tremor	1 (4%)	0	0	0	1 (4%)
Convulsions	0	0	0	1	1 (4%)
Encephalopathy	0	0	0	1	1 (4%)
Headache	4 (17%)	0	0	0	4 (17%)
Myalgia	4 (17%)	0	0	0	4 (17%)

Cytopenias : As expected with a myelosuppresive preparative regimen, cytopenias were observed in all patients. Although neutropenia is not listed as a separate COSTART term, review of the laboratory database indicates that neutropenia occurred in all patients.

Deaths : The reviewer has summarized his findings on review of CRF's for the four patients who died below :

Patient 04-502, an 18 month old with AML and trisomy 21, was intubated on BMT day +6 due to pneumonia and capillary leak syndrome. On day +16, a bone marrow biopsy showed persistent leukemia and support was withdrawn as requested by the family. The patient died of respiratory arrest.

Patient 09-504, a 7 month old with Krabbe's disease, had a post BMT course complicated by veno-occlusive disease and pneumonia. He died on day +28 due to respiratory arrest. This patient had 3 prior failed allogeneic transplant attempts.

Patient 01-501, a 3 year old with AML in partial remission, had a documented relapse on BMT day +48. He died of disease progression on day +70.

Patient 09-502, a 9 year old with beta-thalassemia major, had multiple complications in the post transplant setting including klebsiella pneumonia. She died of multi-organ failure on day +97.

D. Adequacy of Safety Testing

Safety testing in the pediatric population as provided in data from OMC-BUS-5 is limited by the small number of patients and the wide range of diagnoses. The collection of AE data was limited to the first 28 days after stem cell infusion for all AE's and to the first 100 days after stem cell infusion for grade 3 and 4 toxicities and serious AE's.

E. Summary of Critical Safety Findings and Limitations of Data

There is general agreement between FDA and the sponsor on the reported incidence of adverse events in OMC-BUS-5. One area of disagreement is the occurrence of HVOD. The FDA considers that VOD occurred in 5 patients (21%) whereas the sponsor considers that it occurred in 4 patients (17%). Patient 23-501 met the clinical criteria for HVOD but was not considered to have VOD by the investigator based on nonspecific findings on liver ultrasound and liver biopsy. The reviewer considered the patient as

having VOD since the clinical criteria were met, and the liver ultrasound and biopsy did not provide evidence of an alternative diagnosis.

The reviewer suggests that safety information added to the label be limited to adverse events with significant clinical impact such as stomatitis, nausea and vomiting, AGVHD, HVOD, infections such as pneumonia, as well as the four deaths reported in the first 100 days post BMT.

VIII. Dosing, Regimen, and Administration Issues

The currently recommended adult dose of busulfan injection is 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower, administered every 6 hours for 4 days (a total of 16 doses). Cyclophosphamide is given on each of two days as a one-hour infusion at a dose of 60 mg/kg beginning on BMT day –3, six hours following the 16th dose of busulfan injection.

The applicant conducted a trial of busulfan injection in combination with cyclophosphamide as a preparative regimen for a variety of hematologic malignant and non-malignant diseases in 24 pediatric patients. This pharmacokinetic study based initial busulfan dose on body weight, with dose adjustment allowed based on PK data. The sponsor performed a retrospective population pharmacokinetic (PPK) analysis to describe the PK characteristics of busulfan injection in children. Based on this analysis, the sponsor has proposed a 4-step dosing regimen based on weight.

[ ]

Medical and biopharmaceutics reviewers agree that this 4-level dosing regimen is cumbersome and prone to error. The sponsor's division of dosing recommendations into 4 different groups based on weight ranges is derived from a division of the exposure as calculated by the sponsor. There is an increase in the dosing recommendation with increased weight and subsequently a decrease with further weight increases, a pattern likely to be misinterpreted by physicians and pharmacists. The sponsor's silence on specific recommendations for modification of dosing beyond dose 1 based on AUC also raises safety concerns given the known PK/PD relationship between busulfan exposure and clinical outcomes.

The FDA has conducted an independent analysis and developed two simpler dosing regimens. The first is a two-step dosing scheme that is based on actual body weight (1.1 mg/kg if ≤ 12 kg and 0.8 mg/kg if >12 kg). The second

The biopharmaceutics

review team is recommending the first regimen due to the familiarity of the oncology community with body-weight based dosing of intravenous busulfan and the equivalence between the two regimens with respect to achieving target AUC. Because the FDA modeling and simulations indicated that 60% of patients will achieve a target AUC of 900 to 1350 μM-min with the first dose of busulfan, therapeutic drug monitoring is recommended. FDA has devised formulae for dose adjustment to achieve target exposure. The FDA also recommends providing instructions on blood sampling for therapeutic drug monitoring in the label. The FDA biopharmaceutics review team suggested dosing and drug monitoring recommendations are outlined below :

Suggested dosing of BUSULFEX in pediatric patients is shown in the following dosing nomogram:

BUSULFEX Dosing Nomogram

Patient's Actual Body Weight (ABW)	BUSULFEX Dosage
≤ 12 kgs	1.1 (mg/kg)
> 12 kgs	0.8 (mg/kg)

Simulations based on a pediatric population pharmacokinetic model indicate that approximately 60% of pediatric patients will achieve a target BUSULFEX exposure (AUC) between 900 to 1350 μM•min with the first dose of BUSULFEX using this dosing nomogram. Therapeutic drug monitoring and dose adjustment following the first dose of BUSULFEX is recommended.

Dose Adjustment Based on Therapeutic Drug Monitoring

[redacted]

For Pediatric patients ≤ 12 kgs:

Adjusted BUS Dose = First BUS dose (mg) X (1264 ng/ml/$C_{2hrobserved}$)

1 pages redacted from this section of the approval package consisted of draft labeling

In a fax and teleconference on 6/26/02, the sponsor indicated that they agree with the proposed dosing recommendation based on body weight. However, the sponsor did not agree with the FDA's recommendations for therapeutic drug monitoring. They have proposed formulae for dose adjustment based on a calculation of AUC, with a recommendation for 3 blood samples after dose 1 in order to calculate a dose modification. The FDA review team has asked the sponsor to provide the following information regarding their suggested approach for therapeutic drug monitoring:

1. Justification of the choice of the 2, 4 and 6 hr times for sampling Busulfex concentrations.

2. Demonstration that the use of these three samples can be used to accurately determine AUC. It would be useful if a comparison of the Busulfex AUC derived from the complete data for each patient in the OMC-BUS-5, with the AUC derived using the three samples at the proposed time points for each patient is provided.

3. Busulfex labeling instructions that explain how to take the samples and how to calculate the AUC.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Adjusting busulfan dosage based on gender or race has not been adequately studied. In OMC-BUS-5, there were 12 males and 12 females. The small number of patients in the study precludes any definitive conclusions regarding gender or race as it relates to the safety profile of the drug.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age

Five of sixty-one patients treated in the Busulfex adult clinical trial (OMC-BUS-4) were over the age of 55 (range 57-64). All achieved myeloablation and engraftment.

Pediatrics

OMC-BUS-5 was conducted in children up to 16 years of age. Limited dosing and safety information in children will be added to the current label.

C. Comments on Data Available or Needed in Other Populations

Renal or Hepatic Impairment

Busulfan injection has not been studied in patients with renal impairment or hepatic insufficiency.

Pregnancy

Busulfan injection should not be used in pregnant women. The drug is currently labeled as pregnancy class D, due to its teratogenic effects. Teratogenic changes observed in the offspring of mice, rats, and rabbits when given during gestation involved the musculoskeletal system, body weight, and size. In pregnant rats, busulfan produced sterility in both male and female offspring. The solvent, DMA, may also cause fetal harm when administered to a pregnant woman. In rats, DMA given during organogenesis caused significant developmental anomalies.

X. Conclusions and Recommendations

A. Conclusions

Efficacy could not be evaluated properly due to the small number of patients in the trial, the heterogeneity of diagnoses, and the lack of a controlled setting. However, myeloablation was achieved in all 24 patients. Engraftment was documented in 23 patients (96%). Myeloablation and engraftment should be regarded as providing safety information, and do not constitute evidence of benefit.

Preparative regimens for allogeneic hematopoietic stem cell transplantation, including those with busulfan as a component, are associated with a number of serious adverse events which are mostly related to the cytotoxic effect of alkylators and the vulnerability of proliferating cells of the marrow and gastrointestinal tract. Stomatitis, cytopenias, vomiting, and diarrhea are examples of such toxicity. GVHD and VOD are toxicities somewhat unique to the transplant setting, and these were observed in the children treated on OMC-BUS-5 as they have been observed in children and adults undergoing allogeneic hematopoietic cell transplantation in a number of settings.

f. Nausea and Vomiting

Nausea occurred in all patients and vomiting occurred in 83% of patients. However, grade 3 nausea or vomiting occurred in 8% and 13% of patients, respectively.

g. Stomatitis

Nineteen patients (79%) experienced stomatitis. Grade 3 or 4 stomatitis was reported in 17% of patients.

h. HVOD

HVOD occurred in 21% of patients. HVOD was not fatal in any patient. However, one patient who died of pneumonia on BMT day +20 had a concomitant diagnosis of HVOD at the time of death. Although the incidence of HVOD appears to be increased in OMC-BUS-5 over that observed in the adult phase 2 trial of busulfan injection (8% in OMC-BUS-4), the two populations differ in age, diagnosis, and dosing of preparative regimen.

i. Infection

Infections were reported in more than half the patients. Pneumonia was diagnosed in 21% of patients. One patient died of pneumonia on BMT day +20 with a concomitant diagnosis of VOD and another patient died of pneumonia/capillary leak syndrome on BMT day +16.

j. Nervous System

The most common nervous system adverse events reported were agitation (29%) and nervousness (25%). Serious nervous system AE's were uncommon (total 8%). Specifically, one patient had a convulsive episode on BMT day +3 associated with acidosis. Another patient had an episode of hypertensive encephalopathy on BMT day +70.

B. Recommendations

1. Limited safety information from trial OMC-BUS-5 should be added to the special populations – pediatrics section of the label.

2. Information on pediatric dosing should be added to the special populations – pediatrics section of the label. This information should include recommendations for dosage and therapeutic drug monitoring. The sponsor agrees with the FDA's proposed dosing recommendations based on body weight. However, the sponsor did not agree with FDA's recommendations for therapeutic drug monitoring. They have proposed formulae for dose adjustment based on a calculation of AUC, with a recommendation for 3 blood samples after Dose #1 in order to calculate dose modification. Therefore, an approvable letter will be issued with the following items to be outlined for the sponsor to provide:

a. Justification of the choice of the 2, 4 and 6 hr times for sampling Busulfex concentrations.
b. Demonstration that the use of these three samples can be used to accurately determine AUC. This should include a comparison of the Busulfex AUC derived from the complete data for each patient in the OMC-BUS-5 trial with the AUC derived using the three samples at the proposed time points for each patient.
c. Busulfex labeling instructions that explain how to take the samples and how to calculate the AUC.

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/s/

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