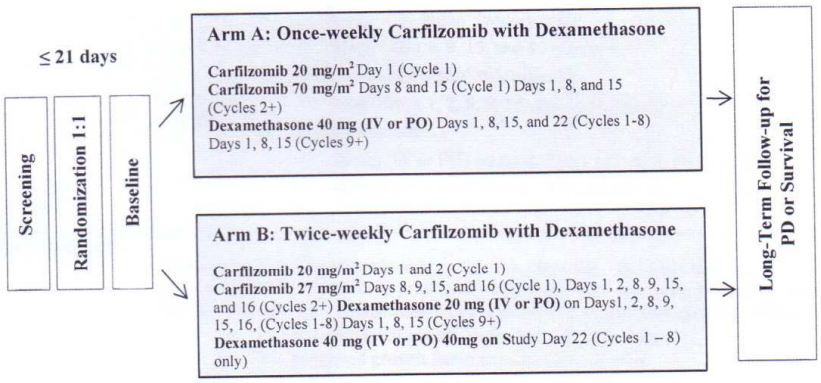
1 SYNOPSIS

Name of sponsor/company:	Onyx Therapeutics
Name of product:	Carfilzomib for Injection
Title of study and protocol number and phase:	A Randomized, Open-label, Phase 3 Study Assessing Safety and Efficacy in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Once-weekly Carfilzomib Compared to Twice-weekly Carfilzomib in Combination with Dexamethasone
Study objective(s):	**Primary Objective** To compare the ORR between once-weekly carfilzomib and twice-weekly carfilzomib when given in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received at least 2 but no more than 3 prior lines of therapy. **Secondary Objectives** To compare the following between treatment groups: • Overall Response Rate (ORR) • Progression-free survival (PFS) • Clinical Benefit Response Rate (CBR rate) o defined as (ORR + minimal response [MR]) • Overall Survival (OS) • Safety and tolerability • Pharmacokinetics (PK) of carfilzomib using sparse sampling **Exploratory Objectives** • PK and pharmacodynamics (PDn) of both carfilzomib treatment groups in a subset of subjects (substudy) • Genomic and transcriptional biomarkers that may predict response and resistance following treatment with carfilzomib. • Global Health Status/QoL as measured by the EORTC QLQ-C30 Global Health Status/QoL scale • All subscales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ)-C30, and the EORTC QLQ-MY20 • EQ-5D; a standardized measure of health status developed by the EuroQol Group • Patient reported convenience questionnaire • Healthcare resource utilization
Study design:	This is an open-label, multicenter, Phase 3 study comparing carfilzomib administered once-weekly to carfilzomib administered twice-weekly when given in combination with dexamethasone to subjects with relapsed and refractory multiple myeloma. The study design is illustrated in the Study CFZ014 Schema below. Eligible patients will be randomized in a 1:1 ratio to receive a regimen consisting of either: • Carfilzomib once-weeklywith dexamethasone or • Carfilzomib twice-weeklywith dexamethasone The randomization will be stratified by: • The ISS Stage at study entry o (Stage 1 versus Stages 2 or 3) • Prior proteasome inhibitor (bortezomib) treatment

	• Age (< 65 versus ≥ 65 years). No crossover between the 2 treatment arms will be allowed. The primary endpoint is ORR. Study treatment will be administered in 28-day cycles. The treatment regimens for each of the arms are depicted in Study CFZ014 Schema below. Patients shall receive the treatment determined by randomization until disease progression, unacceptable toxicity, withdrawal of consent, or death (whichever occurs first). Following termination of study treatment all subjects will be followed for safety, disease status, subsequent antimyeloma treatment, and survival. All subjects will be followed for at least 30 additional days after the last study treatment administration or until initiation of new anticancer therapy. All treatment-related adverse events (AEs) and serious AEs (SAEs) will be followed until resolution or stabilization.
	Study CFZ014 Schema 
Number of investigational sites:	Approximately 100 sites worldwide
Planned number of subjects:	460 subjects 230 each arm
Sample size justification:	The study is designed to have 90% statistical power to detect a significant treatment effect as measured by the odds ratio associated with the response rates in the 2 treatment arms. The analysis is based on the Cochran-Mantel-Haenszel test with a one-sided overall significance level set to 0.025.
Study population:	Adults with relapsed and refractory multiple myeloma will be considered for eligibility. Subjects must have had at least 2 but no more than 3 prior lines of therapy for multiple myeloma.
Treatment regimen(s):	Carfilzomib and dexamethasone will be administered in 28-day cycles in one of two treatment regimens. All cycles will start 28 days (± 2) after the start of the prior cycle. • **Arm A: Once-weekly Carfilzomib with Dexamethasone Regimen**

	○ Carfilzomib 20 mg/m^2 – Cycle 1 Day 1 ○ Carfilzomib 70 mg/m^2 once-weekly – Study Days 8 and 15 (Cycle 1) ○ Carfilzomib 70 mg/m^2 once-weekly – Study Days 1, 8, and 15 (Cycles 2+) ○ Dexamethasone – 40 mg (IV or PO) on Study Days 1,8, and 15 – 40 mg (IV or PO) Study Day 22 (Cycles 1 to 9 only) • **Arm B: Twice-weekly Carfilzomib with Dexamethasone Regimen** ○ Carfilzomib 20 mg/m^2 – Cycle 1 Days 1 and 2 ○ Carfilzomib 27 mg/m^2 twice-weekly – Study Days 8, 9, 15, and 16 (Cycle 1) ○ Carfilzomib 27 mg/m^2 twice-weekly – Study Days 1, 2, 8, 9, 15, and 16 (Cycles 2+) ○ Dexamethasone – 20 mg (IV or PO) on Study Days 1, 2, 8, 9, 15, and 16 – 40 mg (IV or PO) on Study Day 22 (Cycles 1 to 9 only)
Subject selection:	Approximately 460 subjects will be enrolled in this study. Subjects will be evaluated for study entry within the 21 days prior to randomization. All screening laboratory results must be independent of transfusion and hematopoietic stimulating agents as follows: • No non-pegylated growth factor support for ≥ 7 days • No pegylated growth factor support for ≥ 14 days • No platelet or blood transfusions for ≥ 7 days Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed.
Inclusion criteria:	1. Age ≥ 18 years 2. Able to provide written informed consent in accordance with federal, local, and institutional guidelines 3. Relapsed and refractory multiple myeloma 4. At least 2 but no more than 3 prior lines of therapy for multiple myeloma 5. Documented response of at least PR to 1 line of prior therapy 6. Measurable disease with at least 1 of the following assessed within the 21 days prior to randomization: a. Serum M-protein ≥ 0. 5 g/dL b. Urine M-protein ≥ 200 mg/24 hour c. In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio d. For IgA subjects whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA), a qIgA level of ≥ 750 mg/dL (0. 75 g/dL) 7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 8. Left ventricular ejection fraction (LVEF) ≥ 40% within the 21 days prior to

	randomization 9. Adequate organ and bone marrow function within the 21 days prior to randomization defined by: a. Bilirubin < 1. 5 times the upper limit of normal (ULN) b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 times the ULN c. Absolute neutrophil count (ANC) ≥ 1000/mm^3 within 21 days prior to randomization d. Hemoglobin ≥ 8. 0 g/dL within 21 days prior to randomization e. Platelet count ≥ 50,000/mm^3 (≥ 30,000/mm^3 if myeloma involvement in the bone marrow is > 50%) within 21 days prior to randomization f. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/min within 21 days prior to Cycle 1 Day 1 (using a standard formula e. g. , Cockcroft-Gault Equation) 10. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test within the 7 days prior to start of study treatment and a negative urine pregnancy test within the 24 hours prior to the first study treatment administration 11. FOCBP and male subjects who are sexually active with FOCBP must agree to use 2 highly effective concomitant methods of contraception including a male condom during the study and for 90 days following the last study treatment administration
Exclusion criteria:	1. Waldenström macroglobulinemia 2. Multiple myeloma of IgM subtype 3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) 4. Plasma cell leukemia (> 2. 0 × 10^9/L circulating plasma cells by standard differential) 5. Myelodysplastic syndrome 6. Second malignancy within the past 5 years except: a. Adequately treated basal cell or squamous cell skin cancer b. Carcinoma in situ of the cervix c. Prostate cancer < Gleason score 6 with undetectable prostate-specific antigen (PSA) over 12 months d. Ductal breast carcinoma in situ with full surgical resection (i. e. , negative margins) e. Treated medullary or papillary thyroid cancer f. Similar condition with an expectation of > 95% five-year disease-free survival 7. History of or current amyloidosis 8. Cytotoxic chemotherapy within the 28 days prior to randomization 9. Immunotherapy within the 21 days prior to randomization 10. Glucocorticoid therapy within the 14 days prior to randomization that exceeds a cumulative dose of 160 mg of dexamethasone or 1000 mg prednisone 11. Radiation therapy: a. Focal therapy within the 7 days prior to randomization b. Extended field therapy within the 21 days prior to randomization 12. Prior treatment with either carfilzomib or oprozomib 13. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib) 14. Contraindication to dexamethasone or 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