NDA 202714
IND 147187

WRITTEN REQUEST – AMENDMENT 4

Onyx Pharmaceuticals, Inc., a wholly-owned subsidiary of Amgen Inc.
Attention: Sahar Reka, MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 27-2-D
Thousand Oaks, CA 91320-1799

Dear Ms. Reka:[1]

Please refer to your correspondence dated June 30, 2023, requesting changes to FDA's March 17, 2015, Written Request for pediatric studies for Kyprolis (carfilzomib).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on March 17, 2015, and as amended on December 19, 2015; December 10, 2020; and November 14, 2022, remain the same. Refer to the attached document which shows the changes from the previous Written Request.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 17, 2015, as amended by this letter and by previous amendments dated December 19, 2015; December 10, 2020; and November 14, 2022, must be submitted to the Agency on or before April 18, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies

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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:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
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FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[2]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Saumya Nathan, Senior Regulatory Project Manager, at Saumya.Nathan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Complete Copy of the Written Request as Amended, with Changes Marked
- Complete Copy of Written Request as Amended

[2] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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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 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, nelarabine, liposomal vincristine, and most recently blinatumomab, and chimeric antigen receptor T-cell therapy. A commonly used salvage regimen for pediatric ALL is the VXLD regimen (vincristine, dexamethasone, pegylated L-asparaginase, and daunorubicin).

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The study described in your proposed pediatric study report (PPSR) evaluates the potential use of carfilzomib in combination with VXLD 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 of VXLD, is anticipated to show activity within the relapsed or refractory pediatric population with ALL.

While the proposed trial plans to evaluate the use of carfilzomib in combination with the VXLD 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 VXLD 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.

Amendment 4 incorporated a reduction in the minimum sample size of patients with B-cell ALL in Study 2 to a minimum of 310, which is predicted to provide a sufficiently precise estimate of the CR rate in this population to serve as a comparator for Study 1.

- *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 phase 2 portion of this clinical study.

Study 1:

Phase 1b: multicenter, non-randomized, dose-escalation, dose-expansion trial of carfilzomib in combination with dexamethasone, daunorubicin, PEG-asparaginase, and vincristine (VXLD 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 minimum of 6 patients are treated at or above the recommended Phase 2 dose (RP2D), before the Phase 2 portion begins.

Phase 2: multicenter, non-randomized trial of carfilzomib in combination with VXLD for the treatment of pediatric patients with relapsed or refractory ALL.

☐ Efficacy in pediatric patients age 1 month-21 years cannot be extrapolated and will be determined by the studies outlined in the WR.

Study 2: Multicenter, retrospective cohort study of pediatric patients with relapsed and refractory T-cell and B-cell ALL.

- *Objective of each study:*

Study 1:

PRIMARY OBJECTIVES
Phase 1b

- To assess the safety and tolerability of carfilzomib in combination with induction chemotherapy, for the treatment of children with relapsed or refractory ALL
- To determine the RP2D of carfilzomib in combination with induction chemotherapy

Phase 2

- To compare the rate of bone marrow complete response (CR) of the treatment arm at the end of the Induction Cycle relative to a clinically relevant external control group

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 estimate the rate of MRD status < 10-3 and < 10-4 lymphoblasts of subjects treated with carfilzomib in combination with VXLD at the end of the induction cycle
- To assess the safety and tolerability of carfilzomib in combination with VXLD for the treatment of children with relapsed or refractory ALL
- To characterize the PK of carfilzomib in combination with VXLD

Study 2:

Primary objective:

- To estimate the complete remission (CR) rate in patients with refractory or relapsed (first and subsequent) B-ALL, T-ALL treated with curative intent between 29-45 days of initiation of therapy (35-50 days for infants).

Secondary objectives:

- To estimate the overall complete remission (CR) rate (CR, CRh, CRp, CRi) in patients with refractory or relapsed (first and subsequent) B-ALL, T-ALL treated with curative intent.
- To estimate the minimal residual disease (MRD) response rate in patients with refractory or relapsed (first and subsequent) B-ALL, T-ALL, treated with curative intent.
- To estimate the event free survival (EFS) probability in patients with refractory or relapsed (first and subsequent) B-ALL, T-ALL treated with curative intent.
- To estimate the duration of remission (DOR) probability in patients with refractory or relapsed (first and subsequent) B-ALL, T-ALL treated with curative intent.
- To estimate the overall survival (OS) probability in patients with refractory or relapsed (first and subsequent) B-ALL, T-ALL treated with curative intent.
- To estimate the proportion of patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) after initiation of salvage therapy and their subsequent EFS and OS probabilities.

- *Patients to be studied:*
  - *Age group in which study(ies) will be performed*: Subjects will be 1 month to 21 years old across both studies. A minimum of 90% of subjects will be ≤17 years old.

  - *Number of patients to be studied:*
    Study 1:
    Phase 1b
    Up to 18 subjects will be enrolled.
    Phase 2
    A minimum of 100 subjects will be enrolled.

A sample size of 100 was chosen to achieve at least 70% power for testing the primary hypothesis for at least one phenotype at a 2-sided alpha of 0.05 based on:

1. A minimum of 30 enrolled subjects will have refractory or relapsed T-cell ALL.
2. A minimum of 50 enrolled subjects will have post-immunotherapy relapsed or refractory relapsed B-cell ALL.

Study 2:
Data from ~~approximately~~ a minimum of 310 ~~800~~ patients with B-cell ALL and 100 patients with T-cell ALL will be collected and analyzed. For both cohorts, the patients in the external control arm will be selected such that the inclusion criteria are as similar as possible to the inclusion criteria of those enrolled in Study 1.

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 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 RP2D as defined by Cohort Safety Review Committee (CSRC) by evaluating all available data including: subjects clinical history, pharmacokinetics, tolerability, safety and efficacy data

    - ☐ The Phase 2 primary endpoint will be:
      - 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 2 portion, safety and tolerability of carfilzomib in combination with induction chemotherapy is an important secondary endpoint.

Study 1:

- ☐ *Safety endpoints:*
  - ☐ Safety outcomes of subjects treated with carfilzomib in combination with VXLD must include descriptive adverse events, including the incidence of

overall adverse events, of severe adverse events, of grade 3 or higher 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.

- ☐ The study protocol must include instructions for documenting ~~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. The study protocol must include instructions for and ~~monitored~~ monitoring adverse events 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 for pharmacokinetic/ pharmacodynamic analyses to explore exposure-response relationships for clinical safety and efficacy endpoints.

- *Known drug safety concerns and monitoring:* The important identified risks of carfilzomib that have emerged in clinical studies include cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction, and cardiac arrest), pulmonary toxicities (acute respiratory distress syndrome [ARDS], acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease), pulmonary hypertension, dyspnea, hypertension including hypertensive crises, acute renal failure, hemorrhage and thrombocytopenia, tumor lysis syndrome (TLS), infusion reactions, hepatic toxicity, venous thromboembolism, hepatitis B virus (HBV) reactivation, thrombotic microangiopathy, and posterior reversible encephalopathy syndrome (PRES) and important potential risk of carfilzomib includes progressive multifocal leukoencephalopathy (PML). The study protocol must outline procedures for monitoring ~~All of~~ these important risks and other potential adverse reactions of carfilzomib ~~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

    An age-appropriate formulation will be used in the study(ies) described above.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1 Phase 2: A sample size of 100 subjects should provide 70% power for at least one phenotype. The power estimate is dependent on the assumptions around the odds ratio for complete response and the sample size in the external control for each phenotype. The details will be included in the statistical analysis plan.

  An interim analysis for futility will be conducted independently for each phenotype. Additional details will be included in the statistical analysis plan.

  The primary efficacy analysis should be performed based on the primary analysis set, defined as all patients who received at least 1 dose of carfilzomib. The analysis will be performed based on a 2-sided 5% alpha level and will evaluate whether after appropriate adjustment the 95% CI for Odds ratio (OR) between complete response rates of the treatment arm at the end of the Induction Cycle relative to a clinically relevant external control group excludes 1 or each phenotype (B-cell ALL /T-cell ALL) independently. The OR and 95% CI will be estimated via logistic regression model weighted with propensity score weighting for the average treatment effect in the treated (IPTW-ATT). No additional adjustment for multiplicity will be performed.

  The statistical analysis plan (SAP) will be submitted to FDA for review and agreement prior to study analysis. In addition to the primary efficacy analysis, the SAP will describe analyses which assess the comparability of the enrolled patients to the external control group, sensitivity of the results to key model assumptions including unmeasured confounding, and overall model fit.

Supportive analyses will be provided to further assess the primary endpoint of CR. For each cohort, the point estimate of CR and its 95% confidence interval will be provided. In addition, historical estimates of CR in patients treated with best available therapy will be provided via a literature search. Descriptive comparisons will be made in order to assess whether the proposed regimen provides benefit over available therapy.

- *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 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 April 18, 2025. 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 505(A)(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.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

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If you have any questions, contact Saumya Nathan, Regulatory Project Manager, at Saumya.Nathan@fda.hhs.gov.

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{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
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Phase 2: multicenter, non-randomized trial of carfilzomib in combination with VXLD for the treatment of pediatric patients with relapsed or refractory ALL.

☐ Efficacy in pediatric patients age 1 month-21 years cannot be extrapolated and will be determined by the studies outlined in the WR.

Study 2: Multicenter, retrospective cohort study of pediatric patients with relapsed and refractory T-cell and B-cell ALL.

- *Objective of each study:*

Study 1:

PRIMARY OBJECTIVES
Phase 1b

- To assess the safety and tolerability of carfilzomib in combination with induction chemotherapy, for the treatment of children with relapsed or refractory ALL
- To determine the RP2D of carfilzomib in combination with induction chemotherapy

Phase 2

- To compare the rate of bone marrow complete response (CR) of the treatment arm at the end of the Induction Cycle relative to a clinically relevant external control group

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Study 2:

Primary objective:

- To estimate the complete remission (CR) rate in patients with refractory or relapsed (first and subsequent) B-ALL, T-ALL treated with curative intent between 29-45 days of initiation of therapy (35-50 days for infants).

Secondary objectives:

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    Phase 2
    A minimum of 100 subjects will be enrolled.

A sample size of 100 was chosen to achieve at least 70% power for testing the primary hypothesis for at least one phenotype at a 2-sided alpha of 0.05 based on:

1. A minimum of 30 enrolled subjects will have refractory or relapsed T-cell ALL.
2. A minimum of 50 enrolled subjects will have post-immunotherapy relapsed or refractory relapsed B-cell ALL.

Study 2:
Data from a minimum of 310 patients with B-cell ALL and 100 patients with T-cell ALL will be collected and analyzed. For both cohorts, the patients in the external control arm will be selected such that the inclusion criteria are as similar as possible to the inclusion criteria of those enrolled in Study 1.

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 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 RP2D as defined by Cohort Safety Review Committee (CSRC) by evaluating all available data including: subjects clinical history, pharmacokinetics, tolerability, safety and efficacy data

    - ☐ The Phase 2 primary endpoint will be:
      - 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 2 portion, safety and tolerability of carfilzomib in combination with induction chemotherapy is an important secondary endpoint.

Study 1:

- ☐ *Safety endpoints:*
  - ☐ Safety outcomes of subjects treated with carfilzomib in combination with VXLD must include descriptive adverse events, including the incidence of

overall adverse events, of severe adverse events, of grade 3 or higher 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.

- ☐ The study protocol must include instructions for documenting 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. The study protocol must include instructions for and monitoring adverse events 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 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 for pharmacokinetic/ pharmacodynamic analyses to explore exposure-response relationships for clinical safety and efficacy endpoints.

- *Known drug safety concerns and monitoring:* The important identified risks of carfilzomib that have emerged in clinical studies include cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction, and cardiac arrest), pulmonary toxicities (acute respiratory distress syndrome [ARDS], acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease), pulmonary hypertension, dyspnea, hypertension including hypertensive crises, acute renal failure, hemorrhage and thrombocytopenia, tumor lysis syndrome (TLS), infusion reactions, hepatic toxicity, venous thromboembolism, hepatitis B virus (HBV) reactivation, thrombotic microangiopathy, and posterior reversible encephalopathy syndrome (PRES) and important potential risk of carfilzomib includes progressive multifocal leukoencephalopathy (PML). The study protocol must outline procedures for monitoring these important risks and other potential adverse reactions of carfilzomib.

- *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

    An age-appropriate formulation will be used in the study(ies) described above.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1 Phase 2: A sample size of 100 subjects should provide 70% power for at least one phenotype. The power estimate is dependent on the assumptions around the odds ratio for complete response and the sample size in the external control for each phenotype. The details will be included in the statistical analysis plan.

  An interim analysis for futility will be conducted independently for each phenotype. Additional details will be included in the statistical analysis plan.

  The primary efficacy analysis should be performed based on the primary analysis set, defined as all patients who received at least 1 dose of carfilzomib. The analysis will be performed based on a 2-sided 5% alpha level and will evaluate whether after appropriate adjustment the 95% CI for Odds ratio (OR) between complete response rates of the treatment arm at the end of the Induction Cycle relative to a clinically relevant external control group excludes 1 or each phenotype (B-cell ALL /T-cell ALL) independently. The OR and 95% CI will be estimated via logistic regression model weighted with propensity score weighting for the average treatment effect in the treated (IPTW-ATT). No additional adjustment for multiplicity will be performed.

  The statistical analysis plan (SAP) will be submitted to FDA for review and agreement prior to study analysis. In addition to the primary efficacy analysis, the SAP will describe analyses which assess the comparability of the enrolled patients to the external control group, sensitivity of the results to key model assumptions including unmeasured confounding, and overall model fit. Supportive analyses will be provided to further assess the primary endpoint of CR. For each cohort, the point estimate of CR and its 95% confidence interval

will be provided. In addition, historical estimates of CR in patients treated with best available therapy will be provided via a literature search. Descriptive comparisons will be made in order to assess whether the proposed regimen provides benefit over available therapy.

- *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 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 April 18, 2025. 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 505(A)(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.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 17, 2015, as amended by this letter and by previous amendments dated December 19, 2015; December 10, 2020; and November 14, 2022, must be submitted to the Agency on or before April 18, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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.

In accordance with section 505A(k)(1) of the Act, 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:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[2]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Saumya Nathan, Regulatory Project Manager, at Saumya.Nathan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[2] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA B DONOGHUE
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