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Protocol Page

PHASE II STUDY OF SUBCUTANEOUS BORTEZOMIB FOR PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROME 2012-0562

Core Protocol Information

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Protocol Body

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PHASE II STUDY OF SUBCUTANEOUS BORTEZOMIB FOR PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROME

VERSION 2

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1.0 OBJECTIVES

Primary objectives:

1. To determine the efficacy and clinical activity of subcutaneous (SC) bortezomib in patients with low or intermediate-1 myelodysplastic syndrome (MDS)

Secondary objectives:

2. To determine the safety and tolerance of SC bortezomib in low or intermediate-1 MDS

3. To study the effect of SC bortezomib on modulation of NF-Kb activity in patients with low or intermediate-1 MDS by p65 immunohistochemistry staining (ICH)

2.0 BACKGROUND

2.1 MDS

The myelodysplastic syndromes (MDS) consist of a group of clonal myeloid disorders characterized by ineffective hematopoiesis with peripheral blood cytopenias and a tendency towards transformation to acute myelogenous leukemia (AML)[1,2]. The precise incidence of MDS is not known, however incidence rates for MDS in the United States have been estimated at 1.0 to 12.6 per 100,000 individuals. MDS affects more frequently patients of advanced age, particularly those > 60 years of age, that are not generally candidates for intensive chemotherapy or bone marrow transplantation strategies[3]. The risk of MDS also appears to be greater in men than in women. MDS is a heterogeneous disease. In some patients it manifests as an indolent disease whereas in others it is aggressive and may progress rapidly to marrow failure or acute myeloid leukemia (AML). MDS can be classified using different systems, such as the French-American-British (FAB), or the World Health Organization (WHO) classifications[4]. The International Prognostic Score System (IPSS), is a prognostic classification of MDS that is widely used to predict survival and progression to AML[5]. The IPSS combines data on the percentage of marrow blasts, cytogenetic alterations and number of cytopenias to estimate a patient's risk category. With this scoring system, patients are divided into low, intermediate (int-1), int-2 and high-risk disease (Table 1). Based on this data, the

median survival of patients with low or int-1 MDS ranges between 3.5 to 5.7 years. For the majority of low- or int-1 risk patients (excluding only those with the rare 5q deletion or PDGFR gene rearrangement subtypes: approximately 10-15%), specific and highly active therapy is not available or approved. Hence, many physicians, especially in the community tend to "observe" these patients and do not start specific MDS directed therapy. However, patients with low/ int-1 MDS may develop significant cytopenia's. A large number of these patients will become transfusion dependent over time which may result in iron overload with its resultant complications including cardiomyopathy, liver failure, diabetes and hypothyroidism. Thus, there may be an unmet medical need for treatment of low/ int-1 MDS.

Table1. IPSS for MDS

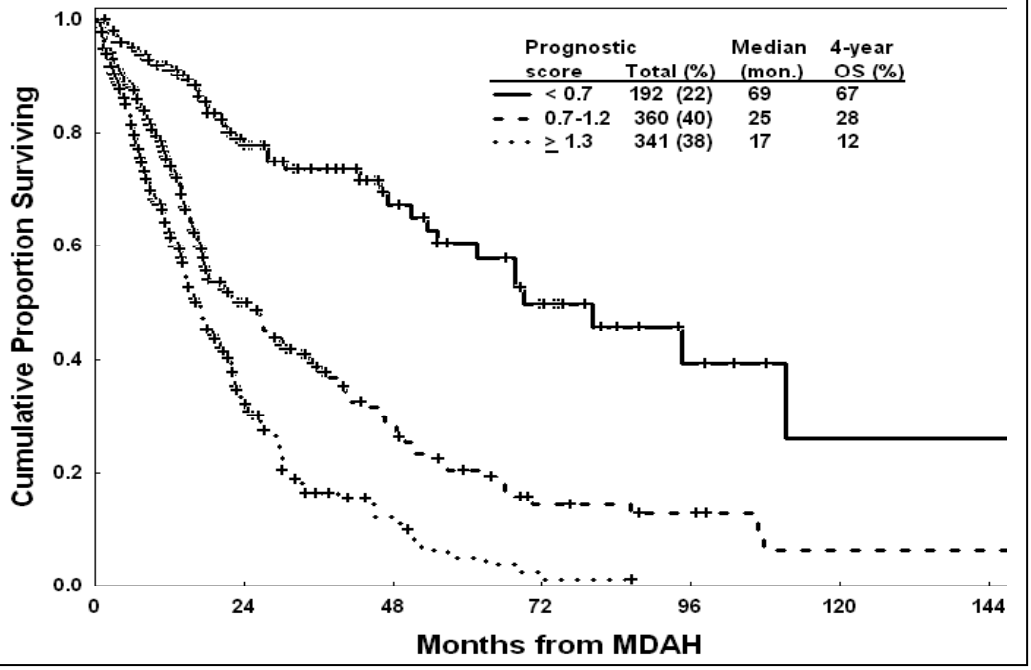
		Score Value			
Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
% BM blasts	<5	5-10	--	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Score are as follows: Low: 0; INT-1: 0.5-1.0; INT-2, 1.5-2.0 and high risk ≥ 2.5 points. Good karyotype includes: diploid, -Y, del(5q), del(20q). Poor karyotype: complex (>3 abnormalities) or chromosome 7 abnormalities. Intermediate karyotype, all others. Cytopenias are considered if the absolute neutrophil count is < 1800 K/uL; hemoglobin less than 10 g/dl and the platelets are less than 10^5 K/uL.

We have recently completed an analysis of the prognosis of patients with lower risk MDS (low and int-1) referred to MDACC over the last 25 years[6]. We analyzed the outcomes of 898 patients previously untreated referred to our center, and have developed a prognostic score. The score is based on patient characteristics including cytogenetics, age, percentage of blasts, hemoglobin and platelet counts. Based on this model, patients with lower-risk MDS can be divided in 3 groups (Figure 1). As can be seen in the figure, over 60% of patients with lower risk MDS have poor prognosis. Of

great importance, it should be noted that only 10% of the patients transformed to AML. This indicates that a majority of patients with lower risk MDS die as a consequence of MDS and not from AML transformation. Therefore the traditional strategy of "watch and wait" used by many physicians in patients with lower-risk MDS may not be indicated. Therefore new therapies are needed for this subgroup of patients. At the present time, 3 therapies are approved for patients with MDS in the US. These include 5-azacitidine[7], lenalidomide[8] , and more recently 5-aza-2'-deoxycitidine (decitabine)[9]. Both 5-azacitidine and decitabine are hypomethylating agents, whereas lenalidomide is a thalidomide derivative. Lenalidomide is indicated for specific subset of patients with MDS, in particular those with alterations of chromosome 5 and anemia with low-risk disease[8]. Of importance, most of the clinical benefit with the hypomethylating agents has been documented for patients with more advance disease, such as those with int-2 and high-risk disease[7,9,10].

Figure 1. Survival of patients with lower risk MDS by MDACC score



2.2 Rationale for the study

At the present time, 3 pharmacological agents are approved for patients with MDS in the United states. These include azacytidine[7], 5-aza-2'-deoxycytidine (decitabine)[9] and lenalidomide[8]. Most of the clinical benefit from hypomethylating agents (azacytidine and decitabine) has been documented in patients with INT-2 or High-risk MDS[7,9,11]. Lenalidomide is only active in a small fraction of patients (those with del5q and anemia, approximately 5-10% of patients). Transplant is offered only to a very small group of patients with Low/ INT-1 disease. Thus, standard of care in lower risk MDS remains suboptimal and there is a need to identify new therapies specifically targeting patients with Low/INT-1 MDS.

Bortezomib is a reversible inhibitor of 26S proteasome and induces apoptosis in human cell lines, especially malignant cells of hematopoietic lineage[12]. Bortezomib induces apoptosis by inhibition of the NF-kB pathway[13]. Leukemic stem cells are highly dependent on NF-kB for survival[14,15]. In-vivo studies have shown that bortezomib can inhibit leukemic cell proteasomes resulting in suppression of NF-kB activity in leukemic cell lines[16,17]. Investigators have further shown that MDS progenitors are also highly dependent on NF-kB activation for survival[18]. In clinical studies bortezomib has shown modest activity in myeloid neoplasms, both as a single agent and in combination with other cytotoxic agents[17,19,20].

We have identified NF-kB activation (p65) in lower risk MDS (Figure 2). We have also detected p65 activation in MDS by performing immunohistochemistry on marrow specimens of patients with lower risk MDS. In fact P65 activation was noted to be a common feature of lower risk MDS. The clinical course of patients with p65 activated MDS and their response to therapy remains poorly understood at this time. However, we expect that patients with activated p65 will have more advanced disease and therefore worse risk. Thus p65 could be a potential target for therapy in MDS. We believe that p65 activation serves as a biomarker of NF-kB activation. Hence, we hypothesize that subcutaneously administered (SC) bortezomib could have clinical activity in patients with lower risk MDS and p65 activation. As mentioned above, in our experience, patients with lower risk MDS but poor prognosis merit therapeutic

intervention. We are encouraged by the activity and safety reported with SC bortezomib in other clinical condition and therefore the interest in this study.

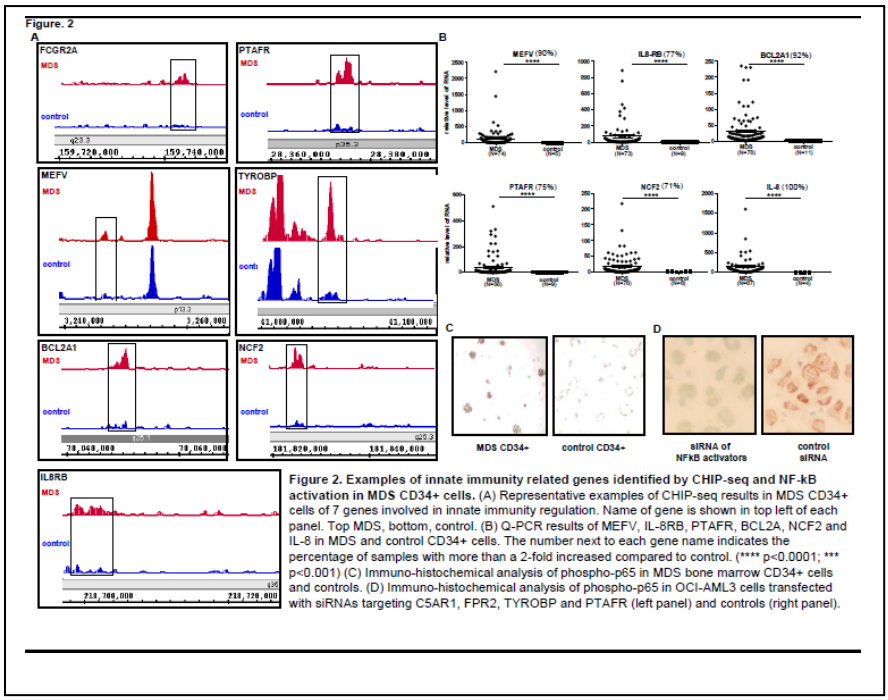


Figure 2. Examples of innate immunity related genes identified by CHIP-seq and NF-kB activation in MDS CD34+ cells. (A) Representative examples of CHIP-seq results in MDS CD34+ cells of 7 genes involved in innate immunity regulation. Name of gene is shown in top left of each panel. Top MDS, bottom, control. (B) Q-PCR results of MEFV, IL-8RB, PTAFR, BCL2A, NCF2 and IL-8 in MDS and control CD34+ cells. The number next to each gene name indicates the percentage of samples with more than a 2-fold increased compared to control. (**** p<0.0001; *** p<0.001) (C) Immuno-histochemical analysis of phospho-p65 in MDS bone marrow CD34+ cells and controls. (D) Immuno-histochemical analysis of phospho-p65 in OCI-AML3 cells transfected with siRNAs targeting C5AR1, FPR2, TYROBP and PTAFR (left panel) and controls (right panel).

2.3 Bortezomib (Velcade, PS-341)

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

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The antineoplastic effect of bortezomib likely involves several

distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration, and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays.[i] 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.[ii,iii,iv,v,vi,vii,viii,ix,x,xi,xii,xiii,xiv] Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.[xv]

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

2.4 Clinical Pharmacokinetics, Pharmacodynamics, Distribution, Metabolism, Elimination, Renal impairment:

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 (Emax) model. The Emax 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.

Subcutaneous administration

Following multiple 1.3 mg/m^2 doses, the mean (SD) maximum plasma bortezomib concentration (C_{max}) was approximately 10 times lower following SC administration (20.4 [8.9] ng/mL) compared with IV administration (223 [101] ng/mL), with a short T_{max} of approximately one-half hour following VELCADE SC injection. However, AUC_{last} was equivalent for both routes of administration with a geometric mean ratio (SC to IV) of 0.992 and 90% CI of 80.18% to 122.80%; ie, within the standard 80 – 125% bioequivalence criteria.

The mean percent inhibition of proteasome activity (E_{max}) was comparable for the SC and IV groups (63.7% vs. 69.3%; respectively) following multiple 1.3 mg/m^2 SC or IV doses of VELCADE. Mean AUE_{72} following SC injection was comparable to that of the IV injection and within the observed variability (CV = 36 - 55%).

The exploratory analyses showed that there were no apparent pharmacokinetic or pharmacodynamic differences related to the site of SC injection (abdomen versus thigh) taking into consideration the small sample size of the pharmacokinetic/pharmacodynamic part of the study.

Bortezomib was reconstituted to a concentration of 2.5 mg/mL for SC administration. In the randomized Phase 1 study CAN-1004, bortezomib was injected subcutaneously in a concentration of 1 mg/mL. The pharmacokinetic and pharmacodynamic parameters of the SC administration were comparable between the 2 studies (Table 1). Thus, the concentration of the SC injected solution does not appear to influence bortezomib pharmacokinetics or pharmacodynamics. The pharmacokinetic and pharmacodynamic parameters following IV administration in the current study were also comparable to those observed previously for IV administration[xxiv].

Table 1: Summary of Pharmacokinetic and Pharmacodynamic Parameters Following Subcutaneous Injections of VELCADE 1.3 mg/m^2 Using 2.5 mg/mL and 1.0 mg/mL Solutions

Parameter	2.5 mg/mL[a]	1.0 mg/mL[b]
C_{max} (ng/mL)[c]	20.4 (8.87)	22.5 (5.36)
T_{max} (h)[d]	0.5 (0.08-1.00)	0.5 (0.25-1.00)
AUC_{last} (ng.h/mL)[c]	155 (56.8)	195 (51.2)
AUE_{72} (%.h)[c]	1714 (617)	1619 (804)
E_{max} (%)[c]	63.7 (10.6)	57.0 (12.8)

AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of last quantifiable time point; AUE_{72}=area under the percent inhibition-time curve from time 0 to 72 hours; E_{max}=observed maximum percent inhibition of 20S proteasome activity (ChT:T); h=hours; SD=standard deviation; T_{max}=time when C_{max} is observed

[a] 26866138-MMY-3021

[b] 26866138-CAN-1004

[c] Mean (SD)

[d] Median (range)

The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3mg/m^2 to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

The pathways of elimination of bortezomib have not been characterized in humans.A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCl) into the following groups: Normal (CrCl _60 mL/min/1.73 m^2, N=12), Mild (CrCl=40-59 mL/min/1.73 m^2, N=10), Moderate (CrCl=20-39 mL/min/1.73 m^2, N=9), and Severe (CrCl < 20 mL/min/1.73 m^2, N=3). A group of dialysis patients who were dosed after dialysis was also included in the study (N=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose normalized AUC and Cmax) was comparable among all the groups.

Clinical Experience

It is estimated that as of June 2011, more than 300,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a phase 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.[xxv] The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

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

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

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

The EBMT response criteria were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm ($p < 0.0001$). CR + PR was 38% with bortezomib versus 18% with dexamethasone ($p < 0.0001$). CR was 6% with bortezomib versus < 1% with dexamethasone ($p < 0.0001$). The CR + nCR (near CR) rate was 13% with bortezomib versus 2% with dexamethasone. In patients who had received only 1 prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs 26% with dexamethasone ($p = 0.0035$). With a median 8.3 months of follow-up, overall survival was significantly longer ($p = 0.0013$) for patients on the bortezomib arm versus patients on the dexamethasone arm. The probability of survival at 1 year was 80% for the bortezomib arm versus 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib ($p = 0.0005$). In patients who had received only 1 prior line of treatment, the probability of survival at 1 year was 89% for the bortezomib arm versus 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib ($p = 0.0098$). Updated response rates and survival data were reported for M34101-039.[xxxiv] The updated CR + PR rate was 43% with bortezomib. The CR + nCR rate was 16% with bortezomib. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm versus patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the bortezomib arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, $p = 0.0272$). The probability of survival at 1 year was 80% for the bortezomib arm versus 67% for the dexamethasone arm ($p = 0.0002$).

The safety and efficacy of bortezomib in relapsed or refractory mantle cell lymphoma (MCL) were investigated in an international, phase 2, multicenter study M34103-053, also referred to as the PINNACLE study.[xxxv] The single-arm study was designed to evaluate the response rates, duration of response (DOR), TTP, overall survival (OS), and safety of bortezomib treatment in patients with relapsed or refractory mantle cell lymphoma. For 141 evaluable patients, the response rate was 31% (8% CR/unconfirmed CR [Cru]). Median time to response was 40 days (range 31-204 days).

The median number of cycles administered across all patients was 4; in responding patients, the median number of cycles was 8. The median DOR by algorithm was 9.2 months and 13.5 months in patients with CR/CRu. Median TTP for both groups was 6.2 months. With a median follow-up of 13.4 months, overall survival had not been reached. The most commonly reported adverse events (AEs) were fatigue, peripheral neuropathy, and gastrointestinal events. A time-to-event update to the PINNACLE study[xxxvi] was reported after a median follow-up of 26.4 months. TTP was 6.7 months for all patients, 12.4 months in all responders. The median DOR was 9.2 months in all responders and had not been reached in patients achieving CR/Cru. Overall survival was 23.5 months in all patients and 36 months in patients with CR/Cru. Survival at 12 months was 69% overall and 91% in responding patients.

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

who received antiviral prophylaxis. Fifteen percent of patients in the VMP group discontinued therapy due to AEs compared to 14% in the MP group.

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

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

In the VISTA study, VMP was associated with prolonged TTP, TNT, TFI, and OS. Patients were successfully treated with subsequent IMiD-based therapy and retreated with bortezomib. After 36.7 months follow-up, OS continued to be superior for VMP. The OS for VMP had not yet been reached compared to MP (43.1 months).[xxxix] In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for VMP was 56.4 months and the MP was 43.1 months, with a hazard ration of 0.695 (95% CI: 0.57, 0.85).[43]

SUBCUTANEOUS ADMINISTRATION

A randomized Phase 1 pilot study in 24 subjects with multiple myeloma demonstrated that both the IV and SC routes of bortezomib administration have similar systemic drug exposure and proteasome inhibition. Importantly, SC and IV administration of bortezomib appeared to result in similar efficacy profiles (ie, response rate) and similar safety profiles. The pilot study also provided preliminary evidence of good local tolerance for SC injection of bortezomib, when administered at 1 mg/mL concentration[xl].

The data from the Phase 1 pilot study formed the basis of the design of a randomized, Phase 3 study that compared the efficacy and safety of subcutaneous versus intravenous bortezomib at the approved 1.3 mg/m(^{2}) dose and twice per week schedule

in patients with relapsed multiple myeloma[xxiv]. 222 patients were randomly assigned in a 2:1 ratio to receive either subcutaneous (n=148) or intravenous (n=74) bortezomib. The response-evaluable population consisted of 145 patients in the subcutaneous group and 73 in the intravenous group. Patients received a median of eight cycles (range one to ten) in both groups.

The ORR (CR+PR) after 4 cycles of treatment, assessed by computer algorithm implementation of EBMT response criteria, was 42 % in both the SC and IV treatment groups for the response-evaluable population. The ORR after 4 cycles in the IV arm was consistent with what was observed in historical single-agent bortezomib trials with relapsed multiple myeloma subjects. The stratified Mantel-Haenszel estimate of the relative risk of achieving response for SC treatment group versus IV treatment group was 0.99 with 95% CI (0.71, 1.37). The 95% CI for ORR_SC - 0.6 ORR_IV was (6.1, 27.1), which excludes 0. Thus the study met the noninferiority objective (p-value for the noninferiority hypothesis was 0.00201). Results in the ITT population were similar; noninferiority of SC versus IV was also demonstrated.

The CR rate after 4 cycles of treatment was 6% in the SC treatment group and 8% in the IV treatment group; the nCR rate after 4 cycles of treatment was 6% in the SC treatment group and 5% in the IV treatment group; the VGPR rate after 4 cycles of treatment was 4% in the SC treatment group and 3% in the IV treatment group. Therefore, 17% subjects in the SC treatment group and 16% subjects in the IV treatment group had obtained at least VGPR after the first 4 cycles.

The ORR (CR+PR) after 8 cycles of treatment was 52% in both the SC and IV treatment groups for the response-evaluable population. The stratified Mantel-Haenszel estimate of the common relative risk of achieving response for SC versus IV was 1.00 with 95% CI (0.77, 1.31). Twenty-five percent of subjects in the SC treatment group and 25% of subjects in the IV treatment group had obtained at least VGPR during the first 8 cycles.

The median TTP (Kaplan-Meier estimate) was 10.4 months in the SC treatment group and 9.4 months in the IV treatment group. The hazard ratio was 0.839 with 95% CI (0.564, 1.249), and the p=0.3866 (stratified log-rank test), indicating similar results between the SC and IV arm.

The median PFS (Kaplan-Meier estimate) was 10.2 months in the SC treatment group and 8.0 months in the IV treatment group. The hazard ratio was 0.824 with 95% CI (0.574, 1.183), and the p=0.2945 (stratified log-rank test), indicating comparable results between the SC and IV arm.

After a median follow-up of 11.8 months, the 1-year survival rate was 72.6% in the SC arm and 76.7% in the IV arm. The p-value for the difference in 1-year survival rate was 0.5037, indicating similar results between the SC and IV arm.

The median time to first response (Kaplan-Meier estimate) was 3.5 months for both the SC and IV treatment groups. The hazard ratio was 1.059 with 95% CI (0.716, 1. 567), and the p=0.7725 (stratified log-rank test), indicating similar results between the SC and IV arm. Among the responders, the median time to first response was 1.4 months (44 days) in the SC arm and 1.4 months (43 days) in the IV arm. Among the responders, the median duration of response (Kaplan-Meier estimate) was 9.7 months in the SC treatment group, compared with 8.7 months in the IV treatment group.

Overall, similar efficacy results were observed in the SC and IV treatment groups, and the study demonstrated that bortezomib SC administration is not inferior to bortezomib IV administration[xxiv].

2.5 Source, Preparation, Handling, Storage, Stability, Administration:

Bortezomib, manufactured under an IND in the same conditions as commercial Velcade™, will be provided by Millennium Pharmaceuticals, Inc. Bortezomib (VELCADE for Injection) is a sterile lyophilized powder for reconstitution and is supplied in vials containing 3.5 mg of bortezomib and 35 mg of mannitol. Unopened vials may be stored at controlled room temperature 25º C (77º F); excursions permitted from 15º to 30º C (59º to 86º F). 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. Retain in original package to protect from light.

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.

Prior to use, the contents of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline (sodium chloride injection). The reconstituted product should be a clear and colorless solution. Bortezomib contains no antimicrobial preservative. When reconstituted as directed, bortezomib may be stored at 25°C (77°F). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 8 hours in a syringe; however, total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting

2.6 Bortezomib Destruction

For commercially-labeled VELCADE for IND-exempt studies, please contact your Millennium Clinical Operations representative to arrange for return of study drug procedures. Any unused or expired VELCADE must be returned to Millennium. Be sure to document drug return on your drug accountability logs.

2.7 Potential Risks

To date, more than 300,000 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 0-1 and Table 0-2. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent

bortezomib dosed at 1.3 mg/m^2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

Table 0-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhoea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*, lower gastrointestinal haemorrhage*± rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction

Table 0-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis∗, bactaeremia*, cellulitis∗, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection∗, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*

Table 0-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea

Table 0-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 15.

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.

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

Table 0-2 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

Table 0-2 Reports of Adverse Reactions From Postmarketing Experience

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

Table 0-2 Reports of Adverse Reactions From Postmarketing Experience

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

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 15 Addendum 1.

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.

SAFETY SUMMARY FOR SUBCUTANEOUS ADMINISTRATION

While the safety profile between the SC and IV treatment groups in general was comparable in most System Organ Classes (SOCs), a difference in incidence in certain safety parameters in favor of the SC treatment group was noted. One hundred and forty (95%) subjects in the SC treatment group and 73 (99%) subjects in the IV treatment group reported at least 1 treatment-emergent adverse event. In the SC treatment group, there was a lower incidence of Grade ≥3 adverse events as compared with the IV treatment group (57% vs. 70%, respectively); a lower incidence of adverse events leading to treatment discontinuations (22% in the SC treatment group and 27% in the IV treatment group); and a lower incidence of adverse events leading to dose modifications

in the SC group: dose reduction (33% in the SC treatment group compared with 45% in the IV treatment group); dose withholding (30% in the SC treatment group compared with 39% in the IV treatment group); or cycle delay (20% in the SC treatment group compared with 34% in the IV treatment group). Serious adverse events were similar between the 2 treatment groups (36% in the SC treatment group and 35% in the IV treatment group). Deaths during treatment (within 30 days of last dose) were 5% in the SC treatment group and 7% in the IV treatment group.

The SC treatment group reported a lower incidence in several adverse events associated with VELCADE toxicity. The incidence of peripheral neuropathy events (all Grades) was 38% in the SC treatment group and 53% in the IV treatment group; the incidence of Grade ≥2 peripheral neuropathy events was 24% in the SC treatment group and 41% in the IV treatment group; and the incidence of Grade ≥3 peripheral neuropathy event was 6% in the SC treatment group and 16% in the IV treatment group. There also appeared to be a trend towards lower incidence in gastrointestinal adverse events (37% for SC and 58% for IV, predominantly due to differences in Grade 1-2 abdominal pain, diarrhea, and dyspepsia); as well as a ≥5% difference in incidence of Grade 3 and 4 hematology laboratory results in the SC treatment group compared with the IV treatment group for WBC (8% in the SC treatment group compared with 18% in the IV treatment group), neutrophil count (22% in the SC treatment group compared with 28% in the IV treatment group) and platelets (18% in the SC treatment group compared with 23% in the IV treatment group).

Local tolerability of SC administration was acceptable. Nine (6%) subjects reported a local reaction to SC administration as an adverse event. Eighty-five (58%) subjects in the SC treatment group reported at least 1 local injection site reaction. The most common local injection site reaction was redness which was reported in 84 (57%) subjects. The majority of subjects with worst injection site reactions were assessed as mild (38%) or moderate (18%). Only 2 (1%) subjects were reported as having severe injection site reactions. All local site reactions resolved completely and rarely led to treatment modifications.

In conclusion, the SC administration of VELCADE has good local tolerance. The systemic safety profile for the SC administration of VELCADE was associated with a lower incidence of Grade ≥3 adverse events, and treatment modifications (discontinuations and dose reductions). In particular, there was a lower incidence of peripheral neuropathy NEC reported[xxiv].

3.0. PATIENT SELECTION

INCLUSION CRITERIA:

1. Voluntary signed informed consent before performance of any study-related procedure not part of normal medical care, indicating that that the patient is aware of the investigational nature of the study in keeping with the policies of MDACC and with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
2. Presence of phosphorylated p65 NF-kB component in at least 5% of bone marrow cells
3. Age ≥ 18 years of age at time of signing consent
4. Confirmed MDS by bone marrow biopsy according to WHO or FAB criteria[21].
5. Classification by the IPSS as low or intermediate-1 risk MDS according to cytogenetics, blood cytopenias and % bone marrow blasts within 28 days of the first dose of treatment in this study.
6. Patients must have received at least one prior therapy for MDS. Patients could have received transplant for MDS
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2.
8. Adequate liver function: Total bilirubin ≤ 1.5 × the upper limit of normal (ULN), unless presence of Gilbert's Syndrome. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 × ULN or ≤ 5.0 x ULN if hepatic involvement is present as determined by the investigator
9. Adequate renal function: Serum creatinine ≤ 2 mg/dL or a calculated creatinine clearance of ≥ 50 mL/min (using the Cockcroft and Gault method).
10. Male patients, even if surgically sterilized (ie, status postvasectomy), who agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study treatment, or agree to completely abstain from heterosexual intercourse
11. Female patients who are postmenopausal for at least 1 year before the Screening visit, or are surgically sterile, or if they are of childbearing potential, must have a negative pregnancy test within 72 hours of treatment start date and agree to practice 2 effective methods of contraception, at the same time, from the time of signing the

informed consent through 30 days after the last dose of study treatment, OR agree to completely abstain from heterosexual intercourse

12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

EXCLUSION CRITERIA

1. Significant medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, to give informed consent, to comply with the study protocol, or to complete the study.

2. Any severe concurrent disease or condition (including active, uncontrolled systemic infection, symptomatic congestive heart failure, unstable angina pectoris or cardiac arrhythmia) that, in the judgment of the Investigator, would make the patient inappropriate for study participation.
3. Pregnant or lactating females.
4. Patient has ≥ Grade 2 peripheral neuropathy
5. Patient had myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
6. Patient has hypersensitivity to bortezomib, boron, or mannitol
7. Current diagnosis of another malignancy, 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.
8. Treatment with other investigational agents, chemotherapy, or immunotherapy within 14 days of the start of this trial and throughout the duration of this trial.
9. 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.

4.0 TREATMENT PLAN

Overview

This open-label, Phase II study is designed to determine the clinical activity, safety and tolerability of Bortezomib in patients with low or intermediate-1 risk MDS. All patients will be registered through Protocol Data Management System (PDMS) or CORe.

Schedule of administration Cycle 1:

Bortezomib will be administered via subcutaneous route at a dose of 1.3 mg/m^2 on days 1, 4, 8 and 11 of a 21 day cycle. A course of treatment will be approximately 21 days. The dose and schedule is adapted based on PK and safety data for subcutaneous Bortezomib as published by Moreau et al[22].

Subsequent cycles:

Patients will receive the first course of therapy without interruption regardless of degree of myelosuppression. Patients can continue to receive therapy for a maximum of 2 years if indicated (see below "Duration of therapy"). After the first course of therapy, interval between cycles of therapy can be spaced out at the discretion of the treating physician, although a schedule as close to possible as the proposed one will be attempted. If prolonged myelosuppression is observed (defined by an absolute neutrophil (ANC) count of less than 1 x10^9/L and a platelet count of less 30 x10^9/L for more than 42 days with evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of recurrent MDS) subsequent courses of bortezomib will be given at the next lower dose, once the counts recover. Count recovery will be considered if the ANC is $\geq$1 x10^9/L, platelets more than 50 x10^9/L. In the rest of potential clinical situations, subsequent courses of therapy will be administered at the discretion of the treating physician.

Cycles will be repeated as long as possible until toxicity or lack of response for at least 6 cycles of therapy. The dose and schedule is adapted from Moreau et al[22]. In that study, the median number of cycles was 8 (range 1 to 10).

Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue up to 2 years until one of the following criteria applies:

a) Clinically significant progressive disease
b) Possibility of undergoing allogeneic bone marrow transplantation
c) Clinically significant intercurrent illness that prevents further administration of treatment
d) Patient request or
e) General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator or treating

5.0 DOSING DELAYS/ DOSE MODIFICATIONS:

Dose modifications will be based on guidelines shown in Table 2

Throughout the study treatment period, 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 Toxicity Criteria for Adverse Events (CTCAE), Version or 4.0 (as preferred by your institution; http://ctep.cancer.gov/reporting/ctc.html).

Dose delay window is +2 days for doses 4,8, and 11. There must be at least 72 hours between each dose of bortezomib.

All previously established or new toxicities observed any time are to be managed as described in Table 3 1. Neuropathic pain and peripheral sensory neuropathy are to be managed as described in Table 4.

Table 2. Bortezomib dose de-escalation. Clinically significant treatment related toxicity and dose management:

Toxicity Grade	***Management/Action***

Toxicity Grade	*Management/Action*
1 or 2	No change required. If the toxicity persists at Grade 1 or 2, then reduction to a lower dose level is allowed according to Investigator judgment and likelihood that the toxicity is related to bortezomib.
3	Hold treatment. Treatment may resume if toxicity is resolved to Grade ≤ 1 or returns to baseline. If the toxicity resolves within 7 days, bortezomib may be resumed at the same level or at the next lower dose level at the discretion of the Investigator.Toxicity lasting more than 7 days will require dose reduction to the next lower dose level.
4	Hold treatment. Treatment may resume if toxicity is resolved to Grade ≤ 1 or returned to baseline at the discretion of the Investigator. Treatment will be reduced by two dose levels from the level at which the toxicity was observed. If Grade 4 toxicity occurs in spite of two dose level reduction, the patient should be discontinued from the study.

Table 3 below summarizes the dose reduction schema to be followed in this study. Patients that require reduction of more than 2 dose levels will be removed from the study.

Table 3. Dose reduction levels for bortezomib:

Starting dose level	**1.3 mg/m2**
Dose level -1	**1.0 mg/m2**
Dose level -2	**0.7 mg/m2**

Clinically significant toxicity management

Toxicity	Grade	Action
Lymphopenia	Any	None

Nonhematological toxicity	3	Hold bortezomib therapy
Hematological Toxicity	4	Hold bortezomib therapy

For any clinically significant and nonhematologic toxicities, bortezomib is to be held for up to 2 weeks until the toxicity returns to Grade 1 or better. For hematologic toxicities, bortezomib is to be held for up to 2 weeks until the patient has a platelet value of 30 k/uL, and neutrophil value of 1 x 10^3

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

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

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

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

If the patient was receiving 0.7 mg/m^2, discontinue drug.

Patients who experience bortezomib-related neuropathic pain or peripheral sensory neuropathy are to be managed as presented in Table 4. Once the dose is reduced for peripheral neuropathy, the dose may not be re-escalated.

Table 4 Management of Patients With bortezomib-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or parasthesias) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting	Reduce bortezomib 1.0 mg/m^2

Table 4 Management of Patients With bortezomib-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	Modification of Dose and Regimen
instrumental Activities or Daily Living [ADL][b])	
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a one dose level reduced dose of bortezomib.
Grade 4 (life-threatening consequence; urgent intervention indicated)	Discontinue bortezomib

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

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

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

Neurotoxicity-Directed Questionnaire

The neurotoxicity-directed questionnaire (see Appendix F) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. It is not a tool intended for direct scoring and toxicity grading. 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.

6.0 AGENT FORMULATION AND PROCUREMENT

SC Bortezomib will be provided by Millennium. This is an FDA approved agent for patients with multiple myeloma.

Bortezomib Administration

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

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

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

INTRAVENOUS AND SUBCUTANEOUS ROUTE OF ADMINISTRATION HAVE DIFFERENT RECONSTITUTED CONCENTRATIONS. CAUTION SHOULD BE USED WHEN CALCULATING THE VOLUME TO BE ADMINISTERED.

SUBCUTANEOUS ADMINISTRATION:

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 1.4 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL for subcutaneous administration.

Subcutaneous Administration Precautions:

- The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose.
- When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated.
- New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.
- If local injection site reactions occur following bortezomib administration subcutaneously, a less concentrated bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the IV route of administration should be considered.
- In clinical trials of bortezomib IV, local skin irritation was reported in 5% of patients, but extravasation of bortezomib was not associated with tissue damage. In a clinical trial of subcutaneous bortezomib, a local reaction was reported in 6% of patients as an adverse event, mostly redness.

Packaging, and Labeling

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

Treatment Compliance

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

Precautions and Restrictions

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

Female patients must meet 1 of the following:

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

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

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

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

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

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

6.1 Concomitant therapies:

a) Anti-emetic therapy
   Prophylactic and therapeutic treatment for nausea and vomiting is recommended.
b) Anti-Diarrheal Therapy
   Treat study treatment-related diarrhea with loperamide 4 mg followed by 2 mg after each loose stool up to a maximum of 16 mg daily. Use alternate approaches in patients intolerant of loperamide. Consider prophylactic loperamide if previous therapeutic treatment was required in same or previous patients.
c) Transfusion to maintain Hgb > 8 gm/dL and platelet count > 10,000/_L is recommended. Higher levels may be targeted if clinically appropriate.
d) G-CSF may be used in cases of neutropenia and suspected or documented infection at physician's discretion. Erythropoietin and darbepoietin are not permissible.
e) Tumor lysis syndrome Monitoring, prophylactic and therapeutic treatment for tumor lysis syndrome is recommended as per institutional criteria.
f) Infection prophylaxis. Prophylaxis with oral antimicrobial agents is permitted for neutropenic patients.
g) Investigators should consider using antiviral prophylaxis in subjects being treated with bortezomib.

6.2 Excluded therapies:

Patients may not receive other investigational agents, chemotherapy, or immunotherapy not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial. Hydroxyurea is not allowed in this group of patients.

7.0 CORRELATIVE STUDIES

We will perform exploratory analysis of the effect of SC bortezomib in patients with lower risk MDS. In particular we will analyze phosphor-p65 and obtain samples for DNA, RNA, and protein analysis approximately at baseline, cycle 1 and 3 day 21. This will be performed in the laboratory of Dr Carlos Bueso-Ramos in Hematopathology using standard accepted immunocytochemistry techniques.

8.0 PATIENT EVALUATION

Pretreatment:

Results from tests performed as standard of care up to 28 days prior to study entry can be used for determining eligibility and establishing baseline measurements. Any clinically significant abnormal results (except for bone marrow aspiration) should be repeated within 48 hours of beginning therapy to establish a baseline.

- A complete history and physical exam including height, weight, and vital signs (blood pressure, heart rate, breathing rate, and temperature), documentation of all measurable disease, and performance status (PS) should be performed 72 hours before initiation of study, and subsequently as indicated.
- Document adverse event assessment and concomitant medications as far as traceable.
- CBC, platelet count, creatinine, total bilirubin, SGPT and/or SGOT, potassium and blood or urine pregnancy test (when indicated) should be performed 72 hours before initiation of study. Pregnancy testing will be conducted for any female that is of childbearing age that has not been surgically sterilized or without a menses for 12 consecutive months.
- Bone marrow aspirate and/or biopsy during the last 28 days preceding study initiation.

- Cytogenetics will be obtained at baseline, if abnormal this will be repeated with Cycle 1 day 21 bone marrow aspirate and/or biopsy and at the time of response as indicated.
- 12 lead EKG
- Pretreatment correlative studies if patient signed for them during consent process.

During Treatment:

- CBC, platelet count, creatinine, SGPT and/or SGOT and total bilirubin weekly during first course of therapy, and then prior to each course of therapy.
- Document adverse event assessment and concomitant at each clinic visit.
- Bone marrow aspiration and/or biopsy will be performed at the end of Cycle 1 (+/- 5 days) and of Cycle 3 (+/- 5 days) to assess for response and every 3 months thereafter as per physicians discretion. Earlier evaluations are allowed as clinically indicated.

End-of-Study:

Thirty days following the last dose of study drug:

- CBC with chemistry
- Bone marrow aspirate, if clinically indicated (per investigator or treating physician)
- Document adverse event assessment and concomitant medications.

9.0 STUDY CALENDAR

Study calendar during therapy:

		CYCLE 1			CYCLE 2 - Subsequent Cycles	CYCLE 3	End of study
	PreTx	**W1**	**W2**	**W3**	**D1**	**D21**	
Complete history, physical exam including height, weight, vital signs, and PS	X				X		
Concomitant medication, adverse event assessment	Continuous						
CBC[1,3]	X	X	X	X	X		X
Chemistries[3]	X	X	X	X	X		X
Pregnancy test[3]	X						
EKG[3]	X						
Bone marrow aspirate and/or biopsy [2,3]	X			X		X	X
Cytogenetics[2,3,4]	X			X		X	X

PreTx:pretreatment (within 72 hrs unless noted otherwise); W:week; D:day

1 CBC/diff/platelets; Chem: creatinine, T. bili, SGPT and/or SGOT, potassium

2 Baseline & repeated on Cycle 1 Day 21

3 all 5 +/- days

4 Cytogenetics will be repeated if abnormal at baseline

10.0 CRITERIA FOR RESPONSE

Criteria for response will follow the modified IWG criteria. This is summarized in appendix below. Response will include complete remission, partial remission, marrow complete remission and any

hematological improvement achieved any time during the duration of the therapy.

Proposed modified International Working Group response criteria for altering natural history of MDS[7]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥11 g/dL
	Platelets ≥100 x 10^9/L
	Neutrophils ≥1.0 x 10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment

Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥50% increase in blasts to > 5% blasts 5%-10% blasts: ≥50% increase to > 10% blasts 10%-20% blasts: ≥50% increase to > 20% blasts 20%-30% blasts: ≥50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS

DFS: time to relapse

Cause-specific death: death related to MDS

Table 6. Proposed modified International Working Group response criteria for hematologic improvement[7]

Hematologic improvement*	Response criteria (responses must last at least 8 wk)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥1.5 g/dL
	Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100 x 10^9/L)	Absolute increase of ≥30 x 10^9/L for patients starting with > 20 x 10^9/L platelets
	Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 x 10^9/L)	At least 100% increase and an absolute increase > 0.5 x 10^9/L†
Progression or relapse after HI‡	At least 1 of the following:
	At least 50% decrement from maximum response levels in granulocytes or platelets
	Reduction in Hgb by ≥1.5 g/dL
	Transfusion dependence

11.0 CRITERIA FOR REMOVAL FROM THE STUDY

This will include:

- Progressive disease

- Possibility of undergoing allogeneic bone marrow transplantation
- Intercurrent illness that prevents further administration of treatment
- Patient request
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

12.0 STATISTICAL CONSIDERATIONS

General Description:

This is a Phase II open-label, efficacy and toxicity study of SC bortezomib in subjects with low and int-1 myelodysplastic syndrome. The primary efficacy outcome is the overall response rate based mainly on hematologic improvement defined by IWG but of course could include complete remission, partial remission and marrow complete remission.

Efficacy monitoring:

A maximum of 40 evaluable patients will be enrolled, but the study will be stopped early if the data suggest that:

$$\Pr(\theta < 0.15 | \text{data}) > 0.95$$

Here θ is the overall response (OR) rate. Since currently the standard practice is to put these patients on observation, an OR rate of about 15% is worth considering. We assume the OR rate has a prior Beta distribution (0.3, 1.7) with mean of 0.15 and variance of 0.0425. The study will be stopped early if:

(The number of patients who hematological improvement) / (The number of patients evaluated) $\leq$ 0/8, 1/24, 2/37, 3/40

That is, if at any time during the study we determine that there is a greater than 95% chance that the average OR rate is less than 15%, we will terminate the study.

The operating characteristics of this design are as follows:

Operating characteristics of response (based on 10000 simulations)			
True OR Rate	Early Stopping Probability	Average sample size achieved	Stopping boundaries
0.05	0.85	16.6	0 /8 1/24 2 /37 3/40
0.10	0.54	25.0	
0.15	0.31	30.8	
0.20	0.18	34.5	
0.30	0.06	38.1	
0.40	0.02	39.46	
0.50	0.004	39.88	
0.60	0.0007	39.97	

Toxicity monitoring

Evidence of Toxicity will be monitored closely in all patients. The study will be terminated if Pr (grade 3 or higher Toxicity >0.15|data)>0.95. Table 10 shows the simulation of the trial. The treatment will be stopped if all the 2 out of first 2 patients experience clinically significant drug related grade 3 or higher toxicity, or $\geq$ 3 out of 4, or $\geq$ 4 out of 7, or $\geq$ 5 out of 11, or $\geq$ 6 out of 15, or $\geq$ 7 out of 19, or $\geq$ 8 out of 23, or $\geq$ 9 out of 28, or $\geq$ 10 out of 32, or $\geq$ 11 out of 37.

Operating characteristics of toxicities (based on 10000 simulations)			
True Probability	Early Stopping Probability	Average sample size achieved	Stopping boundaries
0.05	0.004	39.9	2 /2 3 /4 4 /7
0.10	0.03	39.1	
0.15	0.11	37.0	

Operating characteristics of toxicities (based on 10000 simulations)			
0.20	0.29	32.9	5 /11 6 /15 7/19 8/23 9 /28 10 /32 11/37
0.30	0.77	20.9	
0.40	0.97	11.8	
0.50	1.0	7.3	

Statistical methods:

Data analysis will be performed using SAS or S-plus, as appropriate. The proportion of patients having hematologic improvement and the proportion of patients having grade 3 or higher toxicities will be estimated by a Bayesian posterior credible interval. If the study is completed with 40 patients and there are 6 patients with hematologic improvement, a 90% posterior credible interval for the average rate of hematologic improvement will be 7% to 25%.

13.0 PROTOCOL ADMINISTRATION

Protocol specific data will be entered into PDMS/CORe.

Protocol amendments:

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by the ethics committee of MDAnderson Cancer Center.

Archival of data:

All patient data (including source data) generated in connection with this study will be kept in the archives of the MDACC in accordance with 21 CFR 312.62. All data will be

available for inspection by company representatives of the Medical Department and by regulatory authorities.

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 below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

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

For Product Complaints or Medication Errors,
call MedComm Solutions at
1-866-835-2233 (US sites and International)

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

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