NDA 205552

WRITTEN REQUEST – AMENDMENT 2

Pharmacyclics LLC
Attention: Preeti Sarde
Senior Manager Regulatory Affairs
995 E. Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Sarde:

Please refer to your correspondence dated August 10, 2020, requesting changes to FDA's December 17, 2018 Written Request and for pediatric studies for ibrutinib.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on May 18, 2018, and as amended on December 17, 2018, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- ***Patients to be studied***

Mature B-cell NHL

Study 3: will evaluate pediatric and young adult subjects (age 1 to 30 years, inclusive, with initial diagnosis of mature B-cell NHL at <18 years of age) with relapsed or refractory mature B-cell NHL. A minimum of 65 ~~70~~ pediatric subjects (age < 18 years) will be included in Study 3, including at least 6 subjects age 1 to <6 years, at least 12 subjects age 6 to <12 years, and at least 26 subjects age 12 to <18 years.

- ***Statistical information, including power of studies and statistical assessments:***

Mature B-cell NHL

Study 3: Approximately 72 subjects will be randomized in Part 2. The sample size calculation is based on the assumption of 100% improvement (hazard ratio = 0.5) in median EFS in subjects receiving ibrutinib plus chemoimmunotherapy (CIT; RICE or RVICI) compared with CIT (10 months versus 5 months). Utilizing a 2:1 randomization, and based on 60 events for the two treatment groups, this study will have at least 80% power, given a 1-sided alpha of 0.05. One interim analysis will be conducted when approximately 30 EFS events are reached in Part 2. An independent Data Monitoring Committee will review safety and efficacy data and will determine the appropriateness for early stopping. The Agency has been notified by the Sponsor and agrees with the

IDMC's recommendation that the statistical boundary has been crossed based upon the the interim analysis, as specified in the protocol for Study 3. The Agency has been notified of the plan to close study 3 to further enrollment. The Written Request is hereby amended to reflect the early closure of Study 3 due to futility.

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 May 18, 2018, as amended by this letter and by previous amendments dated December 17, 2018, must be submitted to the Agency on or before September 30, 2024, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) or 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.[1]

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, call Bernetta Lane, Regulatory Project Manager, at 301-796-0937.

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

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Acting Associate Director, Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

WRITTEN REQUEST

Pharmacyclics LLC
Attention: Tania Bekerman
Senior Manager Regulatory Affairs
995 E. Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Bekerman:

Reference is made to your Proposed Pediatric Study Request submitted on March 17, 2018 for ibrutinib.

BACKGROUND:
The following studies investigate the potential use of ibrutinib, in the treatment of pediatric patients with chronic graft versus host disease (cGVHD) and pediatric patients with non-Hodgkin lymphoma.

Chronic Graft versus Host Disease
Chronic GVHD is a serious and life-threatening impediment to the success of allogeneic hematopoietic cell transplantation (allo-HCT). Chronic GVHD is the leading cause of non-relapse mortality in allo-HCT and affects 30% to 70% of patients who survive past the first 100 days. Chronic GVHD is less common in children than in adults, nonetheless children represent a significant proportion of the overall cGVHD population and have substantial morbidity and mortality associated with the disease. Currently, there are no therapies indicated for the treatment of pediatric patients with cGVHD, and ibrutinib is the only therapy indicated for adult patients with cGVHD (after failure of one or more lines of systemic therapy). A significant proportion of children with cGVHD do not maintain sufficient disease control with existing treatments or experience toxicities that limit their effectiveness.

Mature B-cell NHL
In children, mature B-cell NHLs occur rarely, with the most common types being Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). Although these aggressive lymphomas are fatal in weeks to months if untreated, the cure rate in children with BL and DLBCL is between 85% to 90% after initial treatment. Relapsed or refractory disease following treatment with frontline pediatric B-cell NHL protocols is rare and is associated with poor prognosis, with survival rates of less than 20% at 2 years, underscoring the critical unmet medical need in this patient population.

Both chronic graft versus host disease and non-Hodgkin lymphoma are extremely rare in neonates, therefore the Agency is not requesting studies in neonates for either of these indications.

To obtain needed pediatric information on ibrutinib, 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): None.*

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

- *Clinical studies:*

Chronic Graft versus Host Disease
Study 1: Study PCYC-1140-IM, a randomized, double-blind, multicenter, international Phase 3 study of ibrutinib in combination with prednisone versus placebo in combination with prednisone in subjects with new onset cGVHD (including subjects ≥ 12 years of age).

Study 2: Study PCYC-1146-IM, an open-label, multicenter, Phase 1/2 dose finding, safety and efficacy study of ibrutinib in pediatric subjects (≥ 1 and < 22 years of age) with cGVHD. This study is divided in two parts: Part A (dose finding and safety in subjects ≥ 1 and < 12 years of age) and Part B (pharmacokinetics [PK], safety and efficacy in subjects ≥ 1 and < 22 years of age).
Efficacy extrapolation
Efficacy in Study 2 will be supported by data generated in adults and adolescents 12 years and older from studies PCYC-1129-CA and PCYC-1140-IM (Study 1). Given the similar clinical manifestations of cGVHD in adults and pediatrics, similarity of treatment effects, as well as the similarity of exposure-response relationships, the Sponsor will extrapolate efficacy. Supporting PK, pharmacodynamic (PD), safety, and efficacy data will be provided from a single pediatric study, PCYC-1146-IM (Study 2).

Mature B-cell NHL
Study 3: Study 54179060LYM3003, a randomized, open-label, safety and efficacy study of ibrutinib in pediatric and young adult patients ages 1 to 30 years with relapsed or refractory mature B-cell NHL. This study is divided in two parts: Part 1 (run-in part) and Part 2 (randomized part).

Efficacy in pediatric mature B-cell NHL cannot be extrapolated and will be determined by the studies outlined in the WR.

- ***Objective of each study***

Chronic Graft versus Host Disease

Study 1: To evaluate the efficacy of ibrutinib in combination with prednisone versus placebo in combination with prednisone based on the response rate at 24 weeks as determined by National Institutes of Health (NIH) Consensus Development Project Criteria in subjects with new onset moderate to severe cGVHD.

Study 2: Part A: To determine the recommended pediatric equivalent dose (RPED; based on PK and, if applicable, PD data) for use in pediatric subjects (age ≥ 1 and < 12 years) with cGVHD as defined by the 2014 NIH Consensus Development Project Criteria.

Part B To assess the PK and safety of ibrutinib in pediatric subjects (age ≥ 1 and < 22 years) with cGVHD.

Mature B-cell NHL

Study 3:
Part 1: To confirm that the PK in pediatric subjects is consistent with that in adults.
Part 2: To assess efficacy (event-free survival [EFS]) of ibrutinib in combination with rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone (RICE) or rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) background therapy compared to RICE or RVICI background therapy alone.

- ***Patients to be studied***

Chronic Graft versus Host Disease

Study 1: Adults and adolescents (age ≥ 12 years) with new onset cGVHD.

Study 2: ≥ 1 year to < 22 years

A minimum of 35 pediatric subjects age < 18 years will be enrolled across Study 1 and Study 2, including at least 3 subjects age 1 to <6 years, at least 6 subjects age 6 to <12 years, and at least 12 subjects age 12 to <18 years.

Study 1: ≥ 6 subjects (age 12 to < 22 years) with treatment-naïve cGHVD

Study 2:
Part A: ≥ 12 pediatric subjects (age 1 to < 12 years) with relapsed and refractory cGVHD, including at least 3 pediatric subjects age 1 to 6 years.
Part B: ≥ 10 and up to 32 subjects (age 1 to <22 years with treatment naïve or relapsed/refractory cGVHD.

Mature B-cell NHL
Study 3: will evaluate pediatric and young adult subjects (age 1 to 30 years, inclusive, with initial diagnosis of mature B-cell NHL at <18 years of age) with relapsed or refractory mature B-cell NHL. A minimum of 65 pediatric subjects (age < 18 years) will be included in Study 3, including at least 6 subjects age 1 to <6 years, at least 12 subjects age 6 to <12 years, and at least 26 subjects age 12 to <18 years.

- ***Study endpoints***

Chronic Graft versus Host Disease

Study 1*:* The primary endpoint is the response rate at 24 weeks. Response will be defined by the 2014 NIH Consensus Development Project Criteria (Lee et al, 2015).

Study 2:
Part A: The primary endpoint is the PK (area under the plasma concentration-time curve [AUC]) to determine the RPED of ibrutinib for use in pediatric subjects (age ≥ 1 and < 12 years) with cGVHD.
Part B: The primary endpoint is the PK (AUC) and safety (treatment-emergent adverse events [AEs] and laboratory abnormalities) of ibrutinib in pediatric subjects (age ≥ 1 and < 22 years) with cGVHD.

Mature B-cell NHL
Study 3: The primary endpoints for Part 1 are assessment of PK parameters (e.g., exposure [AUC], apparent plasma clearance [CL/F], apparent volume of distribution[Vd/F]), and the relationship between PK parameters and age or measure of body size. The primary endpoint for Part 2 is EFS.

Drug specific safety concerns:
The most common adverse reactions (≥ 20%) in adult patients with cGVHD were fatigue, bruising, diarrhea, thrombocytopenia, muscle spasms, stomatitis, nausea, hemorrhage, anemia, and pneumonia.

The most common adverse reactions (≥ 20%) in adult patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia.

- ***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 forms: include 140 mg capsules, 70 mg capsules, 140 mg tablets and 70 mg/mL oral suspension.
Route of administration: Oral
Regimen:

Chronic Graft versus Host Disease

Study 1*:* Ibrutinib 420 mg will be administered orally once daily.
Study 2:

- **Part A**: Subjects will receive daily oral ibrutinib starting at 120 mg/m^2 (equivalent to approximately 50% of the adult cGVHD dose calculated using mg/m^2), then 240 mg/m^2 (approximately 100% of the adult cGVHD dose). The dose will be increased after 14 days of treatment at 120 mg/m^2, provided there are no safety concerns. If analysis of PK data confirms sub-therapeutic exposure at the 50% dose level, then that dose level may be abandoned. Alternative dose levels may be explored, and the RPED may exceed 240 mg/m^2, based on actual PK observations.
- **Part B**: Subjects age < 12 years will receive daily oral ibrutinib at the RPED determined in Part A of the study. Subjects age ≥ 12 years will receive ibrutinib 420 mg orally once daily.

Mature B-cell NHL

Study 3*:*

- Part 1: Daily oral ibrutinib at a target dose of 329 mg/m^2 per day (up to a maximum of 560 mg per day). If exposures are lower than or exceed the target range set, the dose will be adjusted as appropriate.
- Part 2: Subjects will be randomized in a 2:1 ratio to treatment Arm A (daily oral ibrutinib 329 mg/m^2 or other dose as determined in Part 1, and RICE or RVICI background therapy) or treatment Arm B (RICE or RVICI background therapy only).

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

1. You develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (ie, receives approval);
2. The Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505(A)(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 compounded 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 compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding 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 studies and statistical assessments:***

Chronic Graft versus Host Disease
Study 1: Approximately 186 subjects will be randomized in a 1:1 ratio to receive either ibrutinib in combination with prednisone (Arm A) or placebo in combination with prednisone (Arm B). The null hypothesis is that the two treatment arms have the same response rate at 24 weeks, and the alternative hypothesis is that the response rates of the two arms are different.

Assuming a response rate of 30% at 24 weeks for Arm B, the sample size provides at least an 80% power to detect a 20% difference in the response rates at 24 weeks between the 2 treatment arms (Arm A – Arm B) at an alpha level of 5% (2-sided). Descriptive analyses for the subsets of adult and adolescent subjects will be performed.

Study 2: Descriptive statistics will be used to describe the response rate in pediatric subjects with cGVHD.

Pharmacokinetic/Pharmacodynamic Analysis: PK of ibrutinib may be determined using non-compartmental or population PK approaches. Data from all completed studies in adults and pediatrics should be used for PK-PD analysis to support extrapolation of efficacy in cGVHD and explore exposure-response relationships for safety and efficacy.

Mature B-cell NHL

Study 3: Approximately 72 subjects will be randomized in Part 2. The sample size calculation is based on the assumption of 100% improvement (hazard ratio = 0.5) in median EFS in subjects receiving ibrutinib plus chemoimmunotherapy (CIT; RICE or RVICI) compared with CIT (10 months versus 5 months). Utilizing a 2:1 randomization, and based on 60 events for the two treatment groups, this study will have at least 80% power, given a 1-sided alpha of 0.05. One interim analysis will be conducted when approximately 30 EFS events are reached in Part 2. An independent Data Monitoring Committee will review safety and efficacy data and will determine the appropriateness for early stopping. The Agency has been notified by the Sponsor and agrees with the IDMC's recommendation that the statistical boundary has been crossed based upon the the interim analysis, as specified in the protocol for Study 3. The Agency has been notified of the plan to close study 3 to further enrollment. The Written Request is hereby amended to reflect the early closure of Study 3 due to futility.

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505(A)(j) of the Act, regardless of whether the study(ies) demonstrate that ibrutinib 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 - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

- *Timeframe for submitting reports of the study(ies):*
  All of the final study reports for the above studies must be submitted to the Agency on or before 30 September 2024. 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 (ie, complete or partial response);
2. the status of the application (ie, withdrawn after the supplement has been filed or pending);
3. the action taken (ie, approval, complete response); or
4. the exclusivity determination (ie, 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, callBernetta Lane, Regulatory Project Manager, at 301-796-0937.

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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY H REAMAN
09/18/2020 04:07:28 PM