

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205552Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205552

SUPPL #

HFD # 161

Trade Name Imbruvica® Tablets, 140 mg

Generic Name Ibrutinib (PCI-32765)

Applicant Name Pharmacyclics, Inc.

Approval Date, If Known November 13, 2013

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)

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#

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 ☐

(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:

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 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:

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 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:

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"):

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 #	!
YES <input type="checkbox"/>	! NO <input type="checkbox"/>
	! Explain:

Investigation #2	!
IND #	!
YES <input type="checkbox"/>	! NO <input type="checkbox"/>
	! 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 ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! 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: November 12, 2013

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
11/12/2013

ANN T FARRELL
11/13/2013



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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.

A handwritten signature in black ink, appearing to read 'Urte Gayko', is written over a horizontal line.

June 10, 2013

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

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

NDA/BLA#: 205552 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 (PCI-32765)
Dosage Form: Oral Capsule, 140 mg
Applicant/Sponsor: Pharmacyclics

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) For patients with (b) (4) Mantle Cell lymphoma (MCL)

(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 (b) (4) Mantle Cell lymphoma (MCL)

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); ☒ dosage 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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmts@fda.hhs.gov) OR AT 301-796-0700.

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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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 failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmts@fda.hhs.gov) OR AT 301-796-0700.

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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 DARTS 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
10/22/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 205552 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)
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p> </div> <div style="width: 50%;"> <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> Proposed action November 13, 2013 User Fee Goal Date is February 28, 2014 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

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., new 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 _____	<input checked="" type="checkbox"/> Received
❖ Application Characteristics ³ Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input checked="" type="checkbox"/> Breakthrough Therapy designation NDAs: Subpart H <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date: Approval, November 13, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 	June 28, 2013
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A

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

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 	June 28, 2013
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	June 28, 2013
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 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 15, 2013 Cosigned on behalf of team leader August 16, 2013
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM August 23, 2013 <input checked="" type="checkbox"/> DMEPA August 1, 2013 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) September 20, 2013 <input checked="" type="checkbox"/> OPDP (DDMAC) September 17, 2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	August 23, 2013- RPM filing review <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Designation</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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 (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) 	November 8, October- 31,29,28,23(2),22(2),21,18,17(2) 16,15(2),(2),10, 7(3),4(2),1; September- 30,25,24 (2), 20(7),18, 17,16,13 (2),12(2),(3),10,9,4,3; August- 27(2),26(2),23,21,20,16(3), 14(2), 12,8(3),6, 2(2),1(2); July- 30, 29, 25,23(3), 22,19, 18; June- 28, 20,14(2),13,4,3
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	N/A
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg Pre-NDA MCL April 9, 2013 Pre-NDA-CMC April 9, 2013
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg EOP2-MCL December 3, March 7, 2012
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	Late cycle meeting - October 28, 2013 Midcycle Communications – August 19, 2013
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	

Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None November 12, 2013
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None November 8, 2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None November 8, 2013
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 8 total (7 PMRs/ 1 PMC)
Clinical Information ⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Nov. 6, 2013 Co-signed primary review dated Nov. 6, 2013
• Clinical review(s) (<i>indicate date for each review</i>)	Nov. 6, 2013 Aug. 7, 2013 –filing review
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See page 25 of Clinical Review Dated Nov. 6, 2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None Sept. 17, 2013
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested OSI Letters –Oct. 11, 2013 Sept. 11, 2013 Clinical inspection review - Sept. 17, 2013

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Oct.28, 2013 Co-signed primary review Oct. 28, 2013
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Oct.28, 2013 Co-signed primary review Oct. 28, 2013
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None Oct. 28, 2013 Aug. 14, 2013 filing review
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Nov.1, 2013 Co-signed primary review Nov. 1, 2013
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Nov.1, 2013 Co-signed primary review Nov. 1, 2013
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None Nov. 1, 2013 co-signed Nov. 1, 2013 QT review Oct 3, 2013 Aug. 15, 2013 filing review
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None Aug. 21, 2013
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None Aug. 20, 2013
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> 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)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None Sept 23, 2013, Oct. 18, 2013 cosigned the primary reviews Dated Sept 23, and Oct 18, 2013
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Sept 23, 2013, Oct. 18, 2013 cosigned the primary reviews Dated Sept 23, and Oct 18, 2013
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None ONDQA Primary Oct 18, 2013 & Sept. 23, 2013 Jul. 25, 2013, filing review; Bio pharm Oct. 4, 2013 and Sept. 26, 2013 Bio pharm. -Jul. 30, 2013 filing review
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed Jul. 9, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See page 111-CMC review dated Sept. 23, 2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(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 sites⁷)</i>	Date completed: Oct.17, 2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> 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.

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/s/

EBLA ALI IBRAHIM
11/19/2013

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 assays 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 ($\geq 20\%$) 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

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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 [REDACTED] (b) (4)

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)
(b) (4)

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
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Chris Salido, B.S., Executive Director, Regulatory Affairs, Pharmacyclics (call in)
- Maky Zanganeh, DO, Chief Operating Officer, Pharmacyclics (call in)
- [REDACTED] (b) (4)
- Mann Fung, M.D., Janssen R&D, LLC, Vice President, Compound Development Team Leader
- [REDACTED] (b) (4)

1.0 BACKGROUND

The FDA requested a meeting to discuss the PCI-32765 (ibrutinib) NDA 205552 application, (b) (4)
[REDACTED] 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

(b) (4)
[REDACTED]

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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



ibrutinib (19190) draft-label-final
205552 -- to be... to be sent ...

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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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



ibrutinib (1990) draft-label-test
205552 - to be... to be sent ...

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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DIANE C HANNER
10/28/2013

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 Lonza 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 (b) (4). However (b) (4) does the invoicing for the drug substance. Currently (b) (4) is not listed in the NDA as they are not a manufacturer of drug substance. Should we include (b) (4) 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: 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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DIANE C HANNER
10/23/2013

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

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., “ \geq ” 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



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 (b) (4). We have carefully reviewed your proposals and have the following comments:

(b) (4)

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

Sincerely,

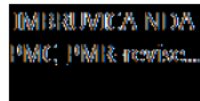
{See appended electronic signature page}

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



Thanks.
Regards

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: Objective is for longer duration of follow-up and completion of extranodal disease outcome assessments: 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 Pharmacocyclics 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-32765/MCL3002) 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 GPIIb-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

PMR: Characterize the bleeding risks associated with ibrutinib therapy in various patient populations by performing enhanced pharmacovigilance (PV) for a period of 4 years. Submit interval and cumulative analyses of hemorrhagic events from both postmarketing and clinical trial sources and make an overall assessment for these events (b) (4)

. The risks of special interest are for major hemorrhagic events and for possible associations with concomitant use of anti-platelet and/or anticoagulant drugs. (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:

1. Perform targeted and expedited surveillance with the use of a guided collection form (as referenced in Pharmacovigilance Plan dated August 23, 2013) to obtain salient additional clinical and diagnostic information related to hemorrhagic events.

Sponsor Comment

Sponsor agrees and would like to submit draft collection forms (Attachment 1) for review by Agency. Are these forms acceptable?

2. Submit as expedited Postmarketing 15-day “Alert Reports” all initial and follow-up reports of major hemorrhagic adverse events from all postmarketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the Standardized MedDRA Query (SMQ) Haemorrhages. (b) (4)

Sponsor Comment

Sponsor agrees to submit 15-day “Alert Reports” for all “serious” cases utilizing the Standardized MedDRA Query (SMQ) Haemorrhages as recommended. We will perform this for a total of 4 years postmarketing.

3. Submit a summary, evaluation, and line listing for all major hemorrhagic events utilizing the SMQ Haemorrhages from all postmarketing sources, including consumer reports, solicited reports, and foreign reports (b) (4)

(b) (4)

4. Assess, summarize, and identify potential risk factors for cumulative major hemorrhagic events from both postmarketing and clinical trial sources and make an overall assessment about these events in the exposed population at 6 month reporting intervals in a separate tab within the PSUR/PBRER. Please comment on whether the cumulative data warrants further detailed assessment, labeling changes and/or other communication about these adverse events.

Sponsor Comment

Sponsor agrees to conduct said analysis included various assessments, as applicable, for labeling/ other safety related communications.

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 patients 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.

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

(b) (4)

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/s/

DIANE C HANNER
10/18/2013

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.

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
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
10/17/2013

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: [URL_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 (b)(4)%
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

Bldg. 22/Room 2119
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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
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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(301) 796-2330
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DIANE C HANNER
10/16/2013

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 $\geq 50\%$ 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 parabrachial node, maximal uptake 4.8, previously 4.7.



PT 217-002
confirmatory PET sc.

5. Patient 217-009

Sponsor Analysis: PR

FDA Analysis: SD

Reason: Patient did not meet PR criteria of $\geq 50\%$ 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

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

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
Bldg. 22/Room 2119
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 inquiries 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
Bldg. 22/Room 2119
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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
10/07/2013

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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(301) 796-2330
FAX (301) 796-9845
E-mail: diane.hanner@fda.hhs.gov

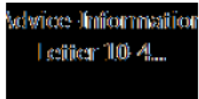
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/s/

DIANE C HANNER
10/07/2013

Hanner, Diane

From: Hanner, Diane
Sent: 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
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
10/04/2013



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.

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(b) (4)

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(b) (4)

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(b) (4)

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
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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

CAPT Diane Hanner
Senior Program Management Officer
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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
Senior Program Management Officer
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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: 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
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
09/25/2013

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
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
09/24/2013

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 cm²), 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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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
09/24/2013

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

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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 orange 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
Bldg. 22/Room 2119
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
09/20/2013

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
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
09/20/2013

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.

Characterize the bleeding risks associated with ibrutinib therapy in various patient populations by performing enhanced pharmacovigilance (PV) for a period of 4 years. Submit interval and cumulative analyses of hemorrhagic events from both postmarketing and clinical trial sources and make an overall assessment for these events (b) (4)

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:

1. Perform targeted and expedited surveillance with the use of a guided collection form (as referenced in Pharmacovigilance Plan dated August 23, 2013) to obtain salient additional clinical and diagnostic information related to hemorrhagic events.

2. Submit as expedited Postmarketing 15-day "Alert Reports" all initial and follow-up reports of major hemorrhagic adverse events from all postmarketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the Standardized MedDRA Query (SMQ) Haemorrhages. (b) (4)

3. Submit a summary, evaluation, and line listing for all major hemorrhagic events utilizing the SMQ Haemorrhages from all postmarketing sources, including consumer reports, solicited reports, and foreign reports (b) (4)

(b) (4)



4. Assess, summarize, and identify potential risk factors for cumulative major hemorrhagic events from both postmarketing and clinical trial sources and make an overall assessment about these events in the exposed population

(b) (4)



Preliminary Protocol Submission:	<u>MM/YYYY</u>
Final Protocol Submission:	<u>MM/YYYY</u>
Study Completion:	<u>MM/YYYY</u>
Final Report Submission:	<u>MM/YYYY</u>

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

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

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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/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).

Characterize the bleeding risks associated with Ibrutinib therapy in various patient populations by performing enhanced pharmacovigilance (PV) for a period of up to 4 years. Submit study reports to FDA annually during the period of study. The risks of special interest are for major hemorrhage events and for possible associations with concomitant use of anti-platelet and/or anticoagulant drugs. The primary enhancements to the current "routine" PV paradigm are the following requirements:

1. Perform targeted and expedited surveillance with the use of a guided collection form (as referenced in Pharmacocyclics' Pharmacovigilance Plan dated August 23, 2013) to obtain salient additional clinical and diagnostic information related to hemorrhagic events.
2. Submit as expedited Postmarketing 15-day "Alert Reports" all initial and follow-up reports of major hemorrhagic adverse events from all postmarketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the Standardized MedDRA Query (SMQ) Haemorrhages. (b) (4)
[REDACTED]
3. Submit a summary, evaluation, and line listing for all hemorrhagic events utilizing the SMQ Haemorrhages, from all postmarketing sources, including consumer reports, solicited reports, and foreign reports (b) (4)
[REDACTED]

(b) (4)
[REDACTED]

(b) (4)

4. Assess, summarize, and identify potential risk factors for cumulative hemorrhagic events from both postmarketing and clinical trial sources and make an overall assessment about these events in the exposed population (b) (4)

Preliminary Protocol Submission:	<u>MM/YYYY</u>
Final Protocol Submission:	<u>MM/YYYY</u>
Study Completion:	<u>MM/YYYY</u>
Final Report Submission:	<u>MM/YYYY</u>

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
09/13/2013

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
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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
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
Silver Spring, Maryland 20993
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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.

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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

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/s/

DIANE C HANNER
09/12/2013



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 (b) (4) Mantle Cell lymphoma (MCL) (b) (4)

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)

Mid-Cycle Communication

- 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

(b) (4)

- (b) (4)

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

Mid-Cycle Communication

- 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, (b) (4)

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.

(b) (4)

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 official 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.

Mid-Cycle Communication

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 use (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 n=6 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 n=6. 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 n=6 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,

(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

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.

PMC

Description: 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.



Table 1. PET
results of patient...

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	<p>2. Minimally metabolically active cavitory 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.</p> <p>3. A punctate FDG-avid focus is noted in the right lobe of the thyroid gland, of uncertain clinical significance.</p>	PR
032-006	(b) (6) , P/ 3/24/2011	<p>3. Persistent active tumor in the right parotid gland.</p> <p>4. Focal hyper-metabolism in the right seminal vesicle is probably related to lymphoma.</p>	PR
032-007	(b) (6) 12/21/2011	<p>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-</p>	PR

		<p>tions within the lesion are stable.</p> <p>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).</p>	
032-015	<div>(b) (6)</div> <p>9/14/2011</p>	<p>3. F18-fluoro-deoxyglucose-avid calcified nodule in the left lobe of the thyroid to be further evaluated.</p>	PR
038-004	<div>(b) (6)</div> <p>5/16/2012</p>	<p>2. Persistent high uptake in the tongue, which may be physiologic. Correlation with clinical exam is recommended. SUV 9.0</p>	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
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
09/04/2013

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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(301) 796-2330
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/s/

DIANE C HANNER
09/03/2013



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, (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** (b) (4) 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
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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
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
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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
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
(301) 796-2330
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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
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(301) 796-2330
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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 "Swallow capsules whole at least 30 minutes before or at least 2 hours after a meal". 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

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
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Silver Spring, Maryland 20993
(301) 796-2330
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/s/

DIANE C HANNER
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.: [REDACTED] (b) (4)

Participant Code: [REDACTED] (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, [REDACTED] (b) (4)

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, (b) (4)
[REDACTED]
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



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. (b) (4) limit in the drug product specification based on batch data or demonstrate that the active ingredient is stable at the proposed acceptance limit ((b) (4) %).
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



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



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. (b) (4) 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 (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)			
032-XXX	Yes	No	Not evaluated	Yes	No	Not evaluated	Yes	No	Not evaluated	Yes	No	Not evaluated	
	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
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
08/08/2013

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
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
08/08/2013



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, (b) (4). The acceptance limits for these impurities were proposed based on the limited batch analysis data using mean \pm 3SD. The statistical approach of using mean \pm 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. (b) (4).
4. It is recommended that you tighten the acceptance criteria for the drug substance and drug product specification for (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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/s/

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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/s/

DIANE C HANNER
08/02/2013



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



NDA 205552

**METHODS VALIDATION
MATERIALS RECEIVED**

Pharmacyclics, Inc.
Attention: Christine Salido, Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521
FAX: (408) 215-3476

Dear Christine Salido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ibrutinib Capsules and to our July 23, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 1, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
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@pcvc.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



NDA 205552

**REQUEST FOR METHODS
VALIDATION MATERIALS**

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

Dear Christine Salido:

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

We will be performing methods validation studies on Ibrutinib capsules, as described in NDA 205552.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

QCM-148 Chiral Impurity in Ibrutinib Drug Substance by HPLC
QCM-129 Impurities in Ibrutinib Drug Substance by HPLC
QCM-130 Content Uniformity, Identification, and Assay for Ibrutinib Capsules, 140 mg, by HPLC or UPLC
QCM-141 Degradation Products in Ibrutinib Capsules, 140 mg by HPLC

Samples and Reference Standards

50 mg of PCI-32765 IMPS system suitability standard
2 x 200 mg of PCI-32765 DS reference standard
2 x 200 mg of PCI-32765 drug substance
150 Ibrutinib capsules, 140 mg
40 placebo capsules

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/23/2013

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. [REDACTED] (b) (4)
[REDACTED]

1.2. Include a warning and precaution [REDACTED] (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: [REDACTED] (b) (4)

Submit the following information:

3.1. For any investigator at [REDACTED] (b) (4) or [REDACTED] (b) (4) who received any fraction of the significant payments of other sorts, including [REDACTED] (b) (4) and [REDACTED] (b) (4), provide details of the investigator involvement in the assessment of efficacy and safety for any patient in clinical trial [REDACTED] (b) (4) or PCYC-1104-CA. 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 [REDACTED] (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



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/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/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

Hanner, Diane

From: Hanner, Diane
Sent: Thursday, June 20, 2013 2:46 PM
To: 'Christine Salido'
Subject: NDA 205552 ibrutinib: rolling submission part 3-information request 6-20-13

Hi Christine,
This is merely for my records, it appears that we will not have a late submission for this NDA.
Please confirm that this is correct.
Thanks.
Regards,
Diane

From: Christine Salido [<mailto:csalido@pcyc.com>]
Sent: Friday, June 14, 2013 11:13 AM
To: Hanner, Diane
Subject: RE: NDA 205552 ibrutinib: rolling submission part 3-information request 6-14-13

Hi Diane,

I can confirm that the 3-month stability data will be included with the 28 June 2013 rolling submission (part 3).

Thanks
Chris

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Friday, June 14, 2013 5:15 AM
To: Christine Salido
Subject: NDA 205552 ibrutinib: rolling submission part 3-information request 6-14-13

Hi Christine,

Please confirm that the 3-month stability update will be received within 30 days of 28 June 2013. This was agreed upon at the preNDA meeting.

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
06/20/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, June 14, 2013 8:51 AM
To: 'Christine Salido'
Subject: NDA 205552 (Ibrutinib) information request -6-14-13 FDA Response

Hi Christine,

FDA Response: One ATC level (the topmost level, equivalent to CMLVL1 in the ADCM analysis dataset) would be acceptable.

Regards,
Diane

From: Christine Salido [<mailto:csalido@pcyc.com>]
Sent: Thursday, June 13, 2013 3:12 PM
To: Hanner, Diane
Subject: RE: NDA 205552 (Ibrutinib) information request

Hi Diane,
Could you please clarify how many ATC levels you need. All 4 levels or some specific number of levels.

Thank you
Chris

From: Christine Salido
Sent: Thursday, June 13, 2013 10:48 AM
To: 'Hanner, Diane'
Subject: RE: NDA 205552 (Ibrutinib) information request

Thank you Diane. Hope all is well.
Chris

From: Hanner, Diane [<mailto:Diane.Hanner@fda.hhs.gov>]
Sent: Thursday, June 13, 2013 10:47 AM
To: Christine Salido
Subject: NDA 205552 (Ibrutinib) information request

Hi Christine,

Please click on the attachments and view the NDA 205552 information request. Please note that we need you to respond to this request by June 20, 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
06/14/2013

Hanner, Diane

From: Hanner, Diane
Sent: Friday, June 14, 2013 8:17 AM
To: 'Christine Salido'
Subject: NDA 205552 ibrutinib: rolling submission part 3-information request 6-14-13

Hi Christine,

Please confirm that the 3-month stability update will be received within 30 days of 28 June 2013. This was agreed upon at the preNDA meeting.

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
06/14/2013



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 (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ibrutinib (PCI-32765).

Please refer to my signed April 24, 2013, Information Request Item 3 Part 2, which upon further review, your submission appears to be incomplete. Specifically, please submit the following information as requested previously (See below). Refer to the attached mock table as provided.

Part 2: Study subject data listings BY clinical site (please identify the corresponding site number), clinical investigator name for this adequate study. The study subject data listings should capture the following:

(3) concomitant medications (non-study medications): (site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped.

(4) prohibited medications (non-study medications): as above with concomitant medications

(5) adverse events, (MEDRA preferred term/investigator entry, detailed drug name, date start/stopped, severity/resolution, SAE (yes, no), death (yes/no))

Please submit the above information on or before June 20, 2013.

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

Mock Table for Concomitant Medications

Subj ID	Age/Sex	A: ATC Level P: Preferred Term V: Verbatim Term	Indication/ Diagnosis	Dose	Unit	Route	Frequency	Start Date/days	Stop date/days	Duration (days)
032-108	63/M	A: CARDIOVASCULAR SYSTEM P: LISINOPRIL V: LISINOPRIL	HYPERTENSION	5	MG	ORAL	QD	24AUG2011 / 365	20SEP2011 / 392	28

Mock Table for Adverse Events

Subj ID	Age/Sex	S: System Organ Class P: Preferred Term V: Verbatim Term	AE Start Date/days	AE Stop Date/days	Duration (days)	Relation- ship to drug	Action	Concom Add'l Tx	SAE	Severity
032-108	63/M	A: GASTROINTESTINAL DISORDERS P: DIARRHOEA V: DIARRHEA	27AUG2010 / 3	28AUG2010 / 4	2	POSSIBLE	DNC	NO	NO	GRADE 1

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/s/

DIANE C HANNER
06/13/2013

From: Hanner, Diane
To: ["Christine Salido"](#)
Bcc: [McGinn, Karen](#); [Verdun, Nicole](#); [De Claro, R. Angelo](#)
Subject: RE: NDA 205552 ibrutinib: mid August safety update
Date: Tuesday, June 04, 2013 1:15:00 PM

Hi Christine,

FDA Response: Yes, the plan is acceptable. However, because the safety review is ongoing, please be prepared to submit the additional lab data upon request.

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](mailto:diane.hanner@fda.hhs.gov)

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Monday, June 03, 2013 9:20 PM
To: Hanner, Diane
Subject: NDA 205552 ibrutinib: mid August safety update

Hi Diane,

Pharmacyclics is planning to submit AE and SAE data for ongoing single agent studies as discussed at our pre-NDA meeting for the upcoming mid August 2013 NDA safety update. While there is one study (PCYC-1104-CA) which has some additional lab data collected, Pharmacyclics is not planning to submit this as part of the mid August safety update. Please note that no lab abnormalities have been identified by Pharmacyclics that warrant information in the draft package insert. Please confirm that this plan is acceptable to FDA for the mid August NDA safety update.

Thank you,

Christine Salido
Regulatory Affairs
Pharmacyclics, Inc.
408-215-3039
csalido@pcyc.com

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
06/04/2013

From: Hanner, Diane
To: ["Christine Salido"](#)
Bcc: [Lee, Shwu-Luan](#); [Saber, Haleh](#); [De Claro, R. Angelo](#); [McGinn, Karen](#); [Verdun, Nicole](#)
Subject: NDA 205552 ibrutinib: Information request
Date: Monday, June 03, 2013 1:53:00 PM

Hi,

Please address the following information request regarding NDA 205552, ibrutinib:

In order to complete our review of the NDA, we need to assess the animal: human exposure ratios for reproductive toxicology studies. Please provide the mean AUC in patients at the recommended human dose. If different doses are proposed for different indications, provide the mean AUCs for the indications/doses proposed.

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](mailto:diane.hanner@fda.hhs.gov)

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/s/

DIANE C HANNER
06/03/2013



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. (b) (4)

(b) (4)

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



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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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**

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: Lymphoma and immune mediated disease
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) (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). 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) 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 batches 1008, 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

IND 102688
Meeting Minutes
Type B

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I

{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) 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) 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 (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 batches 1008, 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.

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

/s/

JEWELL D MARTIN
04/16/2013

ALI H AL HAKIM
04/16/2013

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, (b) (4)

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)

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 (b) (4) 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



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 (b) (4) 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 (b) (4) 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 \pm 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 (b) (4)

(b) (4) 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 (b) (4) 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 Venclebrutinib-Naive	Ibrutinib Venclebrutinib-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

Concordance 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.

AGREEMENT 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 Innovation 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



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B meeting
Meeting Category: EOP 2 meeting
Meeting Date and Time: March 7, 2012, 2:00 p.m.
Meeting Location: CDER WO 1311
Application Number: IND 102688
Product Name: PCI-32765
Indication: Mantle Cell lymphoma
Sponsor Name: Pharmacyclics, Inc.
Meeting Request Date: December 20, 2011
Received Briefing Package February 6, 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
- Angelo De Claro, M.D., Medical Officer, DHP
- LDCR Adam George, Ph.D., Senior Regulatory Review Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Mark D. Rothmann, Ph.D, Statistical Team Leader, DB 5
- 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:

- Eric Hedrick, M.D. Interim Chief Medical Officer, VP of Oncology**
- Alice M. Wei Regulatory Affairs Consultant**
- Lori Kunkel, M.D., Chief Medical Officer**

(b) (4)

1.0 BACKGROUND

The purpose of this meeting is to discuss the acceptability and the design of the development program for PCI-32765 in the treatment of patients with mantle cell lymphoma (MCL). The development program includes a Phase 3 trial PCI-32765MCL3001 of PCI-32765 versus bortezomib for the treatment of patients with MCL who have failed at least one prior systemic chemotherapy and a single arm Phase 2 trial PCI-32765MCL2001 of PCI-32765 in the treatment of patients with relapsed or refractory MCL who are intolerant to or progressed on bortezomib therapy.

The Phase 3 study is intended to support full approval of PCI-32765 for the treatment of patients with MCL who have failed at least one prior therapy. The Phase 2 study is intended to support accelerated approval of PCI-32765 for the treatment of patients with relapsed or refractory MCL who are intolerant to or progressed on bortezomib therapy.

2.0 DISCUSSION

Question 1

Does the Agency agree that the proposed patient population in the Phase 3 study PCI-32765MCL3001 is adequately defined per the study eligibility criteria?

FDA Response: No. Standard first-line therapy for the treatment of patients with MCL consists of combination chemoimmunotherapy regimens that include rituximab. We recommend that you require eligible patients to have received at least 1 prior chemotherapy regimen that includes rituximab. The proposed eligible population would not be applicable to a U.S. population.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment. As recommended by the Agency, we will modify the eligibility criteria to require patients to have received at least 1 prior chemotherapy regimen that includes rituximab.

Question 2

Does the Agency agree the comparator, bortezomib, is appropriate for this patient population?

FDA Response: Yes.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment. No additional response.

Question 3

Does the Agency agree with the proposed dose, schedule, and duration of therapy for PCI-32765 and comparator?

FDA Response: No. Please provide justification for the reduced schedule for bortezomib after 8 cycles. The dose proposed after 8 cycles is also different from the dose used in the Phase 2 study of bortezomib in patients with MCL.

In addition, given the recent approval of the subcutaneous route of administration for bortezomib, the Agency recommends that the Sponsor choose one route of administration, either intravenous or subcutaneous, for use in the Phase 3 PCI-32765MCL3001 trial.

The proposed dose, schedule and duration of therapy for PCI-32765 are acceptable.

Pharmacoclinics Response:

We agree to use the same dose and schedule as that used in the Phase 2 study of bortezomib in patients with MCL (1.3 mg/m²/dose administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a 10 day rest period in a 21 day cycle). Patients will be treated until disease progression or unacceptable toxicity. The intravenous route of administration will be chosen in the PCI-32765/MCL3001 study.

Question 4

Does the Agency agree with the proposed safety plan?

FDA Response: No. You have not included ECG assessments in the safety monitoring plans for the MCL3001 and the MCL2001 trials. The propensity for PCI-32765 to induce prolongation of the QTc interval has not been fully evaluated per the ICH-E14 guidance document. Therefore we request that you evaluate ECGs more frequently in your proposed trials (based upon the PK of the investigational agent).

Pharmacoclinics Response:

In vitro safety pharmacology study suggested that the therapeutic concentrations of ibrutinib achieved with 560mg daily dose are approximately 100 times lower than the median inhibitory concentration for hERG potassium current. No treated-related QTc prolongation effect was observed in cardiovascular study using telemetered dogs. In the first-in-human study (PCYC-04753), ECGs were performed at screening and specified time points during cycle 1. ECG findings from this study, although limited by small numbers of patients in each cohort, the use of different machines at different sites and collecting only QTcB values, showed no evidence for significant QTcB prolongation. At this time, in light of no preclinical and clinical evidence of negative effect of ibrutinib in QT interval, we propose a separate QT study to fully evaluate the effect of ibrutinib in QT interval. For the Phase 3 study, we will perform ECG at baseline and anytime as clinically indicated. We are still on track to submit our plans to the Agency for clinical evaluation of the potential for QT/QTc interval prolongation in Q2 2012.

FDA Response: In addition, the safety plans for the MCL3001 and MCL2001 trials do not include monitoring of serum sodium and magnesium levels. Since diarrhea is one of the most common toxicities observed during clinical trials with PCI-32765, we recommend monitoring of serum sodium and magnesium levels at baseline and at each follow-up visit time point.

Pharmacocyclics Response:

In the single-agent studies of ibrutinib in CLL (PCYC-1102-CA) and MCL (PCYC-1104-CA), serum chemistries, including sodium and magnesium were frequently monitored. In Study PCYC-1102-CA, serum chemistries were obtained on all patients at baseline, on days 8, 15, 22, and 28 of cycle 1, on days 15 and 28 of cycle 2, and on day 28 of all subsequent cycles. As of 14 February 2012, in 116 patients evaluable for adverse events, the incidence of hypomagnesemia was 5%; all cases were Grade 1 in severity. The incidence of hyponatremia was 2% (2 out of 116), with both cases being Grade 3 in severity. In Study PCYC-1104-CA, as of 26 January 2012, in 84 patients evaluable for adverse events, no cases of hypomagnesemia were reported. One case of hyponatremia (Grade 3) was reported (see tables in Appendix 1).

The incidence of both hypomagnesemia and hyponatremia in studies of ibrutinib in which these laboratory values have been monitored frequently is low. On this basis, Pharmacocyclics would propose to monitor serum sodium (in addition to other serum chemistries) once per cycle of treatment, and would propose to monitor serum magnesium as directed by clinical evaluation.

Meeting Discussion: The sponsor agreed to plan scheduled magnesium monitoring at baseline, once per cycle during cycles 1 and 2, and in later cycles as clinically indicated.

FDA Response: Furthermore, your safety plan proposes to conduct more frequent hematologic laboratory assessments for the bortezomib arm following cycle 8 than for the PCI-32765 arm. This plan introduces potential bias for over-reporting of hematologic adverse events in the bortezomib arm compared to the PCI-32765. Please provide a rationale for the imbalance in the schedule of hematologic laboratory assessments between treatment arms.

Pharmacocyclics Response:

In the phase 2 study (PCYC-1104) of ibrutinib in patients with previously treated MCL, grade 3 or 4 neutropenia, thrombocytopenia, and anemia are all less than 5%. Therefore, we anticipate that in the current phase 3 study, hematologic toxicity will not be the predominant toxicity of ibrutinib. To balance the need of similar safety assessment schedule and the consideration on the necessity of the test and patient convenience and comfort, we propose to have a CBC test on days 1 and 8 of during the first 8 cycles in both bortezomib and ibrutinib groups. We expect that this schedule will capture the great majority of hematologic toxicities in both groups.

FDA Response: Please also provide rationale for why patients receiving parenteral anticoagulation with LMWH are eligible for enrollment, given the mechanism of action for PCI-32765 and observed bleeding events in the trials to date.

Pharmacoclinics Response:

In the analysis of four cases of serious adverse events of subdural hemorrhage (in over 300 patients treated with ibrutinib on clinical trials), the use of warfarin was associated with two of these events, amongst twelve patients in total who received warfarin as a concomitant medication on trial. One case of subdural hemorrhage was noted among the 15 patients receiving heparin or low molecular weight heparin; no other serious bleeding adverse events were reported. Although anticoagulant use is a predisposing factor for this event, and the relationship between ibrutinib treatment and subdural hemorrhage cannot be established, in the interest of patient safety, patients who are receiving warfarin at study entry or have a recent history of intracranial bleeding will be excluded from trial. However, the protocol does not exclude patients who receive therapeutic LMWH anticoagulation as there is no evidence that suggest concomitant use of LMWH increase risks of intracranial bleeding. Of note, major hemorrhage has been identified as an event of special interest for studies evaluating ibrutinib. Enhanced reporting and data collection will be mandated for all major bleeding events.

Meeting Discussion: The sponsor agreed to submit a report on the number bleeding events to date in the development program and the number of patients treated to date (including analysis of concomitant medications).

Question 5

Is the proposed plan to collect PK data during the proposed Phase 3 trial using sparse sampling to explore the exposure-response relationship for PCI-32765 acceptable to the Agency?

FDA Response: Yes. We recommend that you provide your population pharmacokinetic analysis plan with a future preNDA submission for Agency review.

Pharmacoclinics Response:

Pharmacoclinics will provide a population pharmacokinetic analysis plan with a future preNDA submission.

Question 6

Is the primary endpoint, (PFS), assessed by blinded 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 is subject to ascertainment bias and any imbalance in assessment dates or a substantial amount of missing data could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS. The magnitude of the treatment effect on PFS will be a review issue.

All patients should be followed for PFS until a PFS event occurs (progression, relapse from CR, or death) or until the data cutoff even when receiving non-protocol therapy. To ensure the integrity of a valid ITT analysis on PFS, missing data/assessments of progression should be kept at a minimum. 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. Sensitivity analyses should include a worst comparison case analysis treating those who had scans discontinue without an event prior to the data cutoff date as censored at their last evaluation on the control arm and as events at the next schedule assessment time on the experimental arm.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment and will perform PFS sensitivity analyses as outlined above.

FDA Response: Please clarify whether IRC tumor assessments are "real-time." If real-time, patients should be followed for PFS until an independent review assessment of a PFS event (progression or death). If not, the sponsor should provide an evaluation of the agreement between the IRC-determined PFS and investigator-determined PFS and the impact on the PFS analysis.

Pharmacyclics Response:

A real-time IRC tumor assessment is not planned for the PCI-32765MCL3001 study. Pharmacyclics will provide an evaluation of the agreement between the IRC-determined PFS and investigator-determined PFS. The IRC's PFS will be used for the primary analyses. However, sensitivity analysis based on investigators' PFS will also be provided.

**FDA Response: Patients receiving subsequent anti-lymphoma therapy before disease progression should be followed for PFS until a PFS event occurs (progression, relapse from CR, or death) or until the data cutoff. A sensitivity analysis including such additional PFS assessment information instead of censoring PFS for that patient by last adequate assessment before subsequent anti-lymphoma therapy is recommended.
See also responses to question 8.**

Pharmacyclics Response:

Pharmacyclics will follow disease assessment until progression irrespective of subsequent anti-lymphoma therapy. In the primary analyses, those who received subsequent anti-lymphoma therapy before progression will be censored at the last adequate tumor assessment before receiving such therapy. Sensitivity analyses including all PFS assessment will be performed as recommended.

Question 7

Does the Agency agree with the sample size calculation and, in particular, the statistical assumptions and analysis plan (including the definition of censoring) with regard to PFS?

FDA Response:

We agree with the sample size calculation. See the response to question 6 and 8 on the analysis of PFS.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment. No Additional response.

Question 8

Does the Agency agree with the proposed interim analysis plan for PFS in study PCI-32765MCL3001?

FDA Response: We discourage the proposed interim analysis of PFS as estimated effects will be less precise, the comparison will be weighted towards early events, and it may be difficult to evaluate the magnitude of PFS benefit. Stopping the trial when 35% of the subjects have an event will provide inadequate subject follow-up.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment. A conservative stopping boundary (O'Brien-Fleming) for efficacy is being proposed, and crossing the interim efficacy boundary will entail an overwhelming PFS effect; the expected HR will be less than 0.56, which corresponds to an at least 78% improvement in median PFS (e.g. from 7 months to at least 12.5 months). We expect the enrollment will be completed at the time that the interim PFS analysis results become available. Analyses from supportive secondary endpoints such as ORR together with various

subgroup analyses will be available at the time of interim analyses to see if the results are internally consistent and robust; this is described in detail in the SAP that accompanies this response (Appendix 2) In the event of a DMC (Appendix 3) recommendation to stop the study because the pre-specified efficacy boundary is crossed, Pharmacyclics does 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 will continue as specified in the protocol until 3 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 of 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.

Question 9

Does the Agency agree that the development program identified for MCL, comprised of one large randomized comparative Phase 3 Study, PCI-32765MCL3001, and one supportive Phase 2 Study PCYC-1104-CA, is adequate in design to characterize the efficacy and safety of PCI-32765 for the treatment of patients with MCL who have received at least one prior therapy and could provide adequate data to support an NDA and regular approval for the proposed indication if a significant PFS benefit and an acceptable toxicity profile is observed?

FDA Response: 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.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment. No additional response.

Question 10

Will the results from an additional single arm Phase 2 Study, PCI-32765MCL2001, with approximately 110 patients with relapsed or refractory MCL who have received at least one rituximab-containing regimen and who have progressed or are intolerant to bortezomib therapy be sufficient to file an NDA under the accelerated approval pathway per 21 CFR 314.500, Subpart H for PCI-32765 if those results provide meaningful therapeutic benefit to patients where no available approved treatment options exist (see APPENDIX B)?

FDA Response: Possibly. The available therapies (against which you must demonstrate an advantage) may change during the conduct of your trial. The FDA is required to make a judgment at the time of the NDA action if the available therapy standard has been met. Should the accelerated approval pathway be unavailable to you at the time of trial completion, because of changes in available therapy, you could utilize the results of this trial (depending upon the results) as a supportive trial in a future NDA.

In addition, you have not provided a definition of bortezomib intolerance in the protocol. Therefore, determining if a truly intolerant population of patients was selected for the trial will be a review issue.

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment. In this study, eligible subjects are required to have received at least two cycles of bortezomib therapy and the documentation of intolerance to bortezomib therapy must be reviewed and approved by the Sponsor prior to enrollment. Detailed information on the toxicities leading to determination of intolerance to bortezomib will be collected and summarized.

Additional Comments:

- 1. Your proposed response and progression criteria for clinical trials MCL2001 and MCL3001 would not be acceptable for the evaluation of patients with FDG-negative disease at baseline.**

Pharmacyclics Response:

According to the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007), MCL is a routinely FDG avid lymphoma. In cases where the disease is FDG-avid at baseline, a PET will need to demonstrate FDG negativity at the time of response assessment to confirm a complete response, as stated in the criteria. In the case that at baseline the disease is FDG-negative, criteria for lymphoma with FDG

avidity unknown or pretreatment FDG-negative lymphoma will be used. Specifically, according to the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007), the response evaluations (CR, PR, or PD) in these instances will be based on CT scan criteria.

Meeting Discussion: The Agency acknowledges your response, however, the criteria described above are not specifically outlined in the protocol. We recommend that the Sponsor include the language above in the protocols for MCL2001 and MCL3001. The Sponsor agrees to clarify the response criteria in the protocols.

2. Your annual report states:

“Lesions of the cornea were observed in dogs treated at high dose levels in non-clinical toxicology studies. This finding prompted specific efforts to identify potential ophthalmologic adverse effects in subjects participating in the initial studies of PCI-32765. The most common ocular adverse events include vision blurred, dry eye, eye pain, visual impairment, and conjunctivitis. All but two events (macular edema and cataract) were of Grade 1 or 2 severity.”

We also note that for clinical trial PCYC-1104-CA, you implemented the following for EU sites:

“Examination of the cornea will be performed by an ophthalmologist at Screening and at the end of Cycles 6, 12, 18, and 24 (± 7 days). Only external and slit lamp examinations are required. If indicated, pupil function, ocular motility, visual field, and intraocular pressure examinations will be done, as well. Visual acuity and fundoscopy should also be assessed during these exams if indicated. If there is a Grade ≥ 3 PCI-32765-related observation, treatment with study drug will be discontinued and the subject will receive monthly follow-up eye exams until abnormalities have resolved or are stable.”

Submit a report regarding ophthalmologic AEs from PCYC-1104-CA.

Discuss your plan for monitoring for ophthalmologic adverse events in your current and proposed development program.

Pharmacoclinics Response:

It is axiomatic that higher doses pose higher risks in a relative sense unless systemic absorption and therefore exposures become saturated at higher doses. Because we have not seen corneal opacities related the PCI-32675 in the clinic, so far, the risk basis would appear to be low at either of our clinical dose levels. The corneal lesion in the dog is not a robust response and does not appear to affect tissue structure microscopically. Briefly:

Corneal dystrophy (opacity) was seen on examination in 3 of 10 dogs in the 4-week toxicity study after 3 weeks of dosing at a dosage level of 150 mg/kg/day. In a recently performed 13-week toxicity study, ophthalmologic examinations revealed the presence of corneal dystrophy at a lower incidence, in 1 of 11 dogs, after 6 weeks of dosing at 220 mg/kg/day followed 6 weeks of dosing at 120 mg/kg/day. In the 13-week toxicity study, frozen Oil-red-O stained sections of corneas were examined from a control group male and the effected 220/120 mg/kg/day group dog. The special stained sections failed to demonstrate corneal stromal lipid inclusions characteristic of corneal dystrophy in dogs, and the corneas were considered to be normal microscopically. No further nonclinical investigations are planned.

In Study PCYC-1104-CA, as of a cut-off date of 26 January 2012, with a median follow up of 4.9 months and 103 subjects enrolled, a total of 15 ophthalmologic adverse events have been reported in 13 patients. The reported adverse events were Grade 1 in severity, with the exception of three Grade 2 events: one event each of retinal detachment, eye dryness, and eye infection. None of the events have been treatment-limiting. The most common events were increased lacrimation (n=5) and eye dryness (n=2). No scleral toxicities have been reported. It should be noted that Study PCYC-1104-CA has a provision for scheduled eye examinations at baseline and after every 6 cycles of treatment until cycle 24; these examinations are being conducted only at European sites participating in Study PCYC-1104-CA. As enrollment at European study sites began in August 2011, there is no data from the planned on-treatment eye examinations as subjects are now just beginning to complete 6 month follow up.

To date, in over 300 patients treated on clinical trials of PCI-32765, the profile of ophthalmologic events has been characterized by a relatively low frequency of reported events, a lack of severe or treatment-limiting events, a lack of consistency in types of events which would suggest an underlying pathophysiologic relationship to PCI-32765, and no events suggesting a correlation to the non-clinical observation of corneal opacities in dogs treated with high doses of PCI-32765. For these reasons, we believe that the plan to monitor ophthalmologic events as part of the routine safety monitoring plan in Studies PCI-32765MCL3001 and PCI-32765MCL2001 is justified.

Meeting Discussion: We recommend that review of systems questions focused on ocular changes be posed to the patients during the visits at baseline and during follow up. Any positive finding (\geq Grade 2) should be referred for formal ophthalmological exam. The Sponsor agreed.

- 3. We recommend that you include determination of circulating MCL cells in your proposed sampling characterization of circulating B-lymphocytes.**

Pharmacyclics Response:

As a part of the biomarker plans, circulating MCL cells will be collected characterized at multiple time points before and during the treatment.

- 4. 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, 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 study-wise type I error rate.**

Pharmacyclics Response:

Pharmacyclics acknowledges the Agency's comment.

- 5. Please provide an analysis plan for overall survival, including the timing of analysis.**

Pharmacyclics Response:

By the protocol design, we will follow the patients for overall survival until study end, which is defined as 3 years after the last patient enrolled or about 80% of the patients have died, whichever is earlier. Overall survival (OS) analyses will be performed at the time of PFS interim analysis, at the time of final PFS analysis and at the end of study.

- 6. We recommend that you continue to assess ECGs in both Study PCI-32765MCL2001 and Study PCI-32765MCL3001. If your ECG data to date suggest that PCI-32765 does not prolong the QT interval and fulfill the ICH E14/QT requirements please submit your data for Agency review and concurrence.**

Pharmacyclics Response:

Please also see response to Question 4. In light of the lack of preclinical and clinical evidence of negative effect of ibrutinib in QT interval, we propose to conduct a separate QT study to fully evaluate the effect of ibrutinib in QT interval. For the registration studies, we will perform ECG at baseline and anytime during treatment as clinically indicated.

Meeting Discussion: The sponsor agreed to submit their QT data and plan for IRT review.

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

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
03/09/2012



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 August 16, 2012, meeting request for a meeting to be held between representatives of your firm and the FDA on December 3, 2012. The purpose of the meeting was to review the clinical development program regarding the treatment of ibrutinib (b) (4) in the treatment of patients with newly diagnosed Mantle Cell Lymphoma (MCL).

A copy of the official minutes of the December 3, 2012, 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}

CDR 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 B

Meeting Category: End of Phase 2

Meeting Date and Time: December 3, 2012

Meeting Location: CDER WO Bldg 22, room 1415

Application Number: IND 102688

Product Name: Ibrutinib

Indication: Mantle Cell Lymphoma

Sponsor/Applicant Name: Pharmacyclics, Inc.

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

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

FDA ATTENDEES

- Edvardas Kaminskas, M.D., Deputy Director, DHP
- R. Angelo de Claro, M.D., Medical Officer, Clinical Team Leader (acting), DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Mark Rothmann, Ph.D., Mathematical Statistician Team Leader, DB 5
- Abhilasha Nair, M.D., Medical Officer, DOP2

SPONSOR ATTENDEES

- Lori Kunkel, M.D., Chief Medical Officer, Pharmacyclics Inc.
- Christine Salido, Executive Director, Regulatory Affairs, Pharmacyclics Inc.
- Urte Gayko, Ph.D., Pharmacyclics, Inc., Vice President, Regulatory Affairs
- Sen Hong Zhuang, M.D., Ph.D., Janssen R&D, LLC, Senior Director, Clinical Research
- Craig Tendler, M.D., Janssen R&D, LLC, Vice President, Late Development and Global Medical Affairs

- Darrin Beaupre, M.D., Senior Director, Clinical Science, Pharmacyclics, Inc
- Steven Sun, Ph.D., Janssen R&D, LLC, Director, Biostatistics
- John Seaman, Pharm.D., Janssen R&D, LLC, Senior Director, Global Regulatory Affairs
- Terri Williams, Ph.D., Janssen R&D, LLC, Associate Director, Global Regulatory Affairs

(b) (4)

- Man-Cheong Fung, M.D., M.B.A., MHCM, FACP, Janssen R&D, LLC Vice President,
Compound Development Team Leader

(b) (4)

- Aleksandra Rizo, M.D., Ph.D., Director, Oncology Drug Development, Janssen R&D, LLC

1.0 BACKGROUND

PHARMACYCLICS REQUESTED AN END OF PHASE 2 MEETING ON AUGUST 16, 2012, TO OBTAIN AGENCY FEEDBACK ON THE FOLLOWING:

- The Sponsor proposed an End of Phase 2/Pre-Phase 3 meeting to review the clinical development program regarding ibrutinib (b) (4) in the treatment of patients with newly diagnosed Mantle Cell Lymphoma (MCL) who are not eligible for intensive chemotherapy and Stem Cell Transplantation (SCT).
- The meeting was granted on August 28 2012, and it was scheduled for December 3, 2012.

2. DISCUSSION

Question 1

Does the Agency concur that the proposed, randomized, double-blind, placebo-controlled Phase 3 Study, PCI-32765MCL3002 is adequate in design to characterize the efficacy and safety of PCI-32765 in combination with bendamustine and rituximab compared with the combination of bendamustine and rituximab with placebo in the treatment of patients with newly diagnosed MCL who are not candidates for high dose chemotherapy (e.g. high-dose Ara-C) or SCT?

FDA Response: Yes, the trial is adequate in design.

Sponsors' Response:

The Sponsors acknowledge the Agency's response.

Meeting Discussion:

No discussion occurred.

Question 2

Does the Agency agree that the proposed patient population for study PCI- 32765MCL3002 is adequately defined per the study eligibility criteria?

FDA Response: No. Please specify what comorbidities would make a patient ineligible for stem cell transplant. Also, please address in the protocol how you will analyze efficacy data in patients who receive a transplant or other anticancer therapies in the absence of progression.

Sponsors' Response:

To simplify the study population and design, the Sponsor will modify the inclusion criteria to include only patients who are 65 years or older.

The primary PFS analysis will censor patients at the last tumor assessment for those who receive a transplant or other anticancer therapies prior to progression. Tumor assessment will continue if patients receive a transplant or other anticancer therapies in the absence of progression. Sensitivity analysis will be performed using all data available.

Meeting Discussion

The Agency considers the Sponsor's proposal to be acceptable.

Question 3

Does the Agency agree the treatment regimen of the combination of bendamustine and rituximab followed by rituximab maintenance treatment as specified in the protocol is an acceptable background therapy for the eligible patients for study PCI-32765MCL3002?

FDA Response: Yes, you can use the treatment regimen.

Sponsors' Response:

The Sponsors acknowledge the Agency's response.

Meeting Discussion:

No discussion occurred.

Question 4

Does the Agency agree with the proposed dose, schedule, and duration of therapy for PCI-32765, bendamustine, and rituximab for study PCI-32765MCL3002?

FDA Response: Yes, you can use the proposed dose, schedule and duration of therapy.

Sponsors' Response:

The Sponsors acknowledge the Agency's response.

Meeting Discussion:

No discussion occurred.

Question 5

Does the Agency agree that the statistical assumptions and key study design elements of study PCI-32765MCL3002, including sample size and power calculations, are adequate?

FDA Response: The median OS is about 4.5 years based on recently published research results. An assumption of 42 months for median PFS in the control arm may be too optimistic.

We discourage the proposed interim analysis of PFS as estimated effects will be less precise, the comparison will be weighted towards early events, and it may be difficult to evaluate the magnitude of PFS benefit.

A disease assessment interval of 24 weeks, after first 12 months after start of the study treatment, may result in inaccurate estimates of PFS. We recommend a scanning frequency of every 3 or 4 months.

Sponsors' Response:

42 month PFS: The published data show the median PFS for bendamustine and rituximab treatment without rituximab maintenance therapy is 36 months (Rummel 2012). An assumption of 42 months for median PFS is based on a longer PFS achieved with rituximab maintenance therapy.

Interim analysis of PFS: The study duration is expected to be very long (~5 years for PFS analysis) with 520 patients. 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.

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, i.e., the estimated HR needs to be less than 0.595, which corresponds to at least 68% improvement in median PFS (e.g. from 42 months to at least 71 months) to claim superiority at the interim analysis. The sponsors expect the interim analysis will take place approximately 14 months after the last patient is randomized.

Analyses from supportive secondary endpoints such as CR, together with various sensitivity analyses and subgroup analyses, will be available at the time of the interim analysis 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 Agency. Overall survival follow-up will continue as specified in the protocol until the study ends, which is defined as when approximately 60% of the patients have died.

Scanning frequency: The sponsors agree with the Agency's recommendation and will revise the protocol to conduct disease assessments every 3 months for the first year and every 4 months thereafter.

Meeting Discussion

The Agency stated that the scanning frequency is acceptable.

The Sponsor should provide the Agency with a comprehensive summary of literature supporting the PFS assumptions of the control arm.

Regarding interim PFS analysis, the Sponsor commits to discussing the results with the Agency prior to taking any action on the clinical trial.

Question 6

Does the agency agree that the primary endpoint, PFS where disease progression determined by the investigator in the context of a double-blind placebo-controlled study design, is appropriate for a Pivotal Phase 3 study supportive of the following proposed indication:

"PCI-32765 (b) (4) is intended for the treatment of patients with (b) (4) MCL (b) (4)
(b) (4)

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 is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms.

Please note that interpretation of investigator-assessed PFS may be confounded if the trial becomes unblinded due to ibrutinib toxicity.

Please clarify whether the study is still double-blinded in the post-treatment follow-up phase.

Sponsors' Response:

The sponsors acknowledge the Agency's response. The sponsors anticipate that the rate of theoretical "unblinding" due to ibrutinib-associated toxicity in the context of concomitant chemoimmunotherapy will be low, thus preserving the robustness of the investigator-assessed PFS. Specifically, the sponsors note that treatment related lymphocytosis of ibrutinib is markedly reduced when ibrutinib is administered in combination with chemotherapy in the CLL studies.

The sponsors also confirm that the study remains double blinded in the post-treatment follow up phase.

Meeting Discussion

The Agency agreed with the proposal of the use of investigator-assessed PFS. The Agency recommended that the Sponsor review the minutes from the July 2012, ODAC meeting, and to submit an auditing plan prior to results of final analysis for investigator-assessed PFS.

Question 7

Does the Agency agree that the proposed secondary endpoints and statistical analyses are appropriate for the proposed Phase 3 registration study and supportive of the proposed indication?

FDA Response: You propose to base the time of the interim analysis for overall survival whenever the PFS results achieve statistical significance. We are concerned that having the time of the interim analysis of OS random and based on when the PFS results achieve statistical significance, but treating the timing as fixed will inflate the strong study-wise type I error rate. For further information see the reference: H. M. James Hung, Sue-Jane Wang, Robert O'Neill. Statistical Considerations for Testing Multiple Endpoints in Group Sequential or Adaptive Clinical Trials *Journal of Biopharmaceutical Statistics*, 17: 1201–1210, 2007.

Sponsors' Response:

The sponsors acknowledge the Agency's concern. The final analysis of OS is event driven, and will occur when approximately 60% of patients have died irrespective of the PFS results. The sponsors will perform the OS analysis at 3 different time points. The first one will be at the time of the planned interim analysis of PFS, which is expected to be approximately 29 months after the first patient is randomized. The anticipated OS events will be about 112. The second analysis of OS will take place at the time of planned final analysis of PFS, approximately 227 OS events will be observed at that time. In case PFS reaches statistical significance at the interim analysis (~132 PFS events), the OS will still be performed when 227 events are observed. The stopping boundaries will be implemented by Lan-Demets spending function with parameter resembling the conservative O'Brien-Fleming boundary to control the 2-sided type I error of 0.05. The efficacy of OS will not be claimed unless the PFS reaches the statistical significance at the first analysis.

Meeting Discussion

The Sponsor's proposal is acceptable.

Question 8

Does the FDA believe additional qualitative research is needed in MCL patients to confirm the FACT-Lym is content valid for supporting a labeling claim should results of the patient reported outcomes (PRO) measure be positive?

FDA Response: No. The scores produced by the FACT-Lym will not support labeling claims for the following reasons.

- **The measurement concepts represented by FACT scores are not well-defined and it is not possible to describe what the subscales are measuring. The subscale names do not appear to represent the item content of those scales.**

- We recommend measurement of symptoms separately from other concerns (e.g., drug toxicity) in order to adequately measure the effect of the treatment on the core symptoms of the disease.
- Items are not worded in a way that makes it possible to assess what aspect of a symptom is assessed, e.g., intensity, frequency or duration of the symptom. We discourage items that ask patients to rate their "bother" consequent to symptom. If a patient responds "not bothered" it will be unclear whether the symptom was not present or the patient experienced the symptom but did not find it bothersome. It is preferable for patients to rate the symptom more directly in terms of its frequency or intensity.
- FACT includes items with response options that do not fit the concept that the item is measuring (e.g., FACT-Lym [5] "I have certain parts of my body that experience pain" response option= "quite a bit"). Results from these items are not interpretable or adequate for labeling because it cannot be determined what the respondent is rating when answering the question.
- The appropriateness of the seven-day recall period used in the FACT for certain concepts has not been established.

As a path forward for the assessment of symptoms, we recommend identifying the core disease-related symptoms of importance to patients that should be assessed as part of an overall symptom severity score. To this end, we recommend literature review, expert input and qualitative research with patients in the target patient population to identify the relevant symptoms of their disease. Consistent with what has been recommended in other oncologic indications, symptom severity might be measured in a daily diary that asks patients to rate each symptom using a 0-10 numeric rating scale, where 0 represents absence of the symptom and 10 represents the worst imaginable symptom experience during the previous 24 hours. Additionally, in order to measure symptom improvement, patients enrolled a clinical trial must have a sufficient severity of symptom at baseline. Finally, it is important to note that clinical trials that are unblinded, either by design or unintentionally (e.g., through differential toxicity profiles of the assigned treatments), are rarely adequate to support labeling claims based on PRO instruments because patient's perceptions may be influenced by knowledge of their treatment assignment. Please also see the final Guidance for industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>).

Sponsors' Response:

The sponsors acknowledge the Agency's response.

Meeting Discussion:

No discussion occurred.

Question 9

Does the Agency agree that in the framework of a supplemental New Drug Application (sNDA), the proposed clinical development plan consisting of 1 large randomized comparative Phase 3 Study, PCI-32765MCL3002, and supportive data from the Phase 2 Studies PCYC-1104-CA and PCI-32765MCL2001, and the Phase 3 study PCI-32765MCL3001 is satisfactory to support the proposed indication?

FDA Response: Your approach to include trials PCYC-1104-CA and PCI-32765MCL2001 with PCI-32765MCL3002 appears reasonable. Please see Response to Question 10 for comments regarding Study PCI-32765MCL3001.

Sponsors' Response:

The sponsors acknowledge the Agency's response. The sponsors would like to inform the Agency that mature data for the Phase 2 study PCYC-1104-CA in relapsed/refractory mantle cell lymphoma is now available. The 111 treated patients had a median age of 68 years, median of 3 prior regimens (range 1-6). In the bortezomib exposed cohort (N = 47 pts), the ORR is 72% (95% CI 57.4 - 84.4%) including 23% CRs. Importantly, the median duration of response and survival have not been reached with time on study ranging from 1.9 to 19.6 months. The median PFS is estimated to be 16.6 months. The safety profile is consistent with previous study results. The sponsors intend to submit a request for Breakthrough Therapy Designation shortly based on these results.

Meeting Discussion

The Agency and the Sponsor had a preliminary discussion regarding Breakthrough Therapy Designation, FDA Expanded Access Program, and the initial NDA.

Question 10

Does the Agency agree that either of the proposed randomized Phase 3 studies PCI-32765MCL3001 or PCI-32765MCL3002, can serve to confirm clinical benefit for the single-arm Phase 2 Study, PCI-32765MCL2001, expected to be filed as a NDA under the accelerated approval pathway per 21 CFR 314.500, Subpart H?

FDA Response: No. Study PCI-32765MCL3001 is problematic because (b) (4) treatment of mantle cell lymphoma. You will need to show that the results of trial PCI-32765MCL3001 are applicable to patients in the U.S.

However, Study PCI-32765MCL3002 appears to be adequate in design, and may be able to support conversion to regular approval if the results show a favorable benefit-risk profile.

Sponsors' Response:

The sponsors acknowledge the Agency's comment that (b) (4) for the treatment of MCL. However, the study population of PCI-32765MCL3001 represents a population that is relevant in the US and outside of US for the following reasons: 1) All patients in MCL-3001 study are required to have receive at least one rituximab containing combination chemotherapy with or without autologous stem cell transplantation, which is a global standard for the initial treatment of patients with MCL; 2) There is no single standard of care for patients

who relapse after initial treatment. Several chemotherapeutic agents such as bendamustine and targeting agents such as bortezomib and (b) (4) have been used.

The sponsors will request a meeting to discuss with the Agency the potential regulatory application of PCI-32765MCL3001 (e.g. supplemental NDA) after the results of the study become available.

Meeting Discussion

The Agency expressed concerns regarding the safety profile of (b) (4) and the (b) (4). The Agency is willing to meet with the Sponsor regarding further discussion of the results of the PCI-32765MCL3001 trial.

Question 11

Orphan Drug Designation has been requested from the Office of Orphan Products Development for the treatment of MCL on 10 October 2012. Does the Agency agree that if Orphan Drug Designation is granted for PCI-32765 for MCL, then PCI-32765 is exempt from the requirement to conduct pediatric studies for the treatment of MCL as stated in 21§CFR 314.55(d) Exemption for Orphan Drugs?

FDA Response: Yes, we agree.

Sponsors' Response:

The sponsors acknowledge the Agency's response.

Meeting Discussion:

No discussion occurred.

Additional FDA Comments:

All patients should be followed for PFS until a PFS event occurs (progression or death) or until the data cutoff. Missing data/assessments of progression should be kept at 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. Sensitivity analyses, including the worst comparison case treating lost-to-follow-ups (missing at least one tumor assessment before data cutoff) as censored at their last evaluation on the control arm and as events at the next schedule assessment time on the experimental arm, should be performed to assess the robustness of the result of the primary analysis of PFS.

Sponsors' Response:

The sponsors acknowledge the Agency's comment.

Meeting Discussion:

No discussion occurred.

3.0 IMPORTANT MEETING INFORMATION

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified that required further discussion.

5.0 ACTION ITEMS

The Sponsor should provide the Agency with a comprehensive summary of literature supporting the PFS assumptions of the control arm.

The Sponsor should submit an auditing plan prior to results of final analysis for investigator-assessed PFS.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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/s/

ROMEO A DE CLARO
12/06/2012

LATE-CYCLE COMMUNICATION
DOCUMENTS



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 Ibrutinib (PCI-32765).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 28, 2013.

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
October 28, 2013, from 2:30 P.M. to 3:00 P.M.

Meeting Location: WO Building 22, Room 2201

Application Number: NDA 205552

Product Name: IMBRUVICA®, PCI-32765 (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.

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., Medical Officer, Clinical Team Leader, DHP
- Karen McGinn, M.S.N., CRNP, Medical Officer, DHP (by phone)
- Nicole Verdun, M.D., Medical Officer, DHP
- Tanya Wroblewski, M.D., Medical Officer, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Lei Nie, Ph.D., Team Leader, DB 5

Late-Cycle Meeting Minutes

- Tamy Kim, Pharm.D., Associate Director of Regulatory Affairs, OHOP
- Haleh Saber, Ph.D., Supervisory Pharmacologist, DHOT
- Shwu-Luan Lee, Ph.D., Pharmacologist, DHOT
- Elimika Pfuma, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Xiao-Hong Chen, Ph.D., CMC Reviewer, ONDQA, Division 3, Branch 5
- Kim Taylor, M.B.A., M.P.H, Operations Research Analyst, OSP
- Vipul Dholakia, Ph.D., Chemist, Office of Compliance (by phone)
- Kate Gelperin, Team Leader (acting), OSE, DPV
- Naomi Redd, Pharm D., Drug Risk Management Analyst, DRISK
- Karen Dowdy, R.N., B.S.N., Patient Labeling Reviewer, DMPP
- Nisha Patel, Pharm D., Regulatory Review Officer, OPDP
- Ebla Ali Ibrahim, M.S., Regulatory Project Team Leader, DHP
- Katherine Coyle, Pharm. D., Safety Evaluator, OPE, DPVII
- Tracy Salaam, PharmD, Safety Evaluator Team Leader, OPE, DPVII
- Janice Brown, Ph.D., CMC Lead, ONDQA, Division 3, Branch 5
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

(b) (4)

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
- Heow Tan, Chief of Quality & Technical Operations, Pharmacyclics
- David Loury, Ph.D., Executive Vice President, Toxicology, Pharmacyclics
- Fong Clow, Sc.D., Vice President, Biometrics, Pharmacyclics

Late-Cycle Meeting Minutes

- Betty Chang, Ph.D., Vice President, Research, Pharmacyclics
- Dana Lee, Vice President, Drug Safety, Pharmacyclics
- Darrin Beaupre, M.D., Ph.D., Vice President, Clinical Medicine & Early Development, Pharmacyclics
- Chris Salido, B.S., Executive Director, Regulatory Affairs, Pharmacyclics
- Usha Ramesh, Ph.D., Senior Director, CMC Regulatory Affairs, Pharmacyclics
- Juthamas Sukbuntherng, Ph.D., Senior Director, Clinical Pharmacology, DMPK, Pharmacyclics
- Danelle James, M.D., M.S., Senior Medical Director, Pharmacyclics
- Sandra Rattray, Ph.D., Vice President, Head of Janssen Oncology Regulatory, Janssen R&D, LLC
- 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
- Jan de jong, Ph.D., Director, Clinical Pharmacology, Janssen R&D, LLC
- Terri Williams, Ph.D., Associate Director, Global Regulatory Affairs, Janssen R&D, LLC

1.0 BACKGROUND

The Late-Cycle Meeting (LCM) teleconference meeting was held on October 28, 2013, to discuss any substantive review issues identified to date.

NDA 205552 was submitted on June 28, 2013, for IMBRUVICA®, PCI-32765 (ibrutinib) capsules, 140 mg.

Proposed indication: Treatment of patients with mantle cell lymphoma (MCL) 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 September 11, 2013.

2.0 DISCUSSION

1. Discussion of Substantive Review Issues

Discussion:

FDA: No substantive review issues have been identified to date for the MCL indication. The Agency also stated that Discipline Review letters will not be issued because of the expedited timelines for the MCL indication. The Agency informed the Applicant that the Agency is in the process of completing primary and summary reviews for the application.

2. Postmarketing Requirements/Postmarketing Commitments

Discussion:

Applicant: The Applicant requested clarification whether the thorough QT trial would be done in a healthy volunteer population.

FDA: The Agency clarified that a healthy volunteer population would be acceptable for the thorough QT trial.

3. Major Labeling Issues

Discussion:

FDA: We reviewed your response and recommend that you keep Renal Toxicity as Warnings & Precautions. Once the applicant has provided a randomized trial this matter may be revisited.

Applicant: That is acceptable.

Applicant: The Applicant asked would it be possible to put the following statement back in the label (b) (4)

FDA: No, this statement is confusing so leave it out.

Applicant: They agreed to leave it out but plans to include this concept in their education materials..

Applicant: The Applicant requested CMC feedback regarding the expiry dating period for the drug product. Does the Agency agree to grant a 24 month expiry dating for the drug product?

FDA: Yes, that is acceptable.

4. Wrap-up and Action Items

Discussion:

FDA: The Agency will be sending the Applicant a courtesy copy of the ASCO burst to primarily verify the results in the document, and not change the content and formatting.

The Agency also inquired regarding the Applicant's marketing plans whether there is sufficient supply to meet the demand for the drug.

Applicant: The Applicant assured that the Agency of adequate supplies for the drug.

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/s/

ROMEO A DE CLARO
11/01/2013



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 (b) (4)
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

Objective is for longer duration of follow-up and completion of extranodal disease outcome assessments: 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:	<u>completed</u>
Trial Completion:	<u>MM/YYYY</u>
Final Report Submission:	<u>MM/YYYY</u>

#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:	<u>completed</u>
Trial Completion:	<u>MM/YYYY</u>
Final Report Submission:	<u>MM/YYYY</u>

#F

(b) (4)

(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 GPIIb-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