Investigator-Sponsored Trial

Chronic Graft Versus Host Disease Consortium

Carfilzomib for Treatment of Chronic Graft vs. Host Disease

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PROTOCOL SYNOPSIS

TITLE:	Carfilzomib for Treatment of Chronic Graft vs. Host Disease
OBJECTIVES:	**Primary Objective:** Determine the proportion of subjects with treatment failure by 6 months after carfilzomib treatment for chronic GVHD. **Secondary Objectives:** 1. Determine 3 month overall (complete + partial), and complete response rate 2. Determine 6 month overall (complete + partial), and complete response rate 3. Report overall survival, non-relapse mortality, primary malignancy relapse, failure-free survival, treatment success, and discontinuation of immune-suppressive therapy at 6 months and 1 year 4. Examine functional outcome (2-minute walk test) and patient-reported outcomes (Lee Chronic GVHD Symptom Scale, quality of life (SF-36, FACT-BMT), Human Activity Profile (HAP)) at study enrollment, 6 months and 1 year 5. Study biologic effects of proteasome inhibition
STUDY DESIGN:	Phase II, single-arm, open-label, multi-center trial.
STUDY POPULATION:	Patients with chronic GVHD (diagnosed according to NIH Consensus Criteria) who have failed at least one prior line of systemic immune-suppressive therapy.
INCLUSION CRITERIA:	*Disease-related:* 1. Diagnosis of chronic GVHD according to NIH Consensus Criteria a. May have either classic chronic GVHD or overlap subtype of chronic GVHD 2. Failure of at least one prior line of systemic immune suppressive therapy for management of chronic GVHD

	3. Subject underwent transplantation at least 3 months prior to enrollment *Demographic:* 1. Age ≥ 18 years 2. Anticipated life expectancy ≥ 6 months *Laboratory:* 1. ALT ≤ 3.5 times the upper limit of normal and bilirubin ≤ 2 mg/dL , unless due to chronic GVHD 2. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L 3. Hemoglobin ≥ 8 g/dL 4. Platelet count ≥ 50×10^9/L 5. Creatinine clearance (CrCl) ≥ 15 mL/minute, either measured or calculated *Other:* 1. Signed informed consent in accordance with federal, local, and institutional guidelines. 2. Females of childbearing potential (FCBP) must agree to a pregnancy test at study enrollment and to practice contraception during the study. 3. Male subjects must agree to practice contraception during the study.
EXCLUSION CRITERIA:	*Concurrent Conditions:* 1. Evidence of recurrent or progressive underlying malignant disease 2. Pregnant or lactating females 3. Surgery within 21 days prior to enrollment a. Does not include placement of venous access device, bone marrow biopsy, GVHD diagnostic biopsy, or other routine procedures in chronic GVHD or post-transplantation care 4. Uncontrolled infection within 14 days prior to enrollment a. Infection treated with appropriate antimicrobial therapy

	and without signs of progression/treatment failure does not constitute an exclusion criterion 5. Documented human immunodeficiency virus (HIV) infection 6. Active hepatitis B or C infection 7. Unstable angina or myocardial infarction within 6 months prior to enrollment, NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities (unless subject has a pacemaker), LVEF < 40, history of torsade de pointe, 8. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment a. Sustained systolic blood pressure > 160 or diastolic blood pressure > 100 despite medical therapy; sustained blood sugar > 300 despite medical therapy b. Chronic hypertension or diabetes on appropriate medical therapy does not constitute an exclusion criterion 9. Non-hematologic malignancy within the past 3 years with the exception of: a. adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer b. carcinoma in situ of the cervix or breast c. prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels d. cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study 10. Significant neuropathy per CTCAE ver. 4.03 or current version (Grade 3 and above, or Grade 2 with pain) 11. History of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib) 12. Contraindication to all available HSV/varicella prophylactic antiviral drugs 13. Pleural effusions requiring thoracentesis, or ascites requiring paracentesis, within 14 days prior to enrollment 14. Any other clinically significant medical or psychological disease or condition that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent

	15. New systemic immune suppressive agent added for the treatment of chronic GVHD within 2 weeks prior to enrollment 16. Treatment with a non-FDA approved drug in the previous 4 weeks
PROCEDURES:	Eligible patients will be treated with carfilzomib for up to 6 cycles per the described treatment schedule, and will be followed for clinical efficacy, patient-reported outcomes and functional measures. Total study follow up will be one year.
STUDY TREATMENT:	**Cycle 1:** Carfilzomib will be administered at 20 mg/m^2 on day 1, and then 36mg/m^2 on days 8 and 15 of a 28-day treatment cycle. **Cycle 2 and subsequent cycles:** Carfilzomib will be administered at 36 mg/m^2 on days 1, 8, and 15 of a 28-day treatment cycle.
PRIMARY ENDPOINT	**6 month treatment failure:** Defined by requirement for an additional line of systemic immune-suppressive therapy, recurrent malignancy, or death.
SECONDARY ENDPOINTS:	**Failure-free survival** This time-to-event outcome will be estimated with the composite event of death from any cause, relapse or addition of secondary immune suppressive agents. This will be estimated at 6 months and 1 year. **Overall response rate** Overall response rate (ORR) at 3 and 6 months following initiation of carfilzomib represents the composite outcome of complete and partial response (CR + PR). ORR will be determined by clinician-defined categories of CR and PR, and separately calculated according to the proposed response definitions of the NIH Consensus Conference.[1] **Complete response rate** Complete response (CR) at 3 and 6 months following initiation of therapy will be determined by clinician-defined CR, and separately calculated according to the proposed response definitions of the NIH Consensus Conference.[1] **Cumulative incidence of non-relapse mortality and primary**

	malignancy relapse The cumulative incidence of non-relapse mortality (defined as death in the absence of primary malignancy relapse after transplant) and relapse (defined as hematologic relapse or any unplanned intervention to prevent progression of disease in patients with evidence (molecular, cytogenetic, flow cytometric, radiographic) of malignant disease after transplantation) will be estimated from time of carfilzomib initiation. These will be treated as competing-risk events, and estimated at 6 months and 1 year. **Overall survival** Overall survival will be determined from date of carfilzomib initiation, with death from any cause as the event of interest, and censoring at last follow up date for those with incomplete observations. This will be determined at 6 months and 1 year. **Use of additional systemic immune suppressive therapies** The use of additional systemic immune suppressive agents will be captured at each study visit, as this constitutes treatment failure. **Discontinuation of all systemic immune suppressive therapies** The incidence of complete discontinuation of all systemic immune-suppressive therapies will be determined at 6 months and 1 year. **Treatment success** This endpoint will be estimated at 6 months and 1 year with a composite outcome of complete resolution of all reversible chronic GVHD manifestations, discontinuation of all systemic immune-suppressive agents, and freedom from death or primary malignancy relapse after transplant. **Patient-reported outcomes and functional measures** Patients will provide assessments of their functional ability (2-minute walk test), symptom burden, and quality of life using validated instruments recommended by the NIH Consensus Development Project on Chronic GVHD (Lee Chronic GVHD Symptom Scale,[2] HAP functional scale,[3] SF-36[4], and FACT-BMT[5]). These will be studied at baseline, 6 months, and 1 year. **Biologic studies** These studies aim to discern the biologic impact of proteasome inhibition in the treatment of chronic GVHD. Peripheral blood samples will be obtained at baseline (study enrollment pre-treatment), and then at

	the 3 and 6 month time points. An additional event-driven blood sample will be obtained when a new systemic immune suppressive therapy is added (treatment failure of carfilzomib).
STATISTICAL METHODS:	The primary endpoint is overall treatment failure at 6 months from study enrollment. Treatment failure represents the composite of addition of a new line of systemic immune-suppressive therapy beyond carfilzomib (objective signal of failure to control GVHD with carfilzomib), non-relapse death, and primary malignancy relapse.[6] The historical benchmark for this outcome based on the analysis of 312 chronic GVHD patients is a 6 month treatment failure rate of 44%. With 20 patients, the standard error of the estimated failure rate will be approximately 10 percentage points. In the analysis of secondary objectives, we will study the 3 and 6 month overall (complete + partial) response and complete response rates, other efficacy measures listed above, patient reported outcomes, and biologic outcome measures. We will study association between biologic outcome measures and clinical parameters (response, treatment failure, mortality).

STUDY THERAPY SCHEMA

Cycle 1:
day 1:
20mg/m2
day 8, 15:
36mg/m2

Subsequent cycles:
day 1, 8, 15: 36mg/m2

Cycle **1**	**2**	**3**	**4**	**5**	**6**
(28d)	**(28d)**	**(28d)**	**(28d)**	**(28d)**	**(28d)**

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1 INTRODUCTION

1.1 Disease Specific Background

1.1.1 Chronic graft vs. host disease

Chronic graft vs. host disease (chronic GVHD) is a major late complication of allogeneic hematopoietic cell transplantation (HCT) that affects up to 70% of HCT survivors. The syndrome is associated with major transplant-related morbidity, mortality, infectious complications, prolonged duration of immune suppression, and impaired patient-reported quality of life.[7-14] Thus, it represents a major obstacle to recovery and survival following HCT, and its prevention and treatment are of significant importance. The syndrome is characterized by diverse clinical manifestations, but the most commonly affected organs are the skin, eyes, mouth, and liver. However, most organs can be involved, with parallels to other systemic immune-mediated disorders.

1.1.2 Chronic GVHD diagnosis and classification

Diagnosis and classification of the syndrome has undergone major revision following the 2005 NIH Consensus Conference on Chronic GVHD. According to the historical classification, acute and chronic GVHD were distinguished by the occurrence of manifestations before or following day 100 post-HCT.[15] According to the proposed NIH Consensus definitions, the diagnosis of chronic GVHD is based on the presence of diagnostic manifestations of the syndrome, rather than the time of onset following HCT. Classic chronic GVHD is defined by the definitive manifestations of the syndrome in the absence of concurrent acute GVHD manifestations. Presence of both chronic and acute GVHD manifestations defines the overlap subtype of chronic GVHD. Chronic GVHD severity is scored according to objective criteria for each organ involved, which is summarized for an overall global severity score of mild, moderate, or severe.[16]

1.1.3 Therapy of established chronic GVHD

Accepted standard primary therapy for chronic GVHD includes 1 mg/kg or greater of prednisone or equivalent with or without a calcineurin inhibitor.[8,17] The addition of other systemic immune-suppressive agents to initial therapy has not provided benefit, as

evidenced by trials adding azathioprine, thalidomide, or hydroxychloroquine to initial treatment with steroids,[18-20] or the more recent randomized trial evaluating the combination of steroids and mycophenolate mofetil.[21] Published primary chronic GVHD therapy trials demonstrate that on average 27% will achieve complete response, and 60% will achieve overall response (complete + partial response) by 6-9 months after starting initial therapy.[17-22]

Based on insufficient response to primary therapy or a flare of chronic GVHD after tapering of initial therapy, many will go on to require additional immune-suppressive agents for chronic GVHD control. “Steroid-refractory” chronic GVHD has most commonly been defined as either progressive manifestations despite one month of treatment, or incomplete response despite two months of 1-2mg/kg of prednisone or equivalent.[8] In addition to steroid-refractoriness, other clinical indications for additional lines of systemic immune suppressive therapy include steroid dependence and steroid intolerance. Patients with steroid-dependent chronic GVHD can’t tolerate tapering prednisone due to recurrent chronic GVHD manifestations. Steroid intolerant patients have medical complications of steroid therapy (e.g. hyperglycemia, edema, psychosis, osteoporosis), and thus require additional immune-suppressive agents to control GVHD and facilitate taper of prednisone. Multiple immune-suppressive therapies, including pharmacologic agents, monoclonal antibodies, and strategies such as extracorporeal photopheresis have demonstrated moderate activity in this setting, both ameliorating objective chronic GVHD manifestations, as well as facilitating taper of systemic steroids.[23] Their effectiveness is suboptimal, however, and many patients will require multiple agents to achieve disease control.

The overall burden of chronic GVHD despite routine pharmacologic GVHD prophylaxis, limited response to primary and secondary therapy, and the attendant morbidity and mortality all support the need for novel approaches in chronic GVHD treatment.

1.1.4 **Assessment of therapeutic response in chronic GVHD**

The established method for response determination in the majority of chronic GVHD therapy trials is clinician-determined response. This method relies on the treating clinician’s

integration of dynamic chronic GVHD manifestations for a summary response categorization of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR indicates complete resolution of all chronic GVHD manifestations; PR signifies reduction in disease activity compared with pre-treatment levels, but without complete resolution; SD indicates no response and no progression; and PD indicates progressive chronic GVHD manifestations from baseline.

Following a 2005 NIH Consensus Conference for Chronic GVHD, several additional means of response assessment in chronic GVHD therapeutic trials have been proposed. These include change in overall NIH severity categories, proposed NIH response criteria, 0-4 and 0-10 ordinal scales that rely on clinician assessment, organ-specific tools such as the Vienna skin scale, as well as patient-determined change in chronic GVHD activity, chronic GVHD-associated symptom burden, functional limitations, and change in quality of life. The Chronic GVHD Consortium is currently assessing these competing measures of disease activity and their relationship to longer-reaching outcomes indicating clinical benefit, such as failure-free survival, discontinuation of all immune suppression, overall survival, or patient-reported benefit.

Interpretation of previously published trials for secondary chronic GVHD treatment is limited by a number of factors, most notably heterogeneity in response determination. A recently published large analysis has examined failure-free survival (FFS) as a proposed outcome among chronic GVHD patients treated with second-line systemic treatment. It included 312 patients who met the following criteria: (1) Had already received systemic steroid treatment for chronic GVHD at a prednisone-equivalent dose of at least 0.5 mg/kg/day, (2) also on an additional systemic immunosuppressive treatment when second-line treatment was started, and (3) received second-line treatment because of progressive GVHD manifestations after at least 1 week of initial treatment or because of lack of improvement after at least 2 weeks of initial treatment. Commonly used second-line treatments included mycophenolate mofetil, tacrolimus, sirolimus, extracorporeal photopheresis, cyclosporine, methotrexate, or other agents. By 6 months of second-line therapy, 44% had experienced treatment failure (composite of requirement of additional systemic immune suppression beyond second-line therapy, death, and malignancy relapse),[6] and thus 6 month failure-free survival (FFS) was 56%. In multivariate analysis, three factors were significant determinants of treatment failure:

high-risk disease at transplantation (defined as diseases other than low risk; low-risk disease categories included chronic myeloid leukemia in chronic phase, acute leukemia in first complete remission, myelodysplastic syndrome without excess blasts, and non-malignant diseases), lower gastrointestinal involvement as second-line treatment was added, and severe NIH global score as second-line treatment was added. These three factors were used to define risk groups: low-risk had no risk factors, intermediate-risk included those with 1 risk factor, and high-risk included those with 2-3 risk factors. The cumulative incidence of 6 month treatment failure was 33% for low-risk, 41% for intermediate risk, and 56% for high risk.

1.1.5 Immune modulation following proteasome inhibition

Proteasome inhibition exerts powerful effects on immune cells implicated in GVHD pathogenesis. Pre-clinical and clinical data provide robust support for this concept.[24,25] Proteasome inhibitors interfere with antigen processing and presentation, as well as signaling cascades involved in immune cell function and survival: In dendritic cells (DC), there is impaired maturation, co-stimulatory molecule expression, and reduction of pro-inflammatory cytokines. T lymphocytes demonstrate apoptosis, reduced proliferation, impaired pro-inflammatory cytokine production, as well as expansion of regulatory T cells (Treg). B cell proliferation is decreased, and reduced antibody production is observed among plasma cells. Thus, proteasome inhibition targets key mediators established to be relevant in GVHD pathogenesis. In a murine GVHD model, bortezomib inhibited alloreactive T cells and protected from GVHD, did not adversely affect donor reconstitution, and did not impair cytotoxic T cell killing of tumor.[26]

1.1.6 Effect of proteasome inhibition on chronic GVHD in the clinical setting

While published clinical trials demonstrate the activity of proteasome inhibition in the primary prevention of GVHD,[27,28] less is known in the setting of chronic GVHD treatment. Emerging clinical data suggest that proteasome inhibition may control chronic GVHD: In a case report, a patient with relapsed multiple myeloma after HCT was successfully treated with bortezomib for oral lichen planus and biopsy-confirmed hepatic chronic GVHD.[29] In a case series (n=8), multiple myeloma patients were treated with bortezomib for relapsed disease after HCT, and those with chronic GVHD (n=4) experienced improvement.[30] Three had remission of chronic GVHD at a median of 150 days after bortezomib discontinuation, and

one had recurrent ocular manifestations of chronic GVHD. Finally, in a larger series, 37 multiple myeloma patients with progressive or residual disease after HCT were treated with bortezomib. Of these, 8 patients had limited chronic GVHD, and 3 had extensive chronic GVHD. Patients were treated with a median of 6 cycles of bortezomib, and this was tolerated well. Common adverse events included peripheral neuropathy, mild thrombocytopenia not requiring transfusion, and fatigue, and there were no treatment related deaths. Of the 3 extensive chronic GVHD cases, 2 responded and were down-graded to limited disease at last evaluation. Of the 8 with limited chronic GVHD, none required additional immune suppressive therapy, and one had resolution of chronic GVHD.[31] Because these limited data are of interest but difficult to interpret in the setting of myeloma relapse or persistence, additional insight should arise from an existing chronic GVHD primary therapy trial (NCT00815919) testing the combination of prednisone and bortezomib.

1.2 Summary of trial rationale

The majority of patients with chronic GVHD will require therapy beyond first-line treatment, and novel therapies are needed in this setting to improve outcomes. Pre-clinical and clinical data demonstrate that proteasome inhibition produces an immunomodulatory effect relevant to GVHD control. Carfilzomib is proteasome inhibitor that has been proven safe and effective in clinical trials of multiple myeloma therapy. We propose a phase II trial of carfilzomib to examine its clinical and biologic activity in the treatment of advanced chronic GVHD.

1.2.1 Proteasome Background

The proteasome is a multi-catalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity (CT-L), a trypsin-like activity (T-L), and a caspase-like (C-L) activity. Proteasome inhibition leads to the accumulation of poly-ubiquitinated protein substrates within cells, with multiple effects including ER stress, alteration of important cellular signaling events, growth arrest, and apoptosis.

1.2.2 Carfilzomib Background

Carfilzomib (PR-171) is a tetrapeptide epoxyketone protease inhibitor specific for the chymotrypsin-like (CT-L) active site of the 20S proteasome. Carfilzomib induces a dose-dependent suppression of proteasome CT-L activity in a wide range of tissues, with the exception of the brain. In human studies, carfilzomib at doses of 15-36mg/m2 lead to 77-86% proteasome inhibition in whole blood and peripheral blood mononuclear cells (PBMC) at 1 hour after dosing. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib.[1,2]

1.2.3 Carfilzomib clinical pharmacology

Mechanism of Action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib has anti-proliferative and pro-apoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibits proteasome activity in blood and tissue and delays tumor growth in models of multiple myeloma, hematologic, and solid tumors.

Pharmacodynamics

Intravenous carfilzomib administration results in suppression of proteasome chymotrypsin-like activity when measured in blood 1 hour after the first dose. On Day 1 of Cycle 1, proteasome inhibition in peripheral blood mononuclear cells (PBMCs) ranged from 79% to 89% at 15 mg/m2, and from 82% to 83% at 20 mg/m2. In addition, carfilzomib administration results in inhibition of the LMP2 and MECL1 subunits of the immunoproteasome ranging from 26% to 32% and 41% to 49%, respectively, at 20 mg/m2. On day 1 of cycle 2, CT-L inhibition in PBMC following a dose of 27mg/m2 was 76% to 92%.

Pharmacokinetics

Absorption: The Cmax and AUC following a single intravenous dose of 27 mg/m2 is 4232 ng/mL and 379 ng•hr/mL, respectively. Repeated doses do not lead to systemic accumulation of carfilzomib. Increased doses are associated with dose-dependent increased exposure.

Distribution: The mean steady-state volume of distribution of a 20 mg/m2 dose of carfilzomib is 28 L. When tested *in vitro*, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

Metabolism: Carfilzomib is rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated *in vitro* by human hepatocytes, are peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism. Cytochrome P450-mediated mechanisms play a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity, and none of the metabolites inhibit the 20S proteasome activity.

Elimination: Following intravenous administration of doses ≥ 15 mg/m2, carfilzomib is rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extra-hepatically. The pathways of carfilzomib elimination have not been characterized in humans.

Age: Analysis of population pharmacokinetics data after the first dose of Cycle 1 (Day 1) in 154 patients who had received an IV dose of 20 mg/m2 showed no clinically significant difference in exposure between patients < 65 years and ≥ 65 years of age.

Gender: Mean dose-normalized AUC and Cmax values are comparable between male and female patients in a population pharmacokinetics study.

Hepatic Impairment: No pharmacokinetic studies were performed with carfilzomib in patients with hepatic impairment.

Renal Impairment: A pharmacokinetic study was conducted in which 43 multiple myeloma patients who had various degrees of renal impairment and who were classified according to their creatinine clearances (CrCl) into the following groups: normal function (CrCl > 80 mL/min, n = 8), mild impairment (CrCl 50–80 mL/min, n = 12), moderate impairment (CrCl 30–49 mL/min, n = 8), severe impairment (CrCl < 30 mL/min, n = 7), and chronic dialysis (n = 8). Carfilzomib was administered intravenously over 2 to 10 minutes, on two consecutive days, weekly for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period every 28 days. Patients received an initial dose of 15 mg/m2, which could be escalated to 20 mg/m2 starting in Cycle 2 if 15 mg/m2 was well tolerated in Cycle 1. In this study, renal function status had no effect on the clearance or exposure of carfilzomib following a single or repeat-dose administration.

Cytochrome P450: In an *in vitro* study using human liver microsomes, carfilzomib showed modest direct and time-dependent inhibitory effect on human cytochrome CYP3A4/5. *In vitro* studies indicated that carfilzomib did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. A clinical trial of 17 patients using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration. Carfilzomib is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates.

P-gp: Carfilzomib is a P-glycoprotein (P-gp) substrate and showed marginal inhibitory effects on P-gp in a Caco-2 monolayer system. Given that Carfilzomib is administrated intravenously and is extensively metabolized, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

1.2.4 Summary of Safety and efficacy experience from human phase I and II trials

Phase I, I-II, and II trials have been conducted in humans with carfilzomib as a single agent, largely focused in relapsed/refractory multiple myeloma. In the first phase I trial, carfilzomib was given at escalating doses for five consecutive days, followed by nine days off therapy for a total 14 day cycle. The 15mg/m2 dose was determined to be the maximal tolerated dose (MTD) due to dose-limiting toxicity (DLT) of thrombocytopenia and febrile neutropenia.

In a second phase I trial, carfilzomib was delivered days 1, 2, 8, 9, 15 and 16 on a four week cycle. No MTD was reached at the maximal dose of 27mg/m^2. Three patients had serious adverse events (SAEs) during phase one (sepsis, elevated liver enzymes, and chemical pancreatitis), possibly related to carfilzomib.

Phase II studies have largely examined the regimen of 20mg/m2 for cycle 1, followed by 27mg/m2 for subsequent cycles. The primary trial used for registration (PX 171-003) tested this regimen as single-agent therapy in 266 pre-treated myeloma patients. Related AE (of any grade) most frequently included fatigue (37%), nausea (34%), and thrombocytopenia. Grade 3/4 hematologic AE included anemia (24%), thrombocytopenia (29%), lymphopenia (20%), and neutropenia (11%). Nonhematologic AEs grade 3/4 included pneumonia (9%), hyponatremia (8.3%), fatigue (7.5%), and hypophosphatemia (6.0%). One-third of the patients experienced mild to moderate dyspnea without detectable lung injury. Peripheral neuropathy was uncommon (12.4%), and was considered related in only 8.3% of patients. Acute renal failure qualifying for a severe AE occurred in 5 of 266 patients. Additional phase II trials have demonstrated activity of carfilzomib in relapsed bortezomib-naïve myeloma patients, safety of standard dose therapy in those with renal insufficiency, and safety of long term therapy.

Additionally, extended infusion time – from 2-10 minutes to 30 minutes – facilitated delivery of higher dose carfilzomib: In a phase I-II trial (PX-171-007), carfilzomib was given as a 30 minute IV infusion on days 1, 2, 8, 9, 15, and 16 of a 28 day cycle. The cycle 1/day 1 and cycle 1/day 2 doses were given at 20mg/m2, and subsequent doses were given at escalating dose cohorts (36, 45, 56, or 70mg/m2). 33 patients were enrolled: 4 at 36 mg/m^2 , 3 at 45 mg/m^2, 24 at 56 mg/m^2, and 2 at 70 mg/m^2. Patients received carfilzomib at stepped-up doses from 36 to 70 mg/m^2: Median number of cycles received was 4 (range 1–17). No DLTs reported in the 36 mg/m^2, 45 mg/m^2, or 56 mg/m^2 dose cohorts. Reversible DLTs were recorded in 2 patients in the 70 mg/m^2 cohort: Grade 3 acute renal failure within 24 hours after the 1st dose (C1D8), and G3 fatigue with fever 4 days after the 4th dose (C1D20). Both patients were successfully re-challenged and continued on treatment at reduced doses. The majority of the AEs in this cohort were Grade 1/2 in severity. The most common grade 3-4 AEs in the 20/56 mg/m^2 cohort were thrombocytopenia (38%), anemia (21%), hypertension (13%), and pneumonia (13%). PK analysis demonstrated a proportional increase in C_{max} and AUC with increasing dose, without affecting $t_{1/2}$ or clearance of carfilzomib.

	20mg/m2 (n=26)	36mg/m2 (n=9)	45mg/m2 (n=9)	56mg/m2 (n=10)
Cmax (ng/mL)	985 +/- 641	1795 +/- 957	1902 +/- 884	2513 +/- 1527
AUC last (hr*ng/mL)	385 +/- 253	690 +/- 365	862 +/- 363	1018 +/- 416
AUC inf (hr*ng/mL)	387 +/- 255	691 +/- 368	864 +/- 366	1025 +/- 424
T ½ (hr)	1.0 +/- 0.5	1.2 +/- 0.8	1.1 +/- 0.2	1.2 +/- 1.0
CL (L/hr)	146 +/- 87	123 +/- 54	129 +/- 54	124 +/- 43

Pharmacodynamic analysis demonstrated an increased inhibition of proteasome chymotrypsin-like activity (CT-L) and all 3 subunits of immunoproteasome (LMP7, MECL1, LMP2) with higher doses of carfilzomib compared to the 20mg/m2 dose.

Summarizing current evidence from phase Ib and II trials with carfilzomib, the following are the most commonly reported **AE** (among those occurring in ≥ 20% of patients): fatigue (55.9%), nausea (43.2%), anemia (42.2%), dyspnea (35.1%), diarrhea (33.8%), thrombocytopenia (32.7%), pyrexia (32.1%), cough (26.8%), headache (26.4%), upper respiratory tract infection (25.4%), vomiting (23.4%), peripheral edema (22.8%), lymphopenia (22.4%), back pain (21.5%), constipation (21.1%), and increased creatinine (20.7%).

Summarizing current evidence from phase Ib and II trials with carfilzomib, the following are the most commonly reported **SAE** (among those occurring in ≥ 1% of patients), regardless of causality: pneumonia (8.1%), disease progression (5.9%), acute renal failure (3.4%), pyrexia (3.4%), congestive heart failure (2.8%), dyspnea (2.7%), pathological fracture (1.6%), hypercalcemia (1.5%), spinal cord compression (1.3%), anemia (1.1%), dehydration (1.1%), sepsis (1.1%), mental status changes (1.0%), and pulmonary embolism (1.0%).

1.3 Dose and schedule Rationale

Dose

Available data supports that proteasome inhibition is augmented with higher dose carfilzomib therapy. In the pre-clinical setting, murine experiments have demonstrated – with selectivity of PR-171 for the chymotrypsin-like (CT-L) proteasome activity – a dose-dependent inhibition of proteasome activity in multiple organ sites (blood, bone marrow, spleen, adrenal, heart, liver, and lung).[32] This therapy leads to accumulation of proteasome substrates, and induction of cell cycle arrest and apoptosis. In the clinical setting, escalated dose is associated with proportional increased Cmax and AUC, without affecting t ½ or clearance of carfilzomib. Doses up to 56mg/m2 have been well tolerated, and 56mg/m2 was defined as the MTD in a phase Ib-II study (PX-171-007) that tested 20mg/m2 in cycle 1 days 1-2, and then escalated dose (36, 45, 56, and 70mg/m2 cohorts) in subsequent doses/cycles.

Human PBMC were tested for the effect of increased dose of carfilzomib in the PX-171-007 trial: In comparison to pre-treatment levels, post-carfilzomib treatment levels of proteasome activity (including CT-L, chymotrypsin-like activity of the constitutive proteasome, LMP7, CT-L activity of the immunoproteasome, LMP2, caspase-like activity of the immunoproteasome, and MECL1, trypsin-like activity of the immunoproteasome) were significantly reduced. Greater inhibition of proteasome and immunoproteasome activity was observed with increased dose carfilzomib. CT-L activity returned to baseline by start of cycle 2 (expected, given the week off therapy at the end of each cycle), but comparable inhibition was then achieved following subsequent therapy in cycle 2. Following the 36mg/m2 dose in cycle 2, potent inhibition (> 80% inhibition of pre-treatment levels) of CT-L (β5 and LMP7) activity was observed. Alongside these pharmacodynamic measures, there was also an association between increasing carfilzomib dose and subsequent clinical response and progression-free survival in this trial. Of note, there were no grade 3/4 treatment-emergent adverse events among those treated in the 36mg/m2 cohort, while a greater proportion of hematologic (anemia, neutropenia, thrombocytopenia) and non-hematologic (dyspnea, fatigue, hypertension, hypoxia, pneumonia) grade 3/4 adverse events were observed in the higher dose cohorts. Taken together, these pre-clinical and clinical data support dose-dependent inhibition of proteasome activity, and support a dose-response therapeutic relationship.

Schedule

The following data support once-weekly dosing of carfilzomib in this trial:

Pre-clinical data support prolonged inhibition of CT-L proteasome activity in murine models: Single dose PR-171 treatment was associated with prolonged inhibition of CT-L activity to 20-25% of control levels through 72 hours in whole blood. By 168 hours (7 days), CT-L activity was < 50% of control levels.[32] Notably, this same trend was not observed following single dose bortezomib therapy, wherein CT-L activity was greater than 50% of control levels by 24 hours and nearly 100% by 72 hours. Single dose PR-171 treatment was also directly compared to two consecutive day (i.e. day 1, day 2) PR-171 treatment. Recovery of CT-L activity in the bone marrow was comparable at 48 and 72 hours. In erythrocyte depleted whole blood, both approaches produced significant inhibition of CT-L activity (< 20% of control) that was sustained for 48-72 hours. These data demonstrate that prolonged inhibition is achieved with a single dose of this irreversible proteasome inhibitor, as recovery of activity is dependent upon production of new functional proteasomes.

Clinical evidence is also supportive of once-weekly dosing of carfilzomib. A single arm, phase I-II study (NCT01677858) has been designed to test the safety and efficacy of once weekly carfilzomib in patients with relapsed/refractory multiple myeloma. Results from the phase I trial have been presented (Berenson, et al. ASH 2013, abstract 1934). Relapsed/refractory multiple myeloma patients who had received 1-3 prior treatment regimens were treated with a 30-minute IV infusion on days 1, 8, and 15 of a 28 day cycle in a phase I trial 3+3 dose escalation design. All received 20mg/m^2 carfilzomib on day 1 of cycle 1; subsequent doses tested were 45 mg/m^2, 56 mg/m^2, 70 mg/m^2, and 88 mg/m^2. Once MTD was determined, an expansion cohort of 9 additional patients was studied. Pharmacokinetic studies were performed in the 70 mg/m^2 and 88 mg/m^2 cohorts using peripheral blood samples on days 1 and 15 of cycle 1 at the following time points: pre-dose, 5, 15, and 30 minutes following start of infusion, and 5, 15, and 30 minutes, and 1, 2, and 4 hours after end of infusion. A total of 27 patients were enrolled on the phase I component of the study. The 45 mg/m^2 and 56 mg/m^2 cohorts enrolled 3 patients each, and no DLT events were observed. The 70 mg/m^2 and 88 mg/m^2 cohorts each enrolled 6 patients, and the 70 mg/m^2 dose level was identified as the maximally tolerated dose: At the 88mg/m^2 dose, 2 DLT events (grade 3 dyspnea and grade 3 vomiting) were observed. At the 70mg/m^2 dose level, 1 DLT was observed (grade 3 dyspnea). An additional 9 patients were studied in the

expansion, thus totalling 15 patients at the 70mg/m^2 dose. In the 45 mg/m^2, 56 mg/m^2, and 70 mg/m^2 dose cohorts, no patients required dose reduction for toxicity. PK analysis demonstrated dose-proportional increase in mean Cmax and AUC from the 20mg/m^2 to 88mg/m^2 dose, and a mean terminal half-life of weekly carfilzomib of 0.8 hours. Treatment with 70mg/m^2 weekly resulted in similar total AUC per cycle (2373h*ng/mL) as the traditional 20/27mg/m^2 twice weekly regimen (2274h*ng/mL), and achieved lower Cmax levels (2640ng/mL vs. 4232ng/mL, respectively). The phase II component of the trial is ongoing, with planned enrollment of 127 patients.

Infusion time: In clinical studies, 27mg/m2 of carfilzomib (bolus administration over 2-10') is well tolerated in MM patients overall and can be tolerated for >12 cycles in late stage MM patients with comorbidities. In the PX-171-007 trial, more recently patients have been treated with carfilzomib given as a 30-minute infusion in order to minimize Cmax-related infusion events. All protocols using ≥36mg/m2 carfilzomib are now administering the drug as a 30-minute infusion. For consistency, all doses of this agent will be delivered over a 30 minute infusion in this trial.

2 OBJECTIVES

2.1 Primary Objective

1. Determine proportion of subjects with treatment failure by 6 months of carfilzomib therapy for chronic GVHD

2.2 Secondary Objectives

1. Determine 3 month overall (complete + partial), and complete response rate
2. Determine 6 month overall (complete + partial), and complete response rate
3. Report overall survival, non-relapse mortality, primary malignancy relapse, failure-free survival, treatment success, and discontinuation of immune suppression at 6 months and 1 year.
4. Examine functional outcome (2-minute walk test) and patient-reported outcomes (Lee Chronic GVHD Symptom Scale, quality of life (SF-36, FACT-BMT), Human Activity Profile (HAP)) at study enrollment, 6 months, and 1 year
5. Study biologic effects of proteasome inhibition

3 EXPERIMENTAL PLAN

3.1 Study Design

In this open-label, phase II, multi-center trial, patients with chronic GVHD who have failed at least one line of systemic immune-suppressive therapy will be treated with intravenous carfilzomib to discern clinical efficacy and biologic activity of this novel therapeutic approach.

3.2 Number of Subjects

Twenty patients will be enrolled in this study.

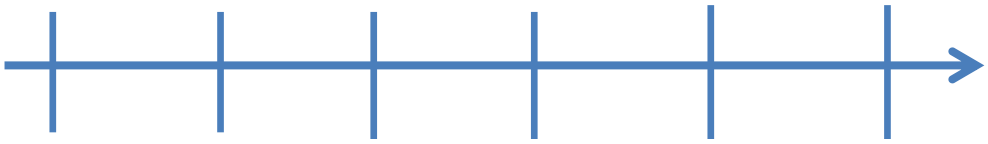
3.3 Estimated Study Duration

Enrolled patients will have up to 6 cycles of treatment, and the primary endpoint will be measured at 6 months. An additional study follow-up for late outcomes will occur at 1 year. Thus, the total duration of time on study for each patient will be one year.

3.4 Treatment Schema

Cycle 1:
day 1:
20mg/m2
day 8, 15:
36mg/m2

Subsequent cycles:
day 1, 8, 15: 36mg/m2



Cycle **1**	**2**	**3**	**4**	**5**	**6**
(28d)	**(28d)**	**(28d)**	**(28d)**	**(28d)**	

Cycle 1:

Carfilzomib will be administered at 20 mg/m2 on day 1, and then 36mg/m2 on days 8 and 15 of a 28-day treatment cycle.

Cycles 2 through 6:

Carfilzomib will be administered at 36 mg/m2 on days 1, 8, and 15 of a 28-day treatment cycle.

***The acceptable window for each dose of carfilzomib is +/- 3 days.**

***See section 6.2 for guidelines on toxicity management and dose reduction.**

4 SUBJECT SELECTION

4.1 Inclusion Criteria

Disease-related:

1. Diagnosis of chronic GVHD according to NIH Consensus Criteria
    a. May have either classic chronic GVHD or overlap subtype of chronic GVHD

2. Failure of at least one prior line of systemic immune suppressive therapy for management of chronic GVHD

3. Subject underwent transplantation at least 3 months prior to enrollment

Demographic:

1. Age ≥ 18 years
2. Anticipated life expectancy ≥ 6 months

Laboratory:

1. ALT ≤ 3.5 times the upper limit of normal and bilirubin ≤ 2 mg/dL, unless due to chronic GVHD
2. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L
3. Hemoglobin ≥ 8 g/dL
4. Platelet count ≥ 50×10^9/L

5. Creatinine clearance (CrCl) ≥ 15 mL/minute, either measured or calculated

Other:

1. Signed informed consent in accordance with federal, local, and institutional guidelines.
2. Females of childbearing potential (FCBP) must agree to a pregnancy test at study enrollment and to practice contraception during the study.
3. Male subjects must agree to practice contraception during the study.

4.2 Exclusion Criteria

Concurrent Conditions:

1. Evidence of recurrent or progressive underlying malignant disease
2. Pregnant or lactating females
3. Surgery within 21 days prior to enrollment
    a. Does not include placement of venous access device, bone marrow biopsy, GVHD diagnostic biopsy, or other routine procedures in chronic GVHD or post-transplantation care
4. Uncontrolled infection within 14 days prior to enrollment
    a. Infection treated with appropriate antimicrobial therapy and without signs of progression/treatment failure does not constitute an exclusion criterion
5. Documented human immunodeficiency virus (HIV) infection
6. Active hepatitis B or C infection
7. Documented unstable angina or myocardial infarction within 6 months prior to enrollment, NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities (unless subject has a pacemaker), LVEF < 40%, history of torsade de pointe,
8. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment
    a. Sustained systolic blood pressure > 160 or diastolic blood pressure > 100 despite medical therapy; sustained blood sugar > 300 despite medical therapy
    b. Chronic hypertension or diabetes on appropriate medical therapy does not constitute an exclusion criterion
9. Non-hematologic malignancy within the past 3 years with the exception of:

a. adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer
b. carcinoma in situ of the cervix or breast
c. prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels
d. cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study

10. Significant neuropathy per CTCAE ver. 4.03 or current version (Grade 3 and above, or Grade 2 with pain) within 14 days prior to enrollment
11. History of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
12. Contraindication to all available HSV/varicella prophylactic antiviral drugs
13. Pleural effusions requiring thoracentesis, or ascites requiring paracentesis, within 14 days prior to enrollment
14. Any other clinically significant medical or psychological disease or condition that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent
15. New systemic immune suppressive agent added for the treatment of chronic GVHD within 2 weeks prior to enrollment
16. Treatment with a non-FDA approved drug in the previous 4 weeks

5 SUBJECT ENROLLMENT

Potentially eligible patients will be approached at participating study centers. The treating clinician will review the informed consent document with them, and eligibility will be confirmed. Eligible patients interested in participating will sign consent and initiate study procedures. Subjects will be registered through the online database system.

6 TREATMENT PROCEDURES

6.1 Drug Preparation and Administration.

Carfilzomib preparation

- Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials.

- The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration.
- The dose will be calculated using the subject's BSA at baseline. BSA will be calculated and updated (if required) according to institutional standards.
- Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.
- Doses may be rounded per institutional standards

Pre-treatment dexamethasone

- Dexamethasone will be administered prior to all carfilzomib doses during the first cycle. For the 20mg/m2 initial carfilzomib dose, the required PO/IV dexamethasone dose is 4mg. For the subsequent 36mg/m2 doses, the required PO/IV dexamethasone dose is 8mg. The timing of dexamethasone administration before carfilzomib and selection of PO or IV dexamethasone will adhere to institutional standards.
- If treatment-related fever, rigors, chills, and/or dyspnea are observed during or after any dose of carfilzomib after dexamethasone pre-medication has been discontinued, dexamethasone (8 mg PO/IV) should be re-started and administered prior to subsequent doses.

IV hydration

- IV hydration will be given immediately prior to carfilzomib during Cycle 1. This will consist of 250mL normal saline or other appropriate IV fluid. Pre-treatment IV hydration is only required before therapy in cycle 1. In all subsequent cycles, hydration may be given before or after carfilzomib according to the treating clinician's judgment, however IV hydration is only required by this protocol before therapy in cycle 1.
- Subjects should be monitored for evidence of fluid overload.

Carfilzomib infusion time

- Carfilzomib should be infused over approximately 30 minutes.

- The dose will be administered at a facility capable of managing hypersensitivity reactions.
- Subjects will remain at the clinic under observation for at least 1 hour following the completion of each dose of carfilzomib in Cycle 1 and following the first dose of Cycle 2.

6.2 Dose Reductions/Adjustments

The dose of carfilzomib should be held and/or reduced according to the following guidelines:

Toxicity	Condition	Action	Toxicity resolution definition	Action post-resolution
Thrombocytopenia	platelets < 30 × 10^9/L Subsequent drop to < 30 × 10^9/L	- Interrupt CFZ - follow CBC* - Interrupt CFZ - follow CBC*	Return to ≥ 30 × 10^9/L Return to ≥ 30 × 10^9/L	Resume at full dose Resume at 1 dose decrement
Neutropenia	ANC < 1.0 × 10^9/L	- Interrupt CFZ - Add filgrastim - follow CBC*	Return to > 1.0 × 10^9/L (if neutropenia was the only toxicity noted)Returns to > 1.0 × 10^9/L (if other toxicity noted) Returns to > 1.0 × 10^9/L	Resume at full dose Resume at 1 dose decrement

	Subsequent ANC < 1.0× 10^9/L	- Interrupt CFZ - Add filgrastim - follow CBC*		Resume at 1 dose decrement
Allergic reaction, Hypersensitivity	Grade 2 or 3	Hold CFZ	Decrease to ≤ Grade 1	Resume at full dose
	Recurrent Grade 2-3 reaction	Hold CFZ	Decrease to ≤ Grade 1	Resume at 1 dose decrement
	Any Grade 4	Discontinue CFZ	n/a	n/a
Infection	Grade 3 or 4	Hold CFZ until infection controlled	Infection controlled per treating clinician	Resume CFZ at full dose **If neutropenic, follow above neutropenic dosing guidelines*
Herpes zoster or simplex reactivation	Any grade	Hold CFZ until lesions are improved and dry	Lesions dry	Resume CFZ at full dose
Neuropathy	Grade 2 treatment-emergent neuropathy with pain or Grade 3 neuropathy (not persistent for > 2 weeks)	Continue CFZ	n/a	n/a

	Grade 2 neuropathy with pain or grade 3 neuropathy (<u>persistent for > 2 weeks</u>)	Hold CFZ until ≤ Grade 2 without pain	Neuropathy improved to ≤ Grade 2 without pain	Resume CFZ at one dose decrement
	<u>Recurrent</u> Grade 2 neuropathy with pain or grade 3 neuropathy (<u>persistent for > 2 weeks</u>)	Hold CFZ until ≤ Grade 2 without pain	Neuropathy improved to ≤ Grade 2 without pain	Resume CFZ at one dose decrement
	Grade 4 neuropathy	Discontinue	n/a	n/a
Renal dysfunction	Creatinine > 2 x baseline	Hold CFZ	Creatinine ≥ 2 x baseline	Resume CFZ at one dose decrement
Congestive heart failure	Clinical evidence of CHF AND <u>either</u> LVEF < 40% or reduction in LVEF below 55% with a drop in LVEF from	Hold CFZ	Control of clinical CHF, and return of LVEF to ≥ 40% or (if held due to drop below LVEF of 55% with > 20%	Resume CFZ at one dose decrement

	prior baseline by > 20%		drop from baseline) return of LVEF to within 15% of baseline value If improvement defined above is not met	Discontinue CFZ therapy
Other non-hematologic toxicity ≥ Grade 3	Other non-hematologic **CFZ-related** ≥ Grade 3 toxicity not listed individually elsewhere	Hold CFZ	Resolved or back to baseline	Resume CFZ at one dose decrement
Pulmonary Hypertension	Grade 3 or 4	Hold CFZ	Resolved or returned to baseline	Resume CFZ at one dose decrement
Pulmonary Complications	Grade 3 or 4	Hold CFZ	Resolved or returned to baseline	Resume CFZ at one dose decrement
Hepatic toxicity	Grade 3 or 4 elevation of transaminases, bilirubin, or other liver abnormalities	Hold CFZ Follow LFT	Resolved or returned to baseline	Resume CFZ at one dose decrement

*CBC – Frequency of CBC monitoring after holding dose for toxicity is directed by treating clinician's judgment, and not mandated by this protocol. A recommended guideline is weekly until return to baseline.

*LFT – Frequency of LFT monitoring is directed by treating clinician's judgment, in keeping with note above regarding CBC monitoring.

Permissible dose decrements:

- 36mg/m2 → 27mg/m2
- 27mg/m2 → 20mg/m2
- 20mg/m2 → 15mg/m2
- If toxicity persists or reoccurs requiring dose reduction below 15mg/m2, then carfilzomib therapy should be discontinued. No more than three dose reductions will be permitted in an individual subject on study. If toxicity continues or recurs after three dose reductions, carfilzomib therapy should be discontinued.
- If toxicity requiring dose reduction occurs on the first dose (i.e. 20mg/m2), only one dose decrement will be possible to 15mg/m2. If toxicity persists or recurs on the 15mg/m2 dose, carfilzomib therapy should be discontinued.

Conditions not requiring dose reduction:

- Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days despite treatment with anti-emetics or anti-diarrheals)
- Grade 3 fatigue (unless persisting continuously for >14 days)
- Alopecia
- Hyperglycemia attributed to steroids

Persistent toxicity for 3 weeks after withholding CFZ therapy:

- If the patient has toxicity attributable to carfilzomib that does not return to baseline or reach < grade 1 in severity by 3 weeks, carfilzomib therapy will be discontinued

Patient tolerates decreased dose following dose reduction for toxicity:

- If the patient tolerates the decreased dose x 2 cycles, full-dose CFZ (i.e. 36mg/m2) should be resumed on subsequent cycles.

- If subsequent toxicity occurs as defined above, the stated rules for dose reduction apply, but a second attempt to resume full-dose therapy should not be made.

6.2.1 **Missed Doses**

Missed doses will not be replaced. If a subject misses doses of planned therapy due to toxicity, they will resume treatment according to planned schedule once the toxicity is resolved (see above guidelines). If toxicity resolves within the acceptable (+3 day) window surrounding planned therapy, that dose may be administered.

6.2.2 **Changes in Body Surface Area (BSA)**

Dose adjustments do not need to be made for weight gains/losses of ≤ 20%. Subjects with a Body Surface Area (BSA) of greater than 2.2 m^2 will receive a capped dose for a BSA of 2.2 m^2. Frequency of weight measurement and subsequent recurring calculation of BSA will be done according to institutional guidelines.

6.3 **Concomitant medications**

6.3.1 **Required Concomitant Medications and contraceptive practices**

Contraception:

Female subjects of child-bearing potential must agree to use contraception (barrier, hormonal, or intrauterine) for the duration of the study. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential. Men who have had a prior vasectomy do not need to use a barrier method for contraception.

Antimicrobial prophylaxis:

Subjects should receive antimicrobial prophylaxis according to institutional treatment standards.

6.3.2 Management of prednisone and other immune suppression

Prednisone:

The management of prednisone will be directed by the treating clinician, and dose/duration of prednisone therapy is not mandated by this protocol.

Additional systemic immune-suppressive agents:

It is expected that patients will be on additional systemic immune-suppressive agents at the time of enrollment, and management of those agents is not mandated by this protocol. Other agents can be tapered or discontinued as directed by the treating clinician.

Addition of new systemic immune-suppressive agents while on trial constitutes treatment failure, regardless of the indication for the agent. Systemic immune-suppressive agents include orally or intravenously administered systemically active immune-suppressive drugs, as well as procedures including extra-corporeal photopheresis (ECP).

Treatment failure does not include the following:

1. Adjustment of dosing of existing immune suppressive agents to maintain therapeutic drug levels (e.g. tacrolimus, cyclosporine, sirolimus), as this is standard practice.
2. Adjustment of prednisone dose up or down according to clinical judgment based on clinical manifestations of chronic GVHD and patient tolerance of steroid treatment.
3. Use of topical therapies, including:
    a. ocular drops or physical interventions (e.g. moisturizing eye drops, ocular cyclosporine drops, punctal plugs, scleral lenses, etc)
    b. oral rinses or agents (e.g. oral steroid rinse, oral topical immune suppressive agents)
    c. non-absorbable gastrointestinal steroid agents (e.g. beclomethasone, budesonide)
    d. topical agents applied to the skin (e.g. topical steroid creams, moisturizing lotion, topical immune suppressive agents such as tacrolimus)
    e. topical agents applied to the vaginal mucosa (e.g. topical steroid creams or topical immune suppressive agents such as tacrolimus)
4. PUVA
5. Fluticasone, azithromycin, or monteleukast

7 STUDY OUTCOMES

Primary endpoint:

Treatment failure

Treatment failure is the cumulative incidence of addition of systemic immune suppressive therapy, recurrent malignancy, and death. The primary endpoint is 6-month treatment failure.

- See above definitions of systemic immune-suppressive therapy (section 6.3.2)
- Recurrent malignancy – This is defined as hematologic relapse or any unplanned intervention (including withdrawal of immune suppression) to prevent progression of disease in patients with evidence (molecular, cytogenetic, flow cytometric, radiographic) of malignant disease after transplantation.
- The date of this event will be the earlier date of the following:

    a. Evidence of relapse

    b. Initiation date of intervention for treatment or prevention of relapse

Secondary endpoints:

Failure-free survival

This time-to-event outcome will be estimated with the composite event of death from any cause, relapse and addition of secondary immune suppressive agents. This will be estimated at 6 months and 1 year.

Overall response rate

Overall response rate (ORR) at 3 and 6 months following initiation of therapy represents the composite outcome of complete and partial response (CR + PR). ORR will be determined by both clinician-defined categories of CR and PR, as well as separately calculated according to the proposed response definitions of the NIH Consensus Conference.[1]

Complete response rate

Complete response (CR) at 3 and 6 months following initiation of therapy. CR will be determined by both clinician-defined CR, as well as separately calculated according to the proposed response definitions of the NIH Consensus Conference.[1]

Cumulative incidence of non-relapse mortality and primary malignancy relapse

The cumulative incidence of non-relapse mortality (defined as death in the absence of primary malignancy relapse after transplant) and relapse (defined as hematologic relapse or

any unplanned intervention to prevent progression of disease in patients with evidence (molecular, cytogenetic, flow cytometric, radiographic) of malignant disease after transplantation) will be estimated from time of study therapy initiation. These will be treated as competing-risk events, and estimated at 6 months and 1 year.

Overall survival

Overall survival will be determined from date of study therapy initiation, with death from any cause as the event of interest, and censoring at last follow up date for those with incomplete observations. This will be determined at 6 months and 1 year.

Use of additional systemic immune-suppressive therapies

The use of additional systemic immune-suppressive agents will be captured at each study visit, as this constitutes treatment failure. See above clarification (section 6.3.2) for definitions of systemic immune-suppressive therapies.

Discontinuation of all systemic immune-suppressive therapies

The incidence of complete discontinuation of all systemic immune-suppressive therapies will be determined at 6 months and 1 year.

Treatment success

This endpoint will be estimated at 6 months and 1 year with a composite outcome of complete resolution of all reversible chronic GVHD manifestations, discontinuation of all systemic immune suppressive agents, and freedom from death or primary malignancy relapse after transplant.

Patient-reported outcomes and functional measures

Patients will provide assessment of their functional ability, symptom burden, and quality of life using validated instruments recommended by the NIH Consensus Development Project on Chronic GVHD (2 minute walk test, Lee Chronic GVHD Symptom Scale,[2] HAP functional scale,[3] QOL instruments SF-36[4] and FACT-BMT[5]). These will be studied at baseline, 6 months, and 1 year.

Biologic studies

These studies aim to discern the biologic impact of proteasome inhibition in the treatment of chronic GVHD. Peripheral blood samples will be obtained at baseline (study enrollment pre-treatment), and then at the 3 and 6 month time points. An additional event-driven blood sample will be obtained when a new systemic immune suppressive therapy is added (treatment failure of carfilzomib).

A total of 15 mL of blood will be drawn at each timepoint, labeled with a study ID and date of draw, and shipped to Moffitt Cancer Center. Samples will be used to confirm effective

proteasome inhibition. In addition, these samples will be used to perform RNA-sequencing discovery studies for therapeutic response vs. nonresponse, and NanoString nCounter validation of any identified targets. Plasma will be used to conduct ELISAs or other tests to validate potential targets.

8 STUDY DISCONTINUATION

8.1 Criteria for study discontinuation

The following conditions require discontinuation of carfilzomib therapy and termination of study follow up:

1. Patient decision to withdraw from study
2. Death
3. Completion of all study follow up

8.2 Discontinuation of carfilzomib therapy

In the following circumstances, carfilzomib therapy will be discontinued, however study follow up will continue:

1. The treating clinician determines that the patient has responded to therapy and does not require any additional carfilzomib treatment
2. Carfilzomib therapy is discontinued due to unresolved toxicity
3. Carfilzomib therapy is discontinued due to patient non-adherence
4. Carfilzomib therapy is discontinued due to the addition of another line of systemic immune suppressive therapy
5. The patient has relapse of their hematologic disorder or malignancy after transplant

*As described below (section 9.2), AE will be collected until 30 days after the last dose of carfilzomib.

9 ADVERSE EVENTS

For more information about reporting and monitoring adverse events, see the DSMB Charter and the Data Safety Monitoring Plan.

9.1 Definitions

Adverse Event

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a drug.

AE Grading Criteria:

The study site will grade the severity of adverse events experienced by study participants on a scale from 1 to 5 according to NCI CTCAE v4.03 or current version. Grade 1 and grade 2 adverse events do not require reporting. Adverse events not included in the NCI CTCAE should be recorded and graded according to the General Grade Definition provided below:

ADVERSE EVENT GENERAL GRADE DEFINITIONS

Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE	Death related to AE

*Instrumental ADL: Preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL: Bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Suspected Adverse Reactions – a subset of Adverse Events based on causality

A suspected adverse reaction is any adverse event for which there is a *reasonable possibility* that the drug caused the event. *Reasonable possibility* means there is evidence to suggest a causal relationship between the drug and the event. Some examples are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug. If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association, event recurs on re-challenge), a single case may be sufficiently persuasive. Often, more than one occurrence is needed before the sponsor-investigator can determine that there is a reasonable possibility that the drug caused the event.
- An aggregate analysis of events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a similar population not receiving the study drug.

If there is reason to conclude with certainty that the drug caused the event, the event is classified as an **Adverse Reaction**.

Unexpected

An adverse event is considered unexpected *if it is not listed in the investigator brochure, or is not listed at the specificity or severity that has been observed in the event*. "Unexpected" also refers to adverse events that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Serious

An adverse event is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

1. Death
2. A life-threatening adverse event (places the subject at an immediate risk of death)
3. Inpatient hospitalization or prolongation of existing hospitalization

4. A persistent or significant disability or incapacitation

5. A congenital anomaly or birth defect

Additionally, events that jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes above may also be considered serious based on appropriate medical judgment.

9.2 Recording of Adverse Events

The study will collect all Grade 3 and above adverse events, regardless of relationship to study therapy or study procedures. Severity grading will be based on the current version of the Common Terminology Criteria for Adverse Events (CTCAE). Grade 1 and 2 events will not be collected.

Adverse events will be collected from the time of first study procedure or first dose of carfilzomib until 30 days after the last dose of carfilzomib. Events that occur after this time will be recorded only if there is a reasonable possibility that the event was caused by a study procedure or carfilzomib. All recordable adverse events will be followed until resolution.

Reporting procedures:

All Grade 3 and above adverse events will be reported through case report forms and must be recorded in the database within 7 calendar days of becoming aware of the event. All AEs are documented and reported as applicable from the time of ICF signature through 30 days after the last dose of study drug.

Exceptions:

The following are frequent events in the chronic GVHD population and will not be recorded as adverse events *as long as they are not serious*:

- Abnormalities present at study enrollment: Will not be considered adverse events, unless such abnormalities worsen (i.e. increase in frequency, intensity, or present new complications or untoward events) during study follow up

- Electrolyte abnormalities: Increase or decrease in sodium, potassium, chloride, bicarbonate, phosphorus, magnesium, calcium, hyperglycemia following steroid therapy

- Ocular: GVHD related eye dryness, discomfort, requirement for moisturizing eye drops or other topical GVHD ocular therapies or interventions (e.g. punctal plugs, scleral lenses), changes in visual acuity.

- Dermatology: Nail changes, GVHD rash (to include erythema, scleroderma, ulceration, lichenoid changes, hyper- or hypo-pigmentation, dry skin and alopecia) or cushingoid appearance due to steroid therapy.
- Gastrointestinal: Xerostomia, oral ulcers or other GVHD associated lesions, oral pain or sensitivity, anorexia, difficulty swallowing due to esophageal stricture or narrowing, nausea/vomiting, salivary gland changes, GVHD associated abdominal pain, bloating, diarrhea, weight loss
- Respiratory: shortness of breath, cough, or oxygen requirement associated with pulmonary chronic GVHD involvement
- Growth and Development: Reduced growth velocity, delayed puberty.
- Musculoskeletal changes: Avascular necrosis, fracture, arthritis, osteoporosis, decrease in range of motion associated with joint or fascial GVHD involvement
- Sexual Function: Erectile dysfunction, infertility, amenorrhea, vaginal stenosis, vaginal dryness or discomfort.
- Events secondary to routine procedures performed for chronic GVHD therapies: Extracorporeal photopheresis, PUVA therapy.

Non-serious adverse events collected in the database will be compiled by the coordinating center and reported to the DSMB approximately every 6 months.

All serious adverse events must be reported in the database within 24 hours of becoming aware of the event. Significant and relevant follow-up information should also be reported immediately within 24 hours of awareness.

Exception:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

The site Principal Investigator must notify the coordinating center and sponsor-investigator when a serious adverse event has been entered. The sponsor-investigator will then determine whether the event meets the criteria for expedited reporting (see below) and will work with the coordinating center to prepare the IND Safety Report.

9.3 **IND Safety Reporting**

An event must meet all three of the following criteria in order to qualify for expedited reporting to the FDA in an IND Safety Report:

1) Serious

2) Unexpected

3) Suspected adverse reaction (i.e. there is a reasonable possibility that the drug caused the event)

The sponsor-investigator is ultimately responsible for determining whether all criteria are met. Details are as follows:

- **Seriousness:** If either the sponsor-investigator or local investigator believes that an event is serious, it must be considered serious and evaluated by the sponsor-investigator for expedited reporting. Similarly, if either the sponsor-investigator or local investigator believes that an event is life threatening, it must be considered life threatening for reporting purposes.

- **Expectedness:** The sponsor-investigator is responsible for determining whether an event is unexpected.

- **Causality:** Although local investigators are required to provide a causality assessment for each serious adverse event originating from their sites, it is ultimately the sponsor-investigator who decides whether the event meets the definition of a suspected adverse reaction.

IND Safety reports will be submitted on a MedWatch3500A form to the FDA and all participating investigators no later than 15 days after the sponsor-investigator determines that the event qualifies for reporting.

Exception: Fatal or life-threatening events will be reported within 7 days of when the sponsor-investigator receives notification of the event.

Relevant additional information should be submitted in a follow-up report as soon as possible, but no later than 15 days after the sponsor-investigator receives the information.

All other adverse events that are collected by the study but do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

Notification of SAE that meet requirement for expedited reporting will also be provided to individual site principal investigators of this trial.

9.4 Reporting to Onyx

The coordinating center is responsible for all communication with Onyx. The sponsor-investigator will submit IND Safety Reports (per above guidelines, namely serious, unexpected, suspected adverse reactions) to Onyx in an expedited manner (same criteria

as above, namely within 24 hours of awareness. This notification will be documented on a MedWatch3500A form.

The initial report will be as complete as possible, at a minimum including the serious adverse event term (s), patient identifier, date of awareness of the event, an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH form. The Onyx protocol number and the institutional protocol number will be included on all reports to Onyx.

All other SAEs (i.e. those not meeting above criteria for expedited reporting) will be sent to Onyx within 30 days of awareness, and include the following: Patient identifier, SAE onset and stop dates, event name (term), outcome, dates of study drug exposure, action taken with study drug, assessment of causality and expectedness.

To report a Serious Adverse Event or other safety related information to Onyx Drug Safety please use:

Drug Safety Hotline: 650.266.2501

Drug Safety Fax: 650.266.0501 or 800-783-7954

Drug Safety Email: AdverseEvents@onyx.com

9.5 Pregnancy

Female participants of child-bearing potential must have a negative pregnancy test prior to treatment and agree to use dual methods of contraception for the duration of the study and for 30 days following completion of study. Male participants must also agree to use a barrier method of contraception for the duration of the study and for 30 days following completion of study if sexually active with a female of child-bearing potential.

If a subject or partner of a subject becomes pregnant during or up to 30 days following administration of the last dose of carfilzomib, Onyx Drug Safety must be notified by the study-investigator within 24 hours of research personnel becoming aware of it. Carfilzomib must be stopped if a subject becomes pregnant. Subjects or pregnant partners will be followed through the outcome of the pregnancy. The outcome must be reported to Onyx Drug Safety. If the outcome qualifies as a serious adverse event, the serious adverse event reporting procedures should be followed.

9.6 Notifying Institutional Review Boards

Study sites are responsible for adhering to their local IRB guidelines. In general, all investigators are required to promptly report to their IRB *all unanticipated problems involving risk to human subjects or others*. IND Safety Reports, which will be distributed to all investigators, will usually require reporting under this category.

10 STATISTICAL ANALYSIS

10.1 Study Design

This is a single arm, pilot phase II trial examining the efficacy of carfilzomib for treatment of chronic GVHD.

10.2 Study Endpoints

The major study endpoints are listed in section 7, 'study outcomes'.

10.2.1 Safety Endpoints

Patients will be monitored for adverse events through 30 days following their last therapy with carfilzomib on trial.

10.3 Sample Size Considerations and Planned Methods of Analysis

The primary endpoint is overall treatment failure at 6 months from study enrollment. Treatment failure represents the composite including addition of new line of systemic immune suppressive therapy beyond carfilzomib (objective signal of failure to control GVHD with carfilzomib), non-relapse death, and primary malignancy relapse.[6] The historical benchmark for this outcome based on this analysis of 312 chronic GVHD patients is a 6 month treatment failure rate of 44%. With 20 patients, the standard error of the estimated failure rate will be approximately 10 percentage points.

The major contribution to the observed treatment failure rate was 34% requiring additional immune suppressive therapy beyond second-line therapy. Assuming effective therapy with ongoing carfilzomib over the treatment period could reduce this risk by 50% (i.e. to 17%) with little or no increased risk for relapse (3% in this published analysis) or non-relapse death (7% in this analysis), the overall improvement in the 6 month treatment failure rate could be 15%. Given the feasible sample size of 20 patients, we do not expect to be able to demonstrate statistically significant differences relative to the historical rate; however, an

observed failure rate in the 30-35% range or better would be considered promising for future study of carfilzomib. Patients who are lost to follow up or otherwise not evaluable will not be replaced.

Although the overall 6 month failure rate in the historical benchmark study was 44%, this varied from 33% to 41% to 56% for patients that were classified as low, intermediate and high risk, respectively. Thus the relative proportions of patients in the different risk categories will need to be considered in order to interpret the possible benefit of carfilzomib therapy.

In the analysis of secondary objectives, we will study the 3 and 6 month overall (complete + partial) response and complete response rates, other efficacy measures listed above, patient reported outcomes, and biologic outcome measures. We will study association between biologic outcome measures and clinical parameters (response, treatment failure, mortality).

10.4 **Study Stopping Rules**

The principal investigators and the Data and Safety Monitoring Board (DSMB) will review safety data on an ongoing basis and formally every 6 months. If any of these reviews conclude that there are significant safety concerns, then the trial could be permanently terminated. The criteria described below provide additional guidance for suspending trial enrollment, analyzing safety data in detail, and deciding whether to continue.

While Carfilzomib has demonstrated safety as a single agent and in combination therapy in multiple myeloma, it has not been previously studied in chronic GVHD therapy after allogeneic hematopoietic cell transplantation. Current evidence suggests that approximately 7% of patients will experience non-relapse mortality during the initial 6 months of therapy.[33] In our current trial, if reasonable evidence exists that non-relapse mortality during the initial 6 months exceeds this threshold, then enrollment to the trial will be halted while data are reviewed. Reasonable evidence indicates that the lower bound of an exact 1-sided 80% confidence interval for the true non-relapse mortality rate exceeds 7%. The data will be evaluated at least every 5 patients, and will be triggered if 2 or more of 5, 2 or more of 10, 3 or more of 15, or 3 or more of 20 patients experience non-relapse mortality within the first 6 months.

The operating characteristics of this stopping rule are provided below:

True rate of event	Probability of stopping*	Average N at stopping*
0.12	51%	16
0.17	73%	13
0.22	88%	11

*Based on 10,000 Monte Carlo simulations

11 INVESTIGATIONAL PRODUCT

11.1 Carfilzomib Description

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

11.2 Formulation

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-□-cyclodextrin (SBE-□-CD, Captisol®).

11.3 Storage

Lyophilized Carfilzomib for Injection must be stored at 2–8ºC under the conditions outlined in the separate Pharmacy Manual, in a securely locked area to which access is limited to appropriate study personnel.

11.4 Accountability

Onyx, Inc. and the Investigator's pharmacy will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of Onyx, by regulatory authorities, and by the Sponsor-Investigator or her designates.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Onyx, by regulatory authorities, and by the Sponsor-Investigator or her designates.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

12 REGULATORY OBLIGATIONS

12.1 Informed Consent

All patients will provide informed consent following review of the informed consent form and discussion with their treating clinician, in keeping with standards at each participating study site.

12.2 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Onyx with a

copy of the IRB approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must be provided to both Onyx and the Sponsor-Investigator as follows:

Onyx Pharmaceuticals, Inc.

Regulatory Department

249 East Grand Ave

South San Francisco, CA 94080

Stephanie Lee, MD, MPH

Fred Hutchinson Cancer Research Center

1100 Fairview Ave

PO Box 19024, D5-290

Seattle, WA 98109

chronicGVHDstudies@fredhutch.org

Onyx will provide study sites with any expedited safety reports generated from any ongoing studies with carfilzomib, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of carfilzomib during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB and other Investigators participating in the study.

Upon completion of the trial, the Investigator must provide the IRB and Onyx with a summary of the trial's outcome.

12.3 **Subject Confidentiality**

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by Onyx, its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB reviews, and FDA inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

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Appendix A: NCI-CTCAE Version 4.03

Common Terminology Criteria for Adverse Events (CTCAE)
National Cancer Institute (NCI) v4.03

Publish Date: June 14, 2010

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

Appendix B: Study Calendar

Procedure	Screening	Baseline	Follow Up****		
			3 months	6 months	12 months
Carfilzomib administration*		X	X	X	
Screening Procedures					
Eligibility criteria**	X				
Informed consent	X				
Efficacy Assessments					
Chronic GVHD activity - NIH score - clinician severity assessments - clinician response assessments - patient-reported severity		X	X	X	X
Patient- reported outcomes - QOL - HAP - Lee symptom scale		X		X	X
Functional measures - 2 minute walk test		X		X	X
Record systemic immune suppressive agents		X	X	X	X
Biologic samples		X	X	X	

Survival and malignancy relapse			X	X	X
Safety Assessments					
Pregnancy test	X				
Physical exam		X	X	X	X
Adverse events***		X	X	X	

*Carfilzomib administration: Weekly for 3 weeks (day 1, 8, 15) out of each 28 day cycle for total of 6 cycles of therapy. Acceptable window for each planned carfilzomib administration date is +/- 3 days. Monitoring of routine laboratory tests (CBC, chemistry, LFT) are per institutional standards.

**Eligibility includes the following:

- Review of patient records for compliance with all listed inclusion and exclusion criteria
- Laboratory studies required to meet laboratory criteria (obtained within 14 days of study enrollment)
    - CBC, chemistry, liver function tests
- EKG to demonstrate no active ischemic changes; other listed cardiac conditions can be addressed by review of patient medical records (EKG should be performed within 14 days of study enrollment)
- Confirmation of no history of HIV or hepatitis B/C
    - If HIV and hepatitis B/C testing has been previously done and documented in the patient record, new testing at time of eligibility screening for this study is not necessary
        - If HIV+, the patient is excluded
    - If Hepatitis B serology indicates prior infection (i.e. core Ab positive, or surface antigen positive), hepatitis B PCR testing on peripheral blood should be done.
        - If PCR negative, the patient is eligible, but if positive, ineligible.
    - If hepatitis C antibody testing is positive, hepatitis C PCR should be tested in peripheral blood.
        - If PCR negative, the patient is eligible, but if positive, ineligible.

***AE/SAE are monitored for duration of therapy through 30 days following the final dose of study therapy

****Acceptable window for study visits at 3 and 6 months is +/- 14 days, and acceptable window for the 12 month study visit is +/- 1 month.