DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202714

WRITTEN REQUEST

Onyx Therapeutics, Inc.
Attention: Margaret Vargo
Vice President, Global Regulatory Affairs
249 E. Grand Avenue
South San Francisco, CA 94080

Dear Ms. Vargo:

Reference is made to your November 17, 2014, Proposed Pediatric Study Request for carfilzomib for injection. This study request proposes to study the potential use of Kyprolis (carfilzomib) in the treatment of pediatric subjects with relapsed or refractory Acute Lymphoblastic Leukemia (ALL).

BACKGROUND:

ALL is the most common pediatric cancer. Leukemia (77% of which are lymphoid leukemias) accounts for 30% of all childhood cancers. Survival rates for pediatric ALL have improved significantly with current 10 year-survival rates estimated at greater than 90%. The successful treatment of children with ALL is largely due to use of multidrug regimens, which includes CNS directed therapy. However, it is estimated that between 6% and 20% of children with ALL may relapse after completion of therapy.

Patients with relapsed/refractory ALL require aggressive re-induction therapy and intensification, often with agents that were not used in the initial treatment protocol. Agents that have been used in this setting include: etoposide, vincristine, asparaginase, doxorubicin, mitoxantrone, cytarabine, cyclophosphamide, methotrexate, dexamethasone, and prednisone. Agents that have been approved for the relapsed setting include: clofarabine, nalarabine, liposomal vincristine, and most recently blinatumomab, although not all of these agents are approved for pediatric populations. A commonly used salvage regimen for pediatric ALL is the UK R3 regimen (dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine).

The study described in your proposed pediatric study report (PPSR) evaluates the potential use of carfilzomib in combination with dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine (UK R3 backbone) for the treatment of pediatric subjects with relapsed or refractory ALL. Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that binds irreversibly to the N-terminal threonine-containing active sites of the 20S proteasome. In vitro, carfilzomib has

been shown to have anti-proliferative and pro-apoptotic activities across a range of solid and hematologic tumor cells, including cells that are resistant to bortezomib. Based on the mechanism of action, carfilzomib combined with a four drug induction platform, consisting of dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine (UK R3 Induction Backbone) is anticipated to show activity within the relapsed or refractory pediatric population with ALL.

The UK R3 induction regimen is commonly used in pediatric patients with relapsed/refractory ALL. This is based on the results of the ALL R3 trial, which demonstrated an improvement in progression-free survival and overall survival when mitoxantrone was added to dexamethasone, PEG-asparaginase, and vincristine compared to idarubicin, dexamethasone, PEG-asparaginase, and vincristine. While the proposed trial plans to evaluate the use of carfilzomib in combination with the UK R3 backbone, it is recognized that the trial attempts to more largely address the issue of the addition of carfilzomib to induction chemotherapy in pediatric patients with relapsed/refractory ALL. The results of this trial may inform the use of carfilzomib when added to other similar induction backbone regimens since the individual agents (or drugs of the same class) of the R3 regimen are common to most induction platforms in the relapsed setting.

FDA is not requesting studies in neonates, because relapsed or refractory ALL by definition would not occur by 28 days of age, and the benefit-risk assessment does not favor use of carfilzomib as first-line therapy at this time.

To obtain needed pediatric information on carfilzomib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

The complete protocol including the statistical analysis plan will be agreed upon with the Agency before initiation of the clinical studies.

Study 1:

Phase 1b: multicenter, non-randomized, dose-escalation, dose-expansion trial of carfilzomib in combination with dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine (UK R3 induction backbone) for the treatment of pediatric subjects with relapsed or refractory ALL. Dose escalation will proceed using a Bayesian design and a cohort size of 2. A small dose-expansion cohort will be enrolled, to ensure a minimum of 12 patients are treated at the maximum tolerated dose (MTD), before the Phase 2 portion begins.

Phase 2: multicenter, randomized trial comparing UK R3 induction backbone alone to the UK R3 induction backbone with the addition of carfilzomib among pediatric patients with relapsed or refractory ALL.

☐ Efficacy in pediatric patients age 0-18 years cannot be extrapolated and will be determined by the studies outlined in the WR.

- *Objective of each study:*

Study 1:

PRIMARY OBJECTIVES
Phase 1b
- To assess the safety and tolerability of carfilzomib, alone and in combination with induction chemotherapy, for the treatment of children with relapsed or refractory ALL
- To determine the MTD of carfilzomib in combination with induction chemotherapy

Phase 2
- To compare the combined rate of bone marrow complete response (CR) and bone marrow CR without platelet recovery (CRp) of the treatment arms at the end of the Induction Cycle

SECONDARY OBJECTIVES
Phase 1b
- To characterize the pharmacokinetics (PK) of carfilzomib alone and in combination with induction chemotherapy
- To evaluate the combined rate of bone marrow CR and bone marrow CRp at the end of the Induction Cycle
- To estimate the proportion of subjects who achieve minimal residual disease (MRD)status $< 10^{-3}$ and $< 10^{-4}$ lymphoblasts at the end of the Induction Cycle

Phase 2
- To compare the proportion of subjects in each treatment arm who achieve MRD status $< 10^{-3}$ and $< 10^{-4}$ lymphoblasts at the end of the Induction Cycle
- To assess the safety and tolerability of carfilzomib in combination with induction chemotherapy, for the treatment of children with relapsed or refractory ALL
- To characterize the PK of carfilzomib in combination with induction chemotherapy

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*: Subjects will be ≤ 18 years old, with a minimum of 3 subjects in each of the following age groups across both phases of the study: 1 to < 24 months; 2 to < 12 years; and 12 to 18 years.

- *Number of patients to be studied:*

  Phase 1b
  Up to 18 subjects will be enrolled.

  Phase 2
  A minimum of 76 evaluable subjects (38 per treatment arm) will be enrolled.

  A sample size of 76 was chosen to achieve 80% power at a 1-sided alpha of 0.1 based on the following 2 assumptions:
  1. Twenty percent (20%) of enrolled subjects experience first relapse while 80% enrolled subjects have refractory or multiply relapsed disease.
  2. A common odds ratio of 2.85 in each diagnosis group (80% combined CR and CRp rate in control arm and 92% in carfilzomib arm from first relapse subjects; 35% rate in control arm and 61% in carfilzomib arm from refractory or multiple relapsed subjects).

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  ☐ *Efficacy Endpoints:*
  - ☐ The Phase 1b primary endpoint will be:
    - Safety and tolerability of carfilzomib alone and in combination with induction chemotherapy as defined by the type, incidence, severity, and outcome of adverse events (AEs); changes from baseline in key laboratory analytes, vital signs, and physical findings.
    - Determination of the MTD as the dose that has the highest posterior probability of having a dose-limiting toxicity (DLT) rate within the target toxicity interval (20%-33%), while the posterior probability of excessive /unacceptable toxicity (> 33%–100%) is less than 40%.

  - ☐ The Phase 2 primary endpoint should be:
    - The proportion of subjects who achieve CR at the end of the Induction Cycle

  - ☐ Important secondary endpoints must include PK parameters, including maximum plasma concentration and area under the curve and the proportion of patients who achieve MRD status $< 10^{-3}$ and $< 10^{-4}$ lymphoblasts at the end of the induction cycle. For the phase II portion, safety and tolerability of carfilzomib in combination with induction chemotherapy is an important secondary endpoint.

- ☐ *Safety Endpoints:*
  - ☐ Safety outcomes must include descriptive adverse events, including the incidence of overall adverse events, of severe adverse events, of serious adverse events, and of fatal adverse events. The type, incidence, and severity of laboratory abnormalities must also be analyzed for each group. Safety analyses must be performed separately for each study, in aggregate, and by age group.

  - ☐ All adverse events with an onset date after the subject or their legally acceptable representative signs the informed consent for participation in the clinical trial through 30 days after any study drug in the combination was received must be documented and monitored until symptom resolution or until the condition stabilizes.

  - ☐ A Data Monitoring Committee (DMC) must be included because of the potential for serious toxicity with carfilzomib. See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf.

  - ☐ *Pharmacokinetic Endpoints:*
    Pharmacokinetic samples must be collected by rich sampling in all patients during the Phase 1B portion of Study 1 and optimal sparse sampling in all patients in the carfilzomib treatment arm during the Phase 2 portion of Study 1. Data from Study 1 must be used to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

- *Known Drug Safety concerns and monitoring:* The important identified risks of carfilzomib that have emerged in clinical studies include thrombocytopenia, tumor lysis syndrome (TLS), dyspnea, and infusion reactions. Cardiac arrest, congestive heart failure, myocardial ischemia, pulmonary hypertension, hepatic toxicity, renal impairment, and embryo-fetal toxicity are considered important potential risks. All of these potential adverse reactions will be monitored throughout the study in all patients.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *dosage form:* Carfilzomib for Injection, 60 mg/vial, is supplied as a white to off-white lyophilized cake or powder in a single-use vial.

- *route of administration:* Intravenous infusion

- *regimen:* Intravenous infusion over approximately 30 minutes

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  The Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

  Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:* The primary efficacy analysis should be performed based on the ITT population. The analysis will be performed based on a 2-sided 5% alpha level. Cochran Mantel Haenszel

(CMH) test will be used for the primary efficacy endpoint analysis. The analysis of the secondary efficacy endpoint will be considered as exploratory analyses.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Carfilzomib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "*Study Data Specifications*," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 30, 2019. Please keep in mind that

pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, complete response); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY H REAMAN
03/17/2015