MERCY01

A Pilot Study of Mitoxantrone-Based Four Drug Reinduction in Combination with Bortezomib for Relapsed or Refractory Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma in Children and Young Adults (NCT02535806)

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This is an investigator-initiated study. The principal investigator, Dr. Keith August, (who may also sometimes be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

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ABSTRACT

This is a pilot study to determine the feasibility and safety of adding bortezomib (Velcade) to four drug reinduction therapy that includes mitoxantrone for patients with relapsed B-precursor cell acute lymphoblastic leukemia (ALL), relapsed T-cell ALL or relapsed lymphoblastic lymphoma (LL). Relapsed ALL or LL in children is associated with a poor prognosis and new strategies for treatment are needed. This study aims to improve outcomes in relapsed ALL and LL by combining bortezomib with the backbone chemotherapy regimen that includes mitoxantrone, which has demonstrated the most success in this population.

The objectives of this protocol are to estimate the toxicity, remission rate, post-induction minimal residual disease, and 2 year event free survival of the above regimen.

This is a pilot study for re-induction therapy only. Upon completion of therapy, it is expected that patients will continue on to further consolidation therapy with either stem cell transplantation or further chemotherapy at the discretion of the treating physician.

EXPERIMENTAL DESIGN

Day	Vincristine	Dexamethasone	Mitoxantrone	PEG-Asparaginase	Bortezomib	Methotrexate (IT)
1	•	Twice Daily	•		•	•
2			•			
3				•		
4					•	
5						
8	•				•	•
10						
11					•	
15	•	Twice Daily				
16						
17				•		
18						
19						
22	•					

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

4.1.1 To evaluate the feasibility and toxicity of using bortezomib in combination with the ALL R3 re-induction regimen in pediatric patients with relapsed or refractory ALL or LL.

4.1.2 To determine the rate of complete response and negative minimal residual disease status following bortezomib combined with R3 reinduction.

2.0 BACKGROUND

Despite the progress that has been made in the treatment of ALL in children, relapse of disease remains a significant treatment problem. By itself, the number of patients with relapsed ALL would be the 4th most common childhood malignancy and overall survival in these patients is poor. Using conventional treatments, second remission rates after bone marrow relapse in ALL are 81-93%(1-6) and long-term event free survival (EFS) is only 27-50%.(2-4, 6-8) Initial standard therapy for children following relapse includes a four drug reinduction strategy, typically using prednisone, vincristine, PEG-asparaginase, and doxorubicin.(5, 9) For children with first marrow relapse of ALL less than 36 months from diagnosis, this four drug reinduction strategy results in a CR rate of 68%.(5) However, 75% of patients in CR2 had minimal residual disease (MRD) that was positive (>0.01%) at the end of reinduction. The presence of MRD in relapsed ALL is strongly associated with worse long term outcomes(5, 10). For children with ALL that relapsed following a second (CR2) remission, outcomes are dismal with 5 year disease free survival of 15%.(2)

In 2010, results were published of the ALL R3 trial from the Children's Cancer and Leukemia Group in the United Kingdom and Ireland. This trial randomized children with first relapse of ALL to receive a four drug reinduction using either mitoxantrone or idarubicin as the anthracycline.(8) The study was closed early due to a statistically significant improvement in survival for children randomized to mitoxantrone. Children who received mitoxantrone had a 3 year disease free survival of 64.6% compared to 35.9% in the idarubicin group. Toxicities in this study were not excessive, and children randomized to receive mitoxantrone had significantly less toxicity than those in the idarubicin group. Based on the results of this trial, the Children's Oncology Group (COG) has begun using this reinduction regimen as the backbone for new clinical trials for children with relapsed ALL.

Despite the improvement in outcomes for the children with relapsed ALL treated with mitoxantrone on the R3 study, there is still a need for continued efforts to improve outcomes in patients with ALL and LL that experience a relapse. This is particularly true for high risk groups such as those who have an early bone marrow relapse (<36 months from diagnosis), second or greater relapse or relapsed LL where long term survival remains less than 50%.(2, 5)

Bortezomib is a proteasome inhibitor that has demonstrated activity in a number of cancer types including acute leukemias. Bortezomib acts by inhibiting the ubiquitin-proteasome pathway

resulting in the blockade of NF-κB activation and the stabilization of multiple proapoptotic proteins including p53, p21, p27, and Bax. Collectively, these effects induce apoptosis and enhance the cytotoxic effects of chemotherapy.(11-13) In the Pediatric Preclinical Testing Program (PPTP), bortezomib showed activity against a number of ALL cell lines.(14) As a single agent, bortezomib was effective at inhibiting NF-κB but there was no clinical response in 9 heavily pretreated children with ALL.(15) Proteasome inhibition is able to induce apoptosis, and may be best utilized in combination with other conventional chemotherapy drugs to help overcome resistance. Preclinical evaluation of bortezomib with a number of drugs commonly used in pediatric ALL therapy demonstrated synergy with dexamethasone and additive effects when given along with vincristine, asparaginase, and doxorubicin.(16)

In a phase 1 study of children with relapsed ALL of bortezomib combined with a four drug reinduction using dexamethasone, vincristine, doxorubicin, PEG-asparaginase and intrathecal therapy, bortezomib at a dose of 1.3 mg/m^2 given on days 1, 4, 8 and 11 was well tolerated.(17) The phase 2 study of this regimen was able to produce a complete response or complete response without platelet recovery in 73% of patients.(18) These results are encouraging as these were heavily pretreated patients treated with 2 or 3 previous regimens. Due to 3 deaths from infectious toxicities, the study was amended to require infectious prophylaxis with vancomycin, levofloxacin, and voriconazole. No further deaths were seen in children following this change. Other toxicities seen on this study include grade 3 peripheral neuropathy in 2 patients.

This is a phase II study designed to investigate the combination of bortezomib with the mitoxantrone reinduction regimen used in the ALL R3 trial. The study will enroll children with high risk ALL relapse including early bone marrow relapse and second or greater relapse of any kind. Patients with relapsed LL will also be eligible. Bone marrow evaluation will be performed after blood counts recover to assess the rate of CR (<5% bone marrow blasts) and MRD status in children following this regimen. Further treatment with or without HSCT will be at the discretion of the primary physician.

2.1 Bortezomib for Injection

2.1.1 Scientific Background

Bortezomib for Injection is a small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. In the European Union (EU), bortezomib in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant. Bortezomib is indicated as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The antineoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration, and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays.(19) In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation.(12, 20-31) Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.(32)

The mechanisms of action leading up to apoptosis have been more clearly defined and include initiation of the unfolded protein response and direct/indirect effects on various molecular targets including cell cycle control proteins p27 and p21, cyclins, signal transduction molecules, transcription factors c-jun and HIF1-α, tumor suppressor protein p53, angiogenesis factors, and many others. Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.(33-40)

2.1.2 Clinical Experience

To date, more than 436,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a phase 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.(41) The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose.

In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, antitumor activity was reported in subjects with Non-Hodgkin's Lymphoma (NHL), MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.(41-44)

The safety and efficacy of bortezomib in subjects with MM were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse)(45) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy).(46) In M34100-025, 202 heavily pretreated subjects with refractory MM after at least 2 previous treatments received bortezomib, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade(47) were utilized to determine disease response. Complete responses (CRs) were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. Partial response (PR) or better was observed in 27% of subjects, and the overall response rate (CR, PR, and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039)(48), also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m^2 IV push twice weekly on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 treatment cycles as induction therapy, followed by 1.3-mg/m^2 bortezomib weekly on Days 1, 8, 15, and 22 of a 5-week cycle for 3 cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to 4 treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on Days 1 to 4 of a 4-week cycle for 5 cycles as maintenance therapy. The EBMT response criteria were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm ($p < 0.0001$). CR + PR was 38% with bortezomib versus 18% with

dexamethasone ($p < 0.0001$). CR was 6% with bortezomib versus < 1% with dexamethasone ($p < 0.0001$). The CR + nCR (near CR) rate was 13% with bortezomib versus 2% with dexamethasone. In patients who had received only 1 prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs 26% with dexamethasone ($p = 0.0035$). With a median 8.3 months of follow-up, overall survival was significantly longer ($p = 0.0013$) for patients on the bortezomib arm versus patients on the dexamethasone arm. The probability of survival at 1 year was 80% for the bortezomib arm versus 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib ($p = 0.0005$). In patients who had received only 1 prior line of treatment, the probability of survival at 1 year was 89% for the bortezomib arm versus 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib ($p = 0.0098$). Updated response rates and survival data were reported for M34101-039.(49) The updated CR + PR rate was 43% with bortezomib. The CR + nCR rate was 16% with bortezomib. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm versus patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the bortezomib arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, $p = 0.0272$). The probability of survival at 1 year was 80% for the bortezomib arm versus 67% for the dexamethasone arm ($p = 0.0002$).

The safety and efficacy of bortezomib in relapsed or refractory mantle cell lymphoma (MCL) were investigated in an international, phase 2, multicenter study M34103-053, also referred to as the PINNACLE study.(50) The single-arm study was designed to evaluate the response rates, duration of response (DOR), TTP, overall survival (OS), and safety of bortezomib treatment in patients with relapsed or refractory mantle cell lymphoma. For 141 evaluable patients, the response rate was 31% (8% CR/unconfirmed CR [Cru]). Median time to response was 40 days (range 31-204 days). The median number of cycles administered across all patients was 4; in responding patients, the median number of cycles was 8. The median DOR by algorithm was 9.2 months and 13.5 months in patients with CR/CRu. Median TTP for both groups was 6.2 months. With a median follow-up of 13.4 months, overall survival had not been reached. The most commonly reported adverse events (AEs) were fatigue, peripheral neuropathy, and gastrointestinal events. A time-to-event update to the PINNACLE study[i] was reported after a median follow-up of 26.4 months. TTP was 6.7 months for all patients, 12.4 months in all responders. The median DOR was 9.2 months in all responders and had not been reached in patients achieving CR/Cru. Overall survival was 23.5 months in all patients and 36 months in patients with CR/Cru. Survival at 12 months was 69% overall and 91% in responding patients.

The phase 3 study (MMY 3002) known as the VISTA study, evaluated the safety and efficacy of the combination of bortezomib, melphalan, and prednisone in previously untreated multiple myeloma patients who were not candidates for stem cell transplant.(51) The study was designed to determine the benefit of adding bortezomib to MP (melphalan and prednisone) as assessed by TTP. Patients (682) were randomized to receive nine 6-week cycles of melphalan 9mg/m^2 and prednisone 60 mg/m^2 on Days 1 to 4, alone or in combination with bortezomib 1.3 mg/m^2 by IV bolus on Days 1, 4, 8, 11, 22, 25, 29, and 32 during Cycles 1 to 4, and on Days 1, 8, 22, and 29 during Cycles 5 to 9. Response was evaluated every 3 weeks using the EBMT criteria. At a preplanned interim analysis, the independent data monitoring committee recommended that the study be stopped since the prespecified statistical boundary end point of TTP had been crossed. Response rates were 30% with 4% CR. The rates of partial response or better were 71% in the bortezomib (VMP) group compared to 34% in the MP group ($p = 0.001$). With follow-up of 16.3 months, the TTP for the VMP group was 24 months compared to 16.6 months in the MP group ($p = 0.000001$) and was associated with a 52% reduced time to progression. The median DOR was 19.9 months in the VMP group and 13.1 months in the MP group. Overall survival had not been reached in either group. Hematologic toxicity was similar in both groups. The incidence of peripheral sensory neuropathy and gastrointestinal symptoms was higher in the VMP group. The incidence of herpes zoster was 3% in patients in the VMP group who received antiviral prophylaxis. Fifteen percent of patients in the VMP group discontinued therapy due to AEs compared to 14% in the MP group.

The VISTA study update after extended follow-up of 25.9 months,(51) confirmed a survival benefit for the VMP group. Overall survival was not reached in either group: VMP group (75) deaths, 3 year OS 72%; MP group (111) deaths, 3 year OS 59% ($p = 0.0032$). Patients on VMP were less likely to start second-line therapy (VMP 38% vs MP 57% at the time of data cut-off) with a longer time to next therapy (TNT) and treatment free interval (TFI). Of the MP patients who received subsequent therapy, 43% went on to receive bortezomib.

Based on investigator-reported best responses to subsequent therapies, patients relapsing after therapy with a novel agent were not intrinsically more resistant than after receiving a traditional agent.

In the VISTA study, VMP was associated with prolonged TTP, TNT, TFI, and OS. Patients were successfully treated with subsequent IMiD-based therapy and retreated with bortezomib. After 36.7 months follow-up, OS continued to be superior for VMP. The OS for VMP had not yet been reached compared to MP (43.1 months).(52) In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for VMP was

56.4 months and the MP was 43.1 months, with a hazard ration of 0.695 (95% CI: 0.57, 0.85).(53)

2.1.3 Potential Risks of Bortezomib

To date, more than 436,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib.

Prescribing physicians and health care practitioners are referred to their locally approved product label for bortezomib regarding Indications and Usage, Contraindications, Warnings, and Precautions.

The known anticipated risks of bortezomib therapy are presented in Table 1-1 and Table 1-2. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent bortezomib dosed at 1.3 mg/m^2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

Table 1-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhoea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*, lower gastrointestinal haemorrhage*± rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±

Table 1-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bactaeremia*, cellulitis*, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*

Table 1-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome ϕ
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 17.

Most common = ≥ 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%.

* Fatal outcomes have been reported.

± Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.

Table 1-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term

ϕ Effective MedDRA update to version 14.0, the term ‘reversible posterior leukoencephalopathy syndrome’ updated to ‘posterior reversible encephalopathy syndrome (PRES)’.

Table 1-2 Reports of Adverse Reactions From Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence[a]
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete	Rare
Cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes	Rare
Optic neuropathy	Rare
Blindness	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic shock	Rare
Progressive multifocal leukoencephalopathy	Very rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Autonomic neuropathy	Rare
Dysautonomia	Unknown
Encephalopathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease[b]	Rare
Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare

Table 1-2 Reports of Adverse Reactions From Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence[a]
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 17.

a Incidence is assigned using the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000, including isolated reports).

b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

Other medical events of interest that are considered not causally related to bortezomib include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Genotoxicity testing has shown that bortezomib is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

Additional details on the potential risks of bortezomib may be found in the current Investigator's Brochure.

3 PATIENT ELIGIBILITY CRITERIA

3.1 The total number of patients to be enrolled in this study is 10.

3.1 Inclusion Eligibility Criteria

The eligibility criteria below are interpreted literally and cannot be waived. Each patient must meet all of the following inclusion criteria to be enrolled in the study. Study procedures must occur within seven days of starting therapy.

3.1.2 Age

Patients must be > 1 month old and < 40 years of age at the time of enrollment

3.1.3 Diagnosis

- Precursor B-cell ALL with bone marrow (BM) or combined BM/extramedullary relapse;
- T-cell ALL with relapsed disease
- LL with relapsed disease
- ALL(T or pre-B) or LL with primary refractory disease after at least two regimens

3.1.4 Performance Score

Karnofsky > 50% for patients > 16 years of age and Lansky > 50% for patients ≤ 16 years of age. (See Appendix I for Performance Scales)

3.1.4 Prior Therapy

3.1.4.1

Patients who relapse while receiving standard ALL maintenance chemotherapy will not be required to have a waiting period before entry onto this study.

3.1.4.2

Patients who relapse on therapy other than standard ALL maintenance therapy must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. In addition, the following requirements must be met:

a. Cytotoxic therapy: At least 14 days since the completion of cytotoxic therapy with the exception of hydroxyurea, which is permitted up to 24 hours prior to the start of protocol therapy.

b. Biologic (anti-neoplastic) agent: At least 7 days since the completion of therapy with a biologic agent or donor lymphocyte infusions (DLI). For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

c. Stem cell transplant or rescue: No evidence of active graft-vs-host disease (GVHD) and ≥ 4 months must have elapsed from time of transplant. Must not be receiving GVHD prophylaxis.

3.1.5 Organ Function Requirements

All patients must have:

3.1.5.1 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2

or

- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.1.5.2 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and

- SGPT (ALT) < 3 x upper limit of normal (ULN) for age, unless elevation due to leukemia infiltration.

3.1.5.3 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram, or

- Ejection fraction of ≥ 50% by gated radionuclide study.

- Please see Section 3.2.6 for prior anthracycline restrictions.

3.1.5.4 Adequate Pulmonary Function Defined As:

- No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry ≥ 94% at sea level (> 90% if at high altitude).

- No evidence of acute pulmonary infiltrates on chest radiograph.

3.1.5.5 Central Nervous System Function Defined As:

- Patients with seizure disorder may be enrolled if on allowed anticonvulsants (see Appendix II) and well controlled. Benzodiazepines and gabapentin are acceptable.

- CNS toxicity < Grade 3.

3.1.5.6 Peripheral Nervous System (PNS) Function Defined As:

- PNS toxicity ≤Grade 2.

3.1.5.7 Reproductive Function

– Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed within 2 weeks prior to enrollment.

– Female patients with infants must agree not to breastfeed their infants while on this study.

– Male and female patients of child-bearing potential must agree to use 2 effective methods of contraception approved by the investigator, at the same time, from the time of signing the informed consent form and for a minimum of 6 months after study treatment, or agree to completely abstain from heterosexual intercourse.

3.2 Exclusion Eligibility Criteria

Patients will be excluded if they meet any of the following criteria

3.2.1 Patients will be excluded if they have a known allergy to any of the drugs on the study with the exception of PEG-asparaginase (see below).

3.2.2 Patients with isolated CNS or isolated testicular disease will be excluded.

3.2.3 Patients will be excluded if they have a systemic fungal, bacterial, viral or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient needs to be off pressors and have negative blood cultures for 48 hours.

3.2.4 Patients with known optic nerve and/or retinal involvement (because it may not be possible to safely delay irradiation) are not eligible. Patients presenting with visual disturbances should have an ophthalmological exam and, if indicated, an MRI to determine optic nerve or retinal involvement.

3.2.5 Patients with concomitant genetic syndrome: patients with Down syndrome, Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome are not eligible.

3.2.6 Cumulative prior anthracycline exposure must not exceed 400 mg/m^2 (each 10 mg/m^2 of idarubicin should be calculated as the isotoxic equivalent of 30 mg/$m^2$of daunorubicin or doxorubicin).

3.2.7 Patients who have previously received bortezomib or other proteasome inhibitors are not eligible.

3.2.8 Patients taking anticonvulsants known to activate the cytochrome p450 system, in particular anticonvulsants such as phenytoin, carbamazepine and phenobarbital, are not eligible. Benzodiazepines and gabapentin are acceptable (see Appendix II). Please see Appendix II for a list of drugs known to be potent inducers/inhibitors of the cytochrome p450 system.

3.2.9 Patients who cannot receive any asparaginase products (E. Coli, PEG-asparaginase, or Erwinia asparaginase) on this study (eg, due to prior severe pancreatitis, stroke or other toxicity) are not eligible. Patients who initially receive asparaginase, but must discontinue due to toxicity, remain eligible. Patients with clinically significant prior allergies to PEG-asparaginase are eligible if Erwinia L-asparaginase can be substituted.

3.2.10 Pregnancy and Breast Feeding: patients who are pregnant or breast-feeding are not eligible for this study as there is as yet no available information regarding human fetal or teratogenic toxicities. Negative pregnancy tests must be obtained in girls who are post-menarchal.

3.2.11 Patients will be excluded if there is a plan to administer non-protocol chemotherapy, radiation therapy, or immunotherapy during the study period.

3.2.12 Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with the protocol treatment or procedures, interfere with consent, study participation, follow up, or interpretation of study results.

3.2.13 Patients with Down syndrome will be excluded.

3.2.14 All patients and/or their parents or legal guardians must voluntarily sign a written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care. Assent from children will be obtained per institutional guidance.

3.2.15 For lymphoma patients with <5% marrow blasts, the platelet count must be $\geq$ 25,000/mm^3 within 7 days before enrollment.

3.2.16 For lymphoma patients with <5% marrow blasts, the absolute neutrophil count must be ≥ 500 cell/mm^3 within 7 days before enrollment.

3.2.17 Patient had myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.

3.2.18 Diagnosed or treated for another malignancy within 2 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.

3.2.19 Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.

3.2.20 Radiation therapy within 3 weeks before randomization. Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy.

3.3 Definitions

Bone marrow status:

M1	< 5%	lymphoblasts
M2	5 - 25%	lymphoblasts
M3	> 25%	lymphoblasts

Leukemia Relapse:

Isolated Bone Marrow Relapse: M3 marrow confirmed by bone marrow aspirate or biopsy.

Isolated CNS Relapse: Positive cytomorphology and WBC ≥ 5/μL OR positive cytomorphology with CSF WBC 0-4/μL on 2 successive occasions 1 month apart.

Isolated Testicular Relapse: Confirmation by testicular biopsy preferred but not required.

Combined Relapse: Documented extramedullary relapse and an M2 or M3 bone marrow.

Lymphoblastic Lymphoma Relapse:

Patients must have histologic verification of lymphoblastic lymphoma at diagnosis or at the time of relapse. Patients must have measurable disease. Measurable disease is defined as any nodal mass with longest transverse diameter > 2 cm, or any measurable, focal mass lesion of a visceral

organ (such as liver, spleen, kidney). Measurable lesions in a visceral organ are lesions that can be accurately measured in 2 axial dimensions by CT.

Central nervous system (CNS) leukemia at relapse diagnosis:

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of WBCs.

CNS 2: In CSF, presence < 5/µL WBCs and cytospin positive for blasts, or ≥ 5/µL WBCs but negative by Steinherz/Bleyer algorithm:

- CNS 2a: < 10/µL red blood cells (RBCs); < 5/µL WBCs and cytospin positive for blasts;
- CNS 2b: ≥ 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts; and
- CNS 2c: ≥ 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below);

CNS 3: In CSF, presence of ≥ 5/µL WBCs and cytospin positive for blasts and/or clinical signs of CNS leukemia:

- CNS 3a: < 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts;
- CNS 3b: ≥ 10/µL RBCs, ≥ 5/µL WBCs and positive by Steinherz/Bleyer algorithm
  (see below);
- CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Method of evaluating initial traumatic lumbar punctures (LPs):
If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/µL and blasts, the following Steinherz/Bleyer algorithm should be used to distinguish between CNS2 and CNS3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/µL blasts, whose CSF WBC/RBC ratio is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.

4.0 TREATMENT PROGRAM

Bortezomib Administration

Drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients may be treated on an outpatient basis, if possible.

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram or calculation .The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time based on clinical judgment.

The appropriate amount of bortezomib will be drawn from the injection vial and administered as an IV push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single-use administration.

There must be at least 72 hours between each dose of bortezomib.

It is strongly recommended that all patients remain inpatient until adequate count recovery due to the risk of serious infection. Antifungal prophylaxis is required (see Section 7.3.1 for appropriate medications) and antibacterial prophylaxis with ciprofloxacin +/- vancomycin is recommended.

Dose calculations should be based on actual BSA. There is no maximum dosing with the exception of vincristine which is capped at a maximum dose of 2 mg.

- Check O2 saturation within 12 hours prior to each dose of bortezomib. In the absence of congestive heart failure or other known cause of hypoxia, O2 saturation must be ≥ 94% at sea level (> 90% at high altitude) prior to bortezomib administration. (Please see Section 5.1 if patient develops drug-induced pulmonary toxicity.)
- Vigorous hydration without potassium should be instituted prior to starting therapy. Allopurinol or urate oxidase may be used as necessary for hyperuricemia.
- No other cytotoxic therapy may be given during this therapy.
- Antiemetics should be given during each chemotherapy course, individualized to the patient's best response. Dexamethasone and aprepitant should not be used as antiemetics.
- Bortezomib has been associated with hypophosphatemia. Phosphorus should be evaluated prestudy. If the level is < 1.5 mg/dL, correct the level to 2 mg/dL or above

prior to beginning chemotherapy. Maintain phosphorus level above 2 mg/dL during the first two weeks of therapy.

- Bortezomib-related hyponatremia has been associated with seizures. Sodium should be monitored and kept > 130 mEq/L during the first two weeks of therapy.

Treatment Plan

Methotrexate: IT - for CNS-negative (CNS1/CNS2) patients only.
Days 1 and 8 (day 1 IT may be given up to 72 hours prior to starting therapy):
Aged – based dosing:

Age (years)	Dose
1 - 1.99	8 mg
2 - 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Triple Intrathecal Therapy (ITT): IT – for CNS-positive (CNS3) patients only.
Days 1, 8, 15, and 22 (day 1 TIT may be given up to 72 hours prior to starting therapy):
Weekly TIT will be continued if necessary beyond the required 4 doses until 2 successive LPs are free of lymphoblasts (up to a maximum of 6 doses ITT). Note that all CNS-positive patients should receive 4 doses of ITT, even if CSF is clear of lymphoblasts prior to Day 15.

Age (years)	Dose (methotrexate (MTX), hydrocortisone (HC), cytarabine (ARAC))
1 - 1.99	MTX: 8 mg; HC: 8 mg; ARAC: 16 mg
2 - 2.99	MTX: 10 mg; HC: 10 mg; ARAC: 20 mg
3 – 8.99	MTX: 12 mg; HC: 12 mg; ARAC: 24 mg
≥ 9	MTX: 15 mg; HC: 15 mg; ARAC: 30 mg

Dexamethasone: PO
Days 1-5 and 15-19
Dose: 10 mg/m^2/dose PO BID (ie, 20 mg/m^2/day PO, divided BID)

Mitoxantrone: IV over 15-30 minutes
Days 1 and 2.
Dose: 10 mg/m^2/dose.

Administer through the tubing of a rapidly infusing solution of D5W or 0.9% NaCl. Avoid extravasation; the use of a central line is suggested.

Bortezomib: IV push over 3-5 seconds followed by a standard saline flush or through a running IV line. Vials are for single-use administration.
Days: 1, 4, 8 and 11. Note: at least 72 hours must have elapsed between doses.
Dose: 1.3 mg/m^2/dose.

Vincristine: IV push over 1 minute
Days 1, 8, 15 and 22
Dose: 1.5 mg/m^2/dose (maximum dose 2 mg).

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vincristine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

PEG-asparaginase: IV over 1 hours
Days 3 and 17.
Dose: 2500 International units/m^2/dose.

Suggested monitoring during administration: Because PEG-asparaginase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for fever, chills, and acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (eg, epinephrine, IV corticosteroids, antihistamines). May prescribe an EpiPen® for home use.

> If allergic to PEG-asparaginase then use Asparaginase *Erwinia Chrysanthemi* 20,000 IU/m^2 IM x 6 doses on a Monday/Wednesday/Friday schedule as a replacement for each scheduled dose of PEG- asparaginase 2,500 IU/ m^2/dose.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for grading and reporting adverse events.

All previously established or new toxicities observed any time are to be managed as described in 5-1. Neuropathic pain and peripheral sensory neuropathy are to be managed as described in table 5-2.

Table 5-1 Toxicity Management

Toxicity	Grade	Action
Lymphopenia	Any	None
Nonhematological toxicity	3	Hold bortezomib therapy
Hematological Toxicity	4	Hold bortezomib therapy

5.1 Bortezomib

For nonhematologic toxicities, bortezomib is to be held for up to 2 weeks until the toxicity returns to Grade 1 or better.

Once bortezomib is reduced for any toxicity, the dose may not be re-escalated.

If after bortezomib has been held, the toxicity does not resolve, then bortezomib must be discontinued.

If the toxicity resolves, as described above, bortezomib may be restarted at the same schedule the patient was on prior to holding therapy, and the dose must be reduced by approximately 25% as follows:

- If the patient was receiving 1.3 mg/m^2, reduce the dose to 1 mg/m^2.
- If the patient was receiving 1 mg/m^2, reduce the dose to 0.7 mg/m^2.

If the patient was receiving 0.7 mg/m^2, discontinue drug unless patient is responding, in which case, this should be discussed with the principal investigator.

Patients who experience bortezomib-related neuropathic pain or peripheral sensory neuropathy are to be managed as presented in 5-1. Once the dose is reduced for peripheral neuropathy, the dose may not be re-escalated.

<u>Peripheral Neuropathy:</u>

For grade 3 peripheral neuropathy, hold bortezomib until symptoms have resolved to ≤ grade 1. Do not make up missed doses. When toxicity resolves, resume bortezomib at 1 mg/m^2/dose.

For grade 4 peripheral neuropathy, discontinue bortezomib.

Table 5-2 Management of Patients With VELCADE-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or parasthesias) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities or Daily Living [ADL][b])	Reduce VELCADE to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequence; urgent intervention indicated)	Discontinue VELCADE

Source: VELCADE USPI issued January 2012.
Abbreviations: ADL = activities of daily living
a Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
b Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc

c Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Patients with mild hepatic impairment (bilirubin ≤ 1.5 × ULN) do not require a starting dose adjustment. Please note that patients with bilirubin levels > 1.5 ULN are excluded from enrollment in this protocol. If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (> 1.5 -3.0 X ULN) while on study, the investigator should hold Bortezomib until the toxicity returns to < Grade 2. Restarting Bortezomib at the next lower dosed level could be considered at the Investigator's discretion and following exclusion of Bortezomib-induced liver impairment and careful consideration of liver disease due to other causes, such as, but not limited to, active infection and multiple myeloma-related liver disease.

Pulmonary Toxicity:

Pulmonary toxicity from bortezomib has been reported including pneumonitis, pneumonia, infiltrates and acute respiratory distress syndrome. All patients should have a CXR prior to starting therapy. Pulse oximetry should be performed prior to each dose of bortezomib.

For grade 3 pulmonary toxicity, hold bortezomib until symptoms have resolved to ≤ grade 1. Do not make up missed doses. When toxicity resolves, resume bortezomib at 1 mg/m^2/dose.

For grade 4 pulmonary toxicity, discontinue bortezomib.

For patients that develop hypoxia (oxygen saturation ≤ 90%) and/or pulmonary infiltrates in the absence of other identifiable causes, steroid treatment is recommended.

5.2 Mitoxantrone

Dose adjustment for hyperbilirubinemia:

Direct bilirubin:

< 2.0 mg/dL	Full dose
2.1-- 3.0 mg/dL	50%
3.1 – 5.0 mg/dL	25% of calculated dose
> 5.0 mg/dL	Hold dose and administer subsequent doses if toxicity has resolved. Do not make up missed doses.

Left Ventricular Systolic Dysfunction:

Hold mitoxantrone for shortening fraction ≤ 27%.

Extravasation:

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines.

5.3 Asparaginase

Allergy:

Continue asparaginase for grade 1 reaction (localized reaction)

Discontinue asparaginase infusion if ≥ grade 2 reaction occurs including anaphylaxis.

For patients that have had a previous allergic reaction to *E. Coli* or PEG-asparaginase, or who react to the first dose on this protocol then *Erwinia* asparaginase should be substituted for each dose at a schedule of 20,000 IU/m^2 on a Monday/Wednesday/Friday schedule for 2 weeks (6 doses).

Coagulopathy:

If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

Hyperglycemia and/or hyperlipidemia:

Do not modify dose. Treat hyperglycemia as medically indicated.

Ketoacidosis:

Hold asparaginase until blood glucose can be regulated with insulin.

Pancreatitis:

Discontinue asparaginase in the presence of hemorrhagic pancreatitis or severe pancreatitis (grades 3 and 4). In the case of mild pancreatitis, asparaginase should be held until symptoms and signs subside, and amylase levels return to normal and then resumed. Severe pancreatitis is a contraindication to additional asparaginase administration.

Thrombosis:

Withhold asparaginase until resolved, and treat with appropriate antithrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing LMWH or antithrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate. For significant thrombosis, not line related, consider evaluation for inherited predisposition to thrombosis. CNS Events (bleed, thrombosis or infarction): Hold asparaginase. Treat with FFP, factors or anticoagulation as appropriate. Resume at full dose when all symptoms have resolved (and evidence of recanalization in case of thrombosis by CT/MRI). Consider evaluation for inherited predisposition to thrombosis.

5.4 Dexamethasone

Hypertension:

Dose should not be reduced. Sodium restriction and anti-hypertensives should be used in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

Hyperglycemia:

Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

Pancreatitis:

Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis.

Infection:

Do not hold steroids for infection unless the infection is life-threatening and discontinuing steroids is thought to provide potential benefit.

Severe Psychosis:

Do not hold steroids for behavioral issues unless they are severe. May reduce dose by 50% if necessary.

5.5 Intrathecal Methotrexate

Neurologic Toxicity

For patients that have ≥ grade 3 neurological toxicity from methotrexate, options include substituting intrathecal cytarabine for future treatments or to treat with leucovorin rescue at a dose of 5 mg/m2 q 12 hrs x 2 doses beginning 48 hours after the LP.

CNS Infection:

For patients with active CNS infection, do not administer intrathecal treatments.

6.0 AGENT INFORMATION

6.1 PEG-Asparaginase

Source and Pharmacology:
PEG-asparaginase is a modified version of the enzyme L-asparaginase. L-asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of PEG-asparaginase is derived from *Escherichia coli* which is purchased in bulk from Merck, Sharp and Dohme. L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. The ability to synthesize asparagine is notably lacking in malignancies of lymphoid origin. Asparaginase depletes L-asparagine from leukemic cells (especially lymphoblasts) by catalyzing the conversion of L-asparagine to aspartic acid and ammonia. In predominately L-asparaginase naive adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration of PEG-asparaginase were determined. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with PEG-asparaginase. The approximate t½ in adult patients is 5.73 days. The enzyme could not be detected in the urine. The half-life is independent of the dose administered, disease status, renal or hepatic function, age, or gender. In a study of newly diagnosed pediatric patients with ALL who received either a single intramuscular injection of PEG-asparaginase (2500 IU/m2), *E. coli* L-asparaginase (25000 IU/m2), or *Erwinia* (25000 IU/m2), the plasma half-lives for the three forms of L-asparaginase were: 5.73 ± 3.24 days, 1.24 ± 0.17 days, and 0.65 ± 0.13 days respectively. The plasma half-life of PEG-asparaginase is shortened in patients who are previously hypersensitive to native L-asparaginase as compared to non-hypersensitive patients. L-asparaginase is cleared by the reticuloendothelial system and very little is excreted in the urine or bile. Cerebrospinal fluid levels are < 1% of plasma levels.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Allergic reactions (total likelihood of local and/or systemic reaction), pain at injection site	Rash	Tachycardia, periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lip edema, arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures (L), hyperuricemia

Prompt: Within 2-3 weeks, prior to the next course	Hyperammonemia (L), coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) (L)	Hyperglycemia, abnormal liver function tests, pancreatitis (L), increased serum lipase/amylase	Pancreatitis (L), hemorrhage (L), DIC, thrombosis, anorexia, CNS ischemic attacks, edema, azotemia and decreased renal function, mild leukopenia and thrombocytopenia, coma and stupor, hypertriglyceridemia, hyperlipidemia, Parkinson-like syndrome with tremor and increase in muscular tone, CNS changes including irritability, depression, confusion, EEG changes, hallucinations
Delayed: Any time later during therapy, excluding the above conditions			Renal failure, urinary frequency, hemorrhagic cystitis, elevated creatinine and BUN, fatty liver deposits, hepatomegaly, liver failure
Unknown Frequency and Timing:	Animal reproduction studies have not been conducted with PEG-asparaginase. It is not known whether PEG-asparaginase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, fetal toxicities and teratogenic effects of asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later.

Formulation and Stability:

Each milliliter of PEG-asparaginase contains: PEG-L-asparaginase 750 IU ± 20%, monobasic sodium phosphate, *USP* 1.20 mg ± 5% dibasic sodium phosphate, *USP* 5.58 mg ± 5%, sodium chloride, *USP* 8.50 mg ± 5% , Water for Injection, *USP* qs to 1 mL. The specific activity of PEG-asparaginase is at least 85 IU per milligram protein. Available in 5 mL vials as Sterile Solution for Injection in ready to use single-use vials, preservative free. Keep refrigerated at 2°-8°C (36°-46°F). Do not use if stored at room temperature for more than 48 hours. **DO NOT FREEZE.** Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

Guidelines for Administration:

See Treatment and Dose Modifications sections of the protocol (Section 4.0 and Section 5.0).

For IV administration: dilute PEG-asparaginase contains in 100 mL of 0.9% sodium chloride injection (NS) or 5% dextrose injection (D5W) and infuse over 1 to 2 hours through a NS or D5W running infusion line. PEG-asparaginase admixed in 100 mL of NS or D5W is stable for 48 hours at room temperature. PEG-asparaginase diluted in 100 mL of NS is stable for up to 72

hours refrigerated (4ºC [39°F]) (refrigerated stability data on file with Sigma-Tau). Avoid excessive agitation. DO NOT SHAKE. Do not use if cloudy of if precipitate is present. Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for ONE hour after administration for signs of hypersensitivity reactions.

6.2 Dexamethasone

Source and Pharmacology:
Dexamethasone is a synthetic fluorinated glucocorticoid devoid of mineralocorticoid effects. Dexamethasone, 0.75 mg, has potent anti-inflammatory activity equivalent to approximately 5 mg of prednisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age: 2.3 to 9.5 hours, 8 to 16 years: 2.82 to 7.5 hours, and adults (age not specified): 3 to 6 hours. The biologic half-life is 36-72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later during therapy, excluding the above conditions	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the

			femoral and humeral heads (L), urolithiasis (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of dexamethasone in children)	
Unknown Frequency and Timing:	**Fetal and teratogenic toxicities**: dexamethasone crosses the placenta with 54% metabolized by enzymes in the placenta. In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. There are no reports of dexamethasone excretion into breast milk in humans; however, it is expected due to its low molecular weight that it would partition into breast milk.		

(L) Toxicity may also occur later.

Formulation and Stability:

Oral:

Available in 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets; liquid formulations are available in 0.5 mg/5 mL and 1 mg/1 mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes.

Injection:

Dexamethasone Sodium Phosphate Solution for Injection is available as 4 mg/mL (1 mL, 5 mL, and 30 mL vials) and 10 mg/mL (1 mL and 10 mL vial sizes). Four milligrams of dexamethasone sodium phosphate is equivalent to 3.33 mg of dexamethasone. IV dexamethasone should be given as 1;1 replacement on study. Vials are available in multi-dose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA.

Guidelines for Administration:

See Treatment and Dose Modifications sections of the protocol (Section 4.0 and Section 5.0).

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid using benzyl alcohol-containing dexamethasone solutions in neonates. Diluted solutions that contain no preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

6.3 Vincristine

Source and Pharmacology:

Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The

initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy, excluding the above conditions	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later.

Formulation and Stability:

Vincristine is supplied in 1 mL and 2 mL vials in which each mL contains vincristine sulfate, 1 mg (1.08 μmol), mannitol 100 mg, Sterile Water for Injection; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol (Section 4.0 and Section 5.0).

Vincristine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecal.
Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only. Fatal if given by other routes."

6.4 Mitoxantrone

Source and Pharmacology:
Mitoxantrone is a substituted alkylaminoanthraquinone and is a potent inhibitor of DNA and RNA synthesis *in vitro* and binds strongly to DNA. Mitoxantrone most likely acts through intercalation between base pairs of the DNA double helix causing crosslinks and strand breaks. In addition, it is a topoisomerase II inhibitor, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on both proliferating and non-proliferating cultured human cells, suggesting lack of cell cycle phase specificity. The drug disappears rapidly from plasma (drug found only in the 3-minute sample) and < 1% appears in the urine in 24 hours. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours (median approximately 75 hours). Primary excretion is biliary with 25% appearing in the feces; renal excretion accounting for only 11% of the total dose. Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin > 3.4 mg/dL) have an AUC more than three times greater than that of patients with normal hepatic function receiving the same dose. Mitoxantrone is approximately 95% protein bound.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, diarrhea, fever, anorexia, green blue discoloration of the urine and/or sclera	Abdominal pain, back pain, headache, phlebitis, constipation	Anaphylaxis, angioedema, cardiac arrhythmias (bradycardia), seizures, extravasation reactions rare but if occur can lead to: (erythema, swelling, pain, burning and/or blue discoloration of the skin

			and rarely tissue necrosis), tumor lysis
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (L), mucositis /stomatitis, immunosuppression, alopecia, fatigue	Transient elevation of LFTs, pruritis with desquamation of the skin due to progressive dryness	Rash, conjunctivitis, (GI) hemorrhage, interstitial pneumonitis
Delayed: Any time later during therapy, excluding the above conditions	Amenorrhea, menstrual disorders, temporary reduction in sperm count	Cardiotoxicity (decreased LVEF) (L)	CHF, hepatotoxicity (L)
Late: Any time after completion of treatment			Secondary malignancy
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mitoxantrone have been noted in animals. Toxicities include: low birth weight and prematurity. Mitoxantrone is excreted in human milk and significant concentrations (18 ng/mL) have been reported for 28 days after the last administration.		

(L) Toxicity may also occur later.

Formulation and Stability:

The concentrate is a sterile, non-pyrogenic, non-preserved, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046% w/v) as inactive ingredients with 0.14 mEq of sodium per mL. Mitoxantrone is provided as 20 mg (10 mL), 25 mg (12.5 mL) and 30 mg (15 mL) vials. Store intact vials at 15°-25°C (59°-77°F). Undiluted mitoxantrone injection should be stored not longer than 7 days between 15°-25°C (59°-77°F) or 14 days under refrigeration. Refrigeration of the concentrate may result in a precipitate, which redisolves on warming to room temperature. DO NOT FREEZE.

Guidelines for Administration:

See Treatment and Dose Modifications sections of the protocol (Section 4.0 and Section 5.0).

Mitoxantrone must be diluted prior to injection. DO NOT GIVE IV PUSH. The dose of mitoxantrone should be diluted in at least 50 mL (or other published dilution concentration) with either 0.9% Sodium Chloride Injection (*USP*) or 5% Dextrose Injection (*USP*). The dilution is stable at room temperature for 48 hours with no loss of potency. Admixture with heparin may result in precipitation. Mitoxantrone is an irritant: Care should be taken to avoid extravasation; the use of a central line is suggested. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be Page 60 placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and surgery consultation obtained early if there is any sign of a local reaction.

6.5 Methotrexate

Source and Pharmacology:
A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 μmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. After oral administration, approximately 60% of a 30 mg/m2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. At doses > 30 mg/m² absorption decreases significantly. Even at low doses absorption may be very erratic, varying between 23% and 95%. The elimination of MTX from the CSF after an intrathecal dose is characterized by a biphasic curve with half-lives of 4.5 and 14 hours. After intrathecal administration of 12 mg/m², the lumbar concentration of MTX is ~100 times higher than in plasma. (Ventricular concentration is ~ 10% of lumbar concentration). MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

Toxicity (Intrathecal):

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, headache	Arachnoditis: (headache, fever, vomiting, meningismus, nuchal rigidity, and pleocytosis)	Anaphylaxis, vomiting, seizures(L), malaise, confusion, back pain, rash, bleeding into subarachnoid or subdural space (risk > with platelet counts < 20,000),
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia, somnolence, cranial nerve palsy, subacute myelopathy (paraparesis/paraplegia), speech disorders, pain in the legs, bladder dysfunction

Delayed: Any time later during therapy, excluding the above conditions		Cognitive disturbances (L), learning disability (L)	Leukoencephalopathy (L)
Late: Any time after completion of treatment			Progressive CNS deterioration

(L) Toxicity may also occur later.

Formulation and Stability:

Methotrexate for Injection is available as a lyophilized powder for injection in 1000 mg vials. The powder for injection contains approximately 7 mEq sodium in the 1000 mg vial. Methotrexate for Injection is also available as a 25 mg/mL solution in 2, 4, 8, 10, and 40 mL preservative free vials and 2 and 10 mL vials with preservative. The 2, 4, 8, 10, and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative.
Sterile methotrexate powder or solution is stable at 20º-25ºC (68º-77ºF); excursions permitted to 15º-30ºC (59º- 86 Fº). Protect from light.

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol (Section 4.0 and Section 5.0).

For intrathecal administration, dilute with 5-10 mL preservative free 0.9% Sodium Chloride Injection, lactated Ringer's, or Elliot's B solution as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Methotrexate dose	Recommended volume	10% CSF volume	CSF Volume*
1–1.99	8 mg	5–10 mL	5 mL	50 + 10 mL (babies)
2–2.99	10 mg	5-10 mL	8 mL	80 + 20 mL (younger children)
3–8.99#	12 mg	5-10 mL	10 mL	100 + 20 mL (older children)
9 or greater	15 mg	5-10 mL	13 mL	130 + 30 mL (adults)

*Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.
Diluted methotrexate for intrathecal administration is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

Diluted methotrexate for intrathecal administration is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

6.6 Asparaginase Erwinia Chrysanthemi

Source and Pharmacology:
L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. Neoplastic cells associated with acute lymphoblastic leukemia, acute myeloid leukemia and lymphoblastic lymphosarcoma are asparagine-dependent but lack asparagine synthetase activity. The administration of L-asparaginase produces an anti-neoplastic effect by catalyzing asparagine into aspartic acid and ammonia. As a result, these cells lack the ability to produce the asparagine necessary for protein metabolism and survival. Deamination of glutamine may also play a role in the antineoplastic activity of asparaginase.

Asparaginase *Erwinia chrysanthemi* (ErwinazeTM) is asparaginase derived from cultures of *Erwinia chrysanthemi*. L-asparaginase is a tetrameric enzyme; each of the four identical subunits has a molecular weight of approximately 35 kDa. Asparaginase *Erwinia chrysanthemi* is immunologically distinct from *E. coli* L- asparaginase and may allow continued asparaginase therapy when a hypersensitivity reaction occurs to *Escherichia coli*-derived asparaginase. The package labeling states that there is insufficient information to characterize the incidence of antibodies to asparaginase *Erwinia chrysanthemi*. Several factors are involved in immunogenicity assay results and the assessment of antibodies, including assay methodology, assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medications, and the underlying disease state.

Effective asparaginase levels have been defined as activity of ≥ 0.1 International Units per mL. Clinical trials with asparaginase *Erwinia chrysanthemi* demonstrated that 100% of patients achieved effective asparaginase levels at 48 and 72 hours (n=35 and n=13, respectively) following the third total dose when given on a Monday, Wednesday, Friday schedule. No formal drug interaction studies have been performed with asparaginase *Erwinia chrysanthemi*.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Allergic reactions Anaphylaxis, urticaria	Local injection site reactions, fever
Prompt: Within 2-3 weeks, prior to the next course	Hyperammonemia (L), coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) (L)	Hyperglycemia, abnormal liver function tests, pancreatitis (L), increased serum lipase/amylase	Pancreatitis, glucose intolerance, thrombosis, hemorrhage, transient ischemic attack, disseminated intravascular coagulation, hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased,

			hyperglycemia, hyperammonemia, vomiting, nausea, abdominal pain, headache, diarrhea, seizure
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of L-asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk. Adequate, well-controlled studies of asparaginase *Erwinia chrysanthemi* have NOT been conducted. It is not known whether asparaginase *Erwinia chrysanthemi* will cause fetal harm or affect the ability to reproduce. It is not known if asparaginase *Erwinia chrysanthemi* is excreted into breast milk. The use of asparaginase *Erwinia chrysanthemi* should be avoided in pregnant or lactating patients.		

Formulation and Stability:
Asparaginase *Erwinia chrysanthemi* is supplied as a sterile, white lyophilized powder for reconstitution in a clear glass vial with a 3 mL capacity. Each vial contains 10,000 International Units of asparaginase *Erwinia chrysanthemi* and the following inactive ingredients: glucose monohydrate (5.0 mg), sodium chloride (0.5 mg). Store between 2°C and 8°C (36° to 46ºF). Store intact vials between 2°C and 8°C (36°- 46ºF). Protect from light.

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol (Section 4.0 and Section 5.0).

Use appropriate precautions for preparation of a hazardous agent. Visually inspect the powder in vial for foreign particles or discoloration prior to reconstitution. The contents of each vial should be reconstituted by slowly adding 1 mL or 2 mL of sterile, preservative-free NS to the inner vial wall. The final concentration is 10,000 International Units per mL when using 1 mL for reconstitution or 5,000 International Units per mL when using 2 mL for reconstitution. Gently mix or swirl the contents to dissolve the contents of the vial. Do not shake or invert the vial. The resulting solution should be clear and colorless. Discard if any particulate matter or protein aggregates are visible. **Withdraw the appropriate dosing volume into a polypropylene syringe within 15 minutes of reconstitution.** Discard any unused drug; do not save or use any unused drug remaining the in the vial.
Administer the dose within a 4 hour time period from reconstitution. If the dose is not used within this time period, discard the dose. Do not freeze or refrigerate the reconstituted solution.
Administer the dose intramuscularly (IM). No more than 2 mL should be given at any one injection site. Doses larger than 2 mL should be divided and given in separate administration sites.

6.7 Bortezomib

Source and Pharmacology:

Formulation and Stability:
Bortezomib for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5mg of bortezomib contain 35mg of mannitol.

Preparation, Handling, Storage, and Destruction of Drugs

Bortezomib

Vials containing lyophilized bortezomib for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); for Europe, do not store above 30ºC (86ºF); excursions permitted from 15 to 30ºC (59-86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

Bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling bortezomib solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Drug is available in sterile, single-use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within 8 hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6.

Reconstituted bortezomib should be administered promptly and in no case more than 8 hours after reconstitution.

Bortezomib Destruction
Investigational bortezomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

Blinding, Packaging, and Labeling
Bortezomib will be supplied in vials as open-label stock. Both the box label and vial label will fulfill all requirements specified by governing regulations.

Treatment Compliance
All drug will be administered to eligible patients under the supervision of the investigator or identified subinvestigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see Appendix 8.1), total drug administered in milliliters and milligrams, and date and time of administration. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

Precautions and Restrictions

It is not known what effects bortezomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.
Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 30 days after the last dose of bortezomib, or agree to completely abstain from heterosexual intercourse.

It is strongly recommended that at least 1 of these 2 methods be highly effective (see examples below).

Highly effective methods	Other effective methods (barrier methods)
Intra-uterine devices (IUD)	Latex condom
Hormonal contraceptives (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide Cervical cap Sponge

If one of the highly effective methods cannot be used, using 2 effective methods at the same time is recommended.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse.

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol (Section 4.0 and Section 5.0).

Bortezomib is to be given without further dilution as an IV push over 3 to 5 seconds.
Consecutive doses must be separated by at least 72 hours.

Special precautions: FOR INTRAVENOUS USE ONLY.
The syringe containing bortezomib should be clearly labeled for intravenous use only. Three fatalities have been reported following accidental intrathecal administration of bortezomib.

Special precautions should be employed to ensure that intravenous bortezomib and intrathecal medications are not inadvertently interchanged.

7.0 SUPPORTIVE CARE AND OTHER CONCOMMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy including chemotherapy, immunotherapy or biologic therapy may not be administered to patients within 14 days of the start of this study and during the study period.

7.2 Investigation Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, anti-hypertensives, fluids, electrolytes, and tumor lysis precautions and general supportive care are to be used as necessary. See Appendix II for drugs that should not be used concomitantly with bortezomib.

7.3.1 Infection Control

Patients with relapsed ALL have a significant risk of morbidity and mortality with intensive chemotherapy.

- It is strongly recommended that patients remain hospitalized from the initiation of therapy until they are clinically stable and have evidence of ANC recovery.
- It is strongly recommended that patients receive broad spectrum antibiotic prophylaxis from the initiation of therapy until there is evidence of ANC recovery. A fluoroquinolone such as ciprofloxacin or levofloxacin is recommended.
- All patients should receive anti-fungal therapy with caspofungin, micafungin or amphotericin unless contraindicated. Azole antifungals are not allowed until 2 days after the last dose of vincristine.

7.3.2 Tumor Lysis Syndrome

Tumor lysis syndrome should be closely monitored at the onset of therapy. Serum chemistries including potassium, phosphorus, calcium and uric acid should be monitored at least daily after initiation of therapy. Allopurinol or urate oxidase should be used for elevated or increasing uric acid levels. IV hydration should be maintained for a minimum of 3 days and there is no laboratory evidence of tumor lysis.

7.3.3 Growth Factors

Growth factors are not recommended for routine use but may be administered at the discretion of the treating physician for infection, severe mucositis or poor wound healing.

7.3.4 Concomitant Medications

Investigators should consider using antiviral prophylaxis in subjects being treated with bortezomib.

The use of enzyme inducing anticonvulsants and antifungals is not permitted until two days following the last dose of vincristine. Please refer to Appendix __ for a list of inhibitors and inducers of CYP3A4.

8.0 STUDY EVALUATIONS

CSF and bone marrow evaluations should be no more than 14 days prior to starting therapy. All other evaluations should take place within 72 hours of the specified time listed in the table below.

Evaluation	Pre-Study	During Therapy	End of Therapy
History	X	Weekly	
Physical Exam	X	Weekly	
Vital Signs including Pulse Oximetry	X	Weekly	
Toxicity Assessments		Weekly	X
SAE Assessments		Weekly	X
Height and Weight	X		X
Performance Status	X		X
CBC with differential	X	Twice weekly	X
Electrolytes (Na, K, glucose, Ca, PO_4)	X	Daily for minimum 3 days, then weekly	X
Uric Acid	X	Daily for minimum 3 days, then weekly	
Creatinine, ALT, Bilirubin	X	Weekly	X
PT, PTT, Fibrinogen	X		
Bone Marrow Aspirate	X		X[1]
Bone Marrow for MRD	X		X[1]
CSF with cell count and cytospin	X	Day 8[5]	
Pregnancy Test[2]	X		
Chest X-ray (2 views)	X		

ECHO/EKG	X		X
CT chest, abdomen and pelvis[3]	X		X
PET scan[4]	X		X

[1] End of Therapy bone marrow evaluation should take place after recovery of blood counts no later than Day 36. If bone marrow is still not recovered (ANC >500) or evidence of leukemia, then follow-up bone marrows should be done every 1-2 weeks.
[2]Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
[3]CT scan only for patients with lymphoma or leukemia patients with extramedullary disease seen on prior scans
[4]PET scan is optional for lymphoma patients, not required for ALL patients
[5]For patients receiving additional IT doses, CSF and cytospin should be performed with each dose

9.0 STATISTICAL CONSIDERATIONS

This is intended as a pilot study to determine the safety and efficacy of the combination of bortezomib with reinduction therapy based on the UK ALL R3 protocol for pediatric relapsed or refractory ALL or LL. There is no control group and no plan to increase or decrease doses of any medications. The goal is to recruit a minimum of 10 patients over a 24 month period to appropriately describe the effects of therapy on patients and resistant leukemia or lymphoma.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

Toxicities occurring during the study period will be reported based on the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE version 4.0 can be found on the CTEP website (http://Ctep.cancer.gov).

10.2 Response Criteria for Patients with Acute Lymphoblastic Leukemia

10.2.1 Complete Remission (CR)

Attainment of an M1 bone marrow (<5% blasts in the bone marrow aspirate or biopsy if aspirate not available) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral counts (absolute neutrophil count (ANC) ≥ 500/μL and platelet count ≥ 50.000/μL)

10.2.2 Complete Remission with Partial Recovery of Platelet Count (CRp)

Attainment of an M1 bone marrow (<5% blasts) with no evidence of circulating blasts or extramedullary disease, but without recovery of ANC or platelet count by day 43 as specified in CR.

10.2.3 Partial Remission (PR)
Complete disappearance of circulating blasts and achievement of M2 marrow status (≥ 5% or < 25% blasts in the bone marrow aspirate or biopsy if aspirate not available). Attainment of a bone marrow CR (above) with proven persistence of extramedullary disease qualifies as a PR.

10.2.4 Progressive Disease (PD)
An increase in the percentage of blasts in either the peripheral blood or bone marrow of >25%

10.2.5 Stable Disease (SD)
This is present when the patient fails to qualify for a CR, PR or PD.

10.3 Response Criteria for Patients with Lymphoblastic Lymphoma

10.3.1 Measurable Disease
Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter) as ≥10 mm by CT scan or ≥10 mm with calipers by clinical exam.

10.3.2 Malignant Lymph Nodes
To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

10.3.3 Non-Measurable Disease
All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, and pleural/pericardial effusions are considered as non-measurable.

10.3.4 Target Lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the

diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

10.3.5 Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

10.4.1 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

10.4.2 Conventional CT and MRI

The same imaging modality should be used to monitor all disease sites for follow-up.

10.4.3 FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not

confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.5 Methods for Evaluation of Measurable Disease

10.5.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis t <10 mm. If immunocytology is available, no disease must be detected by that methodology.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of the target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify for PD.

10.5.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Partial Response (PR):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

11.0 ADVERSE EVENTS

11.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

11.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.

* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

11.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- Is a congenital anomaly/birth defect.

- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations

11.4 Procedures for Reporting Serious Adverse Events

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Adverse Events which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of bortezomib up to and including 30 days after administration of the last dose of bortezomib. Any SAE that occurs at any time after completion of bortezomib

treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

Since this is an investigator-initiated study, the principal investigator Keith August, MD also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance or designee:

> Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event.

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event.

The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- Causality of the event(s): Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium Pharmacovigilance (or designee).

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating

in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: takedaoncocases@cognizant.com

Suggested Reporting Form:

- SAE Report Form (a sample will be provided)
- US FDA MedWatch 3500A:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

- Any other form deemed appropriate by the sponsor-investigator

Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to Millennium Pharmacovigilance or designee (see Section 11.4). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Millennium Pharmacovigilance or designee will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to Millennium Pharmacovigilance or designee (see Section 11.4). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

Pregnancy Report Form (a sample will be provided)

Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product.

Individuals who identify a potential product complaint situation should immediately contact Millennium (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact Millennium (see below) and report the event

For Product Complaints or Medication Errors

- Phone: 1-866-VELCADE (1-866-835-2233)
- E-mail: medical@mlnm.com
- FAX: 1-800-881-6092
- Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 11.4).

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Karnofsky (≥17 years old)		**Lansky (≤16 years old)**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: LIST OF STRONG AND CLINICALLY RELEVENT MODERATE CYP3A4 INDUCERS AND INHIBITORS

Strong CYP3A4 Inducers:	
Generic Name	*Common Trade Name*
Carbamazepine	Tegretol
Phenobarbital	Luminal
Phenytoin	Dilantin
Rifampin	Rifadin
St. John's Wart	N/A
Systemic dexamethasone	Decadron
Strong* and Clinically Relevant Moderate CYP3A4 Inhibitors:	
Generic Name	*Common Trade Name*
Aprepitant	Emend
Clarithromycin*	Biaxin
Erythromycin	Eryc, EryPed
Fluconazole	Diflucan
Grapefruit and its juice	N/A
Itraconazole*	Sporanox
Ketoconazole*	Nizoral
Voriconazole	VFend

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