CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205552 – Original #2 SUPPL # HFD # 161

Trade Name Imbruvica® Tablets, 140 mg

Generic Name ibrutinib

Applicant Name Pharmacyclics, Inc.

Approval Date, If Known February 12, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 205552 – Original #1 Imbruvica was approved on 11/13/13 for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

The applicant submitted a list of published studies.
No statement was received from the sponsor indicating that the publicly available data would not independently support approval of the application.

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

PCYC-1102-CA entitled “A Phase 1b Fixed-dose Study of Bruton’s Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia”.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1: PCYC-1102-CA YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation # 1:PCYC-1102-CA YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

PCYC-1102-CA entitled “A Phase 1b Fixed-dose Study of Bruton’s Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia”.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 102688 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Diane Hanner
Title: Regulatory Project Manager
Date: February 12, 2014

Name of Office/Division Director signing form: Ann T. Farrell, M.D.
Title: Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DIANE C HANNER
02/12/2014

ANN T FARRELL
02/12/2014

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 205552- Originial #2 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DHP PDUFA Goal Date: 2/28/14 Stamp Date: 6/28/2013

Proprietary Name: Imbruvica

Established/Generic Name: ibrutinib

Dosage Form: Oral Capsule, 140 mg

Applicant/Sponsor: Pharmacyclics, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) For patients with chronic lymphocytic leukemia
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For patients with chronic lymphocytic leukemia (CLL) indication

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosing form; ☒ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

DIANE C HANNER
02/12/2014

pharmacyclics
995 EAST ARQUES AVENUE • SUNNYVALE • CA 94085-4521
P: 408-774-0330 • FAX: 408-774-0340 • WWW.PCYC.COM

DEBARMENT CERTIFICATION

Pharmacyclics, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

June 10, 2013

Urte Gayko, Ph.D.
Senior Vice President, Regulatory Affairs
Pharmacyclics, Inc.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205552 Original #2 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: IMBRUVICA Established/Proper Name: Ibrutinib (PCI-32765) Dosage Form: Oral Capsule, 140 mg		Applicant: Pharmacyclics, Inc. Agent for Applicant (if applicable):
RPM: CAPT Diane Hanner		Division: Division of Hematology (DHP)

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action February 14, 2014 • User Fee Goal Date is February 28, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Original #1 Approved on November/13/13

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☒ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

Breakthrough Therapy designation was given for chronic lymphocytic leukemia or small lymphocytic lymphoma with deletion of the short arm of chromosome 17 (del 17p).

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other- BURST-ASCO

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☒ Yes If, yes, NDA/BLA # and date exclusivity expires: Original #1 Approved on November 13, 2013
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date February 12, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	June 28, 2013; January 9, 2014 *via* e-mail
• Original applicant-proposed labeling	N/A
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert January 9, 2014 *via* e-mail ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	June 28, 2013
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	June 28, 2013 November 13, 2013 (final)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Proprietary Name Conditionally Accepted Letter- August 16, 2013 Proprietary Name Review-(DMEPA) August 16, 2013
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM Feb. 4, 2014; ☒ DMEPA August 1, 2013 ☒ DMPP/PLT (DRISK) January 22, 2014; ☒ OPDP (DDMAC) January 17, 2014; ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	August 23, 2013- RPM filing review ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan Designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	**February, 2014.** **10,5,4,3;** **January, 2014.** **27,23,22,16,14,8,7** **November, 2013** **14,8;** **October, 2013.** **31,29,28,23(2),22(2),21,18,17(2)** **16,15(2),11,10,7(3),4(2),1;** **September 2013.** **30,25,24 (2), 20(7),18, 16,** **13 (2),12(2),11(2),10,9,4,3;** **August 2013.** **27(2),26(2),23,21,20,16(3),** **14(2), 12,8(3),6, 2(2),1;** **July 2013.** **30, 29, 25,23(2), 22,19, 18;** **June 2013.** **28.**
❖ Internal memoranda, telecons, etc.	May 7, 2013
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg Pre-NDA CLL April 9, 2013 Pre-NDA-CMC April 9, 2013
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg EOP2-CLL September 26, 2012 EOP2-CLL July 26 , 2012 EOP2-CLL April 30, 2012 EOP2-CLL December 5, 2011
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	LCM – January 23, 2014 Midcycle- August 19, 2013
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	

Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None February 11, 2014
Division Director Summary Review *(indicate date for each review)*	☐ None February 11, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None February 11, 2014
PMR/PMC Development Templates *(indicate total number)*	☐ None 2 total (2 PMRs)
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Feb.11, 2014 Co-signed primary review dated Feb. 11, 2014
• Clinical review(s) *(indicate date for each review)*	Feb. 11, 2014 Aug. 5, 2013 –filing review
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 20 of Clinical Review Dated Feb. 11, 2014
Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None OSE- (DPV) II- Jan.10, 2014 DRISK Sept. 17, 2013
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested OSI Letters – Jan. 9, 2014; Nov. 21, 2013; Oct. 11, 2013; Sept. 11, 2013 Clinical inspection review Sept. 17, 2013

[6] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None Jan. 31, 2014. Co-signed primary review Jan. 31, 2014
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None Jan. 31, 2014. Co-signed primary review Jan. 31, 2014
Statistical Review(s) *(indicate date for each review)*	☐ None Jan. 31, 2014 Aug. 14, 2013 filing review
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None Nov.1, 2013 Co-signed primary review Nov. 1, 2013
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None Jan. 28, 2014 memo Co-signed Jan. 28, 2014 Nov.1, 2013 Co-signed primary review Nov. 1, 2013
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Jan. 28, 2014 memo Nov. 1, 2013 Aug. 15, 2013 filing review
DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None Aug. 21, 2013
• Supervisory Review(s) *(indicate date for each review)*	☐ None Aug. 20, 2013
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Aug. 20, 2013 Aug. 8, 2013-filing review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None Oct. 04, 2013
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None Oct. 18, 2013; Sept. 23, 2013, cosigned the primary reviews Dated: Oct. 18, 2013; and Sept. 23, 2013.
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None ONDQA Primary Reviews Oct. 18, 2013& Sept. 23, 2013 Jul. 25, 2013-filing review Bio pharm Sept. 26, 2013 filing review Bio pharm. -Jul. 30, 2013 filing review
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Jul. 9, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	N/A –See page 111-CMC review dated Sept. 23, 2013
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within 2 **years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: Oct.17, 2013 CMC review ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

From: Hanner, Diane
To: "Christine Salido"
Bcc: Kim, Tamy; Farrell, Ann T
Subject: Ibrutinib PI change- NDA 205552 -Original #2
Date: Monday, February 10, 2014 6:00:00 PM
Attachments: approved.docx

Hi Chris,

An error was found on the NDA 205552 (ibrutinib - Original #2) PI. The number of patients who discontinued treatment due to AEs is incorrect and it should be 5 (10%) instead of (b) (4) (b) (4) Please see the attached revised PI in track change format (see Section 6, page 8).

The current version reads as follows:

(b) (4)

The proposed version should read:

Five patients (10%) discontinued treatment due to adverse reactions in the trial (N=48). These included 3 patients (6%) with infections and 2 patients (4%) with subdural hematomas.

Basis for change:

Subject ID	Adverse Event Leading to Discontinuation
032-102	Subdural hematoma
032-104	Sepsis (death 2 days after drug withdrawal due to infection)
320-401	Gram positive bacteremia (death 15 days after drug withdrawal due to systemic inflammatory response syndrome)
217-105	Multiple infections/AEs (C. difficile infection, dehydration, diarrhea, acute cystitis, generalized weakness, orthostatic hypotension)
123-101	Subdural hematoma, hemorrhage, burr hole procedure

Per our phone conversation, I appreciate your willingness to turn this around by tomorrow a.m.
Thank you.
Regards,
Diane

CAPT Diane Hanner
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FAX (301) 796-9845

E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
02/10/2014

From:	Hanner, Diane
To:	"Christine Salido"
Subject:	IR 2-5-14-response: Please concur with the PMR language regarding NDA 205552 (ibrutinib)- Original #2
Date:	Wednesday, February 05, 2014 4:54:00 PM

Yes!
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Wednesday, February 05, 2014 3:56 PM
To: Hanner, Diane
Subject: RE: response: Please concur with the PMR language regarding NDA 205552 (ibrutinib)- Original #2

Thank you Diane,
Are these considered final and I can now submit to the NDA?

Thank you!
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Wednesday, February 05, 2014 12:44 PM
To: Christine Salido
Subject: RE: response: Please concur with the PMR language regarding NDA 205552 (ibrutinib)- Original #2

Hi,
Your proposed change is acceptable.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Wednesday, February 05, 2014 3:31 PM
To: Hanner, Diane
Subject: response: Please concur with the PMR language regarding NDA 205552 (ibrutinib)- Original #2
Importance: High

Hi Diane,
We agree with the following PMR language but would like to make one clarification noted below.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Wednesday, February 05, 2014 10:04 AM
To: Christine Salido
Subject: Please concur with the PMR language regarding NDA 205552 (ibrutinib)- Original #2
Importance: High

Hi Chris,

Please let me know if you concur with the following PMR language, and if we have an agreement then we will consider this to be the final PMR language.

mit the results of the completed randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 391 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Protocol Submission: Completed (01/2014)
Completion: Completed (01/2014)
Final Report Submission: 06/2014

plete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 578 patients was completed (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Protocol Submission: Completed (09/2013)
Completion: 07/2016
Final Report Submission: 11/2016

Thanks,
Regards,
Diane

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/s/

DIANE C HANNER
02/05/2014

From:	Hanner, Diane
To:	"Christine Salido"
Subject:	NDA 205552 Original #2 CLL (ibrutinib) PI
Date:	Tuesday, February 04, 2014 1:09:00 PM
Attachments:	draft-label-text - CLL draft sent to sponsor 2-4-14.docx
Importance:	High

Hi Chris,

Please click on the attachment and view the NDA 205552 (ibrutinib) CLL label (PI).

Upon completion of your review please accept those changes that you agree with and remember to make all of your changes in tracked changes mode.

Please send me the revised version of the label by 9a.m. –EST- Thurs. 2/6/14.

Thank you.

Regards,
Diane

P.S.
The PPI "Revised: 02/2014" was accepted by the team. The PPI was not sent back to you since this was the only revision noted.

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DIANE C HANNER
02/04/2014

From:	Hanner, Diane
To:	"Christine Salido"
Subject:	FW: Response: Information regarding the NDA 205552/ Original CLL - PMR that will need to have sponsor concurrence
Date:	Monday, February 03, 2014 5:01:00 PM

Hi Chris,
Per our conversation, I need you to re-visit the PMR information that is highlighted below and please provide the dates.

PMR - CONFIRMATORY TRIAL– [redacted (b) (4)] submit the results of the [redacted (b) (4)] randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. [redacted (b) (4)] The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Protocol Submission: Complete
Study/Trial Completion: 01/14
Final Report Submission: 06/14

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

PMR- CONFIRMATORY TRIAL– Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. [redacted (b) (4)] The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Protocol Submission: Complete
Study/Trial Completion: 07/16
Final Report Submission: 11/16

Thank you.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Thursday, January 23, 2014 4:06 PM
To: Hanner, Diane
Subject: Response: Information regarding the NDA 205552/ Original CLL - PMR that will need to have sponsor concurrence

Hi Diane,
Pharmacyclics has no edits and accepts both PMR-9 and PMR-10 as listed below.

Thank you,
Chris

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/s/

DIANE C HANNER
02/03/2014

From:	Hanner, Diane
To:	"Christine Salido"
Subject:	NDA 205552 Original #2 CLL (ibrutinib) PI and PPI
Date:	Monday, January 27, 2014 2:23:00 PM
Attachments:	draft-label-text - 1102 CLL draft 1-27-14.docx ibrutinib (IMBRUVICA) 205552 DMPP OPDP PPI Jan-2014 marked.docx
Importance:	High

Hi Chris,

Please click on the attachments and view the NDA 205552 (ibrutinib) CLL label (PI) and PPI.

Upon completion of your review please accept those changes that you agree with and remember to make all of your changes in tracked changes mode.

Please note that the PI numbering needs to be fixed.

Please send me the revised version of the label by 12:00 p.m., Noon- EST, Thursday, Jan 30.

Thank you.

Regards,
Diane

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DIANE C HANNER
01/27/2014

From: Hanner, Diane
To: "Christine Salido"
Subject: Information regarding the NDA 205552/ Original CLL - PMR that will need to have sponsor concurrence
Date: Thursday, January 23, 2014 11:44:00 AM

Hi Chris,

Please review the PMRs below and please concur by e-mail regarding your acceptance of the

NDA 205552/ ibrutinib –Original #2 PMRs

2060-9 PMR-9: CONFIRMATORY TRIAL– (b) (4) submit the results of the (b) (4) randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission: Complete

Study/Trial Completion: 01/14

Final Report Submission: 06/14

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

2060-10 PMR-10: CONFIRMATORY TRIAL– Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission: Complete

Study/Trial Completion: 07/16

Final Report Submission: 11/16

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

Successful completion of either PMR 9 or PMR 10 could be considered to convert the accelerated approval to regular approval for the Chronic Lymphocytic Leukemia (CLL) indication.

Thank you,

Regards,

Diane

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/s/

DIANE C HANNER
01/23/2014

From: Hanner, Diane
To: "Christine Salido"
Subject: Preamble and PMRs regarding NDA 205552 (ibrutinib)- Original #2
Date: Thursday, January 16, 2014 3:11:00 PM

Hi Chris,

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the previously sent clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later

Some things you can do to expedite this process:
1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:
a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly.

******

Please provide your feedback regarding this NDA 205552 (ibrutinib) – Original #2- CLL indication-
DRAFT PMR listed below and please be sure to include the date information (MM/YYYY).

PMR (F) Description: (b) (4) submit the results of the randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or

relapsed or refractory small lymphocytic lymphoma. [redacted] (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

PMR Schedule Milestones:	Final Protocol Submission:	Completed
	Trial Completion:	Sponsor to propose dates in the form of month/year
	Final Report Submission:	MM/YYYY
		MM/YYYY

PMR (G) Description:

Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. [redacted] (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Completed
	Trial Completion:	Sponsor to propose dates in the form of month/year
	Final Report Submission:	MM/YYYY

Thank you
Regards,
Diane

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/s/

DIANE C HANNER
01/16/2014

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, January 14, 2014 11:34 AM
To: 'Christine Salido'
Subject: NDA 205552- Original #2 (ibrutinib) Information Request

Hi Chris,

Please submit the topline efficacy and safety results of clinical trial PCYC-1112, including DMC minutes, FDA-requested subgroup analyses, and timeline for sNDA submission, to NDA 205552 Original-2.
Thank you.
Regards,
Diane

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/s/

DIANE C HANNER
01/14/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 205552

Pharmacyclics Inc.
Attention: Christine Salido
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Re: Request to submit the PSUR to fulfill the periodic safety reporting requirement under 21 CFR 314.80(c)(2) and request to be waived of the requirement to submit ICSRs for nonserious, labeled adverse events

Dear Ms. Salido:

In your letter dated November 26, 2013, you have requested that Pharmacyclics, Inc. (Pharmacyclics) be waived of certain postmarket reporting responsibilities under 21 CFR 314.80(c)(2). Specifically, you have asked for two waivers: (1) to be allowed to submit the International Conference on Harmonization (ICH) E2C(R1) Periodic Safety Update Report (PSUR) in lieu of the periodic adverse drug experience report (PADER) required under our present regulations at 21 CFR 314.80(c)(2) and (2) to be waived of the requirement to submit individual case safety reports (ICSRs) for nonserious, labeled adverse events. Your requests pertain to Pharmacyclics' approved new drug application (NDA) 205552 Imbruvica (ibrutinib) capsules.

I note that your November 26, 2013 letter also contained a request to alter the submission schedule of reports for Postmarket Requirement (PMR) 2060-4. The Agency will address this request in a separate response.

Waiver request #1: to substitute the PSUR for the PADER with changes in report frequency

In addition to the format change, you have proposed to change the frequency of submission. You proposed to base the DLP on the November 13, 2013 US approval date. You also requested to be waived of the requirement under 21 CFR 314.80(c)(2)(i) to submit your reports on a quarterly basis, but instead proposed to submit them every six months for the first four years post approval. In your December 16, 2013 email correspondence with Mrs. Maureen Melvin of my staff you confirmed that Pharmacyclics would submit quarterly PADERs in the intervening quarters of the 6-month PSUR. You would submit the first 6-month PSUR covering the reporting interval from November 13, 2013 to May 12, 2014.

You proposed to continue semi-annual submissions through the reporting interval that ends on November 12, 2017. Thereafter, you would submit annual PSURs covering the reporting interval

from November 13 through November 12 of the following calendar year. As recommended in the PSUR guideline, you have proposed to submit the PSUR within 60 calendar days of the DLP.

Waiver request #2: to no longer submit ICSRs for nonserious, labeled adverse events
You requested to be waived of the requirement under 21 CFR 314.80(c)(2)(ii)(*b*) to submit, as part of your postmarket periodic safety reporting responsibilities, ICSRs for each adverse experience that is determined to be both non-serious and labeled.

I note the written commitments in your letter: (1) to hold in your corporate drug product safety files the individual case reports of adverse experiences that are both non-serious and labeled, (2) to continue to include the non-serious, labeled adverse experiences in each periodic safety report you submit to FDA for this NDA, in the section that includes a summary tabulation by body system of all adverse experience terms and counts of occurrences submitted during the reporting period, and (3) to submit these individual case reports to FDA within five calendar days after receipt of a request by FDA to do so.

Our response to your two waiver requests:

Based upon our review of the proposals stated in your letter and in you subsequent communications with my staff, I concur that these modifications to your postmarket reporting responsibilities are acceptable at this time for the following approved application:

NDA 205552 Imbruvica (ibrutinib) capsules

Therefore, as of the date of this letter and per 21 CFR 314.90(b), you may submit the PSUR to fulfill the periodic reporting requirement described under 21 CFR 314.80(c)(2), provided that you abide by the conditions listed below. Please note that the waiver of the requirement to submit ICSRs for non-serious, labeled cases is included in condition (4).

(1) The PSUR is prepared according to the guideline developed by the International Conference on Harmonisation (ICH) designated as ICH-E2C and published in the Federal Register on 19 May 1997 [62 FR 27470] and the Addendum to E2C published in the Federal Register on 05 February 2004 [69 FR 5551].

(2) The PSUR for this product is submitted every six months (May 12 and November 12 DLP) through the reporting interval that ends on November 12, 2017, and annually thereafter (November 12 DLP). The first 6-month PSUR will cover the reporting interval from November 13, 2013 through May 12, 2014. The first annual (12-month) PSUR will cover the reporting interval from November 13, 2017 through November 12, 2018. The PSURs will be submitted within 60 calendar days of the DLP.

(3) You submit 3-month PADERs for the intervening quarters of the 6-month cycle (August 12 and February 12 DLPs). You prepare the PADER per our regulations at 21 CFR 314.80 (c)(2), and you submit the PADER within 30 calendar days of the PADER DLPs (August 12 and February 12).

(4) You submit, at the time you submit your PSUR, the ICSRs that you are required to submit as part of a periodic safety report under 21 CFR 314.80(c)(2). You are, however, waived of the requirement to include with the PSUR the ICSRs for adverse experiences that are determined both to be non-serious and to appear in the current labeling for the drug product. You should maintain records of these non-serious, labeled adverse experiences in your corporate drug product safety files. FDA does reserve the right to request these individual case safety reports for the non-serious, labeled adverse experiences and expects that you would send them to us within five calendar days of such a request. Information on these adverse experiences should be submitted in the section that includes a summary tabulation by body system of all adverse experience terms and counts of occurrences submitted during the reporting period.

(5) You submit at the time you submit the PSUR, a narrative that references any changes you believe appropriate, based on the new information received in the reporting period, in your approved U.S. labeling for NDA 205552. Please also include a copy of the most recently approved U.S. labeling for NDA 205552, or include a reference to the section of the eCTD module where this information is readily available.

Additional information regarding the submission of the PSUR and associated ICSRs

Please note that a postmarket periodic safety report submission is comprised of both a descriptive portion and the non-expedited ICSRs received during the reporting interval of the periodic safety report. Each part may be submitted electronically or on paper. You will submit the PBRER as the descriptive portion and submit it to each of the application(s) covered in the report.

For information on how to electronically submit the descriptive portion, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/%20FormsSubmissionRequirements/%20ElectronicSubmissions/ucm153574.htm. For information on how to electronically submit the non-expedited ICSRs, please see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ %20Surveillance/AdverseDrugEffects/ucm115894.htm and http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20Regulatory%20Information/Guidances/UCM072369.pdf.

If you are submitting either the descriptive portion or the non-expedited ICSRs on paper, please submit two copies to:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please do not submit any copies of ICSRs that were previously submitted. We do ask that you include in the PBRER a list of ICSRs that were previously submitted during the reporting interval and their dates of submission.

The waivers outlined in this letter will be in effect until you are notified that they have been discontinued. Also, please note that this letter in no way affects your other reporting responsibilities under our regulations, except as specifically outlined in this letter.

If you have any questions, please contact Mrs. Maureen Melvin, Regulatory Analyst at (301) 796-2380.

Sincerely,

{See appended electronic signature page}

Gerald Dal Pan, M.D., M.H.S.
Director
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

GERALD J DALPAN
01/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

MEETING MINUTES

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Imbruvica ™ ibrutinib (PCI-32765).

The teleconference meeting was held on Monday, January 6, 2014. The purpose of the meeting was to discuss the newly received ibrutinib -Phase 3 data in support of an NDA ibrutinib indication for the treatment of patients with chronic lymphocytic leukemia (CLL).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C

Meeting Category: NDA (Teleconference) meeting- Guidance

Meeting Date and Time: January 6, 2014, at 2:00 p.m.

Meeting Location: CDER WO 5266

Application Number: NDA 205552

Product Name: Ibrutinib (PCI-32765)

Indications: Chronic Lymphocytic Leukemia (CLL)

Sponsor/Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo de Claro, M.D.

Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Richard Pazdur, M.D., Office Director, Office of Hematology and Oncology Products
- Ann Farrell, M.D., Director, DHP
- Robert Kane, M.D., Deputy Director Safety, DHP
- Qin Ryan, M.D., Ph.D., Medical Officer for Safety, DHP
- R. Angelo de Claro, M.D., Team Leader, DHP
- Karen McGinn, M.S.N., CRNP, Senior Clinical Analyst, DHP
- Nicole Verdun, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Lie Nie, Ph.D., Statistical Team Leader, DB 5
- Lara Akinsanya, MS, Regulatory Project Manager (Acting Team Leader)
- Diane Leaman, BS, MT(ASCP), Safety Regulatory Project Manager

- Tamy Kim, Pharm.D., Associate Director of Regulatory Affairs, OHOP
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES:

- Urte Gayko, Ph.D., Senior Vice President, Regulatory Affairs, Pharmacyclics
- Bob Duggan, Chief Executive Officer and Chairman of the Board, Pharmacyclics
- Maky Zanganeh, D.D.S., Chief Operating Officer, Pharmacyclics
- Maria Fardis, Ph.D., M.B.A., Chief of Oncology Operations and Alliances, Pharmacyclics
- Jesse McGreivy, M.D., Chief Medical Officer, Pharmacyclics
- Fong Clow, Sc.D., Vice President, Biometrics, Pharmacyclics
- Linda Gau, Associate Director, Statistical Programming, Pharmacyclics
- Craig Tendler, M.D., Vice President, Late Development & Global Medical Affairs, Janssen R&D, LLC
- Surya Mohanty, Ph.D., Head of Clinical Biostatistics, Janssen R&D, LLC
- Sandra Rattray, Ph.D., Vice President, Head of Janssen Oncology Regulatory, Janssen R&D, LLC
- Chris Salido, B.S., Executive Director, Regulatory Affairs, Pharmacyclics

1.0 BACKGROUND

The Agency and the Sponsor agreed to have a teleconference meeting on January 6, 2014, to discuss the Imbruvica ™ (ibrutinib), NDA 205552 application, for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

The FDA received information from the Sponsor *via* e-mail on January 4, 2014, regarding the study PCYC-1112. The teleconference meeting was held to discuss the interim analysis and the steps forward regarding the CLL application since the sponsor is planning on un-blinding the study.

2.0 DISCUSSION

1. The Agency discussed with the Sponsor that the decision to unblind the Phase 3 clinical trial, PCYC-1112, and the consequences with the unblinding of the clinical trial would be solely the Sponsor's responsibly. However, the Agency had no objections to the Sponsor's proposal to unblind clinical trial PCYC-1112.

   The Sponsor acknowledged that the unblinding of clinical trial PCYC-1112 is the Sponsor's responsibility.

2. The Agency recommended that the Sponsor submit revised labeling by January 9, 2014. The Agency recommended that the labeling for the CLL indication be based upon the primary efficacy and safety analysis of 48 patients as originally discussed.

3. The Agency requested that the Sponsor submit a pre-sNDA meeting request for a supplemental application based on PCYC-1112. The Agency recommended that the Sponsor submit the sNDA after regulatory action for the current application (NDA 205552 Original-2).

3.0 ACTION ITEMS

The following information request was sent to the sponsor immediately after the teleconference meeting.

Clinical Trial PCYC 1102-CA

1. Submit SAS programs used to generate the analysis datasets (adefirc.xpt and adtteirc.xpt) for the IRC assessment of PCYC-1102-CA. Submit by COB today.

2. Submit updated labeling that includes CLL data from PCYC-1102-CA. The primary efficacy and safety population would be the 48 patients with previously treated CLL who received ibrutinib at the 420 mg/day level. Do not include the additional efficacy follow-up from the extension trial (1103-CA) in the labeling. Submit by COB Thursday 1/9/14.

Clinical Trial PCYC 1112

3. Submit PFS analysis tables subgrouped according to 17p deletion status.

4. Submit response rate results (ORR, CR, PR) for both treatment arms. Include subgroup analysis according to 17p deletion status.

Submit #3 and #4 by COB Friday 1/10/14.

4.0 ATTACHMENTS AND HANDOUTS

There were no additional attachments or handouts at the meeting.

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/s/

DIANE C HANNER
01/07/2014

ROMEO A DE CLARO
01/07/2014

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, November 14, 2013 2:53 PM
To: 'Christine Salido'
Subject: FW: Imbruvica; Ibrutinib; NDA 205552; Comments

Hi Chris,

1. Submit the final study report for trial PCI-32765CLL1001 entitled, "An Open-Label, Randomized, 4-Way Crossover Study to Determine the Effect of Food on the Pharmacokinetics of PCI-32765".
2. We recommend you evaluate lower doses of ibrutinib in future clinical development as data from the Phase 1 trial PCYC-04753 showed that maximum BTK occupancy and maximum response were achieved at doses of $\geq$ 2.5 mg/kg.
3. The potential for ibrutinib to inhibit transporters has not been evaluated. We recommend that you evaluate, in vitro, the potential for ibrutinib to inhibit transporters such as BCRP, OATP1B1/OATP1B3, OCT2, OAT1 and OAT3.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
11/14/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, November 08, 2013 2:12 PM
To: 'Christine Salido'
Subject: FW: response: NDA 205552 ibrutinib: MCL label - one additional QC edit
Attachments: draft-label-text - to be sent to the sponsor 10-29-13 CS 110713 clean copy.docx; draft-label-text - to be sent to the sponsor 10-29-13 CS 110713 tracked changes.docx

Importance: High

Hi Chris,
Please send the attached label in officially and we will consider this to be final agreed upon labeling for NDA 205552.
Have a great weekend.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, November 08, 2013 11:08 AM
To: Hanner, Diane
Subject: response: NDA 205552 ibrutinib: MCL label - one additional QC edit
Importance: High

Hi Diane,
Happy Friday! Do you anticipate completing your QC review and/or giving final approval of the MCL label today? Our team is anxiously standing by. If not today, I believe Monday 11/11 is a holiday (Pharmacyclics will be open for business) therefore would the next possibility be on Tuesday 11/12?

I am working offsite today so please feel free to call me at (b) (6) anytime.

Thank you
Chris

From: Christine Salido
Sent: Thursday, November 07, 2013 11:51 AM
To: 'Hanner, Diane'
Subject: response: NDA 205552 ibrutinib: MCL label - one additional QC edit
Importance: High

Hi Diane,
We found one minor QC edit in section 13.1 (see below) for your consideration. I have attached a tracked changes version and a clean version for your reference.

Thank you,
Chris

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay (b) (4) in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

From: Christine Salido
Sent: Monday, November 04, 2013 3:13 PM
To: 'Hanner, Diane'
Subject: response: NDA 205552 ibrutinib: MCL label - one additional QC edit
Importance: High

Hi Diane,
Attached is a copy of the MCL label (tracked changes and clean versions) incorporating the edit below.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Monday, November 04, 2013 7:30 AM
To: Christine Salido
Subject: FW: NDA 205552 ibrutinib: MCL label - one additional QC edit

Hi,
The proposed edits are acceptable.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Saturday, November 02, 2013 1:39 PM
To: Hanner, Diane
Subject: NDA 205552 ibrutinib: MCL label - one additional QC edit

Hi Diane,
Would it be possible under section 6 of the MCL label to add a reference to Table 2? There should be a reference to both Table 1 and to Table 2 because the listed hem tox are listed in Table 2 not in Table 1. See below and the attached MCL label in tracked changes.

"The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (See Tables 1 and 2).

Thank you,

Christine Salido
Regulatory Affairs
Pharmacyclics, Inc.
408-215-3039

csalido@pcyc.com

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DIANE C HANNER
11/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

MEETING MINUTES

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ibrutinib (PCI-32765).

FDA requested to have a face to face meeting with Pharmacyclics, Inc. This meeting was held on Wednesday, October 9, 2013. The purpose of the meeting was to discuss the issues identified during the review specifically regarding the efficacy data in support of an NDA ibrutinib indication for the treatment of patients with chronic lymphocytic leukemia (CLL).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C

Meeting Category: NDA meeting

Meeting Date and Time: October 9, 2013, at 9:00 a.m.

Meeting Location: CDER WO 1309

Application Number: NDA 205552

Product Name: Ibrutinib (PCI-32765)

Indications: Mantle Cell lymphoma (MCL)
Chronic Lymphocytic Leukemia (CLL)

Sponsor/Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo de Claro, M.D.

Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Richard Pazdur, M.D., Office Director, Office of Hematology and Oncology Products
- Jonathan Jarow, M.D. Medical Officer, DOP1
- Ann Farrell, M.D., Director, DHP
- Edvardas Kaminskas, M.D., Deputy Director, DHP
- Robert Kane, M.D., Deputy Director Safety, DHP
- Qin Ryan, M.D., Ph.D., Medical Officer for Safety, DHP
- R. Angelo de Claro, M.D., Team Leader, DHP
- Karen McGinn, M.S.N., CRNP, Medical Officer, DHP
- Nicole Verdun, M.D., Medical Officer, DHP
- Tanya Wroblewski, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Nie Lie, Ph.D., Team Leader, DB 5
- Bahru Habtemariam, Pharm.D., Clinical Pharmacology Reviewer, DCP5

- Brian Booth, Ph.D., Deputy Director, Office of Clinical Pharmacology, DCP5
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES:

- Urte Gayko, Ph.D., Senior Vice President, Global Regulatory Affairs, Pharmacyclics
- Bob Duggan, Chief Executive Officer and Chairman of the Board, Pharmacyclics
- Jesse McGreivy, M.D., Chief Medical Officer, Pharmacyclics
- Maria Fardis, Ph.D., M.B.A., Chief of Oncology Operations and Alliances, Pharmacyclics
- Fong Clow, Sc.D., Vice President, Biometrics, Pharmacyclics
- Danelle James, M.D., M.S., Senior Medical Director, Pharmacyclics
- John Seaman, Pharm.D., Senior Director, Global Regulatory Affairs, Janssen R&D, LLC
- Mann Fung, M.D., Vice President, Compound Development Team Leader, Janssen R&D, LLC
- Sen Hong Zhuang, M.D., Ph.D., Vice President, Clinical Research, Janssen R&D, LLC
- Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Janssen R&D, LLC
- Steven Sun, Ph.D., Director, Biostatistics, Janssen R&D, LLC
- Peter Lebowitz, M.D., Ph.D., Global Therapeutic Area Head (Oncology), Janssen R&D, LLC
- Bill Hait, M.D., Ph.D., Global Head (Pharmaceutical), Janssen R&D, LLC
- (b) (4)
- (b) (4)
- (b) (4)
- Chris Salido, B.S., Executive Director, Regulatory Affairs, Pharmacyclics (call in)
- Maky Zanganeh, DO, Chief Operating Officer, Pharmacyclics (call in)
- (b) (4)
- Mann Fung, M.D., Janssen R&D, LLC, Vice President, Compound Development Team Leader
- (b) (4)

1.0 BACKGROUND

The FDA requested a meeting to discuss the PCI-32765 (ibrutinib) NDA 205552 application, for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

The FDA issues to be discussed were forwarded to the Sponsor on October 4, 2013, and the Sponsor's responses were received *via* e-mail on October 7, 2013, and the meeting was held on October 9, 2013.

2.0 DISCUSSION

1. The Agency discussed with the Sponsor the concerns with the single arm CLL trial submitted for registration, including the following:

- **Small numbers of patients at the proposed dose (n=48) in a common leukemia**
- **Issues with interpretation of the response criteria in the protocol**
- **Unclear statistical analysis plan for efficacy prior to trial initiation**
- **No independent verification of radiologic assessments**

2. The Agency requested clarification whether the CLL study was initially intended for registration purposes. The Sponsor stated that the study was not initially intended for registration.

3. The Agency suggested that the Sponsor consider the submission of data from other ongoing clinical trials to support the CLL indication given the flaws with the current clinical package. The Sponsor stated that they would consider revising the clinical package for the CLL indication and submit a proposal and a timeline to the Agency for review.

3. The Agency discussed the issues with the interpretation of the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria in the setting of the baseline characteristics of the patients enrolled in the CLL trial submitted for registration purposes. The Sponsor agreed that the 2008 IWCLL response criteria are confusing in certain areas and acknowledged outside consultation with the authors to gain clarity. The Sponsor stated that the authors of the IWCLL criteria will re-evaluate the criteria and consider publication of revised criteria in the next several months to clarify.

4. The Agency stated that the review for the MCL indication will be completed earlier than the review for the CLL indication, and that the Agency plans to split the NDA to allow for different action dates per indication.

3.0 ATTACHMENTS AND HANDOUTS

There were no additional attachments or handouts at the meeting.

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/s/

DIANE C HANNER
10/29/2013

ROMEO A DE CLARO
10/31/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, October 29, 2013 7:00 PM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib) PI and PPI -Revised 10-29-13

Hi Chris,

Please click on the attachments and view the revised NDA 205552 (ibrutinib) MCL label and PPI.

Upon completion of your review please make sure that the PI font and spacing are correct.
The font on the PPI is acceptable.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/30/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, October 28, 2013 5:21 PM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib) PI and PPI -Revised 10-28-13

Hi Chris,

Please click on the attachments and view the revised NDA 205552 (ibrutinib) MCL label and PPI.

Upon completion of your review please accept those changes that you agree with and remember to make all of your changes in tracked changes mode.

Once I receive your revised version then we can discuss what needs to be done regarding the "final version" of the label.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/28/2013

From:	Hanner, Diane
To:	"Christine Salido"
Subject:	NDA 205552 (ibrutinib) PI and PPI -Revised 10-23-13
Date:	Wednesday, October 23, 2013 5:57:00 PM
Attachments:	draft-label-text - to be sent to the sponsor 10-23-13.docx ibrutinib (PPI) 205552 - 10-23-13.docx

Hi Chris,

Please click on the attachments and view the revised NDA 205552 (ibrutinib) MCL label and PPI.

Upon completion of your review please accept those changes that you agree with and remember to make all of your changes in tracked changes mode.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/23/2013

From:	Hanner, Diane
To:	Martin, Jewell; Usha Ramesh
Cc:	Christine Salido
Subject:	RE: NDC listing
Date:	Wednesday, October 23, 2013 5:36:00 PM

Hi,
No! Please don't send the revised carton and bottle labels in just yet.
Thank you.
Regards,
Diane

From: Martin, Jewell
Sent: Wednesday, October 23, 2013 5:08 PM
To: Usha Ramesh
Cc: Hanner, Diane; Christine Salido
Subject: RE: NDC listing

Usha,

This question falls under Diane's purview, I will let her answer.

Jewell

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Wednesday, October 23, 2013 4:51 PM
To: Martin, Jewell
Cc: Hanner, Diane; Christine Salido
Subject: RE: NDC listing
Importance: High

Hi Jewell,
Could you inform us if the carton and bottle labels have to be submitted to the NDA?
Thank you
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Martin, Jewell [mailto:Jewell.Martin@fda.hhs.gov]
Sent: Wednesday, October 23, 2013 1:47 PM
To: Usha Ramesh
Cc: Hanner, Diane; Christine Salido
Subject: RE: NDC listing

Hello Usha,

I do not believe [redacted] sales needs to be included in the NDC listing; however, I would recommend contacting eDRLS@fda.hhs.gov for further information. Additionally, the revised labels appear acceptable.

Best,

Jewell

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Tuesday, October 22, 2013 12:22 PM
To: Martin, Jewell
Cc: Hanner, Diane; Christine Salido
Subject: NDC listing
Importance: High

Hi Jewell,

I have a question regarding the drug listing of ibrutinib in the FDA directory. As you are aware the drug substance is manufactured by [redacted] However [redacted] does the invoicing for the drug substance. Currently [redacted] is not listed in the NDA as they are not a manufacturer of drug substance. Should we include [redacted] in the NDC listing? I'd appreciate your prompt feedback on this.

Thank you
Best regards
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

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/s/

DIANE C HANNER
10/23/2013

From: Christine Salido
To: Hanner, Diane
Subject: RE: NDA 205552- ibrutinib- Labeling Instruction
Date: Tuesday, October 22, 2013 5:38:08 PM

Thanks Diane, I will make sure this is done.
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Tuesday, October 22, 2013 2:34 PM
To: Christine Salido
Subject: NDA 205552- ibrutinib- Labeling Instruction

Hi Chris,

Please make sure that in Section 2 of the PI, that you spell out all the symbols (e.g., "≥" should be "greater than or equal to").

Thanks.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/22/2013

From: Hanner, Diane
To: "Christine Salido"
Subject: 10-22-13 -NDA 205552 (ibrutinib) Revised PI and PP
Date: Tuesday, October 22, 2013 5:11:00 PM
Attachments: ibrutinib (PPI) 205552 to be sent to the sponsor 10-22-13..docx
draft-label-text - to be sent to the sponsor 10-22-13.docx

Hi Chris,

Please click on the attachments and view the NDA 205552 (ibrutinib) MCL label and PPI.

Upon completion of your review please accept those changes that you agree with and remember to make all of your changes in tracked changes mode.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

ADVICE/INFORMATION REQUEST

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application Original 2, (NDA 205552), Ibrutinib (PCI-32765).

We also refer to your submission dated October 15 2013, and received October 16, 2013, regarding your Chronic Lymphocytic Leukemia (CLL) proposal. We have carefully reviewed your proposals and have the following comments:

1. For Study 1102, we agree with the proposed information for submission. We agree with the independent review of the response evaluation for all patients treated on the Phase 2 study (1102-CA) and the long term extension study (1103-CA)
2. For Study 1117, we request that you submit data for all patients enrolled. (b) (4)
3. For Study 1112, we decided that the interim results will not be useful for our decision-making process. Therefore do not submit these interim results.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

DIANE C HANNER
10/21/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, October 18, 2013 4:51 PM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib) PMC/PMR for MCL indication.

Hi Chris,
Please take a second look at the PMC/PMRs – NDA 205552 (ibrutinib) which pertain to the MCL indication and let me know if you want to revise your comments, etc.
Thanks.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

IMBRUVICA NDA PMC/PMR –Revised 10-18-13 for MCL indication only

FDA Request #A

PMR1: Evaluate the effect of hepatic impairment on ibrutinib PK. Submit the final study report for trial PCI-32765CLL1006 entitled, "An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects With Varying Degrees of Hepatic Impairment"

Final Protocol Submission: Completed
Trial Completion: 6/30/2014
Final Report Submission: 12/30/2014

FDA Request #B

PMR2: Determine effect of a strong CYP3A Inducer on Ibrutinib PK. Submit the final study report for trial PCI-32765CLL1010 entitled, "An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects"

Final Protocol Submission: Completed
Trial Completion: Completed
Final Report Submission: 04/01/2014

FDA Request #C

PMC1: The Applicant will collect additional dissolution profile data (n=12 at release and n=12 on stability) using USP Apparatus Type 2 (Paddle) at 75 rpm in 3.0% w/v polysorbate 20 (Tween® 20) in 50 mM phosphate buffer pH 6.8 at 37.0°C from at least ten drug product release batches and from the drug product stability-registration/ primary batches through 12 months of storage at the long-term condition. The Applicant will use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria.

The Applicant will submit the final report with the complete dissolution information/data and a proposal for the dissolution acceptance under a supplement to the NDA within 15 months from action date.

Final Protocol Submission: NA
Study Completion: 11/01/2014
Final Report Submission: 02/01/2015

FDA Request #D

PMC2: (b) (4) Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial PCYC-1104-CA with 24 months of minimum follow-up for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each patient. In addition, submit detailed assessment

information regarding all sites of extranodal disease at baseline and follow-up, including assessments for response and progression.

Final Protocol Submission: Completed
Trial Completion: Q3 2014
Final Report Submission: Q1 2015

Sponsor Comment

Study PCYC-1104 was not designed to document the detailed extra-nodal site(s) of progression. As of the NDA cut off, we had 16 patients who progressed at extra-nodal site. Does the agency require Pharmacyclics to go back now and collect this data? Please note that this maybe partial data only. There are currently 31 patients who are still receiving ibrutinib and are being rolled over to the long-term follow-up study, CAN3001 in the next few months. We can amend both studies to collect the site of progression for patients remaining on study. Is this sufficient for fulfillment of the above PMC?

FDA Request #E

PMC 3: Complete and submit the final results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. Enrollment of at approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators . Overall survival is a key secondary endpoint.

Final Protocol Submission: completed
Trial Completion: Q4 2018
Final Report Submission: Q1 2019

Sponsor Comment

Dates are for final PFS analysis.

FDA Request #J

PMC: Determine the effect of a broad range of concentrations of ibrutinib on platelet function by in vitro studies.

Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects

with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

Preliminary Protocol Submission: Q2 2014
Final Protocol Submission: Q4 2014
Study Completion: Q2 2016
Final Report Submission: Q4 2016

(b) (4)

Sponsor Comment

We will commit to conduct a study to determine if ibrutinib has an effect on platelet function. However, we want to seek and incorporate external advice from coagulation experts on this protocol and thereafter present the draft protocol to FDA. We need input from external coagulation experts to determine the feasibility of evaluating such a potential effect in subjects on aspirin, anti-coagulants, and with renal dysfunction. We commit to be aligned with the FDA on the final design of this protocol with the input of external coagulation experts. We have made some wording edits above to keep this PMC a bit more flexible.

FDA Request #K

(b) (4)

The definition of a major hemorrhagic event includes any one of the following criteria:

I. *Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome*

II. *Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells,*

III. *Bleeding resulting in a serious adverse drug experience [as per 21 CFR 314.80(a)]*

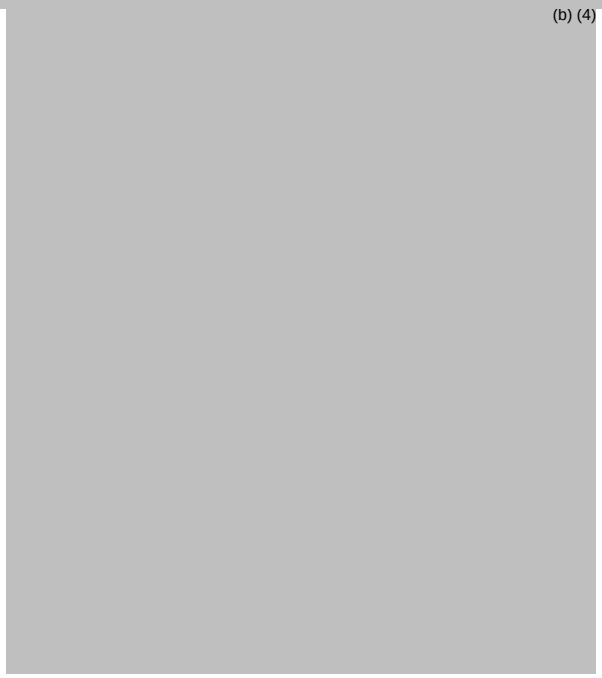
The primary enhancements to the current "routine" PV paradigm are the following requirements:

(b) (4)

Sponsor Comment

(b) (4)

(b) (4)



(b) (4)

Preliminary Protocol Submission: Nov 2013
Final Protocol Submission: Mar 2014
Study Completion: Nov 2017
Final Report Submission: May 2018

FDA Request #L

PMR: Objective: Determine the effect of Ibrutinib on the QT/QTc interval in (b) (4) on one or more therapeutic dose levels.

Conduct and submit results of a thorough QT trial to evaluate the effects of ibrutinib on the QT /QTc interval

(b) (4)

Preliminary Protocol Submission: completed
Final Protocol Submission: Q1 2014
Study Completion: Q1 2015
Final Report Submission: Q3 2015

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/s/

DIANE C HANNER
10/18/2013

From:	Hanner, Diane
To:	"Christine Salido"
Subject:	FDA response to the Urgent Question: NDA 205552 (ibrutinib)
Date:	Thursday, October 17, 2013 2:27:00 PM
Attachments:	URI_final.jmp skin_infections.jmp sinusitis_final.jmp bruising.jmp musculoskeletal_pain.jmp epistaxis.jmp decreased_appetite.JMP

Hi Chris,

Attached are the tables explaining AE counts. Please change the count for sinusitis to 13% and the count for bruising to

30%.

Thank you.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Thursday, October 17, 2013 12:09 PM
To: Hanner, Diane
Subject: FW: Urgent Question: NDA 205552 (ibrutinib)
Importance: High

Hi Diane,
In the AE table, we should like to know the following terms:

Upper respiratory tract infection (b) (4)
Skin infection 14%
Sinusitis (b) (4)
Bruising (b) (4)
Musculoskeletal pain (b) (4)
Epistaxis (b) (4)
Decrease appetite (b) (4)

These are the AE terms that we would like to see how FDA combined these AE total frequency.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Thursday, October 17, 2013 7:26 AM
To: Christine Salido
Subject: Urgent Question: NDA 205552 (ibrutinib)

Hi Chris,

Please clarify which AEs you are questioning.
Thank you.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Wednesday, October 16, 2013 11:10 PM
To: Hanner, Diane
Subject: Urgent Question: NDA 205552 (ibrutinib) PI and PPI -Please send your response by 10-18-13.
Importance: High

Hi Diane,
Our team is having a bit of a challenge validating the numbers in table 1 / AE table. Could you ask the FDA review team if they can help us understand how they came up with their AE preferred terms. We are willing to follow FDA's lead but we cannot replicate their exact numbers without some further instructions.

Would it possible for you to provide a response tomorrow morning PT?

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Wednesday, October 16, 2013 1:29 PM
To: Christine Salido
Subject: NDA 205552 (ibrutinib) PI and PPI -Please send your response by 10-18-13.

Hi Chris,

Please click on the attachments and view the NDA 205552 (ibrutinib) MCL label and PPI.

Upon completion of your review please accept those changes that you agree with and remember to make all of your changes in tracked changes mode.

Please send me the revised version of the label by October 18, 2013.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue

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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/17/2013

From: Hanner, Diane
To: "Christine Salido"
Subject: Urgent Question: NDA 205552 (ibrutinib)
Date: Thursday, October 17, 2013 10:26:00 AM

Hi Chris,
Please clarify which AEs you are questioning.
Thank you.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Wednesday, October 16, 2013 11:10 PM
To: Hanner, Diane
Subject: Urgent Question: NDA 205552 (ibrutinib) PI and PPI -Please send your response by 10-18-13.
Importance: High

Hi Diane,
Our team is having a bit of a challenge validating the numbers in table 1 / AE table. Could you ask the FDA review team if they can help us understand how they came up with their AE preferred terms. We are willing to follow FDA's lead but we cannot replicate their exact numbers without some further instructions.

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Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Wednesday, October 16, 2013 1:29 PM
To: Christine Salido
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Please send me the revised version of the label by October 18, 2013.

Thank you.
Regards,
Diane

CAPT Diane Hanner
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FDA/CDER/OHOP/DHP
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/s/

DIANE C HANNER
10/17/2013

From: Hanner, Diane
To: "Christine Salido"
Subject: NDA 205552 (ibrutinib) PI and PPI -Please send your response by 10-18-13.
Date: Wednesday, October 16, 2013 4:28:00 PM
Attachments: draft-label-text - to sponsor 10-16-13.docx
10-16-13 edits ibrutinib (TRADENAME) 205552 to sponsor.docx

Hi Chris,

Please click on the attachments and view the NDA 205552 (ibrutinib) MCL label and PPI.

Upon completion of your review please accept those changes that you agree with and remember to make all of your changes in tracked changes mode.

Please send me the revised version of the label by October 18, 2013.

Thank you.

Regards,

Diane

CAPT Diane Hanner
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33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DIANE C HANNER
10/16/2013

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, October 15, 2013 4:25 PM
To: 'csalido@pcyc.com'
Cc: Hanner, Diane; Boehmer, Jessica
Subject: RESPONSE NEEDED: NDA 205552: Ibrutinib: Clinical Information Request: Due October 16, 4PM ET

Importance: High

Dear Christine,

In reference to your new NDA for Ibrutinib, NDA 205552, the reviewers have identified the following Clinical Information Request. Please respond via email by the date indicated. You will need to officially submit the information to the NDA as well.

Clinical Information Request:

Provide the timelines for the submission of data for each clinical trial discussed in your information request dated 15 October 2013.

Please respond to this Information Request (send to CAPT Diane Hanner) by **4:00 PM ET Wednesday, October 16, 2013**. Please confirm receipt of this message.

Kind regards,

Jessica

On behalf of CAPT Diane Hanner

Jessica Boehmer, MBA
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
10/15/2013

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, October 15, 2013 10:40 AM
To: 'csalido@pcyc.com'
Cc: Hanner, Diane; Boehmer, Jessica
Subject: RESPONSE NEEDED: NDA 205552: Ibrutinib: Clinical Information Request: Due October 16, 1PM ET

Importance: High

Attachments: PT 217-002 confirmatory PET scan result.pdf

Dear Christine,

In reference to your new NDA for Ibrutinib, NDA 205552, the reviewers have identified the following Clinical Information Request. Please respond via email by the date indicated. You will need to officially submit the information to the NDA as well.

Clinical Information Request:

IR regarding Investigator Assessments for MCL Trial (PCYC-1104-CA): Please see issues below and provide an item-by-item response.

1. Patient 32-004

Sponsor Analysis: CR

FDA Analysis: PR

Reason: Patient had 2 lesions (external iliac 4.1 x 1.2 cm and mesenteric 6.0 x 4.0 cm) that were not FDG-positive at baseline, and the 2 lesions did not regress to ≤1.5 cm. CR for FDG-negative lesions requires lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in greatest diameter for nodes >1.5 cm before therapy).

2. Patient 32-006

Sponsor Analysis: CR

FDA Analysis: SD

Reason: Patient had 1 lesion (retrocaval LN 2.1 x 1.6 cm) that was not FDG-positive at baseline, and the lesion did not regress to ≤1.5 cm. Subsequent measurements were 2.2 x 1.5 cm (C3), 1.9x1.6 cm (C5), 2.1x1.5cm (C7), and 2.3x1.6cm (Unsch D238). Patient also did not meet ≥50% SPD reduction for PR.

3. Patient 32-021

Sponsor Analysis: CR

FDA Analysis: PR

Reason: Patient had a common iliac node 1.6x1.1 cm that was FDG-negative at baseline, and the lesion did not regress to ≤1.5 cm at the date when CR was achieved (D176, 1.6x1.2 cm).

4. Patient 217-002

Sponsor Analysis: CR

FDA Analysis: PR

Reason: FDG-PET scan report (see attached) at the date when CR was first achieved (8/19/11) shows persistent FDG activity within a R parabronchial node, maximal uptake 4.8, previously 4.7.

PT 217-002
onfirmatory PET sc.

5. Patient 217-009

Sponsor Analysis: PR

FDA Analysis: SD

Reason: Patient did not meet PR criteria of ≥50% SPD reduction. Also, according to the CSR for PCYC-1104-CA, page 115, "Errata" states that investigator had downgraded the patient's response to SD.

Please respond to this Information Request (send to CAPT Diane Hanner) by **1:00 PM ET Wednesday, October 16, 2013**. Please confirm receipt of this message.

Kind regards,

Jessica

On behalf of CAPT Diane Hanner

Jessica Boehmer, MBA
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
10/15/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, October 11, 2013 9:50 AM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib) has been administratively split.

Hi Chris,

The administrative split for NDA 205552 (ibrutinib) has been completed in our system.

All future submissions to your NDA should specify the NDA number and all Original numbers to which each submission pertains.

Original #1 is for:

- Mantle cell lymphoma (MCL).

Original#2 is for:

- Chronic lymphocytic leukemia (CLL).

Thanks.
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/11/2013

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, October 10, 2013 4:20 PM
To: Christine Salido
Subject: Question: container /carton labels NDA 205552 (ibrutinib)

Hi Chris,

The container labels and carton labeling appear acceptable.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Tuesday, October 01, 2013 3:32 PM
To: Hanner, Diane
Subject: Question: container /carton labels NDA 205552 (ibrutinib)

Hi Diane,
Do you know if the revised/submitted container/carton labels (see attached labels submitted to the NDA as sequence no. 0039 on 24 September) are acceptable to the FDA and that Pharmacyclics can initiate the printing process for the labels.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, September 20, 2013 8:58 AM
To: Usha Ramesh; Christine Salido
Subject: container /carton labels NDA 205552 (ibrutinib)

Hi,
Please note the following regarding the NDA 205552 (ibrutinib):

The proposed container label and carton labeling are unacceptable.

Container Label and Carton Labeling
1. Ensure the proper name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the proper name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Replace the (b) (4) box on the principal display panel with the statement of strength (i.e. 140 mg).

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP

10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Wednesday, September 18, 2013 9:53 PM
To: Hanner, Diane
Cc: Christine Salido
Subject: container /carton labels NDA 205552

Hi Diane,
Could to provide feedback if the revised container/carton labels that were submitted on 11th Sept. for Imbruvica are acceptable.

Thanks
Best regards
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

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/s/

DIANE C HANNER
10/10/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, October 07, 2013 2:24 PM
To: 'Christine Salido'
Subject: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.

Hi Chris,

We will not be providing additional information outside of the document that was to you on last Friday.

Please note that the purpose for the meeting is to have a general discussion. Specific patient-by-patient discussions may be scheduled at a later date.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, October 07, 2013 1:48 PM
To: Hanner, Diane
Subject: Follow up: Question: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.
Importance: High

Hi Diane,
Would you be able to provide the ID numbers for the 14 CLL patients today? I have been asked about this several times today when we might expect this information.

Thank you,
Chris

From: Christine Salido
Sent: Friday, October 04, 2013 2:15 PM
To: 'Hanner, Diane'
Subject: Question: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.
Importance: High

Hi Diane,
Our team is asking if you could ask the clinical reviewers to provide the ID of the 14 CLL patients they consider confirmed responders per item 1 for CLL.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, October 04, 2013 2:09 PM
To: Christine Salido
Subject: RE: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.

You're welcome!
Have a great week-end.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, October 04, 2013 5:08 PM
To: Hanner, Diane
Subject: RE: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.

Thanks Diane!
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, October 04, 2013 2:08 PM
To: Christine Salido
Subject: RE: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.

Hi Chris,

I'm not sure if additional items will be added…there is always a possibility that more inquires will be made. I'll check in with the clin pharm team and ask if they have anything that is considered a discipline specific topic for the upcoming meeting.

However, please note that the FDA clin pharm reviewers have been invited to attend the meeting on next week.

Regards,
Diane

From: Christine Salido [:csalido@pcyc.com]
Sent: Friday, October 04, 2013 4:15 PM
To: Hanner, Diane
Subject: RE: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.

Thanks Diane. I did not see anything items specifically related to clinical pharmacology. Will you be providing additional clinical pharmacology agenda items prior to next week's meeting?

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, October 04, 2013 12:22 PM
To: Christine Salido
Subject: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.

Hi Chris,

Please click on the attachment and view the letter that contains the itemized list of items that will need to be discussed at the upcoming October 9th meeting which is scheduled for 9:00 a.m.

Upon completion of your review, please let me know if the tentative list of attendees for this meeting will change.
I've already placed the previously sent names into our Lobby guard system so that your notification can be sent to you today if there are no additional attendees.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/07/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, October 07, 2013 1:44 PM
To: 'Christine Salido'
Subject: Response: Question: NDA 205552 Information Request-10-7-13

Hi Chris,

Please note that October 13 is acceptable.

Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, October 07, 2013 12:51 PM
To: Hanner, Diane
Subject: Response: Question: NDA 205552 Information Request-10-7-13

Hi Diane,
Our team will not be able to complete the QC and validation for these 90 patients today (my apology). We expect to have all 111 patient information to you no later than this Sunday night, 13 October.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Monday, October 07, 2013 7:21 AM
To: Christine Salido
Subject: Question: NDA 205552 Information Request-10-7-13

Hi Chris,
Please submit the data for the 90 patients on October 7, and the remainder 21 on October 11.
Thank you.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, October 04, 2013 6:06 PM
To: Hanner, Diane
Subject: Question: NDA 205552 Information Request- 9-30-13
Importance: High

Hi Diane,

Regarding the outstanding information for item 1 highlighted below, 90/111 patient data is currently available and could be submitted by COB PST Monday prior to our Wednesday meeting. Would it be helpful to submit the data for these 90

patients on Monday 7 October or would you prefer that I wait until all 111 patient data is available? The outstanding data for the 21 patients should be available for submission by next Friday 11 October.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Monday, September 30, 2013 12:46 PM
To: Christine Salido
Subject: NDA 205552 Information Request- 9-30-13

Hi Chris,

Please confirm that you have received this information request regarding clinical trial PCYC-1104-CA (MCL trial):

1. Provide documentation that the 111 patients met inclusion criteria 4: "documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen". Acceptable forms of documentation would include reports of imaging studies or biopsy results.

   In addition, we recommend that you include a individual narratives for each of the 111 patients with regards to details on the most recent treatment regimen (prior to ibrutinib), including details of the treatment regimen, duration of treatment, dates (including interval to subsequent ibrutinib treatment), and treatment results (including response and progression).

   We recommend that you submit the above information as soon as possible. Please let us know by Wednesday, October 2 when you can submit the complete information requested in #1.

2. Conduct a sensitivity analysis of efficacy (response rates [CR, PR] and duration of overall response) for PCYC-1104-CA (MCL) wherein you only include target lesions with baseline dimensions of at least 2 cm in at least 1 dimension. Include the analysis datasets and programs in your response.

Please submit your response by Wednesday, October 2nd.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330

FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
10/07/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, October 07, 2013 10:21 AM
To: 'Christine Salido'
Subject: Question: NDA 205552 Information Request-10-7-13

Hi Chris,
Please submit the data for the 90 patients on October 7, and the remainder 21 on October 11.
Thank you.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, October 04, 2013 6:06 PM
To: Hanner, Diane
Subject: Question: NDA 205552 Information Request- 9-30-13
Importance: High

Hi Diane,

Regarding the outstanding information for item 1 highlighted below, 90/111 patient data is currently available and could be submitted by COB PST Monday prior to our Wednesday meeting. Would it be helpful to submit the data for these 90 patients on Monday 7 October or would you prefer that I wait until all 111 patient data is available? The outstanding data for the 21 patients should be available for submission by next Friday 11 October.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Monday, September 30, 2013 12:46 PM
To: Christine Salido
Subject: NDA 205552 Information Request- 9-30-13

Hi Chris,

Please confirm that you have received this information request regarding clinical trial PCYC-1104-CA (MCL trial):

1. Provide documentation that the 111 patients met inclusion criteria 4: "documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen". Acceptable forms of documentation would include reports of imaging studies or biopsy results.

   In addition, we recommend that you include a individual narratives for each of the 111 patients with regards to details on the most recent treatment regimen (prior to ibrutinib), including details of the treatment regimen, duration of treatment, dates (including interval to subsequent ibrutinib treatment), and treatment results (including response and progression).

   We recommend that you submit the above information as soon as possible. Please let us know by Wednesday, October 2 when you can submit the complete information requested in #1.

2. Conduct a sensitivity analysis of efficacy (response rates [CR, PR] and duration of overall response) for PCYC-1104-CA (MCL) wherein you only include target lesions with baseline dimensions of at least 2 cm in at least 1 dimension. Include the analysis datasets and programs in your response.

Please submit your response by Wednesday, October 2nd.

Thank you.

Regards,

Diane

CAPT Diane Hanner
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10903 New Hampshire Avenue
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/s/

DIANE C HANNER
10/07/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, October 04, 2013 3:22 PM
To: 'Christine Salido'
Subject: NDA 205552 (Ibrutinib) Letter containing the specific topics items that will need to be discussed at the upcoming October 9th face to face meeting.

Hi Chris,

Please click on the attachment and view the letter that contains the itemized list of items that will need to be discussed at the upcoming October 9th meeting which is scheduled for 9:00 a.m.

Upon completion of your review, please let me know if the tentative list of attendees for this meeting will change.
I've already placed the previously sent names into our Lobby guard system so that your notification can be sent to you today if there are no additional attendees.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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/s/

DIANE C HANNER
10/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

ADVICE/INFORMATION REQUEST

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (NDA 205552)
Ibrutinib (PCI-32765).

Summary of Mantle Cell Lymphoma (MCL) trial efficacy issue:

1. You have not provided adequate documentation that patients met the following inclusion criteria: "Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen". You have committed to provide this information with the partial information to be submitted by October 11, and the complete information by October 21.

This information is needed to ensure that the treatment effect observed in the trial can be attributed to ibrutinib, and not as a carryover effect from prior therapy. In addition, the lack of a comparator arm in the single-arm trial increases the importance of establishing that the treatment effect in the single-arm trial is due to the trial treatment. Without this information, the clinical and statistical teams cannot identify the patients to be included in the primary analysis for the reviews and labeling.

DHP Assessment for MCL indication: The above deficiency is remediable if you can adequately address this issue.

Summary of Chronic Lymphocytic Leukemia (CLL) trial issues:

1. Efficacy Assessment Issues

There are substantial issues with the CLL portion of the application. Because of the efficacy assessment issues below, the clinical team is uncertain that these issues can be adequately addressed. Currently, the clinical team can verify responses in only 14 of 37 responders (ORR: 29%, all partial responses) in the efficacy population. You had claimed a response rate of 77% (37 of 48 patients).

1.1. Your study enrolled patients with minimal disease burden that would be considered as non-evaluable. The protocol-specified response criteria (standard IWCLL criteria) required a reduction of disease burden in 2 of 4 disease compartments (i.e., peripheral blood, lymph nodes, spleen, liver). Seven patients had a normal sized spleen, liver, and absolute lymphocyte count at baseline. Patients with non-evaluable disease cannot be considered to have responded.

1.2. The clinical team disagrees with your position that maintenance of a normal status already present at baseline, constitutes a response. For example, a patient with a normal-sized spleen at baseline should not be considered as a "spleen responder" if the spleen remains normal during the trial. It is unclear whether maintenance of the normal spleen size is due to the treatment effect of the drug, or from the natural history of the disease.

1.3. The IWCLL criteria required that responses should be documented for a minimum duration of 2 months. However, four patients did not have confirmed responses.

1.4. Additional efficacy issues include assessments of the various disease compartments were not being performed within a 1-month window, or missing assessments.

2. **Available Therapies.** Currently, the following drugs have regular approval for the treatment of CLL: chlorambucil (1957), cyclophosphamide (1959), fludarabine (1991), alemtuzumab (2001 AA, 2007 regular), bendamustine (2008), and rituximab (2010). In the CLL trial, not all of the 48 patients had received the available therapies for CLL (refer to Table below).

Prior therapies	**Number of patients who received available therapies (%)**
Rituximab AND alkylator (chlorambucil, cyclophosphamide, or bendamustine) AND fludarabine	35/48 (73%)
Rituximab AND alkylator (chlorambucil, cyclophosphamide, or bendamustine) AND fludarabine AND alemtuzumab	9/48 (19%)
Rituximab AND alkylator (chlorambucil or cyclophosphamide) AND bendamustine AND fludarabine	10/48 (21%)
Rituximab AND alkylator (chlorambucil or cyclophosphamide) AND bendamustine AND fludarabine AND alemtuzumab	3/48 (6%)

3. **Carryover Effect from Prior Therapies.** You enrolled patients with baseline scans or assessments that show a continuing response to prior therapy. You will be requested to provide additional information to clarify this issue.

DHP Assessment for CLL indication: Given the overall small size of the efficacy population (N=48 patients with CLL treated at 420 mg dose level) and uncertainties in the magnitude of the efficacy treatment effect, the clinical team recommends that you submit interim study reports and data from ibrutinib clinical trials for which trial accrual has been completed (a) PCYC-1112: P3 RCT ofatumumab vs ibrutinib, N=350, relapsed or refractory CLL, and/or (b) PCYC 1117: P2

single-arm trial of ibrutinib in patients with relapsed or refractory CLL with del 17p mutation, N=111.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

DIANE C HANNER
10/04/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, October 01, 2013 11:47 AM
To: 'Christine Salido'
Subject: Clarification: NDA 205552 Information Request- 10-1-13

Hi Chris,

To facilitate the review, please recompile the profiles for the 111 patients with information limited to cancer-related treatment and submit as a PDF document.

Thank you.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, September 30, 2013 11:38 PM
To: Hanner, Diane
Subject: Clarification: NDA 205552 Information Request- 9-30-13

Hi Diane,
In regards to the requested information below:

> "In addition, we recommend that you include a individual narratives for each of the 111 patients with regards to details on the most recent treatment regimen (prior to ibrutinib), including details of the treatment regimen, duration of treatment, dates (including interval to subsequent ibrutinib treatment), and treatment results (including response and progression)."

Pharmacyclics would like to clarify that information for 115 patients (including 4 screen failures) on study PCYC-1104-CA was submitted to the NDA on 31 May 2013 as Sequence No. 0003 (Reviewable Unit 2). This information is located under: Module 5.3.5.4 Other Study Reports, under folder Summary Level Clinical Site Data for Inspection, under Datasets folder, under Profiles folder, under Site-1104 folders.

See the attached example from one patient profile from site 1104-006 that was submitted to the NDA. Please let me know if the patient profiles submitted as Sequence No. 0003 satisfies this request or if additional information is needed.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Monday, September 30, 2013 12:46 PM
To: Christine Salido
Subject: NDA 205552 Information Request- 9-30-13

Hi Chris,

Please confirm that you have received this information request regarding clinical trial PCYC-1104-CA (MCL trial):

1. Provide documentation that the 111 patients met inclusion criteria 4: “documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen”. Acceptable forms of documentation would include reports of imaging studies or biopsy results.

   In addition, we recommend that you include a individual narratives for each of the 111 patients with regards to details on the most recent treatment regimen (prior to ibrutinib), including details of the treatment regimen, duration of treatment, dates (including interval to subsequent ibrutinib treatment), and treatment results (including response and progression).

   We recommend that you submit the above information as soon as possible. Please let us know by Wednesday, October 2 when you can submit the complete information requested in #1.

2. Conduct a sensitivity analysis of efficacy (response rates [CR, PR] and duration of overall response) for PCYC-1104-CA (MCL) wherein you only include target lesions with baseline dimensions of at least 2 cm in at least 1 dimension. Include the analysis datasets and programs in your response.

Please submit your response by Wednesday, October 2nd.

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
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/s/

DIANE C HANNER
10/01/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, September 30, 2013 3:46 PM
To: 'Christine Salido'
Subject: NDA 205552 Information Request- 9-30-13

Hi Chris,

Please confirm that you have received this information request regarding clinical trial PCYC-1104-CA (MCL trial):

1. Provide documentation that the 111 patients met inclusion criteria 4: "documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen". Acceptable forms of documentation would include reports of imaging studies or biopsy results.

   In addition, we recommend that you include a individual narratives for each of the 111 patients with regards to details on the most recent treatment regimen (prior to ibrutinib), including details of the treatment regimen, duration of treatment, dates (including interval to subsequent ibrutinib treatment), and treatment results (including response and progression).

   We recommend that you submit the above information as soon as possible. Please let us know by Wednesday, October 2 when you can submit the complete information requested in #1.

2. Conduct a sensitivity analysis of efficacy (response rates [CR, PR] and duration of overall response) for PCYC-1104-CA (MCL) wherein you only include target lesions with baseline dimensions of at least 2 cm in at least 1 dimension. Include the analysis datasets and programs in your response.

Please submit your response by Wednesday, October 2nd.

Thank you.

Regards,

Diane

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/s/

DIANE C HANNER
09/30/2013

Hanner, Diane

From: Hanner, Diane
Sent: Wednesday, September 25, 2013 10:57 AM
To: uramesh@pcyc.com
Subject: Information Request- NDA 205552 (ibrutinib)(part 4/4) 9-25-13

Hi Usha,

Some of the CT scan reports do not have a corresponding study number written on the document. To ensure that the correct scan is attributed to the correct patient, place the subject number on all of the CT scan reports.

Thank you.
Regards,
Diane

CAPT Diane Hanner
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FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Wednesday, September 25, 2013 2:23 AM
To: Hanner, Diane
Cc: Christine Salido
Subject: RE: Information Request- NDA 205552 (ibrutinib)(part 4/4)
Importance: High

Hi Diane,

Part-4, the final part of the response to the request for information dated sept 20 (see below), is attached. As mentioned in my earlier email, the complete response will be submitted to the NDA as well.

Thank you
Best Regards
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.

Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, September 20, 2013 12:50 PM
To: Usha Ramesh; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha,

Please note that the information request provided on 12 August 2013, indicated that the patients with abnormal spleens at baseline (noted by Pharmacyclics as spleen enlarged (CT), yes) was more than n=8.

Please submit all spleen assessments by CT for all responding CLL patients (n=37) for review at each time point a CT assessment was performed.

Thank you.
Regards,
Diane

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Friday, September 20, 2013 2:00 PM
To: Hanner, Diane
Subject: RE: Information Request- NDA 205552 (ibrutinib)
Importance: High

Hi Diane,

I inadvertently omitted the highlighted portion from my earlier request for clarification. We wish to clarify that we need to provide the radiology reports of the spleen for only the responders with abnormal spleens (n=8).

"*Please confirm that the agency would like submitted the radiology reports of the spleen for all responding CLL patients (n=37) from 1102 study treated at 420 mg with abnormal (enlarged) spleens (n=8) for which the spleen was used as one of the A response criteria.*"

Additionally please note that this data is not available in –house and so it would not be possible to provide the data within the timeframe requested. Pharmacyclics would provide an update on Monday, 23 Sept regarding when we would be able to provide this data.

Thank you
Best Regards
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, September 20, 2013 9:25 AM
To: Usha Ramesh; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha and Chris,

Please address the following NDA 205552 (ibrutinib) information request, and please submit these reports by Monday, September 23, at 9AM.

Submit all radiology reports of the spleen assessments for the patients with relapsed or refractory CLL in clinical trial 1102-CA who received Ibrutinib 420 mg daily.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
09/25/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, September 24, 2013 2:12 PM
To: uramesh@pcyc.com; 'Christine Salido'
Subject: NDA 205552 (ibrutinib) Information Request

Hi Usha and Chris,

Please address this additional information request and please respond by 12:00 noon EST, Friday, September 27, 2013.

Conduct a sensitivity analysis of efficacy (response rates [CR, PR] and duration of overall response) for PCYC-1104-CA (MCL) wherein you only include target lesions with baseline dimensions of at least 1.5 cm in both perpendicular measurements. Include the analysis datasets and programs in your response.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
09/24/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, September 24, 2013 1:01 PM
To: uramesh@pcyc.com; 'Christine Salido'
Subject: NDA 205552 Information Request 9-24-13

Importance: High

Hi Usha and Chris,

Please address the following information request regarding NDA 205552 (ibrutinib), and please submit your response by 12:00 noon EST, Friday, September 27, 2013.

For patients who achieved a CR or PR in clinical trial PCYC-1104-CA (MCL), submit analysis tables (1 per patient) that includes per visit investigator assessments of target lesion information (total and individual), and extranodal assessments. For the individual target lesions, include the lesion site, perpendicular dimensions (2), area (in cm^2), and FDG-avidity. For extranodal assessments, include site, FDG-avidity, and measurements (if available). Include separate columns for bone marrow involvement, progression assessment(s), and overall investigator assessment.

Thank you.
Regards,
Diane

CAPT Diane Hanner
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/s/

DIANE C HANNER
09/24/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 20, 2013 8:41 AM
To: Usha Ramesh; 'Christine Salido'
Subject: Ibrutinib; NDA 205552- IR- 9-20-13

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Chris and Usha,

Please address the following information request and **respond by 10 am on Monday 23rd.**

In the study report for the mass balance Trial # PCI-32765CLL1004, you describe the CYP2D6 phenotypes as poor metabolizers and extensive metabolizers. However, the pharmacogenomics report in Appendix 9.5 lists 2 patients as IM and 1 as either EM or IM. Please submit the data matching the ibrutinib and PCI-45227 PK parameters to the phenotypes that were reported in the pharmacogenomics report.

Thank you,
Regards,
Diane

CAPT Diane Hanner
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/s/

DIANE C HANNER
09/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 20, 2013 11:58 AM
To: uramesh@pcyc.com; Christine Salido
Subject: container /carton labels NDA 205552 (ibrutinib)

Hi,
Please note the following regarding the NDA 205552 (ibrutinib):

The proposed container label and carton labeling are unacceptable.

Container Label and Carton Labeling
1. Ensure the proper name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the proper name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Replace the (b) (4) box on the principal display panel with the statement of strength (i.e. 140 mg).

Regards,
Diane

CAPT Diane Hanner
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10903 New Hampshire Avenue
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(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Wednesday, September 18, 2013 9:53 PM
To: Hanner, Diane
Cc: Christine Salido
Subject: container /carton labels NDA 205552

Hi Diane,
Could to provide feedback if the revised container/carton labels that were submitted on 11th Sept. for Imbruvica are acceptable.

Thanks
Best regards
Usha

Usha Ramesh PhD
Sr. Director

CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

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/s/

DIANE C HANNER
09/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 20, 2013 12:25 PM
To: uramesh@pcyc.com; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha and Chris,

Please address the following NDA 205552 (ibrutinib) information request, and please submit these reports by Monday, September 23, at 9AM.

Submit all radiology reports of the spleen assessments for the patients with relapsed or refractory CLL in clinical trial 1102-CA who received Ibrutinib 420 mg daily.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
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/s/

DIANE C HANNER
09/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 20, 2013 12:50 PM
To: uramesh@pcyc.com
Subject: PMR PMC preamble regarding NDA 205552 (ibrutinib)

Hi Usha,
I'm resending the Preamble regarding NDA 205552 (ibrutinib). Please note that the official copy of the PMR/PMCs is not sent in until we have reached a mutual agreement.
Regards,
Diane

From: Hanner, Diane
Sent: Thursday, September 12, 2013 11:44 AM
To: 'Christine Salido'
Subject: PMR PMC preamble regarding NDA 205552 (ibrutinib)

Hi Chris,

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the previously sent clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later

Some things you can do to expedite this process:
1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:
a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
09/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 20, 2013 2:19 PM
To: uramesh@pcyc.com
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha,

We agree with the clarification of the information needed (radiology reports of the spleen assessments via CT for responding CLL patients treated at 420 mg daily).

Provide the information requested as soon as possible, and at the latest by Wednesday, September 25.
Regards,
Diane

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Friday, September 20, 2013 1:31 PM
To: Hanner, Diane
Cc: Urte Gayko; Christine Salido
Subject: RE: Information Request- NDA 205552 (ibrutinib)
Importance: High

Hi Diane,

Pharmacyclics would like to request some clarification regarding the request below.

"Please confirm that the agency would like submitted the radiology reports of the spleen for all responding CLL patients (n=37) from 1102 study treated at 420 mg with abnormal (enlarged) spleens for which the spleen was used as one of the A response criteria."

Additionally please note that this data is not available in –house and so it would not be possible to provide the data within the timeframe requested. Pharmacyclics would provide an update on Monday, 23 Sept regarding when we would be able to provide this data.

Thank you
Best Regards
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, September 20, 2013 9:25 AM

To: Usha Ramesh; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha and Chris,

Please address the following NDA 205552 (ibrutinib) information request, and please submit these reports by Monday, September 23, at 9AM.

Submit all radiology reports of the spleen assessments for the patients with relapsed or refractory CLL in clinical trial 1102-CA who received Ibrutinib 420 mg daily.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
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/s/

DIANE C HANNER
09/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 20, 2013 3:50 PM
To: uramesh@pcyc.com; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha,

Please note that the information request provided on 12 August 2013, indicated that the patients with abnormal spleens at baseline (noted by Pharmacyclics as spleen enlarged (CT), yes) was more than n=8.

Please submit all spleen assessments by CT for all responding CLL patients (n=37) for review at each time point a CT assessment was performed.

Thank you.
Regards,
Diane

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Friday, September 20, 2013 2:00 PM
To: Hanner, Diane
Subject: RE: Information Request- NDA 205552 (ibrutinib)
Importance: High

Hi Diane,

I inadvertently omitted the highlighted portion from my earlier request for clarification. We wish to clarify that we need to provide the radiology reports of the spleen for only the responders with abnormal spleens (n=8).

"Please confirm that the agency would like submitted the radiology reports of the spleen for all responding CLL patients (n=37) from 1102 study treated at 420 mg with abnormal (enlarged) spleens (n=8) for which the spleen was used as one of the A response criteria."

Additionally please note that this data is not available in –house and so it would not be possible to provide the data within the timeframe requested. Pharmacyclics would provide an update on Monday, 23 Sept regarding when we would be able to provide this data.

Thank you
Best Regards
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, September 20, 2013 9:25 AM
To: Usha Ramesh; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha and Chris,

Please address the following NDA 205552 (ibrutinib) information request, and please submit these reports by Monday, September 23, at 9AM.

Submit all radiology reports of the spleen assessments for the patients with relapsed or refractory CLL in clinical trial 1102-CA who received Ibrutinib 420 mg daily.

Thank you.
Regards,
Diane

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/s/

DIANE C HANNER
09/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 20, 2013 5:01 PM
To: uramesh@pcyc.com
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha,
No, they are not sufficient. Please submit all of the spleen assessments by CT that were completed for the responders.
Thank you,
Regards,
Diane

CAPT Diane Hanner
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Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Friday, September 20, 2013 4:31 PM
To: Hanner, Diane
Cc: Christine Salido
Subject: RE: Information Request- NDA 205552 (ibrutinib)
Importance: High

Hi Diane,
Please note that while there were more than 8 with enlarged spleens at baseline by CT- the 8 listed in the email below was referring to those where spleen was needed to assess response. Based on this could you clarify once again if the radiology reports for these 8 are sufficient?

Thank you
Best regards
usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, September 20, 2013 12:50 PM
To: Usha Ramesh; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha,

Please note that the information request provided on 12 August 2013, indicated that the patients with abnormal spleens at baseline (noted by Pharmacyclics as spleen enlarged (CT), yes) was more than n=8.

Please submit all spleen assessments by CT for all responding CLL patients (n=37) for review at each time point a CT assessment was performed.

Thank you.
Regards,
Diane

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Friday, September 20, 2013 2:00 PM
To: Hanner, Diane
Subject: RE: Information Request- NDA 205552 (ibrutinib)
Importance: High

Hi Diane,

I inadvertently omitted the highlighted portion from my earlier request for clarification. We wish to clarify that we need to provide the radiology reports of the spleen for only the responders with abnormal spleens (n=8).

"*Please confirm that the agency would like submitted the radiology reports of the spleen for all responding CLL patients (n=37) from 1102 study treated at 420 mg with abnormal (enlarged) spleens (n=8) for which the spleen was used as one of the A response criteria.*"

Additionally please note that this data is not available in –house and so it would not be possible to provide the data within the timeframe requested. Pharmacyclics would provide an update on Monday, 23 Sept regarding when we would be able to provide this data.

Thank you
Best Regards
Usha

Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, September 20, 2013 9:25 AM
To: Usha Ramesh; Christine Salido
Subject: Information Request- NDA 205552 (ibrutinib)

Hi Usha and Chris,

Please address the following NDA 205552 (ibrutinib) information request, and please submit these reports by Monday, September 23, at 9AM.

Submit all radiology reports of the spleen assessments for the patients with relapsed or refractory CLL in clinical trial 1102-CA who received Ibrutinib 420 mg daily.

Thank you.
Regards,
Diane

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/s/

DIANE C HANNER
09/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Wednesday, September 18, 2013 3:12 PM
To: 'Christine Salido'
Subject: Revised K-CLL MCL Clinical PMR- NDA 205552 (ibrutinib)

Hi Chris,
Please take a look at this revised PMR regarding NDA 205552 (ibrutinib), and please provide your input regarding this matter especially as it pertains to the MM/YYYY information.

(b) (4)

The definition of a major hemorrhagic event includes any one of the following criteria:

I. *Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome*
II. *Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells*
III. *Bleeding resulting in a serious adverse drug experience [as per 21 CFR 314.80(a)]*

(b) (4)

Preliminary Protocol Submission:	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
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[i] Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005 Apr;3(4):692-4.

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/s/

DIANE C HANNER
09/18/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, September 17, 2013 3:55 PM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib) -L-CLL MCL Thorough QT Study

Hi Chris,

Please provide your feedback regarding this NDA 205552 (ibrutinib) DRAFT PMR listed below and please be sure to include the date information (MM/YYYY).

Conduct a thorough QT trial to evaluate the effects of ibrutinib on the QT /QTc interval

Preliminary Protocol Submission	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

Thank you.
Regards,
Diane

CAPT Diane Hanner
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DIANE C HANNER
09/17/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, September 16, 2013 5:01 PM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib)-Information request 9-16-13
Attachments: Example of Table.doc

Hi Chris,

Please construct a table (example below and attached) of the 12 patients with extranodal disease who achieved CRs and record assessment modality and result for each extranodal site at each assessment timepoint. Include one row per patient, and include one subrow per each site of extranodal disease.

We would appreciate your response no later than noon, Wednesday, September 18, 2013.

Subject ID	Extranodal Site	Screen	C1D1	C2D1	C3D1	C4D1	C5D1
XXX-001	Spleen	PET +					PET -
XXX-001	Skin	Visible on PE L forearm 3 cm (diam)	Skin lesion on PE on L foream 1 cm (diam)	Skin lesion on forearm resolved			No skin lesions
XXX-001	Bone	Bx +					Bx -
XXX-001	Lung	PET+ scattered nodules					No FDG uptake in lungs

Please explain how disease at each extra-nodal site resolved at the time of CR for each patient with extra-nodal disease.
Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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/s/

DIANE C HANNER
09/16/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 13, 2013 6:08 PM
To: 'Christine Salido'; uramesh@pcyc.com
Subject: NDA 205552 Ibrutinib Information Request- PMR- 9-13-13

Importance: High

Hi Chris and Usha,

Please provide feedback regarding this NDA 205552 (ibrutinib) DRAFT PMR and please be sure to include the date information below (MM/YYYY).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Preliminary Protocol Submission:	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

Thank you,
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
09/13/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, September 13, 2013 5:32 PM
To: 'Christine Salido'
Cc: 'uramesh@pcyc.com.'
Subject: NDA 205552 Ibrutinib Information Request 9-13-13

Importance: High

Hi Chris and Usha,

Please address the following NDA 205552 (ibrutinib) information request and please respond by COB, Monday, September 16, 2013.

1. The ADLB datasets for both clinical trial 1104 and 1102 contain multiple rows wherein baseline toxicity grade is missing or blank. Resubmit ADLB datasets that contain baseline toxicity grades for each row wherein baseline toxicity grade can be classified with CTCAE version 4.

2. For clinical trial 1102 (CLL trial), because you did not capture detailed information regarding spleen and liver assessments for all patients, the clinical review team cannot rely on the spleen and liver assessments as a Group A response. Hence, Group A response evaluation would be limited to nodal response and absolute lymphocyte count (ALC) response. Please also note that ALC response for PR as defined in the protocol is a 50% reduction from the baseline.

2.1. Please recalculate the response rate and duration of response from the clinical trial 1102, based on Group A response limited to nodal response and ALC response using the 2008 criteria established by the International Workshop in CLL used in the clinical trial. Include a separate analysis for the subset of 48 patients with relapsed/refractory CLL who received a dose of 420 mg.

2.2. Recalculate the response rate and duration of response for a confirmed response (defined as 2 or more consecutive responses), with the same condition as 2.1. Include a separate analysis for the subset of 48 patients with relapsed/refractory CLL who received a dose of 420 mg.

Include analysis datasets and define file for response to 2.1 and 2.2.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
09/13/2013

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, September 12, 2013 2:45 PM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib)- information request- 9-12-13

Hi Chris,

Please send narratives for all patients in any ibrutinib clinical trial who have experienced leukostasis. You do not need to resend the narratives for the 4 patients (123-401, 367-001, 10001707, 659-002) already included in the safety update.
Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
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/s/

DIANE C HANNER
09/12/2013

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, September 12, 2013 11:44 AM
To: 'Christine Salido'
Subject: PMR PMC preamble regarding NDA 205552 (ibrutinib)

Hi Chris,

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the previously sent clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later

Some things you can do to expedite this process:
1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:
a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue

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(301) 796-2330
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/s/

DIANE C HANNER
09/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

MID-CYCLE COMMUNICATION

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ibrutinib (PCI-32765).

We also refer to the teleconference between representatives of your firm and the FDA on August 19, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 19, 2013 @ 3:00 p.m.

Application Number: NDA 205552

Product Name: Ibrutinib

Indication: For patients with relapsed or refractory Mantle Cell lymphoma (MCL) and Chronic Lymphocytic Leukemia (CLL)

Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo de Claro, M.D.

Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Edvardas Kaminskas, M.D., Deputy Director, DHP
- Robert Kane, M.D., Deputy Director Safety, DHP
- R. Angelo de Claro, M.D., Medical Officer, Clinical Team Leader (acting), DHP
- Karen McGinn, M.S.N., CRNP, Senior Clinical Analyst, DHP
- Nicole Verdun, M.D., Medical Officer, DHP
- Tamy Kim, Pharm.D., Associate Director of Regulatory Affairs, OHOP
- Haleh Saber, Ph.D., Supervisory Pharmacologist
- Shwu-Luan Lee, Ph.D., Pharmacologist
- Elimika Pfuma, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Bahru Habtemariam, Pharm.D., Clinical Pharmacology Reviewer, DCP5
- Brian Booth, Ph.D., Deputy Director, Office of Clinical Pharmacology, DCP5
- Lei Nie, Ph.D., Team Leader, DB 5
- Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst, DRISK
- Kevin Wright, PharmD, Safety Evaluator, Division of Medication Error and Prevention Analysis (DMEPA)

- Yuzhuo Pan, Ph.D., Clinical Pharmacology Reviewer (PBPK modeling and simulation)
- Ping Zhao, Ph.D., Clinical Pharmacology Reviewer (PBPK modeling and simulation)
- Ali Al-Hakim, Ph.D., CMC Branch Chief, Division 1, Branch 2, ONDQA
- John Duan, Ph.D., Biopharmaceutics Reviewer, ONDQA
- Xiao-Hong Chen, Ph.D., CMC Reviewer, ONDQA, Division 3, Branch 5
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Barbara Fuller, R.N., M.S.N., CWOCN, Team Leader (DMPP)
- Kim Taylor, M.B.A., M.P.H, Operations Research Analyst, OSP
- Vipul Dholakia, Ph.D., Chemist, Office of Compliance

EASTERN RESEARCH GROUP ATTENDEES

- Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES

- Urte Gayko, PhD, Senior Vice President, Regulatory Affairs, Pharmacyclics
- Chris Salido, BS, Executive Director, Regulatory Affairs, Pharmacyclics
- Usha Ramesh, PhD, Director, Regulatory Affairs CMC, Pharmacyclics
- Jesse McGreivy, MD, Chief Medical Officer, Pharmacyclics
- Maria Fardis, PhD, MBA, Chief of Oncology Operations and Alliances, Pharmacyclics
- Fong Clow, ScD, Vice President, Biometrics, Pharmacyclics
- Linda Gau, Associate Director, Statistical Programming, Pharmacyclics
- Dana Lee, Vice President, Drug Safety and Pharmacovigilance, Pharmacyclics
- Cindy Chen, Director, Clinical Drug Safety, Pharmacyclics
- Heow Tan, Chief, Quality and Technical Operations, Pharmacyclics
- David Loury, PhD, Executive Vice President, Toxicology, Pharmacyclics
- Juthamas Sukbuntherng, PhD, Senior Director, Clinical Pharmacology and DMPK, Pharmacyclics
- Scott Shearer, PhD, Vice President, Global Quality, Pharmacyclics
- Danelle James, MD, Senior Medical Director, Pharmacyclics
- John Seaman, PharmD, Senior Director, Global Regulatory Affairs, Janssen R&D, LLC
- Sen Hong Zhuang, MD, PhD, Vice President, Clinical Research, Janssen R&D, LLC

- Jerry Retkwa, RPh, MS, Manager, Global Regulatory Affairs, Janssen R&D, LLC
- Mann Fung, M.D., Vice President, Compound Development Team Leader, Janssen R&D, LLC

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

A discussion was held regarding the questions below that were sent to Pharmacyclics:

QUESTION #1

How did you arrive with the dose level of 560 mg for patients with MCL, and 420 mg for patients with CLL/SLL?

Meeting Discussion:

The Applicant referenced their submitted response which was received on August 19, 2013, and officially submitted on August 26, 2013. The Applicant discussed that the selection of the 560-mg once daily dose regimen for patients with MCL was based on pharmacokinetic/ pharmacodynamic sampling and clinical evaluation. The ibrutinib dose was not selected based on a maximum tolerated dose (MTD) determination (as this was never achieved), but on achieving a sustained BTK occupancy, and safety and efficacy profiles. Doses were selected separately for each histology.

The Applicant also conveyed that a determination of the 420-mg once daily dose regimen for the treatment of CLL/SLL in patients was based on pharmacokinetic/pharmacodynamic sampling and clinical evaluation. The ibrutinib dose selection was not based on a MTD determination (as this was never achieved), but on achieving and sustaining occupancy of the active site of BTK, efficacy outcomes, and safety profiles. Two doses (420 and 840 mg/day) were evaluated in the pivotal study PCYC-1102-CA but no clinically meaningful advantages with regard to safety, efficacy, and pharmacodynamic findings with the higher dose were observed. Therefore, the lower dose of 420 mg daily was selected for CLL/SLL.

The Agency advised that the Applicant to revisit the 560 mg dose and stated that would like to see further dose- and exposure-response evaluations in order to further optimize selected doses.

The Agency commented that full BTK occupancy and maximal clinical response (ORR) were achieved at 2.5 mg/kg and asked why the Applicant selected doses that are 2-3-fold higher than the dose needed to achieve maximal BTK occupancy and clinical response-4. The Applicant replied that 5 of 9 patients with MCL treated at 560 mg in study PCYC-04753 (FIH) achieved an overall response therefore based upon this clinical data, Pharmacyclics did not want to take the risk of choosing a lower dose.

QUESTION #2

What efforts have you done to further understand the following safety issues?

QUESTION #2.1 (hemorrhagic risk)

Meeting Discussion:

The Applicant summarized the history of observed CNS hemorrhage including subdural hematoma throughout the clinical development program. The Agency noticed that the AE reporting of mucosal type bleeding (contusion, bruising, etc.) and asked if the Applicant was looking at studies to determine causality. The Applicant mentioned that 4 independent clinical advisors in coagulation reviewed the ibrutinib safety data regarding hemorrhagic events.

The Agency asked if the clinical advisors reviewed all hemorrhagic events or only the severe events and if the Applicant had any additional plans to study platelet function. The Applicant replied that brief summaries of Grade 1-2 AEs included mucosal bleeding events and were provided to the clinical advisors. The Agency requested that the Applicant submit the independent clinical advisors report and any briefing documents provided to the advisors and literature references.

QUESTION #2.2 (second primary malignancies)

Pharmacyclics Response: Please see the Applicant's response received August 19,2013 and officially submission on August 26, 2013.

Meeting Discussion: No discussion was captured.

Other Topics:

3. The Applicant inquired regarding the acceptability of the proposed trade name (IMBRUVICA). The Regulatory Project Manager replied that the proposed trade name had been tentatively approved.

4. The Applicant requested clarification regarding submission of a Pharmacovigilance Plan (PVP). The Agency recommended that the Applicant submit a PVP as requested by the Agency.

3.0 INFORMATION REQUESTS

Several information requests have already been conveyed to the Applicant.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

No major safety concerns regarding Risk Evaluation and Mitigation Strategy (REMS) have been identified at this time.

5.0 ADVISORY COMMITTEE MEETING

At the time of the Midcycle meeting, we have determined that there will not be a need to have an ODAC meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The proposed date for the late-cycle (possible teleconference) meeting is currently scheduled for September 25, 2013, at which time we will discuss the other projected milestones for the remainder of the review cycle.

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/s/

ROMEO A DE CLARO
09/11/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, September 10, 2013 5:08 PM
To: 'Christine Salido'; 'uramesh@pcyc.com'
Subject: PMC - NDA 205552 (ibrutinib)

Hi Chris,

We were willing to accept the proposal of (b) (4) under the condition that insufficient product is available. If this is not the case, a sample size of 12 should be used for stability dissolution testing. Use 12 tablets for the dissolution testing of all the upcoming stability sampling time points, although it is not necessary to redo the already completed stability time points, which used (b) (4) tablets.

Regards,
Diane

From: Usha Ramesh [mailto:uramesh@pcyc.com]
Sent: Friday, August 30, 2013 12:38 PM
To: Hanner, Diane
Cc: Christine Salido
Subject: Re: PMC - NDA 205552 (ibrutinib)
Importance: High

Hi Diane,
Pharmacyclics would like to use a sample size of (b) (4) for stability dissolution testing for the following reasons.
The stability studies that will be used to set the specifications using the Tween method are already under way with (b) (4)
Furthermore, as the RSD of the individual capsules is in general very good and the specification is set on the mean,
Pharmacyclics believes that a sample size of (b) (4) is appropriate; n=12 would not add any significant value.

Please let us know if (b) (4) is acceptable for stability dissolution testing.

Thank you
Best regards
Usha Ramesh PhD
Sr. Director
CMC Regulatory Affairs
Pharmacyclics
997 E. Arques Ave.
Sunnyvale, CA 94085
Phone: (408) 215 3596

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Tuesday, August 27, 2013 8:00 AM
To: Christine Salido
Subject: RE: PMC - NDA 205552 (ibrutinib)

Hi Chris,
Since the stability data will be used for the setting of the final acceptance criteria, we recommend that you consider collecting a sample size of n=12 for the stability dissolution testing. However, if you cannot comply

with our request due to insufficient product under the stability program, we are willing to accept your proposal of (b) (4)
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, August 26, 2013 6:08 PM
To: Hanner, Diane
Subject: FW: PMC - NDA 205552 (ibrutinib)

Hi Diane,
Pharmacyclics agrees with the PMC Study Completion and Final Report Submission dates below. One small clarification/detail (**in red**) has been added below.

Thanks
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Monday, August 26, 2013 1:24 PM
To: Christine Salido
Subject: PMC - NDA 205552 (ibrutinib)

Hi Chris,
Please take a look at this PMC regarding NDA 205552 (Ibrutinib) and let me know if you agree with the trial completion and final report submission information.
Thank you.
Regards,
Diane

PMC Description:	The Applicant will collect additional dissolution profile data (n=12 **at release and** (b) (4) **on stability**) using USP Apparatus Type 2 (Paddle) at 75 rpm in 3.0% w/v polysorbate 20 (Tween® 20) in 50 mM phosphate buffer pH 6.8 at 37.0 °C from at least ten drug product release batches and from the drug product stability-registration/ primary batches through 12 months of storage at the long-term condition. The Applicant will use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria. The Applicant will submit the final report with the complete dissolution information/data and a proposal for the dissolution acceptance under a supplement to the NDA within 15 months from action date.

PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study Completion:	11/01/2014
	Final Report Submission:	02/01/2015

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
09/10/2013

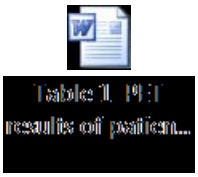
Hanner, Diane

From: Hanner, Diane
Sent: Monday, September 09, 2013 5:46 PM
To: 'Christine Salido'
Subject: NDA 205552 (ibrutinib) Analysis of PET scan reports

Hi Chris,

Please address the following information request regarding NDA 205552 (ibrutinib), and please note the attached table regarding this matter. Also, please respond to this information request by noon, Wednesday, September 11th.

Review of the PET scan reports shows that the following 5 subjects had evidence of disease, did not achieve CR and should be downgraded to PR: 032-004, 032-006, 032-007, 032-015, 038-004. Please explain how these subjects were counted as CRs.



Thank you.
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

Table 1 PET results of patients with CR downgraded to PR

Subject ID	Reader/Date	PET Report	New Response
032-004	(b) (6) / 6/13/2011	2. Minimally metabolically active cavitary focus in the right lung and minimal ground-glass opacity in the left lung remain stable and may be inflammatory, to be followed on CT. 3. A punctate FDG-avid focus is noted in the right lobe of the thyroid gland, of uncertain clinical significance.	PR
032-006	(b) (6) P/ 3/24/2011	3. Persistent active tumor in the right parotid gland. 4. Focal hyper-metabolism in the right seminal vesicle is probably related to lymphoma.	PR
032-007	(b) (6) 12/21/2011	1. Anterior mediastinal/left prevascular hyper-metabolic node that previously had a maximum SUV of 9.3 (image 81, series 2), now has a maximum SUV of 4.3 (image 76, series 5). Previously, the node measured 2.5 cm transversely (image 81, series 2) and now measures 2 cm transversely (image 76, series 2). The calcifica-	PR

		tions within the lesion are stable. 2. The calcified hypermetabolic focus at the level of the AP window (image 92, series 2) that had a maximum SUV of 3.4 now has a maximum SUV of 2.7 (image 88, series 5).	
032-015	(b) (6) 9/14/2011	3. F18-fluoro-deoxyglucose-avid calcified nodule in the left lobe of the thyroid to be further evaluated.	PR
038-004	(b) (6) 5/16/2012	2. Persistent high uptake in the tongue, which may be physiologic. Correlation with clinical exam is recommended. SUV 9.0	PR

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/s/

DIANE C HANNER
09/09/2013

Hanner, Diane

From: Hanner, Diane
Sent: Wednesday, September 04, 2013 1:32 PM
To: 'Christine Salido'
Subject: NDA 205552 ibrutinib - Information Request 9-4-13

Hi,
Please address the following information request and please respond no later than 9AM Monday, September 9th.

For clinical trial PCYC-1104-CA (MCL clinical trial), please submit the bone marrow aspiration and biopsy reports at baseline for all patients, and follow-up reports for patients who achieved PR or CR.

Thank you.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
09/04/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, September 03, 2013 10:31 AM
To: 'Christine Salido'
Subject: NDA 205552 ibrutinib- Information Request 9-3-13

Hi,

Please address the following information request and submit your response by 9 A.M., EST, Monday, Sep 9th:

For clinical trial PCYC-1104-CA (MCL clinical trial)

1. Submit the FDG-PET reports at baseline for all patients, and follow-up FDG-PET reports for patients who achieved PR or CR.

2. For patients who experienced disease progression, what were the site(s) of progression? The CE.xpt and SUPPCE.xpt datasets do not provide sufficient detail. For patients with extranodal site progression, what were the site(s) of progression?

3. Please provide documentation that the simplified MIPI score is prognostic in your proposed indication.

4. Provide efficacy narratives for each patient who achieved a CR. Include assessments of extranodal site(s) of involvement, including bone marrow.

5. Regarding the occurrence of lymphocytosis in patients with MCL, what study(ies) have you conducted to characterize the phenotype of the lymphocytosis? How many patients developed an increase in circulating MCL?

General

6. What data do you have regarding the distribution of ibrutinib to sanctuary sites such as the CNS, eye, or testis?

Thank you.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
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/s/

DIANE C HANNER
09/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) June 28, 2013, received June 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (PCI-32765) (ibrutinib) capsules, 140 mg.

We also refer to your amendments dated, April 25, 2013, May 6, 2013, May 13, 2013, May 31, 2013, June 6, 2013, June 20, 2013, June 28, 2013, July 12, 2013, July 25, 2013 (2), July 26, 2013 (3), July 30, 2013, August 1, 2013, August 2, 2013 (7), August 5, 2013 (2), August 6, 2013, and August 7, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm). Therefore, the user fee goal date is February 28, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by

January 28, 2014. In addition, the internal mid-cycle review meeting was held on August 14, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designations, you are exempt from this requirement.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
08/27/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, August 27, 2013 11:00 AM
To: 'Christine Salido'
Subject: RE: PMC - NDA 205552 (ibrutinib)

Hi Chris,
Since the stability data will be used for the setting of the final acceptance criteria, we recommend that you consider collecting a sample size of n=12 for the stability dissolution testing. However, if you cannot comply with our request due to insufficient product under the stability program, we are willing to accept your proposal of (b) (4)
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, August 26, 2013 6:08 PM
To: Hanner, Diane
Subject: FW: PMC - NDA 205552 (ibrutinib)

Hi Diane,
Pharmacyclics agrees with the PMC Study Completion and Final Report Submission dates below. One small clarification/detail (**in red**) has been added below.

Thanks
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Monday, August 26, 2013 1:24 PM
To: Christine Salido
Subject: PMC - NDA 205552 (ibrutinib)

Hi Chris,
Please take a look at this PMC regarding NDA 205552 (Ibrutinib) and let me know if you agree with the trial completion and final report submission information.
Thank you.
Regards,
Diane

PMC Description:	The Applicant will collect additional dissolution profile data (n=12 **at release and** (b) (4) **on stability**) using USP Apparatus Type 2 (Paddle) at 75 rpm in 3.0% w/v polysorbate 20 (Tween® 20) in 50 mM phosphate buffer pH 6.8 at 37.0 °C from at least ten drug product release batches and from the drug product stability-registration/ primary batches through 12 months of storage at the long-term condition. The Applicant will use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria.

The Applicant will submit the final report with the complete dissolution information/data and a proposal for the dissolution acceptance under a supplement to the NDA within 15 months from action date.

PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study Completion:	11/01/2014
	Final Report Submission:	02/01/2015

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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/s/

DIANE C HANNER
08/27/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, August 26, 2013 4:24 PM
To: 'Christine Salido'
Subject: PMC - NDA 205552 (ibrutinib)

Hi Chris,
Please take a look at this PMC regarding NDA 205552 (Ibrutinib) and let me know if you agree with the trial completion and final report submission information.
Thank you.
Regards,
Diane

PMC Description:	The Applicant will collect additional dissolution profile data (n=12) using USP Apparatus Type 2 (Paddle) at 75 rpm in 3.0% w/v polysorbate 20 (Tween® 20) in 50 mM phosphate buffer pH 6.8 at 37.0 °C from at least ten drug product release batches and from the drug product stability-registration/ primary batches through 12 months of storage at the long-term condition. The Applicant will use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria. The Applicant will submit the final report with the complete dissolution information/data and a proposal for the dissolution acceptance under a supplement to the NDA within 15 months from action date.	
PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study Completion:	11/01/2014
	Final Report Submission:	02/01/2015

CAPT Diane Hanner
Senior Program Management Officer
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/26/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, August 26, 2013 10:39 AM
To: 'Christine Salido'
Subject: NDA 205552 Ibrutinib

Hi Chris,
Please submit as soon as possible or identify location of the Appendices 9.3 (food effects) and 9.5 (pharmacokinetics report) of Trial PCYC-1102-CA with corresponding datasets.
Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/26/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, August 23, 2013 12:21 PM
To: 'Christine Salido'
Subject: FW: Double cking that the DRAFT e-mail regarding NDA 205552 (ibrutinib) PMRs. is okay to send.

Hi Chris,

Please provide your feedback regarding these DRAFT PMRs listed below and please be sure to include if you agree with the Date of Final Protocol Submission, Date of Trial Completion, and Date of Final Report Submission information.

This list is the a Re-cap of the DRAFT - PMRs that I know about to date:

PMRs:

PMR Description:
Objective: Evaluate the effect of hepatic impairment on ibrutinib PK.
Submit the final study report for trial PCI-32765CLL1006 entitled, "An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects With Varying Degrees of Hepatic Impairment"

PMR Schedule Milestones:	Final Protocol Submission:	N/A
	Trial Completion:	02/01/2015
	Final Report Submission:	08/01/2015
	Other:	MM/DD/YYYY

PMR Description:
Determine the effect of a strong CYP3A Inducer on Ibrutinib PK.
Submit the final study report for trial PCI-32765CLL1010 entitled, "An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects"

PMR Schedule Milestones:	Final Protocol Submission:	N/A
	Trial Completion:	Completed
	Final Report Submission:	04/01/2014
	Other:	MM/DD/YYYY

Please let me know if you have any questions.

Thank you.
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP

10903 New Hampshire Avenue
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/s/

DIANE C HANNER
08/23/2013

Hanner, Diane

From: Hanner, Diane
Sent: Wednesday, August 21, 2013 3:58 PM
To: 'Christine Salido'
Subject: Ibrutinib IR- NDA 205552

Hi,
Please address the following information request regarding NDA 205552 (ibrutinib):

In the mass balance trial # PCI-32765CLL1004, ibrutinib and PCI-45227 (M37) only made up 10 percent of the exposure of total radioactivity and the main circulating entities in humans were M21, M25, M34, M37 and unchanged drug. Please specify the contribution of each metabolite (M21, M25, M34, M37), in terms of percentage, to the total radioactivity of the administered drug.
Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/21/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, August 20, 2013 5:14 PM
To: 'Christine Salido'
Subject: QUESTION: NDA 205552 (Ibrutinib)
Attachments: Labels and labeling Guidance.pdf

Hi Chris,
Please see the FDA responses below (in blue) to your NDA 205552 (ibrutinib) questions.
Regards,
Diane

From: Christine Salido
Sent: Thursday, August 15, 2013 3:49 PM
To: 'Hanner, Diane'
Subject: QUESTION: NDA 205552 (Ibrutinib)

Hi Diane,
In regards to the FDA's advice/information request received on 14 August (see attached), Pharmacyclics would like to propose that the tradename on the container and carton labels appear in all capital letters (TRADENAME) rather than in title case. Does the FDA accept this proposal?

FDA Response: No, the trade name should not be in all capital letters. Please refer to the attached Labeling Guidance for Industry, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors".

Also we would like to clarify that the correct safety statement wording should read (b) (4) Is this revised statement acceptable to the FDA?

FDA Response: This is acceptable.

Thank you,
Chris

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/s/

DIANE C HANNER
08/20/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205552

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Pharmacyclics, Inc.
995 East Arques Avenue
Sunnyvale, CA 94085-4521

ATTENTION: Christine Salido
Executive Director, Regulatory Affairs

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) dated June 28, 2013, received June 28, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Ibrutinib Capsules, 140 mg.

We also refer to your July 12, 2013, correspondence, received July 12, 2013, requesting review of your proposed proprietary name, Imbruvica. We have completed our review of the proposed proprietary name, Imbruvica and have concluded that it is acceptable.

The proposed proprietary name, Imbruvica, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 12, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Diane Hanner at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
08/16/2013

From: Hanner, Diane
To: "Christine Salido"
Subject: IR for NDA 205552 (ibrutinib)
Date: Friday, August 16, 2013 11:52:00 AM

Hi Chris,

Please address the following information request regarding NDA 205552 (ibrutinib):

We have just received a safety report of progressive multifocal leukencephalopathy (PML) in a subject enrolled in an investigator initiated trial of ibrutinib. Please send narratives for any subject with PML in any ibrutinib trial.

Thank you.

Regards,

Diane

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/s/

DIANE C HANNER
08/16/2013

From: Hanner, Diane
To: "Christine Salido"
Subject: NDA 205552 (ibrutinib) questions for the Monday post-midcycle meeting
Date: Friday, August 16, 2013 2:06:00 PM
Attachments: Midcycle Communication meeting Agenda.doc

Hi Chris,

Attached please find a DRAFT Agenda for the up-coming NDA 205552 meeting on Monday, August 19, 2013, at 3:00 p.m. to 4:00 p.m.

We will be using the following dial in numbers:

Sponsor's dial in numbers.

Dial in no.: (b) (4)

Participant Code: (b) (4)

Also, please be ready to address the questions at the meeting.

1. How did you arrive with the dose level of 560 mg for patients with MCL, and 420 mg for patients with CLL/SLL?

2. What efforts have you done to further understand the following safety issues?

2.1. hemorrhagic risk

2.2. second primary malignancies

Please let me know if you have any questions.

Thank you.

Regards,

Diane

Agenda
Midcycle Communication
NDA 205552

- Proprietary Name: IMBRUVICA name requested
- Established/Proper Name: Ibrutinib (PCI-32765)
- Dosage Form: Oral Capsule
- Strengths: 140 mg

Item #1

Introductions of the Pharmacyclics, Inc., participants

Item #2

Introductions of the FDA participants

Item #3

Brief introduction regarding the reason for the meeting:

"We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application."

Item #4

Discuss regarding the questions sent to Pharmacyclics:

1. How did you arrive with the dose level of 560 mg for patients with MCL, and 420 mg for patients with CLL/SLL?

2. What efforts have you done to further understand the following safety issues?

    2.1. hemorrhagic risk
    2.2. second primary malignancies

Item #5

Discuss the discipline specific input regarding their reviews of the application including any significant issues identified that need to be discussed.

a. Clinical

b. Statistics

c. Clin Pharm

d. CMC

e. Biopharm

f. Pharm Tox

Item #6

Discuss other disciplines specific input (including consults) regarding their respective reviews of the application including any significant issues identified that need to be discussed.

Item #7

Discuss the disclosure of any important dates that must be conveyed at this time.

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/s/

DIANE C HANNER
08/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552 **INFORMATION REQUEST**

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PCI-32765 (ibrutinib).

We also refer to your June 28, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by August 23, 2013, in order to continue our evaluation of your NDA.

1. For starting material (b) (4) it is unknown whether high levels of residual solvents can impact the subsequent synthesis process. Therefore, add the residual solvent control (with proposed acceptance criteria) to the specification for (b) (4).

2. You have indicated that the analytical method (QCM-132.7) used for determination of drug substance identity and assay will use either an HPLC or UPLC equipment. Please clarify which one is considered as a regulatory method that will be used for routine release and stability testing. The other one could be designated as an alternative analytical method. At a given time only one method should be used for testing.

3. You have also indicated that the analytical method (QCM-130.9) used for determination of drug product identity, assay and content uniformity will use either an HPLC or UPLC equipment. Please clarify which one is considered as a regulatory method that will be used for routine release and stability testing. The other one could be designated as an alternative analytical method. At a given time only one method should be used for testing.

4. Tighten the acceptance limit for total degradation products in the drug product specification based on batch data.

5. [redacted] limit in the drug product specification based on batch data or demonstrate that the active ingredient is stable at the proposed acceptance limit [redacted]%).

6. Revise the long term (25°C/60%RH) testing time points for the annual drug product stability program as follows: 0, 3, 6, 9, 12, 18, 24 and 36 months.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
08/16/2013

Hanner, Diane

From: Christine Salido <csalido@pcyc.com>
Sent: Wednesday, August 14, 2013 3:52 PM
To: Hanner, Diane
Subject: RE: Information request NDA 205552 (ibrutinib)

Hi Diane,
Narrative summaries for the five CLL patients (032-102, 123-101, 032-307, 200-305 and 320-301) who experienced severe bleeding were provided as part of the PCYC-1102-CA CSR (located in module 5.3.5.2), under Attachment 4 (refer to the CSR table of contents) submitted to the NDA. Please let me know if you would like me to resubmit these 5 narrative summaries to the NDA or provide via email.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Wednesday, August 14, 2013 12:15 PM
To: Christine Salido
Subject: Information request NDA 205552 (ibrutinib)

Hi,
Please address the following NDA 205552 (ibrutinib) information request and please respond by the morning of Friday, August 16th:

Please submit a narrative of the history of five CLL patients who experienced severe bleeding in the CLL trial population, including past medical history, concomitant medications, event course, day of study the event occurred, outcome of the event, and dose of study drug at the time of the event.
Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

ADVICE/INFORMATION REQUEST

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (NDA 205552) Ibrutinib (PCI-32765).

We request that you implement the following information:

A. Container Labels

1. Ensure the proprietary name on the container label appears in title case (e.g. Tradename) to optimize the readability of the proprietary name.

2. Ensure the established name appears at ½ the font size as of the proprietary name taking into account all pertinent factors, including font size, typography, layout, contrast, coloring and other printing features.

3. Delete the (b) (4) appearing on the statement of net quantity because this net quantity competes with the product strength for prominence. Thus, the net quantity may be interpreted as the strength of the product. Additionally, relocate the net quantity statement to the lower third of the principle display panel (PDP) away from the statement of strength.

4. Add the safety statement, “Swallow capsule whole on empty stomach”, to the principle display panel of the container label.

5. We note two (b) (4) statements are proposed on the label. We recommend deleting the (b) (4) statement in the upper right portion of the label.

6. Debold the “Rx Only” statement.

B. Carton Labeling

1. Ensure the carton labeling complies with recommendations A1 through A6.

2. Delete the [redacted] (b) (4) from the two side panels to inform practitioners that the panel is a side panel and not the principle display panel.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

DIANE C HANNER
08/14/2013

From: Hanner, Diane
To: "Christine Salido"
Subject: FW: Information request - NDA 205552 (ibrutinib)
Date: Monday, August 12, 2013 1:21:00 PM
Attachments: Ibrutinib IR.DOC

Hi,

I have attached the information request for your ease of reference.

Regards,

Diane

From: Hanner, Diane
Sent: Monday, August 12, 2013 1:17 PM
To: 'Christine Salido'
Subject: Information request - NDA 205552 (ibrutinib)

Hi

Please address the following information request regarding NDA 205552 (ibrutinib). Please response by COB, Wednesday August 14.

1. Provide a summary table for the patients in the CLL clinical trial PCYC-11102-CA (treated at a dose of 420 mg daily, N=51)and their response at each time point during the trial. An example of the format and the information needed is included as an attachment. Please note that the numbers in the table refer to study day, where the reference date is the first day of ibrutinib dose. For the "not evaluated" column, please only include information for missed scheduled visits.

2. Clarify the definition of progressive disease included in Table 1, Group A of the document "Response to Information Request" sent Friday August 9th and whether the criteria "increase > 50%" for lymphadenopathy, hepatomegaly, or splenomegaly is from the previous measurement, nadir measurement, or from baseline measurements.

Thank you.

Regards,

Diane

CAPT Diane Hanner

Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

1. Provide a summary table for the patients in the CLL clinical trial PCYC-11102-CA (treated at a dose of 420 mg daily, N=51)and their response at each time point during the trial. An example of the format and the information needed is included as an attachment. Please note that the numbers in the table refer to study day, where the reference date is the first day of ibrutinib dose. For the "not evaluated" column, please only include information for missed scheduled visits.

Patient	LN Response			Spleen/Liver Response			Peripheral blood lymphocyte response			Hematologic response (ANC, Platelets, Hemoglobin)		
	Yes	No	Not evaluated	Yes	No	Not evaluated	Yes	No	Not evaluated	Yes	No	Not evaluated
032-XXX	D28, D84, D112		D56	D28 (spleen), D84 (spleen/liver), D112 (liver)		D56	D84, D112		D56	D28 (ANC/ platelet) D42 (platelet) D84 (hemoglobin, ANC)		D56

2. Clarify the definition of progressive disease included in Table 1, Group A of the document "Response to Information Request" sent Friday August 9th and whether the criteria "increase > 50%" for lymphadenopathy, hepatomegaly, or splenomegaly is from the previous measurement, nadir measurement, or from baseline measurements.

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/s/

DIANE C HANNER
08/12/2013

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, August 08, 2013 6:16 PM
To: 'Christine Salido'
Subject: IR request for Ibrutinib, NDA 205552

Hi Chris,

Please let me know if a Pharmacovigilance Plan has been submitted to the Ibrutinib, NDA 205552.

If you haven't submitted a Pharmacovigilance Plan then please let me know if you have any intentions on making such a submission.

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **ibrutinib** following market approval.

The following guidance's regarding pharmacovigilance planning have been attached below for your convenience.
Please see the *FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005)*, and the *FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005)* for additional information.

If Pharmacovigilance Plan is available, please include it in the **NDA** application in the appropriate module so it can be reviewed accordingly.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/08/2013

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, August 08, 2013 10:11 AM
To: 'Christine Salido'
Subject: Information Request NDA 205552

Hi Chris,

Please address the following information request and please respond by Friday, August 9th.

1. Provide the full report of the bone marrow evaluation of the patient in CLL trial PCYC-1102-CA with a complete response.
2. Provide the definition used to determine an event for the duration of response measurement. Explain the definition used for a loss of response.
3. Clarify the response assessment criteria used for the CLL trial and if a patient needed to meet peripheral blood assessment criteria AND nodes, liver, and spleen criteria or one or the other.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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/s/

DIANE C HANNER
08/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552 **INFORMATION REQUEST**

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PCI-32765 (ibrutinib).

We also refer to your June 28, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by August 13, 2013, in order to continue our evaluation of your NDA.

1. Your drug substance batch release data showed that impurities (b) (4) (their qualification reports will be submitted post approval) can be controlled well below the ICH qualification threshold (0.15%). Refer to the data from recently manufactured batches, including Drug Substance Commercial Lots 131098, 131097, 131096, and 131061; Drug Substance Registration Stability Lots 121340, 121339 and 121338, and Lots 121312 and 121299; and Drug Substance Primary Stability Lots 121075 and 121074. The stability data did not show significant increases at 25 °C/60% RH. Since the levels of these impurities are consistently low and levels do not appreciably increase over time, tighten the proposed drug substance acceptance limits for impurities (b) (4) at the ICH qualification threshold (0.15%), at present until the general toxicity qualification studies are completed.

2. The description of the drug product manufacturing process is very brief. Specifically, the described manufacturing process parameters consist of (b) (4) Provide updated manufacturing process and controls information in section 3.2.P.3.3 Description of Manufacturing Process and Process Controls that includes this information.

3. Tighten the proposed drug product acceptance limits for the three specified degradation products, [redacted] (b) (4) The acceptance limits for these impurities were proposed based on the limited batch analysis data using mean ± 3SD. The statistical approach of using mean ± 3 SD is not appropriate due to the limited batches used in the analysis. Note that pooling of data for statistical analysis should be justified. In addition, stability data for those two specified impurities did not show discernible increase up to 24 month storage at the long term conditions (25°C/60%RH). In the absence of qualification study to support the safety of those impurities, propose the acceptance limits for the degradation products that have been observed in the clinical batches, i.e. [redacted] (b) (4)

4. It is recommended that you tighten the acceptance criteria for the drug substance and drug product specification for [redacted] (b) (4) based on the batch analysis data and the current manufacturing capability.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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ALI H AL HAKIM
08/08/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, August 06, 2013 1:45 PM
To: 'Christine Salido'
Subject: NDA 205552 Ibrutinib QT/IRT information request

Hi Chris,

This information is acceptable assuming that you will provide the R code and submit the related ECG waveforms to the ECG warehouse.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, August 05, 2013 6:14 PM
To: Hanner, Diane
Subject: QUESTION/CLARIFICATION: NDA 205552 Ibrutinib QT/IRT information request

Hi Diane,
I wanted to provide clarification regarding requested items a - c. Information requested for items a - c was originally submitted in the NDA (Reviewable Unit 2, sequence 0003 dated 31 May 2013):

a. The annotated CRF is located in module 5.3.5.2 under the CSR for PCYC-1102-CA, under folder Datasets, under folder Annotated CRF

b. The data definition file is located in module 5.3.5.2 under the CSR for PCYC-1102-CA, under folder Datasets, under folder Tabulations

c. R programming code was used, not SAS, for the primary statistical and exposure-response analyses submitted in the NDA. The R programming code is immediately available and uses the previously submitted ECG raw and analysis legacy data sets as source. Is this acceptable to the FDA to provide the R code? Replicating the analyses using SAS programming code would take approximately 1 month to complete.

Thank you,
Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, August 02, 2013 10:20 AM
To: Christine Salido
Subject: NDA 205552 Ibrutinib QT/IRT information request

Hi Chris,

Please submit the following information to NDA 205552:

a. Annotated CRF

b. A data definition file which describes the contents of the electronic data sets

c. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses

d. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

e. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

f. Narrative summaries and case report forms for any

   i. Deaths

   ii. Serious adverse events

   iii. Episodes of ventricular tachycardia or fibrillation

   iv. Episodes of syncope

   v. Episodes of seizure

   vi. Adverse events resulting in the subject discontinuing from the study

g. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

h. A completed Highlights of Clinical Pharmacology Table (attached).

Thank you,

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/06/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, August 02, 2013 3:05 PM
To: 'Christine Salido'
Subject: Information requests for ibrutinib (NDA 205552)

Hi Chris,

Please address the following information request regarding ibrutinib NDA 205552:

Also, please let us know when you will be submitting the NDA safety update(s).

NDA Information Request (NDA 205552)
1. Submit modified ADAE datasets for clinical trials PCYC-1102-CA and PCYC-1104-CA that includes the following additional columns:
1.1. Ibrutinib dose (e.g., 420 mg per day) at the AE start date
1.2. Modified ibrutinib dose (e.g., “280 mg every other day”, or “suspended for 10 days then resumed at 420 mg per day”) as a result of the AE (if no change, use the same information as in 1.1)
Please submit the modified datasets by **Monday, August 5, 1pm EST.**

Thank you,
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/02/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, August 02, 2013 10:08 AM
To: 'Christine Salido'
Subject: RE: IR for NDA 205552 (ibrutinib)

Hi Chris,
Please try to respond by c.o.b Wednesday, August 7th.
Thanks,
Diane

From: Hanner, Diane
Sent: Friday, August 02, 2013 9:58 AM
To: 'Christine Salido'
Subject: IR for NDA 205552 (ibrutinib)

Hi Chris,

Please address the following information request regarding NDA 205552 (ibrutinib):

Please provide the death narratives for the following subjects:

364-003
364-007
368-004
368-007

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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Silver Spring, Maryland 20993
(301) 796-2330
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
08/02/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552 **INFORMATION REQUEST**

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PCI-32765 (ibrutinib).

We also refer to your June 28, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by August 9, 2013, in order to continue our evaluation of your NDA.

1. Both (b) (4) and (b) (4) formulations with three different processes (A, B and C) were used in the pivotal clinical trials PCYC-1102 and PCYC-1104. Provide a table listing the patient ID and the corresponding formulation (process) used for each specific patient in these two trails.

2. It is noted that the dissolution values in the batch analysis (3.2.P.5.4) are for the time point at 45 minutes only. Provide the dissolution data at other time points (5, 10, 15, and 30 minutes) and the dissolution method used (QCM-140 or QCM-164).

3. There is a set of dissolution values (mean, min and max) provided in the stability data section (3.2.P.8.3). Clarify what dissolution method was used (QCM-140 or QCM-164) and at what time point the data were collected. Provide the dissolution data at other time points (including 5, 10, 15, 20 and 30 minutes).

4. Provide SAS data of all available Registration, Primary and Supportive stability data for drug product in the format below. Please provide separate SAS files for Registration, Primary and Supportive Stability data.

Test	Storage Temperature	Storage RH	Package	Dose	Batch Number	Time (in Month)	Sample Replicate Number	Result	Unit
Assay									
…									
(b) (4)									
…									

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
08/01/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, July 30, 2013 1:12 PM
To: 'Christine Salido'
Subject: Foreign Inspections- NDA 205552 ibrutinib

Hi Chris,

FDA is currently in the process of scheduling inspections for facilities listed in support of your NDA. FDA is working to ensure that these inspections happen in a timely manner as this product has been designated a breakthrough therapy. Foreign facilities listed in your application will be able to communicate inspection dates to you when they are finalized between the site and the Agency. Inspections dates for August are currently being considered between the Agency and your API facilities. Contact your facilities to determine finalized inspection dates.

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
07/30/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, July 29, 2013 9:39 AM
To: 'Christine Salido'
Subject: NDA 205552 ibrutinib:

Hi Chris,
The revised schedule is acceptable.
Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, July 26, 2013 9:48 PM
To: Hanner, Diane
Subject: Re: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

Thank you Diane!
Chris

Sent from my iPhone

On Jul 26, 2013, at 4:13 PM, "Hanner, Diane" <Diane.Hanner@fda.hhs.gov> wrote:

> Hi,
>
> Thanks for the update. I will pass this information on to the team in order to make sure that they approve the revised schedule.
>
> Regards,
>
> Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, July 26, 2013 7:05 PM
To: Hanner, Diane
Subject: FW: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

Hi Diane,

I wanted to provide an update on the annotated images due 29 July. We are planning to send you images from OSU (on CDs) on Monday or Tuesday next week (29/30 July) via overnight delivery. We are planning to send you the images from MDACC (on CDs) on Wednesday or Thursday next week (31 July/1 August) via overnight delivery.

Thanks

Chris

From: Christine Salido
Sent: Friday, July 26, 2013 9:50 AM
To: 'Hanner, Diane'
Subject: RE: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

Thanks Diane!

I have a few questions regarding the requested annotated images due on July 29. There are 600+ images that need to be hyperlinked/bookmarked and a table of contents generated and I am not sure we will be able to have all images processed/ready by Monday so I wanted to discuss and propose few options.

Thanks again,

Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, July 26, 2013 9:45 AM
To: Christine Salido
Subject: RE: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

Hi,

Sure! I will call you at 2:00 p.m. (EST).

What is the issue that you want to discuss?

Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, July 26, 2013 12:42 PM
To: Hanner, Diane
Subject: RE: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

Hi Diane,

Would you be able to call me at 408-215-3039?

Thanks

Chris

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, July 26, 2013 9:40 AM
To: Christine Salido
Subject: RE: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

You're welcome.

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Friday, July 26, 2013 12:39 PM
To: Hanner, Diane
Subject: RE: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

Thanks Diane!

From: Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]
Sent: Friday, July 26, 2013 9:26 AM
To: Christine Salido
Subject: NDA 205552 ibrutinib: FDA responses regarding sponsor audit

Hi Chris,

Please see the FDA responses below to your inquiry.

Regards,

Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Christine Salido
Sent: Monday, July 15, 2013 11:05 AM
To: Hanner, Diane
Subject: NDA 205552 ibrutinib: follow up to 7/12 sponsor orientation meeting

Hi Diane,

I hope you had a restful weekend! I wanted to follow up on a few items discussed at the 7/12 sponsor orientation meeting:

- Could you please clarify if the FDA has current plans to schedule a sponsor audit of Pharmacyclics' location in Sunnyvale, CA? If so, what would be the proposed timeframe? To date, I have not been contacted by anyone at the FDA regarding the scheduling of this audit.

FDA Response: ORA's San Francisco District Office will contact your firm, for the conduct of the actual site audit as sponsor of NDA 205552. CDER has not been advised when this specific calendar date will be scheduled, as of this morning, July 26, 2013.

- There was mention of a mid-cycle NDA review meeting that could be potentially combined with an in-person label negotiation meeting. Pharmacyclics would propose to schedule this meeting

sometime during the week of 26 August, if possible. In addition, will there also be a need for a late-cycle NDA review meeting?

FDA Response: We will inform you regarding the mid-cycle NDA review meeting after determining the filing status of the application.

Please let me know if there is anything I can do to assist you or the FDA regarding these items.

Thank you,

Christine Salido

Regulatory Affairs

Pharmacyclics, Inc.

408-215-3039

csalido@pcyc.com

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/s/

DIANE C HANNER
07/29/2013

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, July 25, 2013 10:03 AM
To: 'Christine Salido'
Subject: FW: NDA 205552 - Clinical Information Request - 24 July

Hi Chris,

The Division acknowledges your justification to include patients with (b) (4) in the proposed labeling. However, to facilitate the review of the application, we still request that you submit a labeling version (PDF format is acceptable) that does not include the patients with (b) (4). Submit by 8AM EST, Friday, July 26, 2013.

Regards,
Diane

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Wednesday, July 24, 2013 6:41 PM
To: Hanner, Diane
Subject: NDA 205552 - Clinical Information Request - 24 July
Importance: High

Hi Diane,
Attached as a courtesy copy is the revised labeling information (including USPI clean version and tracked changes version) requested by 24 July 2013. This information is being submitted to the NDA today.

Thank you,
Chris

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/s/

DIANE C HANNER
07/25/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, July 23, 2013 11:40 AM
To: 'Christine Salido'
Subject: NDA 205552 - ibrutinib-annotated images should be in PDF and JPEG versions

Hi,

Please see the following request regarding NDA 205552 (ibrutinib):

Because of FDA restrictions with software installation to FDA computers, please send the annotated images in PDF and JPEG versions. Please include a table of contents with hyperlinks to facilitate the navigation of the images.
Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
07/23/2013

Hanner, Diane

From: Hanner, Diane
Sent: Tuesday, July 23, 2013 10:27 AM
To: 'Christine Salido'
Subject: Ibrutinib; NDA 205552- information request 7-23-13

Hi,

Please address the following information request regarding NDA 205552:

Information Request

- Provide information regarding the status of the through QT study (PCI-32765CLL1007) that was submitted for review by FDA QT/IRT as part of a meeting package submitted on 1/4/13.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
07/23/2013

Hanner, Diane

From: Hanner, Diane
Sent: Monday, July 22, 2013 4:57 PM
To: 'Christine Salido'
Subject: NDA 205552 -ibrutinib- Clinical Information Request- FDA response

Hi Chris,

FYI- Below please find the FDA Response regarding NDA 205552 (ibrutinib):

1. OSU data on DVD is acceptable if data cannot fit on 1 CD.
2. MDACC Data: Option A

Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, July 22, 2013 3:26 PM
To: Ali Ibrahim, Ebla
Cc: Hanner, Diane
Subject: FW: NDA 205552 - Clinical Information Request
Importance: High

Hi Ebla,
We are actively working on the requested radiology images for OSU and MDACC. Regarding item 3.4 of your request, we were given the following options on how to provide the information to FDA:

OSU would provide CT images on CD. Is a DVD acceptable if not all data fits on 1 CD, and J-Peg files identifying target lesions and measurements? OSU software will be included on the CD.

MDACC - we have 2 options. Does FDA prefer option A or B:

- Option A: provide all images on CD along with their (different) software for reading or
- Option B: provide a computer with all image data and software on the hard drive.

We are trying to obtain this information as soon as possible but it may take 1 additional business day longer than the requested delivery of 29 July. I hope this potential delay is not going to cause a problem. I will also provide the information via email as a courtesy so you have it readily available.

Thank you,
Chris

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Friday, July 19, 2013 4:34 PM
To: Christine Salido
Cc: Hanner, Diane
Subject: NDA 205552 - Clinical Information Request
Importance: High

Dear Christine Salido,

Please find attached a Clinical Information Request. Please submit your responses per the time line in the attached information request. Please confirm that you have received this email. Thank you.

Ebla Ali Ibrahim, MS
Lead Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

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/s/

DIANE C HANNER
07/22/2013

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, July 19, 2013 7:34 PM
To: 'csalido@pcyc.com'
Cc: Hanner, Diane
Subject: NDA 205552 - Clinical Information Request

Importance: High

Attachments: N205552 Clinical Information Requests.pdf

Dear Christine Salido,

Please find attached a Clinical Information Request. Please submit your responses per the time line in the attached information request. Please confirm that you have received this email. Thank you.

N205552 Clinical Information R...

Ebla Ali Ibrahim, MS
Lead Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

N205552 Clinical Information Request

Submit the following information by the following dates:

24 July 2013: Items 1.1, 1.2, and 1.3

25 July 2013: Items 2, 3.2, 3.3, and 3.5

29 July 2013: Items 3.1 and 3.4

1. Submit revised labeling with the following revisions:

1.1. Exclude patients with (b) (4) Your application does not have enough (b) (4)

1.2. Include a warning and precaution for (b) (4)

1.3. Revise the order of the System Organ Class in Tables 1 and 2 according to clinical significance (top most rows, most significant; bottom rows, less significant).

2. Submit revised TR datasets for clinical trials PCYC-1102-CA and PCYC-1104-CA that include a description of the location of each lymph node measurement (e.g., left axilla, right inguinal, etc.)

3. You have not submitted adequate information to mitigate the concerns for financial conflicts of interest for 2 clinical sites: (b) (6)
Submit the following information:

3.1. For any investigator at (b) (6) or (b) (6) who received any fraction of the significant payments of other sorts, including (b) (6) and (b) (6) provide details of the investigator involvement in the assessment of efficacy and safety for any patient in clinical trial (b) (6) or (b) (6) Include the dates and times of clinical investigator interactions with patients, and nature of assessments. Explain in detail all the steps taken to minimize the potential bias of the clinical study results.

3.2. For clinical trial PCYC-1102-CA, perform additional efficacy and safety analyses that segregates the patients into 3 groups: patients at OSU, patients at MDACC, and other patients. Prove that the efficacy and safety findings in the 3 groups are consistent with each other. Do not include patients with (b) (4) The primary analysis population should consist of the 48 patients with relapsed/refractory CLL treated at the 420 mg dose level.

3.3. For clinical trial PCYC-1104-CA, perform additional efficacy and safety analyses that segregates the patients into 3 groups: patients at OSU, patients at MDACC, and other patients. Prove that the efficacy and safety findings in the 3 groups are consistent with each other. The primary analysis population should consist of the 111 patients with relapsed or refractory MCL.

3.4. For CLL patients at OSU and MDACC enrolled in PCYC-1102-CA and who achieved CR or PR, provide annotated imaging results of CT and FDG-PET scans that document the achievement of CR or PR. The

annotation for each image should include: USUBJID, measurement scale, bidimensional measurement of lymph nodes, location, date, study day. Include the imaging studies at baseline.

3.5. Submit topline results for response rate and safety for patients randomized to the ibrutinib arm in clinical trial PCYC-1112-CA. Include baseline demographic information.

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/s/

EBLA ALI IBRAHIM
07/19/2013

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, July 18, 2013 10:03 AM
To: 'Christine Salido'
Subject: Ibrutinib; NDA# 205552

Hi,
Please address the following information request regarding PBPK Modeling:

We noticed that you used PBPK modeling to predict drug-drug interactions for Ibrutinib.

- You should further investigate the potential PK differences between healthy subjects and oncology subjects (for example under fasted condition) with respect to formulation differences, age differences and/or other factors using your PBPK models.

- Subsequently, the effect of CYP3A4 inhibitors/inducers on ibrutinib PK in the prototype oncology population should be predicted.

- You should also simulate ibrutinib PK in subjects with mild/moderate/severe hepatic impairment.

Please submit model files used to generate the final PBPK simulations (compound and population files, such as .cmp, .lbr, and .wks). The model files should be executable using SimCYP software Version 12.2. These files may be submitted via CD.

Please provide a response by COB, **August 1, 2013.**

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
07/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

NDA ACKNOWLEDGMENT

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
9995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: PCI-32765 (Ibrutinib 140 mg Capsules)

Date of Application: June 28, 2013

Date of Receipt: June 28, 2013

Our Reference Number: NDA 205552

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 27, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 205552** submitted on June 28, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products

5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

DIANE C HANNER
06/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102688

MEETING MINUTES

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ibrutinib (PCI-32765).

We also refer to the teleconference meeting between representatives of your firm and the FDA on May 7, 2013. The purpose of the meeting was to discuss the fact that the Agency did not oppose the use of cross-over in the RESONATE trial. A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C

Meeting Category: Guidance teleconference meeting

Meeting Date and Time: May 7, 2013, at 11:00 a.m.

Meeting Location: CDER WO 2201

Application Number: IND 102688

Product Name: Ibrutinib (PCI-32765)

Indication: Chronic Lymphocytic Leukemia

Sponsor/Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo de Claro, M.D.

Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Richard Pazdur, M.D., Director Office of Oncology Products
- Ann Farrell, M.D., Director DHP
- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst, Clinical Team Leader, DHP
- R. Angelo de Claro, M.D., Team Leader (Acting), DHP
- Nicole Verdun, M.D., Medical Officer, DHP
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES:

- Urte Gayko, Ph.D., Senior Vice President, Regulatory Affairs (Pharmacyclics)
- Lori Kunkel, M.D., Chief Medical Officer (Pharmacyclics)
- Maria Fardis, Ph.D., Chief of Oncology Operations and Alliances (Pharmacyclics)
- Jesse McGreivy, M.D., Vice President, Clinical Science (Pharmacyclics)
- Fong Clow, Sc.D., Vice President, Biometrics (Pharmacyclics)

- Christine Salido, B.S., Executive Director, Regulatory Affairs (Pharmacyclics)
- John Seaman, Pharm. D, Senior Director, Global Regulatory Affairs (Janssen R&D, LLC)
- Sen Hong Zhuang, M.D., Ph.D., Vice President, Clinical Research (Janssen R&D, LLC)
- Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs (Janssen R&D, LLC)
- Jerry Retkwa Manager, R.Ph., M.S., Global Regulatory Affairs (Janssen R&D, LLC)

1.0 BACKGROUND

The Agency requested a Type C teleconference on May 6, 2013, to discuss the PCI-32765 (ibrutinib) Phase 3 clinical trials development program for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have relapsed or have refractory disease and have previously received at least one prior therapy.

The meeting was scheduled for May 7, 2013.

2.0 DISCUSSION

The Agency recommended that the Sponsor allow for cross-over in the RESONATE clinical trial. The Agency discussed that this may be implemented through a protocol amendment or through an expanded access program. The Agency will schedule a meeting to discuss amendments to the statistical analysis plan and protocol regarding the cross-over and interim PFS analysis.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The Agency will have a discussion with EMA regarding the use of cross-over.

5.0 ACTION ITEMS

The Sponsor will submit a meeting request to address the discussion points above.

6.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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/s/

DIANE C HANNER
05/09/2013

ROMEO A DE CLARO
05/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102688

MEETING MINUTES

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ibrutinib (PCI-32765).

We also refer to the meeting between representatives of your firm and the FDA on April 9, 2013. The purpose of the meeting was to discuss the top-line efficacy and safety data in support of an NDA filing for ibrutinib as monotherapy for the treatment of patients with Mantle Cell leukemia (MCL) with at least 1 prior therapy. Your firm also requested that FDA consider mature clinical data from study PCYC-1102-CA as a basis for accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with at least 1 prior therapy as part of the NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-NDA meeting

Meeting Date and Time: April 9, 2013, at 3:00 p.m.

Meeting Location: CDER WO 1419

Application Number: IND 102688

Product Name: Ibrutinib (PCI-32765)

Indication: Chronic Lymphocytic Leukemia

Sponsor/Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo De Claro, M.D.,

Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Ann Farrell, M.D., Director DHP
- R. Angelo de Claro, M.D., Team Leader (Acting) DHP
- Karen McGinn, M.S.N., CRNP, Medical Officer DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Rachelle Lubin, Pharm.D., Clinical Pharmacology Reviewer, DCP5
- Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader DCP5, (phone)
- Shwu-Luan Lee, Ph.D., Pharmacology/Toxicology Reviewer, DHOT
- Christopher Sheth, Ph.D.,Pharmacologist,DHOT
- Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor, DHOT
- Kevin Wright, Pharm D, Safety Evaluator, Division of Medication Error and Prevention Analysis (DMEPA)
- Janice Brown, Ph.D., CMC Lead, ONDQA, Division 3, Branch 5
- Qin Ryan, M.D., Ph.D., Medical Officer for Safety, DHP

- Christopher Sese, Independent Assessor, Eastern Research Group, Inc.
- Nisha Patel, Pharm D., Regulatory Review Officer, OPDP
- Cunlin Wang, M.D.. PhD, Team Leader, OSE
- Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst, DRISK
- Anthony Orencia, M.D., F.A.C.P., Medical Officer, OSI
- James Schlick, R.P.H., Acting Team Leader, DMEPA
- Katherine Coyle, Pharm.D., OSE, DPV
- Tamy Kim, Pharm.D., Associate Director of Regulatory Affairs, OHOP
- Theresa Carioti, M.P.H., Regulatory Project Team Leader, (Acting) DHP
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES:

- Lori Kunkel, M.D., Chief Medical Officer, Pharmacyclics
- David Loury, Ph.D., Pharmacyclics, Inc., Chief Scientific Officer
- Maria Fardis, Ph.D., Pharmacyclics, Inc., Chief of Oncology Operations and Alliances
- Urte Gayko, Ph.D., Pharmacyclics, Inc., Senior Vice President, Regulatory Affairs
- Jesse McGreivy, M.D., Pharmacyclics, Inc., Vice President, Clinical Science
- Fong Clow ScD, Executive Director, Biometrics, Pharmacyclics
- Christine Salido, BS, Pharmacyclics, Inc., Executive Director, Regulatory Affairs
- Juthamas Sukbuntherng, Ph.D., Pharmacyclics, Inc., Senior Director, Clinical Pharmacology, DMPK
- (b) (4)
- John Seaman, Pharm.D., Senior Director, Global Regulatory Affairs, Janssen R&D, LLC
- Sen Hong Zhuang, M.D., Ph.D., Senior Director, Clinical Research, Janssen R&D, LLC
- Terri Williams Ph.D., Associate Director, Global Regulatory Affairs, Janssen R&D, LLC
- Craig Tendler M.D., Vice President, Late Development and Global Medical Affairs, Janssen R&D, LLC

- Mann Fung, M.D., Janssen R&D, LLC, Vice President, Compound Development Team Leader

1.0 BACKGROUND

The Sponsor requested a Type B clinical meeting on February 8, 2013, to discuss PCI-32765 (ibrutinib) which was designated Fast Track on October 29, 2012, for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have relapsed or have refractory disease and have previously received at least one prior therapy.

Additionally, the Sponsor also requested that FDA consider PCI-32765 (ibrutinib) which was designated for Fast Track on December 18, 2012, for the treatment of patients with Mantle Cell lymphoma (b) (4)
(b) (4)

The meeting was granted on February 8, 2013, and it was scheduled for April 9, 2013.

2. DISCUSSION

Question 1

Does the FDA agree that the durable response data (ORR 68.5%, with an estimated median DOR of 17.5 months achieved in study PCYC-1104-CA with 111 MCL patients, and with supporting Phase 1 (PCYC-04753) data, provides adequate efficacy data to support the filing of an NDA under the Breakthrough Therapy Designation for ibrutinib for the treatment of patients with MCL with at least 1 prior therapy?

FDA Response:
The Agency agrees that your durable response data support an NDA submission; however, filing decisions will be made 60 days after the receipt of the NDA.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion

Question 2

Given that ibrutinib has received Breakthrough Therapy designation for the treatment of patients with MCL, would the data provided in the proposed NDA support a full approval rather than an accelerated approval under subpart H?

FDA Response:
The type of approval will be determined during the NDA review. Your current randomized trials in MCL and CLL would be acceptable trials to confirm clinical benefit.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Would comparison to an external, contemporaneous control to estimate response and outcomes to ibrutinib treatment in relapsed MCL patients strengthen our position? Please refer to the ICH E10 guideline, Choice of Control Group and Related Issues in Clinical Trials, in which the external control design is used in situations in which the effect of treatment is dramatic and the usual course of the disease is highly predictable.

Meeting Discussion:
No discussion

Question 3

Would the FDA consider mature clinical data that demonstrates durable responses from study PCYC-1102-CA as a basis for accelerated approval for the treatment of patients with CLL/SLL with at least 1 prior therapy, (b) (4)

FDA Response:
Yes. However, the indication will be a review issue.
Please discuss the timing of the submissions of these two applications at the meeting.

Sponsor Response
Pharmacyclics proposes to submit one NDA to support both the MCL and CLL indications and would like to discuss the implications to the timeline and review process during the meeting. Module 5 will include clinical study reports that supports both the CLL and MCL filing, and there would be no change to the content of the clinical data that was previously proposed. The NDA would include one Integrated Summary of Safety, Integrated Summary of Efficacy and Clinical Overview, respectively. Each of these documents in the eCDT structure will include a subsection for MCL data and a subsection for CLL data.

Pharmacyclics proposes to submit the NDA for relapsed/refractory MCL and CLL as a rolling submission according to the following schedule:

- Module 4 (Nonclinical Study Reports): 30 April 2013
- Module 5 (Clinical Study Reports): 31 May 2013
- Module 1 (Administrative), Module 2 (Summaries), Module 3 (CMC): 28 June to 5 July 2013. Pharmacyclics will communicate the exact date of submission by 1 June 2013.

Meeting Discussion:
The Agency concurs with the Sponsor's proposal. The Agency and the Sponsor agreed to the definition of a complete NDA which will include a late submission for the 3 months stability update within 30 days of the last NDA module submission.

Question 4

Does the FDA agree that the overall safety data base defined below would provide adequate safety data to support an initial NDA for ibrutinib for MCL and CLL/SLL under Breakthrough Therapy Designation?

- N = 120 in monotherapy safety dataset for MCL from 111 patients in study PCYC-1104-CA (560 mg daily) and 9 patients in study PCYC-04753 (range of Phase 1 doses)
- N =148 for CLL/SLL monotherapy from study PCYC-1102-CA (132 patients, doses ranging from 420 mg to 840 mg) and study PCYC-04753 (16 patients, various doses)

FDA Response:
Yes, the proposed datasets are acceptable.

Sponsor Response
Pharmacyclics acknowledges the FDA's response and would like to clarify that of the 148 CLL/SLL patients, 31 are treatment naive and 117 are relapsed/refractory. The Integrated Summary of Safety/Summary of Clinical Safety for the CLL/SLL indication will focus on the 117 patients.

Meeting Discussion:
No Discussion

Question 5

Does the FDA agree that the proposed format/safety data cut-offs for the ongoing clinical studies that will be included in the original NDA and the proposed data cut-offs for the 4 month safety update is acceptable?

FDA Response:
We would like to discuss with you the timing of the data cut-off. We recommend earlier data cut-off dates such that you are able to submit a safety update by mid-August 2013.

Sponsor Response

Pharmacyclics plans to provide a summary of SAEs for all ongoing single agent studies by mid August 2013. These studies include: MCL2001, PCYC-1103-CA, PCYC-1106-CA and PCYC-1117-CA. All patients on study PCYC-1102-CA have been enrolled into the long term follow up study PCYC-1103-CA that will be included in the August submission. Pharmacyclics plans to perform another safety data cut for all AEs on study PCYC-1104-CA which will also be included in the August 2013 safety update.

Meeting Discussion:

The Sponsor will submit final safety datasets for PCYC-1102-CA, and 120 days safety data set for PCYC-1104-CA.

Question 6

The available clinical pharmacology data includes PK, PD, QTc, drug interaction, food effect, and excretion data as well as population PK and simulation data obtained from a physiologically based PK model. Does the FDA agree that the scope of the clinical pharmacology data proposed to be included is adequate to support the filing of an NDA under Breakthrough Therapy Designation?

FDA Response:

We refer you to the clinical pharmacology meeting held on February 20, 2013 in regards to the acceptability of your overall clinical pharmacology development plan for NDA filing.

In regards to dataset format for clinical pharmacology data submission, you should consider the following:

- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.
- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
- For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).

- Also provide in the summary of the report a description of the clinical application of modeling results. Please refer to the following pharmacometric data and models submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm).

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

The datasets for clinical pharmacology and biopharmaceutic studies will include (but not be limited to) the following: datasets used in PK and PK/PD analysis, derived PK parameters, safety (adverse events, and not ADRs), demographics, all lab values including Btk occupancy (for studies applied), conmed (for clinical studies), formulations, feeding status (for food effect evaluation) for studies in healthy volunteers (PCI-32765CLL1002 - DDI with ketoconazole and PCI-32765CLL1004 - mass balance), in patient population (PCYC-04753, PCYC-1102-CA, and PCYC-1104-CA). The safety data for study PCYC-04753 will include data for patients with CLL/SLL and MCL.

The data and models submission will be per FDA guidelines (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm)

Meeting Discussion:
No Discussion

Question 7

Does the FDA agree that the scope of the proposed nonclinical data supports a filing of an NDA for ibrutinib for the proposed indications under Breakthrough Therapy Designation?

FDA Response:
Based on the information provided, the types of nonclinical studies listed in your tables support the filing of an NDA, however, the adequacy of the studies will be a review issue.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion
Question 8

Pharmacyclics plans to submit a rolling NDA for the treatment of patients with MCL and CLL/SLL. Does the FDA agree with the schedule for submission of the portions of the NDA?

FDA Response:
Your proposal appears acceptable. Please submit the request for rolling review as soon as possible to the NDA.

Sponsor Response
Pharmacyclics plans to submit the request for rolling submission for MCL and CLL to the IND on 5 April 2013 as Serial No. 0239.

Meeting Discussion:
No Discussion

Question 9

Does the FDA agree that the proposed NDA table of contents including the list of nonclinical and clinical studies contains the essential components to support the review of the NDA?

FDA Response:
Yes. Refer to question #6 for dataset format for clinical pharmacology data.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion

Question 10

Does the FDA agree with the proposed data/analyses to be included in the Integrated Summary of Safety?

FDA Response:
Yes, with the exception of your plans to only follow ongoing AEs that are related. Because of the single arm trial design, all ongoing AE's should be recorded and followed unless they clearly are not related, e.g., progressive disease.

Sponsor Response
Pharmacyclics would like to clarify that we follow and will include all AEs, regardless of whether related or not, in studies PCYC-1102-CA (patients now enrolled on long term follow up study PCYC-1103-CA), PCYC-1104-CA and PCYC-04753.

Meeting Discussion:
The Sponsor's proposal is acceptable.

Question 11

Does the FDA agree with the proposed data presentation/analyses as presented by the proposed table shells for the Integrated Summary of Efficacy?

FDA Response:
Yes.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion

Question 12

Pharmacyclics proposes to provide completed patient case report forms (CRFs) generated in electronic format using an Electronic Data Capture system for all patients with a safety narrative, ie, deaths within 30 days of last ibrutinib dose, related SAEs, secondary malignancies, major bleeding, and treatment discontinuation, withdrawal or drop-out due to an adverse event(s) for studies PCYC-1104-CA, PCYC-1102-CA and PCYC-04753. Is this proposal acceptable to the FDA?

FDA Response:
No. Submit CRFs and narratives for all SAEs regardless of attribution. Please also note that the Agency may request additional CRFs and narratives.

Sponsor Response
Pharmacyclics acknowledges the FDA's response and plans to provide the following:

- CRFs for all patients with an SAE for studies PCYC-1104-CA, PCYC-1102-CA and PCYC-04753.
- Narratives for all treatment emergent SAEs excluding disease progression for studies PCYC-1104-CA, PCYC-1102-CA and PCYC-04753.

Meeting Discussion:
The Sponsor will submit a summary table for disease progression SAEs.

Question 13

Does the FDA agree with the plan to provide financial disclosure information for the two Phase (b) (6) studies (b) (6) in support of this NDA?

FDA Response:
Yes. The list of investigators should be submitted May 31, 2013 or earlier in order to schedule site inspections as early as possible.

Sponsor Response
Pharmacyclics acknowledges the FDA's response. The list of investigators will be provided as part of the Module 5 rolling submission planned for 31 May 2013.

Meeting Discussion:
No Discussion

Question 14

Does the FDA agree with the plan to submit promotional materials pursuant to requirements in 21 CFR 314, subpart H and the 1999 Guidance for Industry, Accelerated Approval Products - Submission of Promotional Materials?

FDA Response:
Yes, we agree with the plan and would like to add the following additional information:

Any promotional materials (core and non-core) for drugs approved under Subpart H and biologic therapeutic products approved under Subpart E intended to be used in the first 120 days after approval must be submitted to OPDP before the product is approved. The regulations further require that promotional materials intended for dissemination any time after the 120-day post approval period be submitted at least 30 days prior to the intended date of initial dissemination or publication of those materials.

OPDP would also like to communicate the following information regarding the number of pages allowed in order for the promotional materials described above to be considered core launch materials:

- One comprehensive professional labeling piece (e.g., sales aid, visual aid, or detail aid; exhibit panel if there is a major conference within the launch phase) limited to 12 or fewer pages.
- One professional advertisement (e.g., journal ad) limited to four or fewer pages, not including the PI or brief summary.
- One comprehensive direct-to-consumer labeling piece (e.g., patient brochure) limited to 12 or fewer pages.

The goal timeline for review within OPDP (minus the time required for medical officer consult) is within 45 days of receiving the submission. OPDP cannot provide advisory comments on claims that are in the public domain. If you want advisory comments, do not use promotional

pieces with the same or similar claims and presentations as the claims and presentations in the draft materials submitted for advisory review. If you choose to use promotional materials with the same or similar claims or presentations, please let OPDP know immediately so that we can stop the advisory review.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion

Question 15

Which of the four proprietary (trade) names submitted for ibrutinib is acceptable to the FDA?

FDA Response:
We have not determined that any of the four proposed proprietary names are acceptable at this time because our safety review is ongoing. However, (b) (4) and the alternate name (b) (4) were evaluated by the Office Prescription Drug Promotion (OPDP) and found acceptable from a promotional perspective.

Please be advised that although your proprietary name request contained four proprietary names (b) (4) DMEPA is actively evaluating only (b) (4) from a safety perspective since we review only one proprietary name per submission as stated in our Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

Also, please be advised that our timeline for assessment of primary proposed proprietary names submitted as part of an IND is 180 days from the date of submission. Thus, our determination of your proposed primary name, (b) (4) will be communicated to you as soon as we have concluded our safety review and no later than the OSE PDUFA date of August 21, 2013. Should we identify any safety issues with your primary name in the course of our safety review we will contact you to determine whether you would like review of the alternate name to proceed.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion

Question16

Pharmacyclics is not planning on REMS for ibrutinib, however routine pharmacovigilance will be performed post approval. Does the FDA agree?

FDA Response:
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion

Additional Comments:

We have the following recommendations regarding your proposed labeling.

1. Please note that efficacy claims for single-arm trials should be limited to response rate and duration of response. Time-to-event endpoints (such as OS or PFS) and patient-reported outcomes are not evaluable in single-arm trials.

Sponsor Response
Pharmacyclics acknowledges the FDA's response.

Meeting Discussion:
No Discussion

2. For your safety analyses and labeling, include all adverse events regardless of attribution. Please present safety data separately per proposed indication.

Sponsor Response
Pharmacyclics will present safety data separately per proposed indication.

Meeting Discussion:
No Discussion

3. In the SAP for clinical trial PCYC-1104-CA, please be consistent that primary analysis of ORR will be based on all treated population instead of response evaluable patients.

Sponsor Response
Pharmacyclics confirms that the primary analysis of ORR will be based on all treated population.

In addition, Pharmacyclics has now completed the efficacy data for study PCYC-1104-CA by an independent review committee (IRC) demonstrating an ORR of 68.5%, with a 20.7% CR rate and a 47.7% PR rate. There was a concordance rate for ORR of 92%. A summary of the concordance between the investigator and IRC assessment of overall response rate for all treated subjects is provided in the table below.

TEFRSP06: Response Assessments – Concordance Between Investigator and Independent Review Committee; All Treated Population (Study PCYC-1104-CA)

		Ibrutinib	
	ortezomib-Naive	tezomib-Exposed	Combined
Population: all treated	63	48	**111**
Responder (CR or PR) by investigator	43	32	75
Responder (CR or PR) by IRC	40 (63.5%)	31 (64.6%)	**71 (64.0%)**
Complete agreement	33 (52.4%)	26 (54.2%)	59 (53.2%)
CR by investigator but PR by IRC	4 (6.3%)	2 (4.2%)	6 (5.4%)
PR by investigator but CR by IRC	3 (4.8%)	3 (6.3%)	6 (5.4%)
Non responder by IRC	3 (4.8%)	1 (2.1%)	4 (3.6%)
Non responder by investigator	20	16	36
CR by IRC	1 (1.6%)	0	1 (0.9%)
PR by IRC	4 (6.3%)	0	4 (3.6%)
Non responder by IRC	15 (23.8%)	16 (33.3%)	**31 (27.9%)**

= complete response, IRC= independent review committee, PR= partial response

ordance rate for ORR is calculated as: (71+31)/111= 91.9%

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Meeting Discussion:
No Discussion

4. You should include subgroup analyses by age, gender, race and region for primary endpoints in clinical study report for clinical trial PCYC-1102-CA.

Sponsor Response
Pharmacyclics confirms that subgroup analyses by age, gender, and race for primary endpoints will be provided in the clinical study report for study PCYC-1102-CA. Region is not applicable as this study was only conducted in the US.

Meeting Discussion:
No Discussion

3.0 IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Please see the Meeting Discussion under Question 3.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

- A preliminary discussion on the need for a REMS was held and it was concluded that based on the information currently available, FDA does not believe that a REMS will be necessary. A final determination if a REMS is needed will be made during the review of your application.

AGEEMENT FOR LATE SUBMISSION

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

  A late submission regarding the 3 months drug stability update.

- Prominently identify each submission containing your late components with the following wording in bold capital letters at the top of the first page of the submission:

  NDA 205552: LATE COMPONENT - QUALITY

In addition, we note that a chemistry pre-submission meeting was held on April 9, 2013. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovaton ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.

Because none of the criteria apply to your application, you are exempt from these requirements/Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified which required further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no additional attachments or handouts at the meeting.

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

/s/

ROMEO A DE CLARO
04/19/2013

Reference ID: 3460668

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

¶
¶
IND 102688

MEETING MINUTES

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Ave
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ibrutinib (PCI-32765).

We also refer to the meeting between representatives of your firm and the FDA on April 9, 2013. The purpose of the meeting was to discuss product development plans for ibrutinib (PCI-32765).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	CMC, Pre-NDA
Meeting Date and Time:	April 9, 2013, 2:00 PM – 3:00 PM (EST)
Meeting Location:	White Oak Building 22, Conference Room: 1415
Application Number:	IND 102688
Product Name:	Ibrutinib (PCI-32765)
Indication:	(b) (4)
Sponsor/Applicant Name:	Pharmacyclics, Inc.
Meeting Chair:	Janice Brown, CMC Lead
Meeting Recorder:	Jewell Martin, ONDQA Project Manager

FDA ATTENDEES
Janice Brown, MS, CMC Lead, ONDQA
Sarah Pope Miksinski, Division Director, ONDQA
Jean Tang, PhD, CMC Reviewer, ONDQA
John Duan, PhD, Biopharmaceutics Reviewer, ONDQA
Jewell Martin, MA, MBA, MBA, Project Manager, ONDQA
Haleh Saber, PhD, Supervisory Pharmacologist, DHOT
Christopher Sheth, PhD, Pharmacologist, DHOT
Shwu-Luan Lee, PhD, Pharmacologist, DHOT
Angelo De Claro, MD, Medical Officer, DHP
Karen McGinn, MSN, CRNP, Senior Clinical Analyst, DHP
Vipul Dholakia, PhD, Compliance Officer, OC
Amy Devine, Consumer Safety Officer, ORA
Kevin Wright, PharmD, Pharmacist, DMEPA
James Schlick, PhD, Lead Health Scientist, DMEPA

SPONSOR ATTENDEES
Heow Tan, MS, MBA, Pharmacyclics, Inc. - Chief, Technical Operations
Urte Gayko, PhD, Pharmacyclics, Inc. – Sr. Vice President, Regulatory Affairs
David Loury, PhD, Pharmacyclics, Inc. - Chief Scientific Officer
Scott Shearer, PhD, Pharmacyclics, Inc. - Vice President, Global Quality
Usha Ramesh, PhD, Pharmacyclics, Inc. - Director, CMC Regulatory Affairs
Maria Fardis, PhD, MBA, Pharmacyclics, Inc. - Chief of Oncology Operations and Alliances
Man-Cheong Fung, M.D. , Janssen R&D, LLC - Vice President, Compound Development TL
Hans Vermeersch, PhD, Janssen R&D, LLC – Sr. Scientific Director, CMC Development TL

John Seaman, Pharm.D., Janssen R&D, LLC – Sr. Director, Global Regulatory Affairs
Lillian Malahias, MS, Janssen R&D, LLC - Director, CMC Regulatory Affairs
Lea De Rycke, Janssen JSC - Senior Manager, Product Quality
Sandra Snook, DVM, DACVP, Janssen R&D, LLC- Sr. Scientific Director Drug Safety Sciences
(b) (4)

1.0 BACKGROUND

In a letter dated February 8, 2013, Pharmacyclics, Inc. requested a Pre-NDA, Chemistry, Manufacturing, and Controls (CMC) meeting. The purpose of this meeting is to discuss drug development plans for ibrutinib (PCI-32765). The Office of New Drug Quality Assessment (ONDQA) issued a Meeting Granted letter to Pharmacyclics, Inc. on February 13, 2013. Pharmacyclics, Inc. submitted their meeting background package on February 28, 2013.
On February 6, 2013, following the September 19, 2012, Type B, CMC, End of Phase 2 meeting, Pharmacyclics submitted an amendment to their IND containing additional information on the selection of (b) (4) as a starting material for ibrutinib drug substance. The Agency sent a General Advice Letter to Pharmacyclics on February 14, 2013, stating that the proposal to designate (b) (4) as a starting material was not acceptable.

On February 28, 2013, a teleconference was held between Pharmacyclics and ONDQA. During the meeting Pharmacyclics agreed to provide follow-up information regarding the designation of the regulatory starting material for ibrutinib production. On March 27, 2013, Pharmacyclics submitted an amendment to their IND providing this follow-up information. The Agency's comments regarding the March 27, 2013, amendment are addressed in these preliminary meeting comments. Pharmacyclics provided responses to FDA preliminary comments on April 8, 2013 and requested further discussion on responses to Question 2, Question 7, Question 4 and Question 6 in this order. Pharmacyclics responses are included throughout the meeting minutes and attached for convenience.

2.0 DISCUSSION

Pharmacyclics, Inc. Question 1:
The additional technical information to justify (b) (4) as a starting material was recently submitted as an IND amendment (Serial No. 0199, dated 6 February 2013), in accordance with the agreement made at the End-of-Phase 2 meeting. Pharmacyclics received an FDA Advice Letter (dated 14 Feb 2013; received 22 Feb 2013) and on 23 Feb 2013 requested a teleconference with FDA to clarify the guidance in the advice letter. Based on the additional technical information provided in IND Amendment 0199, does the Agency agree that (b) (4) is acceptable as a starting material?

FDA Response to Question 1:
No. (b) (4) is not acceptable as a starting material.

- **Pharmacyclics, Inc. Revised Question 1 per March 27, 2013 communication:**
  Based upon the designation of (b) (4) as a regulatory starting material, Pharmacyclics is proposing to replace Question 1 from the pre-NDA briefing document with the question outlined below.

  As (b) (4) is a well-established material that is available from multiple vendors, is a (b) (4)

  a. Does the Agency agree with designation of (b) (4) as a regulatory starting material?
  b. Does the Agency agree with the proposed data to be included in the NDA to support (b) (4) as a regulatory starting material?

FDA Response to Revised Question 1 per March 27, 2013 communication:
The Agency does agree that (b) (4) may be designated as a starting material. The overall acceptability of any proposed starting materials will be assessed during the NDA review.

Meeting Discussion: No Further Discussion Required.

Pharmacyclics, Inc. Question 2:
Consistent with the premise of Breakthrough Therapy Designation and the accelerated development timeline, does the Agency agree with the proposed approach for the qualification of impurities in drug substance and drug product?

FDA Response to Question 2:
In general, for impurities above the threshold defined by ICH Q3A(R2) or ICH Q3B(R2), it is recommended that two different SAR prediction methods be applied, such as an expert rule-based and a statistical-based model. No further genotoxicity testing is needed for (b) (4) (b) (4) (DEREK positive but AMES negative). Impurities (b) (4) (b) (4) did not indicate a positive response in DEREK. These 4 impurities may be further evaluated using a statistical-based SAR analysis (or may be evaluated by AMES assay). If after review of the 2 SAR analyses (or the Ames test) we conclude that the impurities are negative for mutagenicity, no further genotoxicity testing will be necessary. Please submit the SAR analyses for our review; include the version of DEREK used. With regard to the general safety of impurities, impurities above the qualification threshold defined by ICH Q3A(R2) or ICH Q3B(R2) may be qualified using the levels of impurities present in batches used in either nonclinical or clinical studies. Based on the information provided, impurities (b) (4) appear to be qualified based on safety data in rats.

Pharmacyclics Response Received April 8, 2013:

FDA Response 2: *"In general, for impurities above the threshold defined by ICH Q3A(R2) or ICH Q3B(R2), it is recommended that two different SAR prediction methods be applied, such as an expert rule-based and a statistical-based model. No further genotoxicity testing is needed for* (b) (4) *(DEREK positive but AMES negative). Impurities* (b) (4) (b) (4) *did not indicate a positive response in DEREK. These 4 impurities may be further evaluated using a statistical-based SAR analysis (or may be evaluated by AMES assay)."*

Pharmacyclics Response

- *Ames testing of* (b) (4) *has been completed and preliminary information indicates a negative test result. This data will be shared in the NDA.*
- *Pharmacyclics agrees to use two different SAR prediction methods, an expert rule-based and a statistical-based model, for evaluation of impurities above the threshold defined by ICH Q3A(R2) or ICH Q3B(R2).*
- *For impurities* (b) (4) *that were negative for mutagenicity in the expert rule-based application DEREK NEXUS (3.0.1), Pharmacyclics proposes a second evaluation using the statistical-based SAR application MultiCase*
- *Pharmacyclics proposes to use Module A7A FDA Mutagenicity Microbial composite (Sal_Ecoli_Bac).* ***Does the Agency concur with the choice of this module?***

Meeting Discussion:
FDA stated that MultiCase modules are under review. Currently the Agency's preference is to use salmonella-based modules (A7B, A2H, or AZ2/AZ3 Databases) because the E.coli based approaches seem to result in many "no calls". The A7A module may be acceptable for this breakthrough therapy; however the Agency may ask for additional evaluations in the future.

FDA Response: *"If after review of the 2 SAR analyses (or the Ames test) we conclude that the impurities are negative for mutagenicity, no further genotoxicity testing will be necessary. Please submit the SAR analyses for our review; include the version of DEREK used."*

Pharmacyclics Response

- *Analyses from the Derek Nexus and MultiCase analyses of* (b) (4) (b) (4) *will be included in the NDA submission.*
- *If the DEREK-Nexus and MultiCase analyses are concordant, no additional genotoxicity testing will be conducted*

- *In the event of discordant results from Derek Nexus and MultiCase, Pharmacyclics will propose post-approval approaches for additional genotoxicity qualification in the NDA, as needed.* ***Does the Agency concur with our strategy?***

Meeting Discussion:
Considering the breakthrough therapy designation, the sponsors approach is acceptable.

FDA Response: *"With regard to the general safety of impurities, impurities above the qualification threshold defined by ICH Q3A(R2) or ICH Q3B(R2) may be qualified using the levels of impurities present in batches used in either nonclinical or clinical studies. Based on the information provided, impurities* (b) (4) *appear to be qualified based on safety data in rats."*

Pharmacyclics Response

- *Pharmacyclics acknowledges that the safety information obtained for impurities* (b) (4) *in rat studies supports their qualification.*
- *For impurities* (b) (4) *Pharmacyclics plans to perform a general toxicology study in rats as outlined in the briefing book. The final report for this study will be available by December 2013.* ***Does the Agency agree with this approach?***

Meeting Discussion:
Considering the breakthrough therapy designation, the sponsors approach is acceptable.

Pharmacyclics, Inc. Question 3:
Consistent with the premise of Breakthrough Therapy Designation, does the Agency agree that the following drug substance stability data, to be provided in the NDA, is sufficient to support the NDA submission?

- 6 months of long-term and accelerated stability data for three drug substance registration batches (121338, 121339, and 121340) manufactured at the (b) (4) site (future commercial site),
- 12 to 24 months of long-term stability data and 6 months of accelerated stability data from three supportive drug substance batches [111132 (24 months), 121074 (12 months), and 121075 (12 months)] manufactured at the (b) (4) manufacturing facility using the same synthesis method, and
- 24 months of long-term and 6 months of accelerated stability data from one supportive drug substance batch (101044) manufactured at (b) (4)

FDA Response to 3:
Your proposal appears reasonable. The assessment of the re-testing period is a review issue.

Meeting Discussion: No Further Discussion Required.

Pharmacyclics, Inc. Question 4:
Does the Agency agree that overall stability plan for drug product is adequate to support NDA submission and that the amount of stability data provided from the eight registration/primary and supportive stability batches of drug product is sufficient to support a 24-month expiration dating period?

FDA Response to Question 4:
Your proposal appears reasonable, provided that your NDA comes in with three months long term and three months accelerated data for the three primary batches. However, the assessment of the expiration dating period is a review issue.

Pharmacyclics Response Received April 8, 2013:

Sponsor Response 4: Drug Product Stability Data

- *Pharmacyclics commits to submit three months of long term and accelerated stability data for the three registration batches, within 30 days of NDA submission in accordance with PDUFA V.* ***Does the FDA agree with our strategy?***

Meeting Discussion:
The Agency stated that this approach is reasonable; however further discussion is required.

Pharmacyclics, Inc. Question 5:
Does the Agency agree with the proposed strategy to support (b) (4) as a packaging and labeling site in the NDA?

FDA Response to Question 5:
For the facility evaluation, the strategy appears acceptable. The compliance status of the proposed primary commercial drug product packaging and labeling facility will be evaluated during the review cycle and may be inspected, if required. The actual protocols, acceptance criteria and study outcomes of the validation studies will be evaluated during an inspection.

Meeting Discussion: No Further Discussion Required.

Pharmacyclics, Inc. Question 6:
Does the Agency agree with the plans for submission of the SLS method as the regulatory method for dissolution testing in the NDA and the phase-in plans for the improved Tween 20 method post-approval?

FDA Response to Question 6:
While we understand the timing issues, we recommend that you implement the new Tween method as soon as feasible. Pharmacyclics is asked to agree to a post marketing commitment (PMC) to submit a prior approval supplement (PAS) for the full implementation of the Tween method within one year of approval.

Note the additional comments below as you prepare a future submission in fulfillment of the aforementioned PMC:

1. **From Table 12 of the briefing package, clarify which clinical studies used (b) (4) drug substance and which clinical studies used (b) (4) drug substance.**
2. **In the dissolution method development report to-be-submitted in the NDA, include the following information in addition to that you provided in the current briefing package:**
   - **Justification for the proposed rotation speed (include data at 50 rpm).**
   - **Justification for the proposed type and concentration of surfactant (include data with no surfactant and different concentrations of the tested surfactant).**

Pharmacyclics Response Received April 8, 2013:
Sponsor Response 6: Dissolution
PCYC agrees to submit a prior-approval supplement (PAS) within one year of NDA approval to implement the Tween 20 dissolution method.

- *PCYC would like to clarify that all clinical batches were produced with (b) (4) ibrutinib. (b) (4) ibrutinib was never used to produce clinical supplies. Dissolution data was generated from drug product manufactured with (b) (4) drug substance to determine the discriminatory nature of the method.*
- *All additional information requested in the FDA response (i.e., justification of rotational speed and concentration of Tween 20) will be provided in the NDA.*

Meeting Discussion:
The Agency concurs that the Sponsors approach appears reasonable.

Pharmacyclics, Inc. Question 7:
(A) Does the Agency agree that drug substance batches 1008, 1009, and 1010 manufactured prior to PPQ can be considered commercial batches contingent upon successful completion of the drug substance PPQ campaign at (b) (4)

(B) Does the Agency agree that drug product successfully produced from drug substance batches 1008, 1009, and 1010 during the planned drug product PPQ campaign can be used as the commercial launch supplies?

FDA Response to Question 7:
FDA does not approve process validation approaches, protocols, or number of specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Additional Comments:
The use of the drug substance batches 1008, 1009 and 1010 manufactured at the (b) (4) (b) (4) facility prior to completion of process performance qualification (PPQ) study *may* be considered acceptable for use in manufacturing drug product under a breakthrough therapy designation. However, there are risk factors that should be evaluated as part of your decision. For example, there is a risk that you learn during or after PPQ that these drug substances batches are not of appropriate quality. As stated in your meeting package, the acceptability of the batches needs to be evaluated in your comparability assessment to show equivalence of these batches to the acceptable PPQ batches (e.g., manufacturing processes, laboratory methods, stability studies, and testing results). As a second example, it is unclear why one batch was produced at (b) (4)% of target commercial scale and how this may impact the quality of the drug substance. The difference in manufacturing scale, as well as the amount of material rejected, should be evaluated to determine if there is an impact on drug substance quality.

Further, should you manufacture drug product with these drug substance batches prior to completion of drug substance PPQ, issues that may arise in your comparability assessment can have an impact on the acceptability of the drug product batches made with drug substance batches 1008, 1009, and 1010. Circumstances and rationale for releasing these drug substance batches for use in the drug product process qualification should be fully described in the drug product PPQ protocol and must comply with all CGMPs, regulatory approval requirements, and PPQ protocol lot release criteria. If, after considering factors relevant to use of these drug substance batches, you have determined that the drug substances batches were appropriate for use, the process qualification (PPQ) drug product batches may be released for commercial distribution provided they conform to applicable quality standards as defined in the process performance qualification protocol.

Pharmacyclics Response Received April 8, 2013:
We appreciate and acknowledge the FDA comments provided on our process validation approach. To ensure that the District Offices are aware of the Breakthrough Therapy designation for ibrutinib and of our strategy for process validation, Pharmacyclics is requesting that the Chemistry Review team provide information on Breakthrough Therapy designation and

the Office of Compliance provide the pre-NDA CMC briefing book and the meeting minutes to the District Offices responsible for site inspections.

The main points outlined in the FDA feedback on our process validation approach are summarized as follows:

1. *Drug substance batches 1008, 1009 and 1010 will be considered acceptable for commercial distribution contingent upon:*
    a. *Successful completion of the drug substance PPQ campaign at* (b) (4)
    b. *Successful completion of* (b) (4) *PPQ at* (b) (4) *using batches 1008, 1009 and 1010*
    c. *Drug substance batches 1008, 1009, and 1010 can be designated as commercial batches upon completion of the comparability assessment with results showing equivalency of batches 1008, 1009 and 1010 to the PPQ batches;*
2. *Successful completion of drug product process validation with drug substance batches 1008, 1009 and 1010 is contingent upon:*
    a. *Drug substance batches 1008, 1009 and 1010 can be identified as commercial batches in the PPQ protocol for drug product. The drug product PPQ batches can be commercially distributed upon the successful completion of the drug substance PPQ at* (b) (4) *Pharmacyclics does not plan to conduct additional drug product PPQ activities*
    b. *Successful completion of packaging validation at* (b) (4)
3. *Upon successful completion of Items 1 and 2, Pharmacyclics intends to commercially distribute the drug product batches produced using drug substance batches1008, 1009 and 1010 to support product launch upon NDA approval.*

Note: We want to clarify that batch 1008 was intentionally targeted to be produced at (b) (4) *% of the intended commercial scale. The overall percent yield and quality is consistent among batches 1008, 1009, and 1010. There was no product rejected for drug substance batch 1008.*

In summary, we agree with the Agency that the use of drug substance batches 1008, 1009 and 1010, manufactured at the (b) (4) *facility prior to completion of the drug substance PPQ study, may be considered acceptable for use in manufacturing of drug product under a Breakthrough Therapy designation. In addition, we agree with the Agency that the drug product PPQ batches may be released for commercial distribution provided Pharmacyclics successfully completes the contingency items listed above.*

Meeting Discussion:
Yes, the meeting minutes will be distributed to the District Office. The sponsor agreed to provide copies of the briefing book to the District Office.

The sponsor will submit a list of the commercial manufacturing sites in the first submission of the NDA at the end of April.

Pharmacyclics, Inc. Question 8:
Does the Agency agree with our proposed commercial imprinting code for the drug product, ibrutinib capsule, 140 mg?

Yes, the Agency agrees that the proposed capsule as described in the CMC meeting package is in accordance with 21 CFR 206.10(a).

Meeting Discussion: No Further Discussion Required.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

5.0 ATTACHMENTS AND HANDOUTS

Handout provided by Pharmacyclics Inc. on April 8, 2013, see attached.

6.0 CONCURRENCE

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Janice Brown, MS
CMC Team Lead, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Sponsor Additional Discussion Points

Ibrutinib pre-NDA CMC meeting: 9 April 2013 (1400-1500 EST)

We appreciate the FDA feedback received on 5 April 2013.

1. No further discussion needed for responses to Q1, Q3, Q5 and Q8
2. We respectfully request further discussion on responses to Q2, Q7, Q4 and Q6 in this order.

Sponsor Response 2: Qualification of Impurities

We appreciate and acknowledge the FDA comments provided on Qualification of Impurities. Below is the FDA response divided into sections with the corresponding Pharmacyclics response and/or questions.

FDA Response 2: "In general, for impurities above the threshold defined by ICH Q3A(R2) or ICH Q3B(R2), it is recommended that two different SAR prediction methods be applied, such as an expert rule-based and a statistical-based model. No further genotoxicity testing is needed for (b) (4) (DEREK positive but AMES negative). Impurities (b) (4) did not indicate a positive response in DEREK. These 4 impurities may be further evaluated using a statistical-based SAR analysis (or may be evaluated by AMES assay)."

Pharmacyclics Response

- Ames testing of (b) (4) has been completed and preliminary information indicates a negative test result. This data will be shared in the NDA.
- Pharmacyclics agrees to use two different SAR prediction methods, an expert rule-based and a statistical-based model, for evaluation of impurities above the threshold defined by ICH Q3A(R2) or ICH Q3B(R2).
- For impurities (b) (4) that were negative for mutagenicity in the expert rule-based application DEREK NEXUS (3.0.1), Pharmacyclics proposes a second evaluation using the statistical-based SAR application MultiCase
- Pharmacyclics proposes to use Module A7A FDA Mutagenicity Microbial composite (Sal_Ecoli_Bac). **Does the Agency concur with the choice of this module?**

FDA Response: "If after review of the 2 SAR analyses (or the Ames test) we conclude that the impurities are negative for mutagenicity, no further genotoxicity testing will be necessary. Please submit the SAR analyses for our review; include the version of DEREK used."

Pharmacyclics Response

- Analyses from the Derek Nexus and MultiCase analyses of (b) (4) (b) (4) will be included in the NDA submission.
- If the DEREK-Nexus and MultiCase analyses are concordant, no additional genotoxicity testing will be conducted
- In the event of discordant results from Derek Nexus and MultiCase, Pharmacyclics will propose post-approval approaches for additional genotoxicity qualification in the NDA, as needed. **Does the Agency concur with our strategy?**

FDA Response: "With regard to the general safety of impurities, impurities above the qualification threshold defined by ICH Q3A(R2) or ICH Q3B(R2) may be qualified using the levels of impurities present in batches used in either nonclinical or clinical studies. Based on the information provided, impurities (b) (4) appear to be qualified based on safety data in rats."

Pharmacyclics Response

- Pharmacyclics acknowledges that the safety information obtained for impurities (b) (4) (b) (4) in rat studies supports their qualification.

- For impurities [redacted] (b) (4) Pharmacyclics plans to perform a general toxicology study in rats as outlined in the briefing book. The final report for this study will be available by December 2013. **Does the Agency agree with this approach?**

Sponsor Response 4: Drug Product Stability Data

1. Pharmacyclics commits to submit three months of long term and accelerated stability data for the three registration batches, within 30 days of NDA submission in accordance with PDUFA V. **Does the FDA agree with our strategy?**

Sponsor Response 6: Dissolution

PCYC agrees to submit a prior-approval supplement (PAS) within one year of NDA approval to implement the Tween 20 dissolution method.

1. PCYC would like to clarify that all clinical batches were produced with (b) (4) ibrutinib. (b) (4) ibrutinib was never used to produce clinical supplies. Dissolution data was generated from drug product manufactured with (b) (4) drug substance to determine the discriminatory nature of the method.
2. All additional information requested in the FDA response (i.e., justification of rotational speed and concentration of Tween 20) will be provided in the NDA.

Sponsor Response 7: Process Validation

We appreciate and acknowledge the FDA comments provided on our process validation approach. To ensure that the District Offices are aware of the Breakthrough Therapy designation for ibrutinib and of our strategy for process validation, Pharmacyclics is requesting that the Chemistry Review team provide information on Breakthrough Therapy designation and the Office of Compliance provide the pre-NDA CMC briefing book and the meeting minutes to the District Offices responsible for site inspections.

The main points outlined in the FDA feedback on our process validation approach are summarized as follows:

1. Drug substance batches 1008, 1009 and 1010 will be considered acceptable for commercial distribution contingent upon:
    a. Successful completion of the drug substance PPQ campaign at (b) (4)
    b. Successful completion of micronization PPQ at (b) (4) using batches 1008, 1009 and 1010
    c. Drug substance batches 1008, 1009, and 1010 can be designated as commercial batches upon completion of the comparability assessment with results showing equivalency of batches 1008, 1009 and 1010 to the PPQ batches;
2. Successful completion of drug product process validation with drug substance batches 1008, 1009 and 1010 is contingent upon:
    a. Drug substance batches 1008, 1009 and 1010 can be identified as commercial batches in the PPQ protocol for drug product. The drug product PPQ batches can be commercially distributed upon the successful completion of the drug substance PPQ at (b) (4) Pharmacyclics does not plan to conduct additional drug product PPQ activities
    b. Successful completion of packaging validation at (b) (4)
3. Upon successful completion of Items 1 and 2, Pharmacyclics intends to commercially distribute the drug product batches produced using drug substance batches1008, 1009 and 1010 to support product launch upon NDA approval.

Note: We want to clarify that batch 1008 was intentionally targeted to be produced at (b) (4)% of the intended commercial scale. The overall percent yield and quality is consistent among batches 1008, 1009, and 1010. There was no product rejected for drug substance batch 1008.

In summary, we agree with the Agency that the use of drug substance batches 1008, 1009 and 1010, manufactured at the (b) (4) facility prior to completion of the drug substance PPQ study, may be considered acceptable for use in manufacturing of drug product under a Breakthrough Therapy designation. In addition, we agree with the Agency that the drug product PPQ batches may be released for commercial distribution provided Pharmacyclics successfully completes the contingency items listed above.

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/s/

JEWELL D MARTIN
04/16/2013

ALI H AL HAKIM
04/16/2013

FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B meeting
Meeting Category:	EOP2 meeting (Teleconference)
Meeting Date and Time:	September 26, 2012, 1:00 p.m.
Meeting Location:	CDER WO 2201
Application Number:	IND 102688
Product Name:	Ibrutinib (PCI-32765)
Indication:	Chronic Lymphocytic Leukemia/Small lymphocytic lymphoma
Sponsor Name:	Pharmacyclics, Inc.
Meeting Request Date:	August 20, 2012
Received Briefing Package	August 26, 2012
Meeting Chair:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
Meeting Recorder:	CDR Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES:

- Ann T. Farrell, M.D., Division Director, DHP
- Anthony Murgo, M.D., Associate Director for Regulatory Science, OHOP
- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- Angelo De Claro, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Brenda Gehrke, Ph.D., Pharmacologist/Toxicologist, DHOT
- Gregory Reaman, M.D., Associate Director for Oncology Sciences, OHOP
- Elizabeth Mansfield, Ph.D., Director Personalized Medicine, CDRH
- Maria M. Chan, Ph.D., Division Director for DIHD, CDRH
- Tremel Faison, M.S., Regulatory Review, OIVD, CDRH
- Lea Carrington, M.S., M.B.A. Team Leader, OIVD, CDRH
- Meghna Alimchandrani, Staff Fellow

- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

- **SPONSOR ATTENDEES:**
- Lori Kunkel, M.D., Chief Medical Officer, Pharmacyclics Inc.
- David Loury, Ph.D., Chief Scientific Officer, Pharmacyclics Inc.
- Urte Gayko, Ph.D., Vice President, Regulatory Affairs, Pharmacyclics Inc.
- Jesse McGreivy, M.D., Vice President, Clinical Science, Pharmacyclics Inc.
- Fong Clow, ScD., Vice President, Biometrics, Pharmacyclics Inc.
- Alvina Chu, M.D., Medical Director, Pharmacyclics Inc.
- Man-Cheong Fung, M.D., M.B.A., MHCM, FACP, Vice President, Compound Development Team Leader, Janssen R&D, LLC
- John Seaman, Pharm D., Senior Director, Global Regulatory Affairs, Janssen R&D, LLC
- Sen Hong Zhuang, M.D., Ph.D., Senior Director, Clinical Research, Janssen R&D, LLC
- Debra Rasmussen, M.B.A., Senior Director, Diagnostics Regulatory Affairs Leader, Janssen R&D, LLC
- Terri Williams, Ph.D., Associate Director, Global Regulatory Affairs, Janssen R&D, LLC
- Abhijit (Ron) Mazumder, Ph.D., M.B.A., Global Head, Research & Product Development, Janssen Diagnostics
- (b) (4)
-

1.0 BACKGROUND

PHARMACYCLICS REQUESTED AN EOP2 MEETING ON JUNE 29, 2012, TO OBTAIN AGENCY FEEDBACK ON THE FOLLOWING:

- The clinical development plan regarding a pivotal Phase 2 trial (PCYC-1117-CA) of ibrutinib administered as a single oral agent in CLL/SLL patients with del 17p who require treatment after at least one prior systemic therapy.

- The adequacy of clinically meaningful results from a single-arm Phase 2 study (PCYC-1117-CA), in approximately 111 evaluable patients with CLL/SLL who have confirmed del 17p, have received at least one prior systemic therapy, who require therapy for relapsed or refractory disease, and who have no available approved therapeutics options, to serve as the basis of a NDA for consideration under the accelerated approval pathway per 21 CFR 314.500, subpart H.
- The adequacy of a randomized Phase 3 trial (PCYC-1112-CA) of ibrutinib versus ofatumumab for the treatment of CLL/SLL patients (which includes del 17p CLL patients) to serve as a confirmatory trial, if a clinically meaningful response rate is demonstrated in Study PCYC-1117-CA.

The EOP2 meeting was granted on August 7, 2012 and scheduled for September 26, 2012.

2.0 DISCUSSION

Question 1

Does the Agency agree that a clinically meaningful, durable, objective response from a single-arm Phase 2 study, PCYC-1117-CA, in approximately 111 evaluable patients with relapsed or refractory CLL/SLL with del 17p, who have received at least one prior treatment regimen and who require treatment by IWCLL guidelines, is adequate to support an NDA filing for ibrutinib under the accelerated approval pathway per 21 CFR 314.500, Subpart H?

FDA Response: Possibly. You should note that an application for accelerated approval requires demonstration of meaningful therapeutic benefit over available therapy. The determination of available therapy is made at the time of regulatory action.

Please also note that the fileability of an NDA is determined at the time of NDA submission.

For the NDA submission, we recommend that all patients must have at least 6 months of follow-up data.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response and commits to provide a minimum of 6 months of follow-up data on all patients for the NDA submission.

No meeting discussion occurred.

Question 2

Does the Agency agree that a single, large, randomized comparative Phase 3 confirmatory trial (PCYC-1112-CA), previously discussed with the Agency at an End of Phase 2 meeting on 5 December 2011, could provide adequate demonstration of clinical benefit for conversion to full approval if a clinically significant improvement in PFS in the 17 p subset is demonstrated in this study?

FDA Response: Although conversion to regular approval may be possible with a single large, randomized Phase 3 confirmatory trial, we recommend that you have at least two ongoing randomized Phase 3 trials at the time of regulatory action for your application for accelerated approval. The Agency does not require that the clinical trial population for the confirmatory trials should be exactly the same as the application for accelerated approval. Please also refer to ODAC meeting minutes for the February 2011 ODAC meeting for committee recommendations regarding number of confirmatory trials needed to convert accelerated approvals.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response. At least two randomized Phase 3 trials will be ongoing at the time of regulatory action for our accelerated approval application.

No meeting discussion occurred.

Question 3

Does the Agency agree that the CLL/SLL del 17p relapsed and/or refractory patient population as defined in protocol PCYC-1117-CA would support an accelerated approval pathway?

FDA Response: Yes. Please see also response to question 1.

A broader population of patients with previously treated (not limited to chemoimmunotherapy or alemtuzumab-based therapy) CLL or SLL del 17p with relapsed or refractory disease requiring treatment would also be acceptable.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response. The eligibility criteria will be broadened to include patients who have received at least two cycles of prior chemotherapy or immunotherapy and have relapsed or refractory disease.
No meeting discussion occurred.

Question 4

Does the Agency agree with the application of the IWCLL criteria to assess response according to the updated addendum for response definition for treatment related lymphocytocysis (Hallek e-letter Blood June 2012)?

FDA Response: The Agency has no regulatory experience with how these modifications to the existing IWCLL criteria will perform. Therefore, this will be a review issue.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response.

No meeting discussion occurred.

Question 5

Does the Agency agree that an ORR of 39% (with lower boundary of 95% CI above 25%) represents a clinically meaningful benefit from which the success of Study PCYC-1117-CA can be judged?

FDA Response: Possibly. An ORR of 39% with an adequate duration may be reasonably likely to predict clinical benefit. The magnitude and duration of response will be a review issue based upon the safety profile of ibrutinib.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response.

No meeting discussion occurred.

Question 6

Does the Agency agree that the design elements of the trial including trial size, duration of on-study, and general statistical approach, including primary endpoint of ORR assessed by IRC, is appropriate for a Phase 2 study supportive of the following proposed indication:

> "Ibrutinib is indicated for the treatment of patients with CLL (b) (4) with 17p deletion who require treatment after at least one prior systemic therapy"

FDA Response: Please note that the indication granted would depend on the actual population enrolled in the clinical trial. We recommend that the efficacy population for analysis (primary efficacy population) be defined as all eligible patients who received study drug.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response. The primary efficacy analysis will be performed on all eligible patients who have received study drug.

No meeting discussion occurred.

Question 7

Does the Agency agree that the secondary endpoints including duration of response (including patients who achieve a PR with lymphocytosis). (b) (4) (b) (4) are appropriate for a Phase 2 study supportive of this indication?

FDA Response: No. (b) (4) **are not evaluable in a single-arm clinical trial due to confounding effects of the natural history of the disease.** (b) (4) **is not acceptable as a key secondary endpoint because this endpoint is not evaluated in the primary efficacy population.**

However, duration of response is an acceptable secondary endpoint. The acceptability of duration of response in patients who achieve PR with lymphocytosis will be a review issue.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response. The PFS, OS, and hematologic improvement will be captured as supportive endpoints for clinical benefit.

No meeting discussion occurred.

Question 8

Does the Agency agree that the use of an analytically validated and commercially available del 17p by FISH diagnostic test in the proposed patient population is adequate to define the study population?

FDA Response: Yes, we agree that the use of an analytically validated del 17p FISH assay is necessary. If you intend to use a FISH test for selection of patients for ibrutinib therapy then the assay will likely require premarket approval as a companion diagnostic. Contact CDRH with a pre-submission to discuss the necessity of an IDE in your study as well as for premarket approval studies.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response. Discussions with (b) (4) have been initiated for development of a FISH assay to be used in the clinical studies. Pharmacyclics plans to implement the existing 510 (k) cleared (b) (4) that detects deletion 17p used to (b) (4) (b) (4) CDRH will be contacted regarding the IDE.

Meeting Discussion:

(b) (4)

The Sponsor stated that for clinical trial 1112, the cutoff that will be used will be amended to 7% for 17p. The Sponsor also stated that all markers other than 17p will be used for exploratory purposes only.

FDA stated that if the Sponsor intends to use the -17p FISH assay to select patients for ibrutinib therapy this is a new companion diagnostic selective claim that will likely require a separate premarket submission. This will be discussed separately with CDRH. The Sponsor should contact CDRH to discuss the IDE. We will then discuss whether simultaneous clearance or approval is needed.

Question 9

Does the Agency require simultaneous approval of a del 17p test with ibrutinib treatment?

FDA Response: If the del 17p test is needed to select the population of patients who will benefit from ibrutinib treatment, a simultaneous device approval may be necessary.

Pharmacyclics Response

Would a simultaneous device approval be necessary if the existing 510 (k) cleared assay is used as a prognostic indicator in Study PCYC-1117-CA for the identification of CLL patients with del 17p?

Discussion: See discussion under Question 8.

Question 10

Ibrutinib was granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of CLL on 27 March 2012. Does the Agency agree that ibrutinib is exempt from the requirement to conduct pediatric studies for the treatment of CLL as stated in 21§CFR 314.55(d) Exemption for Orphan Drugs?

FDA Response: Yes.

Pharmacyclics Response

Pharmacyclics acknowledges the Agency's response.

No discussion occurred.

Additional Comments:

1. **We recommend that for patients who proceed to other antineoplastic treatment (including hematopoietic stem cell transplant) in the absence of disease progression, that these patients should be censored for duration of response at the time of initiation of other antineoplastic treatment. Responses that occur after the initiation of subsequent antineoplastic treatment should not be attributed to ibrutinib in the analysis.**

Pharmacyclics Response

Pharmacyclics will report the duration of response analysis as described by the Agency. An exploratory measurement of time to event, which would not censor patients who proceed on to other antineoplastic treatment, will also be conducted.

2. Please capture details of prior therapies for CLL including dates of treatment, best response, progression, etc.

Pharmacyclics Response

Pharmacyclics agrees to require documentation and will capture dates of prior treatment, best response, and dates of progression on eligible patients.

3. Clinical trials PCYC-1112 and PCYC-1117 target similar patient populations. Please comment on your plan to enroll to these two clinical trials concurrently.

Pharmacyclics Response

Study PCYC-1112-CA is currently enrolling both del 17p patients and patients without del 17p. Study PCYC-1117-CA will be conducted at sites that have either met their enrollment quota (10% of population or 35 patients) or sites that are not participating in Study PCYC-1112-CA.

Pharmacyclics anticipates that final analysis of Study PCYC-1117-CA will be performed after Study PCYC-1112-CA has been completely enrolled but before the final study analysis for PCYC-1112-CA. If requested by the Agency, Pharmacyclics will commit to submit a summary of the PFS, OS, and safety data on all of the del 17p patients enrolled in Study PCYC-1112-CA as supportive data for risk benefit analysis at the time of the PCYC-1117-CA NDA submission.

No discussion occurred for any of the additional comments.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified requiring further discussion.

4.0 ACTION ITEMS

No issues identified requiring further actions.

5.0 ATTACHMENTS AND HANDOUTS

No issues identified requiring further actions.

Meeting Chair

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,
Clinical Team Leader, DHP

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

/s/

VIRGINIA E KWITKOWSKI
09/27/2012

FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B meeting
Meeting Category:	EOP2 meeting
Meeting Date and Time:	July 26, 2012, 12:00 p.m.
Meeting Location:	CDER WO 1309
Application Number:	IND 102688
Product Name:	Ibrutinib (PCI-32765)
Indication:	Chronic Lymphocytic Leukemia
Sponsor Name:	Pharmacyclics, Inc.
Meeting Request Date:	May 7, 2012
Received Briefing Package	June 15, 2012
Meeting Chair:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
Meeting Recorder:	CDR Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES:

- Edvardas Kaminskas, M.D., Acting Deputy Director, DHP
- Anthony Murgo, M.D., Associate Director for Regulatory Science
- Gerald Marti, M.D., Medical Officer, OIVD, DIHD, CDRH

- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- R. Angelo De Claro, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Mark D. Rothmann, Ph.D., Team Leader, DB 5
- Phillip Koo, Clinical Pharmacology Staff Fellow, DCP5
- Rachelle Lubin, Pharm.D., Clinical Pharmacology Reviewer, DCP5
- Bahru Habtemariam, Pharm.D., Acting Team Leader Clinical Pharmacology, DCP5
- Gregory Reaman, M.D., Associate Director for Oncology Sciences
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES:

- Steven Sun, Ph.D., Director, Biostatistics, Janssen R&D, LLC
- John Seaman, Pharm.D., Senior Director, Global Regulatory Affairs
  Janssen R&D, LLC
- Sen Hong Zhuang, M.D., Ph.D., Senior Director, Clinical Research, Janssen R&D, LLC
- Terri Williams PhD, Associate Director, Global Regulatory Affairs, Janssen R&D, LLC
- (b) (4)
- Craig Tendler MD, Vice President, Late Development and Global Medical Affairs, Janssen R&D, LLC
- Cindy Lopez, Senior Manager, Regulatory Affairs, Pharmacyclics
- Fong Clow ScD, Executive Director, Biometrics, Pharmacyclics
- Danelle James, M.D., Associate Medical Director, Pharmacyclics
- Jesse McGreivy M.D., Vice President, Clinical Science, Pharmacyclics
- Lori Kunkel, M.D., Chief Medical Officer, Pharmacyclics

1.0 BACKGROUND

On May 7, 2012, Pharmacyclics submitted a Type B, End of Phase 2 meeting request to discuss their development their Sponsor's Phase 2 trial (PCYC-117-CA) of ibrutinib administered as a single oral agent in CLL/SLL patients with deletion of the short arm of chromosome 17 who have relapsed or have refractory disease and have previously received at least one prior therapy. The Division of Hematology Products (DHP) issued a Meeting Granted letter to Pharmacyclics on May 22, 2012. Pharmacyclics submitted the meeting background package on June 15, 2012. On July 19, 2012, DHP provided Pharmacyclics with the preliminary responses to their questions in preparation for discussion at the meeting. Pharmacyclics provided their response to the FDA preliminary responses and comments via e-mail on July 25, 2012.

2.0 DISCUSSION

List of Specific Questions

1. Does the Agency agree with the choice of patient population and how they are defined in the study eligibility criteria for the proposed Phase 3 study PCYC-1115-CA?

FDA Response: No. The (b) (4) does not identify a population of patients who would not be eligible for chemo-immunotherapy. (b) (4) has not been validated for CLL or in any other cancer setting. In addition, the patient heterogeneity as a result of using (b) (4) would be a problem in labeling a patient population based on (b) (4) data.

Please clarify the term "clinically significant autoimmune cytopenia" in Inclusion Criterion #1. Did you mean to use the same definition as in Inclusion Criterion #3 (i.e., "autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy")?

A population of patients ≥ 65 years of age with CLL/SLL who require treatment would be acceptable. You can use clinical information such as performance status, creatinine clearance, autoimmune cytopenias, and co-morbidities to further describe the baseline characteristics of your population. You can also use this clinical information for exploratory subgroup analyses.

Pharmacyclics Response:

Pharmacyclics agrees not to use the [redacted] (b) (4) for defining the population for labeling criteria.

Yes, Pharmacyclics will use the same definition as in Inclusion #3 that defines autoimmune complications that is poorly responsive to corticosteroids or other therapies in the same fashion for eligibility as the IWCLL criteria defining active disease and indications for anti-leukemia therapy.

Automimmune hemolytic anemia will be defined for this study as a patient with at least one marker of hemolysis (elevated indirect bilirubin not due to liver disease, increased lactate dehydrogenase without alternative etiology, or increased absolute reticulocytosis or bone marrow erythropoiesis in the absence of bleeding) AND at least one marker of direct or indirect autoimmune mechanism (positive direct antiglobulin for IgG or C3d, Cold agglutins) (DingClin Adv Hematol Oncol. 2007 Apr;5(4):257-61. Review). Immune thrombocytopenia is defined as a patient with thrombocytopenia (platelets ≤100,000) and increased megakaryocytes on the bone marrow exam. Pharmacyclics will exclude patients with uncontrolled autoimmune cytopenias as defined by a declining platelet counts within 4 weeks prior to the first dose of study drug or the need for daily corticosteroids > 20 mg daily.

Based on the Agency's recommendation and European Scientific Advice, Pharmacyclics proposes that patients ≥65 years are eligible, but patients younger than 70 years must have a co-morbidity that may preclude the effective and/or safe use of intensive fludarabine based chemoimmunotherapy. These criteria will be defined in the protocol and will include compromised performance status (ECOG ≥1), significant cytopenias (platelets <100,000 or hemoglobin <10g/dL), creatinine clearance <70 mL/min, and clinical apparent autoimmune cytopenias.

Meeting Discussion: The Agency acknowledges the Sponsor's responses. The Agency encourages submission of the proposed trial under an SPA agreement request.

2. Does the Agency agree with the choice of chlorambucil as the comparator for the Phase 3 registration study PCYC-1115-CA and the doses, schedules, and treatment durations of both ibrutinib and chlorambucil?

FDA Response: No. In the submitted briefing package, we note that your previous trials enrolled patients < 65 and ≥ 65 years old and patients ≥ 65 years old had approximately a 3-fold higher AUC than those < 65 years old. We also note that your proposed phase 3 trial will only enroll patients ≥ 65 years old. In light of the higher exposure observed in patients ≥ 65

years old, you should justify the selected phase 3 dose using exposure-response analyses for safety and effectiveness based on data collected in clinical trials thus far.

In addition, you state that (b) (4) **We recommend that you administer ibrutinib at least 1 hour before or 2 hours after a meal. Also, refer to Additional Comment #2.**

However, your proposed dose, schedule, and treatment duration of chlorambucil are acceptable.

Pharmacyclics Response:

The Agency has noted a higher ibrutinib AUC exposure in CLL patients ≥ 65 years old than those < 65 years old in Study PCYC-1109-CA. It should be noted that the difference in AUC between age groups across other studies and treatment cohorts at the 420 mg/day dose level is considerably less than 3-fold. In combined analysis of PK data from 420 mg/day cohorts in Studies PCYC-1102-CA and PCYC-1109-CA, the ibrutinib AUC in patients ≥ 65 years old was on average 916 ng·h/mL where the mean AUC in patients < 65 years old was 571 ng·h/mL (a 60% greater in the older patients) (Table 1). This is within the variability measurement of AUC and is not associated with an increased identifiable safety risk.

In Study PCYC-1109-CA, the mean AUC in patients ≥ 65 years old was 1320 ng·h/mL (comparable to the AUC measured in the 840 mg/day group in Study PCYC-1102-CA) and 474 ng·h/mL for patients < 65 years old (comparable to the AUC measured in the 420 mg/day group in Study PCYC-1102-CA). Safety data in Study PCYC-1109-CA can only be analyzed for the first 28 days of treatment due the fact that ofatumumab was initiated thereafter and confounds the interpretation of single agent comparison. When the safety profiles of these two subgroups were compared, no substantial differences were observed (Table 2).

In Study PCYC-1102-CA, the mean AUC in relapsed/refractory patients that received a dose of 840 mg/day was 1210 ng·h/mL whereas the mean AUC in patients that received 420 mg/day was 536 ng·h/mL. Safety profiles in patients with low exposure (420 mg/day) were compared to patients with a higher exposure (840 mg/day) and no significant difference was observed between those groups (Table 3).

This analysis supports the selection of once-daily 420 mg dose of ibrutinib for the Phase 3 Study PCYC-1115-CA. The 420 mg/day dose in Studies PCYC-1102-CA and PCYC-1109-CA has been demonstrated to provide continuous Btk target occupancy in over 90% of CLL patients. This level of Btk occupancy has been associated with clinical benefit in both studies.

Pharmacyclics has completed a pilot food effect study for ibrutinib as part of Study PCYC-1102-CA. This study demonstrated that a lower AUC was achieved under fasting conditions. All of Pharmacyclics Phase 1 and 2 studies have been conducted with the modified fasting conditions as defined as 30 minutes before or 2 hours after meals. Pharmacyclics does not want to modify these dosing conditions in Phase 3 given the current efficacy and safety profile, and changing the administration of ibrutinib to at least 1 hour before may result in decreased exposure. See detailed results in Table 1 and Table 2.

Table 1: Preliminary Mean Ibrutinib Steady-state (Cycle 1) Pharmacokinetics at 420 mg/day by Age Range

		Age Group		Mean ± SD			
Study No.	Group	Median (Range) (Years)	N	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-24} (ng·h/mL)
PCYC-1102-CA	Naïve	≥ 65 71 (66, 84)	26	144 ± 97.5	1.79 ± 0.96	6.33 ± 1.89[a]	824 ± 524
	R/R	< 65 57 (40, 64)	14	74.5 ± 48.3	1.96 ± 1.45	7.92 ± 2.93[b]	491 ± 328
		≥ 65 70 (68, 79)	12	119 ± 105	1.58 ± 0.51	8.22 ± 3.87[c]	587 ± 338
	R/R (high risk)	< 65 53 (37, 58)	10	132 ± 68.3	1.50 ± 0.53	8.32 ± 4.53[d]	809 ± 361
		≥ 65 73 (66, 82)	14	210 ± 191	2.04 ± 0.97	6.88 ± 3.34	965 ± 753
PCYC-1109-CA	R/R	< 65 59 (51, 64)	13	70.4 ± 55.6	3.85 ± 6.08	6.23 ± 2.18[c]	474 ± 367
		≥ 65 74 (66, 85)	14	215 ± 164	2.43 ± 1.16	9.35 ± 6.26[b]	1320 ± 855

Combined Data	**< 65**	**37**	**88.6 ± 61.3**	**2.50 ± 3.77**	**7.47 ± 3.26[e]**	**571 ± 372**
	56 (37, 64)					
	≥ 65	**66**	**169 ± 141**	**1.94 ± 0.97**	**7.41 ± 3.89[f]**	**916 ± 666**
	73 (66, 85)					

R/R = relapsed/refractory; CV = coefficient of variation

[a] N = 25; [b] N = 13; [c] N = 11; [d] N = 9; [e] N = 33; [f] N = 63

Table 2: Ibrutinib AEs Within the First 28 Days in Cohort 1 by Age Group in Study PCYC-1109-CA

Pharmacyclics, Inc. >>>> Draft <<<< Protocol PCYC-1109-CA

BTK (Data Cut: 03JUL2012)

AEs within First 28 Days (>=30% for Grade 1&2 or >=2% for Grade >=3) by Age 65 Groups, Max NCI-CTC Grades and Preferred Term

Safety Population (Cohort 1)

	< 65 Years (N=13)		>= 65 Years (N=14)	
Preferred Term	Grades 1-2	Grades 3-5	Grades 1-2	Grades 3-5
Diarrhoea	3 (23%)	1 (8%)	6 (43%)	0 (0%)
Anaemia	0 (0%)	1 (8%)	0 (0%)	1 (7%)
Hyponatraemia	0 (0%)	0 (0%)	0 (0%)	2 (14%)
Dyspnoea	0 (0%)	1 (8%)	0 (0%)	0 (0%)
Electrolyte imbalance	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Hyperuricaemia	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Stridor	0 (0%)	1 (8%)	0 (0%)	0 (0%)

Note: Patients who had more than one occurrence of an adverse event are counted once within the preferred term by its maximum grade.

MedDRA version: 15.0

source: BTK\PCYC-1109-CA\Development\Programs\adhoc_t_ae_age65_28days.sas sc 22JUL2012:22:04 Page 1 of 1

Table 3: Ibrutinib AEs in Patients with R/R CLL at 420 and 840 mg/day in Study PCYC-1102-CA

Pharmacyclics, Inc. >>> D R A F T <<< Protocol PCYC-1102-CA

BTK (Data Cut: 03JUL2012)

Adverse Events (>=30% for Grade 1&2 or >=5% for Grade >=3) by Treatment Group, Max NCI-CTC Grades and Preferred Term

Relapsed/Refractory Safety Population (Cohorts 1,3)

	R/R 420mg (N=27)		R/R 840mg (N=34)	
Preferred Term	Grades 1-2	Grades 3-5	Grades 1-2	Grades 3-5
Diarrhoea	16 (59%)	2 (7%)	15 (44%)	0 (0%)
Upper respiratory tract infection	15 (56%)	0 (0%)	10 (29%)	0 (0%)
Cough	9 (33%)	0 (0%)	14 (41%)	0 (0%)
Fatigue	8 (30%)	2 (7%)	10 (29%)	0 (0%)
Pyrexia	7 (26%)	0 (0%)	8 (24%)	3 (9%)
Contusion	10 (37%)	0 (0%)	7 (21%)	0 (0%)
Oedema peripheral	5 (19%)	0 (0%)	11 (32%)	0 (0%)
Sinusitis	2 (7%)	0 (0%)	7 (21%)	2 (6%)
Hypertension	2 (7%)	0 (0%)	5 (15%)	2 (6%)
Pneumonia	2 (7%)	1 (4%)	0 (0%)	6 (18%)
Anaemia	1 (4%)	2 (7%)	3 (9%)	2 (6%)
Asthenia	3 (11%)	2 (7%)	3 (9%)	0 (0%)
Neutropenia	0 (0%)	1 (4%)	1 (3%)	5 (15%)
Abdominal pain	2 (7%)	0 (0%)	2 (6%)	2 (6%)
Atrial fibrillation	1 (4%)	2 (7%)	2 (6%)	0 (0%)
Dehydration	0 (0%)	2 (7%)	1 (3%)	1 (3%)
Thrombocytopenia	0 (0%)	2 (7%)	1 (3%)	1 (3%)
Febrile neutropenia	0 (0%)	1 (4%)	0 (0%)	2 (6%)

Hyperkalaemia	0 (0%)	0 (0%)	1 (3%)	2 (6%)
Bacteraemia	0 (0%)	0 (0%)	0 (0%)	2 (6%)
Clostridial infection	0 (0%)	2 (7%)	0 (0%)	0 (0%)
Hypoglycaemia	0 (0%)	0 (0%)	0 (0%)	2 (6%)
Subdural haematoma	0 (0%)	2 (7%)	0 (0%)	0 (0%)

Note: Patients who had more than one occurrence of an adverse event are counted once within the preferred term by its maximum grade.
MedDRA version: 15.0
source: BTK/PCYC-1102-CA/Development/Programs/adhoc_t_ae_RR13.sas sc 21JUL2012:17:06 Page 1 of 1

Meeting Discussion: The Sponsor proposes to submit plans for future Clinical Pharmacology studies. The Agency reiterated the initial response to question 2 that extensive PK and exposure response analysis should be done to optimize the dose in patients 65 years and older. The Agency reiterates the recommendation that the drug be given 1 hour before or 2 hours after a meal. The dose justification should be submitted with the SPA.

3. Does the Agency agree that the primary endpoint PFS, as assessed by independent review, is appropriate for the Phase 3 study supportive of the proposed indication as stated below:

(b) (4)

FDA Response: IRC-assessed PFS is an acceptable primary endpoint. However, the indication granted depends on the actual population studied in the clinical trial.

All patients should be followed for PFS until a PFS event has occurred (progression or death) or until the data cutoff. Missing data/assessments of progression should be kept to a minimum. A substantial amount of missing data could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS.

We recommend that IRC reviews of disease status occur simultaneously or shortly after the investigator's review, and that patients should continue to undergo disease assessment until progression has been confirmed by the independent review committee.

Pharmacyclics Response:

We agree. This is our planned approach for IRC reviews in PCYC-1115-CA.

4. Does the Agency agree that the secondary endpoints including ORR as assessed by the IRC, hematologic improvement, and overall survival are appropriate for a Phase 3 study supportive of the proposed indication?

FDA Response: ORR, MRD-negative CR, and OS are acceptable secondary endpoints. (b) (4) is not acceptable as a secondary endpoint for labeling purposes because (b) (4) is evaluated in a subset of patients with cytopenias, rather than the ITT population.

In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints, subgroups, or further analysis of the primary endpoint cannot result in (either singly or in combination) an efficacy claim. In the event that there is a statistically

significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future submission, any secondary endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee an overall 2-sided 0.05 level for the tests of such secondary endpoints.

Pharmacyclics Response:

In consideration of the Agency's comments (as well as European Scientific Advice from CHMP), the secondary endpoints for Study PCYC-1115-CA will be revised as the following:

1. ORR according to standard IWCLL criteria (see below), as assessed by the IRC
2. Event-free-survival, where progressive disease (PD), death and non-responders at 3 months are defined as events. Overall Response (OR) as defined by CR, Cri, PR, nPR plus PR with lymphocytosis will be counted as responders.
3. Overall Survival (OS)
4. Fatigue measure by FACIT-5
5. Hematological Improvement

To address the multiple inferential tests among the secondary endpoints, inferential testing of the first secondary endpoints, ORR, will be conducted only if the primary analysis of PFS achieves statistical significance at 2-sided alpha=0.05. Only if the first secondary endpoint achieves statistical significance at 2-sided alpha=0.05, the second secondary endpoint, event-free-survival, will be tested at alpha=0.05 level. Following a positive outcome of the second secondary endpoint, event-free-survival, the overall Type I error rate is maintained at 0.05 by a Hochberg adjustment for multiple comparisons (Hochberg 1988) for the subsequent three secondary endpoints: OS, Fatigue and Hematological Improvement.

The Hochberg adjustment for these three multiple comparisons is conducted as follows:

- All 3 comparisons are significant if the largest 2-sided p-value is ≤ 0.05.
- The 2 strongest comparisons are significant if the second smallest 2-sided p-value is ≤ 0.025 (0.05/2)
- The strongest comparison is significant if the smallest 2-sided p-value is $\leq$ 0.0167 (0.05/3)

With this strategy, an overall 2-sided 0.05 level for the test of all secondary endpoints will be maintained.

All subcategories of ORR will be presented in the table of ORR analysis but no formal statistical test will be used.

Pharmacyclics agrees with the Agency's comments on (b) (4) and does not intend to obtain label claims of (b) (4)

Meeting Discussion: The Agency expressed concerns regarding limitations of an EFS endpoint. The Sponsor will provide justification for EFS with the SPA submission. The Agency suggested that the Sponsor may consider providing different SAPs to US FDA and other international regulatory agencies.

5. Does the Agency agree that the statistical analysis approach and analysis of the primary endpoint in the Phase 3 study PCYC-1115-CA are adequate to support the proposed indication?

   FDA Response: The statistical analysis approach is acceptable.

   Pharmacyclics Response:

   Pharmacyclics Acknowledges the Agency's comment.

6. Does the Agency agree that the data cut-off for the primary analysis is acceptable, namely, at the time when all patients have a minimum of 12 months of treatment/follow-up AND either 81 progression events have occurred OR 15 months have elapsed after the last patient was randomized, which comes first?

   FDA Response: Based on your analysis plan for PFS, the Agency is concerned that the size of PFS benefit may not be reliably estimated (e.g., there may not be an estimate of median PFS for the experimental arm).

   Pharmacyclics Response:

   The Hazard Ratio (HR) was select to describe the outcome of this study as it has the advantage of using all available information, including patients who have not completed or have failed protocol therapy. It is the most comprehensive measure of effect size.

   It is expected that the number of chlorambucil PFS events will exceed the number of ibrutinib PFS event considerably. This assumption is based on the results of the Phase 2 study of ibrutinib in treatment-naive patients (>85% PFS at 22 months). The assumption of a median PFS of 15 months from the chlorambucil arm seems very reasonable based on the historic literature. The alternative cut-off rule for the final analysis is reasonable in order to shorten the study duration as much as possible and still maintain an acceptable power (85%).

Although Study PCYC-1115-CA may have variable power, the study is adequately powered for various reasonable study assumptions (Tables 4-6). The attempt to ensure the maturity of the PFS outcome data is accomplished by defining a minimal median follow-up of 15 months, which is supported by the cut-off criteria based on the design of 81 events or the minimal median follow-up of 18 months with the 15 month cut-off criteria.

Table 4: Expected Study Duration (Months) Based on 10,000 Simulations

	Median PFS (Months) for Chlorambucil				
HR	**15**	**17**	**20**	**22**	**25**
0.1	19.9	21.0	21.9	22.0	22.0
0.3	19.0	19.2	20.2	21.1	21.8
0.5	19.0	19.0	19.1	19.5	20.6
0.6	19.0	19.0	19.0	19.2	19.9

Table 5: Expected No. Events at the End of Study Based on 10,000 Simulations

	Median PFS (Months) for Chlorambucil				
HR	**15**	**17**	**20**	**22**	**25**
0.1	82	79	73	68	61
0.3	96	88	82	79	74
0.5	111	101	89	84	80
0.6	117	107	94	88	83

Assumptions: 1-sided $\alpha = 0.025$; 40-90 % risk reduction between groups; Total n = 272; enrollment rate: 40/month

Table 6: Power Calculations for Varying PFS Medians

	Median PFS (Months) for Chlorambucil				
HR	**15**	**17**	**20**	**22**	**25**
0.1	1.00	1.00	1.00	1.00	1.00
0.3	1.00	1.00	1.00	1.00	1.00
0.5	0.95	0.93	0.90	0.88	0.86
0.6	0.79	0.74	0.69	0.66	0.63

Assumptions: 1-sided $\alpha = 0.025$; 40-90 % risk reduction between groups

Thus the magnitude of difference between the two groups will be made substantial and will be captured by an HR of <0.5. Pharmacyclics is committed to follow all patients in a longitudinal database for long term follow-up including PFS events for ibrutinib, subsequent anti-cancer therapy, and survival.

Meeting Discussion: Whether the Agency will be able to assess the size of the benefit will be a review issue.

7. Does the Agency agree to Study PCYC-1116-CA as an extension protocol to PCYC-1115-CA for long-term follow-up of patients randomized into PCYC-1115-CA and for monitoring of subsequent anticancer therapy (alternative treatment arm or investigator choice) after patients' first progression?

FDA Response: No. Because ibrutinib is not approved or marketed, we recommend not allowing patients on the control arm (Arm A: chlorambucil) to receive ibrutinib after progression. Allowing such cross-in may confound comparison of long-term outcomes between arms.

Pharmacyclics Response:

Pharmacyclics recognizes that subsequent anti-cancer therapy can confound the ability to interpret long-term outcomes such as survival in randomized Phase 3 studies, while the integrity of the primary endpoint, IRC assessed PFS, is preserved. PFS is an acceptable endpoint for clinical trial evaluation of new agents for CLL. It is recognized that some patients will receive alternative anti-cancer treatment following IRC confirmed disease progression in the extension study. In this context, it is important to implement study conduct measures to ensure compliance with the assigned treatment while minimizing the potential impact of subsequent therapy, including investigational treatment, on long term outcomes. Accordingly, only those patients who have received at least 3 cycles of chlorambucil and experience a documented IRC confirmed disease progression and progress within 12 months will be eligible to receive second-line therapy and including investigational agents in the setting of the extension study (see details bulleted below). These patients who relapse during treatment or within 12 months of treatment are by definition resistant to alkylating agent therapy, by eligibility criteria for PCYC-1115-CA are inappropriate for intensive fludarabine-based therapy, and are considered at high risk for decreased survival. There is no Phase 3 data to support effective and safe salvage therapy in this population and as such, an investigational agent is within the standard of care. The extension study to PCYC-1115-CA, PCYC-1116-CA will allow for collection of long-term safety and efficacy longitudinal data in all patients randomized in the main study for 5 years following first patient enrolled enabling a robust analysis of long term outcomes.

The initial CLL approval in the US will be based on the currently enrolling phase 3 study PCYC-1112-CA, in CLL patients with relapse refractory disease who are considered inappropriate for treatment or retreatment with purine analog based therapy. It is designed to demonstrate superiority over a standard of care without the allowance for crossover and overall survival is an important secondary end point which will not be compromised. Based on the results of PCYC-1112-CA, Pharmacyclics anticipates that ibrutinib may become commercially available for relapsed/refractory CLL during the conduct of the proposed front-line Phase 3 study,

PCYC-1115-CA, such that patients randomized to chlorambucil may ultimately receive ibrutinb for relapsed disease. The proposed extension study (PCYC-1116-CA) provides a robust mechanism by which these patients can be retained and closely followed so that long term outcomes with respect to safety and efficacy can be shared with FDA.

Criteria necessary for ibrutinib as an investigational therapy in PCYC-1116-CA:

- Ibrutinib will only be offered to a subset of patients, when all the following criteria are met:
  - Patients with IRC confirmed disease progression
  - Patients who have received at least 3 cycles of chlorambucil therapy
  - Patients with documented protocol defined reason for chlorambucil discontinuation
    - No response at 3 months, no further response after at least 6 cycles, or could not tolerate treatment (a situation defined by the recurrence of toxicity of at least Grade 3 despite appropriate dose reductions and optimal symptomatic management, or a maximum treatment of 12 cycles
  - Patients who are considered high-risk due to progressive disease confirmed by IRC within 12 months of chlorambucil therapy
    - Standard treatment of these patients is in a clinical trial with an investigational agent
  - Patients who continue to have adequate organ function, performance status, and meet other criteria that define eligibility for ibrutinib
- Ibrutinib requests will be stripped of identifiers and evaluated by the study-management committee to confirm the above criteria are met

Meeting Discussion: The Agency recommends that the Sponsor include additional data that are available to support the justification for cross over in the high risk population. The Sponsor will submit protocol and SAP for study 1116 to support the SPA submission for study 1115.

8. Does the Agency agree that the pharmacokinetic data and population pharmacokinetics assessed in the Phase 3 trial of relapsed/refractory CLL patients (Study PCYC-1112-CA, which is anticipated to include at least 50% patients of age of 65 years or older), in combination with the pharmacokinetic data collected in association with ECG assessment in Study PCYC-1115-CA plus data from elderly patients in the Phase 1b/2 Study PCYC-1102-CA, will be sufficient to support of the registration of ibrutinib for the treatment of (b) (4) CLL/SLL?

FDA Response: No. In order to conduct a reliable exposure-response analysis for safety and effectiveness, we recommend that you collect steady state sparse PK samples (pre-dose) in all patients receiving ibrutinib. In addition, your current phase 3 study protocol does not include a PK sampling plan. You should amend your protocol to include the PK sampling plans. Whether your data are sufficient to support an approval will be a review issue.

Pharmacyclics Response:

This is an elderly frail population with multiple co-morbidities and compromised performance status. Pharmacyclics proposes to collect steady-state sparse PK samples in approximately 50 evaluable patients. The PK sampling plan will be incorporated into protocol PCYC-1115-CA. This is in addition to the following:

- sampling of 100 ibrutinib treated patients from Phase 3 Study PCYC-1112-CA of whom 50% are anticipated to be 65 years or older.
- Data from 98 patients ≥ 65 years old who have had extensive PK evaluations in Phase 1 and Phase 2 ibrutinib studies.

Pharmacyclics believes this should provide sufficient characterization of the PK profile in the patient population ≥ 65 years old, does the Agency agree?

9. Does the Agency agree that our clinical development plan is satisfactory to support approval of ibrutinib for the (b) (4) with CLL/SLL who require treatment by standard guidelines?

FDA Response: Your development plan would be acceptable if you adequately define the patient population. See response to #1.

In general, two adequate and well controlled studies are required for approval. FDA may accept a single pivotal study to support approval if results show a highly statistically significant and clinically meaningful effect that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. For further information please refer to the FDA document "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comments. Please refer to Pharmacyclic's response to question #1. It should be noted that PCYC-1115 is anticipated to be as (b) (4) and that Pharmacyclics/Janssen is conducting a number of other randomized controlled clinical trials in CLL.

10. (b) (4)

FDA Response: No. See responses to questions 1, 2, and 4.

Pharmacyclics Response:

Has Pharmacyclics adequately addressed the Agency's comments to questions 1, 2, and 4? Are Pharmacyclics revisions acceptable for consideration for a Special Protocol Assessment (SPA) designation?

Meeting Discussion: The SPA submission should contain the protocol, final SAP, and informed consent document.

Additional comments:

1. The Agency cannot confirm the sample size justification in study PCYC-1115-CA based on your assumptions of a HR=0.5 (median PFS of 15 months for the control arm), one-sided type I error rate of 0.025 and power of 86%, 7 months accrual, and at least 15 months follow-up.

Pharmacyclics Response:

1) Assuming HR=0.5, 81 events will ensure 85% power, given the median PFS=15 months for the control and 40/month enrollment rate, we anticipate 81 events will occur approximately 7.5 months after the last patient is randomized with total sample size of 272 (Table 7).
2) To enhance the data maturity, we mandate minimal follow-up of 12 months for every subjects. Given the assumptions above, we expect 111 events will occur at the cutoff of 12 months after last patient is enrolled, the actual power for the study will be approximately 94%.

3) The study is not event driven only. The clinical cutoff is also calendar based to avoid unnecessarily prolonging the study duration in the case of an exceedingly beneficial effect of ibrutinib. At this scenario, the actual power varies with the different median PFS of the control group. If the median for the control is <25 months, then the study will have at least 86% power (Table 6).

Table 7: East Output for Sample Size, Events, and Study Duration Estimate

Plan ID	Plan1		
Test Parameters			
1-Sided or 2-Sided Test	1-Sided		
Significance Level (Alpha)	0.025		
Power (1 - Beta)	0.85		
Assigned Fraction (Treatment)	0.5		
Boundary Parameters			
Planned Number of Looks	1		
Spacing of Looks			
Hypothesis to be Rejected			
Boundary Family			
Boundary to Reject H0			
Boundary to Reject H1			
Survival Parameters			
Subject Accrual Per Unit Time	40.0		
Median Time (Control)	15.0		
Median Time (Treatment)	30.0		
Committed Accrual	Min		Max
Committed Accrual (Duration)	1.869	6.8	11.677
Committed Accrual (Subjects)	75	272	467
Max. Duration and Events			
Maximum Study Duration		13.901	
Maximum Number of Events		81	
Expected Values under...	H0	H1	H½
Expected Accrual (Subjects)	272	272	272
Expected Study Duration	11.154	13.901	12.271
Expected Number of Events	81	81	81

2. We strongly recommend that you conduct your food effect study prior to starting your phase 3 trial as per the Guidance for Industry entitled *Food-Effect Bioavailability and Fed Bioequivalence Studies*.

Pharmacyclics Response:

The fed-fast study was conducted in 16 subjects with CLL as a sub-study of PCYC-1102-CA. Ibrutinib 420 mg was administered once daily under modified fasting conditions (at least 30 minutes before or 2 hours after meal). The effect of food was evaluated at steady-state on Days 8 and 15 of Cycle 1 as cross-over fasted or fed prior to dosing. These fasted and fed exposure data

were also compared to exposure on Day 1 under modified fasting conditions. Since there was no accumulation of ibrutinib exposure after repeated dosing, Pharmacyclics considers the comparison of data on Day 1 and at steady-state is valid. Preliminary results of the fed-fast sub-study will be submitted to the IND prior to years end.

The preliminary results demonstrated that a slightly higher ibrutinib exposure (1.8-fold for AUC and 2.4-fold for C_{max}) was obtained after administration with high fat meal when compared to ibrutinib dosing post an overnight fasted (Table 8 and Table 9). Similarly, a 1.6-fold higher AUC and a 1.4 higher C_{max} with high fat meal were observed when compared to modified fasting conditions. Since ibrutinib has been dosed at least 30 minutes before or 2 hours after meal in all Phase 2 trials to obtain preliminary safety and efficacy information, Pharmacyclics prefers to use the same conditions for ibrutinib administration in the Phase 3 studies.

Table 8: Preliminary Pharmacokinetics of Ibrutinib under Modified Fasted, Fasted or Fed Conditions in Sub-Study PCYC-1102-CA

Daily Dose	N	Treatment	Mean ± SD			
			C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-24} (ng·h/mL)
420 mg	16	Modified Fasted[a]	86.3 ± 63.0	1.94 ± 0.93	7.72 ± 4.21[b]	548 ± 370
		Fasted	50.4 ± 45.4	2.00 ± 1.26	9.05 ± 4.09[c]	449 ± 256
		Fed	120 ± 95.4	3.44 ± 1.63	4.03 ± 0.95[b]	792 ± 400

[a] at least 30 minutes before or 2 hours after meal

[b] N = 13; [c] N = 15

Table 9: Geometric Mean Ratios (Fed/Fasted or Fed/Modified Fasted) and 90% Confidence Intervals for Ibrutinib Pharmacokinetic Parameters Following Administration of 420 mg

Parameter	Geometric Mean Ratio			
	Fed/Fasted		Fed/Modified Fasted	
	Point Estimate	90% Confidence Interval	Point Estimate	90% Confidence Interval
C_{max}	2.43	1.71, 3.47	1.41	0.93, 2.16
AUC_{0-24}	1.83	1.43, 2.34	1.55	1.20, 1.99

3. Your proposed protocol states that strong CYP3A4/5 inhibitors/inducers, CYP2D6 inhibitors, grapefruit and Seville oranges should be used with caution. Because the term (b) (4) is difficult to put into practice, you should revise your protocol to explicitly state that the use of CYP3A4/5 inhibitors/inducers, CYP2D6 inhibitors, grapefruit and Seville oranges should be avoided.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's recommendations and will revise the protocol to state that the use of CYP3A4/5 inhibitors/inducers, CYP2D6 inhibitors, grapefruit and Seville oranges should be avoided.

4. The clinical evaluation of the potential for QT/QTc interval prolongation needs to be addressed. We encourage submitting your plan for review by the Agency.

Pharmacyclics Response:

Pharmacyclics submitted the plan for clinical evaluation of the potential for QT/QTc interval prolongation to the Agency on 29 June 2012 (Serial No. 0086). The submission included the following information:

- QT data and Interim reports (Part 1 and Part 2) from Study PCYC-1102-CA
- Definition of ECG parameters for Study PCYC-1102-CA
- SAS transport files : ecg.xpt and adecg.xtp

- ECG waveforms for Study PCYC-1102-CA provided to the Agency by iCardiac Technologies through the Agency's ECG warehouse

- Proposed synopsis of the clinical pharmacology study PCI32765CLL1107 to assess the effects of ibrutinib on ECG parameters in general and the QT interval in particular in healthy volunteers as detailed in the ICH Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified requiring further discussion.

4.0 ACTION ITEMS

No issues identified requiring further actions.

5.0 ATTACHMENTS AND HANDOUTS

The sponsor submitted extensive responses via email at 4:29 p.m., July 25, 2012, the day before the sponsor meeting. This timing did not permit the Agency to review the responses prior to the Face to Face meeting.

Meeting Chair

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,

Clinical Team Leader, DHP

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

/s/

VIRGINIA E KWITKOWSKI
08/07/2012

FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B meeting
Meeting Category:	EOP2 meeting
Meeting Date and Time:	April 30, 2012, 12:00 p.m.
Meeting Location:	CDER WO 1309
Application Number:	IND 102688
Product Name:	Ibrutinib (PCI-32765)
Indication:	Chronic Lymphocytic Leukemia
Sponsor Name:	Pharmacyclics, Inc.
Meeting Request Date:	February 15, 2012
Received Briefing Package	March 16, 2012
Meeting Chair:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
Meeting Recorder:	CDR Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES:

- Edward Kaminskas, M.D., Acting Deputy Director DHP
- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- R. Angelo De Claro, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Mark D. Rothmann, Ph.D., Team Leader, DB 5
- Rachelle Lubin, Pharm.D., Clinical Pharmacology Reviewer, DCP5
- Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5
- Gregory Reaman, M.D., Associate Director for Oncology Sciences
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES:

- Angela Howes, Medical Leader, Janssen R&D, LLC, Janssen R&D, LLC8
- Jan de Jong, Director, Clinical Pharmacology8
- Steven Sun, Ph.D., Director, Biostatistics, Janssen R&D, LLC8
- Jerry Retkwa, Manager, Global Regulatory Affairs, Janssen R&D, LLC8
- John Seaman, Pharm.D., Senior Director, Global Regulatory Affairs Janssen R&D, LLC8
- Sen Hong Zhuang, M.D., Ph.D., Senior Director, Clinical Research, Janssen R&D, LLC8
- Man C. Fung, M.D., Vice President, Compound Development Team Leader, Janssen R&D, LLC 8
- Alice M. Wei, Pharmacyclics, Regulatory Affairs Consultant8
- Danelle James, M.D., Pharmacyclics, Associate Medical Director8
- Lori Kunkel, M.D., Pharmacyclics,Clinician8

1.0 BACKGROUND

The purpose of this meeting was to discuss the proposed Phase 3 protocol (PCI-32765CLL3001) for the treatment of patients with previously treated CLL/SLL. The proposed study design is a multicenter, double-blind, placebo-controlled randomized Phase 3 study to determine the benefits and risks of combining ibrutinib with bendamustine and rituximab (BR) in patients with relapsed or refractory CLL/SLL. Approximately 580 patients will be randomized in a 1:1 ratio to receive either BR with oral placebo (Treatment Arm A) or BR with oral ibrutinib (Treatment Arm B).

2.0 DISCUSSION

Question 1.

Does the Agency agree that the proposed Phase 3 Study, PCI-32765CLL3001, is adequate in design to characterize the efficacy and safety of ibrutinib in combination with bendamustine and rituximab for the treatment of patients with relapsed or refractory CLL/SLL (b) (4)

FDA Response: No. The Agency discourages the proposed interim analysis of PFS as estimated effects will be less precise, the comparisons will be weighted towards early events, and it may be difficult to evaluate the magnitude of the PFS benefit.

Stopping the trial when only 29% of the subjects have an event will provide inadequate subject follow-up.

Pharmacyclics and Janssen Response:
The sponsors acknowledge the Agency's comment. An interim analysis will provide the Data Monitoring Committee (DMC) with a mechanism to determine superiority of the experimental group in case of overwhelming efficacy results. The ongoing phase 2 single agent ibrutinib PCYC-1102-CA study and combination of ibrutinib with BR PCYC-1108-CA study suggest that CLL3001 may confirm a robust treatment benefit of ibrutinib in refractory and relapsed CLL/SLL patients. (See results based on the March 2012 cutoff in Appendix 1).

A conservative stopping boundary (O'Brien-Fleming) for efficacy is being proposed, and an overwhelming PFS effect will be required to cross the interim efficacy boundary. The expected HR will be less than 0.63, which corresponds to an at least 58% improvement in median PFS (e.g. from 15 months to at least 24 months). We expect the enrollment into PCI-32765CLL3001 will be completed at the time of the interim PFS analysis cut-off, approximately 19 months after the first patient is randomized.

To further explore the impact of potential differences between early and late events on overall study results, we calculated the conditional probability of showing superiority of ibrutinib over placebo at the final PFS (342 events) analysis assuming the HR of late events is less than that observed at the interim analysis. The calculation is based upon an observed HR=0.63 at the interim analysis (171 events) and continuation of the study to the final analysis. As can be seen from the table, even if the true HR=0.8 for the second half of events, we will still have more than 94% chance of showing statistically significant results at the planned final analysis.

True effect size by HR	Conditional Probability
0.70	99.3%
0.73	98.5%
0.75	97.8%
0.78	96.0%
0.80	94.3%
0.85	88.2%

Analyses from supportive secondary endpoints such as ORR, together with various sensitivity analysis and subgroup analyses, will be available at the time of interim analyses to see if the results are internally consistent and robust. In the event of a DMC determination that the pre-specified efficacy boundary is crossed, the sponsors do not intend to stop assigned study treatment, or take other actions that may jeopardize final analysis of the study, prior to seeking advice from the FDA. Overall survival follow-up will continue as specified in the protocol until the study ends, which is defined as either 4 years after the last patient is enrolled or 80% of the patients have died, whichever occurs first.

Meeting Discussion: The Agency does not encourage use of an interim PFS analysis for regulatory action. An interim futility analysis is acceptable. The Sponsor may submit a meeting request with the interim PFS data upon boundary crossing.

The Sponsor agreed to continue following patients for the PFS endpoint until final analysis.

FDA Response:
In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints or subgroups can not result in (either singly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. You should include in a future submission, your plan for testing secondary endpoints for which claims may be included in the labeling.

Pharmacyclics and Janssen Response:
The sponsors acknowledge the Agency's comment and will include our plan for testing secondary endpoints in a future submission.

FDA Response:
In addition, your protocol does not adequately address the risk of tumor lysis syndrome.

Pharmacyclics and Janssen Response:
The sponsors acknowledge that the risk of tumor lysis syndrome was not addressed in the submitted Protocol Elements Document. In the full protocol it is addressed with the following text:

For subjects considered at risk for tumor lysis syndrome (TLS):

Subjects with more than 1 of the factors listed below are considered to be at increased risk of TLS and should be considered for hydration and treatment with a uric acid-lowering agent as well as for frequent monitoring of tumor lysis associated signs and symptoms. Uric-acid lowering agents may include xanthine oxidase inhibitor allopurinol or Uloric [febuxostat] with or without rasburicase per the drug product package inserts.

- Serum creatinine ≥1.5 x ULN or calculated creatinine clearance <60mL/minute
- White blood cell (WBC) ≥50,000/μL
- Uric acid > 450 μmol/L or 7.5mg/dl
- Bulky disease (e.g. lymph node >10cm or massive splenomegaly)

- Elevated LDH >2 x ULN

CBC and blood chemistry, including LDH, phosphate, potassium, creatinine, uric acid, are also added to Day 2 of Cycle 1 for additional monitoring of TLS risk factors

Meeting Discussion: The Agency considers the Sponsor's proposal to be acceptable.

Question 2.

Does the Agency agree that the proposed patient population is adequately defined per the study eligibility criteria?

FDA Response: Yes. However, your definition of refractory is not consistent throughout the protocol (b) (4) vs. 12 month time frame).

Pharmacyclics and Janssen Response:
The sponsors acknowledge the inconsistency in the document. The protocol now defines refractory using the 12 month timeframe throughout the protocol.

Question 3.

Does the Agency agree with the treatment regimen of the combination of bendamustine and rituximab with ibrutinib compared to the combination of bendamustine and rituximab with placebo?

FDA Response: Yes.

Pharmacyclics and Janssen Response:
The sponsors acknowledge the Agency's comment.

Question 4.

Does the Agency agree with the proposed dose, schedule, and duration of therapy for bendamustine, rituximab, and ibrutinib?

FDA Response: Yes. Your planned dose and schedule for ibrutinib is acceptable. A specific claim for (b) (4) would not be possible based upon the current study design which does not isolate the individual contributions of ibrutinib to induction or continuation therapy.

Pharmacyclics and Janssen Response:
The sponsors acknowledge the Agency's comment.

Question 5.

5a. Is the primary endpoint, progression free survival (PFS), assessed by independent review, adequate for the demonstration of clinical benefit in the proposed patient population?

FDA Response: In general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision. However, you should be aware that PFS may be influenced by any imbalance in assessment dates or substantial missing data between treatment arms.

Pharmacyclics and Janssen Response:
The sponsors acknowledge the Agency's comment.

5b. Does the Agency agree that the study design with objective to detect hazard ratio of 0.70 and a significance level of 0.025 (1-sided) is sufficient to demonstrate meaningful clinical benefit?

FDA Response: Refer to 5a.

Pharmacyclics and Janssen Response:
The sponsors acknowledge the Agency's comment.

Question 6.

Is the proposed application of the 2008 IWCLL criteria with modification for assessment of response and disease progression acceptable?

FDA Response: The Agency has no regulatory experience with how these modifications to the existing IWCLL criteria will perform. Therefore, this will be a review issue.

Pharmacyclics and Janssen Response:

The sponsors acknowledge the Agency's comment. The Company also notes that in January 2012 the NCCN (National Cancer Center Network) published revised criteria to address treatment-related lymphocytosis observed in various BCR (B-cell receptor) targeting agents. The text is as follows: "Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease" This modification is consistent with the Agency's advice during the EOP2 meeting on 05 December 2011.

The IWCLL response criteria are currently under revision to account for treatment-related lymphocytosis (TRL) in the definition of disease progression. It is anticipated to be published in 2012.

In the PCI-32765CLL3001 protocol, this class effect of TRL has been addressed as follows: For disease progression: TRL, in isolation, is not a criterion for progression in the setting of unequivocal benefit in at least 1 other parameter of response: lymph node size, spleen size, hematologic parameters (hemoglobin and platelet count), or disease-related symptoms.

For partial response, IWCLL 2008 requires at least a 50% reduction in 2 tumor burden criteria, which may include lymphadenopathy, hepatomegaly, splenomegaly, blood lymphocytes, or bone marrow infiltrate/nodules. Subjects in the CLL3001 protocol will not be classified as PR until response in lymphocytes is met. The criteria will be applied equally to both treatment arms.

Meeting Discussion: The Agency reiterated that the exclusion of treatment-related, isolated lymphocytosis from the criteria for progression of disease is novel to the Agency's approval of drugs for CLL and can not be formally accepted at this time.

The isolated lymphocytosis should be accompanied by reduction in nodal measurements to be considered a non-PFS event. The sponsor is welcome to conduct the trial using the modifications to the CLL criteria, however, the findings will be a review issue at the time of NDA submission.

Question 7.

Does the agency agree that our clinical development plan is satisfactory to support approval of ibrutinib (b) (4) for the treatment of patients with relapsed or refractory CLL/SLL who have received at least 1 prior systemic therapy?

FDA Response: Your clinical development plan appears acceptable. Whether the data from PCI-32765CLL3001 and PCYC-1108-CA will support approval will be a review issue.

Pharmacyclics and Janssen Response:
The sponsors acknowledge the Agency's comment.

Additional Comments and Questions:

1. Provide a timeline for the initiation and completion of your planned Phase 3 trials: PCI-32765CLL3001, PCYC-1112-CA, and PCI-32765MCL3001.

Pharmacyclics and Janssen Response:

PCI-32765CLL3001*: First patient dosed- 3Q 2012

Phase 3 Top line results- 3Q 2015

PCYC-1112-CA*: First patient dosed- 2Q 2012

Phase 3 Top line results- 3Q 2015

PCI-32765MCL3001*: First patient dosed- 4Q 2012

Phase 3 Top line results- 3Q 2015

* Final design of all three studies is currently pending EMA scientific advice.

2. The Agency recommends that you evaluate ECGs more frequently in your proposed clinical trials (based upon the PK of the investigational agent). The propensity for PCI-32765 to induce prolongation of the QTc interval has not been fully evaluated as per the ICH E14 guidance document.

Pharmacyclics and Janssen Response:
In the Phase 3 study PCI-32765CLL3001, an ECG will be performed at baseline and any time when clinically indicated. This study is not considered suitable for evaluation of cardiac effects of ibrutinib because the drug will be given in combination with BR for the first 6 cycles and the study is double blinded. In a phase 2 study PCI-32765MCL2001, in which subjects with mantle cell lymphoma will receive single-agent ibrutinib, ECGs will be performed at baseline and at Day 1 of cycle 1 and 2 with corresponding PK sampling predose and at 2 hr post-dose, around the anticipated C_{max} of ibrutinib. At this time, there is no preclinical or clinical evidence suggesting a negative effect of ibrutinib on QT interval. We plan on submitting the ibrutinib QT data from the phase 2 study 1102 as well as our complete plan to further evaluate the effect of ibrutinib on QT/QTc interval prolongation in a separate study to the Agency by the end of June 2012.
We are enclosing preliminary ECG data from study PCYC-1102. See Appendix 3.

Meeting Discussion: The Agency recommends that the Sponsor continue ECG monitoring in the Phase 3 trial until the IRT has a chance to review the data the Sponsor plans to submit in June 2012. Monitoring should include sampling during cycle 1 at T_{max} and some point after T_{max}. This should also be repeated in a subsequent cycle. This can be done in a subset of patients at one to two sites.

3. Regarding patient reported outcomes, the Agency requires a validated instrument in the population studied and alpha allocation in order for patient reported outcomes to be included in labeling.

Pharmacyclics and Janssen Response:

The sponsors acknowledge the Agency's comment. The EORTC-QLQ-CLL16 assesses issues relevant to CLL patients. This instrument is in the process of being validated as per the FDA guidance. The scoring algorithm and validation data will be provided. The FACIT-fatigue total score will be used to assess fatigue and further validation data for

this instrument will be provided. Appropriate alpha will be allocated and submitted in the SAP at a later date.

4. The potential for a PK interaction between ibrutinib and bendamustine and rituximab will need to be evaluated during development. We recommend that you collect PK samples for bendamustine, rituximab along with ibrutinib in study PCI-32765CCL3001.

Pharmacyclics and Janssen Response:

In developing the sparse sampling plan to allow population PK for the ibrutinib pivotal trials, which we will share in more detail with the Agency before submission of the NDA, we took into account the current knowledge about metabolic routes of clearance of ibrutinib and its major metabolite, PCI-45227. In addition, we assessed the risks associated with ibrutinib and PCI-45227 as potential perpetrators of clearance mechanisms of concomitant medications. Based on this assessment, we have determined that enzymatic drug-drug interactions between ibrutinib and bendamustine and rituximab would not be expected and hence, PK evaluations for either bendamustine or rituximab should not be needed for safety and/or efficacy evaluations.

For bendamustine, the justification is based on the following:

Bendamustine is an alkylating agent primarily metabolized by CYP1A2 (from the bendamustine Package Insert: "bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2").

- Neither ibrutinib nor PCI-45227 inhibit CYP1A2 (in text of Investigator's Brochure, plus specific data in Tables 1 and 2 below)
- Neither ibrutinib nor PCI-45227 are inducers of CYP1A2, as measured both functionally by phenacetin *O*-dealkylase activity and via mRNA expression in cultured human hepatocytes from 3 different donors (preliminary data)

Table 1: Inhibitory Potential of Ibrutinib Towards Human Hepatic Microsomal Cytochrome P450 Isoenzymes

CYP enzyme	Substrate	Substrate Conc (μM)	IC_{50} (μg/mL)	Ki [a] (μg/mL)	[I]/Ki	Prediction
1A2	Ethoxyresorufin	1	>44.0	--	--	Remote
2B6	Bupropion	100	4.23	2.1	0.07	Remote
2C8	Paclitaxel	10	10.6	5.3	0.03	Remote
2C9	Diclofenac	10	5.29	2.6	0.06	Remote
2C19	Omeprazole	0.5	5.73	2.9	0.05	Remote
2D6	Dextromethorphan	5	11.0	5.5	0.03	Remote
2E1	Chlorzoxazone	100	NC	--	--	Remote
3A4/5	Midazolam	5	10.6	5.3	0.03	Remote
3A4/5	Testosterone	50	8.81	4.4	0.04	Remote

Note: Mean steady-state maximum concentration of ibrutinib after oral administration at 420 mg/day was 0.155 ng/mL obtained from Study PCYC-1109-CA.

a. Assuming competitive inhibition. NC – Not calculated due to no inhibition.

Table 2: Inhibitory Potential of PCI-45227 Towards Human Hepatic Microsomal Cytochrome P450 Isoenzymes

CYP Enzyme	Substrate	Substrate Conc (μM)	IC_{50} (μg/mL)	Ki [a] (μg/mL)	[I]/Ki	Prediction
1A2	Phenacetin	10	NC[c]	--	--	Remote
2B6	Bupropion	100	8.08	4.04	0.03	Remote
2C8	Paclitaxel	10	15.7	7.84	0.02	Remote
2C9	Diclofenac	10	27.6	13.8	0.01	Remote
2C19	Omeprazole	0.5	>47.5	--	--	Remote
2D6	Dextromethorphan	5	36.1	18.1	0.01	Remote
2E1	Chlorzoxazone	100	NC[c]	--	--	Remote
3A4/5	Midazolam	5	NC[c]	--	--	Remote
3A4/5	Testosterone	50	>47.5	--	--	Remote

Note: mean steady-state maximum concentration of PCI-45227 after oral administration of PCI-32765 at 420 mg/day was 0.129 ng/mL obtained from Study PCYC-1109-CA.

b. Assuming competitive inhibition.

c. NC= not calculated due to no inhibition.

For rituximab, the justification is based on the following:

- Rituximab is a monoclonal antibody, which is metabolized and eliminated by catabolic degradation into individual protein fragments and ultimately amino acids, which will then be recycled into other peptides/proteins. In view of this pathway unique to proteins, which is independent of small molecule metabolism (i.e., no involvement of CYP and other drug metabolizing enzymes), it is unlikely that its pharmacokinetic profile will be influenced by ibrutinib.

Another possible interaction could occur through an effect of rituximab or bendamustine on drug metabolizing enzymes involved in the clearance of ibrutinib, i.e., as a perpetrator drug. With regard to bendamustine, it is known that it inhibits neither CYP3A4 nor CYP2D6 (from the bendamustine PI: "based on in vitro data, bendamustine is not likely to inhibit metabolism via human CYP isoenzymes CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes"), which appear to be the main enzymes involved in ibrutinib metabolism (see Investigator's Brochure and study protocol).

With regard to rituximab, it has been reported (Appendix 2: Zidek 2009) that protein drugs which exert their effect through mediation of cytokine production are able to affect the expression of certain CYPs. Rituximab does not act through this kind of mechanism and hence is not expected to influence CYP-mediated metabolism of ibrutinib.

However, even if the possibility of a drug-drug interaction is remote, the meta-analysis of the population PK data from this and other ibrutinib trials will allow us to more fully evaluate this effect.

Meeting Discussion: The Agency's policy is that the drug-drug interaction potential in combination therapy should be addressed regardless of mechanism principles. This can be done in a subset of patients and pharmacokinetics can be compared to

the historical controls. If the Sponsor believes timing of administration negates a drug interaction, they can submit that justification.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified requiring further discussion.

4.0 ACTION ITEMS

No issues identified requiring further actions.

5.0 ATTACHMENTS AND HANDOUTS

Attachments below include the following:

Appendix 1: Data results from March 2012 data snapshot
Figure 1: PFS KM Curve from ongoing study PCYC-1108-CA (based on March 2012 data snapshot)
Figure 2: PFS KM Curve from ongoing study PCYC-1102-CA (based on March 2012 data snapshot)

Attachments below do not include the following:

Appendix 2: Reference; Zidek, 2009

Appendix 3: Prelim

Meeting Chair

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,
Clinical Team Leader, DHP

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/s/

VIRGINIA E KWITKOWSKI
05/11/2012

FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B meeting
Meeting Category:	EOP2 meeting
Meeting Date and Time:	December 5, 2011, 9:00 a.m.
Meeting Location:	CDER WO 1309
Application Number:	IND 102688
Product Name:	PCI-32765
Indication:	Chronic lymphocytic leukemia
Sponsor Name:	Pharmacyclics, Inc.
Meeting Request Date:	September 6, 2011
Received Briefing Package	October 31, 2011
Meeting Chair:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
Meeting Recorder:	CDR Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES:

- Edward Kaminskas, M.D., Acting Deputy Director DHP
- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- Angelo De Claro, M.D., Medical Officer, DHP
- Nicole Gormley, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Mark D. Rothmann, Ph.D, Team Leader, DB 5
- Haleh Saber, Ph.D., Supervisory Pharmacologist , DHOT
- Brenda Gehrke, Ph.D., Pharmacologist, DHOT
- Rachelle Lubin, Pharm.D., Clinical Pharmacology Reviewer, DCP5
- Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES:

- Fong Clow, Sc.D., Sc.M. Executive Director Biometrics
- Eric Hedrick, M.D. Interim Chief Medical Officer, VP of Oncology
- William B. Jones, Ph.D. Director Regulatory Affairs
- David Loury, Ph.D, DABT Chief Scientific Officer
- Christine Salido Sr. Director Regulatory Affairs
- Alice M. Wei Regulatory Affairs Consultant
- (b) (4)
- Danelle James, M.D., Associate Medical Director
- Lori Kunkel, M.D., Clinician

1.0 BACKGROUND

The purpose of this meeting is to discuss the proposed Phase 3 protocol for the treatment of patients with CLL/SLL and the acceptability of the clinical and nonclinical programs for registration and approval. The proposed indication for PCI-32765 is for the treatment of patients with CLL or SLL (b) (4) (b) (4)

The proposed design of the Phase 3 study PCYC-1112-CA of PCI 32765 versus ofatumumab is for the treatment of CLL/SLL patients (b) (4) (b) (4) (b) (4) This Phase 3, randomized controlled multicenter study will evaluate PFS among approximately 350 patients (1:1) randomized to PCI 32765 versus the approved dose and schedule of ofatumumab in relapsed CLL/SLL.

2.0 DISCUSSION

CLINICAL

Question 1: Does the Agency agree that the proposed Phase 3 Study, PCYC-1112-CA, is adequate in design to characterize the efficacy and safety of PCI-32765 for the treatment of patients with CLL or SLL (b) (4) (b) (4)

FDA Response: No.

Should median PFS for PCI-32765 be around 12 months, increasing PFS assessment interval to 24 weeks after 12 months may make it difficult to reliably evaluate the size of a PFS benefit. See other responses below.

Pharmacyclics Response:

Thank you for your comment. We have reviewed the schedule of assessments and have identified an oversight. The original intent was to perform clinical monitoring of subjects by blood work and physical exam every 12 weeks after 12 months as well as by CT every 24 weeks after 12 months. A corrected schedule of assessments reflecting this information is attached (Appendix 1).

Question 1a: Does the Agency agree that the proposed patient population is adequately defined per the study eligibility criteria?

FDA Response: Yes.

A broader patient population may be also acceptable, given that not all patients can tolerate chemoimmunotherapy.

Pharmacyclics Response:

We agree that a broader population to encompass those who are not candidates for chemoimmunotherapy would be appropriate for the planned Phase 3 clinical study.

We propose that subjects who are not appropriate candidates for treatment with

(b) (4)

[redacted]

FDA Response Continued:

See response to question 8 regarding the acceptability of any trial population for accelerated approval.

Meeting Discussion: The Agency stated that the proposed trial population is acceptable. The population identified has available therapies and would not be supportive for an accelerated approval for this indication.

Question 1b: Does the Agency agree that the comparator, ofatumumab, is appropriate for this patient population?

FDA Response: Yes.

Question 1c: Does the Agency agree with the proposed dose, schedule, and duration of therapy for PCI-32765 and ofatumumab?

FDA Response: Yes. The Agency notes differences in treatment duration between treatment arms. You should be aware that differences in actual timings of response assessments between treatment arms would affect the interpretability of PFS.

Pharmacyclics Response:

Pharmacyclics acknowledges the concern of the Agency regarding potential for imbalance of scheduled assessments between arms in the interpretability of PFS. In the Phase 3 study design, we have ensured that the scheduled tumor assessments are balanced between arms, including after the period of ofatumumab administration in the control arm of the trial. Pharmacyclics acknowledges a potential for imbalance in the frequency of assessments between the arms in the first 8 weeks of the study. In order to address the potential bias this may create in detection of progressive disease in the early phase of the trial, Pharmacyclics will address, in the Statistical Analysis Plan, sensitivity analyses to address the potential for this bias in PFS interpretation.

Question 2a: Does the Agency agree that the existing safety data is adequate to support the initiation of the proposed Phase 3 PCYC-1112-CA clinical trial?

FDA Response: No. You have reduced the minimum eligibility criteria for platelet count from 50,000/mm^3 (as in the earlier trials) to 30,000/mm^3 (in the proposed Phase 3 trial). You have not adequately evaluated the safety of the proposed regimen in patients with lower platelet counts.

Pharmacyclics Response:

In the Phase 2 clinical trial PCYC-1102-CA, an amendment in August 2010 allowed for the enrollment of subjects with platelet counts <50,000/ul in the event of documented bone marrow involvement. This resulted in 13 subjects being enrolled to study PCYC-1102-CA with platelet counts below 50,000/ul (range 2,000 - 49,000/ul). Adverse events, including bleeding events, in this subset of subjects, versus the overall population of the study (Groups 1-3) is described below. Thus, we believe this supports the inclusion of subjects with platelet counts above 30,000/ul (Appendix 2).

Meeting Discussion: The sponsor's proposal to enroll patients with a minimum platelet count of 30,000/ mm^3 with provisions for expedited reporting of hemorrhagic events is acceptable. The Agency requests that the sponsor capture pertinent platelet activity and functional evaluations on patients with bleeding events to further evaluate a potential safety signal.

Question 2b: Does the Agency agree that the size of the safety database inclusive of the proposed Phase 3 study [redacted] (b) (4)

FDA Response: No. The adequacy of your safety database [redacted] (b) (4) [redacted] (b) (4) **The Agency does not agree beforehand on the adequacy of the safety database.**

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment.

Question 3: Does the Agency agree with the proposed efficacy, safety and interim analyses?

FDA Response:

[redacted] (b) (4)

Pharmacyclics Response:

Pharmacyclics strongly believes that the inclusion of a single interim efficacy analysis is necessary for the proper and ethical conduct of this clinical trial. In the mature cohorts of relapsed or refractory CLL patients (Groups 1 and 3) in the Phase 2 clinical trial PCYC-1102-CA, amongst 61 treated subjects, only 4 disease progression events have been noted (1 progression event has been observed since the August 2011 data cut-off date); thus it is not possible at this time to estimate the median PFS of PCI-32765 treatment in this disease setting. Please note that all cases of disease progression have been clinically suspected or confirmed Richter's transformation; no cases of "classical" progression of underlying CLL have been observed.

Based on these data, the potential exists for an overwhelming difference in PFS in favor of the PCI-32765 arm. In this circumstance, it will be important to provide the Data Monitoring Committee (DMC) overseeing the trial a mechanism to issue a recommendation regarding trial continuation.

Additionally, though the Phase 2 data make this scenario less likely, it will similarly be important to provide the DMC a mechanism to recommend trial closure in the event of futility for PFS. A futility boundary for the interim analysis will be described in the Statistical Analysis Plan.

The planned interim analysis of efficacy will be performed after either 50% information fraction, after 116 PFS events have been reached, estimated to be approximately 15 month after initiation of the enrollment under current enrollment assumptions of 20 subjects per month. Table 1 below describes the possible timing of the interim analysis under different subject accrual and PFS effect size scenarios. An O'Brien-Fleming boundary ($\alpha = 0.0001$) will be used at the interim analysis, which will required the observed hazard ratio of 0.47 to reach the statistical significance. If the median PFS of ofatumumab-treated control arm of 8 months is observed, with a hazard ratio of 0.47 for

PFS, the median PFS of PCI-32765 group would be a minimum of 17 months, a 9-month increase in median PFS.

FDA Response Continued:

In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints or subgroups can not result in (either singly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label.

Please include in a future submission, your plan for testing secondary endpoints for which claims may be included in the labeling.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comments. A full description of analysis of secondary endpoints will be included in the Statistical Analysis Plan for the Phase 3 study PCYC-1112-CA, which we anticipate submitting to the Agency in January 2012.

FDA Response Continued:

Provide an analysis plan for overall survival, including the timing of analysis.

Pharmacyclics Response:

The analysis plan for overall survival, including timing of analysis, will be included in the Statistical Analysis Plan for the Phase 3 study PCYC-1112-CA, which we anticipate submitting to the Agency in January 2012.

FDA Response Continued:

Provide further details on anticipated accrual rate and anticipated length of the study.

Pharmacyclics Response:

Table 1 presents estimations of the study duration and analysis timing based on various assumptions of the median PFS for the control versus experimental arm of the study, under various potential enrollment rate assumptions, assuming a total sample size of 350 subjects and power of 90% with alpha level of 0.01 and 0.0001 for the final and interim analysis, respectively.

Table 1

Median PFS and HR Assumptions			# Subject Enroll per Month	Enrollment Duration (Month)	Estimated Analysis Time (Month)	
Ofa Median PFS (Month)	PCI Median PFS (Month)	Hazard Ratio			Interim (events=116)	Final (events=232)
6	10	0.6	20	17.5	14	22
			25	14	12	20
			30	11.6	11	19
8	13.3	0.6	20	17.5	15	26
			25	14	13	24
			30	11.6	12	23
10	16.7	0.6	20	17.5	17	30
			25	14	15	28
			30	11.6	14	27

FDA Response Continued:

Missing data/assessments of progression should be kept at a minimum. Patients should be followed for PFS until an IRF assessment of a PFS event (progression or death). Additionally, you should provide sensitivity analyses to study the impact on the analysis of PFS due to any missing data/assessments, and any loss to follow-up or discontinuation of assessments of PFS not due to an event.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment and concern. Sensitivity analyses to account for the potential effect of missing data on PFS will be described in the Statistical Analysis Plan, which we anticipate submitting to the Agency in January 2012.

FDA Response Continued:

However, your proposed safety analyses appear acceptable.

Question 3a: Is the primary endpoint of PFS, assessed by a central independent review, an adequate primary endpoint in the proposed patient population?

FDA Response: Yes. However, the magnitude of the treatment effect on PFS is a review issue. Please also refer to question 1c.

Pharmacyclics Response:

Pharmacyclics acknowledges that the magnitude of PFS effect is a review issue. Table 1 above describes potential PFS effect sizes detectable as statistically significant in the design of this trial.

Question 3a(2): Does the Agency agree that the study objective of an improvement in hazard ratio for PFS of 0.6 at an $\alpha = 0.01$ and an 90% power is sufficient in a single trial to demonstrate efficacy in this study population?

FDA Response: In general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit

profile may be considered for regulatory decision. However, you should be aware that PFS may be influenced by any imbalance in assessment dates or substantial missing data between treatment arms.

Pharmacyclics Response:

Pharmacyclics acknowledges the concern of the Agency regarding potential effect of assessment imbalance or missing data on PFS interpretation. Please see responses to comments on Questions 1c and 3 above.

FDA Response Continued:

You should provide an estimate of the magnitude of the treatment effect on median PFS for the proposed trial population.

Pharmacyclics Response:

Please refer to Table 1 above.

FDA Response Continued:

For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide clinically meaningful and statistically persuasive efficacy findings with an acceptable risk benefit profile. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's response. It should be noted that Pharmacyclics is conducting a number of other clinical trials in CLL. In the future we plan to conduct other Phase 3 trials in B-cell malignancies.

Meeting Discussion: The Agency does not encourage use of an (b) (4) **for regulatory action. An interim futility analysis is acceptable. The sponsor may submit a meeting request with the interim PFS data upon boundary crossing.**

Question 3b: Does the Agency agree with the proposed application of the 2008 IWCLL response criteria?

FDA Response: For regulatory approval in CLL, all criteria defined by the 2008 IWCLL Criteria used for assessment of disease response and/or progression must be considered in the response assessment of each patient. Refer to comments below on each of your proposed modifications to the 2008 IWCLL Criteria.

Also, we recommend that you use the 2008 IWCLL response criteria for determination of response and progression in patients with SLL because progression in patients with SLL may manifest as CLL progression (i.e., cytopenias due to bone marrow involvement, lymphocytosis) which may not be adequately captured by the 2007 Cheson Criteria.

Pharmacyclics Response:

Pharmacyclics will apply the IWCLL criteria (b) (4)

FDA Response Continued:

1. CT scans of the chest, abdomen, and pelvis, as well areas of evaluable peripheral lymphadenopathy (eg, neck) will be a required during scheduled response assessments.

FDA Response: Your proposal is acceptable.

(b) (4)

FDA Response: We disagree. Refer to response to question 3b.

Pharmacyclics Response: Pharmacyclics acknowledges the concern from the Agency regarding the specific application of IWCLL criteria in this study. To clarify, our proposal is to apply the criteria equally to both arms of the trial, to all subjects on the trial, and to apply all parameters to the response assessment for all subjects. Best response will be assessed according to the IWCLL as currently written. Regarding disease progression, in a strict interpretation of the IWCLL criteria, we have significant concerns that subjects may be inaccurately categorized as having progressive disease, and thus unnecessarily discontinued prematurely from study treatment, if an isolated lymphocytosis is considered sufficient for declaration of disease progression. These concerns are supported by the data as summarized below.

In the ongoing Phase 1b/2 study PCYC-1102-CA, in the cohorts of relapsed or refractory subjects included in this submission (Groups 1 and 3), as of an October 25, 2011 cut-off date, 48 of 61 treated subjects (79%) had a $\geq$50% elevation in circulating lymphocytes (to at least 5,000/ul) after initiation of treatment. In 44 of these 48 subjects, the elevation of circulating lymphocytes was observed at the 1- week laboratory assessment, and in all cases lymphocytosis was evident within 3 weeks of treatment initiation. Under the current version of the IWCLL criteria, this could be potentially interpreted as "progressive disease". However, in 47 of these 48 subjects, the level of circulating lymphocytes peaked within 3 months of treatment initiation and subsequently decreased. Thirty-six of these 48 subjects were ultimately documented to have achieved at least a partial remission by IWCLL criteria (requiring a greater than or equal to 50% reduction in absolute lymphocyte count relative to baseline). These data support the hypothesis that initial lymphocytosis reflects the mechanism of action of PCI-32765, rather than being an indicator of disease progression. Moreover, the strict application of IWCLL criteria in this study, where lymphocytosis in isolation would have sufficed for determination of "disease progression", would have inappropriately categorized the vast majority of responding subjects as having disease progression within 3 weeks of treatment initiation.

These data support the proposal to apply the IWCLL criteria as a true composite criterion in this trial, wherein disease progression must be supported by objective findings (including radiographic, laboratory, and functional evidence) rather than isolated

laboratory findings. The criteria will be applied equally to both arms of the trial, and adjudicated by blinded independent review, thus minimizing bias.

Meeting Discussion: The Agency reiterated that the (b) (4) (b) (4) **Agency's approval of drugs for CLL and can not be formally accepted at this time. The isolated lymphocytosis should be accompanied by reduction in nodal measurements to be considered a non-PFS event. The sponsor is welcome to conduct the trial using the modifications to the CLL criteria, however, the findings will be a review issue at the time of NDA submission. The sponsor should consider anchoring this endpoint to a different clinical endpoint such as OS or symptom improvement.**

FDA Response Continued:

3. **The presence of new lymph nodes (>1.5 cm), in the absence of other criteria for progressive disease will require evaluation by two serials exams at least 2 weeks apart to confirm progressive disease.**

FDA Response: This modification is not clear. In cases where the new lymph nodes are only detected on imaging studies, do you intend to repeat CT or MRI studies?

Pharmacyclics Response

Yes

Question 4: Is a minimum of 15% subject participation in this Phase 3 registration trial acceptable to the Agency?

FDA Response: The Agency does not require a minimum percentage of patients to come from the US. However, you will need to demonstrate that your trial results can be extrapolated to the US population.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment.

Question 5: Does the Agency agree that the proposed Clinical Pharmacology Development Plan, including completed and planned studies summarized in Section 10.2, is adequate to support the registration of PCI-32765 for the treatment of patients with CLL or SLL (b) (4) (b) (4)

FDA Response: No, following issues still need to be addressed:

1) **Your food effect study should be conducted prior to Phase 3.**

Pharmacyclics Response:

Pharmacyclics confirms that the food effect study, summarized in the meeting package (see Section 10.2.5.1 Fast/Fed PK Study), will be conducted prior to the Phase 3 study (PCYC-1112-CA).

The synopsis for Fast/Fed PK study is provided as Appendix 3.

2) **Determine bioavailability of PCI-32765 in humans per Guidance for Industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations***

Pharmacyclics Response:

Pharmacyclics agrees to determine the absolute bioavailability of PCI-32765 in humans per the Guidance for Industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations.*

3) **The clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14) needs to be addressed. We encourage submitting your plan for review by the agency.**

Pharmacyclics Response:

Pharmacyclics will submit our plan for clinical evaluation of the potential for QT/QTc interval prolongation to the Agency Q2 2012.

4) **Based on results of your ADME study, you may need to conduct organ impairment trial(s). Please refer to the Guidances for Industry *Pharmacokinetics in Patients with Impaired Renal Function* and *Pharmacokinetics in Patients with Impaired Hepatic Function* for more information.**

Pharmacyclics Response:

Pharmacyclics plans to use the results of our ADME study in humans to determine which type(s) of organ impairment trial(s) to conduct.

5) **You should validate the analytical method(s) used to measure the parent drug and any active metabolites according to the principles described in the Guidance for Industry entitled "Bioanalytical Method Validation".**

Pharmacyclics Response:

The analytical methods used to measure the concentrations of PCI-32765 and its major metabolite PCI-45227 in human plasma are validated according to the principles described in the Guidance for Industry entitled "Bioanalytical Method

Validation". Pharmacyclics will develop and validate bioanalytical assay(s) for other major metabolite(s) or important active metabolite(s) identified in the mass balance study in humans.

Question 6: Does the Agency agree that the proposed Nonclinical Development Program, including completed and planned studies summarized in Section 10.3 is adequate to support the Phase 3 study PCYC-1112-CA as well as the registration of PCI-32765 for the treatment of patients with CLL or SLL (b) (4) (b) (4)

FDA Response: The proposed nonclinical development program appears sufficient to support the Phase 3 study and registration of PCI-32765 for the proposed indication. The adequacy of the nonclinical studies to support a NDA will be a review issue.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment.

Question 7: Does the Agency agree that a clinical development program comprised of a single adequate and well-controlled Phase 3 study (PCYC-1112-CA), and the two supporting Phase 2 studies, PCYC-04753 and PCYC-1102-CA, is satisfactory to support full approval of PCI 32765 for the treatment of patients with CLL or SLL (b) (4) (b) (4)

FDA Response: Refer to response to question 3a(2).

Question 8: Does the Agency concur with plans for an (b) (4) (b) (4) based upon the proposed interim analysis of PCYC-1112-CA?

FDA Response: No. Your proposed trial population does not meet the available therapy standard (b) (4) See also response to question 3 regarding interim PFS analysis.

Pharmacyclics Response:

Pharmacyclics acknowledges that our proposed Phase 3 trial does not address all available therapy. However, should an overwhelming difference in PFS in favor of the PCI-32765 arm be observed during the interim analysis, we would like to meet with the Agency to discuss an acceptable means by which to obtain approval.

Additional Comments:

1. The meeting package identified serious bleeding events in patients receiving PCI-32765. These include 3 patients with subdural hematoma, 1 patient with hemorrhagic stroke, and 2 patients each with GI hemorrhage and hematuria. On 23 Nov 2011, you submitted safety reports on 3 patients who developed subdural hematomas.

1a. How many cases of intracranial hemorrhage have been reported in your clinical program for PCI-32765?

Pharmacyclics Response:

There have been a total of 5 events of intracranial hemorrhage reported in the clinical program for PCI-32765. One event of CVA/hemorrhage was previously reported (IND Serial No. 026) and was included in the discussion of subdural hemorrhage in the recently submitted expedited report (IND Serial No. 051). Five events of subdural hematoma (one event included intracranial hemorrhage) have also been observed; one subdural hematoma event reported previously (IND Serial No. 022), three serious events of subdural hematoma/subdural hematoma plus intracerebral hemorrhage included in the most recent expedited report (IND Serial No. 051) and one non-serious event of subdural hematoma, that occurred following a fall and resolved without drug interruption or sequelae, also noted in the most recent expedited report.

1b. What is your plan to mitigate the risk of serious bleeding in your Phase 3 clinical trial?

Pharmacyclics Response:

Pharmacyclics plans to exclude subjects receiving full-dose warfarin from future clinical trials of PCI-32765, including the proposed Phase 3 study PCYC-1112. Additionally, subjects with a prior history of intracranial hemorrhage will be excluded. In subjects who require the institution of full-dose warfarin during the course of the study, PCI-32765 treatment will be held until stable levels of anti-coagulation, as measured by the INR, are achieved. Precautionary language for management of subjects requiring full-dose warfarin will be included in the protocol, and bleeding events overall, and subdural hemorrhage specifically, will be identified as events of special interest for the DMC overseeing the trial.

2. The Agency requires a validated instrument in the population studied and alpha allocation for patient reported outcomes to be included in labeling. Also, patient reported outcome information is unlikely to be evaluable in an open-label trial.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment. The intent of the patient reported outcomes is to support pharmacoeconomic analyses of PCI-32765.

3. Do you have any data on MRD in patients treated with your product?

Pharmacyclics Response:

Pharmacyclics has not included monitoring for minimal residual disease in PCI-32765 CLL clinical trials thus far. However, at least two subjects have achieved IWCLL complete remissions with no morphologic evidence of CLL on follow-up bone marrow assessment. We plan to incorporate minimal residual disease monitoring into future initial therapy trials of PCI-32765, and may ultimately conduct trials specifically in the setting of treatment of minimal residual disease after clinical remission in CLL.

4. We recommend you collect sparse PK samples in all patients as a part of the standard assessments. This will allow you to explore the exposure-response relationship for PCI-32765, for measures of both effectiveness and toxicity.

Pharmacyclics Response:

Pharmacyclics will incorporate the collection of sparse PK samples in subjects participating at clinical sites in the US in the Phase 3 study PCYC-1112-CA. The sample collection schedule will be detailed in the Phase 3 PCYC-1112-CA study protocol. The sparse PK samples are in addition to extensive PK sampling already collected during Cycle 1 on Day 1 and Day 8 from approximately 200 subjects across 5 studies (Table 2).

Table 2: PK Sample Collections During Phase 1 and Phase 2 Studies with PCI-32765

Study	Study No	Population	Treatment	Dose per day	N	PK collection (h)
Phase 1a	04753	Mixed	PCI-32765	1.25 mg/kg 2.5 mg/kg 5 mg/kg 8.3 mg/kg 12.5 mg/kg 560 mg	56	Cycle 1 Day 1: 0, 0.5, 1, 2, 4, 6, 24 Day 8: 0, 0.5, 1, 2 Day 28: 20-26
Phase 1b	1102	CLL/SLL	PCI-32765	420 mg 840 mg	77	Cycle 1 Day 1: 0, 0.5, 1, 2, 4, 6, 24 Day 8: 0, 0.5, 1, 2, 4, 6 Day 15: 0, 2 Day 22: 0, 2 Day 28: 0, 2
Phase 2	1104	MCL	PCI-32765	560 mg	26	Cycle 1 Day 1: 0, 1, 2, 4, 7, 24 Day 8: 0, 1, 2, 4, 7, 24 Day 15: 0, 2 Day 22: 0, 2

Phase 2	1106	ABC or DLBCL	PCI-32765	560 mg	12	Cycle 1 Day 1: 0, 1, 2, 4, 7, 24 Day 8: 0, 1, 2, 4, 7, 24 Day 15: 0, 2 Day 22: 0, 2
Phase 1b/2	1109	CLL/SLL	PCI-32765 ofatumumab	420 mg	27	Cycles 1 and 2 Day 1: 0, 2, 4, 6, 24 Day 8: 0, 2, 4, 6, 24 Day 15: 0, 2 Day 22: 0, 2
				Total	198	

***5. In vitro* studies with human liver microsomes indicated that PCI-32765 is metabolized by CYP2D6 and 3A4. Given this finding, your protocol should exclude patients taking strong CYP3A4 and CYP2D6 inhibitors or inducers.**

Pharmacyclics Response:

Pharmacyclics is conducting an analysis of systemic exposure and adverse events in subjects who have received strong inducers or inhibitors of CYP3A4 and/or CYP2D6 in the course of PCI-32765 clinical trials and would propose to base the inclusion or exclusion of such medications in the proposed Phase 3 study PCYC-1112-CA on the basis of this analysis.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified requiring further discussion.

4.0 ACTION ITEMS

No issues identified requiring further actions.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Meeting Chair

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,
Clinical Team Leader, DHP

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/s/

DIANE C HANNER
12/05/2011

VIRGINIA E KWITKOWSKI
12/05/2011

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

LATE-CYCLE MEETING MINUTES

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) dated June 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica®, (ibrutinib) capsules, 140 mg.

We also refer to the Late-Cycle Meeting (LCM) teleconference between representatives of your firm and the FDA on January 23, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, M.D.
Medical Officer Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: Teleconference meeting

January 23, 2014, from 10:00 A.M. to 10:30 A.M.

Meeting Location: WO Building 22, Room 5201

Application Number: NDA 205552- Original #2

Product Name: IMBRUVICA®, (ibrutinib) capsules, 140 mg.

Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo de Claro, M.D.

Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

- Richard Pazdur, M.D., Office Director, Office of Hematology and Oncology Products
- Ann Farrell, M.D., Director, DHP
- Robert Kane, M.D., Deputy Director Safety, DHP
- Qin Ryan, M.D., Ph.D., Medical Officer for Safety, DHP (by phone)
- R. Angelo de Claro, M.D., Medical Officer, Clinical Team Leader, DHP
- Nicole Verdun, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Lei Nie, Ph.D., Mathematical Statistician ,Team Leader, DB 5
- Tamy Kim, Pharm. D., Associate Director of Regulatory Affairs, OHOP
- Kim Taylor, M.B.A., M.P.H, Operations Research Analyst, OSP
- Joyce Weaver, Pharm D., Drug Risk Management Analyst, DRISK
- Dr. Olanrewaju Okusanya, Pharm D., Clinical Pharmacology Reviewer, DCP5
- Julie Bullock, Pharm. D., Team Leader, Office of Clinical Pharmacology, DCP5

- Sonny, Saini, Pharm. D., M.B.A., Team Leader, OSE
- Diane Leaman, B.S, Safety Regulatory Project Manager
- Nisha Patel, Pharm D., Regulatory Review Officer, OPDP
- Tracy Salaam, Pharm. D, Safety Evaluator Team Leader, OPE, DPVII
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

EASTERN RESEARCH GROUP ATTENDEES

- Hyun Kim, Independent Assessor (by phone).

APPLICANT ATTENDEES

- Bob Duggan, Chief Executive Officer and Chairman of the Board, Pharmacyclics
- Urte Gayko, Ph.D., Senior Vice President, Global Regulatory Affairs, Pharmacyclics
- Jesse McGreivy, M.D., Chief Medical Officer, Pharmacyclics
- Maria Fardis, Ph.D., M.B.A., Chief of Oncology Operations and Alliances, Pharmacyclics
- Fong Clow, Sc.D., Vice President, Biometrics, Pharmacyclics
- Dana Lee, Vice President, Drug Safety, Pharmacyclics
- Chris Salido, B.S., Executive Director, Regulatory Affairs, Pharmacyclics
- Juthamas Sukbuntherng, Ph.D., Senior Director, Clinical Pharmacology, DMPK, Pharmacyclics
- Danelle James, M.D., M.S., Senior Medical Director, Pharmacyclics
- John Seaman, Pharm. D., Senior Director, Global Regulatory Affairs, Janssen R&D, LLC
- Mann Fung, M.D., Vice President, Compound Development Team Leader, Janssen R&D, LLC
- Sen Hong Zhuang, M.D., Ph.D., Vice President, Clinical Research, Janssen R&D, LLC
- Steven Sun, Ph.D., Director, Biostatistics, Janssen R&D, LLC
- Terri Williams, Ph.D., Associate Director, Global Regulatory Affairs, Janssen R&D, LLC
- Sandra Rattray, Ph.D., Vice President, Head of Janssen Oncology Regulatory, Janssen R&D, LLC

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

1.0 BACKGROUND

NDA 205552 was submitted on June 28, 2013, for Imbruvica®, (ibrutinib) capsules, 140 mg.

The NDA 205552, Original #1 was approved on November 13, 2013, for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

The proposed indication for Original #2 is for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

PDUFA goal date: February 28, 2014.

FDA issued a Background Package in preparation for this meeting on January 22, 2014.

2.0 DISCUSSION

1. **Discipline Review Letters**
   No Discipline Review letters have been issued to date for NDA 205552 Original-2.
   Discussion: None

2. **Substantive Review Issues**
   No substantive review issues have been identified to date.
   Discussion: The Agency noted that no substantive review issues have been identified.

3. **Postmarketing Requirements/Postmarketing Commitments –10 minutes**

   2060-# CONFIRMATORY TRIAL– (b) (4) submit the results of the (b) (4) randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of (b) (4) (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	Complete
Study/Trial Completion:	1/14
Final Report Submission:	06/14

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

2060-# CONFIRMATORY TRIAL– Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. (b) (4) (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	Complete
Study/Trial Completion:	07/16
Final Report Submission:	11/16

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

Sponsor response to PMR (above): Pharmacyclics would like the FDA to consider changing the proposed PMR to a post approval commitment (PMC) because study PCYC-1112-CA should be sufficient to accomplish regular (full) approval for the current indication for single agent ibrutinib therapy.

Discussion: The Agency informed Pharmacyclics that successful completion of either of the PMRs mentioned above could be considered in order to convert the accelerated approval to regular approval for the Chronic Lymphocytic Leukemia (CLL) indication.

These PMRs were originally sent to Pharmacyclics but they no longer apply.

(b) (4)

(b) (4)

Discussion: None.

4. REMS or Other Risk Management Actions

Not applicable

Discussion: None.

5. Major labeling issues – 5 minutes

No major labeling issues have been identified to date. Minor revisions were identified and will be sent to the Applicant within the next 2 weeks.

Discussion: The Agency noted that no major labeling issues have been identified.

6. Review Plans

Clinical reviews of efficacy results reported by the independent review committee are ongoing.

Discussion: The Agency will send the sponsor a draft copy of the ASCO burst once labeling is almost complete.

7. Wrap-up and Action Items – 5 minutes

Discuss whether Applicant plans to request a wrap up meeting.

Discussion: The Sponsor noted that they wanted a wrap up meeting.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

ROMEO A DE CLARO
01/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

LATE CYCLE MEETING
BACKGROUND PACKAGE

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
9995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IMBRUVICA®, (ibrutinib) capsules, 140 mg.

We also refer to the Late-Cycle Meeting (LCM) teleconference which has been re-scheduled for January 23, 2014, to discuss the Chronic Lymphocytic Leukemia (CLL) indication. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, M.D.
Medical Officer Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: January 23, 2014, room 10:00 a.m. to 10:30 a.m.

Meeting Location: WO Building 22, Room 5201

Application Number: NDA 205552 Original-2

Product Name: IMBRUVICA®, (ibrutinib) capsules, 140 mg.

Indication: Treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL)

Applicant Name: Pharmacyclics, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) teleconference is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE:

1. **Discipline Review Letters**
   No Discipline Review letters have been issued to date for NDA 205552 Original-2.

2. **Substantive Review Issues**
   No substantive review issues have been identified to date.

3. Postmarketing Requirements/Postmarketing Commitments –10 minutes

2060-# CONFIRMATORY TRIAL– [redacted] submit the results of the [redacted] randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of [redacted] The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission: Complete
Study/Trial Completion: 12/13
Final Report Submission: 06/14

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

2060-# CONFIRMATORY TRIAL– Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of [redacted] The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission: Complete
Study/Trial Completion: 07/16
Final Report Submission: 11/16

Sponsor response to PMR (above): Pharmacyclics would like the FDA to [redacted] because study PCYC-1112-CA should be sufficient to accomplish regular (full) approval for the current indication for single agent ibrutinib therapy.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

These PMRs were originally sent to Pharmacyclics but they no longer apply.

4. REMS or Other Risk Management Actions

Not applicable

5. Major labeling issues – 5 minutes

No major labeling issues have been identified to date. Minor revisions were identified and will be sent to the Applicant within the next 2 weeks.

6. Review Plans

Clinical reviews of efficacy results reported by the independent review committee are ongoing.

7. Wrap-up and Action Items – 5 minutes

Discuss whether Applicant plans to request a wrap up meeting.

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/s/

ROMEO A DE CLARO
01/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

LATE CYCLE MEETING
BACKGROUND PACKAGE

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
9995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IMBRUVICA®, PCI-32765 (ibrutinib) capsules, 140 mg.

We also refer to the Late-Cycle Meeting (LCM) teleconference scheduled for September 25, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, M.D.
Medical Officer Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 25, 2013, from 3:00 P.M. to 4:00 P.M.

Meeting Location: WO Building 22, Room 2201

Application Number: NDA 205552

Product Name: IMBRUVICA®, PCI-32765 (ibrutinib) capsules,140 mg.

Indication: Treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and Mantle Cell lymphoma (MCL).

Applicant Name: Pharmacyclics, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE:

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments –40 minutes

   No additional discussion is deemed necessary regarding the 3 previously sent Postmarketing Requirements/Postmarketing Commitments. The alphabetical listing (of D-J below) has been added merely for ease of reference.

   #D

   [redacted] (b) (4) Continue follow-up of patients (on treatment and in protocol-defined post-treatment follow-up) and submit a final analysis report of trial PCYC-1104-CA with 24 months of minimum follow-up for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each patient. In addition, submit detailed assessment information regarding all sites of extranodal disease at baseline (b) (4) [redacted] and progression.

Final Protocol Submission:	completed
Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

   #E

   Complete and submit the final results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. Enrollment of at approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by (Sponsor's input is requested to determine this date). Overall survival is a key secondary endpoint.

Final Protocol Submission:	completed
Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

   #F

   [redacted] (b) (4) submit the results of the (b) (4) [redacted] randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of [redacted] (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	completed
Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

#G

Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of (b) (4) The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	completed
Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY
Other: _____	MM/YYYY

(b) (4)

#J

Determine the effect of ibrutinib on platelet function by in vitro studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from patients with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

Preliminary protocol submission	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

The itemized list above is not inclusive of all of the Postmarketing Requirements/Postmarketing Commitments that should be anticipated.

3. Major labeling issues – 5 minutes

4. Review Plans – 5 minutes

5. Wrap-up and Action Items –5 minutes

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/s/

ROMEO A DE CLARO
09/11/2013