

3.4 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.

3.4.1 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.

3.4.2 Concomitant Medications

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

- 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: Five institutions accrued patients to this study and it is not clear if and how these institutions differed in terms of supportive care 'institutional guidelines.

3.4.3 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.

For marrow procurement, 1200-1800 ml of marrow containing $\geq 1 \times 10^8$ mononuclear cells/kg was to be obtained using standard techniques. If $>3 \times 10^8$ cells/kg were collected, and if malignant cells were reactive with antibodies against CD2, CD3, CD4, CD10, CD11, CD19, or DR, the marrow could be immunopurged using immunomagnetic separation. The remainder of cells were to be cryopreserved without treatment.

If the patient was to receive peripheral stem cell transplant, peripheral blood stem cells mobilized by filgrastim were to be collected by apheresis and cryopreserved. The apheresis collection was to contain at least 4×10^6 autologous PBSC within $\geq 4 \times 10^4$ CFU-GM and/or $\geq 4 \times 10^6$ CD34+ cells/kg.

Instructions for marrow and/or PBSC infusion included rapid thaw of the marrow, drawing the marrow up into a syringe and infusing it through a line running with normal saline. Patients were to be premedicated for the marrow and/or PBSC's with hydrocortisone 100 mg and benadryl 25 mg IV, or as per institutional guidelines. Intravenous fluids without bicarbonate were to be infused through 24 hours after marrow infusion, or again, per institutional guidelines.

Reviewer Comment: An ACCESS query of the sponsor's ACCESS Table "Bone Marrow" found no patients who received a purged marrow transplant. The majority of patients (35) appear to have received peripheral blood stem cells. Three patients appear to have received both marrow and peripheral blood stem cells, and 4 patients received marrow only.

3.4. 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 forms had pages for post-study surveillance data collection regarding patient status and survival. This included a question about whether the patient had experienced graft failure, and a page for collection of adverse events.

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.

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 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 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.

3.4.5 Pharmacokinetic Studies

Heparinized blood for busulfan levels were to be drawn immediately before the first busulfan infusion, and at 15, 30, and 45 minutes after the start of infusion, as well as 5 minutes prior to the end of the two hour infusion and at 15, 30, 60, 120, 180, 240, 300, and 360 minutes post infusion. Since the busulfan infusion was to occur over a two-hour period and doses were to be repeated every 6 hours, the last 3 pharmacokinetic blood levels were scheduled to be drawn during the second busulfan infusion. Blood samples were also scheduled at the same time intervals during the ninth busulfan infusion (on BMT Day -5). At dose 13 a trough was to be drawn immediately before the start of the infusion, and a peak was to be drawn five minutes prior to the end of its infusion.

3.5 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.
- $\geq 1 \times 10^8$ marrow derived mononuclear cells/kg with $\geq 1 \times 10^4$ CFU-GM/kg and/or $\geq 0.7 \times 10^6$ CD34+ cells/kg harvested and cryopreserved while in remission as documented by bilateral aspirates and biopsies within four weeks prior to harvest or $> 4 \times 10^8$ peripheral mononuclear blood cells/kg with $\geq 4 \times 10^4$ CFU-GM/kg and/or $\geq 4 \times 10^6$ CD34+ cells/kg.

3.6 Protocol Amendments

The content and dates of four protocol amendments are summarized below. Enrollment on this study started June 24, 1996, and the last patient was completed January 7, 1998.

3.6.1 Amendment #1: February 28, 1997

- The upper limit of enrollment was increased to 45 patients. (The upper limit of enrollment was not found by the reviewer to be clearly defined in the original protocol.)
- Eligibility was expanded to include:
 - (a) Patients between the physiologic ages of 15 – 55. (Changed from “age 18 – 55.”)
 - (b) Patients with CML in chronic phase. (Addition to the previous CML in accelerated phase or blast crisis.)
 - (c) Acute leukemia patients in first or subsequent relapse. (Previously read “AML past first remission, in first remission with a high risk for relapse, or induction failure.”)
 - (d) Patients with MDS. (Not previously included.)
- Entry criteria for certain laboratory values were changed:
 - (a) Serum creatinine criteria were changed to “within accepted laboratory standard normal limits or considered clinically non-significant” from ≤ 1.5 mg/dl.
 - (b) Serum bilirubin criteria were changed to “within accepted laboratory standard normal limits or considered clinically non-significant” from ≤ 1.0 mg%.
 - (c) Alkaline phosphatase requirement was changed to “within accepted laboratory standard normal limits or considered clinically non-significant” from alkaline phosphatase ≤ 100 .

- The busulfan concentration assay was changed from _____ and the centralized laboratory was changed to the _____
- The defined study periods and data to be collected within these periods were standardized.
- Appendices were added listing the expected adverse events of high dose BU/CY therapy to "clarify and standardized AE reporting requirements".

3.5.2 Amendment #2: July 30, 1997

Corrected word processing errors and inconsistencies in Amendment #1.

3.6.2 Amendment #3: October 1, 1997

Increased the maximum number of patients participating from 45 to 100 to allow for collection of additional safety data.

3.6.3 Amendment #4: October 14, 1997

Allowed for at least 12 patients to receive a single dose of oral busulfan as the first dose on study, followed by 15 doses of intravenous busulfan, to enable a comparison to be made between the pharmacokinetic data between the oral and intravenous formulations using _____ assay.

3.7 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

January 9, 1998, the clinical data cut-off date, was the date that all patients (N=42) had completed the "Study Period." There were Short-Term Post-Study Surveillance data available through January 9, 1998 on 31/42 patients and Long-Term Post-Study Surveillance data available on 18/42 patients.

The 42 patients on study were treated in five centers participating in this study. All 42 patients received the entire course of busulfan infusions as outlined in the protocol, but one patient requested withdrawal from the study prior to Day +28 because of progressive disease after completing treatment. That patient began alternative chemotherapy on BMT Day +15.

Additional data was submitted in the 120-day Safety Update sent 12/3/98 and received by the Agency on 12/7/98. This report included post-study surveillance data through July 31, 1998. In this report the sponsor noted that as of the Safety Update Report clinical cut-off date, 93% (39/42) of the 42 patients had been observed through Day +100. The three patients who were not

followed through that point included the patient who withdrew consent on Day +15, mentioned above, another patient who withdrew consent on Day +91, and a patient lost to follow-up on Day +30. Fifteen of the 39 who completed 100 day post-transplant subsequently became unavailable for follow-up, including 6 who withdrew consent, 8 who died, and one who was lost to follow-up. All patients who withdrew from the study were reported to have had relapse or disease progression when they withdrew.

3.7.1 Protocol Violations Based on Eligibility Criteria

There were 24 protocol violations based on eligibility criteria. These are summarized below:

- Age Violations = 6, based on chronological age >55 yo, but all were considered physiologically <55 yo by the attending physician (in keeping with Amendment #1). One of the six (01-305) was entered before Amendment #1 changed eligibility to "physiological" age <55 yo.
- "Cell Number for Transplant" Violations = 6 (fewer than the required number of cells). Four came one center (4/7 entered at that center).
- LVEF <50% = 2
- Blood Laboratory Values Outside Eligibility Criteria = 9
 - Serum Bilirubin = 1 (considered clinically non-significant)
 - Alkaline phosphatase = 8 (but Amendment #1 made this an optional entrance requirement) Only two of these patients entered the study before that amendment.
- Effusion ≥ 1 L = 1

3.7.2 Protocol Violations Based on Study Medication/Transplant Deviations

- Dose Delay of Busulfan = 2 (each a single dose)
- Treatment with study drug started prior to registration with sponsor. Patient received 8 doses (2 days) of study drug prior to registration.
- Transplant infused over multiple consecutive days = 4: Due to large number of cells to be infused or large volume of infusion. Two of these patients received PBSC's as the first infusion and marrow as the second infusion. Patients who received multiple infusions on consecutive days had BMT Day 0 defined as the first day any stem cell infusion occurred.

3.7.3 Protocol Violations Based on Scheduled Assessments/Evaluations

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

3.8 Patient demographics and baseline characteristics; tumor characteristics

The median patient age on study was 34 yo (range = 18-60). Fifty-seven percent were male and 67% were Caucasian. Twenty-four percent were Hispanic and only 5% were African American. Most patients had lymphoma (83%) and most of those had Hodgkin's disease (24/35). The lymphomas were primary refractory or disease in resistant relapse. The remaining seven patients had acute leukemia. Four of those had disease beyond first remission, and 3 were in first remission but considered at high risk for relapse.

Eight-one percent of patients (34/42) 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. Three patients had undergone a previous transplant and all of those 3 had received prior radiation and ≥ 3 prior chemotherapy regimens.

A table summarizing the baseline characteristics of the participants on OMC-BUS-3 is provided below.

Table 3 Baseline Characteristics of Participants; Derived From Sponsor Table 11.1 Summary of Patient Disease/Disease Status at Enrollment, Volume 1.35.

Disease	No. with Active Disease	No. with Prior Transplant	No. with ≥ 3 Prior Chemotx Regimens	No. with Prior Radiotherapy	No. with Both Prior Radiotherapy and ≥ 3 Chemotx
Acute Leukemia (N = 7)					
> CR#1 (N = 4)	1	0	4	0	0
CR#1 with high risk for relapse (N=3)	0	0	1	0	0
Lymphoma (N = 35)					
Hodgkin's Disease (N=24) Primary Refractory or Resistant Relapse	23	2	7	6	10

Disease	No. with Active Disease	No. with Prior Transplant	No. with ≥ 3 Prior Chemotx Regimens	No. with Prior Radiotherapy	No. with Both Prior Radiotherapy and ≥ 3 Chemotx
Non-Hodgkin's Lymphoma (N=11) Primary Refractory or Resistant Relapse	9	1	4	0	2
TOTAL	33	3	16	6	12

Reviewer Comment: Heavy pretreatment in the setting of transplantation has its greatest impact on observed regimen related toxicity and subsequent relapse of disease. As the study was designed to primarily examine engraftment after transplantation, only the regimen related toxicity would be expected to be readily discernible from data collected through Day +28.

3.9 On-Study Therapy

All patients received the planned 16 doses of intravenous busulfan on study (as full dose), and review of the sponsor's tabular information provided on cyclophosphamide dose delivery revealed that all patients received the intended cyclophosphamide dosage on study. The protocol provided that the busulfan infusion would be administered in a 2-hour infusion. The protocol cautioned against rapid infusion as a bolus or IV push. Review of Appendix 16.2.19 Listing of IV Busulfan Record in the NDA submission reveals that there was one patient, who received Dose #10 as a 2-minute infusion. It is not clear whether this was a typographic error in the case report form, but the table indicates that the infusion was tolerated without unusual side effect. Two additional patients, are also listed in the same appendix as having received a dose delivered as a one hour infusion, and both had no unusual ill-effects recorded associated with those infusions.

3.10 Endpoints/Statistical Considerations

The efficacy variables selected for analysis in this study were **myeloablation, engraftment, relapse, and survival**. The endpoints of myeloablation and time to engraftment were accepted as primary surrogate endpoints by the Division of Oncology Drug Products in a pre-NDA meeting with the sponsor

3.10.1 Definitions of Efficacy Endpoints

- Myeloablation was defined as any one or combination of the following:

- (a) Absolute neutrophil count (ANC) $<0.5 \times 10^9/L$.
- (b) Absolute lymphocyte count (ALC) $<0.1 \times 10^9/L$.
- (c) Platelet count $<20,000/mm^3$ or bleeding requiring platelet transfusion.

The first of two consecutive days for which cell counts dropped to below these cut-off levels was recorded as the date of myeloablation. In addition, for the purpose of the sponsor's study report, because some institutional guidelines allowed platelet transfusion before platelet counts fell below $20,000/mm^3$, thrombocytopenia was defined as the first day a patient required platelet transfusion.

- **Engraftment** was defined as the day that ANC was $>0.5 \times 10^9/L$.
- **Nonengraftment** was defined as failure to reach an ANC $>0.5 \times 10^9/L$ by BMT Day +100.
- **Late Graft Failure or Late Rejection** was defined as development of ANC $<0.5 \times 10^9/L$ after having engrafted within the first 100 days.
- **Relapse** was recorded as the day it was detected.
- **Survival** was recorded as the date of death. Cause of death was to be recorded.

The statistical analysis plan treated patients who did not complete the study period (through BMT Day +28) because of death, withdrawal of consent, failure to engraft, or disease progression with subsequent alternative treatment as censored.

3.11 Efficacy Analysis

3.11.1 Myeloablation

The definitions used to describe this endpoint were described in the preceding section, 3.9.1 Definitions of Efficacy Endpoints. The median time to achieving myeloablation based on neutrophil count was BMT Day +4. The median time to myeloablation based on the first platelet transfusion was BMT Day +6. The median time to lymphopenia-defined myeloablation was BMT Day +2.

Reviewer Comment: A query of the sponsor's ACCESS database (Table-Laboratory Hematology and Table-Transfusion) revealed that the majority of patients received their first platelet transfusion on study when the platelet count was $<20,000/mm^3$. Thirteen patients were exceptions. Seven of those patients platelet counts were $\geq 20,000/mm^3$ and $<30,000/mm^3$ at the time of first platelet transfusion. The remaining patients had platelet counts of 54,000, 55,000, 56,000, 39,000, and 104,000. Patient did not have a platelet count listed in the database on the date of first platelet transfusion.

3.11.2 Engraftment

Engraftment was recorded as the day that ANC exceeded $0.5 \times 10^9/L$. All patients treated in this study are reported to have engrafted. The median time to engraftment was BMT Day +10 (range = 8-19).

Reviewer Comment: All patients on study, except three were treated with G-CSF. An ACCESS query of the sponsor's ACCESS Concomitant Medications table using "GCSF", "G-CSF", and "Neupogen" accounted for all the patients who received

this therapy, but demonstrated that stop dates were not always provided in the data base, and because multiple stop and start dates were found for some patients, this therapy appears to have been sporadic. In addition, when the serial WBC's and ANC's were examined by patient, the possibility was raised that not all sporadic use of G-CSF was always recorded. For example, a patient's granulocyte could be noted to drift downward after the stop date for G-CSF in the concomitant medication data base, and then suddenly jump significantly, only to start a slow drift downward again – similar to the drift seen after the documented prior stop of G-CSF (but no G-CSF usage was documented with the subsequent rise).

Because CBC data after 28 days was not provided in most patients, the reviewer questioned whether the ANC was maintained after discharge from the hospital in those patients who had ANC's drifting significantly downward at the time of dismissal. Patient in fact, appears to have met the criteria for graft rejection as defined in the study (Late Graft Failure or Late Rejection = development of ANC $<0.5 \times 10^9/L$ after having engrafted within the first 100 days), although the drop in ANC to <0.5 occurred early after initial recovery. According to the dataset information, this patient had an ANC of $0.038 \times 10^9/L$ on BMT Day +4. ANC recovered to $2.1 \times 10^9/L$ on Day 12 and was as high as $9.67 \times 10^9/L$ on Day +14. GCSF was reported to have been stopped after Day 12. The next recorded ANC was $1.38 \times 10^9/L$ on Day 17, followed by 16.9×10^9 on Day 18, and then $1.6 \times 10^9/L$ on Day 20. By Day 22 the ANC was $0.493 \times 10^9/L$. On Day 23 the ANC was up to 13.4×10^9 , but on Day 26 was 0.95×10^9 and on Day +29 was $0.39 \times 10^9/L$. No additional information regarding this patient's blood counts beyond Day +29 could be found. According to the information on this patient in Table 14.3.12 Serious Adverse Event/Death Narratives, this patient was discharged from the hospital on Day +13 "after engraftment on Day +10" (on Day 10 her ANC was $0.246 \times 10^9/L$). She was subsequently re-admitted on Day +14 with abdominal pain, diarrhea, nausea and vomiting. A stool culture was positive for *C. difficile* toxin infection and the patient was treated with vancomycin, imipenem, metronidazole, and ciprofloxacin. She was discharged again on Day +20.

Two additional patients were found to have similar issues on review of their serial hematology laboratory – The pertinent laboratory for these 3 patients is summarized below in tabular form. Two of 3 have evidence of marrow recovery in terms of what appears to be a self-sustaining platelet count. None of these patients had hematological adverse events identified in the Post-Study Surveillance ACCESS data set. That data set appears to have been derived from the Post-Study Surveillance Adverse Events Record (BMT Day +29 to BMT Day +100) sheet in the case report form. This sheet provided the investigator a place to record the adverse events during that time period, along with the associated grade, start and stop dates, coding for severity, relationship to busulfan, and the action taken to address the event. Pt.

Post-Study Surveillance data did indicate that on Day +29 (ANC drop to 390) a grade 2 infection leading to hospitalization was reported as an SAE

Table 4 Summary Patient Hematology Data in Patients with a Significant Drop in ANC After Engraftment

Pt.					
BMT Day	WBC	ANC	Platelet	GCSF	Transfusion
Day +4	0.1	38	26		Platelets
Day+12	3.1	2,108	27		
Day +14	10.4	9,672	47	stop	
Day +17	2.0	1,380	65	Dose x 1	