Abbreviated Protocol Synopsis

Name of Sponsor:	Onyx Therapeutics, Inc.
Name of Product:	Carfilzomib
Title of Study and Protocol Number:	A Randomized, Open-label Phase 3 Study of Carfilzomib, Melphalan and Prednisone versus Bortezomib, Melphalan and Prednisone in Transplant-ineligible Patients with Newly Diagnosed Multiple Myeloma
Phase of Development:	3
Study Objectives:	**Primary Objective:** To compare the progression free survival (PFS) of transplant-ineligible patients newly diagnosed with multiple myeloma who are treated with carfilzomib, melphalan and prednisone (CMP) versus those treated with bortezomib (Velcade®), melphalan and prednisone (VMP). **Secondary Objectives:** To compare the following between the treatment groups: • Overall Survival (OS) • Time to Progression (TTP) • Overall Response Rate (ORR) per International Myeloma Working Group (IMWG) [defined as the proportion of best overall response of stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), and Partial Response (PR)] • CR rate • Duration of Response (DOR) • Neuropathy Events (defined from Grade 2 or higher peripheral neuropathy incidence, and FACT/GOG-NTx [version 4; "Additional Concerns" questionnaire] score) • Health-related quality of life (HR-QOL) (measured by European Organization for Research and Treatment of Cancer [EORTC] Core Module [QLQ-C30], Multiple Myeloma Module [QLQ-MY20)], and FACT/GOG-NTx [version 4; "Additional Concerns"] questionnaires) • Safety and Tolerability **Exploratory Objectives:** To evaluate the following between the treatment groups: • Pre-treatment analysis of biomarkers that predict for response following treatment with proteasome inhibitors from all patients who consent to biomarker analysis from both treatment groups (CMP and VMP)

Study Design:

This is a Phase 3 multicenter, open-label, randomized trial in transplant-ineligible patients with newly diagnosed, untreated multiple myeloma.

Patients are randomized to receive 1 of 2 treatment regimens: CMP or VMP, as outlined below:

Study Design: Treatment Regimens		
CMP Regimen: Nine 42-Day Cycles		
Cycles	Days	Carfilzomib (mg/m^2)
1	1, 2	20
1	8, 9, 22, 23, 29, 30	36
2-9	1, 2, 8, 9, 22, 23, 29, 30	36
Cycle 1- Dexamethasone 4 mg, days 8, 9, 22, 23, 29, 30		
All cycles, Days 1-4: Oral melphalan 9 mg/m^2, oral prednisone 60 mg/m^2		
VMP Regimen: Nine 42-Day Cycles		
Cycles	Days	Bortezomib (mg/m^2)
1-4	1, 4, 8, 11, 22, 25, 29, 32	1.3
5-9	1, 8, 22, 29	1.3
All cycles, Days 1-4: Oral melphalan 9 mg/m^2, oral prednisone 60 mg/m^2		

The randomization will be stratified on the basis of:

1) International Staging System (ISS) stage
   - Stage 1
   - Stages 2 or 3
2) Choice of route of bortezomib administration (intravenous [IV] versus subcutaneous [SC])
3) Region

The estimated sample size is 882 patients.

Physicians are encouraged to maintain patients on the same route of bortezomib administration (SC or IV) throughout the study. Any switch in route of administration requires documentation of the switch, and the reason for the switch, in the designated electronic case report form (eCRF).

Patients shall receive the treatment determined by randomization until confirmed disease progression, physician decision, unacceptable toxicity, withdrawal of consent, mortality, or completion of 9 treatment cycles (whichever occurs first). Patients will be assessed for response using central laboratory results every 3 weeks irrespective of treatment delays or the timing of treatment cycles.

Long-term follow-up (LTFU) for disease status (only in cases where patients

<table>
<tr><td></td><td>discontinued treatment prior to completion of 9 treatment cycles or prior to PD) and for survival shall continue after treatment discontinuation or until the patient has withdrawn consent for further participation, is lost to follow-up, has died, or the Sponsor makes a decision to close the study. No cross-over between the two arms will be allowed. For patients who discontinue treatment before disease progression occurred (such as for an adverse event [AE], noncompliance, etc), disease response assessments using central laboratory results shall be performed every 3 weeks. Disease response assessments will continue until disease progression.

Follow up for survival will continue every 3 months for all patients until study closure. For any patient who is lost to follow-up, the study site shall attempt to ascertain survival information via public database search.

The trial is designed to detect a 35% improvement in PFS (hazard ratio [HR] 0.74) with 85% power and a 1-sided significance level of 0.025. It is assumed that the PFS for the control arm (VMP regimen) is 21 months. The enrollment period is anticipated to be 21 months. One interim analysis will be performed when 75% of the total PFS events have occurred.</td></tr>
<tr><td>Number of Investigational Sites:</td><td>Approximately 200 globally.</td></tr>
<tr><td>Planned Number of Patients:</td><td>882 patients (441 per arm) will be enrolled.</td></tr>
<tr><td>Study Population:</td><td>Transplant-ineligible patients with newly diagnosed, untreated multiple myeloma.</td></tr>
<tr><td>Study Treatment:</td><td>
<table>
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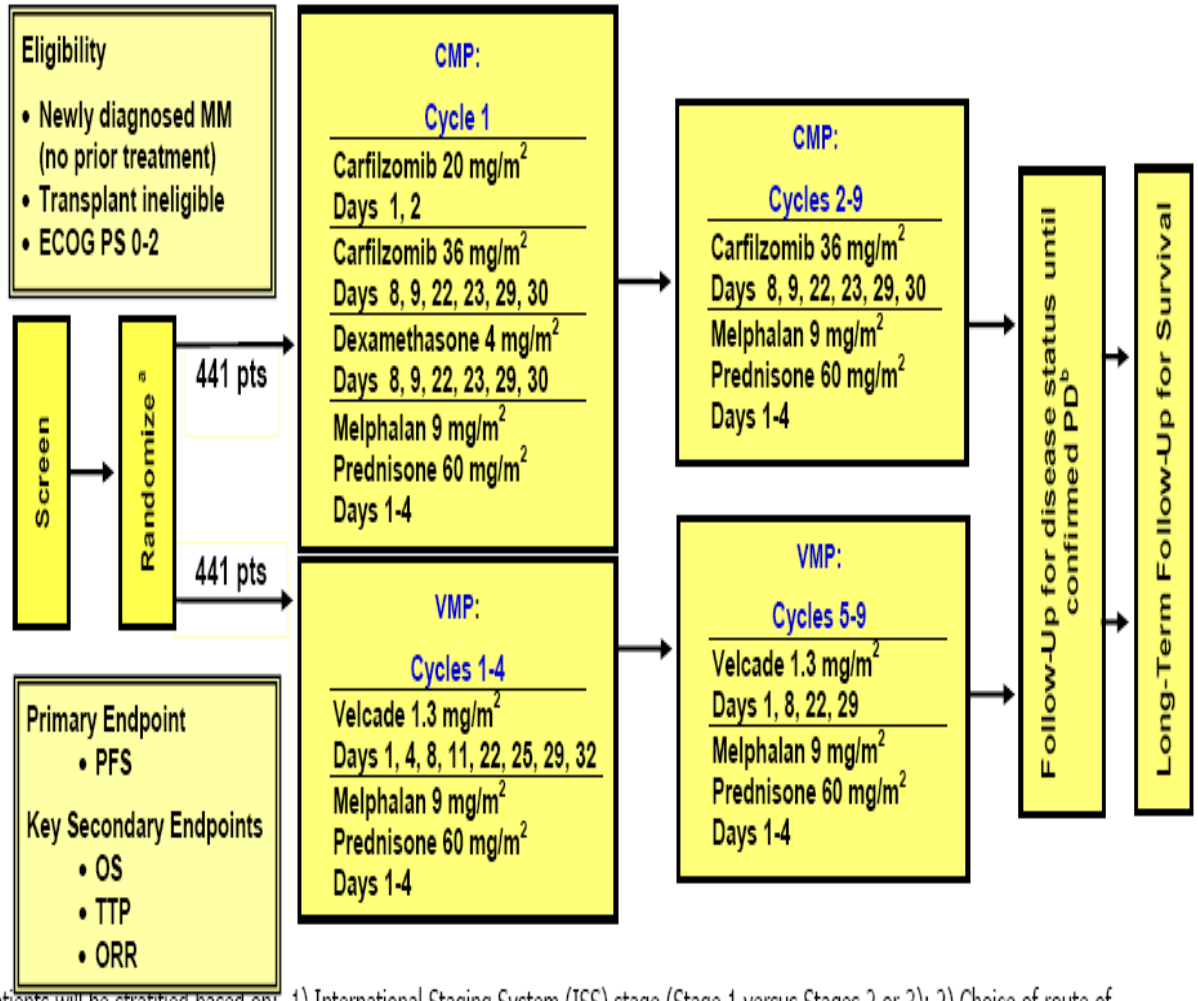
	Treatments (CMP or VMP) are continued until confirmed disease progression, physician decision, unacceptable toxicity, withdrawal of consent, mortality, or completion of 9 treatment cycles (whichever occurs first).
Inclusion Criteria:	1. Newly diagnosed multiple myeloma. 2. Transplant-ineligibility. 3. Measurable disease, as defined by one or more of the following (assessed within 21 days prior to randomization): • Serum M-protein ≥ 0.5 g/dL, or • Urine M-protein ≥ 200 mg/24 hours, or • In patients without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal κ/λ ratio (>4:1 or <2:1), or • For IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA) ≥ 750 mg/dL (0.75 g/dL). 4. No prior treatment for multiple myeloma. 5. Males and females ≥ 18 years of age. 6. Eastern Cooperative Oncology Group (ECOG) performance status 0–2. 7. Adequate hepatic function within 21 days prior to randomization, with bilirubin < 1.5 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 times the ULN. 8. Absolute neutrophil count (ANC) ≥ 1000/mm3 within 21 days prior to randomization. Screening ANC should be independent of growth factor support for ≥ 1 week. 9. Hemoglobin ≥ 8.0 g/dL within 21 days prior to randomization. Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed, however the most recent RBC transfusion may not have been done within 7 days prior to obtaining screening hemoglobin. 10. Platelet count ≥ 50,000/mm3 (≥ 30,000/mm3 if myeloma involvement in the bone marrow is > 50%) within 21 days prior to randomization. Patients should not have received platelet transfusions for at least 1 week prior to obtaining the screening platelet count. 11. Calculated or measured creatinine clearance (CrCl) of ≥ 15 mL/min within 21 days prior to randomization. Calculation should be based on standard formula such as the Cockcroft and Gault: [(140 – Age) × Mass (kg) / (72 × Creatinine mg/dL)]; multiply result by 0.85 if female. 12. Female patients of child-bearing potential (FCBP) must have a confirmed negative serum pregnancy test within 21 days prior to randomization (performed at central laboratory) and agree to use an effective method of contraception during and for 3 months following last dose of drug (more frequent pregnancy tests may be conducted if required by local regulations). This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy, or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). 13. Male patients must use an effective barrier method of contraception during study and for 3 months following the last dose if sexually active with a

	female of child-bearing potential. 14. Written informed consent in accordance with federal, local, and institutional guidelines.
Exclusion Criteria:	1. Multiple Myeloma of IgM subtype. 2. Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 14 days prior to randomization. 3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). 4. Plasma cell leukemia (> 2.0 × 109/L circulating plasma cells by standard differential). 5. Waldenstrom's Macroglobulinemia. 6. Patients with known amyloidosis. 7. Chemotherapy with approved or investigational anticancer therapeutics within 21 days prior to randomization. 8. Focal radiation therapy within 7 days prior to randomization. 9. Radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to randomization (i.e., prior radiation must have been to less than 30% of the bone marrow). 10. Immunotherapy within 21 days prior to randomization. 11. Major surgery within 21 days prior to randomization. 12. Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, or conduction abnormalities uncontrolled by conventional intervention. Myocardial infarction within four months prior to randomization. 13. Acute active infection requiring systemic antibiotics, antiviral (except antiviral therapy directed at hepatitis B as noted below) or antifungal agents within 14 days prior to randomization. 14. Known HIV seropositive, hepatitis C infection, and/or hepatitis B (except for patients with hepatitis B surface antigen [SAg] or core antibody receiving and responding to antiviral therapy directed at hepatitis B: these patients are allowed). 15. Patients with known cirrhosis. 16. Second malignancy within the past 3 years except: • adequately treated basal cell or squamous cell skin cancer, • carcinoma in situ of the cervix, or • prostate cancer < Gleason score 6 with stable prostate-specific antigen (PSA) over 12 months, or • breast carcinoma in situ with full surgical resection • treated medullary or papillary thyroid cancer 17. Patients with myelodysplastic syndrome. 18. Significant neuropathy (Grades ≥ 2) within 14 days prior to randomization. 19. Female patients who are pregnant or lactating. 20. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib). 21. Patients with hypersensitivity to boron, or mannitol (associated with parenteral bortezomib administration).

	22. Patients with a contraindication to prednisone or dexamethasone. 23. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment. 24. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomization.Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent. 25. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomization. 26. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.
Biomarker Analyses:	Analysis of pre-treatment biomarkers that predict for response following treatment with proteasome inhibitors will be performed on all patients who consent to biomarker analyses. Biomarker analyses will be performed on bone marrow biopsies and blood samples.

Figure 1: Study Schema



a Patients will be stratified based on: 1) International Staging System (ISS) stage (Stage 1 versus Stages 2 or 3); 2) Choice of route of bortezomib administration (IV versus SC); and 3) Region

b Follow up for disease status will only occur in cases where patients discontinued treatment prior to completion of 9 treatment cycles or PD.

Abbreviations (Figure 1): CMP = carfilzomib, melphalan and prednisone; ECOG PS = Eastern Cooperative Oncology Group performance score; HR = hazard ratio; HR-QOL= Health-related Quality of Life; MM = multiple myeloma; MP = melphalan and prednisone; ORR = Overall Response Rate; OS = Overall Survival; PD = progressive disease; PFS = Progression-Free Survival; pts = patients; VMP = bortezomib, melphalan and prednisone.

Note (Figure 1): Patients shall receive the treatment determined by randomization until disease progression, physician decision, unacceptable toxicity, withdrawal of consent, mortality or completion of 9 treatment cycles (whichever occurs first). Patients are followed for disease status until confirmed PD. Follow up for disease status (in cases where patients discontinued treatment prior to completion of 9 treatment cycles or PD) and for survival shall continue after treatment discontinuation or until the patient has withdrawn consent for further participation, is lost to follow-up, has died, or the Sponsor makes a decision to close the study.