Clinical Trial Protocol

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Title: Comparing and Combining Bortezomib and Mycophenolate in SSc Pulmonary Fibrosis

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SUMMARY OF PROPOSED WORK

Background: Systemic sclerosis (SSc) is a chronic multisystem autoimmune connective tissue disease for which the etiology remains unknown. The prevalence for SSc is between 19-75 cases per 100,000 and it is more frequent in women, with a peak occurrence in the 4th or 5th decade of life. Morbidity and Mortality in SSc are substantial and pulmonary complications are now the leading cause of death among patients with SSc. The most profound SSc pulmonary manifestations are pulmonary arterial hypertension (PAH) and pulmonary fibrosis (PF). Skin fibrosis is also a significant cause of morbidity. Pulmonary and skin fibrosis is marked by fibroblast activation, increased extracellular matrix synthesis and progressive replacement of normal tissue architecture. While the role of resident fibroblasts in development of pulmonary fibrosis is not questioned, the specific cells, signals and mechanisms that trigger and sustain their activation are subjects of extensive investigation. Transforming growth factor-beta (TGF-β) has been implicated as a central mediator in the pathogenesis of both pulmonary and skin fibrosis as well as pulmonary hypertension.

SSc is an orphan disease and as such resources devoted towards investigating pathophysiological mechanisms and developing novel therapies for SSc associated fibrosis are limited. Treatment approaches for SSc associated fibrosis or tissue fibrosis in general represents a significant unmet need in medicine. Despite the absence of proven for SSc associated pulmonary fibrosis, Mycophenolate Mofetil has become 1st line therapy at many SSc Centers.

The SSc program at Northwestern is one of the leading programs in the country. There are robust clinical and research efforts devoted to providing state of the art patient care as well as exploring the pathophysiology of tissue fibrosis and identifying novel therapeutic targets. The program has exceptional resources to identify new potential therapies and translate them efficiently to the clinic. As part of our effort, we began experiments exploring the role of proteasomal inhibition in tissue fibrosis. Our interests coalesced around our expertise in the ubiquitin proteasomal protein degradation pathway and intriguing hints in the literature that proteasomal inhibition may protect against tissue fibrosis in some animal models. We decided to use bortezomib a small molecule proteasome inhibitor in our experiment since it was FDA approved and there was extensive human safety experience already. In our initial experiments, bortezomib was administered to mice beginning seven to fourteen days after the intratracheal (pulmonary fibrosis model) or intradermal administration of bleomycin (skin fibrosis model) and lung and skin fibrosis were measured after 21 (and 28) or 40 days, respectively. We also found similar efficacy for bortezomib in the asbestos model of lung fibrosis. Further, to examine the mechanism of this protection, bortezomib was administered to primary normal lung fibroblasts and primary lung and skin fibroblasts obtained from patients with idiopathic pulmonary fibrosis and scleroderma, respectively. Our results showed that bortezomib promoted normal repair and showed dramatic reduction in lung and skin fibrosis when administered beginning 7-14 days after the initiation of bleomycin. In primary human lung fibroblasts from normal individuals and patients with idiopathic pulmonary fibrosis and in skin fibroblasts from patients with scleroderma, bortezomib inhibited TGF-β mediated transcription by inhibiting transcription induced by activated Smads. This inhibition required an increase in the abundance and activity

of the nuclear hormone receptor Peroxisome proliferator-activated receptor-gamma (PPAR-γ) a repressor of Smad-mediated transcription. Based on these results we have developed the following hypothesis.

Hypothesis: Proteasomal Inhibition will result in TGF-β antagonism and a potent anti-fibrotic effect. Thus we hypothesize that bortezomib will lead to stabilized FVC in patients with SSc at high risk for disease progression.

Proposal: A randomized pilot trial in which bortezomib or placebo is added to MMF for 24 weeks in SSc-ILD patients. Toxicity and tolerability data are the primary endpoints. The primary clinical endpoint is the annualized change forced vital capacity (FVC) and there are multiple secondary endpoints.

In summary our published results are tremendously exciting since they identify an FDA approved drug that may show efficacy in pulmonary and skin fibrosis, diseases for which there are no effective treatments. Our proposed trial will provide the rationale for a pivotal, multi-center trial of proteasomal inhibition in SSc.

PROTOCOL SUMMARY

TITLE: PROTEASOMAL INHIBITION IN SYSTEM SCLEROSIS (PRISS)

Objectives

THE PRIMARY OBJECTIVE OF THIS STUDY IS TO:

- To assess the safety and tolerability of bortezomib with MMF in System Sclerosis (SSc) patients at high risk of progression of pulmonary disease
- To assess the effect of bortezomib with MMF on lung function in SSc patients at high risk of progression of pulmonary disease

THE SECONDARY OBJECTIVES OF THIS STUDY ARE TO:

- To assess the effect of bortezomib with MMF on Quality of Life and respiratory symptoms in SSc patients at high risk of progression of pulmonary disease
- To assess the effect of bortezomib with MMF skin fibrosis in System Sclerosis (SSc) patients at high risk of progression of pulmonary disease

Exploratory objective

- To assess the effect of bortezomib with MMF on serum biomarkers
- To assess the effect of bortezomib with MMF on aberrant gene expression in skin biopsies from SSc patients at high risk for disease progression

STUDY DESIGN

Study Overview

This is a pilot randomized clinical trial of adding bortezomib or placebo to MMF in SSc System Sclerosis (SSc) patients at high risk of progression of pulmonary disease

Primary Efficacy Endpoint

- Annualized change in forced vital capacity (FVC)

Primary Safety Endpoint

- Incidence of Serious Adverse Events (SAEs)

Secondary Endpoints

- Change in Modified Rodnan Skin Score
- Change in SF-36
- Change in St. George's Respiratory Dyspnea Score
- Change in Hopkins Skin Score (Exploratory)
- Change in Promis-29 (Exploratory)
- Change in FACIT-dyspnea Score (Exploratory)

Exploratory Endpoints

- Change in Serum Biomarkers
- Change in Gene Expression Profile (Skin Biopsies and monocyte/macrophages)

PATIENT POPULATION

- Patients with SSc who have active pulmonary disease (as defined below)

NUMBER OF PATIENTS

- 30

Enrollment: An expert panel has recently recommended that efforts be made to enrich SSc cohorts at greater risk for disease progression(1). With this in mind and in order to maximize the risk-benefit ratio of a novel therapy in SSc patients we have identified risk factors associated with pulmonary disease progression. The rationale is provided below.

Rationale: In the NIH-funded SLS-1 study of SSc patients, the forced vital capacity (FVC) was 4.16% higher in the cyclophosphamide (CYC) treated group compared to the placebo treated group after 12 months. This improvement dissipated after 24 months. The overall magnitude of the non-durable response to CYC was modest, which combined with the potential toxicity of CYC has led to limited enthusiasm for treating SSc patients with CYC. Another observation from the SLS-1 study was the considerable heterogeneity in clinical course in the placebo and CYC treated cohorts. Investigation of factors that were associated with accelerated loss of FVC in the placebo treated patients and significant treatment response in those randomized to CYC identified extent of pulmonary and skin fibrosis as assessed by HRCT (Fib_{max}) and the Modified Rodnan Skin Score (MRSS) (2). Further these factors were most useful in those diagnosed with SSc within 2-3 years of trial entry(3). These data are similar to a large observational cohort in which disease extent on chest HRCT or an FVC < 70% predicted was associated with a higher mortality(4). Another subset of patients who is at increased risk of mortality is that with rapid loss of lung function, regardless of disease duration (5). Based on these considerations we propose inclusion criteria designed to enrich SSc subjects at high risk for disease progression and most likely to benefit from treatment.

INCLUSION CRITERIA

1. Meet established criteria for diffuse or limited SSc and evidence of pulmonary at high risk of progression with or without progressive skin disease.
    - **a.** Definition includes subjects who meet the ACR criteria for scleroderma
    - **b.** High Risk of disease progression (see rationale) will be defined as follows
        - **i.** If first non-Raynaud's manifestation of SSc ≤ 36 months, then if any of the following are true:
            1. FVC <70% predicted
                or
            2. HRCT Fib_{max} >3
                or
            3. FVC < 85% and MRSS increase > 5 over 6 months
        - **ii.** Regardless of disease duration
            1. Fall in FVC > 10% over the preceding 12 months or less in the absence of prior therapy or another identified causative process as assessed by the primary scleroderma physician
            2. Fall in FVC > 10% over 12 months on at least 12 months of prior therapy
2. Age ≥ 18 years
3. Ability to give informed consent.
4. Willingness to discontinue present therapy for the duration of the study

5. Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.
6. Male subject agrees to use an acceptable method for contraception for the duration of the study.
7. No evidence of acute infection
8. ANC >1000
9. Platelets ≥75,000
10. Stable MMF dose for 8 weeks

Exclusion Criteria

1. Inability to give informed consent or comply with protocol procedures
2. FVC < 40% or DLCO <30% predicted
3. Patient has a platelet count of less than 50,000 within 14 days before enrollment.
4. Patient has an absolute neutrophil count of less 1000 within 14 days before enrollment.
5. Patient has a calculated or measured creatinine clearance of < 20 ml/minute within 14 days before enrollment.
6. Patient has ≥Grade 2 peripheral neuropathy by history within 14 days before enrollment.
7. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.4), 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 has to be documented by the investigator as not medically relevant.
8. Patient has hypersensitivity to bortezomib, boron or mannitol.
9. Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
10. Patient has received other investigational drugs within 4 weeks before enrollment
11. Serious medical co-morbidity which in the opinion of the investigator makes participation in the study too high risk
12. Psychiatric illness likely to interfere with participation in this clinical study.

STUDY DESIGN AND METHODOLOGY

- This is a pilot study in which patients who meet entry criteria will be randomized to receive bortezomib or placebo as add on treatment for MMF for 24 weeks. Fifteen patients will be randomized to receive bortezomib or placebo.

TREATMENTS ADMINISTERED

Rationale: The standard dose of bortezomib in multiple myeloma is 1.3 mg/m^2. This is also the dose of bortezomib which has been well tolerated in an ongoing study of GVHD patients. Thus

we will use this dose of bortezomib in our study. The MMF dose is the standard dose used in clinical practice for SSPF.

- Bortezomib 1.3 mg/m^2 once a week x 2 by Subcutaneous injection or IV infusion (every 4 weeks Monthly) or placebo x 3 4-week cycles (12 weeks) and then Bortezomib 1.3 mg/m^2 once a week by Subcutaneous injection or IV infusion (every 4 weeks Monthly) or placebo x 3 4-week cycles (12 weeks)
- MMF 1.5 g twice a day orally for 24weeks.

STATISTICAL PROCEDURES

Based on a previous study (2), we will assume that the high risk subgroup of SSc-ILD patients in this study will have had an annualized fall in FVC of 5% if not treated. We will assume that bortezomib/MMF group will work at least as well as CYC in SLS1 and better than placebo/MMF which will lead to a non-worsening and perhaps improvement in FVC. We will define non-worsening as a flat (0%) slope in FVC. The reported standard deviation of the difference from baseline was 5%. These data in addition to SLS2 results will facilitate future phase 3 trial design and corresponding power calculations, by providing estimates of variability and plausible effect size after each treatment. Additional analyses will involve linear random effects model to fit observations over time for each subject, as well as for all (random) subjects together to compare the two treatment groups. This will provide information about components of variance present in this type of data, under such or similar circumstances, to be used in future study planning. Thus we will be able to use the proposed study to estimate the range of within subject variability as well as between subjects variability inherent in a general mixed model. We will use command xtmixed in Stata statistical software (www.stata.com).

ANALYSIS PLAN

Patients who receive at least 1 dose of bortezomib/ placebo will be termed the intention to treat (ITT) population. Patients who complete at least 2/3 of the bortezomib/placebo doses in the trial will be termed per protocol population (PP) and analyzed separately. The main analysis will be performed on the ITT group where measurements will be taken at the enrollment and the primary endpoint visit. In an alternative statistical analysis we will incorporate as a covariate the actual length of time between ‘first’ and ‘last’ measurements as it may vary from patient to patient if there is dropout prior to completing treatment. The primary and secondary endpoints will be analyzed using the ITT and PP populations. Results from the ITT analysis will take precedence over findings from the PP analysis. In addition, where possible, pattern mixture models will be used to assess the level of ‘randomness’ for missing data.

Contents

ABBREVIATION LIST

Abbreviation	Definition
°C	degrees Celsius
μM	micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
BSA	body surface area
cm	centimeter
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
dL	deciliter
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
FVC	Forced Vital Capaciy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ht	height
HSCT	Hematopoietic Stem cell transplantation
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
Ki	inhibitory constant
lbs	pounds
m^2	square meters
mg	milligram
min	minute
ml	milliliter
mm^3	cubic millimeters
MMF	Mycophenolate mofetil
mmol	millimole
NF-κB	nuclear factor-κB
ng	nanogram
nM	nanomole
PFT	Pulmonary Function Testing
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
SAE	serious adverse event
SSc	Systemic Sclerosis
TGF-β1	Transforming Growth Factor-beta1
US	United States
USP	United States Pharmacopeia
wt	weight

1.0 BACKGROUND AND STUDY RATIONALE

1.1. Overview of Disease

Prevalence estimates for systemic sclerosis (i.e. scleroderma) vary from 138 to 660 per million population. There two distinct subtypes, diffuse cutaneous and limited cutaneous though both have multi-organ manifestations. Pulmonary disease is now the most common cause of mortality. Overall 30%-40% of patients will develop pulmonary fibrosis, usually within 2-4 years of diagnosis. Scleroderma lung disease is marked by loss of the alveolar capillary units which can be quantified on pulmonary function testing as a fall in the total lung capacity (TLC) and the diffusing capacity for carbon monoxide (DLCO). Radiologically scleroderma lung disease is marked by increased interstitial infiltrates which can progress to honeycombing at end-stage.

Lung Fibrosis-Abnormal Lung Repair

While the etiology and pathogenesis of SSc remain incompletely understood, the initial insult is likely to be vascular. After injury, the recovery of normal tissue function can be prevented or delayed by the development of fibrosis (6). Fibroblast activation in response to alveolar epithelial injury is required for tissue repair and recovery of lung function (7), but if not properly regulated may also lead to impaired compliance and gas exchange, and pulmonary fibrosis. In animal models, investigators have reported that activation of the cytokine Transforming growth factor-beta (TGF-β) is required and sufficient for the development of fibrosis in the lung and other organs (8). In the lung the intratracheal administration of bleomycin results in acute lung injury followed by TGF-β dependent lung fibrosis (8). In addition to in vitro and animal data there is also compelling human data on the importance of TGF-β in tissue fibrosis. Gene expression analysis of tissue obtained by lung and skin biopsies showed upregulation of many TGF-β regulated genes(9,10). In addition we and others have detected active TGF-β in the alveolar fluid of pulmonary fibrosis patients which is transcriptionally active (11).

Active TGF-β binds to its plasma membrane receptors inducing signaling cascades that transcriptionally regulate myofibrobast differentiation, collagen expression and endothelial/epithelial to mesenchymal cell transition (12). Full expression of TGF-β mediated gene expression requires canonical smad and non-smad pathways (12). The transcriptional program activated by TGF-β is therefore an attractive therapeutic target for the prevention of organ fibrosis after injury (8,13,14).

TGF-B IN TISSUE REPAIR

Fibroblast activation after lung injury is characterized by elevations of the pro-fibrotic cytokine TGF-β (15,16) . TGF-β

interstitium in a latent form. Upon injury to the epithelium or endothelium, TGF-β is converted from a latent to active form (17-21) and binds to one of a family of TGF-β receptors present on the cell surface, activating multiple downstream signaling cascades. Binding of TGF-β with the ALK5 receptor has been shown to be required for the development of fibrosis in multiple models. Activation of the ALK5 receptor induces the phosphorylation of one of the small mothers against decapentaplegic

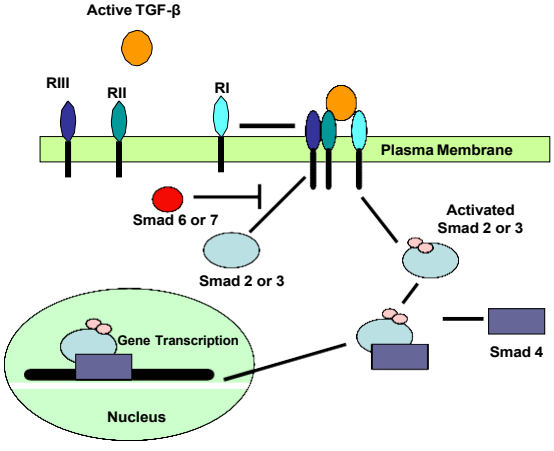


Figure 1. Signaling by TGF-β.

(Smads) (Smad2). Smad2 forms a complex with other Smad proteins, which translocates to the nucleus where it interacts with transcriptional co-activators or repressors to regulate gene transcription (Figure 1).

The consequences of Smad mediated transcription are cell type specific. In resident lung fibroblasts or fibroblasts recruited from circulating fibrocytes, TGF-β stimulates proliferation and transformation to myoyfibroblasts (22-24). Myofibroblasts are specialized fibroblasts important in tissue repair and fibrosis that express alpha-smooth muscle actin (α-SMA), secrete increased extracellular matrix and release fibrogenic cytokines (i.e. connective tissue derived growth factor (CTGF), platelet derived growth factor (PDGF) and others). In addition, stimulation of myofibroblasts with TGF-β stimulates them to release active TGF-β, amplifying the fibrotic signal (24). Myofibroblasts have been reported in biopsy specimens obtained from patients with ARDS and patients with idiopathic pulmonary fibrosis. In epithelial cells, Smad signaling can induce apoptosis or a transition to a mesenchymal phenotype (EMT) (25,26). In rodent models of lung fibrosis, preventing the activation of TGF-β, blocking the TGF-β receptor, inhibiting Smad activation in response to receptor binding and inhibiting Smad dependent gene transcription have all been shown to attenuate lung fibrosis in response to bleomycin (8). A similar requirement for TGF-β signaling has been observed in lung fibrosis that develops in response to ionizing radiation and asbestos (27). TGF-β signaling has also been shown to play a critical role in the fibrosis that develops in the liver, skin, gut and kidney in response to different fibrogenic stimuli(13). Collectively, this has led investigators to hypothesize that the activation of TGF-β serves as a "fibrotic switch" that is turned on in response to injury and turned off after repair. Excessive fibrosis likely results from unregulated activation of TGF-β or from its failed downregulation after repair of injury.

Smad-dependent pathways are required for the normal regulation of tissue regeneration, inflammation and fibrosis. As a result, strategies that completely inhibit Smad signaling have been associated with significant toxicity. To overcome these difficulties, investigators have focused on pathways that modulate the intensity of Smad signaling or act independent of the Smad pathway in mediating the full TGF-β mediated cellular response (28-30). For example, activation of the mitogen-activated protein kinase (MAPK) pathways including p38 (28), extracellular signal-regulated protein kinase (ERK) (30), or the c-Jun N-terminal kinase (JNK) (31) is often required for effective TGF-β signaling (32). Imatinib (Gleevec) is an example of a small molecule designed to inhibit Smad-independent signaling by TGF-β. Imatinib inhibits TGF-β-induced activation of the tyrosine kinase, c-Abelson (c-Abl), which is required for extracellular matrix expression in fibroblasts. The administration of imatinib to mice was shown to prevent pulmonary fibrosis in the bleomycin model, but only when the drug was administered before the administration of bleomycin (33,34).

PPAR- INHIBITS TGF-B1 MEDIATED SIGNALING/FIBROSIS

Peroxisome proliferator-activated receptor-gamma (PPAR-γ) is a nuclear hormone receptor and transcription factor that is essential for normal adipogenesis and glucose homeostasis. PPAR-γ exists as two isoforms in human cells that are splice variants of a single gene. PPAR-γ_1 is ubiquitously expressed and plays an important role in glucose metabolism. PPAR-γ_2 is expressed only in adipocytes where it functions as a master switch in adipocyte development. Endogenous lipids and eicosanoids such as 15-deoxy-Δ12,14-prostaglandin J_2 (15d-PGJ_2) act as natural PPAR-γ ligands. Activation of PPAR-γ can also be induced by thiazolidinedione anti-diabetic drugs such as rosiglitazone.

We have previously reported that in normal skin fibroblasts, PPAR-γ ligands block the upregulation of collagen synthesis and α-SMA expression induced by TGF-β (35). Ectopic

PPAR-γ elicited a similar response in these cells even in the absence of PPAR-γ ligand. Recently they reported that mouse embryonic fibroblasts (MEFs) lacking PPAR-γ displayed substantially elevated basal levels of collagen gene expression. Collagen gene expression persisted despite the administration of PPAR-γ ligands, but was normalized by the expression of ectopic PPAR-γ. In addition, PPAR-γ null MEFs had increased TGF-β production and elevated levels of expression of the type I TGF-β receptor (TβRI). Furthermore, PPAR-γ null MEFs showed constitutive activation of endogenous Smad2/3 in the absence of PPAR-γ exogenously added ligand (36). Together, these results suggest that cellular PPAR-γ plays an important physiological role in negatively modulating the intensity of intracellular TGF-β signaling and target gene expression. Further, PPAR-γ agonists, if administered prior to bleomycin instillation, have been shown to be protective against pulmonary fibrosis (37).

PROTEASOMAL DEGRADATION OF PROTEINS

Since its original description by Dr. Aaron Ciechanover and colleagues, the ubiquitin/proteasome system has emerged as a key pathway which defines cellular protein turnover and consequently the levels and activity of numerous intracellular proteins. Proteins are targeted for degradation by the covalent linkage of ubiquitin to a lysine residue in the target protein. Ubiquitin is a small, ubiquitously expressed protein that is highly conserved throughout evolution. In most cases, ubiquitin is linked to the substrate protein through an isopeptide bond between the ε-amino group of a lysine in the target protein and the COOH-terminal glycine of ubiquitin. Cycles of these reactions link additional ubiquitins to lysines within the previously added ubiquitin.

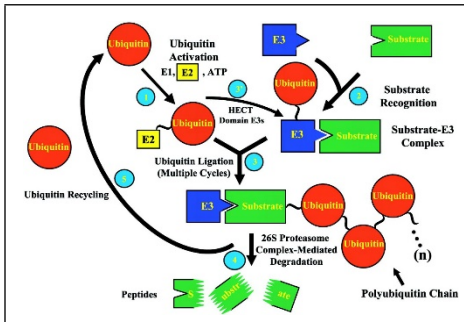


Figure 2. The targeting of proteins for degradation by the ubiquitin-proteasome system. From reference ((38)).

The conjugation of ubiquitin to protein substrates involves a series of hierarchically organized steps (Figure 2). An E1 ubiquitin-activating enzyme that is present in all mammalian cells catalyzes the formation of an E1 ubiquitin thioester adduct with the COOH-terminal glycine of ubiquitin in a reaction that requires ATP. The E1 enzyme transfers the ubiquitin to members of the E2 ubiquitin-carrier protein family (also called ubiquitin-conjugating enzymes). For the majority of proteins the transfer of ubiquitin from the E2 ligase to the protein targeted for degradation requires the participation of an E3 ubiquitin ligase. The E3 ligases are a large class of a structurally diverse family of proteins that may number in the hundreds in humans (38). They provide selectivity to the ubiquitin process by serving as docking proteins that bring the substrate protein and the E2 carrier protein with activated ubiquitin together. In some instances, accessory proteins also interact with E3 ubiquitin ligases to facilitate substrate recognition.

Signaling through TGF-β is known to be regulated by the ubiquitin conjugating system. HECT domain E3 ligases, facilitate the degradation of receptor regulated Smads 2,3 and some of the proteins that comprise the TGF-β receptor. The RING finger E3 ligase Arkadia is activated upon binding to Smad7 and targets it and the transcriptional repressors SnoN and c-Ski for degradation. By removing these three independent inhibitors of Smad transcription, Arkadia enhances TGF-β signaling.

The 26S Proteasome

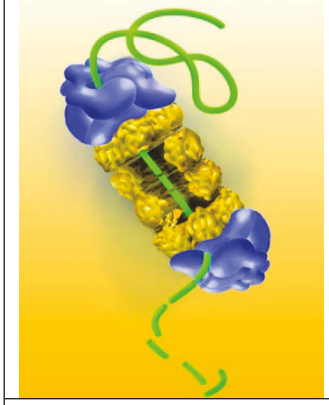
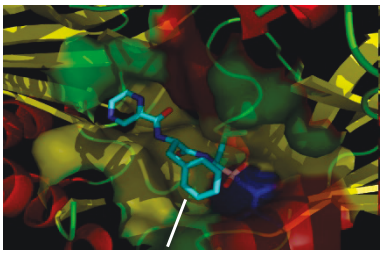


Figure 3. The 26S proteasome.

In addition to its role in removing damaged proteins, the ubiquitin/proteasome system has been shown to play a critical role in the regulation of proteins that affect inflammatory processes, cell growth, and differentiation. The proteasome is located both in the cytoplasm and the nucleus (38). It has a barrel-like structure that is capped at each end by regulatory 19S proteins (Figure 3). The barrel moiety or core 20S particle has both a scaffold-like and proteinase functions. The active site threonine residues whose hydroxyl groups function as the catalytic nucleophils have three distinct cleavage preferences termed: chymotryptic, tryptic, and caspase. Inhibitors of the proteasome can bind to one of more of these sites to inhibit enzymatic function. The regulatory 19S complex at each end of the barrel functions to recognize, bind and unwind proteins prior to degradation. The 20S core and the 19S regulatory units are collectively referred to as the 26S proteasome. Inhibiting the activity of the proteasome prevents substrate degradation which leads to modulation of associated proteins that are involved in disease states. Inhibition of these "activated" proteins (e.g., transcription factors such as nuclear factor-κB (NF-κB) or HIF) can modulate molecular pathways, and the resulting phenotype in disease models. Proteasomal inhibitors have been shown to ameliorate liver steatosis/fibrosis (39,40), myelofibrosis (41) cardiac fibrosis (42) and renal fibrosis (43) in animal models. The mechanism by which proteasomal inhibition protects against injury/fibrosis is not known; investigators have proposed that proteasomal inhibition might prevent TGF-β1 activation (41), the expression of TGF-β regulated fibrotic genes (44) or an increase in fibroblast apoptosis (40).



Bortezomib

Figure 4. Binding of bortezomib with a catalytic domain in the 26s proteasome to reversibly inhibit its chymotrypsin like activity.

Bortezomib is a modified dipeptidyl boronic acid that intercalates into an active site of the proteasome to specifically and reversibly inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells (Figure 4). It is the first proteasomal inhibitor approved by the FDA for clinical use for the treatment of multiple myeloma, mantle cell lymphoma and other malignancies.

TGF- , PPAR- and Ubiquitin/Proteasomal system Little is known regarding the proteasomal degradation of PPAR-γ. We have data that bortezomib inhibits TGF-β mediated gene expression, prevents PPAR-γ degradation and promotes normal healing by protecting against bleomycin pulmonary and skin fibrosis when begun 7 or days after bleomycin instillation. We also have data that BAL fluid from pulmonary fibrosis patients induces profibrotic gene expression which is inhibited by bortezomib. In addition we have shown that bortezomib inhibits profibrotic gene expression in lung and skin fibroblasts obtained from pulmonary and skin fibrosis patients respectively.

1.2 BORTEZOMIB (BORTEZOMIB FOR INJECTION)

1.2.1 Scientific Background

Bortezomib for Injection is a small molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) and it is registered in Europe for the treatment of multiple myeloma patients who have received at least one prior therapy.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays (45). 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 (46,47). 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 (48).

1.2.2 Nonclinical Pharmacology

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

The pharmacodynamic action of bortezomib is well established and can be measured through an ex vivo assay (20S proteasome activity) (49). This assay was used to determine the duration of drug effect in lieu of the PK data in the early preclinical toxicology studies as well as to set a guide for dose escalation in humans. Following dosing with bortezomib in the rat and cynomolgus monkey, proteasome inhibition in peripheral blood had a half-life less than 24 hours, with proteasome activity returning to pretreatment baseline within 24 hours in monkey and within 48 to 72 hours in rat after a single dose of bortezomib. Further, intermittent but high inhibition (>70%) of proteasome activity was better tolerated than sustained inhibition. Thus, a twice-weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations.

1.2.3 Nonclinical Toxicity

Single-dose IV toxicity studies were conducted with bortezomib in the mouse, rat, dog, and monkey to establish the single-dose maximum tolerated dose (MTD). The MTDs were 0.25 mg/kg (1.5 mg/m^2) and 0.067 mg/kg (0.8 mg/m^2) in the 2 most sensitive species, rat and monkey, respectively.

Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic

toxicity of bortezomib when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.10 mg/kg (0.6 mg/m^2) and the key target organs were the gastrointestinal (GI) tract, hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m^2) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date.
In general, the nature of the toxicity of bortezomib is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of bortezomib in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD. The cause of death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of bortezomib on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.

1.2.4 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.

1.2.5 Clinical Experience

It is estimated that as of August 31, 2006, more than 44,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003. The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (50). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.

The safety and efficacy of bortezomib in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) (51)and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy) (52). In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma after at least 2 previous treatments received bortezomib, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of subjects, and the overall response rate (CR, PR and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039) (53), 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 bortezomibwas associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2 bortezomib weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in

TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm (*P*<.0001). CR (complete response) + PR (partial response) was 38% with bortezomib vs. 18% with dexamethasone (*P*<.0001). CR was 6% with bortezomib vs. <1% with dexamethasone (*P*<.0001). The CR + nCR rate was13% with bortezomib vs. 2% with dexamethasone. In patients who had received only one prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs. 26% with dexamethasone (*P*=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (*P*=.0013) for patients on the bortezomib arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (*P*=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (*P*=.0098). Updated response rates and survival data were reported for M34101-039 (53). The updated CR (complete response) + PR (partial response) rate was 43% with bortezomib. The CR + nCR rate was 16% with bortezomib. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm vs. patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the bortezomib arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, *P*= 0.0272). The probability of survival at one year was 80% for the bortezomib arm vs. vs 67% for the dexamethasone arm (*P*=0.0002).

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

1.2.6 Potential Risks of bortezomib

To date, more than 100,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib. Please see table 1 and section 5.5 of the bortezomib Investigators' Brochure (IB, V17 Apr 2014) for the known anticipated risks of bortezomib and a consolidated table listing the approximate incidence of those risks.

Table 1 **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*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and labyrinth disorders	
Uncommon	Deafness, hearing impaired
Eye disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal disorders	
Most common	Constipation, diarrhoea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*, lower gastrointestinal haemorrhage*±, rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction
General disorders and administration site conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune system disorders	
Uncommon	Drug hypersensitivity, angioedema

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

System Organ Class Observed Incidence	Preferred Term
Infections and infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bactaeremia*, cellulitis*, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, poisoning, and procedural complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and nutritional disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and connective tissue disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, benign, malignant, and unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*
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, posterior reversible encephalopathy syndromeϕ

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

System Organ Class Observed Incidence	Preferred Term
Psychiatric disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and urinary disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, thoracic, and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and subcutaneous tissue disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

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 Table 4-9, however the event is deemed medically important and so is included.

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

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.

1.3 STUDY RATIONALE AND SELECTION OF DRUG DOSES

The study is being conducted to establish the safety and tolerability of bortezomib in SSc patients at high risk for pulmonary disease progression. In addition the study will examine the effect of bortezomib on the rate of FVC decline (a physiologic parameter closely associated with disease outcome) and other clinical parameters. In addition we will also measure the effect of bortezomib on biomarkers associated with fibroblast activation. If successful, the study will provide the rationale for a multi-center placebo controlled trial to test the efficacy of bortezomib in SSc patients at high risk for progressive pulmonary disease.

Rationale for drug dosing: The standard dose of bortezomib in multiple myeloma is 1.3 mg/m^2. In our mouse bleomycin experiments we observed antifibrotic effects at this dose (proportional to body surface area of a mouse) as well as doses up to ten fold lower. In addition we detected efficacy when given weekly for two weeks out of four. In a separate study we have found that bortezomib at a dose of 1.3mg/m^2 weekly is well tolerated in patients with pulmonary GVHD, a non-oncologic population. Thus, we propose to test a dose of bortezomib 1.3 mg/m^2. We will also administer bortezomib for 2 weeks out of a 4 week cycle and the cycle will be repeated 3 times. We will then administer bortezomib for 1 week out of a 4 week cycle and the cycle will be repeated for 3 cycles.

Benefits

In SSc patients with progressive pulmonary disease, mortality is substantial and most patients die from their pulmonary disease. Thus strategies effective at preventing progressive fibrosis are likely to have to have salutary effects on mortality. Bortezomib is an FDA approved therapy for the treatment of multiple myeloma and other malignancies. We have data that bortezomib inhibits TGF-β signaling in vitro and promotes normal repair and prevents against lung fibrosis in the TGF-β mediated intratracheal bleomycin mouse model as well as in a mouse model for skin fibrosis (54). This is consistent with other data in the literature that proteasomal inhibition can prevent the development of fibrosis (41,55). Further there are multiple reports on the efficacy of bortezomib in ameliorating cGVHD in patients after allogeneic HSCT for multiple myeloma (56,57). Bortezomib was also well tolerated in the large clinical trials of multiple myeloma patients with neuropathy and thrombocytopenia the primary adverse events (53). No pulmonary toxicities were reported in these studies.

Risk

Studies in monkeys have shown that acute administration of bortezomib at twice the recommended clinical dose resulted in cardiovascular collapse and death 12-14 hours after administration. Doses $\geq$ 1.3 mg/m^2 induced dose-proportional changes in cardiac parameters. bortezomib distributes to most tissues in the body except for the CNS, testes and eyes. Toxicity observed with chronic administration at dose and schedule used in multiple myeloma patients, 1.3 mg/m^2, twice a week for 2 weeks followed by 1 week rest, included peripheral neuropathy, thrombocytopenia, anemia, GI, neurologic and lymphoid system toxicities.

There are, however, reports of patients who developed pulmonary toxicity following bortezomib administration (58) on a twice weekly basis. The vast majority of these patients were in Japan. At the time of the earliest report, bortezomib was not approved in Japan and was imported from abroad for administration. In addition no consideration was given to patient's performance status or chest x-ray findings and acute infection was not excluded. After this report was published, it was recommended that bortezomib be administered only to patients with a good performance status and no evidence of infection. Implementation of these guidelines has led, in 2 different studies (59), to a 10-fold reduction in incidence of pulmonary complications, including a post-marketing surveillance cohort of 666 patients(60). Based in part on these studies, bortezomib was approved in Japan in 2006. Though there are sporadic case reports of bortezomib induced pulmonary toxicity from elsewhere (61,62), there are no reports suggesting the high rate of bortezomib induced pulmonary toxicity seen in Japan and pulmonary toxicity was not reported in the pivotal US phase 2 study(52). In addition we have pulmonary function data on 73 patients after induction treatment with bortezomib comprising 12-24 doses and have found no unexpected abnormalities of pulmonary function (see appendix). These patients have undergone high-dose chemotherapy with HSCT subsequently without any unanticipated lung problems. We also have anecdotal experience of administering

bortezomib to 6 critically ill multiple myeloma patients in the intensive care unit with no specific

pulmonary adverse effects. Finally based upon our experience and recent data from an Italian study (63)in myeloma, it is expected that administration of bortezomib for 2 weeks out of 4 for 3 cycles and then 1 week out of 4 for 3 cycles will be associated with a substantial reduction in all types of toxicity.

1.4 Mycophenolate Mofetil (MMF)

ADMINISTRATION ROUTE: ORAL

Dosing unit: Capsules containing 500 mg MMF.

Dosing: up to 1.5 g twice daily for 24 weeks:

Subjects will be on a stable dose of MMF for at least 8 weeks prior to enrolling in the study. Dosing may be held or down-titrated at any time if indicated by study criteria for safety and/or tolerability. Participants will continue their MMF for the duration of the study of 24 weeks.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

- To assess safety and tolerability of bortezomib in combination with MMF in System Sclerosis (SSc) patients at high risk of progression of pulmonary disease
- To assess the effect of bortezomib in combination with MMF on lung function in SSc patients at high risk of progression of pulmonary disease

2.2 Secondary objectives

- To assess the effect of bortezomib in combination with MMF on Quality of Life and respiratory symptom scores in SSc patients at high risk of progression of pulmonary disease
- To assess the effect of bortezomib in combination with MMF on skin fibrosis in System Sclerosis (SSc) patients at high risk of progression of pulmonary disease

2.3 Exploratory objective

- To assess the effect of bortezomib in combination with MMF on serum biomarkers
- To assess the effect of bortezomib in combination with MMF on aberrant gene expression in skin biopsies and from SSc patients at high risk for disease progression

3.0 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

This is a pilot randomized double blind clinical trial in which bortezomib or placebo is added to MMF in System Sclerosis (SSc) patients at high risk of progression of pulmonary disease (defined below).

3.2 Selection of Patients

The total number of patients to be enrolled is 30.

Enrollment is defined as the first day of bortezomib or placebo (i.e. day 1 of cycle 1).

3.2.1 **Inclusion Criteria**

1. Meet established criteria for diffuse or limited SSc and evidence of pulmonary at high risk of progression with or without progressive skin disease.
    - **i.** Definition includes subjects who meet the ACR criteria for scleroderma
    - **ii.** High Risk of disease progression (see rationale) will be defined as follows
        - **1.** If SSc diagnosis ≤ 36 months then if any of the following are true:
            - **a.** FVC <70% predicted
            - or
            - **b.** HRCT Fib_{max} >3
            - or
            - **c.** FVC < 85% and MRSS increase of 5 over 6 months
        - **2.** Regardless of disease duration
            - **a.** Fall in FVC > 10% over the preceding 12 months or less in the absence of prior therapy or another identified causative process as assessed by the primary scleroderma physician
            - **b.** Fall in FVC > 10% over 12 months on at least 6 months of prior therapy
2. Age ≥ 18 years
3. Ability to give informed consent.
4. Willingness to discontinue present therapy for the duration of the study
5. Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.
6. Male subject agrees to use an acceptable method for contraception for the duration of the study.
7. No evidence of acute infection
8. ANC >1000
9. Platelets ≥75,000
10. Stable dose of MMF at least 8 weeks prior to enrollment

3.2.2 **Exclusion Criteria**

1. Inability to give informed consent or comply with protocol procedures
2. FVC < 40% or DLCO <30% predicted
3. Patient has a platelet count of less than 50,000 within 14 days before enrollment.
4. Patient has an absolute neutrophil count of less 1000 within 14 days before enrollment.
5. Patient has a calculated or measured creatinine clearance of < 20 ml/minute within 14 days before enrollment.

6. Patient has ≥ Grade 2 peripheral neuropathy by history within 14 days before enrollment.
7. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.4), 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 has to be documented by the investigator as not medically relevant.
8. Patient has hypersensitivity to bortezomib, boron or mannitol.
9. Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
10. Patient has received other investigational drugs within 4 weeks before enrollment
11. Serious medical co-morbidity which in the opinion of the investigator makes participation in the study too high risk
12. Psychiatric illness likely to interfere with participation in this clinical study.

3.3 STUDY TREATMENTS

3.3.1 CLINICAL TRIAL MATERIALS

Bortezomib for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing Bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of Bortezomib contain 35 mg of mannitol. MMF will be purchased as capsules.

Preparation, Handling and Storage of Drugs

Bortezomib

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

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

Drug is available in sterile, single use vials containing 3.5 mg of Bortezomib. Each vial of Bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains Bortezomib at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted Bortezomib should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

MMF
MMF will be distributed to study subjects in a bottle from their specific pharmacy. Subjects are responsible for the cost of the MMF.

Drug administration and dosage schedule
Bortezomib, 1.3 mg/m^2 by subcutaneous injection or intravenously (only done if subcutaneous injection is not possible) once a week x 2 weeks for 3 cycles and then once a week for 3 cycles.
MMF 1.5 g twice a day orally.

Bortezomib is being provided by Millennium Pharmaceuticals at no cost to the subjects and Northwestern University is receiving no monetary compensation form Millennium Pharmaceuticals.

Bortezomib or Normal Saline (placebo) Administration
Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients may be treated on an out-patient basis, if possible. The pharmacist will prepare the drug under aseptic conditions. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (see section 8.2). The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight (e.g. loss or gain of ≥8 lbs or 3.6 kg) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time.

The appropriate amount of Bortezomib will be drawn from the injection vial and administered by subcutaneous injection. The intent is for all subjects to receive the medication subcutaneously, but if that is not possible it will be administered as an intravenous (IV) push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

MMF will be prescribed to patients by their primary care physician. The research subjects will be responsible for filling their prescription and purchasing the MMF from their local pharmacy. Subjects will take the medication at home on their own. Each subject will record their use in a diary and bring it at their research visits.

3.3.2 Dose modification and Delay

Bortezomib

Dose escalation will not be allowed in any patient, and there must be at least 1 week between each dose of bortezomib. Dosing will be modified in patients with evidence of moderate or severe hepatic impairment. Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s).All previously established or new toxicities observed any time, with the exception of neuropathic pain and peripheral sensory neuropathy, are to be managed as follows: If the patient experiences febrile neutropenia, a Grade 4 hematologic toxicity (including a platelet count $<25 \times 10^9$/L) or any ≥Grade 3 non-hematologic toxicity considered by the investigator to be related to bortezomib, then drug is to be held.

For non-hematologic 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 hemoglobin value of >8, platelet value of 20K and neutrophil value of >1000. Dose interruption or study discontinuation is **not** required for lymphopenia of any grade. If, after bortezomib has been held, the toxicity does not resolve, as defined above, then drug must be discontinued. If the toxicity resolves, as defined above, and bortezomib is to be restarted, the dose must be reduced by approximately 25% as follows: If the patient was receiving 0.7 mg/m^2, reduce the dose to 0.5 mg/m^2. Patients who experience bortezomib-related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 3.

Management of Patients with Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy.

Table 3: Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Periphe Sensory or Motor Neuropathy

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

*Grading based on NCI Common Terminology Criteria CTCAE v4.0

**Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc;

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

The neurotoxicity-directed questionnaire (see section 8.4) 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.

MMF

The toxicity profile for is MMF is well established as outlined below and drug discontinuation and/or dose modification will be managed by the Clinical Investigator (see below) using the following specific criteria.

Reasons for withholding the dose of study drug: The following abnormalities and laboratory tests require study drug discontinuation, either temporary (until normalization) or permanent, as indicated by the nature of the event, its severity and/or course of resolution upon discontinuation of therapy.

- Allergic reaction associated with drug administration
- WBC <2500, or < 1000 neutrophils
- Platelet count < 20,000
- Hemoglobin < 8.0 gm/dl
- Documentation of gastrointestinal ulcer, bleeding or abdominal emergency
- Pregnancy or initiation of breastfeeding
- Intractable congestive heart failure
- Serum creatinine > 2.0 mg/dl, or increase in serum creatinine of> 50% over baseline, or decrease of estimated GFR to < 45 mIIminl1.73 m2 (corrected) in the absence of other etiology
- Ongoing infection whose management would be significantly compromised by continued drug-associated immunosuppression
- Any adverse event felt by the investigator to be possibly or probably related to a study drug and of a clinical significant sufficient to warrant drug discontinuation

Management of drug dosing in response to specified toxicities. If any of the above toxicity occurs, the dose of study medication will be altered as follows:

- Allergic reaction; pregnancy or breastfeeding; proven malignancy: Study drug will be stopped and subject withdrawn from study.
- Bone Marrow Suppression: For leukopenia (WEC < 2500 and/or ANC < 1000), thrombocytopenia « 20,000), or anemia (Hgb < 8 gm/dl) the study drug will be managed as follows:
  - Hold study drug until there is a stabilization of the hematologic abnormality at a value above the toxicity threshold levels (Hgb > 8.0 gm/dl , WBC > 2500, platelets > 20,000). In addition, if another cause for the reduction in hemoglobin is found (e.g., gastrointestinal bleeding), that cause should be appropriately treated and determined by the study physician to be stable before restarting on study drug.
  - Once threshold values are exceeded, the MMF will be reintroduced at by starting over at the lowest dose and the dose advanced every week as tolerated. At the clinical investigator discretion, after taking into account

whether the study drug was likely or probably related to the adverse event, the final maintenance dose may be either the last regular dose taken by the patient or 500 mg/day less for MMF.

- For hospitalizations, surgery or infections requiring antibiotics for which the immunosuppressive effects of the study drugs are determined by the investigator to likely complicate the clinical course: The study drug should be discontinued until the potential interaction with the medical condition in question has resolved. Once the patient is stable, the study drug can be restarted without dose modification.
- Other severe or dangerous adverse events: For adverse events that are considered clinically serious by the investigator, the study drug will be managed as follows:
  - Hold study drug until there is resolution of the adverse event.

Once stable, the MMF will be reintroduced by starting over at the lowest dose with the dose advanced every week as tolerated. At the site investigator's discretion, after taking into account whether the study drug was likely or probably related to the adverse event, the final maintenance dose may be either the last regular dose taken by the patient or 500 mg/day less.
Follow-up should be every 1-2 weeks, as clinically indicated, until the investigator is satisfied that it is safe to return to the protocol-defined dosing schedule. In the event of repeat toxicity, the same cycle should be repeated except with the intention of achieving a maintenance dose equal to 1000 mg/day less.

- For severe diarrhea, the MMF will be stopped and the subject will receive antidiarrheal medications until the diarrhea has resolved. The MMF will be reintroduced with a more gradual dose escalation and if necessary a goal dose of 1.5 grams to 2 grams per day. If diarrhea recurs and the subject is intolerant of at least 1.5 grams to 2 grams of MMF per day, the subject will be removed from the study.

For less severe or dangerous adverse events (e.g., dyspepsia) not responding to concomitant medications: the study drugs are to be discontinued until the adverse event disappears, at the clinical discretion of the study physician. At that point the subject can be restarted at one-half of the original dose. The subject can return to the full dose of medications or one capsule less than the full dose, as clinically indicated, after 1 week at the half dose of medications.
Discontinuation of study drug for unresolved toxicity: If the subject cannot resume study medication at some dose within one month of discontinuing, secondary to adverse or other events: the subject should be discontinued from the trial and the subject should complete the end of the study visits.

3.3.4 Treatment Assignment
Patients will be randomized to a 1:1 ratio to bortezomib or placebo for the study which will be added to MMF.

3.3.5 Blinding Packaging and Labeling

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

3.3.6 CONCOMITANT TREATMENT

Required Concurrent Therapy

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

- Patients will be administered their usual therapies at the discretion of the treating physician.
- **Acyclovir**

Varicella zoster virus (VZV) reactivation is a common and serious adverse effect of bortezomib treatment. Acyclovir 400 mg once daily has been shown to be sufficient to protect from VZV reactivation in patients treated with bortezomib. All subjects will be required to take acyclovir 400 mg by mouth once per day after they have qualified for the study and prior to the first dose of bortezomib/placebo. Subjects will be required to have the prescription written by their primary medical doctor or the primary investigator. Subjects will be responsible for filling their prescription and purchasing the acyclovir from their local pharmacy.

Prohibited Concurrent Therapy

- Any investigational agent other than Bortezomib.

3.3.7 Treatment Compliance

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see section 8.2) and total drug administered in milliliters and milligrams and number of capsules. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

3.3.8 Concurrent Medications

Concurrent medications will be recorded at each visit. In addition, participants will be instructed to contact study physician in case their medication is changed by another physician. As this is a double-blind study, management of concurrent medications will be the same for all participants.
The following drugs have significant interactions with MMF: Hormonal Contraceptives, Antacids, Acyclovir, gancylovir, valcylorvir, Cholestyramine, Echinacea. Patients will be advised of these interactions and appropriate actions will be taken to prevent complications.
The following drugs are contraindicated: Azathioprine, Cyclcosporine, D-penicillamine, Methotrexate, Potab, Rituximab, Etanercept, Inflixamab, Adalimiumab. Corticosteroid use will be allowed if the dose is lower than equal

to 15mg of prednisone per day.

3.4 Duration of Treatment, Patient Participation and Study Procedures

Once enrolled patients randomized to bortezomib will receive either weekly subcutaneous injections or IV infusions of bortezomib/placebo for first 2 weeks of a 4 week cycle for 12 weeks or 3 cycles and then once per week for 12 weeks or 3 cycles and oral daily MMF. The 4 week cycle of bortezomib or SC/IV placebo will be repeated 6 times for a total of 24 weeks. The completion visit at the end of the 48 weeks will serve as the primary endpoint visit. There will also be a visit 3 months after the primary endpoint visit.

3.4.1 Summary of Study Visits

EVALUATIONS BY VISIT

Visit 0 Screening-SSc

Screening Protocol: After providing informed consent, patients will begin a staged screening protocol. Prospective patients will undergo a history and physical (H&P) and a Spirometry at a screening visit. Screen-eligible patients will be asked to undergo a high resolution computerized x-ray examination of the lungs (chest HRCT scan). If the patient recently completed a chest HRCT scan (within the past 3 months), the scan may be considered in place of completing another scan for this study. The thoracic HRCT will be assessed for study purposes and inclusion criteria within 4 weeks of the screening visit by Dr. Hart. Patients meeting HRCT or alternative criteria will begin the enrollment visit. To be randomized the FVC from the screening and enrollment must be within 7% of each other to ensure a stable baseline. If not, a repeat FVC will be obtained within 7 days and if it agrees within 7% of the FVC at screening, the patient can be randomized.

- Medical Chart Review
- H&P
- Demographics
- Vital signs
- Assess AE's and Concomitant medications
- ECG
- HRCT (If not done within 3 months of the visit for standard of care)
- Spirometry
- MRSS
- Blood Work-CBC, Chemistries, urine dipstick pregnancy for women of child bearing potential
- Distribute/collect MMF diary

Visit1 Enrollment-Study Day 1 (Cycle 1, Day 1)

- Interim H&P (if applicable)
- Full PFTs
- Vital signs
- Assess Ae's and concomitant medications
- MRSS and Hopkins Skin Score
- Skin Biopsy (If consented)
- Blood Work
- QOL assessment and NU PRO
- St. George's and FACIT-dyspnea
- 6MW
- Interim H&P

- Blood Work/Serum for Biomarkers, urine dipstick pregnancy for women of child bearing potential
- 1st Dose of Randomized Bortezomib/ Placebo SC or IV Administration
- Distribute/collect MMF Diary

Visits for Drug Administration Only (Visits 2-6, 8-&9)

- Interim H&P(if applicable)Vital signs
- Assess AE's and concomitant medications
- Toxicity Assessment for Neuropathy (Subjects will complete the FACT/GOG-Ntx Functional Assessment Tool [see appendices 8.4])
- Spirometry
- Blood Work, urine dipstick pregnancy for women of child bearing potential
- Bortezomib/ Placebo SC or IV Administration
- Distribute/collect MMF Diary

Visits for Quarterly Assessments and Drug Administration (Visit 7)

- Interim H&P(if applicable)
- Vital signs
- Assess Ae's and concomitant medications
- Spirometry
- MRSS and Hopkins Skin Score
- QOL assessment and NU PRO
- St. George's and FACIT-dyspnea
- 6MW
- Interim H&P
- Toxicity Assessment for Neuropathy (Subjects will complete the FACT/GOG-Ntx Functional Assessment Tool [see appendices 8.4])
- Blood Work/Serum for Biomarkers, dipstick pregnancy for women of child bearing potential
- Bortezomib/ Placebo SC or IV Administration

Visit for Primary Endpoint Evaluation/ Completion of Phase 2 (Visit 10)

- Interim H&P (if applicable)
- Vital Signs
- Assess AE's and concomitant medications
- PFTs
- Skin Biopsy (If consented)
- MRSS and Hopkins Skin Score
- QOL assessment and NU PRO
- St. George's and FACIT-dyspnea
- 6MW
- Toxicity Assessment for Neuropathy (Subjects will complete the FACT/GOG-Ntx Functional Assessment Tool [see appendices 8.4])
- Blood Work/Serum for Biomarkers

Early Termination Visit (For toxicity, disease progression or patient request)

- Interim H&P(if applicable)
- Vital signs
- Assess AE's and concomitant medications
- PFTs
- Skin Biopsy (If consented)
- MRSS and Hopkins Skin Score
- QOL assessment and NU PRO
- St. George's and FACIT-dyspnea
- 6MW
- Toxicity Assessment for Neuropathy (Subjects will complete the FACT/GOG-Ntx Functional Assessment Tool [see appendices 8.4])
- Blood Work/Serum for Biomarkers

Follow-up visit (3 months after Primary Endpoint or Early Termination Visit)

- Interim H&P(if applicable)
- Vital signs
- Assess AE'
- Spirometry
- HRCT (If not done within 3 months of the visit for standard of care)
- Skin Biopsy (If consented)
- MRSS and Hopkins Skin Score
- QOL assessment and NU PRO
- St. George's and FACIT-dyspnea
- 6MW
- Toxicity Assessment for Neuropathy (Subjects will complete the FACT/GOG-Ntx Functional Assessment Tool [see appendices 8.4])
- Blood Work

3.4.2 STUDY PROCEDURES

Informed Consent

The Investigator will explain the benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness and

obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study related procedure and administration of study drug). The PI will provide the informed consent. The final, version dated, form must be agreed to by the PI and the IRB and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the physician conducting

The informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects or their legally authorized representative with a copy of their signed informed consent and assent where appropriate The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the IRB and existing subjects informed of the changes and re-consented. This is documented in the same way as previously described. The Investigator should with the consent of the subject or subject's legally acceptable representative, inform the subject's primary physician about participation in the clinical trial.

Eligibility Criteria
Subjects will be reviewed for eligibility against the inclusion and exclusion criteria.

Medical History
A comprehensive medical history will be undertaken by the investigator to determine past and current medical conditions and procedures.

Demographic Information
The following information will be collected: date of birth, height and weight, race, gender, age at diagnosis.

Concomitant medications
Medication use that is current will be recorded. In addition all prior therapy and duration for SSc will be noted. Generic names are to be used where possible, though trade names may be used for combination drugs. Start and stop dates, total daily dose, route and indication for use should be recorded. Where possible the use of all concomitant medications at the start of the treatment period should be maintained throughout the treatment period, and wherever possible, institution of new concomitant medications should be avoided.

Physical Examination and Vital Signs
A physical examination must include as a minimum: Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature), chest auscultation, height and weight. The physical examination should be conducted by a physician, but where timing prohibits this, a suitably trained nurse may undertake this task. If any doubt exists about the physical status of the subject the physician should be consulted.

Pulmonary Function Testing and Spirometry

All study pulmonary function and spirometric testing must be conducted according to the ATS/ERS criteria 2005 (64). When possible, pulmonary function testing should be performed as close as possible to the same time of the day at each visit. All pulmonary function testing should be done in the sitting position, unless the subject is obese, who will commonly obtain a deeper inspiration when tested in the standing position.

Skin Thickness and Function Scores

Modified Rodnan Skin Score-Clinical assessment of skin thickness will be made in

each of 17 body areas with 0-3 score with a maximum score of 51. (0=normal, 1=mild thickness, 2= moderate, 3= severe)

Hopkins Skin Score- Patient reported assessment of skin disease will be evaluated based on a 6 component questionnaire using a Likert Scale with a range of 0-10 on each component. The score can vary from 0-60.

SKIN BIOPSIES (OPTIONAL)

Two to four total punch biopsies will be performed each time as indicated in the protocol. A 3 mm punch will be obtained from the lesional forearm (1x) and from non-involved skin like buttocks (x2). 1 piece will be used for RNA (microarrays and qPCR-Ancillary Project) and 1 piece will be paraffin embedded for histology and immunohistochemistry.

SERUM COLLECTION, PREPARATION AND STORAGE

All blood tests that are obtained for routine clinical care will be recorded in the CRF. Subjects will be asked to provide a blood sample for study purposes from an existing catheter (i.e. central venous line or arterial catheter) prior to study drug initiation and weekly thereafter before and 1 hour after drug administration until study drug is stopped. Serum will be aliquotted in 1ml tubes and frozen at -80° C.

HIGH RESOLUTION CHEST CT

Thoracic HRCT will be obtained at the screening visit and at the last visit of the study (three-month follow-up visit). If subjects recently completed a chest HRCT scan (within the past three months of each visit), the scan may be considered in place of completing another scan specifically for the study. The HRCT at screening will be assessed for inclusion criteria by Dr. Hart.

SIX-MINUTE WALK TEST

The 6MW walk test will be administered using ATS guidelines (65). The distance walked in meters by the patient over 6 minutes will be recorded.

PATIENT REPORTED OUTCOMES

RESPIRATORY SYMPTOM SCORES

St. George's Respiratory Questionnaire- Symptoms and activity scores are calculated using item weights provided in the instrument. The total score is calculated from 16 items and their respective weights.

FACIT-Dyspnea- Contains 10 common tasks and respondent is asked to rate the severity of dyspnea when performing each task over the previous 7 days. They are also asked to rate the difficulty in completing each task due to dyspnea. If a task was not completed respondents are asked whether the task was not completed due to shortness of breath or because no opportunity to perform the task arose.

QUALITY OF LIFE INSTRUMENTS

Short-form-36(SF-36)- The SF-36 is a quality of life questionnaire which yields scores for eight domains, as well as two summary scores, a mental component summary score (MCS) and a physical component summary score (PCS) (66).

Promis-29- This Promis-29 is an instrument that contains 7 domains that relate to physical, mental and social health and cover most of the relevant areas of self-reported health. It includes 4 items in each of the 7 domains as well as one11-point rating scale for pain intensity.

Study Drug Administration

The bortezomib and matching placebo will be prepared by the research pharmacy at NMH and delivered to the CRU. The CRU staff will be responsible for administering the SC injections or IV Infusions (bortezomib or placebo).

3.5 TERMINATION OF TREATMENT AND/OR STUDY PARTICIPATION

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

- Occurrence of an unacceptable adverse event
- Patient request
- Protocol violations
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease at any time
    - > Persistent 10% drop in FVC from Enrollment Visit
    - MRSS score increase of 5 or aggressive skin disease progression as judged by the investigator

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents. The participant will also be asked to participate in an exit visit, either by phone or in person, to document the reason for withdrawal and the status of the participant at the time of the withdrawal. Should the participant die, the cause of death will be determined and recorded if possible. This additional data will be utilized in the statistical analysis of the primary and secondary study outcomes and any missing data handled by appropriate statistical methods.

3.6 EFFICACY, PHARMACODYNAMIC/CORRELATIVE STUDIES, AND SAFETY MEASUREMENTS

3.6.1 Efficacy Measurements

Primary Endpoints

- Incidence of serious adverse events (SAE's)
- Annualized change in Forced Vital Capacity

Secondary Endpoints

- Change in Modified Rodnan Skin Score
- Change in SF-36
- Change in St. George's Respiratory Dyspnea Score
- Change in Hopkins Skin Score (Exploratory)
- Change in Promis-29 (Exploratory)
- Change in FACIT-dyspnea Score (Exploratory)

Exploratory Endpoints

- Change in Serum Biomarkers

- Change in Gene Expression Profile (Skin Biopsies)

3.6.2 Pharmacogenomic/Correlative Studies

- Change in serum proteasomal activity

3.6.3 Safety Measurements

Safety will be assessed by tracking the number and percentage of adverse events at 48 weeks. In addition subjects will be monitored for changes in a standard panel of blood tests. There will interim safety analysis after 8 and 16 patients. Specific stopping rules will be in place (See section 5.4.3)

Adverse events

The number and percentage of patients experiencing adverse events will be tabulated.

Additional summary data will be presented for:

• Serious adverse events,
• Treatment related adverse events (defined as being possibly, probably or definitely related to treatment in the opinion of the investigator),
• Treatment related serious adverse events,
• Adverse events leading to study withdrawal,
• Treatment related adverse events leading to study withdrawal
· Deaths

4.0 ADVERSE EVENTS

4.1 Definitions

4.1.1 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.

4.1.2 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 **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 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.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant eCRF must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication? – other medication?".

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.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".
Other significant adverse events
Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment will be classified as OAEs.

4.2 PROCEDURES OF AE AND SAE REPORTING

All Investigators and sub-investigators must report all serious adverse events (SAE) regardless of relationship with any study drug or expectedness to it's own IRB and the primary investigator-sponsor as soon as possible, but no later than 5 calendar days of the investigator's or sub-investigators observation or awareness of the event. Serious adverse events will be captured and reported for 30 days post treatment on the study. All sub-investigators must report all SAEs to the investigator-sponsor so that the investigator-sponsor can meet his/her foregoing reporting obligations to the IRB at Northwestern.
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). 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.

SAES MUST BE FAXED OR EMAILED TO MILLENNIUM PHARMACOVIGILANCE (OR DESIGNEE):
Toll-Free Fax#: 1-800-963-6290
Email: takedoncocases@cognizant.com

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 4.03, as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

4.3 MONITORING OF ADVERSE EVENTS AND PERIOD OF OBSERVATION

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

5.0 STATISTICAL PROCEDURES

5.1 SAMPLE SIZE ESTIMATION

This is a pilot study which will provide data for a sample size estimation for a phase 3 study.

5.2 POPULATIONS FOR ANALYSIS

Patients who receive at least 1 dose of bortezomib/ placebo will be termed the intention to treat (ITT) population. Patients who complete at least 2/3 of the bortezomib/placebo doses in the trial will be termed per protocol population (PP) and analyzed separately. The main analysis will be performed on the ITT group where measurements will be taken at the enrollment and the primary endpoint visit. In an alternative statistical analysis we will incorporate as a covariate the actual length of time between 'first' and 'last' measurements as it may vary from patient to patient if there is dropout prior to completing treatment. The primary and secondary endpoints will be analyzed using the ITT and PP populations. Results from the ITT analysis will take precedence over findings from the PP analysis. In addition, where possible, pattern mixture models will be used to assess the level of 'randomness' for missing data.

5.3 PROCEDURES FOR HANDLING MISSING, UNUSED, AND SPURIOUS DATA

The primary and secondary endpoints will be analyzed using intention to treat (ITT) and PP populations. Results from the ITT analysis will take precedence over findings from the PP analysis. Where a subject has missing data on a continuous outcome measure, we will use the last measure. The pattern of missing data for the primary endpoint variable will be summarized descriptively. In addition, where possible, pattern mixture models will be used to assess the level of 'randomness' in the missing data patterns.

5.4 STATISTICAL METHODS

5.4.1 BASELINE VARIABLES

Continuous demographic and clinical variables will be collected in source documents and displayed as descriptive statistics. Categorical variables will be presented in a tabular form.

5.4.2 Efficacy Analysis

Primary efficacy endpoint of annualized FVC decline will compare bortezomib and placebo treated cohorts using a t-test.
This is a pilot study in which the primary goal will be to establish safety and tolerability of bortezomib or placebo with MMF in SSc-IID patients. Efficacy will be judged by the annualized change in FVC from the enrollment visit to the primary endpoint visit of the study. The inclusion criteria for the study identifies a cohort that his likely to have a fall in FVC of 5% in 1 year if untreated (2). Bortezomib/MMF and Placebo/MMF treated cohorts will have annualized change in FVC assessed independently. An annualized change in the FVC of 0 will be considered pulmonary disease stabilization though we expect FVC improvement (See above). Skin scores and QOL measures will also be important secondary endpoints and will be assessed similarly to lung function changes. Success or failure of secondary endpoints will be based on established norms and minimally important clinical differences already established for each parameter.

5.4.3 Safety Analysis and stopping rules

Extent of exposure: A summary of exposure to study drug and the duration of exposure will be provided.
Adverse events and Serious adverse events: Treatment-emergent adverse events (TEAEs) (events which were not present at baseline or worsened in severity following the start of treatment) will be presented. Any AEs starting after a patient has terminated from the study will not be presented. The following summaries will be provided:

• A summary of the number and percentage of patients reporting any TEAE, at least one severe TEAE, at least one TEAE possibly related to study drug, and at least one TEAE leading to withdrawal from study drug.

For each patient and each TEAE, the worst severity recorded will be attributed and used in the by-severity summaries.
The following by-patient listing will be provided:
• A listing of all AEs (including non-treatment-emergent events), date of onset, date of resolution, duration, severity, seriousness, action taken, outcome and relationship to study treatment
Safety will be assessed after the first 8 patients have completed the study. The chair of the DSMB will have the option to be unblinded to the treatment assignment and the study statistician will compare and SAE including mortality in three groups. Safety will be reassessed after the next 8 (total of 16) and at the end of study. All serious adverse events will be examined by the DSMB. It will be up to the discretion of the DSMB to continue or stop the study after each safety analysis.

- 1st Safety Analysis (after first 8 patients (~25 % of the total) have completed the trial): If more than 60% or more patients have died or dropped out, the study will be unblinded and if all are in the bortezomib group the study will be terminated.
- 2nd Safety Analysis (after 12 patients (60% of the total) have completed the trial): If more than 50% or more patients have

died or dropped out and more than 80% are in the bortezomib group the study will be terminated.

5.5 PROCEDURES FOR REPORTING DEVIATIONS TO ORIGINAL STATISTICAL ANALYSIS PLAN

- All deviations from the proposed statistical analysis plan will be reported to the DSMB

6.1 ADMINISTRATIVE REQUIREMENTS

6.2 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.

6.3 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see section 8.5). The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

6.4 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).

6.5 PATIENT CONFIDENTIALITY

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) to the sponsor or his designee 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.

6.6 PROTOCOL COMPLIANCE/QUALITY CONTROL

All **the** study procedures for each visit will be conducted by the nursing staff in the Clinical Research Unit (CRU) of Northwestern in collaboration with the research coordinator. The CRU staff and the research coordinator will be blinded with respect to randomization. The CRU staff and study coordinator will attend an initiation/training session conducted by the PI. This session will include a detailed review of the study protocol, study procedures, data collection forms, duties of the CRU staff, study coordinator and the procedures for handling blood specimens, etc. Quality assurance monitoring for essential study procedures and outcomes will be handled by the PI who will prepare independent manuals of operation and monitor quality features of every study performed. The PI will meet quarterly with the CRU staff to assure that training, staff and instrumentation are in place and being properly used to collect these outcome measures. Blinding will be assessed by asking each participant whether they received bortezomib or MMF in phase 1 of the trial.

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from sponsor and written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to sponsor and the regulatory authority(ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

6.7 ON-SITE AUDITS

Regulatory authorities, the IRB and/or the sponsor designee 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.

6.8 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 Bortezomib will be treated and disposed of as hazardous waste in accordance with governing regulations.

6.9 PREMATURE CLOSURE OF THE STUDY

This study may be prematurely terminated, if in the opinion of the investigator or sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or sponsor 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.

6.10 RECORD RETENTION

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

7.0 REFERENCES

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	SCREENING	CYCLE 1		CYCLE 2		CYCLE 3	
		ENROLLMENT VISIT 1/DAY 1	VISIT 2/DAY 2	VISIT 3/DAY 1	VISIT 4/DAY 2	VISIT 5/DAY1	VISIT 6/DAY 2
INFORMED CONSENT	X						
REVIEW MEDICAL HISTORY	X						
INTERIM HISTORY	X	X	X	X	X	X	X
DEMOGRAPHICS	X						
PHYSICAL EXAM (IF APPLICABLE)	X	X	X	X	X	X	X
PFTS	X	X					
6 MINUTE WALK TEST		X					
VITAL SIGNS	X	X	X	X	X	X	X
ASSESS AES	X	X	X	X	X	X	X
ASSESS CONCOMITTANT MEDICATIONS	X	X	X	X	X	X	X
SPIROMETRY (PRE-BRONCHODILATOR ONLY)	X	X	X	X	X	X	X
RODNAN SKIN SCORE	X	X					
St. George's and FACIT dyspnea		X					
HRCT (IF NOT DONE FOR STANDARD OF CARE WITHIN 3 MONTHS OF THE VISIT)	X						
LABORATORIES(CHEMISTRY/HEMATOLOGY)	X	X	X	X	X	X	X
URINE DIPSTICK PREGNANCY (FEMALES OF CHILDBEARING POTENTIAL ONLY)	X	X	X	X	X	X	X
ECG	X						
SKIN BIOPSY (OPTIONAL)		X					
BLOOD COLLECTION (PROTEASOMAL ACT/BIOMARKERS) OPTIONAL		X					
QOL ASSESSMENT		X					
PATIENT SELF ASSESSMENT		X					
HOPKINS SKIN SCORE ASSESSMENT		X					
TOLERABILITY AND TOXICITY ASSESSMENT		X	X	X	X	X	X
BORTEZOMIB/PLACEBO ADMINISTRATION		X	X	X	X	X	X

MYCOPHENOLATE (MMF) DIARY DISTRIBUTION/COLLECTION	X	X	X	X	X	X	X

	CYCLE 4	CYCLE 5	CYCLE 6	PRIMARY ENDPOINT/EARLY WITHDRAWL	3 MONTH FOLLOW UP
	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
INFORMED CONSENT					
REVIEW MEDICAL HISTORY					
INTERIM HISTORY	X	X	X	X	X
DEMOGRAPHICS					
PHYSICAL EXAM (IF APPLICABLE)	X	X	X	X	X
PFTS	X	X	X	X	X
6 MINUTE WALK TEST	X			X	X
VITAL SIGNS	X	X	X	X	X
ASSESS AES	X	X	X	X	X
ASSESS CONCOMITTANT MEDICATIONS	X	X	X	X	X
SPIROMETRY (PRE-BRONCHODILATOR ONLY)	X	X	X	X	X
RODNAN SKIN SCORE	X			X	X
St. George's and FACIT dyspnea	X			X	X
HRCT (IF NOT DONE FOR STANDARD OF CARE WITHIN 3 MONTHS OF THE VISIT)					X
LABORATORIES(CHEMISTRY/HEMATOLOGY)	X	X	X	X	
URINE DIPSTICK PREGNANCY (WOMEN OF		X	X		X

CHILDBEARING POTENTIAL ONLY)					

	CYCLE 4	CYCLE 5	CYCLE 6	PRIMARY ENDPOINT/EARLY WITHDRAWL	3 MONTH FOLLOW UP
	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
ECG				X	
SKIN BIOPSY (OPTIONAL)	X			X	X
BLOOD COLLECTION (PROTEASOMAL ACT/BIOMARKERS) OPTIONAL	X			X	X
QOL ASSESSMENT	X			X	X
PATIENT SELF ASSESSMENT	X			X	X
HOPKINS SKIN SCORE ASSESSMENT	X			X	X
TOLERABILITY AND TOXICITY ASSESSMENT	X	X	X	X	X
BORTEZOMIB/PLACEBO ADMINISTRATION	X	X	X		
MYCOPHENOLATE (MMF) DIARY DISTRIBUTION/COLLECTION	X	X	X	X	X

8.2 Body Surface Area and Creatinine Clearance Calculations

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

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

or

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

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows: $\text{CrCl (ml/min)} = \frac{(140\text{-age})\ (\text{actual wt in kg})}{72 \times \text{serum creatinine (mg/dl)}}$ For females use 85% of calculated CrCl value.

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

8.3 Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

8.4 FACT/GOG- Neurotoxicity Questionnaire, Version 4.0

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

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

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

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

8.5 New York Heart Association Classification

Class 1-No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).

Class 2-Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class 3-Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class 4-Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.