CITY OF HOPE NATIONAL MEDICAL CENTER
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DIVISION OF HEMATOLOGY

TITLE: **A PHASE II STUDY OF MAINTENANCE TREATMENT WITH SEQUENTIAL BORTEZOMIB, THALIDOMIDE AND DEXAMETHASONE FOLLOWING AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANT IN PATIENTS WITH MULTIPLE MYELOMA**

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DISEASE SITE: **Bone Marrow**

STAGE (*If applicable*)**:** **I - III**

MODALITY(IES):
TYPE (*e.g., Pilot, Phase I*)**:** **Phase II**

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PROTOCOL SUMMARY

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A PHASE 11 STUDY OF MAINTENANCE TREATMENT WITH SEQUENTIAL BORTEZOMIB, THALIDOMIDE AND DEXAMETHASONE FOLLOWING AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANT IN PATIENTS WITH MULTIPLE MYELOMA

OBJECTIVES:

The primary objectives of this study are:

- To assess the feasibility and toxicities of maintenance therapy with sequential bortezomib, thalidomide, and dexamethasone following high dose melphalan and autologous peripheral blood stem cell transplant in patients with multiple myeloma.

- To assess whether administration of maintenance therapy with sequential bortezomib, thalidomide, and dexamethasone can improve progression-free survival following autologous peripheral stem cell transplant.

The secondary objectives of this study are :

- To assess whether administration of maintenance therapy with sequential bortezomib, thalidomide, and dexamethasone can increase complete remission (CR) rate and duration of response following autologous peripheral stem cell transplant.

- To assess the impact of maintenance therapy with sequential bortezomib, thalidomide, dexamethasone on overall survival following autologous peripheral stem cell transplant.

- To evaluate the influence of chromosome abnormalities on outcome by performing cytogenetics, and fluorescence in situ hybridization (FISH) studies on baseline and post transplant bone marrow specimens.

PATIENT POPULATION:

1. Stage II - III MM
2. Progressive Stage I MM
3. Patients with Peripheral Neuropathy no greater than grade I
4. No evidence of resistance to bortezomib and thalidomide prior to transplant

NUMBER OF PATIENTS:

A total of 45 patients will be accrued.

STUDY DESIGN AND METHODOLOGY:

AUTOLOGOUS PERIPHERAL STEM CELL PROCURMENT — A minimum of 4 x 10^6 CD 34 + cell/kg is obtained

TRANSPLANT

DAY –2 Melphalan 100 mg/m^2 IV

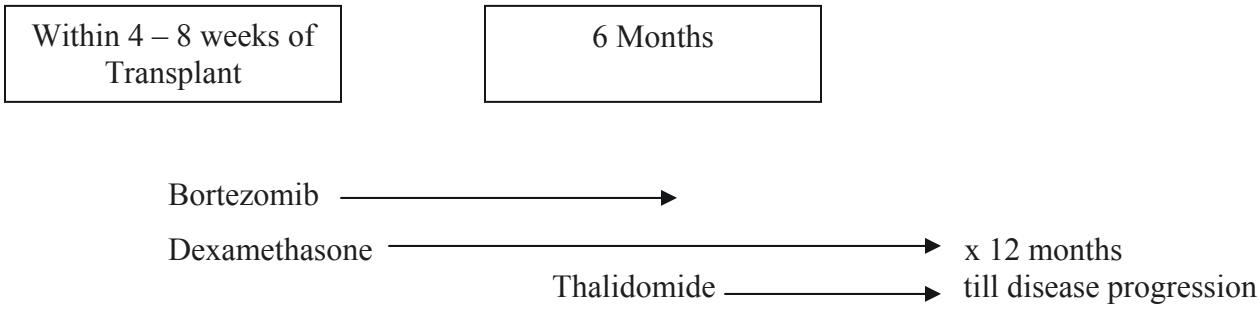
DAY –1 Melphalan 100 mg/m^2 IV

DAY 0 Reinfusion of collected stem cells (mimimum cell dose of 2x10^6 CD 34 + cell/kg)

DAY +5 Start Filgrastim 5mcg/kg, Daily, IV

MAINTENANCE

Within a minimum of 4–8 weeks after autologous peripheral stem cell transplantation bortezomib will be administered as maintenance treatment at 1.3 mg/m^2 once a week for three weeks followed by one-week rest for a maximum of 6 months. Additionally, patients will receive dexamethasone at 40 mg/day D 1-4 of every month. Dexamethasone will be given for a total of 12 months. Two weeks after completion of bortezomib maintenance therapy patients will be started on thalidomide at 50 mg per day and thalidomide dose will be escalated to target dose of 200 mg per day till disease progression.



STATISTICAL PROCEDURES:

Sample Size

The objectives of this Pilot study are to evaluate the feasibility and toxicities of maintenance therapy, complete response rate, duration of response, 3-year progression-free and overall survival rates.

The maintenance therapy is considered feasible if more than 70% of the subjects are able to receive a minimum of 4 months of bortezomib therapy (patients able to receive bortezomib but on a reduced dose per protocol would not be considered "unable to tolerate"). The maintenance therapy is considered not feasible if less than 50% of the subjects are able to tolerate bortezomib therapy. With the early stopping rules, and more than 25/45 tolerating considered a success, this study has 85% power to determine feasibility with a type I error of 10% and an 84% chance of early stopping if not feasible (based on 5000 simulations). A second feasibility marker regarding thalidomide will be also be assessed, but is not the basis of the sample-size and no related interim stopping rules are formalized for that component of the maintenance therapy.

To evaluate for feasibility during the study while preventing excess patients from receiving the therapy if it is clearly not feasible, we will enforce the following:

Early Stopping Rules

Inability to continue to receive bortezomib for a minimum of 4 months per protocol dose modification guidelines will constitute intolerance. The study will hold accrual, if the following numbers of patients able to tolerate bortezomib are observed (patients accrued will continue therapy per protocol):

Patients with 4 Months Follow-up	Stop if the Number Able to Tolerate Bortezomib is:
5	0
15	<=8
25	<=13
35	<=19

In order to accommodate the fact that several patients may be undergoing maintenance therapy when the stopping rule is activated, the following rule is to be followed: If after a hold on study accrual, the percent of patients unable to tolerate maintenance therapy remains above 50%, the study will not re-open. If the percent of patients unable to tolerate drops below 50%, accrual may re-start if the stopping condition was at 25 patients or less (if stopped at 35 patients with 4 months of follow-up, with <=19 able to tolerate, there will be no restart).

The regimen, if feasible, will also be evaluated for its potential to improve three-year progression-free survival. Historical data suggest approximately 52% of the patients are expected to be progression-free at 3 years after autologous stem cell transplant followed by maintenance thalidomide (Attal et al., Blood Nov 2006; 108 (10), P3289-3294). With 45 patients, there is 81% power to detect an improvement to a 66% 3-year progression-free survival with the proposed

maintenance therapy with a one-sided type I error of 10%. This assumes an accrual time of 24 months, and a minimum follow-up of 36 months. The critical value for 3-year PFS rate is 60%, which, if observed, would suggest that the proposed therapy is a promising new maintenance therapy. This calculation is based on a constant hazard model, and on a parametric exponential estimate.

Criteria for Feasibility

If the study accrues to the full 45 patients, the trial will be considered a success on the primary endpoint of feasibility if 26 or more patients tolerated treatment. If the estimated feasibility rate in the study group is equal to 70% then the 95% confidence interval would range from 57% to 83%.

Analytic Plan

The primary endpoint of feasibility will be estimated as a proportion along with the 95% confidence interval for the binomial. If our accrual goal is met with no premature termination due to significant toxicity, a secondary goal of assessing response, progression-free survival (PFS), and overall survival (OS) will be carried out. Survival estimates will be made using the product-limit method of Kaplan and Meier, with 95% confidence limits calculated using the logit transformation. It is hoped that PFS and OS will be further improved with the use of the proposed maintenance therapy. If the patient discontinues maintenance therapy due to adverse events or personal choice, patient will be taken off protocol.

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1.0 SCHEMA

AUTOLOGOUS PERIPHERAL STEM CELL PROCURMENT — A minimum of 4 x 10^6 CD 34 + cell/kg is obtained

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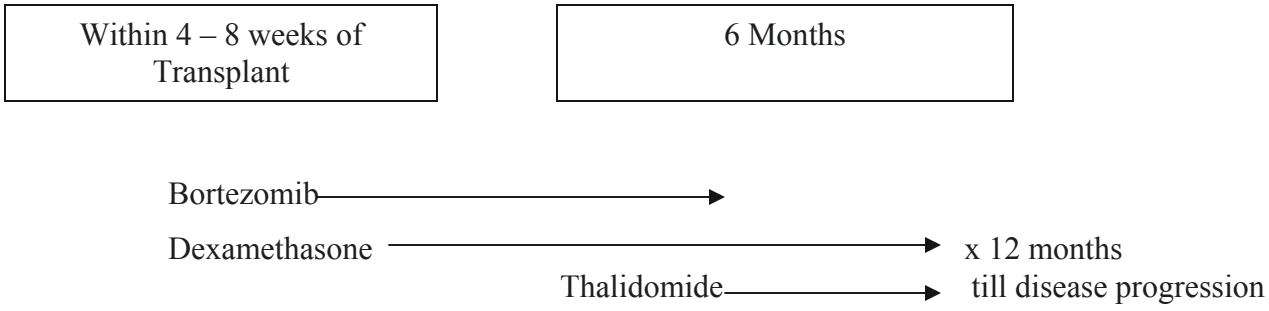
Within a minimum of 4 – 8 weeks after autologous peripheral stem cell transplantation bortezomib will be administered as maintenance treatment at 1.3 mg/m^2 once a week for three weeks followed by one-week rest for a total duration of 6 months. Additionally, patients will receive dexamethasone at 40mg/day D 1-4 of every month. Dexamethasone will be given for a total of 12 months. Two weeks after completion of bortezomib maintenance therapy patients will be started on thalidomide at 50mg per day. The dose will be escalated at 50mg per week to a target dose of 200mg per day. Dose reduction to a minimum dose of 50 mg every other day is allowed for thalidomide related toxicities. Thalidomide will be continued till disease progression.



2.0 OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

- To assess the feasibility and toxicities of maintenance therapy with sequential bortezomib, thalidomide, and dexamethasone following high dose melphalan and autologous peripheral blood stem cell transplant in patients with multiple myeloma.

- To assess whether administration of sequential bortezomib, thalidomide, and dexamethasone can improve progression-free survival

2.1.2 SECONDARY OBJECTIVE

- To assess whether administration of sequential bortezomib, thalidomide, and dexamethasone can increase complete remission (CR) rate and duration of response in patients with multiple myeloma.

- To assess the impact of maintenance therapy with sequential bortezomib, thalidomide, dexamethasone following transplant on overall survival.

- To evaluate the influence of cytogenetic abnormalities including but not limited to chromosome 13 deletion, 14 q32 abnormality, t (4;14), chromosome 1 q21 amplification and chromosome 17 deletion on outcome by performing conventional cytogenetic study and fluorescence in situ hybridization (FISH) studies on baseline and post transplanted bone marrow specimens.

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3.0 BACKGROUND AND RATIONALE

3.1 The incidence of multiple myeloma (MM) has been on the rise accounting for approximately 10% of all hematological malignancies and 1% of all cancer-related death in Western countries. Five in 100,000 Americans suffer from MM; the entire spectrum of plasma cell dyscrasias affects an even greater percentage of the population. These diseases include benign gammopathy, macroglobulinemia, and solitary plasmacytoma and, within the category of MM, smoldering and indolent forms as well as immunoblastic lymphoma and plasma cell leukemia[1]. Adverse prognostic factors such as high plasma cell labeling index, elevated beta-2 microglobulin and C-reactive protein, the presence of specific chromosomal abnormalities, plasmablastic morphology and abnormal renal function, poor performance status at diagnosis and elevated serum levels of interleukin-6 are of grave clinical significance.[2-4] Chemotherapy with melphalan and prednisone, a

combination of alkylating agents, or vincristine, doxorubicin is effective in 50-70% of patients with newly diagnosed MM; however, less than 10% of patients will achieve complete remission[5,6]. Unfortunately, the effects of chemotherapy are usually short lasting. The median survival of patients with MM is 30-36 months. The lack of long-term effectiveness is due to either primary, or acquired resistance. Attempts to improve overall response and response duration have been focusing on overcoming drug resistance due to over expression of the MDR-1 gene product[7], or utilizing myeloablative therapy followed by autologous or allogeneic peripheral blood progenitor cell rescue (PBPC).[8]

3.2 High-dose chemo-/radiotherapy in the treatment of MM.

Single agent high-dose melphalan therapy results in response rates of > 80% with complete response rates of > 30% as described in earlier studies without the use of stem cell support. In a recent update, 1/3 of the patients from the original cohort treated with high-dose melphalan were reported to be alive at 9 years[9, 10.] Thousands of patients with multiple myeloma have received dose-intense bone marrow ablative therapy followed by autologous bone marrow, or peripheral stem cell rescue, worldwide[8, 11, 16] A prospective randomized study (IFM90) comparing high-dose consolidation therapy and stem cell rescue following induction therapy to conventional chemotherapy alone, reported higher complete response rates (22% versus 5%) and improved progression-free and overall survivals with transplant (projected 5 year event-free and overall survivals 28% and 52% versus 10% and 12%). [17] Comparison of early vs. late (at the time of progression) autologous transplants favor early high-dose therapy resulting in prolonged progression-free survival and quality of life while in response.[18] Tandem cycle high-dose chemo/radiotherapy in the setting of a total therapy in the largest series by a single institution suggested additional benefit associated with the second transplant in a series of 231 patients, independent of the presence of unfavorable cytogenetics and elevated beta 2 microglobulin; with a median follow-up of 4.2 years among surviving patients actuarial 5-year event-free and overall survivals were 42% and 58%, respectively.[19] A recent prospective randomized study by the French group (IFM 94) reported seven year event-free and overall survival of 20% and 40% respectively with tandem autologous transplant twice the rate obtained with single transplant, suggesting a benefit in favor of tandem autologous transplant.[20] However, the benefit was observed only in patients who did not have a very good partial response (VGPR) within three months after first autologous transplant. Furthermore a recent randomized study by an Italian group reported only PFS advantage with no difference in OS with tandem autologous stem cell transplant as compared to single autologous transplant. [42] Overall the benefit from tandem autologous transplant remains marginal and majority of the patients still experience recurrent disease.

Allogeneic bone marrow transplantation has been associated with a disappointing median overall survival of 13 months in a registry review by the European Group

for Blood and Bone Marrow Transplantation, with approximately 40% early, treatment-related mortality, caused by regimen-related toxicities, infections, and acute or chronic graft versus host disease.[16] More recent data suggest diminished early mortality rates possibly due to incorporation of PBPC reinfusions in addition to ongoing assessment of the role of the so called mini transplants.[21] Currently early utilization of myeloablative therapy is recommended with autologous stem cell transplantation in order to consolidate complete or partial response to conventional treatment. In addition, even patients with previously untreated or refractory disease may respond to high-dose therapy, with the possibility of long-term disease control.[8]

3.3 Chromosomal abnormalities as prognostic indicators in MM

Cytogenetic abnormalities can be detected in significant numbers of MM cases; the presence of 11q, -13 and deletion 13q, t (4;14) have been associated with worse survival.[19] Frequent abnormalities observed in MM include t(4;14) (p16;q32), t(11;14) (q13;q32), t(8;14) (q24;32), t(14;18) (q32;q21), t (14;16) (q32; q23), 13q14 (Rb loss), chromosome 17 deletion, and others. [22]One of these translocations, t(4;14) may lead to dysregulations of two separate oncogenes providing one of many potential targets for specific interventions in the future. More recently high amplification of chromosome 1q21 has been linked to worse outcome following transplant.[23] Global gene expression profiling on highly purified malignant plasma cells from 351 newly diagnosed patients with multiple myeloma treated with autologous stem cell transplantation revealed a statistically significant over representation of chromosome 1 gene in a group of 70 genes whose expression was linked to poor outcome. In particular, over expression of CKS1B, which maps to an amplicon at 1 q21 in myeloma and regulates proteolysis of the cyclin dependent kinase inhibitor P27kip1 was significantly over expressed in patients with poor prognosis. [24]

3.4 Maintenance therapy after autologous stem cell transplant in MM

Despite prolongation of disease free survival and overall survival with autologous stem cell transplant majority of the patients experience relapse within a few years of transplant. Maintenance therapy might prolong response and survival by inhibiting proliferation and inducing apoptosis of malignant cells that have not been eliminated by chemotherapy. The use of maintenance therapy post autologous stem cell transplant was initially studied using alfa-interferon. This approach was shown to exert anti-myeloma activity but was associated with significant toxicities and no statistical difference in overall survival in a randomized study. [25]

A phase II study conducted at COH investigated the role of maintenance thalidomide after single autologous stem cell transplant. A total of 29 patients were enrolled. With a median follow up of 27.7 months, estimated 2 year overall survival was 83% and progression free survival was 49%. At 6 months 45% of patients

achieved CR or near CR, suggestive of additional benefits from maintenance thalidomide.[26] In this study patients with chromosome 13 abnormality had a PFS of only 16% despite maintenance thalidomide. A randomized study (IFM9902) reported improvement in event free survival with maintenance thalidomide post tandem autologous stem cell transplant with a 3 year post randomization probability of EFS of 52% as compared to 36% in the observation arm and 37% in the pamidronate arm. They also reported an overall survival advantage in favor of maintenance thalidomide with 4-year post diagnosis probability of survival of 87% versus 77% in the observation arm and 74% in the pamidonate arm. [27] In this study the benefit from maintenance thalidomide was seen in patients who had no chromosome 13 abnormality suggesting that the negative impact of chromosome 13 abnormality cannot be overcome by maintenance thalidomide alone. A study by the Arkansas group also reported an increase in CR rate and 5 - year EFS with the addition of thalidomide to tandem autologous transplant plan throughout (Total Therapy II) with no difference in OS. [37] They reported shorter survival from relapse in patients who received thalidomide. This shorter post relapse survival was traced to high amplification of chromosome 1q21, which was more often present on the thalidomide arm. It must be noted that the shorter post relapse survival may be related to the fact that relapse occurred later on maintenance thalidomide, as OS was similar in the two treatment arms in Total Therapy II. Furthermore French (IFM9902) study reported a similar post relapse survival in the 3 treatment groups. [27] Another randomized study by an Australian group compared thalidomide as maintenance therapy following single autologous stem cell transplant in combination with prednisone to prednisone alone. In this study thalidomide was continued for 12 months post transplant and prednisone was continued till disease progression. The thalidomide maintenance arm demonstrated superior PFS (P=0.0003) and OS (P=0.02) compared to prednisone arm supporting the use of maintenance thalidomide post autologous stem cell transplant. [43]

Based on these results, further studies investigating the potential role of newer anti-myeloma agents such as bortezomib, in combination with dexamethasone and thalidomide as maintenance therapy following autologous stem cell transplantation are warranted especially in patients with adverse prognostic features. Furthermore, the results of recent studies with bortezomib indicate that response rate, EFS and OS are all independent of chromosomal abnormalities such as chromosome 13 deletion in patients with relapsed or refractory multiple myeloma supporting the addition of bortezomib to thalidomide as maintenance therapy in the high risk patients. [39]

4.0 THERAPEUTIC AGENTS

4.1.1 Bortezomib

-Mechanism of action: Bortezomib is a first-in-class inhibitor of proteasome activity that effectively interrupts the degradation of proteins involved in cell cycle regulation and apoptosis. 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).

-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. . 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 VELCADE 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 VELCADE 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. Bortezomib has demonstrated no irreversible adverse effect on hematopoietic stem cells.[28]

-Clinical Experiences: Several studies have reported encouraging results using bortezomib alone or in combination with dexamethasone in both relapsed/refractory multiple myeloma and previously untreated disease. The SUMMIT STUDY (The study of uncontrolled MM managed with proteasome inhibitor therapy) was a prospective open-label phase II study in 202 patients with relapsed/refractory multiple myelomas.[29] The median number of previous treatment was 6 with 64% of patients having had stem cell transplant and 83% were previously treated with thalidomide. The overall response rate of 35% with complete or near complete response rates of 10%, partial response rate of 18% and minimal response rate of 7%. The most commonly reported adverse events were GI (such as nausea, diarrhea, and vomiting), fatigue, transient thromocytopnia (40%) and peripheral neuropathy (31%). A phase III randomized study, APEX TRIAL (The Assessment of Proteasome Inhibition of Extending Remission) compared bortezomib with high dose dexamethasone in 669 patients with relapsed or refractory multiple myeloma with one to three previous treatments.[30] In this study bortezomib was administered at 1.3mg/m^2 on day 1, 4, 8, and 11 for eight five-week cycles, followed by weekly treatment on days 1, 8, 15, and 22 for three five-week cycles. The dexamethasone arm of the trial was stopped after a preplanned interim analysis revealed significant clinical benefits in survival and time to disease progression for patients receiving bortezomib. Significant activity in previously untreated patients with

multiple myeloma treated with bortezomib has also been reported. A phase II study of bortezomib alone and in combination with dexamethasone in 32 previously untreated patients reported an overall response rate of 88% with CR + nCR rate of 20%. The most common adverse events were sensory neuropathy (31%), constipation (28%), myalgia (13%), and neutropenia (13%).[31] Another phase II study of bortezomib in high risk newly diagnosed multiple myeloma was conducted by the Eastern Cooperative Oncology Group (E2A02). High risk patients were defined B2 – microglobulin levels of $\geq$ 5.5mg/L, ch13q deletion or plasma cell labeling index $\geq$ 1. Patients received induction treatment with bortezomib 1.3mg/m^2 on day 1, 4, 8, and 11 every 21 days for 8 cycles. After induction, patients were scheduled to receive bortezomib 1.3mg/m^2 every other week indefinitely. Alternatively, eligible patients could undergo PBSC mobilization after 4 cycles. In patients with progressive disease during maintenance treatment, the induction was repeated. A total of 44 patients were enrolled. Preliminary data were presented in 19 patients, 13 patients (68.4%) achieved a partial response. One of 2 evaluable patients with deletion 13q, 6 of 8 evaluable patients with LI $\geq$ 1 and 11 of 15 evaluable patients with B2 - microglobulin $\geq$ 5.5 mg/L achieved a partial response [(38).]

Potential Risks of Bortezomib

More than 55,000 people have been exposed to Bortezomib (Velcade).

Known Anticipated Risks of VELCADE 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 that may increase the risk of bleeding*, anemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*
Uncommon	Febrile neutropenia
Cardiac Disorders	
Common	Arrhythmias including tachycardia, atrial fibrillation, and palpitations; acute development or exacerbation of cardiac failure, including congestive heart failure*; pulmonary edema*
Uncommon	Cardiogenic shock*, new onset of decreased left ventricular fraction*, atrial flutter, cardiac tamponade*, bradycardia, atrioventricular block (complete)
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impairment
Eye Disorders	
Common	Blurred vision, conjunctival infection and irritation

Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Uncommon	Conjunctival hemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhea*, nausea, vomiting*
Very common	Gastrointestinal and abdominal pain, excluding oral and throat
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, stomatitis and mouth ulceration, dysphagia, gastrointestinal hemorrhage (upper and lower gastrointestinal tract)*, rectal hemorrhage (includes hemorrhagic diarrhea)
Uncommon	Eructation, tongue ulceration, retching, upper gastrointestinal hemorrhage*, hematemesis*, oral mucosal petechiae, ileus paralytic*, odynophagia, enteritis, colitis, oesphagitis, fungal oesphagitis, enterocolitis, acute pancreatitis*
General Disorders and Administration Site Conditions	
Most common	Asthenic conditions, including weakness, fatigue, lethargy, and malaise; pyrexia
Very common	Rigors, edema of the lower limbs
Common	Neuralgia, chest pain, mucosal inflammation*
Uncommon	Injection site pain and irritation, injection site phlebitis, general physical health deterioration*, injection site cellulitis, catheter site cellulitis, injection site infection
Hepatobiliary Disorders	
Common	Abnormal liver function tests
Uncommon	Hyperbilirubinemia, hepatitis*
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, lower respiratory tract and lung infections*, pneumonia*, Herpes zoster*
Common	Herpes zoster disseminated,*, postherpetic neuralgia, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, catheter-related infection*, sepsis and bacteremia*, cellulitis and other skin infections*, Herpes simplex
Uncommon	Bronchitis, gastroenteritis*, septic shock*, urosepsis*, aspergillosis*, tinea infections, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic
Injury, Poisoning, and Procedural Complications	
Common	Catheter-related complication
Investigations	
Common	Increased ALT, increased AST, increased alkaline phosphatase

Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Uncommon	Increased GGT, oxygen saturation decreased*, blood albumin decreased
Metabolism and Nutritional Disorders	
Most common	Decreased appetite and anorexia, which may result in dehydration and/or weight loss
Very common	Dehydration*
Common	Hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, pain in limb, myalgia, arthralgia
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA high-level term peripheral neuropathy NEC)
Very common	Paresthesia and dysesthesia; dizziness, excluding vertigo; headache
Common	Polyneuropathy, syncope, dysgeusia
Uncommon	Convulsions, loss of consciousness, ageusia, encephalopathy, paralysis*, reversible posterior leucoencephalopathy syndrome
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumor lysis syndrome*
Psychiatric Disorders	
Very common	Anxiety
Common	Confusion
Renal and Urinary Disorders	
Common	Renal impairment, including renal failure and increased serum creatinine*; hematuria
Uncommon	Difficulty in micturition
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnea
Common	Epistaxis, exertional dyspnea, pleural effusion*, rhinorrhea, hypoxia*
Uncommon	Hemoptysis*, acute respiratory distress*, respiratory failure*, pneumonitis*, lung infiltrates, pulmonary alveolar hemorrhage*, interstitial lung disease*, pulmonary hypertension*
Skin and Subcutaneous Tissue Disorders	
Very common	Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis
Common	Urticaria
Uncommon	Leukocytoclastic vasculitis
Vascular Disorders	
Very common	Hypotension*
Common	Orthostatic/postural hypotension, petechiae

Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Uncommon	Cerebral hemorrhage*

Source: VELCADE Investigator's Brochure, Edition 10

ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma glutamyl transferase

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

* Fatal outcomes have been reported

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

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. 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 Velcade may be found in the Investigator's Brochure.

Preparation, Handling, and Storage of Bortezomib (Velcade)

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

Drug is available in sterile, single use vials containing 3.5 mg of VELCADE. Each vial of VELCADE 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 VELCADE 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 VELCADE 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.

4.1.2 Thalidomide

Mechanism of action of thalidomide is not fully understood. In multiple myeloma, thalidomide has been shown to block different pathways for disease progression. In addition to anti-angiogenic properties, thalidomide also possesses immunomodulatory and anti-inflammatory properties. Thalidomide reduces production of vascular endothelial growth factor (VEGF) and interleukin6 (IL-6), a growth factor for proliferation of myeloma cells, by bone marrow stromal cells. [40] This drug can modulate the expression of cell surface adhesion molecules like TNF-alpha, ICAM- 1 and VCAM 1. Thalidomide also generates apoptotic signals through activating capspase-8 mediated cell death, promoting c-jun terminal kinase (JNK) which leads to increased permeability of mitochondrial pores, and increasing production of pro-apoptotic proteins such as cytochrome C and second mitochondrial-derived activator of caspase (Smac). In addition, thalidomide modulates host immune response by augmenting the activity of natural killer (NK) cells through increased production of IL-2 from activated T-cells. [41]

Teratogenecity is the most serious side effect of thalidomide. S.T.E.P.S (System for Thalidomide and Prescribing Safety) program has been designed to minimize the chance of fetal exposure to thalidomide. Under this program, women of childbearing age are monitored for pregnancy, and both male and female patients are instructed to abstain from sexual intercourse or to use highly effective contraceptive methods.

The incidence of toxicities with thalidomide usually correlates with the dose of the drug. Patients usually tolerate doses of 200 mg/day or less well and experience more side effects with higher doses. Incidence of certain toxicities such as constipation and sedation decreases with time, whereas incidence of peripheral neuropathy and hypothyroidism increases in frequency. Somnolence (~75%), constipation (~85%), xerostomia (~10%), tremors (~35%), skin rash (~45%), and neutropenia (15-25%) are the most common side effects of thalidomide. Severe incidence of somnolence (~5-10%), constipation (~5%), and peripheral neuropathy (~3-5%) has been reported in less than 10% of patients. Less common side effects of thalidomide include: bradycardia (~25%), peripheral edema (~15%), anasarca (~3%), ataxia (~15%), hearing loss (~3%), Steven- Johnson syndrome (<3%), and headaches (~10%). Although rare, seizures, confusion, impotence, elevation of liver enzymes, hypothyroidism, menstrual irregularities, hyperglycemia, and hypoglycemia have also been reported. Peripheral neuropathy can occur in about

80% of patients, with grade 3-4 neuropathy occurring in about 3-5% of all patients. This side effect usually occurs after 6 months of therapy. Deep venous thrombosis (DVT) and pulmonary embolism (PE) are serious side effects occurring in ~ 1-3% of patients receiving single-agent thalidomide. The incidence of thrombosis can climb to 15-25% when thalidomide is added to standard chemotherapy. Use of prophylactic low-molecular weight heparin, warfarin, and aspirin for all patients receiving thalidomide is being studied. Currently they are recommended during induction treatment with combination of thalidomide and dexamethasone when tumor burden is high. The incidence of DVT during maintenance therapy with thalidomide post autologous stem cell transplant has not been reported to be high [27] and role of DVT prophylaxis in this setting remains to be determined. Therefore no anticoagulation therapy will be used during maintenance therapy in this study.

How supplied: Oral capsule: 50, 100, and 200 mg

5.0 PATIENTS ELIGIBILITY

5.0a INCLUSION CRITERIA

5.1a Multiple Myeloma patients with symptomatic disease, stage II or III at diagnosis or progressive stage I requiring chemotherapy and/or radiation therapy (by Salmon-Durie classification), who are not eligible for tandem transplant study using TMI; (protocol 04064) because of previous radiation or eligibility criteria. Documentation of disease staging by both Salmon-Durie classification and International Staging System (ISS) is required.

5.2a Patients with non-secretory myeloma should have measurable serum free–light chain protein by the Free-lite test or measurable disease such as a soft tissue myeloma.

5.3a A minimum of 4×10^6 of CD 34 Positive cell/kg has been harvested.

5.4a Patients must be $\leq$ 70 years old at the time of enrollment.

5.5a A KPS of $\geq$ 70 % is required unless the KPS is impaired due to bone disease.

5.6a No contraindication to the collection of a minimum of 4×10^6 CD34+ cells/kg by apheresis.

5.7a All patients must have signed a voluntary, informed consent in accordance with institutional and federal guidelines.

5.8a Adequate hepatic function as demonstrated by bilirubin, ≤ 1.5 mg/dl, and SGOT and SGPT < 2.5 x upper limits of normal.

5.9a Acceptable renal function as demonstrated by measured creatinine clearance of ≥ 40cc/min.

5.10a Absolute neutrophil count of > 1000/µl, platelet count of > 100,000/µl.

5.11a Cardiac ejection fraction ≥ 45% by MUGA scan and/or by echocardiogram.

5.12a Adequate pulmonary function as demonstrated by DLCO ≥ 50% of predicted lower limit.

5.13a HIV antibody tests negative.

5.14a No other medical, or psychosocial problems which in the opinion of the primary physician or principal investigator would place the patient at unacceptably high risk from this treatment regimen.

5.0b EXCLUSION CRITERIA

5.1b Presence of peripheral neuropathy ≥ grade II.

5.2b Patients with evidence of disease progression (with ≥ 25% increase in M protein) on bortezomib and or thalidomide therapy prior to transplant.

5.2c Pregnant or nursing women, as well as women of child bearing age, who are unwilling to use a dual method of contraception and men who are unwilling to use condom.

5.2d Patients with history of hypersensitivity to bortezomib, boron or mannitol.

6.0 TREATMENT PLAN

6.1 Pre-treatment Evaluation to be done within 6 weeks of enrollment. If PSC collection is prolonged beyond 3 days, an additional 7-10 days will be allowed for the pre-treatment evaluations.

6.1.1 History and physical examination.

6.1.2 Radiographic evaluation: Bone survey, MRI of the involved area as indicated clinically.

6.1.3 Chest X-ray.

6.1.4 Pulmonary function tests

6.1.5 MUGA scan or echocardiogram.

6.1.6 CBC, differential count, platelet count, renal and liver function tests, electrolyte, blood sugar, ca, and uric acid (should be done within 4 weeks of enrollment).

6.1.7 Urine analysis (should be done within 4 weeks of enrollment).

6.1.8 24 urine collection for total protein, protein electrophoresis, immuno electrophoresis, and creatinine clearance. Creatinine clearance will be repeated after transplant prior to start of bortezomib.

6.1.9 Hepatitis panel, HIV antibody, HSV and CMV antibody.

6.1.10 Unilateral bone marrow biopsy and aspirate and biopsy for morphology, cytogenetics and FISH.

6.1.11 Serum protein electrophoresis, quantitative serum immunoglobulins, serum immunofixation electrophoresis, and free light chain assay (FLC).

6.1.12 Beta-2 Microglobulin level and albumin level for International Staging System (ISS) documentation.

6.1.13 Serum pregnancy test for women of childbearing potential (should be done within 4 weeks of enrollment and repeated every 4 wks while on maintenance therapy).

6.1.14 HLA, ABO and Rh typing. These tests may be done prior to autologous PSCT.

6.1.15 Double lumen Hickman catheter will be placed prior to stem cell harvest. (CBC, Comprehensive metabolic panel, pregnancy test for patients in child bearing age should be done immediately prior to start of melphalan).

6.2 Patient Registration

After all pre-treatment evaluations have been performed and autologous PSC at a minimum dose of 4 x 10^6 CD34 + cell /kg has been harvested and separated into 2 bags with a minimum of 2 x 10^6 CD34 + cell /kg per bags. Eligibility requirements must be reviewed by a member of the department of Biostatistics and the principal investigator. Patients will be registered to the trial after completion of stem cell collection and signing the informed consent form.

6.3 High-Dose Chemotherapy

6.3.1 Melphalan

6.3.1.1 DAY –3, -2 and -1

Admission (patients will be admitted on day -3 per COH standard practice), history and physical, Comprehensive Metabolic Panel 18, Mg, CBC, differential and PLT count. Review of required laboratory, screening and radiographic data.

Prophylactic IV, or p.o. fluconazole at 400 mg daily will be given to patients on D +1, after melphalan started.

Intravenous hydration per standard bone marrow transplant procedure is initiated on admission. After 4 hours of hydration on day –2 and –1 melphalan 100 mg/m^2 will be infused in $\leq$ 30 minutes. Hydration is continued for at least 24 hours after the last dose of melphalan.

Appropriate intravenous antiemetics will be given.
Melphalan should be dosed based on ideal body weight for patients who weigh 100 – 120% of their ideal body weight. For patient who weigh less than 100% of their ideal body weight, dosing is based on actual bodyweight. For patients who weigh above 120% of their ideal body weight, the adjusted ideal body weight (AIBW) should be used:
AIBW = Ideal Body Weight + [(0.25) x (Actual BW – Ideal BW)]

6.3.1.2 DAY 0

A minimum cell dose of 2 x 10^6 CD-34 + cell/kg of previously collected peripheral blood stem cells will be reinfused. The remainder of cryo-preserved autologous peripheral blood stem cells could be stored at the discretion of the treating physician for possible future use in the event of disease progression for a second autologous PSCT. Patients will be taken off study at the time of disease progression.

6.3.1.3 Day +5

Filgrastim 5 μg/kg daily, IV, or SQ will be started. Continue with Filgrastim until ANC > 1000/ is achieved per COH standard practice or per physician's discretion.

6.3.3 Maintenance Therapy

Patients will be started on maintenance therapy approximately within 4 – 8 weeks after transplant. Patients should have at least a WBC $\geq$ 3.0 and or ANC > 1000, platelet count $\geq$ 100,000 and no peripheral neuropathy $\geq$ grade II, within 14 days before bortezomib. Creatinine clearance is repeated prior to start of bortezomib and should be > 20 ml/min.

6.3.3a Bortezomib: will be administered IV bolus at 1.3 mg/m^2 once a week for 3 weeks (days 1, 8, & 15) followed by 1 week rest. The Bortezomib cycle should be repeated every 28 days +/- 4 days for patient schedule flexibility. Bortezomib will be started within 4-8 weeks after transplant and continued for 6 cycles after transplant. Patients should have WBC $\geq$ 3000, ANC $\geq$ 1000, and platelets $\geq$ 100, 000 on day 1 of each cycle.

6.3.3b Dexamethasone: will be started at 40 mg daily D1-4 of every month for approximately a total duration of 12 months.

6.3.3c Thalidomide: Two weeks after completion of bortezomib patient will be started on thalidomide at 50mg per day. The dose will be escalated by 50mg per week if tolerated to a target dose of 200mg/day till disease progression. Dose reduction to a minimum of 50 mg every other day allowed for thalidomide related toxicities.

6.4 Dose Adjustments – Only 2 dose reductions are allowed. Patients who require dose reductions below 0.7 mg/m^2 will be taken off study.

Dose Level	Bortezomib Dose
1	1.3 mg/m^2
-1	1 mg/m^2
-2	0.7 mg/m^2

6.4.1 Bortezomib: For grade ≥ II peripheral neuropathy bortezomib will be held. It may be resumed at the next lower dose level if peripheral neuropathy resolved or decreased to $\leq$ grade I. For persistent peripheral neuropathy grade ≥ II with no improvement after 12 weeks bortezomib is discontinued permanently.

For grade III hematologic toxicities bortezomib will be held for up to 4 weeks until the patient has WBC $\geq$ 3.0, ANC > 1000 and PLT $\geq$ 100,000 before bortezomib is restarted at the next lower dose level. If a patient experiences grade II hematologic toxicities, bortezomib is held until the day 1 parameters are met. Bortezomib should be restarted at the same dose, unless a dose-reduction is approved by the PI, but NOT dose reduces when

treatment parameters are met. If treatment is delayed by more than 4 weeks due to allow for recovery of hematologic toxicity, the patient will be taken off study. Dose interruption or discontinuation is not required for lymphopenia of any grade.

For days 8 and 15, patients must have WBC $\geq$ 2000, ANC $\geq$ 1000, and platelets $\geq$50,000.

For any other grade $\geq$ III toxicity bortezomib will be held until toxicity is resolved or is grade $\leq$ I. The dose then will be reduced to next lower level from 1.3mg/m^2 to 1mg/m^2 and from 1mg/m^2 to 0.7mg/ m^2. Dose interruption or discontinuation is not required for lymphopenia of any grade.

6.4.2 Dexamethasone: for any grade III or more toxicity dexamethasone will be held. Dose can be reduced by 50% to 20mg D1-4 for the subsequent cycles.

6.4.3 Thalidomide: For any grade $\geq$ III toxicities thalidomide will be held until the toxicity is resolved. Dose will be reduced by 50% to a minimum of 50mg every other day. Dose may be later on escalated to the target dose of 200mg per day at the discretion of the treating physician. If bortezomib is discontinued prior to completion of 6 months, patients can start thalidomide earlier, at least 2 weeks after the last dose of bortezomib. Patients must not have peripheral neuropathy $\geq$ grade II, before the start of thalidomide.

6.4.4 Patients unable to tolerate lowest dose of bortezomib, dexamethasone, and thalidomide need to stop the treatment with that agent permanently.

7.0 SUPPORTIVE CARE POST TRANSPLANT

Prophylactic IV, or p.o. fluconazole at 400 mg daily will be given to patients on D +1, after melphalan started.

Patients will be supported through IV hydration and TPN, red cell and platelet transfusions as needed. CBC, PLT and SMA7, SMA 12, and Mg and weekly chest x-ray (as needed) as well as the necessary fever workup will be done. Patients can be followed in the outpatient unit unless they develop neutropenic fever, uncontrollable diarrhea or other problems requiring inpatient care. Inpatient care will be provided in rooms equipped with HEPA filter and they will be in protective isolation. All blood products will be filtered and radiated.

Patients should receive prophylaxis against PCP and varicella – zoster according to City of Hope standard practice. Patients will also receive bisphosphonate therapy as clinically indicated, once a month. Bisphosphonate therapy will be continued till CR is achieved. It can be discontinued in patients who remain in CR per COH guidelines.

DVT prophylaxis: No DVT prophylaxis is recommended during Velcade phase of maintenance study. However, during Thalidomide phase of the study, prophylactic aspirin or low molecular weight heparin or warfarin are suggested only in patients with a past medical history of DVT on Thalidomide or at high risk of developing DVT/PE unless contraindicated. High risk will be defined as history of DVT/PE in the past, significant family history of DVT/PE, smoking history, use of oral contraceptives, and concurrent use of epoetin.

8.0 EVALUATION AND TOXICITIES

Physical evaluation, laboratory and radiographic evaluation will be performed as outlined in the treatment regimen. When evaluating toxicity, the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 3.0 will be used.

Table 8.a. Management of Patients with Bortezomib (VELCADE) Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 2 (interfering with function but not with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves or if ≤ gr I reinitiate with a reduced dose of VELCADE at the next dose level.
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves or if ≤ gr I reinitiate with a reduced dose of VELCADE at the next dose level
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VELCADE
Grading based on NCI Common Terminology Criteria CTCAE v3.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living

The neurotoxicity-directed questionnaire (see FACT/GOG- Neurotoxicity Questionnaire, Version 4, Appendix 18.1) 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.

9.0 STUDY PARAMETERS

	Within 6 Wks Prior to enrollment##	Melphalan PBSCT	Post PBSCT Prior to Start of Bortezomib	Bortezomib Maintenance Therapy Day 1, 8, & 15 (Q28 days +/- 4 days)	Q 1 mo** Post PBSCT ± 2 weeks for the first year	Q 3 mos** Post PBSCT ± 2 weeks for the first year	Post PBSCT after 6 cycles of bortezomib	Q yr+ Post PBSCT ± 2 weeks 2 – 4 years
History and Physical	X	X	X			X	X	X
CBC, DIFF, PLT/SMA7	X	X	X	X#		X	X	X
Renal, liver function tests,	X	X	X			X	X	X
Ca, uric acid	X							
Urinalysis	X							
Chest X-ray	X							
Bone x-rays, MRI (if indicated),	X						X	X
SPEP, QIG, IEP, Beta-2 Microglobulin, serum FLC	X		X			X	X	X
24 hr urine for PEP, IEP, total protein, creatinine clearance*	X		X				X	X
MUGA Scan/ or echo	X							
EKG	X							
PFT	X							
AB, RH, HLA Typing	X							
BM, ASP, BX, for flow cytometry, morphology, cytogenetics,	X		X				X	X
Serum B-HCG**	X	X	X	X**	X			X
HIV, Hepatitis Panel to include A,B,C; Herpes and CMV Titer	X							
FACT-GOG Neurotoxicity Questionnaire to be completed***	X		X		X			X

*creatinine clearance is obtained at enrollment and prior to start of bortezomib.

**B-HCG is repeated in women of childbearing age prior to start of melphalan and then monthly as long as receiving maintenance therapy.

***FACT- GOG Neurotoxicity questionnaire will be completed at baseline (within 6 wks prior to enrollment) and at 2 months post transplant and once a month after that for the first year. For the second year the questionnaire will be completed every 3 months as long as on thalidomide for the duration of the study.

CBC, PLT, and Diff only.

An additional 7-10 days will be allowed if PSC collection is prolonged beyond 3 days.

+ SPEP, QIg, IEP and Serum FLC are repeated every 3-4 months in years 2-4.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Response is evaluated based on a new International myeloma working group uniform response criteria.[36]

Table 1 International Myeloma Working Group uniform response criteria: CR and other response categories

Response subcategory	Response criteria[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disapperance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on Electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100mg per 24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200mg per 24 h If the serum and urine M-protein are unmeasurable,d a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a . 50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an Indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR. complete response: FLC, free light chain; PR, partial response; SD, stable disease;sCR, stringent complete response; VGPR, very good partial response.

[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
[b]Confirmation with repeat bone marrow biopsy not needed.
[C]Presence/absence of clonal cells is based upon the κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.
[d]Refer to table 4 for definitions of measurable disease.

Table 2 International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	Relapse criteria
Progressive disease[a] To be used for calculation of time of progression and progression-free survival end points for all patients including those in those in CR (includes primary progression disease and disease progression on or off therapy)	Progression Disease: requires any one or more of the following: Increase of ≥ 25% from baseline in Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved anduninvolved FLC levels. The absolute increase must be >l0mg/dl. Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[C] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/1) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)b It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.Smg/dI) [2.65 mmol/l] 4. Decrease in hemoglobin of ≥ 2 g/dl [1.25 mmol/1] (see Table 3 for further details) 5. Rise in serum creatinine by 2mg/dl or more [177 μmol/l or more)
Relapse from CR[a] (To be used only if The end point studied is DFS)[d]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥ 5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR. complete response: DFS, disease-free survival.
[a]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of $\geq$ 1 gm/dl are sufficient to define relapse if starting M-component is $\geq$ 5g/dl.
[C]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

11.0 REPORTING DATA

11.1 All primary data will be maintained by the Department of Biostatistics, City of Hope National Medical Center. This includes on study flow sheets, consent forms and off-study forms.

11.2 Removal of patients from protocol therapy: If at any time the constraints of this protocol are detrimental to the patient's health, the patient experience disease progression and /or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued and patient to be removed from the study. In this event:

- Document the reason(s) for discontinuation of therapy.
- Follow the patient for survival, progression, and relapse, per study parameters.

12.0 STATISTICAL CONSIDERATIONS

12.1 Sample Size

The objectives of this Phase II study are to evaluate the feasibility and toxicities of maintenance therapy, complete response rate, duration of response, 3-year progression-free and overall survival rates.

The maintenance therapy is considered feasible if more than 70% of the subjects are able to receive a minimum of 4 months of bortezomib therapy (patients able to receive bortezomib but on a reduced dose per protocol would not be considered "unable to tolerate"). The maintenance therapy is considered not feasible if less than 50% of the subjects are able to tolerate bortezomib therapy. With the early stopping rules, and more than 25/45 tolerating considered a success, this study has 85% power to determine feasibility with a type I error of 10% and an 84% chance of early stopping if not feasible (based on 5000 simulations). A second feasibility marker regarding thalidomide will be also be assessed, but is not the basis of the sample-size and no related interim stopping rules are formalized for that component of the maintenance therapy.

To evaluate for feasibility during the study while preventing excess patients from receiving the therapy if it is clearly not feasible, we will enforce the following:

12.2 Early Stopping Rules

Inability to continue to receive bortezomib for a minimum of 4 months per protocol dose modification guidelines will constitute intolerance. The study will hold accrual, if the following numbers of patients able to tolerate bortezomib are observed (patients accrued will continue therapy per protocol):

Patients with 4 Months Follow-up	Stop if the Number Able to Tolerate Bortezomib is:
5	0
15	<=8
25	<=13
35	<=19

In order to accommodate the fact that several patients may be undergoing maintenance therapy when the stopping rule is activated, the following rule is to be followed: If after a hold on study accrual, the percent of patients unable to tolerate maintenance therapy remains above 50%, the study will not re-open. If the percent of patients unable to tolerate drops below 50%, accrual may re-start if the stopping condition was at 25 patients or less (if stopped at 35 patients with 4 months of followup, with <=19 able to tolerate, there will be no restart).

The regimen, if feasible, will also be evaluated for its potential to improve three-year progression-free survival. Historical data suggest approximately 52% of the patients are expected to be progression-free at 3 years after autologous stem cell transplant followed by maintenance thalidomide (Attal et al., Blood Nov 2006; 108 (10), P3289-3294). With 45 patients, there is 81% power to detect an improvement to a 66% 3-year progression-free survival with the proposed maintenance therapy with a one-sided type I error of 10%. This assumes an accrual time of 24 months, and a minimum follow-up of 36 months. The critical value for 3-year PFS rate is 60%, which, if observed, would suggest that the proposed therapy is a promising new maintenance therapy. This calculation is based on a constant hazard model, and on a parametric exponential estimate.

12.3 Criteria for Feasibility

If the study accrues to the full 45 patients, the trial will be considered a success on the primary endpoint of feasibility if 26 or more patients tolerated treatment. If the estimated feasibility rate in the study group is equal to 70% then the 95% confidence interval would range from 57% to 83%.

12.4 Analytic Plan

The primary endpoint of feasibility will be estimated as a proportion along with the 95% confidence interval for the binomial. If our accrual goal is met with no premature termination due to significant toxicity, a secondary goal of assessing response, progression-free survival (PFS), and overall survival (OS) will be carried out. Survival estimates will be made using the product-limit method of Kaplan and Meier, with 95% confidence limits calculated using the logit transformation. It is hoped that PFS and OS will be further improved with the use of the proposed maintenance therapy. If the patient discontinues maintenance therapy due to disease progression or personal choice, patient will be taken off protocol. Patients who discontinue maintenance treatment due to toxicities will remain on the study and will be followed for the study endpoints including disease response, PFS and overall survival. We will summarize the duration and the dose of boretzomib therapy and the duration and the dose of sequential thalidomide therapy.

12.5 Toxicity Grading

When evaluating toxicities of maintenance therapy The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0 will be used to grade adverse events as well as to assign perceived attribution of these events to the study treatment regimen. By these criteria, toxicity is defined as an adverse event considered to possibly, probably or definitely related to treatment.

13.0 GENDER AND ETHNICITY STATEMENT

The City of Hope has a plan in place to increase minority recruitment to our studies in compliance with the National Institute of Health policy for recruitment of women and minorities.

The table below shows the distribution by sex and race of the patients accrued to therapeutic clinical studies at City of Hope for the past five years. Our goal is to maintain our high accrual of women while continuing to increase the accrual of minority subjects.

Accrual Goal by Sex and Ethnicity								
		By Sex		By Ethnicity				
Site	Accrual Goal	Female	Male	White	Hispanic	Black	Asian/ Other	Unknown
Multiple Myeloma	45	21 (47%)	24 (53%)	24 (53%)	9 (20%)	10 (22%)	2 (4%)	0 (1%)

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study is to be approved by the Institutional Review Board of the City of Hope. All patients will have signed an informed consent for participation in research activities, and will have been given a copy of the Experimental Subject's Bill of Rights.

When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence, according to current legal requirements. However, they will be made available for review, as required by the Food and Drug Administration (FDA) or to other authorized users such as the National Cancer Institute (NCI) under the guidelines established by the Federal Privacy Act.

15.0 DATA AND SAFETY MONITORING

A) Definition of Risk Level

This is a Risk Level 3 study, as defined in the "Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope", http://www.infosci.coh.org/ocrqa/forms/guidance.doc because it is a phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

B) Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.
Data and safety will be reported to the COH DSMB. Protocol specific data collection will include toxicities $\geq$ grade 3 based on NCI CTCAE, version 3.0. Reporting of data and safety to the DSMB will occur after the first 5 patients were enrolled and then after every 10 patients enrolled using the PMT report.

16.0 DEFINITIONS

A. Adverse Event Definition:

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

B. Serious Adverse Event Definition

A **serious adverse event** (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

C. Procedures for AE and SAE Reporting

Investigator-sponsor must report all serious adverse event (SAE) regardless of relationship with any study drug or expectedness to the COH DSMB and IRB and Millennium as soon as possible, but no later than 5 calendar days of the investigator-sponsor's observation or awareness of the event. All sub-investigators must report all SAEs to the investigator-

sponsor so that the investigator-sponsor can meet his/her foregoing reporting obligations to Millennium.

SAE Reporting to COH: Adverse events must be reported to the COH DSMB and IRB according to definitions and guidelines at http://www.infosci.coh.org/ocrqa/forms/guidance.doc and http://resadmin.coh.org/doc/irb3810.doc, which are defined below. AEs will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports.

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's Product Safety Department will send to the investigator-sponsor a monthly 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.

SAE Reporting to Millennium, Contact Information (North America Reporting)
Millennium Product Safety
Fax: (617) 551-3746
Telephone: (617) 551-2972
E-mail: productsafety@mpi.com

For both serious and non-serious adverse events, the investigator or sub-investigator must determine both the intensity of the event and the relationship of the event to drug administration.

Relationship to drug administration will be determined by the investigator or sub-investigator responding yes or no to the question: Is there a reasonable possibility that the adverse event is associated with the drug?
Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 3.0, as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

17.0 ADMINISTRATIVE REQUIREMENTS

17.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). 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.

17.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see section 8.5). The IRB/IEC 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/IEC 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/IEC by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

17.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

17.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, tudy 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.

17.5 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC 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/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.
Any departures from the protocol must be fully documented in the source documents.

17.6 On-site Audits

Regulatory authorities, the IEC/IRB and/or Millennium's clinical quality assurance group 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.

17.7 Drug Accountability

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator 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 or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

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

17.8 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- 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.

17.9 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

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