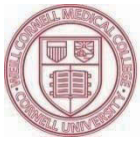

Weill Cornell Medical College

Amendment #6.1, Version: October 26, 2015
IRB Number: 1005011049

TITLE: A Prospective Randomized Trial Comparing Three Different Peripheral Stem Cell Mobilization Regimens in Patients with Symptomatic Multiple Myeloma or Lymphoma

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*VELCADE is the exclusive trademark of Millennium Pharmaceuticals, Inc., registered in the United States and internationally.

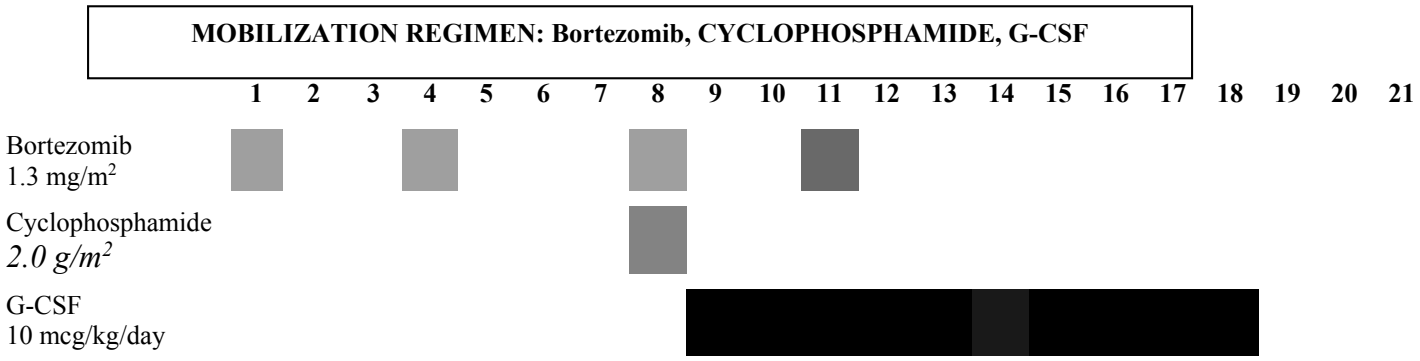
[redacted]

Amendment History:

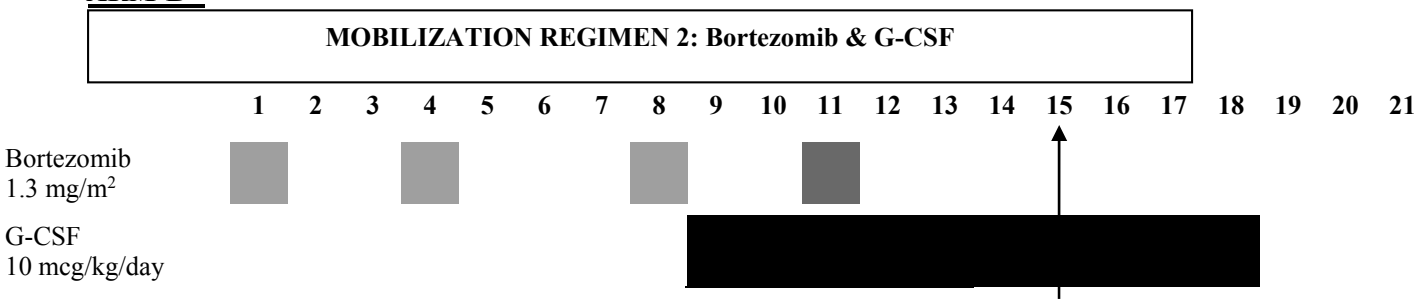
Original Protocol Date: July 8, 2010
Amendment #1: December 20, 2010
Amendment #2: March 28, 2011
Amendment #3 : March 12, 2012
Amendment #4 : February 15, 2013
Amendment #5 : May 31, 2014
Amendment #6 : July 22, 2015
Amendment #6.1 : October 26, 2015

TREATMENT SCHEMA

ARM A

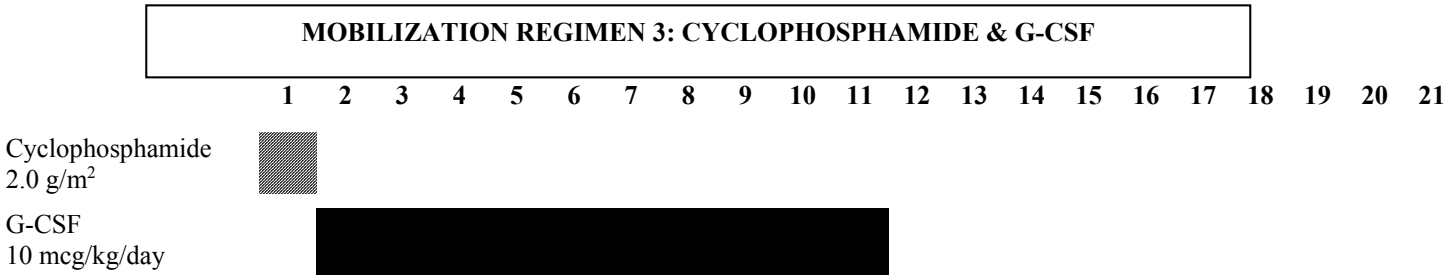


ARM B*



Start apheresis – Day 15 (or when wbc > 50K/µl, whichever occurs first)

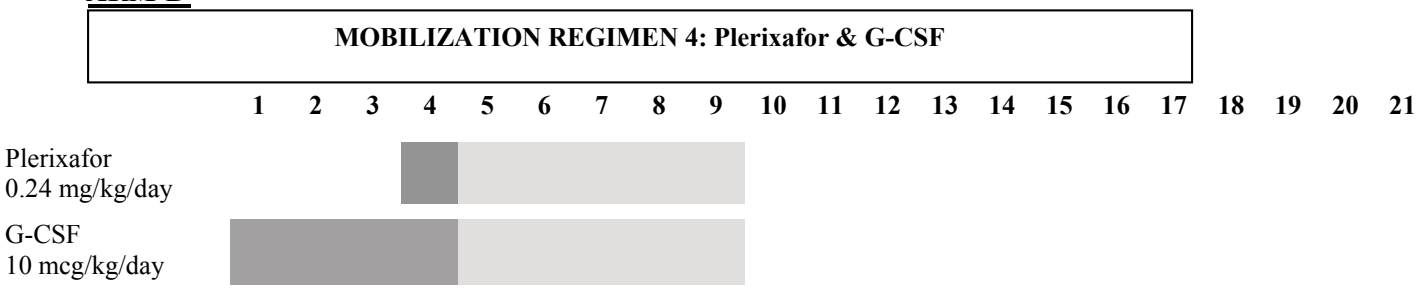
ARM C*



*Effective January 16, 2013, Arm B is closed to further accrual.

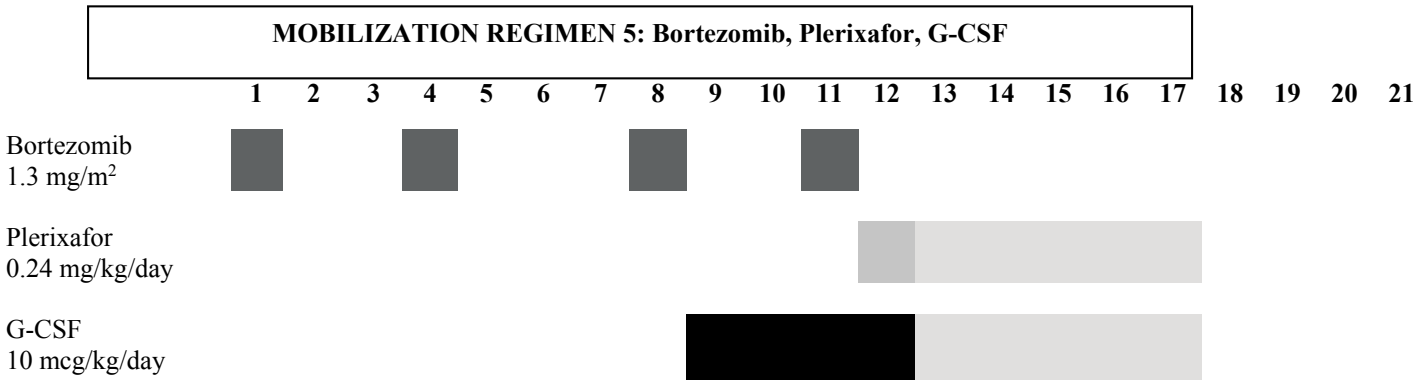
**Effective July 9, 2015, Arm C is closed to further accrual.

ARM D



Start apheresis – Day 5; continue G-CSF and plerixafor daily until stem cell harvest is complete.

ARM E



Start apheresis – Day 13; continue G-CSF and plerixafor daily until stem cell harvest is complete.

TABLE OF CONTENTS

1. OBJECTIVES

1.1. Study Objectives

PRIMARY STUDY OBJECTIVES

- To compare the efficacy of the following peripheral stem cell mobilization regimens for Multiple Myeloma (MM):
    A. High dose cyclophosphamide, Bortezomib, and G-CSF
    B. Bortezomib and G-CSF
    C. High dose cyclophosphamide and G-CSF
    D. Plerixafor and G-CSF
    E. Bortezomib, plerixafor, and G-CSF

SECONDARY STUDY OBJECTIVES

- To evaluate biomarkers as surrogate markers of mobilization in each arm.
- To evaluate changes in tumor mass as defined by standard response parameters.
- To evaluate the safety of each of the arms.

EXPLORATORY OBJECTIVE

- To attempt to establish the predictive value and correlation of Hematopoietic Progenitor Cells (HPC) and Absolute Neutrophil Count (ANC) in each arm. This objective is only applicable to Weill Cornell Medical College as sub-sites will not participate in the correlative studies.

This is a phase III, randomized trial comparing three different peripheral stem cell mobilization regimens for patients with multiple myeloma who have received primary induction therapy. Effective January 16, 2013, Arm B is closed to further accrual due to futility. Effective July 9, 2015, Arm C is closed to further accrual due to futility.

1.2 Study Endpoints

PRIMARY STUDY ENDPOINTS

- Percentage of patients able to collect >6 x 10^6 CD34+ cells/kg in $\leq$ 2 collections.

SECONDARDY STUDY ENDPOINTS

- Engrafting: Neutrophil recovery (ANC >0.5 in $\leq$20 days), Platelet recovery (>20K untransfused $\leq$20 days) after melphalan 200 based transplant.
- Toxicities

2. BACKGROUND

2.1 Disease

Multiple Myeloma (MM) is a neoplastic disorder of unknown etiology characterized by an abnormal accumulation and proliferation of monoclonal plasma cells producing excess quantities of a single immunoglobulin protein isotype (M-protein). It is estimated that 14,000 new cases of myeloma are diagnosed in the US each year[1] accounting for approximately 1% of all cancers, and 10-15% of all hematological malignancies[2]. The disease is twice as common in blacks as whites[3]. MM usually occurs in older individuals with a median age of 69 years old.

Lymphoma, neoplasm originating from lymphoid tissue, has many different subtypes corresponding to the complexity of the human immune system. Prognosis and growth rate vary widely, but all lymphomas are characterized by exquisite sensitivity to chemotherapy. High dose chemotherapy with stem cell support is standard of care for patients with recurrent lymphoma and, depending on the subtype and chemotherapy sensitivity, can result in cure or in prolonged remission.

2.2 Prognosis of myeloma

The overall median survival for patients with MM is 36 months, with stage I, II, and III patients surviving a median of >60, 41, and 23 months respectively[4]. Several prognostic factors have been identified. An elevated serum level of beta-2 microglobulin (ß$_2$M), a component of the class I HLA molecule, is a powerful prognostic indicator of shortened survival[5]. ß$_2$M is excreted by the kidney and renal insufficiency will increase serum levels of ß2M. The plasma cell labeling index (PCLI) identifies the percentage of proliferating plasma cells in S-phase of the cell cycle and is a powerful independent predictor of progression and survival[6]. An elevated serum lactate dehydrogenase (LDH) predicts an aggressive course with lymphoma-like features[7]. Translocations such as t(4,14) and t(14,16) confer poor prognosis[8]. Investigators have found that achieving a complete remission early in the disease may be important in predicting long-term survival[9,10]. Indeed, Kyle et al suggested that an objective response to standard therapy is by far the most important feature of long-term survivors[11]. Major controlled trials have confirmed this seminal observation even in the context on high-dose chemotherapy[12]. Based on those observations, the goal of achieving an early CR should allow patients to sustain long-term survival and perhaps lead to a cure.

2.3 Rationale

2.3.1 Treatment: Stem Cell Transplant and Mobilization

Though more targeted and effective therapies have been evolving over the last 10 years, multiple myeloma (MM) remains incurable[13],[14]. For newly diagnosed patients, treatment with high dose chemotherapy and stem cell transplantation (PBSCT) has extended median survival from 3 to 5-7 years and has thus emerged as the standard of care. Most groups agree that for PBSCT candidates, those patients who are young enough and fit enough to endure the rigorous therapy, initial therapy is based on a two-phase treatment approach. Typically this consists of induction

therapy and consolidation therapy with high-dose melphalan and subsequent PBSC rescue. When this two-phase model was pioneered, most transplant candidates received dexamethasone (Dex) based regimens. [15] However, PBSC harvests are not always successful and still are associated with significant morbidity[16]. Typical regimens for stem cell collection in MM include G-CSF alone or in combination with high dose cyclophosphamide. Though a "successful" harvest usually describes a CD34+ yield of 2-5 x 10^6 cells/kg, the newer evidence for the efficacy of double autologous transplant would necessitate CD34+ collections closer to 10 million cells. Thus there is both room and need to optimize the transplant process, specifically in terms of PBSC mobilization and collection. For transplant candidates, initial therapies must be tailored with the transplant end goal in mind, as it seems that they will affect the success and robustness of stem cell harvest and subsequent re-infusion. Induction regimens, therefore, cannot include stem cell toxic drugs such as alkylators like nitrosureas and melphalan, which are known to hinder the success of PBSC harvests[17]. Most recently, the newest immunomodulatory drug, lenalidomide, has come under scrutiny as well. Lenalidomide treated patients suffer of poor mobilization and their collection is substantially reduced[18]. We and others have noted that the addition of cyclophosphamide to GCSF will overcome the inhibitory effect of lenalidomide. [19] The routine use of cyclophosphamide however is often complicated by neutropenia and sepsis requiring hospitalizations, hence, delaying the transplant and causing significant increase in morbimortality and costs.

Recently a new molecule, plerixafor (Mozobil™, Genzyme Corp.) a CXCR4 inhibitor has been FDA approved for use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin lymphoma (NHL) and MM who fail prior mobilization attempts or who are at high risk of failure.

The efficacy and safety of plerixafor in combination with G-CSF in NHL and MM were evaluated in two placebo-controlled studies. Patients were randomized to receive either plerixafor 0.24 mg/kg or placebo each evening prior to apheresis. All patients received G-CSF 10 micrograms/kg daily for four days prior to the first dose of plerixafor or placebo and prior to apheresis. Results from 302 patients with MM were analyzed.

In the MM study, only 72 percent of patients who were mobilized with plerixafor and G-CSF collected ≥ 6 X 10^6 CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions compared with 34 percent of patients who were mobilized with placebo and G-CSF ($p < 0.001$).). Of note only about 54% of pts reached target CD34+ collection after 1 pheresis, 78% after 2 pheresis sessions, 87% after 3 and 4 pheresis sessions, suggesting a plateau effect) [20].

Safety data for plerixafor in combination with G-CSF were obtained from 983 patients enrolled in 16 clinical studies (593 patients enrolled in randomized Studies 1 and 2 plus 410 patients enrolled in 14 additional non-randomized studies). Patients were primarily treated with plerixafor at daily doses of 0.24 mg/kg SC. Median exposure to plerixafor was two days (range one to seven days).

The most common adverse reactions ($\geq$ 10 percent) reported in patients who received plerixafor in conjunction with G-CSF that were more frequent than in patients who received placebo were diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness and vomiting.

Prescribing physicians and patients should be aware of the potential for tumor cell mobilization in leukemia patients, increased circulating leukocytes and decreased platelet counts, splenic enlargement, and fetal harm when administered to pregnant women. Plerixafor has a cumbersome dosing schedule: GCSF is given for 4 days prior to the first dose of plerixafor then on each morning of apheresis. Plerixafor is administered in the evening starting on day 5. Plerixafor should be given approx. 11 hours prior to the initiation of apheresis for up to 4 consecutive days. Dose modifications are required for renal impairment. Pts with a Cr CL $\leq$ 50 ml/min should have their plerixafor dose reduced by 1/3 to 0.16mg/kg not to exceed 27mg/day[21].

2.3.2 **Treatment: Response and Outcomes**

A substantial body of data suggests that patients fare better if meaningful responses are achieved during therapy. Such evidence makes a case for the use of agents known to achieve an effective cell kill during stem cell mobilization and harvest, even if patients have just been subjected to a substantial amount of anti-myeloma therapy. Recent studies, such as the French IFM 94 and U.S TT1,2,3 trials suggest that a double rather than single autologous transplant correlates with longer progression free and overall survival. In consideration of some of these newer developments, the importance of a robust PBSC collection has become increasingly evident[22].[23]

2.4 **Working Hypothesis**

Given the known in vitro and in vivo synergy between alkylating agents and proteasome inhibitors, we sought to optimize the potential for concurrent cytoreduction by adding bortezomib to a standard cyclophosphamide mobilization regimen. This pilot study, included 22 evaluable patients, whose prior therapy consisted of six cycles of chemotherapy were mobilized. Patients received IV push bortezomib at 1.3 mg/m^2 on days 1, 4, 8, and 11 in combination with high-dose cyclophosphamide at 3 g/m^2 on day 8. G-CSF was given for 10 consecutive days starting on day 9.

2.5 **Preliminary Findings (See Table Below)**

The number of CD34+ cells collected far exceeded the study goal of 10x10^6 cells/kg, a collection result typical of standard mobilizations using cyclophosphamide and/or G-CSF alone. Twenty-two (100%) patients had more than adequate collections in a single day. Median CD34+ collection was 21x10^6 cells/kg in 1-5 collection days (range of 9.3-294.2 x 10^6). Mobilization with this regimen was not only robust but the mobilization window was highly predictable, eliminating the need for guess work in collection timing; furthermore, the amount of collection days was limited to only one day in the great majority of patients, thus suggesting that this regimen will allow efficient planning of pheresis sessions and will reduce the number of pheresis needed, ultimately reducing costs. Noteworthy is that all patients who began mobilization with less than a CR continued to respond positively to treatment, including one transition from nCR to CR and one from SD to PR. No patients progressed or moved to lower response categories. This suggests that this is the only regimen which contributes to tumor mass reduction, thus, improving ultimately outcomes. So far 20 patients were able to high dose melphalan supported by autologous stem cell transplantation post protocol mobilization. All showed typical and adequate

engraftment after CD34+ infusions. The median number of days to ANC recovery was 11 days (range 10-17). Platelet recovery median 18 days (range 13-24) [24].

Patient	Days Required for Collection	Days to collection	CD34+ Stem Cells (million/kg)	Stem Cells Infused (x10^6/kg)	Viability	Day of neutrophil engraftment	Day of platelet engraftment
1	1	18	21.2	5.778	85%	14	20
2	1	18	47.4	13.22	80%	11	13
3	1	19	22	9.87	60%	13	22
4	1	18	17.9	9.03	90%	10	15
5	4	19	40.6	5.44	97%	11	21
6	1	18	19.9	9.24	94%	10	16
7	3	19	294.157	17.73	91%	10	17
8	2	17	13.8	6.32	80%	13	24
9	5	18	9.25	4.25, 2.74	80%, 94%	11	18
10	2	17	21.4	9.05	93%	16	21
11	1	24	50.033	no transplant	no transplant		
12	2	19	66.149	12.83	85%	11	11
13	1	18	30.377	7.38	93%	11	11
14	2	16	43.637	10.02	92%	12	15
15	1	19	50.984	12.72	87%	13	11
16	1	17	15.584	5.31	93%	11	13
17	1	17	6.794	6.66	92%	12	13
18	1	17	31.668	9.2	95%	11	20
19	1	17	7.769	7.397	92%	10	11
20	1	16	43.89	11.06	98%	10	21
21	1	18	23.22	no transplant	no transplant		
22	1	17	13.996	3.47	90%	16	16

Early data from work in mouse models indicates that bortezomib may have a mobilization effect through effects on SDF-1 where as CXCR4 is the target for plerixafor. Data in mouse models shows the combination of G-CSF + Bortezomib is significantly better than either agent alone in terms of increasing the white blood count (WBC), colony-forming unit – granulocyte/macrophage (CFU-GM), and colony-forming unit – erythroid (CFU-E). The combination appears to be additive[26] . We can therefore conclude that the use of bortezomib for mobilization may offer a less cumbersome, safer and effective regimen.

2.6 **Conclusions**

Bortezomib in addition to high-dose cyclophosphamide (Cytoxan) followed by G-CSF is a novel, well-tolerated and efficacious combination for stem cell mobilization in patients with multiple myeloma (MM). This regimen not only yields a high number of stem cells within a short collection time, but also provides the potential for further cytoreduction. Of particular

importance is that this regimen overcomes any inhibitory effect of lenalidomide, which is the most common induction regimen in MM. Our objectives, therefore, are to critically test this new mobilization regimen against standard of care (Cyclophosphamide and G-CSF) and a control group of Bortezomib and G-CSF in a prospective, randomized fashion. This trial is of particular interest given the following issues:

1) Consistency in number of collections required and predictability of the timing in stem cell collection when bortezomib is used.
2) Potential benefit on engraftment and co-morbidities when a higher than average number of stem cell are infused
3) Advantage of mega-mobilization in order to adequately cryopreserve for future use (in the relapse setting)
4) Potential benefit in lenalidomide treated patients and high risk patients
5) New biological insights in stem cell biology
6) If this trial shows that bortezomib/GCSF is as good as cyclophosphamide/GCSF could potentially eliminate chemotherapy as mobilizing agent. (Less toxicity in terms of myelosupression, renal/kidneys etc.)
7) Not all patients with MM successfully collect with plerixafor and G-CSF alone. This trial may show that adding bortezomib to plerixafor and G-CSF increases the chances of a successful collection.

Bortezomib, a recently approved 26S proteasome inhibitor, appears to be effective even in patients with poor prognostic features for transplant such as del 13q14 and has been shown to be non-stem cell toxic. Our objective is to achieve maximum response before transplant as well as a successful mobilization and harvest of PBSCs, which we defined as at least 10 x 106 CD34+ cells/kg in under 2 leukapheresis procedures.

Bortezomib also has activity in lymphoma and its use in stem cell mobilization may also be useful in this disorder.

Use of Peripheral Blood CD34 counts as a measure of stem cell mobilization and collection. The yield of a stem cell collection is determined by the peripheral blood CD34, the volume of collection and to a lesser degree by a number of other factors such as the instrument utilized for collection, the hematocrit, WBC and even serum albumin (see for example Hosing 2013, Ford 1998, Hollingsworth 1999). The peripheral blood CD34 on the first day of collection is the best measure of "mobilizing" efficiency and is widely utilized (Hosing 2013) and will be the primary outcome measure for this study.

3. INVESTIGATIONAL AGENTS

3.1 VELCADE® (bortezomib) for Injection

3.1.1 Scientific Background

VELCADE® (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) and it is registered in Europe for the treatment of multiple myeloma patients who have received at least one prior therapy.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic 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 (Adams et al., 1999). 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 (Steiner et al., 2001; Teicher et al., 1999; Cusack et al., 2001; LeBlanc et al., 2002; Pink et al., 2002). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey et al., 1999).

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 (Hideshima et al., 2001).

3.1.2 **Nonclinical Pharmacology**

Pharmacokinetic (PK) and pharmacodynamic studies were conducted in the rat and cynomolgus monkey. Upon intravenous (IV) bolus administration, bortezomib displays a rapid distribution phase ($t_{1/2}\alpha$ <10 minutes) followed by a longer elimination phase ($t_{1/2}\beta$ 5–15 hours). Bortezomib has a large volume of distribution (range 5–50 L/kg). The plasma PK profile is well described by a 2-compartment model.

The pharmacodynamic action of bortezomib is well established and can be measured through an ex vivo assay (20S proteasome activity) (Lightcap et al., 2000). This assay was used to determine the duration of drug effect in lieu of the PK data in the early preclinical toxicology studies as well as to set a guide for dose escalation in humans. Following dosing with bortezomib in the rat and cynomolgus monkey, proteasome inhibition in peripheral blood had a half-life less than 24 hours, with proteasome activity returning to pretreatment baseline within 24 hours in monkey and within 48 to 72 hours in rat after a single dose of bortezomib. Further, intermittent but high inhibition (>70%) of proteasome activity was better tolerated than sustained inhibition. Thus, a twice-weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations.

3.1.3 **Nonclinical Toxicity**

Single-dose IV toxicity studies were conducted with bortezomib in the mouse, rat, dog, and monkey to establish the single-dose maximum tolerated dose (MTD). The MTDs were 0.25

mg/kg (1.5 mg/m^2) and 0.067 mg/kg (0.8 mg/m^2) in the 2 most sensitive species, rat and monkey, respectively.

Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic toxicity of bortezomib when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.10 mg/kg (0.6 mg/m^2) and the key target organs were the gastrointestinal (GI) tract, hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m^2) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date.

In general, the nature of the toxicity of bortezomib is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of bortezomib in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD. The cause of death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of bortezomib on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.

Additional detailed information regarding the nonclinical pharmacology and toxicology of bortezomib may be found in the Investigator's Brochure.

3.1.4 **Clinical Experience**

It is estimated that more than 100,000 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 I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 2002). 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, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.

The safety and efficacy of bortezomib in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) (Jagannath et al, 2004) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy) (Richardson et al, 2003). In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma 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, (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. 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) (Richardson et al, 2005), 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 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight 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 three 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 four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) 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<.0001). CR (complete response) + PR (partial response) was 38% with bortezomib vs. 18% with dexamethasone (P<.0001). CR was 6% with bortezomib vs. <1% with dexamethasone (P<.0001). The CR + nCR rate was13% with bortezomib vs. 2% with dexamethasone. In patients who had received only one prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs. 26% with dexamethasone (P=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (P=.0013) for patients on the bortezomib arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (P=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (P=.0098). Updated response rates and survival data were reported for M34101-039 (Richardson ASH, 2005). The updated CR (complete response) + PR (partial response) 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

vs. 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 one year was 80% for the bortezomib arm vs. 67% for the dexamethasone arm (*P*=0.0002).

Studies using **bortezomib** as monotherapy and in combination with other chemotherapy agents are continuing.

3.2 High-dose Cyclophosphamide (CYTOXAN)

3.2.1 Scientific Background

Cyclophosphamide is an alkylating agent that prevents cell division primarily by cross-linking DNA strands. The cell continues to synthesize other cell constituents (RNA and protein), an imbalance occurs and the cell dies. Cyclophosphamide is considered cell cycle phase non-specific. Cyclophosphamide is bio-transformed principally in the liver to active alkylating metabolites that cross-link to tumor-cell DNA.

3.3 G-CSF (NEUPOGEN)

3.3.1 Scientific Background

NEUPOGEN is the trademark name for G-CSF also known as Filgrastim, a human granulocyte colony-stimulating factor. It is a 175 amino acid protein manufactured by recombinant DNA technology. NEUPOGEN is produced by *Escherichia coli* (E. coli) bacteria into which has been inserted the human granulocyte colony-stimulating factor gene.

Colony stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. NEUPOGEN regulates the production of neutrophils from the bone marrow. NEUPOGEN® is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care.
NEUPOGEN® is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing Filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by a cell mitogenesis assay). The product is available in single use vials and prefilled syringes. [25]

3.4 Plerixafor

Plerixafor (Mozobil), a hematopoietic stem cel1 mobilizer, is indicated in combination with grulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma. Plerixafor acts by inhibiting the interaction

between SDF-1 (stem cell derived factor 1) and CXCR4 (chemokine receptor type 4) which abrogates the main force binding CD34 cells to the bone marrow stroma. Plerixafor has been shown to enhance stem cell harvest yield when used in combination with G-CSF as opposed to G-CSF alone in patients with non-Hodgkin lymphoma and multiple myeloma.[11]

4. PATIENT SELECTION

4.1 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be eligible to participate in this study:

- Subject has voluntarily agreed to participate by giving 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. Informed Consent must be obtained prior to mobilization.
- Subject has a confirmed diagnosis of multiple myeloma as specified by the International Myeloma Working Group criteria, detailed in Appendix G or subject has a diagnosis of lymphoma and is in need of stem cell transplant.
- Subject is ≥ 18 years of age at the time of signing the informed consent form.
- Subject has a Karnofsky performance status above 60%.
- Subjects must have measurable monoclonal protein, free light chains, and/or M-spike in blood or urine and/or measurable disease by imaging techniques such as MRI and PET scan.
- Female subject is either post-menopausal for at least 1 year before screening visit, is surgically sterilized 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.
- Male subject, even if surgically sterilized (i.e., status post vasectomy) 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.
- Subject has a life expectancy of > 12 weeks.
- Subject must meet the following laboratory parameters within 14 days before enrollment:
    - Absolute neutrophil count (ANC) ≥1500 cells/mm^3 (≥1000 for patients with bone marrow biopsy displaying ≥50% involvement by myeloma). In study centers that have the equipment capability, ANC > 1.0 will not be the benchmark to start stem cell collection. *A minimum requirement of ≥ 20 x 10^6 $CD34^+$ cells/ml will be required to start stem cell collection.*
    - Platelets count ≥ 50,000/mm^3 (≥ 30,000 for patients with bone marrow biopsy displaying ≥50% involvement by myeloma)

- Hemoglobin > 9.0 g/dL
- Serum SGOT/AST <3.0 x upper limits of normal (ULN)
- Serum SGPT/ALT <3.0 x upper limits of normal (ULN)
- Serum creatinine ≤ 2.5 mg/dL or creatinine clearance > 40ml/min
- Serum total bilirubin < 1.5 x ULN

- Subject must have a MUGA scan or echo with LVEF ≥50% within 6 months of enrollment.

4.2 **Exclusion Criteria**

Subjects meeting any of the following exclusion criteria are not eligible to participate in this study.

- Subject has a history of allergic reactions to compounds containing boron, mannitol, or VELCADE
- Subject has a prior history of other malignancies (except for basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix or breast) unless disease free for ≥ 5 years.
- Subject has a NYHA Class III or IV heart disease and/or a history of active unstable angina, congestive heart disease, severe uncontrolled cardiac arrhythmia, electrocardiographic evidence of acute ischemia, active conduction system abnormalities or myocardial infarction within 6 months prior to enrollment. Prior to study entry, any ECG abnormality at Screening has to be documented by the investigator as not medically relevant.
- Female subjects who are pregnant or breastfeeding. Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
- Subject has a known HIV or hepatitis A, B, or C positivity---ONLY IF ACTIVE
- Subject has active viral or bacterial infections or any coexisting medical problem that would significantly increase the risks of this treatment program.
- Subject has concurrent, uncontrolled medical condition, laboratory abnormality, or psychiatric illness which could place him/her at unacceptable risk, including, but not limited to, uncontrolled hypertension, uncontrolled diabetes, active uncontrolled infection, and/or acute chronic liver disease (i.e., hepatitis, cirrhosis).
- Subject has ≥Grade 2 peripheral neuropathy.
- Subject has participated 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 participation in this trial.
- Subject has been diagnosed or treated for another malignancy within 3 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.

- Subject has received 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.
- Subject has had prior mobilization or stem cell transplant.

5. REGISTRATION PROCEDURES

5.1 Central Patient Registration

Patients will be centrally randomized and registered with the Weill Cornell Medical College (WCMC), Division of Hematology and Medical Oncology, Joint Clinical Trials Office. To register a patient, email the following documents to Christina Persaud at cpp2005@med.cornell.edu. You may also fax the documents to the Clinical Trials Office at 646-962-1610:

- WCMC Patient Enrollment Form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes are required.
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers requested
- For inpatients, signed consent documentation template

Central registration information is reviewed and entered into the HemOnc centralized research database. For patients enrolled at Weill Cornell Medical College, documentation of patient registration will be faxed to the Investigational Pharmacy to allow for release of study agent. All participating sub-sites will notify their pharmacy for release of study drug as per institutional guidelines.

6. TREATMENT PLAN

6.1 Study Design

This phase III, randomized trial compares three different peripheral stem cell mobilization regimens for patients with multiple myeloma who have received primary induction therapy rev or other therapies. Up to 198 patients will be enrolled. Effective January 16, 2013, Arm B is closed to further enrollment due to futility. Effective July 9, 2015, Arm C is closed to further enrollment due to futility. Patients eligible for treatment will be randomized to one of the following mobilization regimens:

A. Arm A:

Bortezomib at 1.3 mg/m^2 IVP on days 1, 4, 8 and 11 in combination with high-dose cyclophosphamide at 2.0 g/m^2 on day 8. G-CSF is given for ten (+/- two) consecutive days starting on day 9 at a dose of 10 micrograms/kg/day. Pheresis will commence once absolute neutrophil count (ANC) of 1.0 is reached*.

B. Arm B: **This Arm is closed to further accrual.**

Bortezomib at 1.3 mg/m^2 IVP on days 1, 4, 8 and 11. G-CSF is started on day 9 at a dose of 10 micrograms/kg/day. Pheresis collection is started on Day 15 or whenever the total white blood cell count is > 50,000 / μl, whichever occurs first*. G-CSF is continued until pheresis goal has been met.

C. Arm C: **This Arm is closed to further accrual.**

High-dose cyclophosphamide at 2.0 g/m^2 on day 1. G-CSF is given for ten (+/- two) consecutive days starting on day 2 at a dose of 10 micrograms/kg/day. Pheresis will commence once ANC of 1.0 is reached*.

D. Arm D:

G-CSF is given for ten (+/- two) consecutive days starting on day 1 at a dose of 10 micrograms/kg/day. Plerixafor is given on day 4, approximately 11 hours prior to stem cell collection attempt on Day 5. Both G-CSF and plerixafor are continued daily until collection is complete. Pheresis will commence for everyone on Day 5 regardless of ANC status.

D. Arm E:

Bortezomib at 1.3 mg/m^2 IVP on days 1, 4, 8 and 11. G-CSF is given for ten (+/- two) consecutive days starting on day 9 at a dose of 10 micrograms/kg/day. Plerixafor is given on day 12, approximately 11 hours prior to stem cell collection attempt and is continued daily until collection is complete. Pheresis will commence for everyone on Day 13 regardless of ANC status.

The decision to collect is at the discretion of the primary physician/ Principal Investigator.

* In study centers that have the equipment capability, ANC > 1.0 will not be the benchmark to start collection. Instead, peripheral blood $CD34^+$ cells/ ml will be determined by flow cytometry on a subject's blood sample on each morning of proposed collection and will be the primary determinant of whether stem cell collection is attempted for the day. A minimum requirement of $\geq 20 \times 10^6$ $CD34^+$ cells/ml will be required to start stem cell collection. If the subject fails to reach this benchmark, stem cell collection for the day will be aborted for futility and the patient will return the next day for reevaluation. If the subject fails to achieve an adequate peripheral blood $CD34^+$ cell count after 14 days of G-CSF on Arms A and C, or 10 days of G-CSF on Arm B, D and E, the collection attempt will be deemed a failure and the patient will be taken off study. HPC analysis will not be used to determine eligibility to start stem cell collection. In study centers without ready access to flow cytometry analysis of CD34+ cell content of peripheral blood, ANC will be the sole marker to start stem cell collection.

6.2 **Stopping Rules**

Stopping rules will be implemented once 10 patients are accrued in each arm and the rule will not allow more than 4 failures in the 10 accrued patients per arm. Failure is defined as: If > 40%

of patients fail to collect the target CD34+ cells in two or less collections in any arm, then the arm will be terminated.

Due to futility, Arm B is closed to further accrual effective January 16, 2013. Arm C is closed to further accrual effective July 9, 2015. For arms A and C, three out of four subjects randomized to mobilize sufficiently. Accrual will continue on Arms A and D and E as planned.

After 10 patients are evaluated in each arm we are going to attempt to establish the predictive value and correlation of HPC and ANC in each arm. We will later use that data to better define the optimal time for commencing leukapheresis.

6.3 **Risks of Insufficient Stem Cell Collection**

The risk of insufficient stem cell collection is a risk associated with any mobilization program. Usually a patient who fails to mobilize with one strategy will succeed at a second attempt by adding a medication called Mozobil (plerixafor). Failure to mobilize stem cells successfully will preclude the performance of an autologous stem cell transplant. In this protocol, patients who fail any of the three mobilization arms will be offered standard of care mobilization plerixafor.

6.4 **Concomitant Treatment**

6.4.1 Required Concurrent Therapy

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

Mesna may be given at the discretion of the study doctor as per institutional guidelines.

The following medications/supportive therapies are required during study participation, as applicable:

- Antiviral agent

6.4.2 Prohibited Concurrent Therapy

- 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.

Treatment Compliance

All drug will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(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 D), and total drug administered in milliliters and milligrams. 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) Hormonal contraceptives (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Latex condom 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 (i.e., status post vasectomy) 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.

6.5 **Duration of Therapy and Criteria for Removal from Study**

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw, and in some cases is required to withdraw, patients from the study for any of the following reasons:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Occurrence of unacceptable adverse event(s),
- Suspected or confirmed pregnancy,

- The patient achieves a stable plateau and is eligible to proceed to high dose chemotherapy and stem cell transplantation,
- The development of any co-morbid condition or excessive toxicity that would make further participation in the protocol unsafe,
- Protocol violations,
- Non-compliance,
- Administrative reasons,
- Failure to return for follow-up,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

At the time of study withdrawal or completion of the study, all study procedures outlined for the End of Treatment visit must be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

The duration of the study includes a 21-day treatment schedule, an end of study visit, and a specified period time for survival follow up.

6.6 **Duration of Follow Up**

Patients who do not withdraw consent will be followed for survival after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed for life, unless they withdraw consent.

7. DOSING DELAYS/DOSE MODIFICATIONS

Patients will be evaluated for toxicity throughout treatment. Doses of study medications will be held for neuropathy toxicity Grade ≥ 2 with pain.

Dose escalation will not be allowed in any patient, and there must be at least 72 hours between each dose of bortezomib.

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

All previously established or new toxicities observed any time, with the exception of neuropathic pain and peripheral sensory neuropathy, are to be managed as follows:

- If the patient experiences febrile neutropenia, a Grade 4 hematologic toxicity (including a platelet count $<25 \times 10^9$/L) or any ≥Grade 3 non-hematologic toxicity considered by the investigator to be related to bortezomib, then drug is to be held.
- For hematologic toxicities, bortezomib is to be held for up to 2 weeks until the patient has a hemoglobin value of > 9.0 g/dL , platelet value of ≥ 50,000/mm^3 (≥ 30,000 for patients with bone marrow biopsy displaying ≥50% involvement by myeloma), and neutrophil

value of ≥1500 cells/mm^3 (≥1000 for patients with bone marrow biopsy displaying ≥50% involvement by myeloma)

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

No dose modifications or reductions will be made. Subjects are anticipated to receive four doses in each respective arm. If the four doses are interrupted at any point, no further attempts to re-dose will be made.

Patients who experience bortezomib-related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 7.1 Management of Patients with bortezomib Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy. Once the dose is reduced for peripheral neuropathy, the dose may not be re-escalated.

Table 7-1 Management of Patients with VELCADE Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Recommended Dose Modification for bortezomib related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Motor Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated	No action
Grade 1 with pain or Grade 2: Moderate Symptoms; limiting instrumental activities of daily life (ADL)	Reduce bortezomib to 1.0 mg/m^2
Grade 2 with pain or Grade 3: Severe Symptoms; limiting self-care ADL; assistive device indicated	Withhold* VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7mg.m^2 and change treatment schedule to once per week.*
Grade 4 : Life-threatening consequences; urgent intervention indicated	Discontinue bortezomib
Severity of Peripheral Sensory Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1: Asymptomatic; loss of deep tendon reflexes or paresthesia	No action
Grade 1 with pain or Grade 2: Moderate symptoms; limiting instrumental ADL	Reduce bortezomib to 1.0 mg/m^2
Grade 2 with pain or Grade 3: Severe symptoms; limiting self-care ADL	Withhold* bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 and change treatment schedule to once per week*
Grade 4: Life-threatening consequences; urgent intervention indicated	Discontinue bortezomib
Grading based on NCI Common Terminology Criteria CTCAE v4.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living

*Key:

Reduce by one dose level: bortezomib dose reduction from 1.3 to 1.0, or 1.0 to 0.7 mg/m^2/dose.

Reduce by two dose levels: bortezomib dose reduction from 1.3 or 1.0 to 0.7 mg/m^2/dose.

Hold: Interrupt bortezomib for up to 2 weeks until the toxicity returns to Grade 1 or better.

Schedule change: Schedule change from bortezomib twice per week (Days 1, 4, 8 and 11 on a Q3W cycle) to once

per week (Days 1, 8, 15, and 22 on a Q5W cycle). If the treatment schedule is already once weekly, then it should remain once weekly.

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 dose 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.

The neurotoxicity-directed questionnaire (see Appendix E) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

8. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

8.1 **Study Agents / Method Risks**

8.1.1 Bortezomib

To date, more than 100,000 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 8-1 Known Anticipated Risks of bortezomib and Table 8-2 Reports of Adverse Reactions from Post-marketing Experiences. 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 8-1 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*, anemia*
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 hemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal hemorrhage*, lower gastrointestinal hemorrhage*± rectal hemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal hemorrhage*, hematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, esophagitis, enterocolitis, diarrhea hemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, edema 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	Hyperbilirubinemia, hepatitis*±

Table 8-1 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*, bacteremia*, 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 esophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural hematoma
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	Hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia*
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	Tumor lysis syndrome*

Table 8-1 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, post herpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, 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*, hematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnea
Common	Epistaxis, dyspnea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary edema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar hemorrhage*, 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 hemorrhage*

Source: VELCADE® Investigator's Brochure Edition 16.

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.

ϕ Prior to MedDRA version 14.0, posterior reversible encephalopathy syndrome (PRES) was termed 'reversible posterior leukoencephalopathy syndrome (RPLS)'.

Table 8-1 Known Anticipated Risks of bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term

Table 8-2 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

Table 8-1 Known Anticipated Risks of bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: VELCADE® Investigator's Brochure Edition 16.

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.

8.1.2 **High-dose Cyclophosphamide (CYTOXAN)**

Possible serious side effects associated with cyclophosphamide include malignancy, sterility, hemorrhagic cystitis, congestive heart failure, immunosuppression, anaphylaxis, leukopenia, thrombocytopenia and cardiomyopathy.

Possible common side effects associated with cyclophosphamide include alopecia, nausea, vomiting, cystitis, anorexia, diarrhea, rash, headache, dizziness, darkened skin, darkened nails and stomatitis.

8.1.3 **G-CSF (NEUPOGEN)**

Possible serious side effects associated with G-CSF include splenic rupture, Adult Respiratory Distress Syndrome (ARDS), anaphylaxis and thrombocytopenia.

Possible common side effects associated with G-CSF include bone pain, musculoskeletal pain, splenomegaly, injection site reactions, elevated alkaline phosphatase, elevated lactate dehydrogenase (LDH), hyperuricemia, nausea, abdominal pain, flank pain, headache, thrombocytopenia, anemia, hypotension, and leukocytosis.[3]

8.1.4 **Plerixafor (Mozobil)**

Possible side effects associated with plerixafor include diarrhea, nausea, and local injection site reaction (observed in over 10% of patients). Other problems with digestion and general symptoms like dizziness, headache, and muscular pain were found in more than 1% of patients. Allergies occur in less than 1% of cases. Most adverse effects in clinical trials were mild and transient

8.2 **Adverse Event Characteristics**

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

8.3 **Recording of Adverse Events**

All adverse events will be recorded on a patient specific adverse event (AE) log. The AE log will be maintained by the research staff and kept in the patient's research chart. Adverse events will be entered into the RedCap database. Additional information about RedCap can be found in Section 12.1.1.

8.4 **Serious Adverse Event (SAE) Reporting**

8.4.1 **Definition of SAE**

SERIOUS ADVERSE EVENTS include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies, suspected or positive pregnancy, and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2 **Reporting of SAE to IRB**

All SAEs occurring on this study will be reported to the IRB according to the IRB policy. The

IRB requires immediate reporting of all unexpected and study-related (definite or probable) adverse events. The following procedure will be followed for reporting SAE to the IRB:

- Complete the SAE Cover Sheet (See Appendix B)
- If the event is unexpected AND definitely or probably related to the study, complete the IRB Unexpected, Study-related Adverse Events, Incidents, and Information Reporting Form. This form should be submitted within 24 hours of investigator notification of the event.
- If the event is expected OR possibly or unrelated to the study, only the SAE Cover Sheet must be completed. These events will be reported to the IRB at the time of continuing renewal on the Adverse Event & IND Safety Reporting Cumulative Table.

Forms may also be downloaded from the IRB website at:
http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html

8.4.3 **Reporting of SAE to Millennium**

Adverse events (AEs) may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. AEs which are serious must be reported to Millennium. Pharmacovigilance (or designee) from first dose of bortezomib up to and including 30 days after administration of the last dose of bortezomib. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any SAE that occurs at any time after completion of bortezomib treatment or after the designated follow-up period that the investigator-sponsor and/or sub-investigator considers to be related to any study drug must be reported to the 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).

This is an investigator-initiated study. The principal investigator, Dr. Ruben Niesvizky, (who may also sometimes be referred to as the investigator-sponsor), 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.

Investigator-sponsor must report all serious adverse events (SAE) regardless of relationship with any study drug or expectedness to Millennium Pharmacovigilance (or designee) as soon as possible, but no later than 5 calendar days of the investigator-sponsor's observation or awareness of the event. In the event that this is a multisite study, the investigator-sponsor 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 investigator-sponsor so that the investigator-sponsor can meet his/her foregoing reporting obligations to Millennium Pharmacovigilance, unless otherwise agreed between the investigator-sponsor and sub-investigator(s). Millennium Pharmacovigilance (or designee) may request follow-up

information to a reported SAE, which the investigator-sponsor will be responsible for providing to Millennium Pharmacovigilance (or designee).

The SAE report must include event term(s), serious criteria, and the investigator-sponsor's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration.

Intensity for each SAE, including any lab abnormality, will be determined by using the NCI CTCAE, version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to all study drugs for each SAE will be determined by the investigator-sponsor 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)?

Investigator-sponsor must also provide Millennium with a copy of all communications related to the Study or Drug with the applicable regulatory authority, including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of that communication.

Millennium will send to the investigator-sponsor a quarterly listing of the SAE reports received for SAE verification. Investigator-sponsor will be responsible for forwarding such reports to any sub-investigator(s) and providing any follow-up safety information requested by Millennium

Millennium Pharmacovigilance
SAE and Pregnancy Reporting Contact Information:
North America
PPD, Inc.
Safety and Medical Management, US
[redacted]

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 must permanently discontinue study drug(s). All pregnancies and suspected pregnancies must be reported to Millennium Pharmacovigilance (or designee; see Section 8.4.3 for contact information) immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the investigator-sponsor.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance (or designee) immediately (see Section 8.4.3 for contact information). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

8.4.4 **Adverse event updates and IND safety reports**

Millennium shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Millennium and the IRB, on file.

9. PHARMACEUTICAL INFORMATION

9.1 **Clinical Pharmacology**

9.1.1 **Clinical Pharmacokinetics and Pharmacodynamics**

The clinical pharmacology characterization of bortezomib has been determined from phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in phase 2 studies in subjects with multiple myeloma.

Bortezomib demonstrates multi-compartmental pharmacokinetics. Following intravenous administration of 1.0 mg/m^2 and 1.3 mg/m^2 dose, the mean first-dose maximum observed plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively in 11 patients with multiple myeloma and creatinine clearance values >50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

The time course of proteasome inhibition in subjects is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity. On the Day 1, 4, 8, and 11 schedule, variable (10%–30%) levels of proteasome inhibition have been observed at next scheduled dosing. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.

The relationship between bortezomib plasma concentrations and proteasome inhibition can be described by a maximum effect (E_{max}) model. The E_{max} curve is initially very steep, with small changes in plasma bortezomib concentration over the range of 0.5 to 2.0 ng/mL relating to large increases in the percent inhibition (0–60%). After that, a plateau occurs where marginal increases of proteasome inhibition are observed in spite of large changes in plasma bortezomib concentrations.

9.2 **Bortezomib Supply and Dosage**

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 eight 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. 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.

9.2.1 Bortezomib Administration

Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients may be treated on an out-patient basis, if possible. The pharmacist will prepare the drug under aseptic conditions. 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 (see Appendix E). 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 (e.g., loss or gain of ≥8 lbs or 3.6 kg) 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 intravenous (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. The initial dose of bortezomib administered will be 1.3 mg/m^2. The dose may be modified. Please refer to section 6.0.

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

9.2.2 Bortezomib Storage and Special Handling Instructions

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 3.5 mg of bortezomib contain 35 mg of mannitol.

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); excursions permitted from 15 to 30ºC (59 to 86ºF). For Europe, do not store above 30ºC (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.

Bortezomib Return

For commercially-labeled bortezomib for IND-exempt studies, please contact Millennium to arrange for study drug return procedures. Any unused or expired bortezomib must be returned to Millennium. Drug return activity must be documented in the drug accountability log.

Millennium Study Drug 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 MedComm Solutions (see the following contact information 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.

For Product Complaints, call MedComm Solutions at [redacted]

9.2.3 Bortezomib 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.

9.3 **G-CSF, or Neupogen (filgrastim):**

9.3.1 Description

Filgrastim is a human granulocyte colony stimulating factor (G-CSF), produced by recombinant DNA technology. NEUPOGEN is the Amgen Inc. trademark for filgrastim, recombinant methionyl human granulocyte colony stimulating factor (rmetHu G-CSF). Other names:

- G-CSF
- Granulocyte Colony Stimulating Factor
- Neupogen
- recombinant methionyl human granulocyte - colony stimulating factor; r - methHuG – CSF

9.3.2 Contraindications

NEUPOGEN is contraindicated in patients with known hypersensitivity to E. coli - derived proteins, filgrastim, or any component of the product.

9.3.3 Dilution/Storage

If required, NEUPOGEN may be diluted in 5% dextrose. NEUPOGEN diluted to concentrations between 5 and 15 mcg/ml should be protected from adsorption to plastic materials by addition of albumin (Human) to a final concentration of 2mg/ml. Do not dilute with saline at any time; product may precipitate.

NEUPOGEN should be stored in the refrigerator at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking. Prior to injection, NEUPOGEN may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded.

9.3.4 How Supplied

Commercial NEUPOGEN is available in 1ml and 1.6ml vials at a concentration of 300mcg/ml and 480mcg/ml. Discard unused portions. Use only one dose per vial; do not reenter the vial. Do not save unused drug for later administration.

9.3.5 Toxicity

The only consistently observed clinical toxicity described with NEUPOGEN is medullary bone pain. Other clinical adverse events that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of NEUPOGEN, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase."

9.4 **High-dose Cyclophosphamide (Cytoxan)**

Commonly used brand name(s): *Cytoxan; Neosar; Procytox.*

Cyclophosphamide is classed as an alkylating agent of the nitrogen mustard type. An activated form of cyclophosphamide, phosphoramide mustard, alkylates or binds with many intracellular molecular structures, including nucleic acids. Its cytotoxic action is primarily due to cross-linking of strands of DNA and RNA, as well as to inhibition of protein synthesis.

9.4.1 Other actions/effects

Cyclophosphamide is a potent immunosuppressant. It also causes marked and persistent inhibition of cholinesterase activity

9.4.2 Absorption

Well absorbed after oral administration (bioavailability greater than 75%)

9.4.3 Distribution

Crosses blood-brain barrier to limited extent.

9.4.5 Protein binding

Very low (some active metabolites greater than 60%)

9.4.6 Biotransformation

Hepatic (including initial activation and subsequent degradation

9.4.7 Half-life

Unchanged drug 3 to 12 hours

9.4.8 Time to peak concentration

Plasma Metabolites: 2 to 3 hours after intravenous administration

9.4.9 Elimination

Renal, 5 to 25% unchanged
In dialysis Cyclophosphamide is dialyzable

9.4.10 Side/adverse effects

Signs of potential side effects, especially, amenorrhea, leukopenia, infection, cardiotoxicity,

SIADH, hemorrhagic cystitis, hyperuricemia, uric acid nephropathy, nonhemorrhagic cystitis, nephrotoxicity, pneumonitis, interstitial pulmonary fibrosis, anemia, thrombocytopenia, anaphylactic reaction, hemorrhagic colitis, hepatitis, hyperglycemia, redness or swelling or pain at site of injection, and stomatitis

Physician or nurse can help in dealing with side effects

Possibility of hair loss; normal hair growth should return after treatment has ended; new hair may be slightly different in color or texture

9.5 **Plerixafor (Mozobil)**

Plerixafor is a macrocyclic compound and a bicyclam derivative. It is a strong base; all eight nitrogen atoms accept protons readily. The two macrocyclic rings form chelate complexes with bivalent metal ions, especially zinc, copper and nickel, as well as cobalt and rhodium. The biologically active form of plerixafor is its zinc complex.

9.5.1 Pharmacokinetics

Following subcutaneous injection, plerixafor is absorbed quickly and peak concentrations are reached after 30 to 60 minutes. Up to 58% are bound to plasma proteins, the rest mostly resides in extravascular compartments. The drug is not metabolized in significant amounts; no interaction with the cytochrome P450 enzymes or P-glycoproteins has been found. Plasma half-life is 3 to 5 hours. Plerixafor is excreted via the kidneys, with 70% of the drug being excreted within 24 hours.

9.5.2 Pharmacodynamics

In the form of its zinc complex, plerixafor acts as an antagonist (or perhaps more accurately a partial agonist) of the alpha chemokine receptor CXCR4 and an allosteric agonist of CXCR7.[10] The CXCR4 alpha-chemokine receptor and one of its ligands, SDF-1, are important in hematopoietic stem cell homing to the bone marrow and in hematopoietic stem cell quiescence. The in vivo effect of plerixafor with regard to ubiquitin, the alternative endogenous ligand of CXCR4, is unknown. Plerixafor has been found to be a strong inducer of mobilization of hematopoietic stem cells from the bone marrow to the bloodstream as peripheral blood stem cells.

10. STUDY EVALUATIONS

Table 4: Study Calendar

Schedule of Assessments for Arms A, B, and E

	Screening[11]	Day 1	Day 4	Day 8		Day 11	Day 21	On days of Stem Cell collection	End of Treatment[10]
Complete Medical History	X								X
Physical Exam, KPS	X								X
Neuropathy Assessment	X	X X		X		X			X
Vital Signs	X	X X		X		X			X
Weight and Height	X								X
EKG	X								X
CBC w. Diff and Platelets	X[9]	X	X	X [4, 6]		X			X
Complete Metabolic Profile[1]	X[9]								X
SPEP, IF, Quantitative IGs	X								X
24-Hr U for UTP, UPEP, UIF	X								X
Serum Free Light Chains	X								X
Urinalysis	X								X
Serum Pregnancy Test (WCBP)[2]	X								
Bone Marrow Biopsy & Aspirate	X								X[3]
MUGA or Echo	X						X[5]		
VELCADE Dispensing		X	X	X		X			
Cyclophosphamide Dispensing				X[4]					
CD 34 analysis [8]	X	X X		X		X	X	X[6]	
Correlative Studies [7]	X	X X		X		X	X	X[6]	
Concomitant Medications		CONTINUOUS							
Toxicity Assessment		CONTINUOUS							

1 Includes sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphate, total bilirubin, SGOT/AST, SGPT/ALT, lactate dehydrogenase (LDH), uric acid

2 Within 7 days of start of treatment (Day 1)

3 To confirm complete response or when clinically indicated

4 Only for patients randomized to Arm A

5 Screening MUGA to be performed within 6 months prior to treatment then repeated when clinically indicated

6 +/- 2 days

7 Patients undergo hematopoietic colony-forming assays, flow cytometry and viability testing for mobilized CD34+ cells, and plasma chemokine levels (SDF-1 and KitL). DNA/RNA will be extracted for genomics. Correlative studies will only be performed at WCMC and for subjects enrolled at WCMC only. Approved for 6 patients in Arm A and 6 patients in Arm B.

8 In study centers that have the equipment capability, ANC > 1.0 will not be the benchmark to start collection. Instead, peripheral blood CD34+ cells/ ml will be determined by flow cytometry on a subject's blood sample on each morning of proposed collection. A minimum requirement of ≥ 20 x 106 CD34+ cells/ml will be required to start stem cell collection. If the subject fails to reach this benchmark, stem cell collection for the day will be aborted for futility and the patient will return the next day for reevaluation. If the subject fails to achieve an adequate peripheral blood CD34+ cell count after 14 days of G-CSF on Arms A and C, or 10 days of G-CSF on Arm B, the collection attempt will be deemed a failure and the patient will be taken off study. HPC analysis will not be used to determine eligibility to start stem cell collection. In study centers without ready access to flow cytometry analysis of CD34+ cell content of peripheral blood, ANC will be the sole marker to start stem cell collection.

9 To be performed within 14 days of enrollment

10 All subjects will undergo an End of Treatment visit. End of Treatment visits are to be performed within 3 days of study withdrawal or Day 21

11 Screening procedures will be performed within 28 days of enrollment, unless otherwise indicated

Schedule of Assessments for Arms C and D

	Screening[8]	Day 1	Day 8	On days of Stem Cell collection	End of Treatment[7]
Complete Medical History	**X**				**X**
Physical Exam, KPS	**X**				**X**
Vital Signs	**X**	**X**			**X**
Neuropathy Assessment	**X**				**X**
Weight and Height	**X**	**X**			
EKG	**X**				**X**
CBC w. Diff and Platelets	**X[5]**	**X**	**X[9]**		**X**
Complete Metabolic Profile[1]	**X[5]**	**X**			
SPEP, IF, Quantitative IGs	**X**				**X**
Serum Free Light Chains	**X**				**X**
24-Hr Urine collection for UTP, UPEP, UIF	**X**				**X**
Urinalysis	**X**				**X**
Serum Pregnancy Test (WCBP)[2]	**X**				
Bone Marrow Biopsy & Aspirate	**X**				**X[6]**
MUGA or echo	**X**				
Cyclophosphamide Dispensing		**X**			
CD 34 analysis [4]	**X**			**X[9]**	
Correlative Studies [3]				**X[9]**	
Concomitant Medications	**CONTINUOUS**				
Toxicity Assessment	**CONTINUOUS**				

1 Includes sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphate, total bilirubin, SGOT/AST, SGPT/ALT, lactate dehydrogenase (LDH), uric acid

2 Within 7 days of treatment

3 Patients undergo hematopoietic colony-forming assays, flow cytometry and viability testing for mobilized CD34+ cells, and plasma chemokine levels (SDF-1 and KitL). DNA/RNA will be extracted for genomics. Correlative studies will only be performed at WCMC and for subjects enrolled at WCMC only. Approved for 6 patients in Arm C.

4 In study centers that have the equipment capability, ANC > 1.0 will not be the benchmark to start collection. Instead, peripheral blood CD34+ cells/ ml will be determined by flow cytometry on a subject's blood sample on each morning of proposed collection. A minimum requirement of ≥ 20 x 106 CD34+ cells/ml will be required to start stem cell collection. If the subject fails to reach this benchmark, stem cell collection for the day will be aborted for futility and the patient will return the next day for reevaluation. If the subject fails to achieve an adequate peripheral blood CD34+ cell count after 14 days of G-CSF on Arms A and C, or 10 days of G-CSF on Arm B, the collection attempt will be deemed a failure and the patient will be taken off study. HPC analysis will not be used to determine eligibility to start stem cell collection. In study centers without ready access to flow cytometry analysis of CD34+ cell content of peripheral blood, ANC will be the sole marker to start stem cell collection. This is being done for subjects enrolled at WCMC only.

5 To be performed within 14 days of enrollment.

6 To confirm complete response or when clinically indicated

7 All subjects will undergo an End of Treatment visit. End of Treatment visits are to be performed within 3 days of study withdrawal or Day 21

8 Screening procedures will be performed within 28 days of enrollment, unless otherwise indicated

9 +/- 2 days

10.1 **Correlative Studies**

Correlative studies will be done on select patients enrolled at Weill Cornell Medical College only.

Daily CD34 quantification (When possible, excluding weekends):

Arm A: starting day 9
Arm B: starting day 9 (approved for 10 patients only)
Arm C: starting day 5
Arm D: starting day 4
Arm E: starting day 12

Selected patients will undergo hematopoietic colony-forming assays, flow cytometry and viability testing for mobilized CD34+ cells, and plasma chemokine levels (SDF-1 and KitL). DNA/RNA will be extracted for genomics.

10.2. **Evaluation of Response**

10.2.1 Efficacy Evaluations

- Percentage of patients able to collect >6 x 10^6 CD34+ cells/kg in $\leq$ 2 collections.
- Engrafting: Neutrophil recovery (ANC >0.5 of $\leq$20 days), Platelet recovery (>20K untransfused $\leq$20 days) after mel 200 based transplant.
- Toxicities

10.2.2 Tumor Response

Hematological parameters and paraprotein levels will be monitored at screening and end of treatment. Formal response evaluations will be performed between 2-6 weeks after stem cell collection. This evaluation will be according to the International Uniform Response Criteria for Multiple Myeloma (EBMT criteria) presented in Appendix C. For quantitative immunoglobulins, and M-protein in serum and 24-hour urine, the investigator will use results provided by the New York- Presbyterian Hospital Laboratories. Serum free light chain data will be used for exploratory analysis only.

Myeloma Protein Measurements in Serum and Urine:
Blood samples for quantitation of immunoglobulins and M-protein by serum protein electrophoresis (SPEP), and a 24-hour urine sample for quantitation of M-protein by urine electrophoresis (UPEP) are to be collected from all subjects during the Screening Phase and at the End of Treatment Visit. If the assessment of progressive disease is based on one of these tests, then confirmation is required.

Blood and 24-hour urine samples for M-protein measurement (including immunofixation at screening and after complete response [CR]) will be analyzed by the NewYork-Presbyterian Hospital Laboratories.

Bone Marrow Examination:
Bone Marrow aspiration and biopsy are to be performed for all subjects during the Screening

Phase, and for any subject who achieves a CR. Repeat collection and evaluation of bone marrow is not required to confirm CR if the monoclonal antibody remains undetectable in a second assay 6 weeks after the initial observation of a CR.

Our response criteria will follow the modified version of EBMT and International Uniform Response Criteria (IURC). Therefore, no scans are required.

10.3 **Post study follow-up**

All attempts will be made to follow patients until progression or death. Subjects who have been discontinued from study will still be followed in a clinic setting to the fullest extent possible on a monthly to bi-monthly basis. Those who choose not to resume regular clinic follow-up will be contacted every 6 months by telephone or electronically to collect post study information. The post-study collection information will consist of telephone interview between the clinical investigator and the discontinued patient. The information requested will be current disease status, current treatment use, and physical status of the patient.

10.4 **Procedure for early removal from study**

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB, regulatory authorities, etc.).

The responsible Clinical Investigator and/or Millennium have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

11. MEASUREMENT OF EFFECT

11.1 **Disease Response**

Disease response category (e.g. partial response, very good partial response, complete response, stringent complete response) will be as defined by the International Uniform Response Criteria for Multiple Myeloma (Appendix C).

11.2 **Duration of Response**

Duration of overall response*:* The duration of overall response is measured from the time measurement criteria are met for complete response or partial response (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

12. DATA REPORTING / REGULATORY CONSIDERATIONS

12.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, and efficacy data for all enrolled patients.

12.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill Cornell Medical College Clinical and Translational Science Center (CTSC). It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA. REDCap will be used by all participating sites for data collection for this study.

12.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. Millennium will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

12.3 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) at Weill Cornell Medical College will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DSMB is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DSMB may request additional meetings or safety reports as deemed necessary upon discussion with Millennium and its representatives. The Principal Investigator, Dr. Ruben Niesvizky, will be the safety contact for all DSMB related analysis outcomes.

Dr. Niesvizky's office is located at: [redacted]

The phone number to Dr. Niesvizky's office is: [redacted]

The DSMB may stop the study following review of results from each interim analysis. The first interim analysis will examine only safety information from the first ten patients accrued to each arm. **Safety will be evaluated by CTC criteria. Any grade 5 toxicity that is due to treatment will be considered unacceptable, and the study arm will be terminated.** The

second interim, conducted when the database is more mature (60 patients enrolled – 20 patients in each arm A, D and E), will examine both safety and efficacy, **including toxicity data, protocol adherence, and protocol deviations.** Appropriate efficacy and safety data summaries will be provided to the DSMB after each interim analysis.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Primary Endpoints

The primary endpoint in all five treatment arms is the percentage of patients who are able to achieve greater than 6 x 10^6 CD34+ stems cells/kg harvested (defined as effectiveness). Ninety-five percent confidence intervals will be estimated for the effectiveness proportions in all three treatment arms via binomial proportions. As well, 95% confidence intervals for the differences in effectiveness proportions between the three treatment arms will be estimated via binomial proportions. The chi-square test will be used to compare the effectiveness proportion between the three groups and pair-wise group comparisons will be performed with adjustment for multiple comparisons (Scheffe). Multivariate logistic regression will be used to compare the effectiveness proportions between pairs of treatment arms, controlling for demographic and prognostic factors that may not have been successfully balanced after randomization.

13.2 Sample Size/Accrual Rate

With the closures of the CTX-GCSF (standard of care) arm and the Bortezomib-GCSF arm, approximately 66 patients each in the CTX-Bortezomib-GCSF arm (Arm A), Plerixafor-GCSF arm (Arm D), and Plerixafor-Bortezomib-GCSF arm (Arm E), will allow for the detection of 1) a ≥18% absolute difference between the percentage of patients in arm A vs. E who are able to achieve greater than 6 x 10^6 CD34+ stems cells/kg harvested (defined as effectiveness), and 2) a ≥28% absolute difference between the percentage of patients in arm D vs. E who are able to achieve greater than 6 x 10^6 CD34+ stems cells/kg harvested (defined as effectiveness), with 90% and 95% power, respectively, and a two-sided alpha level of 5%. This calculation assumes an effectiveness proportion of 70% in the Plerixafor-GCSF arm, 80% in the CTX-Bortezomib-GCSF arm, and 98% in the Plerixafor-Bortezomib-GCSF arm.

For the comparison of the CTX-Bortezomib-GCSF arm (Arm A) and the Plerixafor-GCSF arm (Arm D), with 66 patients per arm, an observed ≥10% absolute difference between the percentage of patients in each arm who experience effectiveness will only be considered exploratory (i.e., hypothesis-generating) and not formally powered.

The above sample size/power calculation has been adjusted for the possibility of early stopping as discussed in section 6.2 (i.e., stopping rules will be implemented once 10 patients are accrued in each arm and the rule will not allow more than 4 failures in the 10 accrued patients per arm). The overall alpha level (type I error rate) has been modified to account for the possibility of early stopping of an arm after the accrual of 10 patients per arm. The final analysis comparing the efficacy proportions between the treatment arms (A vs. E and D vs. E) will use an adjusted

significance level that accounts for the possibility of early stopping.

13.3 **Analysis of Secondary Endpoints**

Secondary endpoints include 1) the mean and median number of stem cells collected for the patients in each treatment arm, 2) measures of tumor mass change (as defined by standard response parameters), 3) the prevalence of biomarkers as surrogate markers of mobilization, 4) patient safety, and 5) patient toxicity. The ANOVA test (or nonparametric Kruskal-Wallis test, as appropriate) will be performed for comparing the mean (or median) number of stem cells collected in each treatment arm. The chi-square test (or Fisher's exact test, as appropriate) will be used to compare tumor mass change response proportions (i.e., CR, PR, SD, etc.) between the three treatment arms and to compare the prevalence of specific biomarkers between the three treatment arms.

The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

13.4 **Randomization**

Stratified and blocked randomization will be performed at all participating sites. Randomization will be stratified by participating institution. A series of randomized blocks of 6 will be generated for each participating institution, using a 1:1:1 allocation ratio (for accrual into arms A, D, and E going forward). This will provide assurance that after six patients are enrolled at any participating site, there will be two patients assigned to each of the three treatment arms. After the closing of arms B and C, and the addition of arms D and E, randomization will still commence in a 1:1:1 allocation ratio. Since some accrual has already occurred on arm A, however, it will finish accrual before arms D and E. After arm A completes accrual, the randomization scheme will be adjusted to provide a 1:1 allocation into the remaining arms D and E. A block size of 6 will still be utilized, but after six patients are enrolled at any participating site, there will be three patients assigned to arm D and 3 patients assigned to arm E. This will ensure that we have 66 patients in each of the three treatment arms at study completion (assuming none of the current arms are subject to early closure).

14. PROTOCOL AMENDMENTS AND DEVIATIONS

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

All protocol amendments and consent form modifications will be made by the Principal Investigator. Changes to the protocol will require approval from Millennium and written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.

Written verification of IRB approval will be obtained before any amendment, which affects subject safety or efficacy, is implemented. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information purposes.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB.

Any departures from the protocol must be fully documented in the source documents.

15. REGULATORY CONSIDERATIONS

15.1 Institutional Review Board Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

The Investigator will be responsible for preparing documents for submission to the relevant IRB and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

All protocol amendments will be reviewed by Millennium prior to submission and approval by the Institutional Review Board (IRB) before they can be implemented. The investigator is also responsible for notifying the IRB of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB submission.

15.2 **Informed Consent Procedures**

The Investigator must obtain written informed consent from a subject or his/her guardian or legal representative prior to study participation as per GCP's as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. At the pre-admission consultation, patients will be fully informed as to the purposes and potential risks and benefits involved in this study. Patients will have ample opportunity to ask questions before consenting. Legal guardians will sign informed consent for legally incompetent patients in accordance with hospital policy.

15.3 **Protecting Privacy and Confidentiality**

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.4 **Study records requirements**

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with ICH-GCP and applicable regulatory requirement(s) (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

15.5 **Protection of Human Rights**

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to Weill Cornell Medical College IRB guidelines. Patients will be eligible for this trial regardless of gender or racial/ethnic background.

15.6 **Premature Discontinuation of Study**

The responsible local clinical Investigator as well as Millennium have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party. Possible reasons for termination of the study could be but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.
- Serious adverse events, intolerability of drug regimen, or sudden/unexpected death in any of the early trial (up to three patients) participants, as outline in section 9.2.
- Plans to modify, suspend or discontinue the development of the drug. Should the study be closed prematurely, all study materials must be returned to Millennium.

15.7 **Benefits of the Protocol**

The potential benefit of this study is the discovery of a superior mobilization regimen for MM patients. Knowledge will be acquired about this treatment program, its tolerability, and the effectiveness of the combination of VELCADE, high-dose cyclophosphamide (CYTOXAN) and G-CSF in mobilizing peripheral stem cells in patients with multiple myeloma.

15.8 **Risks in Relation to Anticipated Benefit**

The risks associated with participation in this trial are commensurate with the expected risks of other potential therapies and are reasonable given the potential benefit to patients with multiple myeloma.

15.9 **Alternative Treatments**

Patients who refuse to participate in the study or decided to withdrawal from the study will be given the option to choose standard chemotherapy, other investigation studies, supportive care, or no anti-cancer treatment at all. Some patients treated with standard chemotherapy do benefit. While the results of this therapy have been encouraging, long-term remissions are rare, no patients are cured and none of the drugs used in these standard treatments are free of side effects. We believe that this novel regimen will improve response rates and duration of remission.

15.10 **Incentives**

No incentives will be offered to patients/subjects for participation in the study. Participation is voluntary.

15.11 **Costs**

Patients and/or their medical insurance coverage will be responsible for paying for their hospitalization, doctor visits, diagnostic tests, chemotherapy drugs, and other medicines used in their care directly. These costs are expected to be equivalent to those of standard treatment. Bortezomib will be provided to research subjects by Millennium Pharmaceuticals, Inc. for the duration of their participation in this trial at no charge to the subject or their insurance providers. G-CSF and high dose cyclophosphamide (Cytoxan) will be obtained through normal commercial channels.

16. ADMINISTRATIVE REQUIREMENTS

16.1 **On-Site Audits**

Regulatory authorities, the IRB and/or Millennium may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

16.2 **Drug Accountability**

Accountability for the drug at all study sites (including sub-sites, if applicable) is the responsibility of the investigator-sponsor. The investigator-sponsor will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Millennium will be maintained by the site and/or sub-sites. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

Any unused or expired commercially labeled bortezomib must be returned to Millennium. Bortezomib destruction at any study site is not allowed for commercially labeled product that is associated with this Investigator Initiated Study.

All material containing bortezomib will be treated and disposed of as hazardous waste in accordance with governing regulations.

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky[1] Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Source:Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. *Cancer* 1984;53:2002-2007.
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APPENDIX B: WCMC IRB SAE Reporting Forms

http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html

APPENDIX C: International Uniform Response Criteria for Multiple Myeloma

Stringent Complete Response (sCR) requires all of the following:

- ❑ All of the criteria of complete response
- ❑ Normal serum free light chain ratio
- ❑ Absence of monoclonal cells on bone marrow aspirate by immunohistochemistry or immunofluorescence

Complete Response (CR) requires all of the following:

- ❑ Absence of the original monoclonal protein in serum and urine by inmmunofixation. The presence of oligoclononal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- ❑ ≤5% plasma in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
- ❑ No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response)
- ❑ Disappearance of soft tissue plasmacytoma.

Very Good Partial Response (VGPR) requires all of the following:

- ❑ Negative serum and urine protein electrophoeresis with persistence of monoclonal protein detectable on immunofixation OR
- ❑ ≤90% reduction in serum monoclonal protein level with urine monoclonal protein level < 100mg in 24 hour collection.

Partial Response (PR) requires all of the following:

- ❑ ≥50% reduction in the level of the serum monoclonal paraprotein.
- ❑ Reduction in 24h urinary light chain excretion either by ≥90% or to <200mg.
- ❑ For patents with light chain only disease, then a 50% reduction in the difference between the involved and uninvolved free light chain level may be substituted for the M-protein measurement.
- ❑ For patients with non-secretory myeloma only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine bone biopsy, if biopsy is performed.
- ❑ ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- ❑ No increase if size or number of lytic bone lesion (development of a compression fracture does not exclude response)

Stable Disease (SD) requires the following:

- ❑ Not meeting the criteria stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)

Plateau:

- ❑ Stable values (within 25% above or below value at the time response is addressed)

Patients in which no significant change (<50% decrease or <25% increase from baseline) in the production rate of the monoclonal serum protein or Bence-Jones protein excretion and no new lytic lesions and/or plasmacytomas are detected.

Relapse from CR requires at least one of the following:

- ❑ Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
- ❑ ≥5% plasma in a bone marrow aspirate or trephine bone biopsy.
- ❑ Development of new lytic lesions of soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
- ❑ Development of hypercalcemia (corrected serum calcium >11.5mg/dl or 2.8 mmol/l) not attributable to any other cause.

Progressive disease (PD) for patients not in CR requires one or more of the following:

- ❑ >25 increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5g/L and confirmed by at least one repeated investigation.
- ❑ >25 increase in the 24h urinary light chain excretion, which must also be an absolute increase of at least 200mg/24h and confirmed by at least one repeated investigation.
- ❑ >25% increase in plasma cells in a bone marrow aspirate and on trephine bone biopsy, which must also be an absolute increase of at least 10%.
- ❑ Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- ❑ Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
- ❑ Development of hypercalcemia (corrected serum calcium >11.5mg/dl or 2.8 mmol/l) not attributable to any other cause.

APPENDIX D: Body Surface Area and Creatinine Clearance Calculations

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m^2):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \text{ (actual wt in kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

For females use 85% of calculated CrCl value.

Note: In markedly obese patients, the Cockroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

APPENDIX E: FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands…….	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.

APPENDIX F: New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256

APPENDIX G: International Myeloma Working Group Diagnostic Criteria

Diagnosis	Diagnostic Criteria: All Three Required
Symptomatic multiple myeloma[a]	• Monoclonal plasma cells in the bone marrow >/=10% and/or presence of a biopsy-proven plasmacytoma • Monoclonal protein present in the serum and/or urine[b] • Myeloma-related organ dysfunction (>/=1)[c] [C] Calcium elevation in the blood (serum calcium >10.5 mg/l or upper limit of normal [R] Renal insufficiency (serum creatinine >2mg per 100 ml) [A] Anemia (hemoglobin <10 g per 100 ml or 2 g <normal) [B] Lytic bone lesions or osteoporosis[d]
Monoclonal gammopathy of undetermined significance (MGUS)	• Serum monoclonal protein low[e] • Monoclonal bone marrow plasma cells <10% • No evidence of end-organ damage attributable to the clonal plasma cell disorder: • Normal serum calcium, hemoglobin level and serum creatinine • No bone lesions on full skeletal X-ray survey and/or other imaging if performed • No clinical or laboratory features of amyloidosis or light chain deposition disease
Smoldering or indolent myeloma[f]	• Monoclonal protein present in the serum 3 g per 100 ml or higher or • Monoclonal plasma cells 10% or greater present in the bone marrow and/or a tissue biopsy • No evidence of end-organ damage attributable to the clonal plasma cell disorder: • Normal serum calcium, haemoglobin level and serum creatinine • No bone lesions on full skeletal X-ray survey and/or other imaging if performed • No clinical or laboratory features of amyloidosis or light chain deposition disease
Solitary plasmacytoma of bone	• Biopsy-proven plasmacytoma of bone in a single site only. X-rays and magnetic resonance imaging and/or • FDG PET imaging (if performed) must be negative outside the primary site.

	• The primary lesion may be associated with a low serum and/or urine M-component • The bone marrow contains no monoclonal plasma cells • No other myeloma-related organ dysfunction

Adapted with permission from Kyle and Rajkumar, Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma..*Leukemia* 2009; 23: 3–9.

[a]These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.

[b]If no monoclonal protein is detected (non-secretory disease), then >/= 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

[c]A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

[d]If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then >/= 30% plasma cells are required in the bone marrow.

[e]Low is defined as serum M protein <3.0 g per 100 ml.

[f]These criteria identify Stage IA myeloma by Durie/Salmon stage.

Source: International Myeloma Foundation. IMWG Criteria for the Diagnosis of Myeloma and Guidelines for the Diagnostic Work-Up of Myeloma. 2010. 14 Mar 2011 <http://myeloma.org/ArticlePage.action?articleId=2970>

APPENDIX H: Common Terminology Criteria for Adverse Events

http://ctep.cancer.gov/reporting/ctc.html