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*APPLICATION NUMBER:*

**205552Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template PMR 2060-# 1:

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA# 205552  
Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

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PMR Description: 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 a minimum follow-up of 24 months 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. Summarize extranodal disease characteristics at baseline and at time of progression. Request further documentation as necessary from clinical trial sites in order to summarize the details of the extranodal disease progression.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	Completed 01/2013
	Trial Completion:	09/ 2014
	Final Report Submission:	03/ 2015

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Relapsed or refractory mantle cell lymphoma (MCL) is a life-threatening condition. The median overall survival for this population is less than two years. In clinical trial PCYC-1104-CA, the applicant reports an overall response rate of 68% with a median duration of response of 17.5 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The Agency has previously accepted overall response rates supported by duration of response from a single-arm clinical trial as a basis for initial approval. The goal for this PMR would be to obtain 2-year follow-up data from clinical trial PCYC-1104-CA. In addition, the applicant will be required to submit a more detailed evaluation of extranodal disease, in order to better characterize the efficacy profile of ibrutinib for the proposed indication.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: minimum 2-year patient follow-up of PCYC-1104-CA (ongoing) including detailed information on extranodal disease

Required

- Observational pharmacoepidemiologic study
  - Registry studies
  - Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  
2-year follow-up of PCYC-1104-CA (ongoing) including detailed information on extranodal disease
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed



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/s/  
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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013

## PMR/PMC Development Template PMR 2060-#2:

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA# 205552  
Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

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PMR Description: 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 approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators. Overall survival is a key secondary endpoint.

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PMR Schedule Milestones:	Final Protocol Submission:	Completed 04/2013
	Trial Completion:	12/ 2018
	Final Report Submission:	03/ 2019

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Relapsed or refractory mantle cell lymphoma (MCL) is a life-threatening condition. The median overall survival for this population is less than two years. In clinical trial PCYC-1104-CA, the applicant reports an overall response rate of 68% with a median duration of response of 17.5 months.

There are no curative therapies for MCL, virtually all patients will develop recurrent disease.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The Agency has previously accepted overall response rates supported by duration of response from a single-arm clinical trial as a basis for initial approval.

The goal for this PMR would be to obtain long-term efficacy outcomes including progression-free survival from a randomized clinical trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: Submit the final clinical study report and data from 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.

Required

- Observational pharmacoepidemiologic study
  - Registry studies
  - Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Confirmatory clinical trial under subpart H
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**



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/s/  
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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013

### PMR/PMC Development Template- 2060-#3

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

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NDA# 205552

Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

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PMR Description: Determine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function by conducting *in vitro* studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

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PMR Schedule Milestones:	Preliminary protocol submission	06/ 2014
	Final Protocol Submission:	12/ 2014
	Study Completion:	06/ 2016
	Final Report Submission:	12/ 2016

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Relapsed or refractory mantle cell lymphoma (MCL) is a life-threatening condition. The median overall survival for this population is less than two years. In clinical trial PCYC-1104-CA, the applicant reports an overall response rate of 68% with a median duration of response of 17.5 months. 48% of patients experienced a bleeding event.

Relapsed or refractory chronic lymphocytic leukemia (CLL) is a life-threatening condition. Although most patients who undergo chemotherapy for CLL achieve an initial response, disease relapse invariably occurs. In the single-arm clinical trial PCYC-1102-CA, the applicant reports a 77% overall response rate in 48 patients with relapsed or refractory CLL. The median duration of response had not been reached with a median follow-up of 16.4 months. 63% of patients experienced a bleeding event.

BTK is expressed in platelets. However, the function of BTK in platelet signaling and activation is not fully understood.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal for this PMR is to determine the effect of ibrutinib on platelet function. Assessment methods should evaluate for effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include patients with concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of aspirin, use of other anticoagulants).  
If the *in vitro* data are not definitive, clinical trials may be required.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: LABORATORY STUDIES: Assess the effect of ibrutinib on platelet function. Assessment methods should evaluate for effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include patients with concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction).

Required

- Observational pharmacoepidemiologic study
  - Registry studies
  - Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks

- Information cannot be gained through a different kind of investigation
  - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
  - The trial will emphasize risk minimization for participants as the protocol is developed
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

    RCK      
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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013

## PMR/PMC Development Template PMR 2060-#4:

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA# 205552

Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

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PMR Description: Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica<sup>®</sup>, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs. Major hemorrhagic events are defined as any one of the following:

- 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)]

This enhanced Pharmacovigilance study will include:

1. Targeted and expedited surveillance with a guided collection form (as referenced in Pharmacocyclics' Pharmacovigilance Plan dated August 23, 2013) to obtain additional salient clinical and diagnostic information related to major hemorrhagic events.
  2. Submission of Post-marketing 15-day Alert Reports for all initial and follow-up reports of serious hemorrhagic adverse events from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) – Haemorrhages.
  3. Submission of interval and cumulative analyses, as well as line listing for all major hemorrhagic events (utilizing the SMQ Haemorrhages) from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports.
-

4. The interval and cumulative analyses should assess potential risk factors for cumulative major hemorrhagic events identified from both clinical trials and all postmarketing sources, and an overall assessment about these events in patients treated with Imbruvica<sup>®</sup> (ibrutinib) Capsules. In the overall assessment, discuss whether the data warrants further detailed assessment, labeling changes and/or other communication about these adverse events.

Continue the study for a period of four years from the date of final protocol submission as noted below. Prior to starting the study, submit for FDA review, a protocol describing how you will conduct the study and report results, according to the timeline below.

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PMR Schedule Milestones:

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Draft Protocol Submission:	03/2014
Final Protocol Submission:	06/2014
#1 Interim Report Submission	12/2014
#2 Interim Report Submission	06/2015
#3 Interim Report Submission	12/2015
#4 Interim Report Submission	06/2016
#5 Interim Report Submission	12/2016
#6 Interim Report Submission	06/2017
#7 Interim Report Submission	12/2017
Study Completion:	06/2018
Final Report Submission:	11/2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Relapsed or refractory mantle cell lymphoma (MCL) is a life-threatening condition. The median overall survival for this population is less than two years. In clinical trial PCYC-1104-CA, the applicant reports an overall response rate of 68% with a median duration of response of 17.5 months. Of 111 enrolled patients, 53 (48 %) experienced a bleeding event...

Relapsed or refractory chronic lymphocytic leukemia (CLL) is a life-threatening condition. Although most patients who undergo chemotherapy for CLL achieve an initial response, disease relapse invariably occurs. In the single-arm clinical trial PCYC-1102-CA, the applicant reports a 77% overall response rate in 48 patients with relapsed or refractory CLL. The median duration of response had not been reached with a median follow-up of 16.4 months. 63% of patients experienced a bleeding event...

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The objective for this PMR is to characterize the risk of minor and major bleeding events in ibrutinib-treated patients based on submission of periodic pharmacovigilance reports every 6 months for up to 4 years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

**Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

**Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: Pharmacovigilance plan to characterize the risk of major and minor hemorrhagic events in ibrutinib-treated patients.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

  RCK    
(signature line for BLAs)

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/s/  
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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013

## PMR/PMC Development Template (PMR # 5)

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA# 205552  
Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

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

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PMR Schedule Milestones:	Final Protocol Submission:	<u>11/28/2012</u>
	Trial Completion:	<u>06/30/2014</u>
	Final Report Submission:	<u>12/30/2014</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Ibrutinib is extensively metabolized in the liver. Increased ibrutinib exposures (plasma concentrations) are expected to be seen in patients with hepatic impairment. A clinical trial evaluating ibrutinib in patients with varying levels of hepatic impairment is currently recruiting. The final study report may provide informative labeling recommendations including possible dose adjustments in patients with varying levels of hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Increased ibrutinib exposures are expected in patients with hepatic impairment. Increased ibrutinib exposure would likely result in increases in toxicities such as neutropenia, thrombocytopenia, diarrhea and infections. Results of the hepatic impairment trial will allow for informative labeling recommendations including possible dose adjustments in patients with varying levels of hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This trial is an open-label, single-dose, multi-center, non-randomized study to assess the pharmacokinetics of ibrutinib in volunteers who either have mild, moderate, or severe hepatic impairment or qualify for the control group (normal liver function).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013



The co-administration of ibrutinib with strong CYP3A4 inducers will result in reduced ibrutinib exposure. A large magnitude of exposure reduction could lead to a partial or complete loss of efficacy. A clinical drug-drug interaction study with strong CYP3A4 inducers will allow the identification of an efficacies dose of ibrutinib when co-administered with strong CYP3A inducers. Strong CYP3A4 inducers include some commonly used drugs such as carbamazepine, phenytoin and rifampin.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This completed trial was an open-label, single center, sequential trial to evaluate the potential effects of rifampin on the pharmacokinetics of ibrutinib in healthy volunteers

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK  
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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013

## PMR/PMC Development Template 2060-7

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

NDA# 205552  
Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

---

PMR Description: Objective Determine the effect of ibrutinib on the QT/QTc interval in healthy subjects 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.

---

PMR Schedule Milestones:

Preliminary Protocol Submission	03/2014
Final Protocol Submission:	06/2014
Study Completion:	06/2015
Final Report Submission:	12/2015

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Relapsed or refractory mantle cell lymphoma (MCL) is a life-threatening condition. The median overall survival for this population is less than two years. In clinical trial PCYC-1104-CA, the applicant reports an overall response rate of 68% with a median duration of response of 17.5 months.

Relapsed or refractory chronic lymphocytic leukemia (CLL) is a life-threatening condition. Although most patients who undergo chemotherapy for CLL achieve an initial response, disease relapse invariably occurs. In the single-arm clinical trial PCYC-1102-CA, the applicant reports a 77% overall response rate in 48 patients with relapsed or refractory CLL. The median duration of response had not been reached with a median follow-up of 16.4 months.

From the pharmacology-toxicology primary review, “Ibrutinib inhibited hERG channel currents with an IC50 value of approximately 1 μM and may be considered a low-potency blocker. In a single-dose safety pharmacology study in Beagle dogs, an oral ibrutinib dose up to 150 mg/kg did not induce QT interval prolongation; increases in the RR interval were observed. Dose-dependent RR interval prolongation and decreased heart rate was reported in dogs in the 13-week toxicology study during Weeks 1 and 12. The effect occurred at 1 hour post-dose. One of the major metabolites of PCI-32765, PCI-45227, inhibited hERG channel currents with an IC50 value of 9.6 μM, i.e. ten fold less potency for blocking the I<sub>Kr</sub> current compared to the parent drug. QTc prolongation was not reported in patients treated with ibrutinib.”

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal for this PMR is to determine the effect of ibrutinib on the QT/QTc interval in humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

**Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: CLINICAL TRIAL: Assess the effect of ibrutinib on the QT/QTc interval by conducting a "Thorough QT/QTc Study"

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013

## PMR/PMC Development Template 2060-PMC #8

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA# 205552  
Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

---

PMC Description: 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. Use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria.

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:

Study Completion:	<u>11/2014</u>
Final Report Submission:	<u>02/2015</u>

---

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Tween 20 dissolution method QCM-168 is superior over the currently proposed SLS dissolution method QCM-164. However, since limited GMP QC data are available for drug product tested using the Tween 20 method and virtually no GMP QC stability testing data have been obtained with the Tween 20 method, the FDA agreed to use method QCM-164 as interim dissolution method considering the status of breakthrough therapy. Therefore, additional Tween 20 GMP QC dissolution data are needed and should be collected for the drug product under this PMC.

2. Describe the particular review issue and the goal of the study. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The currently proposed dissolution method is as follows:

Apparatus: USP 2 (paddle). (b) (4)

Temperature: 37.0 ± 0.5 °C

Speed: 75 rpm

Volume: 900 mL

Medium: 0.3% SLS in Purified water

However, at low pH the positively charged ibrutinib interacts with the negatively charged capsule excipient SLS causing incomplete dissolution and a low recovery. To eliminate this interaction and to improve ibrutinib solubility in the aqueous dissolution medium, a Tween 20 surfactant concentration at 3.0% w/v in phosphate buffer pH 6.8 was selected and this medium would achieve a complete dissolution for ibrutinib capsules. Since limited GMP QC data are available for drug product tested using the Tween 20 method and no GMP QC stability testing data have been obtained with the Tween 20 method, the FDA agreed to use method QCM-164 as interim dissolution method considering the status of breakthrough therapy for this NDA.

Under this PMC, the collection of additional Tween 20 GMP QC dissolution data would result in a better dissolution methodology. At the end of this PMC, more appropriate acceptance criteria would be set to better control the quality of the drug product.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant will collect 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. These data will be used for the setting of the final dissolution acceptance criteria.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Dissolution studies

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK

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DIANE C HANNER  
11/12/2013

ROBERT C KANE  
11/12/2013

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>NDA</b>	205552
<b>Generic Name</b>	Ibrutinib
<b>Sponsor</b>	Pharmacyclics, Inc.
<b>Indication</b>	Treatment of patients with mantle cell lymphoma (MCL) [REDACTED] (b) (4)
<b>Dosage Form</b>	Capsule (140 mg)
<b>Drug Class</b>	Bruton's Tyrosine Kinase Inhibitor
<b>Therapeutic Dosing Regimen</b>	560 MCL [REDACTED] (b) (4)
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Not determined
<b>Submission Number and Date</b>	SDN 003 May 30, 2013
<b>Review Division</b>	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

For the objective of a dedicated QTc assessment following treatment with ibrutinib, we conclude that the current QTc study is inconclusive due to the following limitations in trial design:

- Baseline ECGs were not adequately collected. The Sponsor used screening ECGs that were collected at any time point up to two weeks before the drug was administered.
- Single on-treatment ECGs were collected in this study. Triplicate ECGs should be collected to reduce variability in QT measurements.

In a previous review (1/30/13), QT-IRT recommended that a thorough QT study be conducted for ibrutinib and the results be submitted as a post-marketing requirement. After reviewing the current study we reaffirm our previous recommendation.

#### 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

This study is inconclusive. QT-IRT will provide labeling language once the TQT study is reviewed.

## 2 BACKGROUND

The following information was extracted from the Meeting package

### 2.1 PRODUCT INFORMATION

PCI-32765 (JNJ-54179060) is a first-in-class, selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed for the treatment of B-cell malignancies.

### 2.2 MARKET APPROVAL STATUS

Ibrutinib is not approved for marketing in any country.

### 2.3 PRECLINICAL INFORMATION

The IC<sub>50</sub> for inhibitory effect by ibrutinib on hERG channel current was 970 nM (427 ng/mL). The IC<sub>50</sub> for inhibitory effect by the major metabolite PCI-45227 on hERG channel current was 9,600 nM (4229 ng/mL).

In 4 male telemetry-monitored dogs administered with single oral doses of 0 (vehicle), 1.5, 24, and 150 mg/kg of ibrutinib, no QRS effects or QTc prolongation were observed.

Significant shortening of the QTC interval was observed from 1 to 6 hours postdose overall with a peak effect noted at 3 hours postdose (14 msec shorter) after administration of the 150 mg/kg dose. Based on toxicokinetic data obtained from dogs after the first dose in a companion 4-week toxicity study, mean C<sub>max</sub> values for total ibrutinib plasma levels are estimated to range from 745 to 949 ng/mL for the 24 and 150 mg/kg dose range in dogs. These estimated mean exposures are 4.1 to 5.3 times the mean C<sub>max</sub> (180 ng/mL) in patients receiving ibrutinib at a dose of 560 mg per day.

*Reviewer's comments: Ibrutinib blocks hERG current with high affinity. Based on in vivo data there is a potential for Ibrutinib to shorten QT.*

### 2.4 PREVIOUS CLINICAL EXPERIENCE

Cardiovascular safety data is available as of 06 April 2012 for 408 subjects treated with ibrutinib in 8 clinical studies. The cardiovascular safety of ibrutinib was evaluated by monitoring of adverse events in all studies; in addition, formal ECG monitoring was performed in 2 single-arm, uncontrolled studies (PCYC-04753 [n = 45] and PCYC-1102-CA [n = 67]). To date there is no evidence of ECG morphological changes or prolongation of QTc interval in patients treated with ibrutinib. The most common cardiovascular adverse events reported in the 408 subjects were atrial fibrillation (n=17), tachycardia (n=7), sinus tachycardia (n=4) and sinus bradycardia (n=3). Events of Grade 3 or greater severity included only atrial fibrillation (n=6), supraventricular tachycardia (n=2) and tachycardia (n=1). These findings are consistent with expectations in the elderly population, many of whom have known cardiovascular disease at baseline.

*Reviewer's comments: No seizures, sudden cardiac death or ventricular arrhythmias were reported. Atrial fibrillation was reported (4%), grade ≥3 in 1.5% of the total number of cases.*

## **2.5 CLINICAL PHARMACOLOGY**

Appendix 5.1 summarizes the key features of ibrutinib's clinical pharmacology.

## **3 SPONSOR'S SUBMISSION**

### **3.1 OVERVIEW**

The QT-IRT reviewed a protocol synopsis for a TQT study (PCI-32765CLL1007) on two occasions (8/28/12 and 1/30/13). Based on summary results from study PCYC-1102-CA we advised that the TQT study could be submitted as a post-marketing requirement and that routine on-treatment ECGs be collected in the registration trial(s). The sponsor submitted the study report for Protocol PCYC-1102-CA, including electronic datasets and waveforms to the ECG warehouse. This protocol was not reviewed by QT-IRT. Nevertheless, the Division requested that QT-IRT thoroughly review the ECG results of this study.

### **3.2 TQT STUDY**

#### **3.2.1 Title**

A Phase 1b/2 Fixed-dose Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia

#### **3.2.2 Protocol Number**

PCYC-1102-CA

#### **3.2.3 Study Dates**

Study Initiated: May 20, 2010

Study Completed: December 18, 2012

#### **3.2.4 Objectives**

- To determine the safety of a fixed-dose daily regimen of ibrutinib at 2 dose levels (420 mg and 840 mg) in subjects with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
- To assess the preliminary efficacy, pharmacokinetics (including the effects of the fed-versus-fasted state), pharmacodynamics, and long-term safety of ibrutinib

#### **3.2.5 Study Description**

##### **3.2.5.1 Design**

This was an open-label, nonrandomized, multicenter, Phase 1b/2 study of ibrutinib in subjects with treatment-naïve or relapsed/refractory CLL/SLL conducted in the United States. Cohorts were defined by the disease population (treatment-naïve or relapsed/refractory) and by the ibrutinib dose level (420 mg or 840 mg). Subjects received study treatment once daily until disease progression, unacceptable drug-related toxicity, or other reason for treatment discontinuation. After a minimum of 12 cycles of

treatment or at the closure of this study, in the absence of disease progression, subjects could continue treatment in a long-term extension study PCYC-1103-CA (Study 1103). Subjects enrolled in Cohort 6 participated in a randomized crossover substudy to assess the effects of the fed-versus-fasted state on the pharmacokinetics of ibrutinib in conjunction with Days 8 and 15 administration of study drug. These subjects received 6 cycles on Study 1102 and were then transferred into Study 1103.

### 3.2.5.2 Controls

Neither placebo nor positive (moxifloxacin) controls were used in the study.

### 3.2.5.3 Blinding

This was an open label study.

## 3.2.6 Treatment Regimen

### 3.2.6.1 Treatment Arms

Group	Population	PCI-32765 Once Daily Dose (mg)	All Treated Population	QT/QTc Analysis Set
1	Relapsed/refractory	420	27	24
2	Treatment-naïve (elderly)	420	27	23
3	Relapsed/refractory	840	34	34
4	High-risk relapsed/refractory	420	24	22
5	Treatment-naïve (elderly) <sup>a</sup>	840	4	5 <sup>b</sup>
6	Relapsed/refractory (food effect cohort)	420	16	16

<sup>a</sup> Cohort closed prior to full accrual.

<sup>b</sup> ECG population is based on dose assignment. Patient 217-501 was assigned to Treatment Group 5, 840mg dose, but received 420 mg dose throughout treatment.

### 3.2.6.2 Sponsor's Justification for Doses

The present study was initiated to test the utility of fixed continuous dosing (ie, not weight-based and without a 7-day rest period). The starting dose of 420 mg was based on pharmacodynamic results from Study PCYC-04753 which indicated that, at equivalent weight-based doses (8.3 mg/kg/day or less), over 90% of the BTK active site was occupied by drug. A fixed dose of 420 mg/day was therefore expected to exceed the minimum area under the curve (AUC) required for saturation of the active binding site. \ This dose also displayed an acceptable safety profile and was showing promising clinical activity. Daily dosing was deemed desirable as it is a common regimen for other kinase inhibitors.

Reviewer's Comment: Acceptable.

(b) (4)

### 3.2.6.3 Instructions with Regard to Meals

For cohorts 1 through 5, the ibrutinib dose was to be taken at least 2 hours after the previous meal and at least 30 minutes before the next meal. Patients enrolled in Cohort 6 were randomized on Days 8 and 15 of Cycle 1 to be given the 420 mg dose either on an empty stomach or after a high-calorie high-fat breakfast. Serial blood sampling was conducted over 24 hours post-dose.

*Reviewer's Comment: The Sponsor included a cohort to investigate the effect of food. A high-fat meal doubled  $C_{max}$ . To study the worst case clinical scenario, ibrutinib should be administered with food. In this study there were 16 patients who received an ibrutinib dose with a high-fat meal.*

### 3.2.6.4 ECG and PK Assessments

Serial blood samples for analysis of drug levels were drawn from all subjects during Cycle 1 as follows:

- Day 1 predose and at 0.5, 1, 2, 4, 6, and 24 hours postdose (prior to Day 2 dose)
- Day 8 predose and at 0.5, 1, 2, 4, and 6 hours postdose
- Days 15, 22, and 28 predose and 2 hours postdose

For the food effect substudy (see Section 3.6), subjects in Cohort 6 were randomized to receive 420 mg ibrutinib either on an empty stomach or after a high-calorie high-fat breakfast served in the clinic prior to dosing (after both groups fasted overnight) on Day 8 of Cycle 1, and then crossing over to the alternate food regimen on Day 15. Serial blood sampling for pharmacokinetics was conducted predose and at 0.5, 1, 2, 4, 6, and 24 hours postdose.

ECG:

Study Segment	Day	ECG Acquisition Time
Screening	-14 to -1	Triplicate at least 1 min apart
Cycle 1	1-2	Pre-dose, and 1, 2, 4, 6, and 24 hours (before Day 2 dose) after 1st dose. Window for ECGs at 1, 2, 4, and 6 hours was $\pm 10$ min. The 24-hour ECG had to be pre-dose on Day 2.
Cycle 1	8	Pre-dose, and 1, 2, 4, and 6 hour after 8th dose. Window for ECGs at 1, 2, 4, and 6 hour was $\pm 10$ min.
Cycle 1	15, 22, 28	Single ECG 2 hour ( $\pm 30$ min) post-dose
Cycle 3, 6, 12, 18, and 24	28	Single ECG anytime during the visit
30-day follow-up	n/a	Single ECG anytime during the visit

*Reviewer's Comment: The timing of ECGs is adequate to capture potential effects at  $C_{max}$  and at steady-state.*

### 3.2.6.5 Baseline

Baseline ECGs at screening were used.

### **3.2.7 ECG Collection**

A central cardiac safety monitoring facility [REDACTED]<sup>(b) (4)</sup> was used in this study for ECG readings. Standard 12-lead ECGs were collected using Global Instrumentations M12R Digital recorders that were provided to the study centers with appropriate training. ECGs were transmitted electronically to the central ECG laboratory.

Baseline ECGs were collected in triplicates, only single ECG were collected post-treatment.

### **3.2.8 Sponsor's Results**

#### **3.2.8.1 Study Subjects**

One hundred seventeen subjects were enrolled into Cohorts 1 through 5, of whom 116 were treated. The enrollment breakdown by cohort is shown in Table 3. Subject 217-501, who was enrolled into Cohort 5 to receive 840 mg/day ibrutinib, was treated with 420 mg/day at the investigator's discretion due to potential safety concerns, and was therefore analyzed in Cohort 2. 78 subjects received 420 mg/day ibrutinib and 38 received 840 mg/day.

**Table 1: Subject Demography**  
(All Treated Population)

	<b>Treatment-naïve (N = 31)</b>	<b>Relapsed/ Refractory (N = 85)</b>	<b>Total (N = 116)</b>
Age (years)			
Mean (SD)	72.4 (4.7)	63.7 (10.5)	66.0 (10.0)
Median	71.0	66.0	68.0
Range	65, 84	37, 82	37, 84
≥ 65 years, n (%)	31 (100.0)	43 (50.6)	74 (63.8)
≥ 70 years, n (%)	23 (74.2)	30 (35.3)	53 (45.7)
Sex, n (%)			
Male	19 (61.3)	65 (76.5)	84 (72.4)
Female	12 (38.7)	20 (23.5)	32 (27.6)
Race, n (%)			
White	28 (90.3)	81 (95.3)	109 (94.0)
Black	0 (0.0)	4 (4.7)	4 (3.4)
Other	3 (9.7)	0 (0.0)	3 (2.6)

Cross-reference: Attachment 1 [Table A.1.3](#)

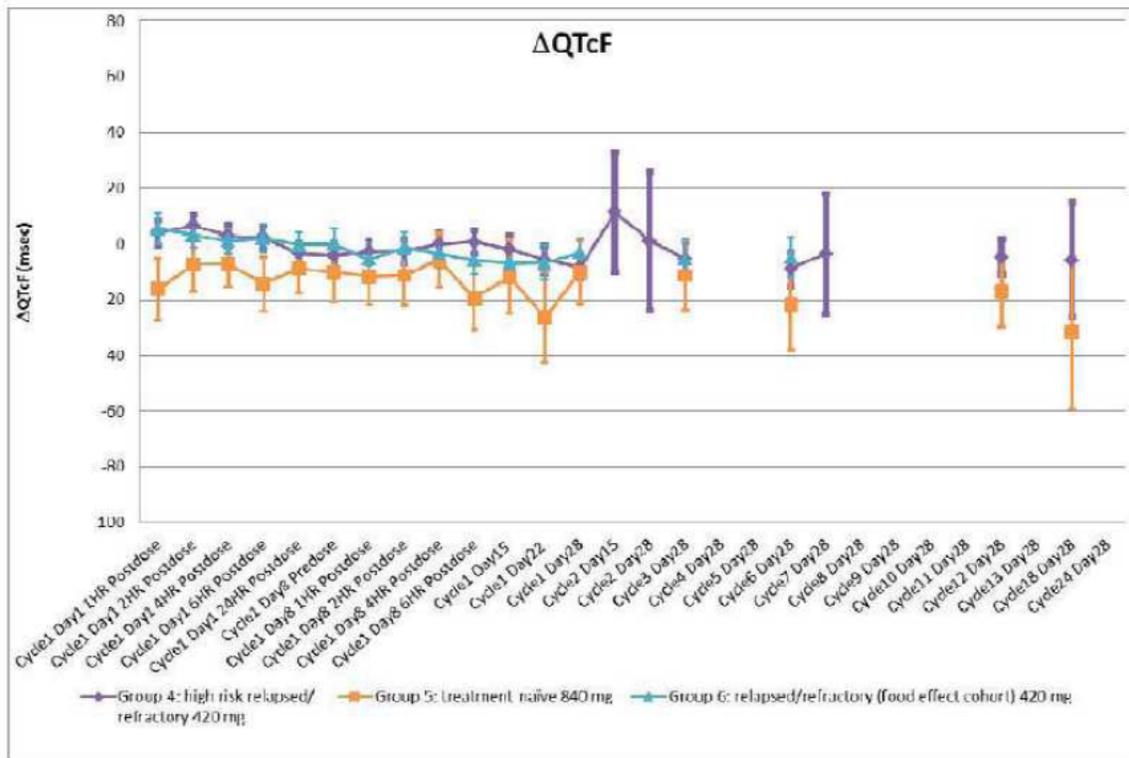
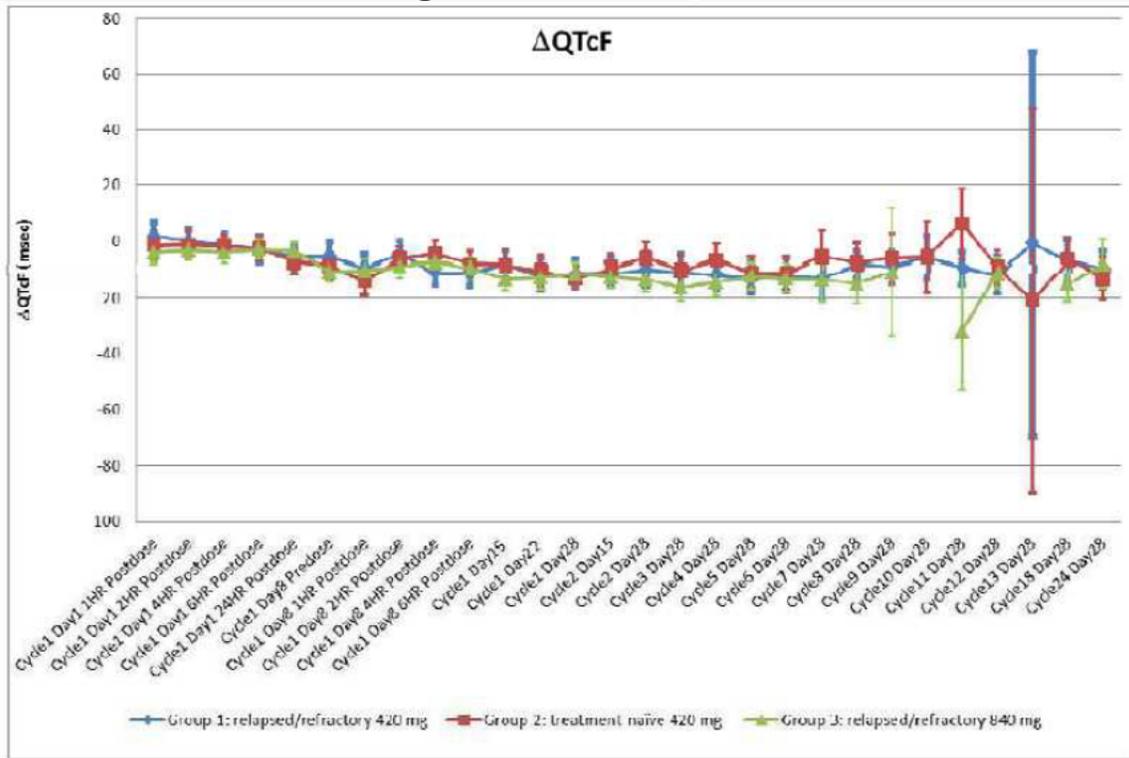
Source: CSR, Table 5.

### 3.2.8.2 Statistical Analyses

#### 3.2.8.2.1 Primary Analysis

Subjects in Treatment Group 1 (relapsed/refractory 420 mg), Treatment Group 2 (treatment naïve 420 mg), and Treatment Group 3 (relapsed refractory 840 mg) showed statistically significant decrease in QTcF duration ranging on average from 5 msec to 13 msec in comparison to baseline for most of the cycles. This decrease is not considered a clinical concern. In Treatment Group 4 (high risk relapsed/refractory 420 mg) and in Treatment Group 6 (relapsed refractory food effect cohort 420 mg), QTcF did not change significantly in comparison to baseline. Treatment Group 5 (treatment naïve 840 mg) included only a few subjects showing a decrease in QTcF. When assessing mean change in QTcF in Treatment Group 1 (relapsed/ refractory 420 mg) vs. Treatment Group 3 (relapsed/refractory 840 mg) there was no indication of dose-dependency of decreasing QTcF between these two doses (as seen in the top panel in Figure 4).

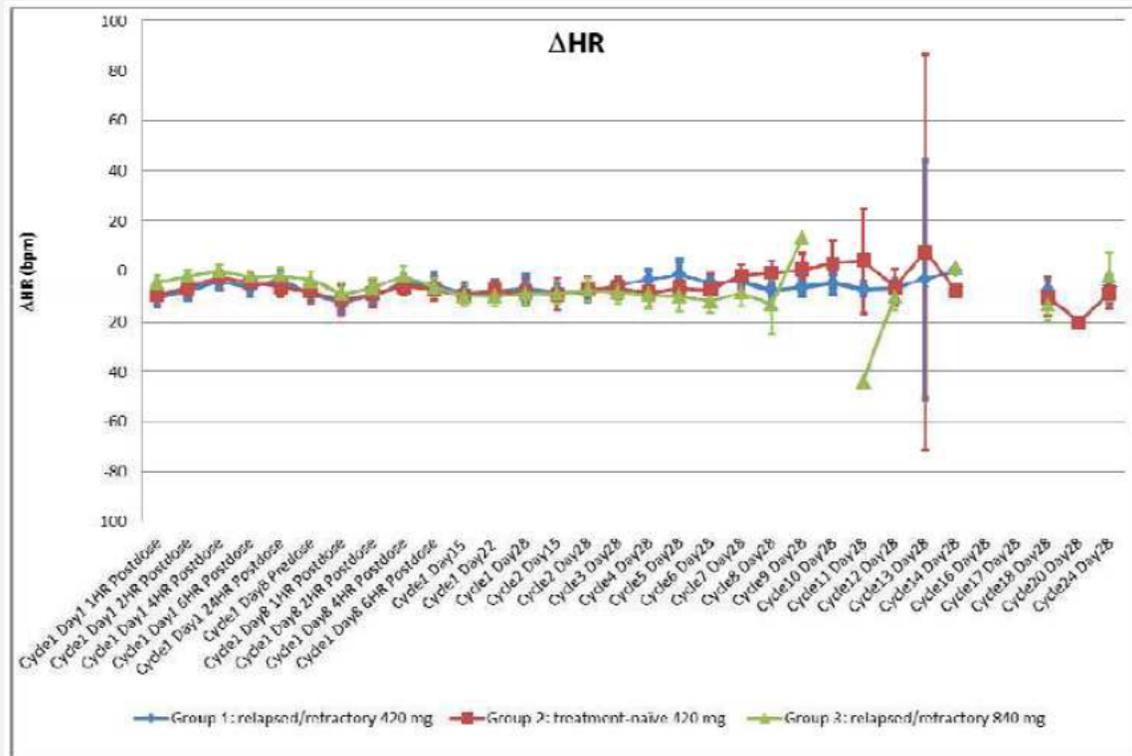
**Figure 1: Profile of  $\Delta$ QTcF**

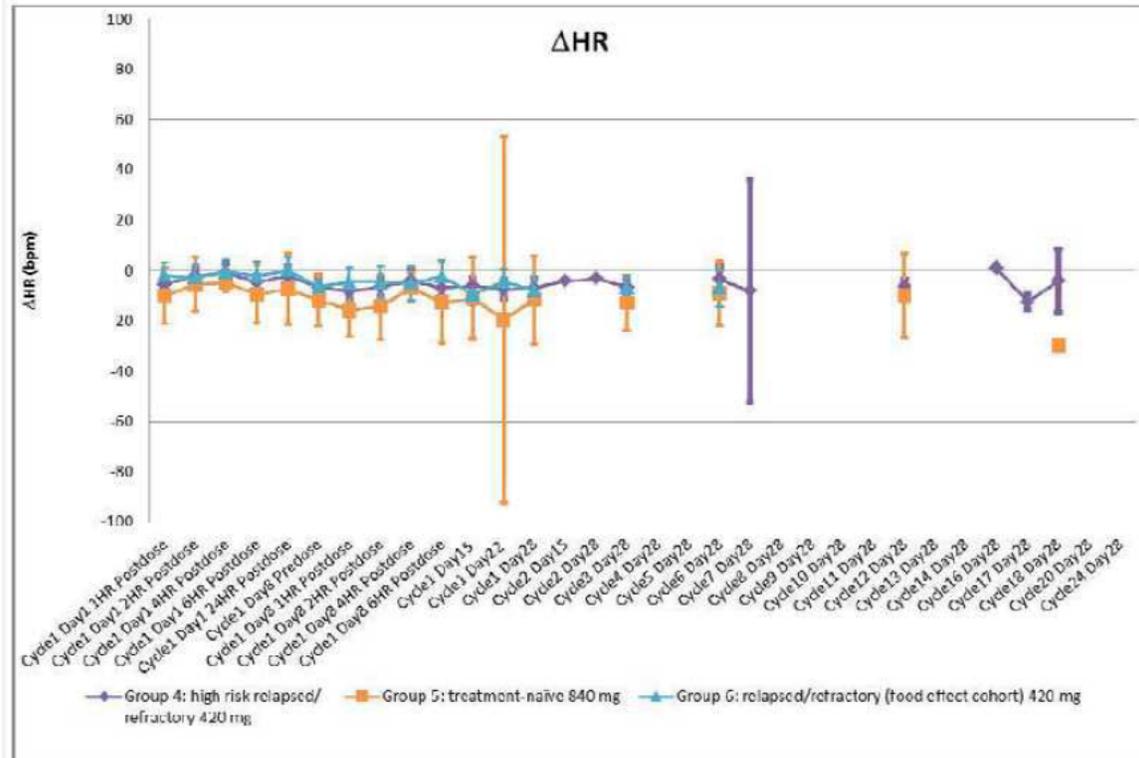


Source: CSR Figure 4

Subjects in Treatment Group 1 (relapsed/refractory 420 mg), Treatment Group 2 (treatment naïve 420 mg), Treatment Group 3 (relapsed refractory 840 mg), and Treatment Group 4 (high risk relapsed/refractory 420 mg) showed statistically significant decrease in mean heart rate ranging on average from 2 to 13 beats per minute in comparison to baseline for most of the cycles. When assessing mean change in heart rate for respective timepoints for Treatment Group 1 (relapsed/refractory 420 mg) vs. Treatment Group 3 (relapsed/refractory 840 mg) there was no indication of dose-dependency of decrease in heart rate between these two doses (as it could be seen in the top panel of *Figure 1*). In Treatment Group 6 (relapsed refractory food effect cohort 420 mg), there was less evidence for heart rate decrease with only few timepoints reaching significance. Treatment Group 5 (treatment naïve 840 mg) included only a few subjects, but non-significant trends and few significant changes were observed pointing in the same direction of heart rate decrease by 5 to 15 beats per minute.

**Figure 2: Profile of  $\Delta$ HR**

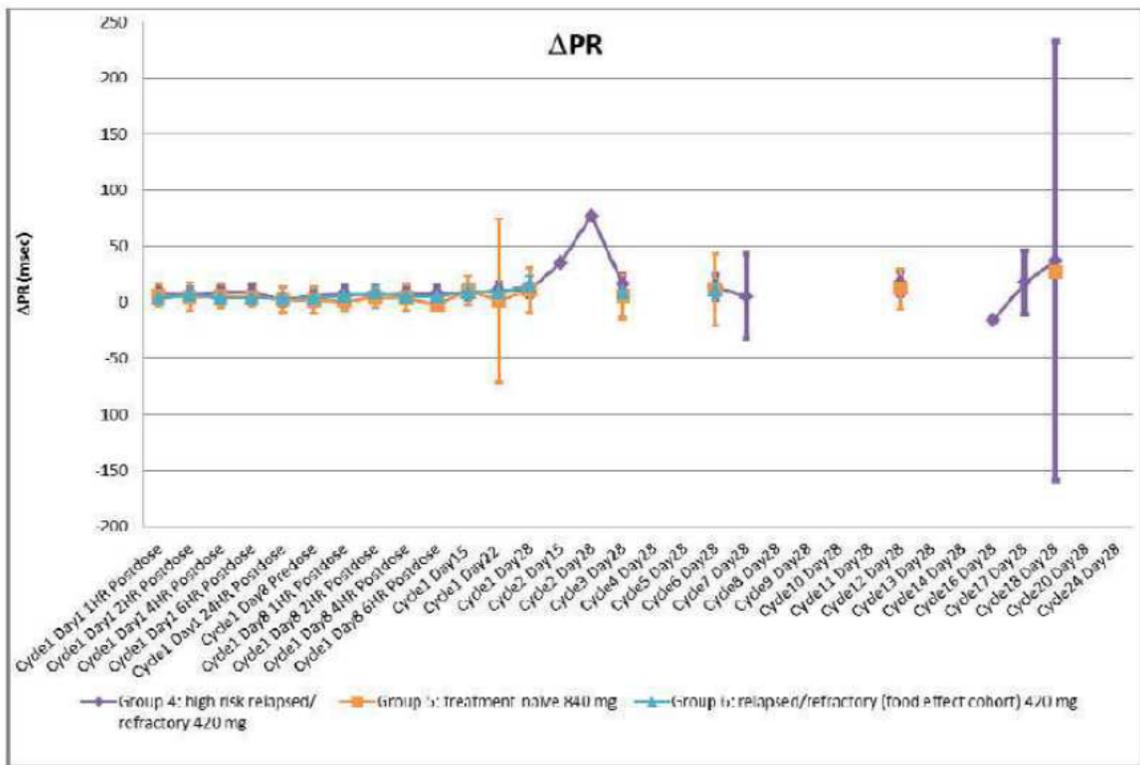
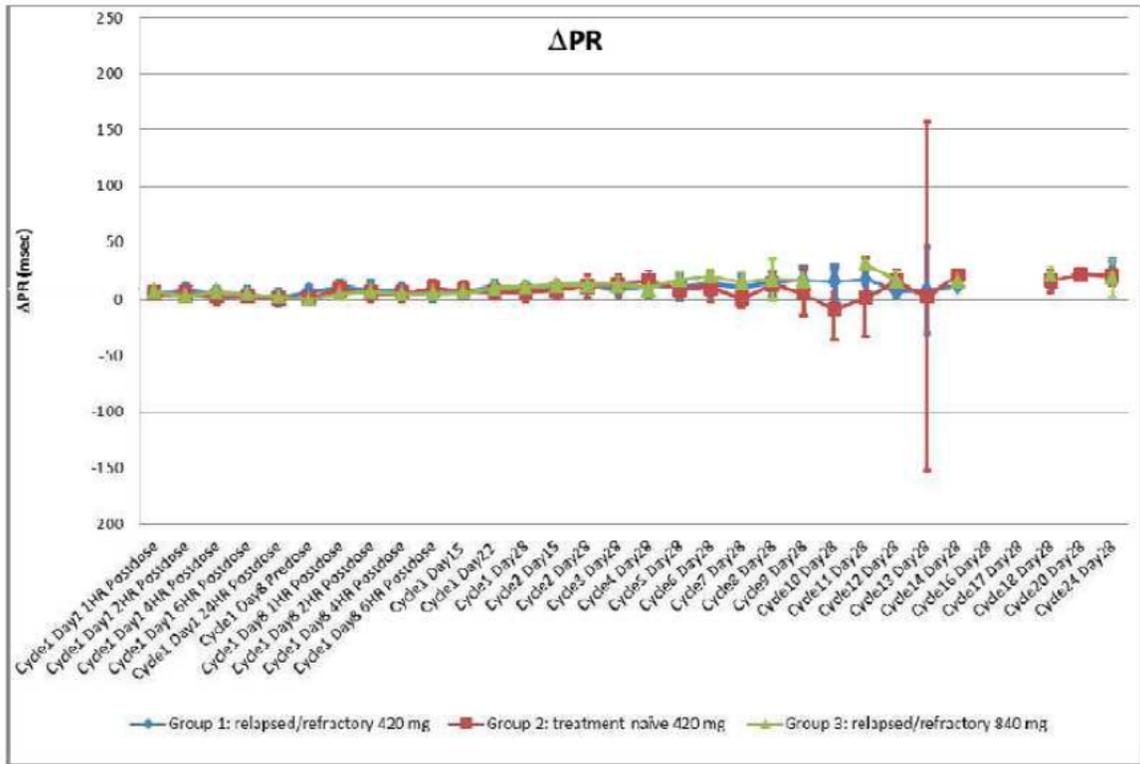




Source: CSR Figure 1

Subjects in Treatment Group 1 (relapsed/refractory 420 mg), Treatment Group 2 (treatment naïve 420 mg), Treatment Group 3 (relapsed refractory 840 mg), and Treatment Group 4 (high risk relapsed/refractory 420 mg) showed statistically significant increase in mean PR interval ranging on average from 5 msec to 20 msec in comparison to baseline for most of the cycles. When assessing mean change in PR interval in Treatment Group 1 (relapsed/refractory 420 mg) vs. Treatment Group 3 (relapsed/refractory 840 mg) there was no indication of dose-dependency of increasing PR interval between these two doses (as it could be seen in the top panel in [Figure 2](#)). In Treatment Group 6 (relapsed refractory food effect cohort 420 mg), there was less evidence for PR interval prolongation with only few timepoints reaching significance. Treatment Group 5 (treatment naïve 840 mg) included only a few subjects and changes in PR interval were not significant in this group.

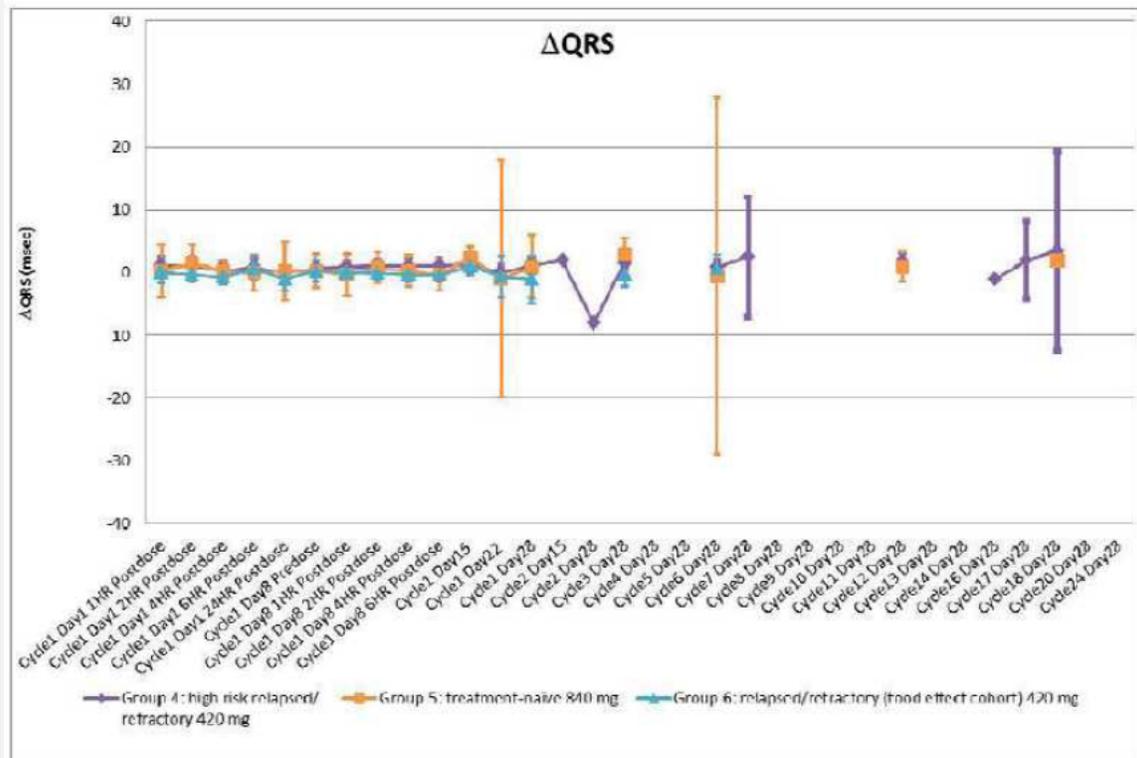
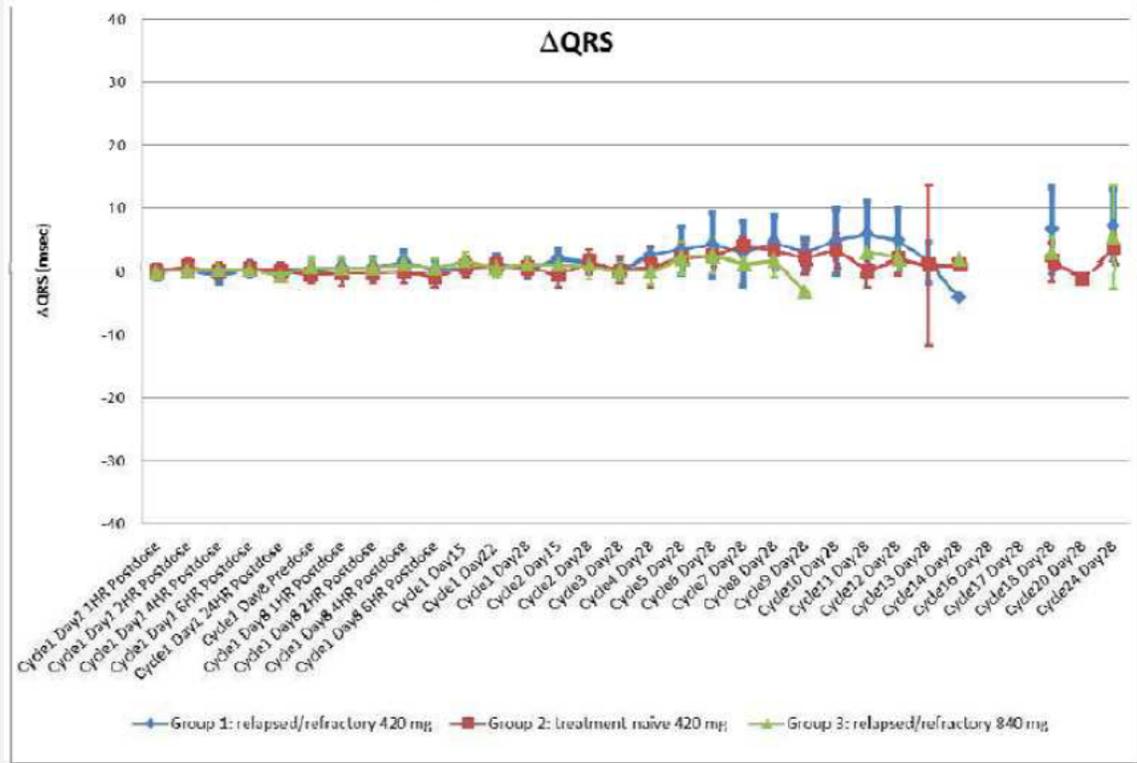
**Figure 3: Profile of  $\Delta$ PR**



Source: CSR Figure 2

Figure 3 demonstrates that tested treatment did not have a meaningful effect on QRS duration regardless of treatment group. (Table III in the Appendix A provides details regarding statistical significance for each timepoint.) Although there were some findings of significant QRS prolongation by up to 5 msec - 7 msec, there was no consistency of the findings across cycles and across Treatment Groups.

**Figure 4: Profile of  $\Delta$ QRS**



Source: CSR Figure 3

### 3.2.8.2.2 Categorical Analysis

Table 9 describes the frequency of outliers regarding QTcF prolongation as per the pre-specified protocol. No QTcF values exceeding 480 msec existed in the studied individuals and only 11 (9%) subjects had QTcF increases by > 30 msec and none by > 60 msec across all Treatment Groups.

Classically, normal PR interval should not exceed 200 msec; nevertheless, it is known that upper limit of normal values can be up to 240 msec in elderly individuals. Importantly, very few occurrences of PR interval > 200 msec (Table 8) and no occurrences of PR interval > 240 msec were observed.

**Table 2: Incidence of PR Interval > 200 msec**

Cycle	Day	Time	Total N	PR Interval > 200 msec N (%)	Total N	PR Interval > 200 msec N (%)	Total N	PR Interval > 200 msec N (%)	Total N	PR Interval > 200 msec N (%)	Total N	PR Interval > 200 msec N (%)	Total N	PR Interval > 200 msec N (%)	
			Group 1		Group 2		Group 3		Group 4		Group 5		Group 6		
1	1	1	20	0	20	2 (10%)	33	2 (6%)	22	4 (18%)	4	0	14	0	
		2	20	0	19	2 (11%)	30	1 (3%)	22	3 (14%)	4	0	15	0	
		4	20	0	22	NA	32	1 (3%)	20	3 (15%)	4	0	15	0	
		6	20	0	19	2 (11%)	32	1 (3%)	21	5 (24%)	4	0	14	0	
		24	22	0	19	1 (5%)	32	1 (3%)	20	3 (15%)	4	0	15	0	
	8	0	18	0	23	1 (4%)	31	1 (3%)	20	3 (15%)	4	0	14	0	
		1	19	1 (5%)	18	0	31	1 (3%)	22	3 (14%)	4	0	14	0	
		2	20	1 (5%)	23	2 (9%)	31	1 (3%)	22	3 (14%)	4	0	14	1 (7%)	
		4	20	0	21	3 (14%)	31	1 (3%)	22	3 (14%)	4	0	13	0	
		6	17	0	19	2 (11%)	30	1 (3%)	21	2 (10%)	3	0	13	0	
		15	N/A	21	0	18	2 (11%)	31	1 (3%)	21	3 (14%)	3	0	13	0
		22	N/A	19	0	20	1 (5%)	30	2 (7%)	20	3 (15%)	2	0	12	0
		28	N/A	18	0	22	2 (9%)	31	2 (6%)	19	3 (16%)	3	0	13	1 (8%)
	2	15	N/A	20	0	19	3 (16%)	32	1 (3%)	1	0				
28		N/A	19	0	21	3 (14%)	30	2 (7%)	1	1 (100%)					
3	28	N/A	16	0	22	3 (14%)	29	2 (7%)	17	2 (12%)	3	0	12	0	
4	28	N/A	19	2 (11%)	19	3 (16%)	23	1 (4%)							
5	28	N/A	19	1 (5%)	16	3 (19%)	22	2 (9%)							
6	28	N/A	16	1 (6%)	17	3 (18%)	24	1 (4%)	13	2 (15%)	2	0	9	0	
7	28	N/A	16	1 (6%)	12	0	15	2 (13%)	2	0					
8	28	N/A	18	1 (6%)	9	1 (11%)	9	1 (11%)							
9	28	N/A	15	2 (13%)	7	2 (29%)	1	0							
10	28	N/A	14	1 (7%)	5	0									
11	28	N/A	14	2 (14%)	3	0	1	0							

Source: CSR table 8

The incidence of classical definition of bradycardia (< 60 beats per minute; data not shown) and clinically significant bradycardia (< 50 beats per minute; data shown in Table 7) was very low in all Treatment Groups.

**Table 3: Incidence of HR < 50 bpm**

Cycle	Day	Time	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	
			Group 1		Group 2		Group 3		Group 4		Group 5		Group 6		
1	1	1	20	0	20	2 (10%)	33	0	22	2 (9%)	4	0	15	0	
		2	20	0	19	3 (16%)	30	0	22	1 (5%)	4	0	16	0	
		4	20	0	22	1 (5%)	32	0	20	1 (5%)	5	0	16	0	
		6	20	0	19	1 (5%)	32	0	21	2 (10%)	4	0	15	0	
		24	22	1 (5%)	19	1 (5%)	32	0	20	1 (5%)	4	0	16	0	
	8	0	18	2 (11%)	23	2 (9%)	31	0	20	2 (10%)	4	0	15	0	
		1	19	2 (11%)	18	2 (11%)	31	0	22	2 (9%)	4	0	16	0	
		2	20	1 (5%)	23	2 (9%)	31	0	22	2 (9%)	4	0	16	0	
		4	20	0	21	0	31	0	22	1 (5%)	4	0	15	0	
		6	17	1 (6%)	19	0	30	0	21	0	3	0	15	0	
	15	N/A	21	0	18	2 (9%)	31	0	21	1 (5%)	3	0	15	0	
	22	N/A	19	0	20	1 (5%)	30	0	20	2 (10%)	2	0	14	0	
	28	N/A	19	0	22	2 (9%)	31	0	19	2 (10%)	3	0	14	0	
	2	15	N/A	20	1 (5%)	19	3 (16%)	32	0	1	0				
		28	N/A	19	1 (5%)	21	3 (14%)	30	0	1	0				
3	28	N/A	16	0	22	3 (14%)	29	0	17	2 (12%)	4	0	13	0	
4	28	N/A	19	0	19	2 (10%)	23	1 (4%)							
5	28	N/A	19	0	16	1 (6%)	22	0							
6	28	N/A	16	0	17	2 (12%)	24	0	14	0	2	0	11	0	
7	28	N/A	16	1 (6%)	12	0	15	0	2	1 (50%)					
8	28	N/A	18	1 (6%)	9	1 (11%)	9	1 (11%)							
9	28	N/A	15	0	7	0	1	0							
10	28	N/A	14	0	5	0									
11	28	N/A	14	0	3	0	1	0							
12	28	N/A	15	0	19	1 (5%)	23	1 (4%)	15	1 (7%)	4	0			
Cycle	Day	Time	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	Total N	HR < 50 bpm N (%)	
			Group 1		Group 2		Group 3		Group 4		Group 5		Group 6		
13	28	N/A	2	0	2	0									
14	28	N/A	1	0	1	0	1	0							
16	28	N/A							1	0					
17	28	N/A							2	0					
18	28	N/A	12	1 (8%)	14	2 (14%)	20	2 (10%)	2	0	1	0			
20	28	N/A			1	0									
24	28	N/A	14	2 (14%)	11	1 (9%)	8	1 (13%)							
Total			24	4 (17%)	23	6 (26%)	34	4 (12%)	22	3 (14%)	5	0	16	0	

Source: CSR table 7

### 3.2.8.3 Safety Analysis

Grade 3 and higher events that were considered related to ibrutinib occurred in 25.0% of all treated subjects. The most common events in relapsed/refractory subjects were neutropenia, diarrhea, fatigue, and thrombocytopenia; diarrhea was the most common in treatment-naïve subjects (Table 4).

**Table 4: Adverse Events of a Severity of Grade 3 and Higher and Related to Ibrutinib in More than 2% of Subjects in Descending Order of Incidence (All Treated Population)**

Preferred Term	Treatment-naïve (N = 31)	Relapsed/ Refractory (N = 85)	Total (N = 116)
Neutropenia	0 (0.0)	9 (10.6)	9 (7.8%)
Diarrhea	3 (9.7)	1 (1.2)	4 (3.4%)
Fatigue	1 (3.2%)	3 (3.5)	4 (3.4%)
Thrombocytopenia	0 (0.0)	4 (4.7)	4 (3.4%)
Asthenia	0 (0.0)	3 (3.5)	3 (2.6%)
Pneumonia	0 (0.0)	3 (3.5)	3 (2.6%)

Cross-reference: Attachment 3 [Table A.3.1.3.4](#)

Source: CSR, Table 33

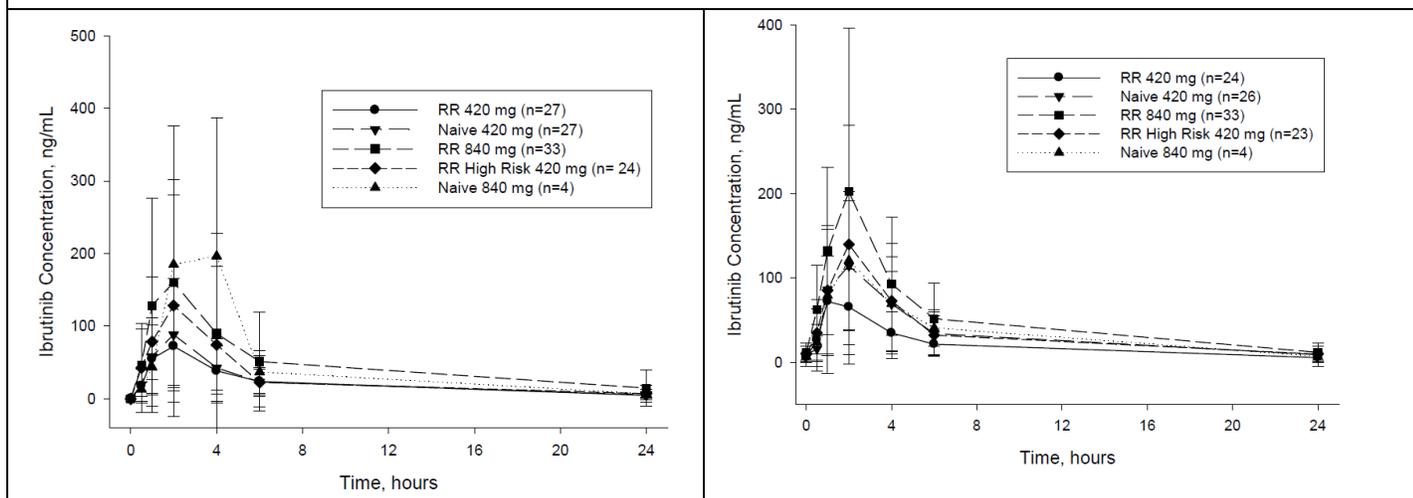
No dose reduction, discontinuation or death was due to cardiovascular events.

### 3.2.8.4 Clinical Pharmacology

#### 3.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented for ibrutinib in Table 5 (Day 1) and Table 6 (Day 8). PK results for the metabolite PCI-45227 are presented in Table 7 (Day 1) and Table 8 (Day 8). Concentration-time profiles are illustrated in Figure 5 and Figure 6 for ibrutinib and PCI-45227, respectively. Ibrutinib  $C_{max}$  increased approximately proportional with increasing dose from 420 mg to 840 mg.

**Figure 5: Mean (SD) Plasma Ibrutinib Concentration-Time Profiles on Day 1 (left) and Day 8 (right) Following Oral Administration of Ibrutinib**



Source: Pharmacokinetics Report, Figure 1 and 2, Pages 8 and 9.

**Table 5: Summary of Ibrutinib Pharmacokinetic Parameters on Day 1**

Cohort	Dose Level		C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>0-24</sub> (ng · hr/mL)	t <sub>1/2, term</sub> (hr)
1 (R/R)	420 mg	n	27	27	27	15
		Mean (SD)	84.9 (64.4)	1.75 (0.83)	520 (516)	6.57 (2.68)
		% CV	75.9	47.6	99.2	40.8
		Geometric mean	64.3	1.57	385	6.04
4 (HR)	420 mg	n	23	23	23	9
		Mean (SD)	168 (195)	2.75 (4.72)	701 (567)	4.83 (1.25)
		% CV	116	171	81.0	25.9
		Geometric mean	101	1.73	523	4.69
1 + 4	420 mg	n	50	50	50	24
		Mean (SD)	123 (145)	2.21 (3.26)	603 (542)	5.92 (2.38)
		% CV	118	147	89.9	40.2
		Geometric mean	79.2	1.64	443	5.5
2 (TN)	420 mg	n	27	27	25	11
		Mean (SD)	95.6 (74.4)	1.81 (0.84)	528 (359)	5.98 (2.14)
		% CV	77.8	46.5	68.0	35.9
		Geometric mean	68.4	1.61	401	5.64
3 (R/R)	840 mg	n	33	33	32	13
		Mean (SD)	208 (166)	1.97 (1.01)	1184 (1056)	6.27 (2.61)
		% CV	79.6	51.4	89.2	41.6
		Geometric mean	148	1.74	864	5.74
5 (TN)	840 mg	n	4	4	4	2
		Mean (SD)	299 (190)	2.51 (1.00)	1126 (485)	4.13 (0.58)
		% CV	63.4	39.7	43.1	14.0
		Geometric mean	249	2.39	1054	4.11

Abbreviations: R/R = relapsed/refractory; HR = relapsed/refractory high-risk; TN = treatment-naïve

Source: *Clinical Study Report, Table 11 Page 47.*

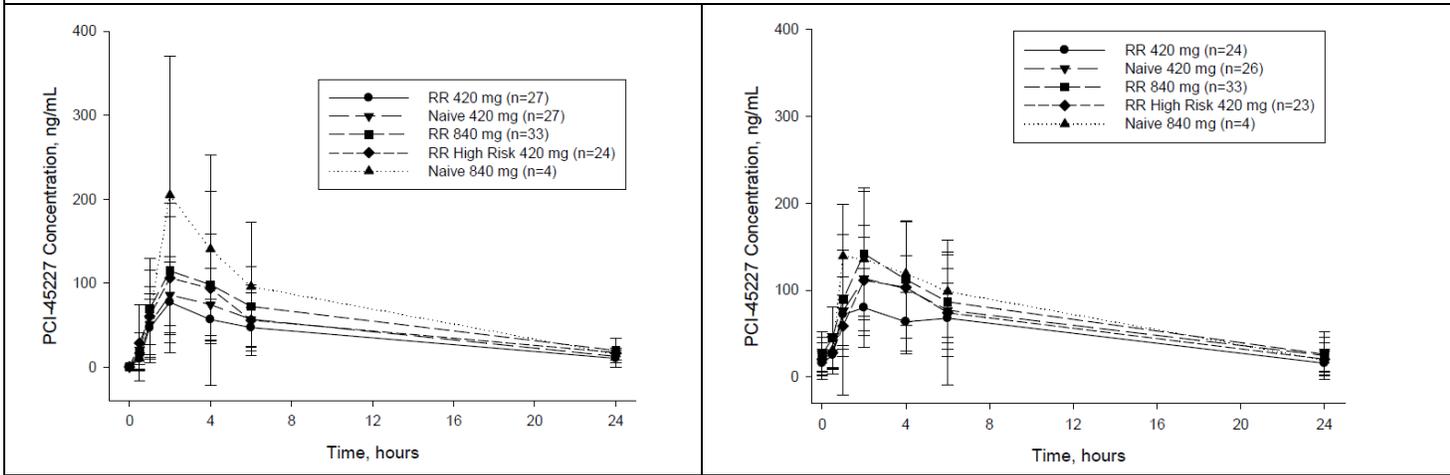
**Table 6: Summary of Ibrutinib Pharmacokinetic Parameters on Day 8**

Cohort	Dose Level		C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>0-24</sub> (ng · hr/mL)	t <sub>1/2, term</sub> (hr)	Accumulation Ratio AUC <sub>0-24</sub>
1 (R/R)	420 mg	n	24	24	22	14	22
		Mean (SD)	93.2 (81.1)	1.81 (1.33)	463 (280)	7.72 (3.65)	1.33 (0.63)
		% CV	87.0	73.2	60.4	47.3	47.6
		Geometric mean	69.1	1.53	388	6.83	1.19
4 (HR)	420 mg	n	23	23	23	11	22
		Mean (SD)	173 (157)	1.87 (0.91)	888 (606)	7.74 (4.27)	1.77 (1.49)
		% CV	90.7	48.6	68.2	55.1	84.4
		Geometric mean	120	1.67	711	6.89	1.35
1 + 4	420 mg	n	47	47	45	25	44
		Mean (SD)	132 (129)	1.84 (1.13)	680 (517)	7.28 (3.85)	1.55 (1.16)
		% CV	97.6	61.4	76.0	52.9	74.5
		Geometric mean	90.5	1.60	529	7.03	1.27
2 (TN)	420 mg	n	26	26	26	14	24
		Mean (SD)	146 (96.4)	1.82 (0.98)	823 (525)	6.16 (1.9)	1.70 (0.78)
		% CV	66.3	53.6	63.8	30.9	45.9
		Geometric mean	115	1.60	656	5.91	1.55
3 (R/R)	840 mg	n	32	32	32	22	31
		Mean (SD)	221 (193)	1.63 (0.70)	1246 (921)	7.4 (2.68)	1.17 (0.62)
		% CV	87.2	42.9	73.9	36.2	52.9
		Geometric mean	164	1.48	956	6.91	1.03
5 (TN)	840 mg	n	4	4	4	3	4
		Mean (SD)	122 (81.8)	1.52 (0.61)	853 (406)	7.42 (3.7)	0.829 (0.448)
		% CV	66.9	40.2	47.5	49.9	54.0
		Geometric mean	104	1.43	762	6.88	0.723

Abbreviations: R/R = relapsed/refractory; HR = relapsed/refractory high-risk; TN = treatment-naïve

Source: *Clinical Study Report, Table 12 Page 48.*

**Figure 6: Mean (SD) Plasma PCI-45227 Concentration-Time Profiles on Day 1 (left) and Day 8 (right) Following Oral Administration of Ibrutinib**



Source: Pharmacokinetics Report, Figure 7 and 8, Pages 15 and 16.

**Table 7: Summary of PCI-45227 Pharmacokinetic Parameters on Day 1**

		$C_{max}$	$t_{max}$	$t_{last}$	$AUC_{0-24h}$	$AUC_{last}$	$AUC_{\infty}$
		ng/mL	h	h	h.ng/mL	h.ng/mL	h.ng/mL
<b>RR 420 mg Day 1</b>	n	27	27	27	27	27	15
	Mean	86.4 (45.0)	2.68 (1.59)	23.92 <sup>b</sup>	828 (326)	828 (326)	890 (389)
	%CV	52.1	59.5	0.90	39.4	39.4	43.7
	Range	32.2 - 195	0.83 - 6.00	23.33 - 24.50	334 - 1550	334 - 1550	349 - 1663
	GeoMean	76.9	2.32	23.95	765	765	809
<b>RR High Risk 420 mg Day 1</b>	n	23	23	23	23	23	16
	Mean	134 (129)	3.24 (4.68)	23.92 <sup>b</sup>	1111 (718)	1111 (718)	1357 (803)
	%CV	96.0	144.3	2.29	64.6	64.6	59.2
	Range	25.1 - 568	0.50 - 23.97	21.50 - 24.25	252 - 3297	252 - 3297	397 - 3608
	GeoMean	95.5	2.24	23.74	911	911	1156
<b>All RR 420 mg Day 1</b>	n	50	50	50	50	50	31
	Mean	108 (95)	2.94 (3.36)	23.92 <sup>b</sup>	958 (555)	958 (555)	1131 (666)
	%CV	88.1	114	1.72	57.9	57.9	58.9
	Range	25.1 - 568	0.50 - 23.97	21.50 - 24.50	252 - 3297	252 - 3297	349 - 3608
	GeoMean	84.9	2.28	23.85	829	829	973
<b>Naïve 420 mg Day 1</b>	n	27	27	27	25	27	12
	Mean	94.6 (46.2)	2.43 (1.13)	23.92 <sup>b</sup>	976 (505)	982 (530)	1181 (712)
	%CV	48.9	46.5	16.1	51.7	54.0	60.3
	Range	36.4 - 192	0.50 - 4.17	6.05 - 31.00	272 - 2096	272 - 2096	279 - 2540
	GeoMean	85.2	2.15	22.85	862	850	996
<b>RR 840 mg Day 1</b>	n	33	33	33	32	33	16
	Mean	132 (69.4)	2.34 (1.22)	23.92 <sup>b</sup>	1331 (760)	1303 (766)	1275 (799)
	%CV	52.5	52.1	13.5	57.1	58.8	62.7
	Range	21.0 - 259	1.00 - 5.92	6.00 - 25.00	156 - 2947	156 - 2947	247 - 2672
	GeoMean	111	2.08	22.96	1085	1053	1022
<b>Naïve 840 mg Day 1</b>	n	4	4	4	4	4	2
	Mean	205 (166)	2.01 (0.01)	23.54 <sup>b</sup>	1693 (1248)	1693 (1248)	2851 (394)
	%CV	81.0	0.70	3.70	73.8	73.8	13.8
	Range	24.9 - 412	2.00 - 2.03	22.25 - 24.08	266 - 3014	266 - 3014	2572 - 3130
	GeoMean	136	2.01	23.34	1202	1202	2837

Source: Pharmacokinetics Report, Table 4, Page 18.

**Table 8: Summary of PCI-45227 Pharmacokinetic Parameters on Day 8**

		$C_{max}$ ng/mL	$t_{max}$ h	$t_{last}$ h	$AUC_{0-24h}$ h.ng/mL	$AUC_{last}$ h.ng/mL
<b>RR 420 mg Day 8</b>	n	24	24	24	22	24
	Mean	114 (105)	2.60 (1.71)	24.00 <sup>b</sup>	1121 (926)	1068 (906)
	%CV	92.4	65.8	22.5	82.6	84.9
	Range	29.6 - 465	0.92 - 7.00	6.08 - 24.00	305 - 4608	222 - 4608
	GeoMean	88.6	2.17	21.41	893	837
<b>RR High Risk 420 mg Day 8</b>	n	23	23	23	23	23
	Mean	131 (80.8)	2.72 (1.21)	24.00	1370 (748)	1370 (748)
	%CV	61.5	44.5	0.00	54.6	54.6
	Range	30.0 - 361	1.00 - 6.05	24.00 - 24.00	273 - 3145	273 - 3145
	GeoMean	109	2.50	24.00	1178	1178
<b>All RR 420 mg Day 8</b>	n	47	47	47	45	47
	Mean	122 (93.5)	2.66 (1.47)	24.00 <sup>b</sup>	1248 (840)	1216 (838)
	%CV	76.4	55.4	15.7	67.3	68.9
	Range	29.6 - 465	0.92 - 7.00	6.08 - 24.00	273 - 4608	222 - 4608
	GeoMean	98.2	2.32	22.64	1029	989
<b>Naïve 420 mg Day 8</b>	n	26	26	26	26	26
	Mean	127 (42.6)	2.44 (1.19)	24.00 <sup>b</sup>	1436 (606)	1436 (606)
	%CV	33.5	49.0	0.00	42.2	42.2
	Range	64.5 - 220	0.88 - 4.08	24.00 - 24.00	487 - 2978	487 - 2978
	GeoMean	120	2.14	24.00	1322	1322
<b>RR 840 mg Day 8</b>	n	32	32	32	32	32
	Mean	152 (70.0)	2.23 (0.82)	24.00 <sup>b</sup>	1653 (913)	1653 (913)
	%CV	45.9	37.0	0.00	55.3	55.3
	Range	36.1 - 296	1.00 - 4.00	24.00 - 24.00	236 - 4023	236 - 4023
	GeoMean	135	2.10	24.00	1389	1389
<b>Naïve 840 mg Day 8</b>	n	4	4	4	4	4
	Mean	178 (66.6)	2.75 (1.48)	24.00 <sup>b</sup>	1704 (874)	1704 (874)
	%CV	37.4	53.9	0.00	51.3	51.3
	Range	95.0 - 246	1.08 - 4.00	24.00 - 24.00	696 - 2747	696 - 2747
	GeoMean	167	2.40	24.00	1514	1514

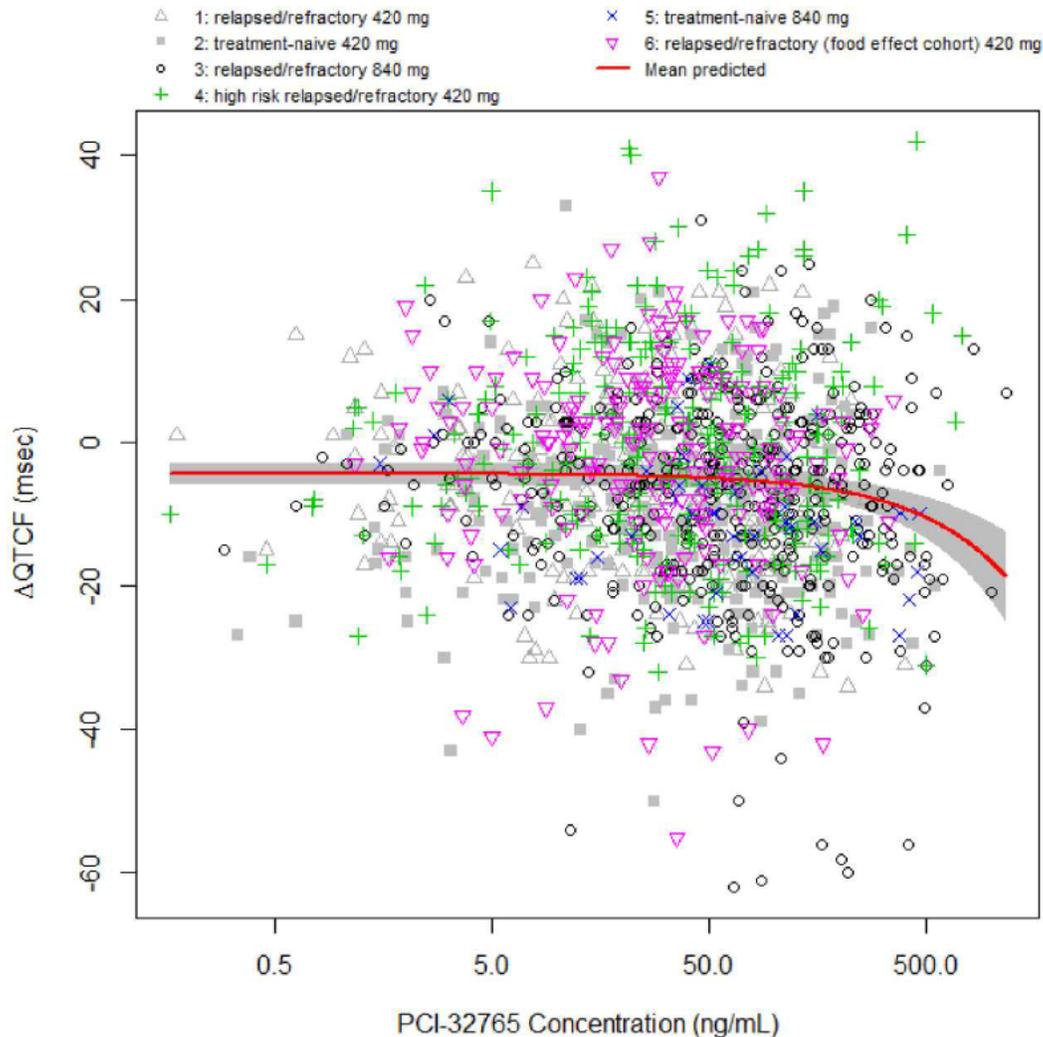
Source: Pharmacokinetics Report, Table 5, Page 19.

#### 3.2.8.4.2 Exposure-Response Analysis

The relationships between plasma concentrations (of ibrutinib and PCI-45227) and  $\Delta Q T c F$  were investigated by a linear mixed-effects modeling approach. The estimates

(90% CI) of intercept and slope were -4.39 (-5.94; -2.83) ms and -0.0122 (-0.0177; -0.0068) ms per ng/mL, respectively for ibrutinib. The negative slope was statistically significant ( $p=0.0002$ ). The relationship is visualized in Figure 7.

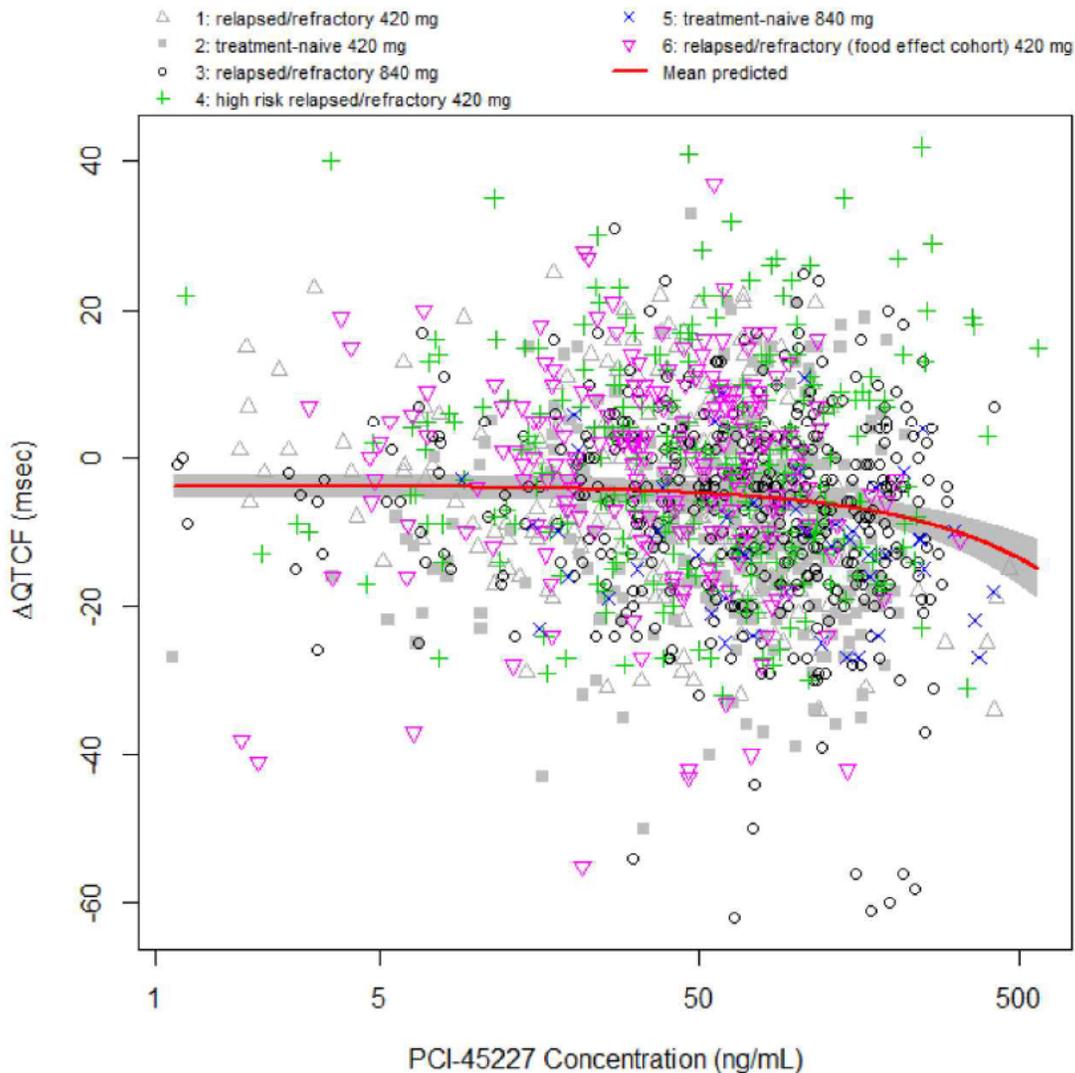
**Figure 7: Observed  $\Delta$ QTcF vs. Ibrutinib Concentration with Population Mean Prediction (solid red line)**



Source: ECG Report, Part 2, Figure 5a, Page 13.

For PCI-45227, a negative relationship was also observed ( $p<0.0001$ ). The estimates (90% CI) of intercept and slope were -3.81 (-5.45; -2.18) ms and -0.0197 (-0.0272; -0.0122) ms per ng/mL, respectively. The relationship is visualized in Figure 8.

**Figure 8: Observed  $\Delta$ QTcF vs. PCI-45227 Concentration with Population Mean Prediction (solid red line)**



Source: ECG Report, Part 2, Figure 5b, Page 21.

Reviewer's Analysis: The reviewer's independent analysis is included in Section 5.

## 4 REVIEWERS' ASSESSMENT

### 4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based

on the results listed in Table 9, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

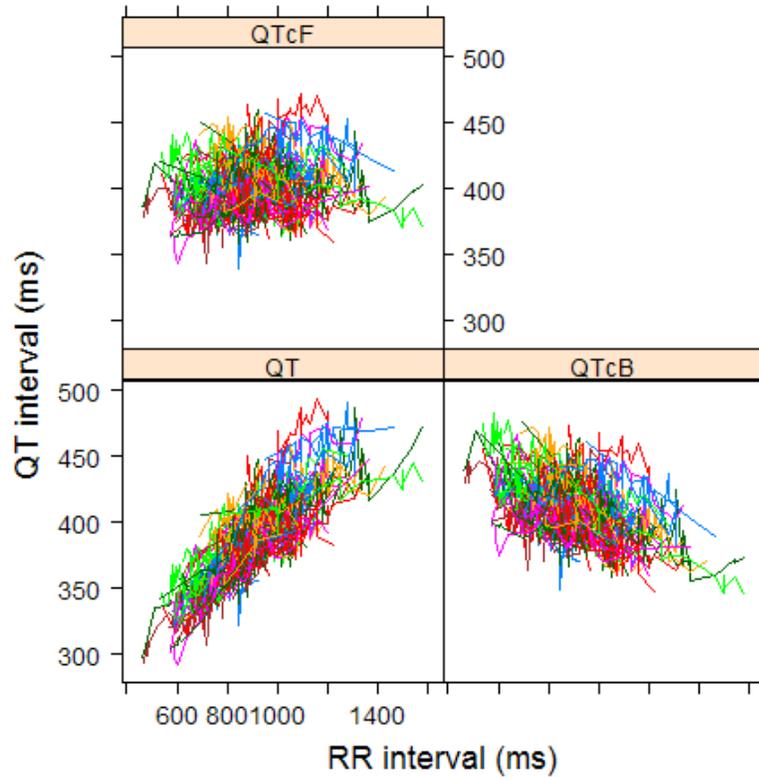
**Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

method	Treatment					
	High-Risk Relapsed/Refractory 420		Relapsed/Refractory 420		Relapsed/Refractory 840	
	N	MSSS	N	MSSS	N	MSSS
QTcB	24	0.0122	27	0.0105	34	0.0105
QTcF	24	0.0039	27	0.0043	34	0.0023

Treatment							
Relapsed/Refractory/Food Effect 420		Treatment-Naive 420		Treatment-Naive 840		ALL	
N	MSSS	N	MSSS	N	MSSS	N	MSSS
16	0.0136	26	0.0112	4	0.0143	131	0.0114
16	0.0048	26	0.0031	4	0.0089	131	0.0037

The relationship between different correction methods and RR is presented in Figure 9.

**Figure 9: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)**



## 4.2 STATISTICAL ASSESSMENTS

### 4.2.1 QTc Analysis

#### 4.2.1.1 The Primary Analysis for Ibrutinib

Descriptive analysis was applied. Means and the 90% confidence intervals of dQTcF, dHR, dPR, dQRS at each visit for each treatment cohort were displayed in following tables

**Table 10: Means and C.I. for dQTcF**

Treatment	Day	Visit	dQTcF	
			Change from Baseline (ms)	90% CI (ms)
High-Risk Relapsed/Refractory 420	1	CYCLE 1	3.8	( 1.3, 6.4)
	8	CYCLE 1	-1.4	(-3.7, 0.9)
	15	CYCLE 1	-2.0	(-9.6, 5.5)
	22	CYCLE 1	-5.4	(-11.5, 0.7)
	28	CYCLE 1	-8.3	(-13.7, -2.9)
		CYCLE 12	-4.8	(-14.0, 4.4)
		CYCLE 3	-4.5	(-11.6, 2.6)
		CYCLE 6	-11.4	(-19.6, -3.2)
Relapsed/Refractory 420	1	CYCLE 1	0.5	(-1.5, 2.5)
	8	CYCLE 1	-7.5	(-9.7, -5.3)
	15	CYCLE 1	-6.3	(-10.7, -1.8)
		CYCLE 2	-9.7	(-14.9, -4.4)
	22	CYCLE 1	-10.4	(-16.1, -4.7)
	28	CYCLE 1	-9.6	(-14.6, -4.7)
		CYCLE 10	-6.2	(-11.4, -1.0)
		CYCLE 11	-8.2	(-13.8, -2.7)
		CYCLE 12	-9.1	(-13.5, -4.8)
		CYCLE 18	-5.2	(-12.6, 2.3)
		CYCLE 2	-7.4	(-13.1, -1.6)
		CYCLE 24	-7.9	(-16.1, 0.2)
		CYCLE 3	-9.0	(-15.0, -3.0)
		CYCLE 4	-10.4	(-16.6, -4.2)
	CYCLE 5	-12.1	(-16.6, -7.5)	
	CYCLE 6	-8.9	(-13.6, -4.1)	
	CYCLE 7	-10.9	(-20.1, -1.8)	
	CYCLE 8	-7.7	(-12.6, -2.7)	
	CYCLE 9	-8.9	(-14.0, -3.9)	
Relapsed/Refractory 840	1	CYCLE 1	-3.3	(-5.0, -1.5)
	8	CYCLE 1	-8.2	(-10.3, -6.1)
	15	CYCLE 1	-12.2	(-17.1, -7.3)
		CYCLE 2	-11.8	(-16.8, -6.8)

			dQTcF	
Treatment	Day	Visit	Change from Baseline (ms)	90% CI (ms)
	22	CYCLE 1	-11.9	(-16.5, -7.4)
	28	CYCLE 1	-10.4	(-14.3, -6.4)
		CYCLE 12	-11.0	(-16.1, -6.0)
		CYCLE 18	-14.1	(-19.6, -8.6)
		CYCLE 2	-11.4	(-17.0, -5.8)
		CYCLE 24	-8.4	(-17.9, 1.1)
		CYCLE 3	-15.6	(-20.7,-10.4)
		CYCLE 4	-13.2	(-18.1, -8.4)
		CYCLE 5	-12.0	(-16.6, -7.4)
		CYCLE 6	-12.4	(-18.0, -6.8)
		CYCLE 7	-13.7	(-20.3, -7.0)
		CYCLE 8	-15.0	(-24.6, -5.4)
Relapsed/Refractory/Food Effect 420	1	CYCLE 1	2.9	( 0.2, 5.6)
	8	CYCLE 1	-3.9	( -7.0, -0.9)
	15	CYCLE 1	-7.3	(-14.6, -0.0)
	22	CYCLE 1	-7.4	(-15.1, 0.3)
	28	CYCLE 1	-3.5	(-10.2, 3.2)
		CYCLE 3	-6.6	(-15.7, 2.5)
		CYCLE 6	-5.3	(-18.4, 7.8)
Treatment-Naive 420	1	CYCLE 1	-4.0	( -6.1, -1.8)
	8	CYCLE 1	-10.0	(-12.5, -7.6)
	15	CYCLE 1	-11.7	(-16.1, -7.3)
		CYCLE 2	-12.8	(-18.1, -7.6)
	22	CYCLE 1	-12.8	(-18.6, -7.0)
	28	CYCLE 1	-14.3	(-18.7, -9.9)
		CYCLE 12	-11.9	(-20.3, -3.4)
		CYCLE 18	-8.1	(-19.3, 3.0)
		CYCLE 2	-10.3	(-17.8, -2.8)
		CYCLE 24	-15.1	(-21.3, -8.9)
		CYCLE 3	-13.3	(-19.2, -7.4)
		CYCLE 4	-9.2	(-16.3, -2.0)
		CYCLE 5	-12.9	(-20.4, -5.4)

			dQTcF	
Treatment	Day	Visit	Change from Baseline (ms)	90% CI (ms)
		CYCLE 6	-13.1	(-18.1, -8.0)
		CYCLE 7	-8.8	(-21.1, 3.4)
		CYCLE 8	-8.7	(-14.0, -3.4)
		CYCLE 9	-5.6	(-19.9, 8.8)
Treatment-Naive 840	1	CYCLE 1	-11.6	(-15.5, -7.8)
	8	CYCLE 1	-15.9	(-20.1,-11.7)

**Table 11: Means and C.I. for dHR**

			dHR	
Treatment	Day	Visit	Change from Baseline (bpm)	90% CI (bpm)
High-Risk Relapsed/Refractory 420	1	CYCLE 1	-3.3	( -4.7, -2.0)
	8	CYCLE 1	-6.4	( -8.1, -4.7)
	15	CYCLE 1	-6.0	( -9.5, -2.5)
	22	CYCLE 1	-7.4	(-11.4, -3.4)
	28	CYCLE 1	-6.9	(-11.2, -2.7)
		CYCLE 12	-6.4	( -9.4, -3.4)
		CYCLE 3	-6.6	( -9.8, -3.4)
		CYCLE 6	-3.4	( -8.6, 1.9)
Relapsed/Refractory 420	1	CYCLE 1	-7.2	( -8.6, -5.7)
	8	CYCLE 1	-8.2	( -9.9, -6.5)
	15	CYCLE 1	-8.3	(-11.5, -5.2)
		CYCLE 2	-8.2	(-11.1, -5.2)
	22	CYCLE 1	-7.9	(-11.6, -4.2)
	28	CYCLE 1	-6.7	(-11.1, -2.2)
		CYCLE 10	-5.1	( -9.1, -1.2)
		CYCLE 11	-7.1	( -9.6, -4.5)
		CYCLE 12	-6.9	(-10.3, -3.5)
		CYCLE 18	-7.6	(-11.4, -3.7)
		CYCLE 2	-8.4	(-11.3, -5.6)

			dHR	
Treatment	Day	Visit	Change from Baseline (bpm)	90% CI (bpm)
		CYCLE 24	-7.4	(-12.4, -2.5)
		CYCLE 3	-5.9	(-8.8, -3.0)
		CYCLE 4	-3.8	(-7.6, -0.0)
		CYCLE 5	-1.7	(-7.4, 3.9)
		CYCLE 6	-4.8	(-7.0, -2.6)
		CYCLE 7	-4.6	(-8.5, -0.8)
		CYCLE 8	-7.3	(-10.1, -4.4)
		CYCLE 9	-6.5	(-9.3, -3.6)
Relapsed/Refractory 840	1	CYCLE 1	-2.4	(-3.6, -1.2)
	8	CYCLE 1	-6.0	(-7.8, -4.2)
	15	CYCLE 1	-9.4	(-12.9, -5.8)
		CYCLE 2	-8.8	(-12.6, -5.0)
	22	CYCLE 1	-9.7	(-13.9, -5.4)
	28	CYCLE 1	-8.8	(-13.1, -4.5)
		CYCLE 12	-9.8	(-15.3, -4.4)
		CYCLE 18	-13.2	(-19.5, -6.8)
		CYCLE 2	-7.4	(-11.4, -3.4)
		CYCLE 24	-2.3	(-11.6, 7.1)
		CYCLE 3	-8.1	(-12.4, -3.8)
		CYCLE 4	-9.3	(-14.7, -3.9)
		CYCLE 5	-9.6	(-15.9, -3.4)
		CYCLE 6	-11.8	(-16.3, -7.3)
		CYCLE 7	-8.3	(-14.0, -2.7)
		CYCLE 8	-12.9	(-24.8, -1.0)
Relapsed/Refractory/Food Effect 420	1	CYCLE 1	-1.7	(-4.0, 0.6)
	8	CYCLE 1	-4.1	(-7.0, -1.3)
	15	CYCLE 1	-9.3	(-13.8, -4.8)
	22	CYCLE 1	-4.4	(-9.7, 0.8)
	28	CYCLE 1	-7.9	(-13.3, -2.4)
		CYCLE 3	-6.9	(-11.6, -2.2)
		CYCLE 6	-7.1	(-14.3, 0.1)
Treatment-Naive 420	1	CYCLE 1	-5.7	(-7.2, -4.2)

			dHR	
Treatment	Day	Visit	Change from Baseline (bpm)	90% CI (bpm)
	8	CYCLE 1	-8.3	(-10.4, -6.1)
	15	CYCLE 1	-9.5	(-12.9, -6.1)
		CYCLE 2	-9.2	(-15.3, -3.1)
	22	CYCLE 1	-7.7	(-11.4, -4.0)
	28	CYCLE 1	-8.7	(-13.5, -3.9)
		CYCLE 12	-6.2	(-12.8, 0.4)
		CYCLE 18	-10.1	(-17.6, -2.5)
		CYCLE 2	-7.1	(-11.3, -2.9)
		CYCLE 24	-8.4	(-14.3, -2.4)
		CYCLE 3	-6.9	(-10.6, -3.1)
		CYCLE 4	-8.5	(-14.2, -2.7)
		CYCLE 5	-6.6	(-11.6, -1.6)
		CYCLE 6	-7.6	(-13.6, -1.6)
		CYCLE 7	-2.2	(-6.5, 2.2)
		CYCLE 8	-1.0	(-5.8, 3.8)
		CYCLE 9	0.3	(-6.4, 7.0)
Treatment-Naive 840	1	CYCLE 1	-7.7	(-12.0, -3.4)
	8	CYCLE 1	-13.2	(-18.1, -8.2)

**Table 12: Means and C.I. for dPR**

Treatment	Day	Visit	dPR	
			Change from Baseline (ms)	90% CI (ms)
High-Risk Relapsed/Refractory 420	1	CYCLE 1	8.4	( 5.8, 11.0)
	8	CYCLE 1	7.6	( 4.9, 10.3)
	15	CYCLE 1	8.1	( 3.0, 13.2)
	22	CYCLE 1	11.2	( 5.7, 16.6)
	28	CYCLE 1	10.9	( 5.6, 16.2)
		CYCLE 12	17.5	( 6.6, 28.4)
		CYCLE 3	16.4	( 8.5, 24.3)
		CYCLE 6	13.9	( 3.0, 24.9)
	Relapsed/Refractory 420	1	CYCLE 1	6.3
8		CYCLE 1	8.0	( 5.5, 10.5)
15		CYCLE 1	7.5	( 2.7, 12.4)
		CYCLE 2	11.3	( 7.3, 15.3)
22		CYCLE 1	10.3	( 6.0, 14.6)
28		CYCLE 1	8.3	( 3.8, 12.7)
		CYCLE 10	14.5	( 0.7, 28.3)
		CYCLE 11	16.3	( 4.0, 28.6)
		CYCLE 12	7.5	( 3.1, 11.9)
		CYCLE 18	13.3	( 7.3, 19.4)
		CYCLE 2	11.9	( 8.8, 15.0)
		CYCLE 24	23.1	( 12.9, 33.4)
		CYCLE 3	8.6	( 3.1, 14.2)
		CYCLE 4	11.1	( 3.3, 18.8)
		CYCLE 5	10.8	( 0.6, 21.1)
	CYCLE 6	13.0	( 4.1, 21.9)	
	CYCLE 7	10.9	( 2.8, 19.1)	
	CYCLE 8	13.2	( 5.9, 20.4)	
	CYCLE 9	15.6	( 4.0, 27.2)	
Relapsed/Refractory 840	1	CYCLE 1	5.5	( 3.8, 7.3)
	8	CYCLE 1	5.6	( 4.1, 7.1)
	15	CYCLE 1	6.2	( 2.6, 9.8)
		CYCLE 2	12.3	( 8.4, 16.3)

			dPR	
Treatment	Day	Visit	Change from Baseline (ms)	90% CI (ms)
	22	CYCLE 1	9.9	( 5.5, 14.3)
	28	CYCLE 1	10.8	( 6.4, 15.2)
		CYCLE 12	16.1	( 8.6, 23.6)
		CYCLE 18	20.9	( 13.7, 28.0)
		CYCLE 2	12.3	( 7.9, 16.8)
		CYCLE 24	18.3	( 2.4, 34.1)
		CYCLE 3	12.6	( 7.2, 18.1)
		CYCLE 4	9.5	( 4.1, 14.8)
		CYCLE 5	16.8	( 10.9, 22.6)
		CYCLE 6	19.3	( 13.1, 25.4)
		CYCLE 7	14.5	( 6.0, 23.1)
		CYCLE 8	17.1	( -0.7, 34.9)
Relapsed/Refractory/Food Effect 420	1	CYCLE 1	4.6	( 2.4, 6.7)
	8	CYCLE 1	6.4	( 3.7, 9.2)
	15	CYCLE 1	9.6	( 2.8, 16.4)
	22	CYCLE 1	8.7	( 3.2, 14.1)
	28	CYCLE 1	14.8	( 5.8, 23.8)
		CYCLE 3	8.4	( 1.1, 15.8)
		CYCLE 6	11.4	( 3.4, 19.5)
Treatment-Naive 420	1	CYCLE 1	4.4	( 1.9, 7.0)
	8	CYCLE 1	7.3	( 4.1, 10.5)
	15	CYCLE 1	8.1	( 1.8, 14.3)
		CYCLE 2	8.1	( 0.3, 15.8)
	22	CYCLE 1	6.6	( 0.7, 12.5)
	28	CYCLE 1	7.3	( -0.6, 15.1)
		CYCLE 12	14.9	( 5.5, 24.2)
		CYCLE 18	15.6	( 6.5, 24.8)
		CYCLE 2	11.2	( 2.2, 20.2)
		CYCLE 24	19.8	( 11.9, 27.7)
		CYCLE 3	12.5	( 4.9, 20.1)
		CYCLE 4	15.3	( 6.7, 23.8)
		CYCLE 5	9.4	( 0.1, 18.6)

			dPR	
Treatment	Day	Visit	Change from Baseline (ms)	90% CI (ms)
		CYCLE 6	10.8	(-0.2, 21.9)
		CYCLE 7	1.3	(-6.9, 9.6)
		CYCLE 8	13.1	( 3.0, 23.3)
		CYCLE 9	5.6	(-14.0, 25.1)
Treatment-Naive 840	1	CYCLE 1	1.7	(-0.3, 3.6)
	8	CYCLE 1	-0.7	(-3.0, 1.7)

**Table 13: Means and C.I. for dQRS**

			dQRS	
Treatment	Day	Visit	Change from Baseline (ms)	90% CI (ms)
High-Risk Relapsed/Refractory 420	1	CYCLE 1	0.9	( 0.2, 1.5)
	8	CYCLE 1	1.1	( 0.6, 1.6)
	15	CYCLE 1	1.3	(-0.0, 2.6)
	22	CYCLE 1	0.1	(-1.0, 1.2)
	28	CYCLE 1	1.2	( 0.1, 2.2)
		CYCLE 12	1.9	( 0.5, 3.3)
		CYCLE 3	1.5	( 0.8, 2.2)
		CYCLE 6	0.9	(-0.0, 1.9)
Relapsed/Refractory 420	1	CYCLE 1	0.0	(-0.4, 0.5)
	8	CYCLE 1	0.9	( 0.3, 1.6)
	15	CYCLE 1	0.6	(-0.6, 1.7)
		CYCLE 2	2.0	( 0.6, 3.3)
	22	CYCLE 1	1.3	( 0.2, 2.5)
	28	CYCLE 1	0.5	(-0.7, 1.7)
		CYCLE 10	4.8	(-0.2, 9.8)
		CYCLE 11	5.8	( 0.4, 11.2)
		CYCLE 12	4.9	(-0.0, 9.9)
		CYCLE 18	6.6	(-0.1, 13.2)

			dQRS	
Treatment	Day	Visit	Change from Baseline (ms)	90% CI (ms)
		CYCLE 2	1.6	( 0.7, 2.6)
		CYCLE 24	7.2	( 1.4, 13.0)
		CYCLE 3	0.4	(-1.0, 1.9)
		CYCLE 4	2.6	( 1.4, 3.9)
		CYCLE 5	3.4	(-0.3, 7.1)
		CYCLE 6	4.2	(-0.8, 9.1)
		CYCLE 7	2.9	(-2.1, 8.0)
		CYCLE 8	4.6	( 0.4, 8.7)
		CYCLE 9	2.9	( 0.7, 5.1)
Relapsed/Refractory 840	1	CYCLE 1	0.3	(-0.1, 0.6)
	8	CYCLE 1	0.9	( 0.3, 1.4)
	15	CYCLE 1	1.7	( 0.4, 3.0)
		CYCLE 2	1.1	(-0.7, 2.8)
	22	CYCLE 1	0.7	(-0.6, 2.1)
	28	CYCLE 1	1.3	( 0.2, 2.4)
		CYCLE 12	2.2	( 0.1, 4.4)
		CYCLE 18	3.0	( 0.5, 5.4)
		CYCLE 2	0.9	(-1.1, 2.8)
		CYCLE 24	5.5	(-2.5, 13.5)
		CYCLE 3	0.1	(-1.3, 1.5)
		CYCLE 4	0.1	(-1.9, 2.1)
		CYCLE 5	2.2	(-0.3, 4.7)
		CYCLE 6	2.5	(-0.2, 5.1)
		CYCLE 7	1.3	( 0.4, 2.1)
		CYCLE 8	1.7	(-0.6, 4.0)
Relapsed/Refractory/Food Effect 420	1	CYCLE 1	-0.0	(-0.8, 0.7)
	8	CYCLE 1	-0.2	(-0.7, 0.4)
	15	CYCLE 1	1.1	(-0.4, 2.5)
	22	CYCLE 1	-0.6	(-3.8, 2.7)
	28	CYCLE 1	-1.1	(-4.9, 2.6)
		CYCLE 3	-0.3	(-2.2, 1.5)
		CYCLE 6	0.7	(-1.4, 2.9)

			dQRS	
Treatment	Day	Visit	Change from Baseline (ms)	90% CI (ms)
Treatment-Naive 420	1	CYCLE 1	0.6	( 0.1, 1.1)
	8	CYCLE 1	-0.1	(-0.8, 0.7)
	15	CYCLE 1	0.9	(-0.4, 2.2)
		CYCLE 2	-0.4	(-2.4, 1.5)
	22	CYCLE 1	0.9	(-0.6, 2.4)
	28	CYCLE 1	0.8	(-0.5, 2.2)
		CYCLE 12	2.1	(-0.3, 4.4)
		CYCLE 18	1.6	(-1.4, 4.6)
		CYCLE 2	1.6	(-0.1, 3.4)
		CYCLE 24	3.6	( 1.6, 5.6)
		CYCLE 3	0.5	(-1.4, 2.5)
		CYCLE 4	0.9	(-2.3, 4.1)
		CYCLE 5	2.1	(-0.2, 4.4)
		CYCLE 6	2.4	( 1.0, 3.9)
	CYCLE 7	4.0	( 2.6, 5.4)	
	CYCLE 8	3.3	( 1.6, 5.0)	
	CYCLE 9	2.0	(-0.2, 4.2)	
Treatment-Naive 840	1	CYCLE 1	-0.5	(-1.3, 0.4)
	8	CYCLE 1	-0.3	(-1.4, 0.7)

#### 4.2.1.2 Categorical Analysis

Table 14 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 14: Categorical Analysis for QTcF**

Treatment Group	Total N		Value $\leq 450$ ms		450 ms < Value $\leq 480$ ms		Value > 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
High-Risk Relapsed/Refrac	24	298	20 (83.3%)	291 (97.7%)	4 (16.7%)	7 (2.3%)	0 (%)	0 (0.0%)
Relapsed/Refractory 420	27	487	25 (92.6%)	484 (99.4%)	2 (7.4%)	3 (0.6%)	0 (%)	0 (0.0%)

Treatment Group	Total N		Value<=450 ms		450 ms<Value<=480 ms		Value>480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Relapsed/Refractory 840	34	579	34 (100%)	579 (100%)	0 (0.0%)	0 (0.0%)	0 (%)	0 (0.0%)
Relapsed/Refractory/Food	16	191	14 (87.5%)	189 (99.0%)	2 (12.5%)	2 (1.0%)	0 (%)	0 (0.0%)
Treatment-Naive 420	26	442	24 (92.3%)	425 (96.2%)	2 (7.7%)	17 (3.8%)	0 (%)	0 (0.0%)
Treatment-Naive 840	4	39	4 (100%)	39 (100%)	0 (0.0%)	0 (0.0%)	0 (%)	0 (0.0%)

Table 15 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 15: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
High-Risk Relapsed/Refrac	22	284	18 (81.8%)	278 (97.9%)	4 (18.2%)	6 (2.1%)	0 (%)	0 (0.0%)
Relapsed/Refractory 420	24	442	23 (95.8%)	441 (99.8%)	1 (4.2%)	1 (0.2%)	0 (%)	0 (0.0%)
Relapsed/Refractory 840	34	579	32 (94.1%)	577 (99.7%)	2 (5.9%)	2 (0.3%)	0 (%)	0 (0.0%)
Relapsed/Refractory/Food	16	191	14 (87.5%)	189 (99.0%)	2 (12.5%)	2 (1.0%)	0 (%)	0 (0.0%)
Treatment-Naive 420	24	427	22 (91.7%)	418 (97.9%)	2 (8.3%)	9 (2.1%)	0 (%)	0 (0.0%)
Treatment-Naive 840	4	39	4 (100%)	39 (100%)	0 (0.0%)	0 (0.0%)	0 (%)	0 (0.0%)

**Table 16: Categorical Analysis for HR**

Treatment Group	Total N		Value<=50 bpm		50 bpm<Value<=100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
High-Risk Relapsed/Refrac	24	298	4 (16.7%)	29 (9.7%)	24 (100%)	269 (90.3%)	0 (0.0%)	0 (0.0%)
Relapsed/Refractory 420	27	487	4 (14.8%)	16 (3.3%)	23 (85.2%)	466 (95.7%)	4 (14.8%)	5 (1.0%)
Relapsed/Refractory 840	34	579	5 (14.7%)	12 (2.1%)	25 (73.5%)	533 (92.1%)	9 (26.5%)	34 (5.9%)
Relapsed/Refractory/Food	16	191	1 (6.3%)	1 (0.5%)	15 (93.8%)	188 (98.4%)	1 (6.3%)	2 (1.0%)

Treatment Group	Total N		Value<=50 bpm		50 bpm<Value<=100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Treatment-Naive 420	26	442	7 (27%)	45 (10.2%)	25 (96.2%)	396 (89.6%)	1 (3.8%)	1 (0.2%)
Treatment-Naive 840	4	39	1 (2.6%)	1 (2.6%)	4 (100%)	38 (97.4%)	0 (0.0%)	0 (0.0%)

**Table 17: Categorical Analysis for PR**

Treatment Group	Total N		Value<=200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
High-Risk Relapsed/Refrac	24	297	18 (75.0%)	253 (85.2%)	6 (25.0%)	44 (14.8%)
Relapsed/Refractory 420	27	486	24 (88.9%)	472 (97.1%)	3 (11.1%)	14 (2.9%)
Relapsed/Refractory 840	34	579	28 (82.4%)	545 (94.1%)	6 (17.6%)	34 (5.9%)
Relapsed/Refractory/Food	16	172	15 (93.8%)	170 (98.8%)	1 (6.3%)	2 (1.2%)
Treatment-Naive 420	26	442	18 (69.2%)	393 (88.9%)	8 (30.8%)	49 (11.1%)
Treatment-Naive 840	4	37	4 (100%)	37 (100%)	0 (0.0%)	0 (0.0%)

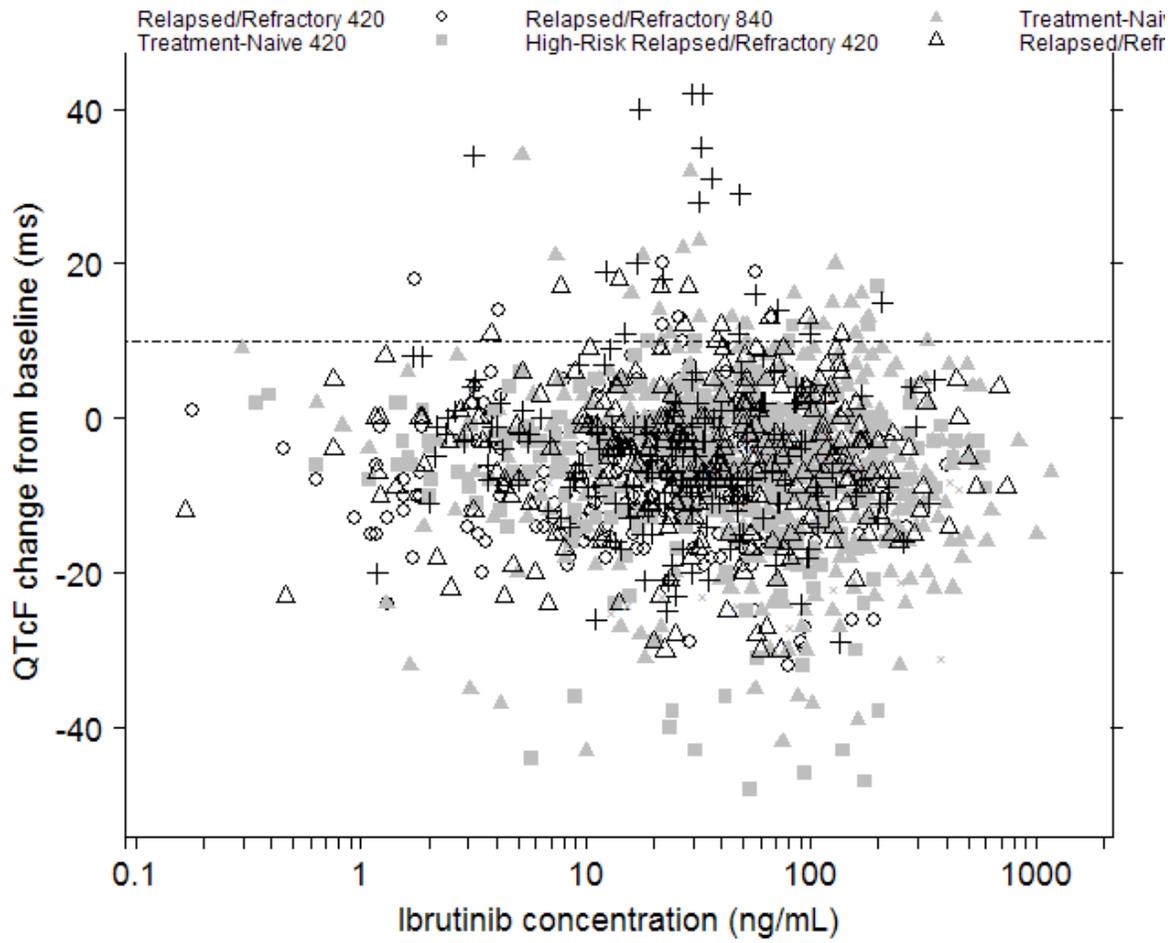
**Table 18: Categorical Analysis for QRS**

Treatment Group	Total N		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
High-Risk Relapsed/Refrac	24	298	8 (33.3%)	139 (46.6%)	10 (41.7%)	107 (35.9%)	6 (25.0%)	52 (17.4%)
Relapsed/Refractory 420	27	487	4 (14.8%)	202 (41.5%)	18 (66.7%)	232 (47.6%)	5 (18.5%)	53 (10.9%)
Relapsed/Refractory 840	34	579	5 (14.7%)	222 (38.3%)	16 (47.1%)	235 (40.6%)	13 (38.2%)	122 (21.1%)
Relapsed/Refractory/Food	16	191	4 (25.0%)	78 (40.8%)	6 (37.5%)	73 (38.2%)	6 (37.5%)	40 (20.9%)
Treatment-Naive 420	26	442	4 (15.4%)	162 (36.7%)	15 (57.7%)	179 (40.5%)	7 (26.9%)	101 (22.9%)
Treatment-Naive 840	4	39	1 (25.0%)	9 (23.1%)	1 (25.0%)	19 (48.7%)	2 (50.0%)	11 (28.2%)

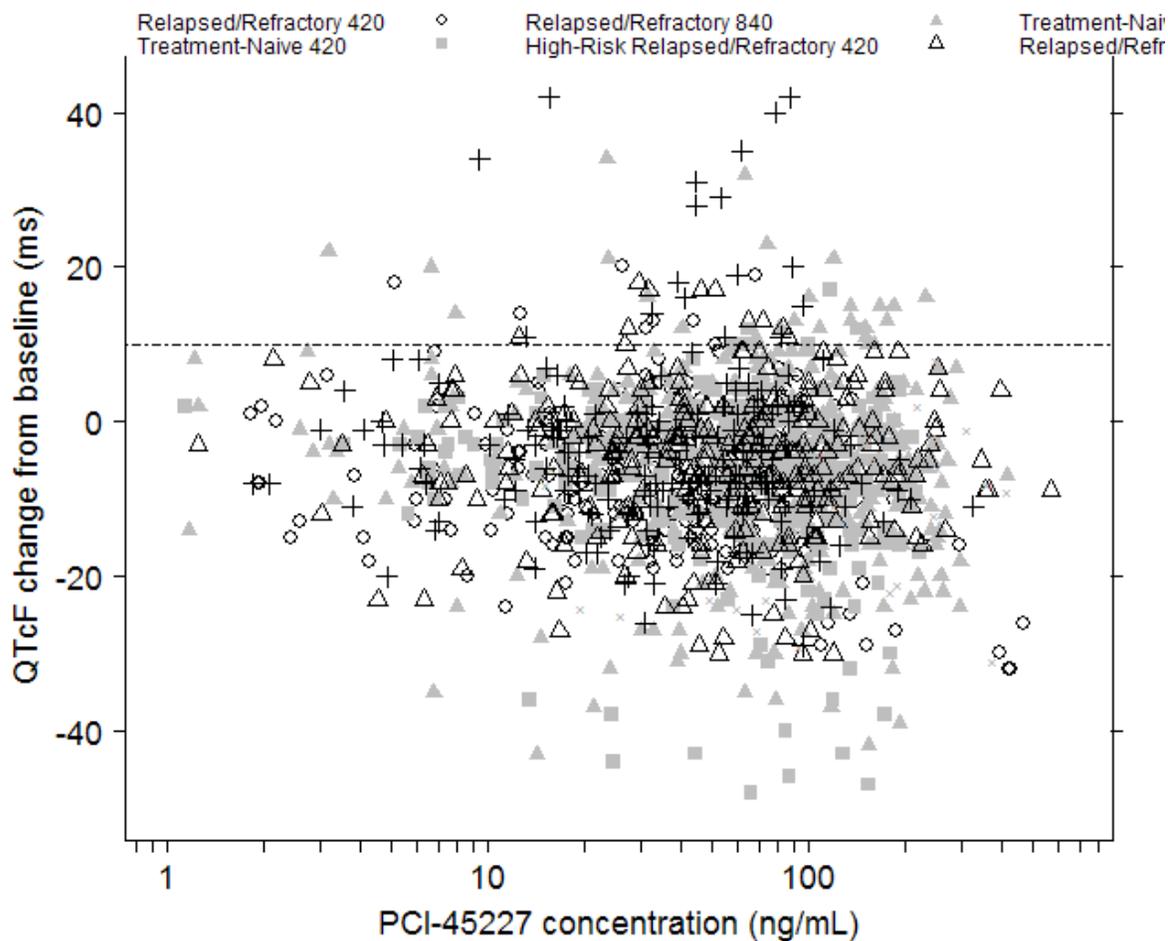
### **4.3 CLINICAL PHARMACOLOGY ASSESSMENTS**

The relationships between  $\Delta\text{QTcF}$  and ibrutinib and PCI-45227 concentrations are visualized in Figure 10 and Figure 11, respectively, with no evident exposure-response relationship.

**Figure 10:  $\Delta$  QTcF vs. Ibrutinib concentration**



**Figure 11:  $\Delta$  QTcF vs. PCI-45227 concentration**



#### 4.4 CLINICAL ASSESSMENTS

##### 4.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

##### 4.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 100% of the ECGs were annotated in the primary lead II, with less than 1.5% of ECGs reported to have significant QT bias, according to the automated algorithm.

Baseline ECGs were collected at screening at unknown study days. Only single ECGs were collected posttreatment.

#### **4.4.3 PR and QRS Interval**

Twenty four patients had a postbaseline PR > 200 ms. One subject had an increase of 40% over baseline and a PR of 240 ms. Three subjects experience 30% increase in PR, with PR up to 230 ms.

Thirty nine patients had a QRS > 110 ms. Two subjects had a QRS > 130 ms at baseline. One patient had a postbaseline increase of 40%, QRS reached 140 ms.

It is very difficult to draw any conclusion from these data because of the high variability due to the study design. Single ECGs were collected on-treatment instead of triplicate and baseline ECGs were collected at screening without a pre-specified time.

## 5 APPENDIX

### 5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

		(b) (4)
Therapeutic dose		MCL: 560 mg once daily
Maximum tolerated dose	Monotherapy: $\geq 12.5$ mg/kg once daily (mean of $\geq 1040$ mg once daily). No dose limiting toxicities identified at 12.5 mg/kg once daily, therefore no MTD determined.	
Principal adverse events	Most common adverse events: diarrhea, nausea/vomiting, fatigue, upper respiratory tract infection, arthralgia, cough, peripheral edema, dyspnea and pyrexia. No dose limiting toxicities identified.	
Maximum dose tested	Single Dose	No SAD study conducted
	Multiple Dose	Body weight based dose: <u>12.5 mg/kg/day</u> Fixed dose: 840 mg/day
Exposures Achieved at Maximum Tested Dose Mean (%CV)	Single Dose Phase 1	At 12.5 mg/kg on Day 1 $C_{max}$ [ng/mL] = 383 (72%) $AUC_{0-24}$ [ng·h/mL] = 1445 (60%)
	Single Dose Phase 2	At 840 mg on Day 1 $C_{max}$ [ng/mL] = 218 (77%) $AUC_{0-24}$ [ng·h/mL] = 1177 (85%)
	Multiple Dose Phase 2	At 840 mg/day on Day 8 (steady-state) $C_{max}$ [ng/mL] = 210 (64%) $AUC_{0-24}$ [ng·h/mL] = 1202 (73%)
Range of linear PK	1.25 to 12.5 mg/kg once daily (absolute range from 40-1400 mg once daily – doses rounded to closest available capsule dose)	
Accumulation at steady state Mean (%CV)	(b) (4)  Accumulation ratio after once daily dosing of 560 mg: Parent PCI-32765: 1.40 (54%) Metabolite PCI-45227: 1.41 (63%)	
Metabolites	The dihydrodiol of PCI-32765 (PCI-45227) is a prominent metabolite with 1/15th intrinsic reversible Btk inhibitory activity compared to the parent compound and plasma exposures comparable to or slightly exceeding parent. Three other prominent metabolites (not yet quantified at steady state) are: M21 (sulphate conjugate of hydroxylated phenyl moiety), M25 (opening of the piperidine ring with further oxidation to a carboxylic acid), M34 (opening of the piperidine ring with further reduction to a primary alcohol).	
Absorption	Absolute/Relative Bioavailability	Not known, but predicted to be <5% (based on data from CYP3A inhibition DDI study)  (b) (4)
	$T_{max}$ (560 mg) Median (range)	Parent PCI-32765: 2.0 h (0.8 to 22.8) metabolite PCI-45227: 2.0 h (0.9 to 6.1)
Distribution Mean (%CV)	Vd/F (population PK)	Central compartment: 246 L (153%) Peripheral compartment: 9620 L (47%)
	% bound to plasma protein healthy subjects (12-083-Hu-X-PB (FK10375))	97.3% (0.05%)

Elimination	Route	Hepatic; 80% of total radioactivity renal; ~8% of total radioactivity
	Terminal t <sub>1/2</sub>	parent: 14-15 h (population PK) PCI-45227: 7-10 h
	CL/F Mean (%CV) (population PK)	1060 L/h (22%)
Intrinsic Factors	Age (population PK)	No significant changes
	Sex (population PK)	No significant changes
	Race (population PK)	No significant changes
	Renal Impairment (population PK)	No significant changes
	Hepatic Impairment	Child-Pugh class B (moderate impairment): 6-fold increase in AUC (preliminary data; submitted 1 August as Sequence 0013 in response to FDA Information Request email dated 18 July 2013)
Extrinsic Factors	Drug interactions (observed)	<b>Healthy Subjects</b> Ketoconazole study: compared to fasted state condition, dose-normalized exposure increase = 24-fold in AUC <sub>last</sub> and 29-fold in C <sub>max</sub> (at sub- therapeutic dose) <sup>(b) (4)</sup> <b>Patients with <sup>(b) (4)</sup> MCL</b> Although there is no reference baseline ibrutinib exposure data in patients on concomitant CYP3A4/5 inhibitors, exposure data from patients taking concomitant mild or moderate inhibitors indicate a lower magnitude of increase than was observed in healthy volunteers. At least 80% of the patients treated with mild and moderate CYP3A4/5 inhibitors had ibrutinib exposure within the range of those who did not receive the inhibitors. For those patients with exposure above this range, the ibrutinib AUC was still ≤ 2-fold the upper limit of the range observed in absence of inhibitors. No data for concomitant administration of ibrutinib with strong inhibitors of CYP3A4/5 is available in patients.
	Drug interactions (simulated using PBPK model for fasted healthy subjects)	Fluvoxamine, diltiazem and erythromycin increase AUCs by 2-7.5x Predictions for ketoconazole confirmed accuracy of PBPK model
	Food Effects	High-fat breakfast increases C <sub>max</sub> 2.24x and AUC <sub>last</sub> 1.65x (420 mg once daily, steady-state conditions)
Expected High Clinical Exposure Scenario	Worst case scenario is CYP3A inhibition with a strong inhibitor (see above). An agreement was reached with IRT to target 1.5-fold mean C <sub>max</sub> at steady state (560 mg once daily) for the thorough QTc study.	

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/s/  
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KEVIN M KRUDYS  
10/02/2013

QIANYU DANG  
10/02/2013

MONICA L FISZMAN  
10/02/2013

NORMAN L STOCKBRIDGE  
10/03/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: September 20, 2013

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**  
Robert Kane, MD  
Deputy Director for Safety  
**Division of Hematology Products (DHP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Nisha Patel, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (ibrutinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 205552

Applicant: Pharmacyclics, Inc.

## 1 INTRODUCTION

On June 28, 2013, Pharmacyclics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 205552 for TRADENAME (ibrutinib) capsules, with the proposed indication for the treatment of patients with:

- mantle cell lymphoma (MCL) who have received at least one prior therapy

(b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Hematology Products (DHP) on June 21, 2013, and June 5, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (ibrutinib) capsules.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (ibrutinib) PPI received on June 28, 2013, and received by DMPP and OPDP on September 12, 2013.
- Draft TRADENAME (ibrutinib) Prescribing Information (PI) received on June 28, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on September 12, 2013.
- Draft TRADENAME (ibrutinib) Prescribing Information (PI) received on June 28, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on September 16, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/  
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KAREN M DOWDY  
09/20/2013

NISHA PATEL  
09/20/2013

BARBARA A FULLER  
09/20/2013

LASHAWN M GRIFFITHS  
09/20/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** September 17, 2013

**To:** Diane Hanner, Senior Program Management Officer  
Division of Hematology Products (DHP)

**From:** Nisha Patel, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Karen Rulli, Team II Leader, OPDP

**Subject:** Comments on draft labeling (Package Insert) for  
Imbruvica™ (ibrutinib) capsules, for oral use  
NDA 205552

In response to your consult dated June 5, 2013, we have reviewed the draft Package Insert (PI) for Imbruvica™ (ibrutinib) capsules, for oral use (Imbruvica) and offer the following comments. OPDP has made these comments using the version dated, 9/16/13.

Section	Statement from draft	Comment
Highlights AND Full Prescribing Information (PI)		Please place a general note in the PI requesting that the sponsor update all cross-references to other sections of the PI.
Highlights, Warnings and Precautions	(b) (4)	(b) (4)
Highlights, Adverse Reactions	The most common adverse reactions ( $\geq 20\%$ ) in patients with MCL are diarrhea, fatigue, musculoskeletal pain, (b) (4) rash, nausea, bruising, upper respiratory infection, abdominal pain, dyspnea, constipation, vomiting, and decreased appetite. (b) (4)	We note that the Review Division has requested that the sponsor round all values in the tables included in the Adverse Reactions section of the full PI. We note that "cough" from Table 1 of the full PI will be rounded to (b) (4). Please ensure that the sponsor includes

Section	Statement from draft	Comment
	(b) (4)	<p>“cough” in the Highlights, Adverse Reactions section for MCL patients.</p> <p>We also recommend revising the term (b) (4) to “peripheral edema” to ensure consistency with the full PI and the Highlights, Adverse Reactions section (b) (4)</p>
<p>Highlights, Drug Interactions</p> <p>2 Dosage and Administration</p> <p>7 Drug Interactions</p> <p>12 Clinical Pharmacology</p>		<p>We note that (b) (4) “CYP3A” (emphasis added) are used throughout these sections of the PI. Should (b) (4) CYP3A be used throughout the PI?</p>
6 Adverse Reactions	(b) (4)	<p>Please revise the list of the most commonly occurring non-hematological adverse reactions to ensure consistency with the Highlights, Adverse Reactions section and Table 1 from the full PI.</p>
6 Adverse Reactions	(b) (4)	(b) (4)
6 Adverse Reactions	<p>The most common Grade 3/4 adverse reactions (<math>\geq 5\%</math>) were: (b) (4)</p> <p>The most common Grade 3/4 adverse reactions (<math>\geq 5\%</math>) were: (b) (4)</p>	<p>We note that the Review Division has requested that the sponsor round all values in the tables included in the Adverse Reactions section of the full PI and that the sponsor present laboratory information in separate tables.</p> <p>Please revise these statements to ensure consistency with Tables 1 and 2 of the full PI once the values are rounded.</p>
12 Clinical Pharmacology	<p>Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a <b>covalent</b> bond with a cysteine residue in the BTK active site, leading to (b) (4) <b>inhibition</b> of BTK enzymatic activity. (emphasis added)</p>	<p>The terms “covalent” and (b) (4) “inhibition” are promotional in tone and the sponsor could use these terms to overstate the efficacy of the drug. Please consider deleting these terms. We also note that the term “covalent” was deleted from the Description section of the full PI.</p>

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/s/  
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NISHA PATEL  
09/17/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

DATE: September 17, 2013

TO: Diane Hanner, M.P.H., M.S.W., Regulatory Project Manager  
Nicole Verdun, M.D., Medical Officer  
Karen McGinn, M.S.N., C.R.N.P., Clinical Analyst  
R. Angelo de Claro, M.D., Cross Discipline Team Leader  
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.  
Medical Officer, GCP Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.  
Team Leader, GCP Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief, GCP Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA#: 205552

APPLICANT: Pharmacyclics, Inc.

DRUG: ibrutinib

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority (breakthrough therapy)

INDICATION: Treatment of mantle cell lymphoma with at least one prior therapy (b) (4)

CONSULTATION REQUEST DATE: June 13, 2013 (Signed)  
INSPECTION SUMMARY GOAL DATE: September 16, 2013 (Original)  
September 23, 2013 (DHP Extension)  
DIVISION ACTION GOAL DATE: October 31, 2013 (Original)  
PDUFA DATE: October 31, 2013

## I. BACKGROUND:

Ibrutinib is a selective and irreversible inhibitor of the Bruton tyrosine kinase protein. Ibrutinib blocks activation of B-cells, arresting cell growth and inducing apoptosis in the human B-cell lymphoma cell lines in vitro, and inhibiting tumor growth in vivo in xenograft models.

(b) (4) relapsed or refractory mantle cell lymphoma (MCL), (b) (4) are serious and life-threatening illnesses with approximate median overall survival of two years and five years, respectively. Breakthrough therapy designation is granted by the FDA for therapies such as ibrutinib, where there is preliminary clinical evidence of substantial improvement over existing therapies, for conditions that are serious and life-threatening. Given the high level of activity of ibrutinib in the above hematologic malignancy populations, ibrutinib, if approved, may transform the pharmacological management of patients with (b) (4) MCL.

The sixth version of the investigational brochure lists diarrhea (40.4%), fatigue (32.1%), and nausea (24.0%) as the most commonly reported treatment-emergent adverse events in studies of ibrutinib administered as monotherapy to 312 subjects. The NCI Common Terminology Criteria for Adverse Events with a severity of Grade 3 and 4 were uncommon, were primarily hematologic in nature, and include anemia, neutropenia, and thrombocytopenia. Serious AEs in the monotherapy studies were commensurate with the disease or its complications, the most common being pneumonia (4.5%) and febrile neutropenia (3.2%).

Two clinical studies were submitted in support of the sponsor's NDA. The CDER review division selected two clinical investigator sites for inspection for each of two studies, Protocols PCYC-1104-CA and PCYC-1102-CA, principally based on the highest number of enrolled patients, highest (b) (4) treatment responders, and/or highest reported serious adverse events (SAEs).

### Study Protocol PCYC-1104-CA

Study PCYC-1104-CA was a Phase 2, open-label, nonrandomized, multicenter, monotherapy study in subjects with histologically-documented mantle cell lymphoma who had relapsed after one or more but not greater than five prior treatment regimens. All subjects meeting eligibility criteria received ibrutinib (PCI-32765) capsules at a dosage of 560 mg once daily for a 28-day cycle until disease progression, unacceptable toxicity, or enrollment in a long-term extension study. The study had two treatment groups in parallel, which were stratified based on prior bortezomib exposure. Efficacy evaluation for overall response and duration of response was performed by the investigator. Overall response was defined as a subject achieving either a partial response or complete response according to the revised International Working Group Criteria for Non-Hodgkins Lymphoma. In addition, the efficacy profile of single agent ibrutinib therapy was confirmed by independent response assessment for the bortezomib-treated cohort.

### Study Protocol PCYC-1102-CA

Study PCYC-1102-CA was a Phase 1b/Phase 2, open-label, nonrandomized, multicenter study in subjects with treatment-naïve chronic lymphocytic lymphoma or small lymphocytic lymphoma, relapsed/refractory chronic lymphoma, or high-risk relapsed/refractory chronic lymphocytic lymphoma or small lymphocytic lymphoma. The primary objective was to determine the safety of two fixed dose daily regimens of ibrutinib (PCI-32765) capsules in subjects with chronic lymphocytic lymphoma or small lymphocytic lymphoma. Treatment with ibrutinib was continued until disease progression, withdrawal of consent, or an unacceptable drug-related toxicity occurred. The ibrutinib treatment cohorts consisted of the following: (1) subjects with relapsed/refractory disease on 420 mg/day, (2) treatment-naïve subjects 65 years or older on 420 mg/day, (3) subjects with relapsed/refractory disease on 840 mg/day, (4) subjects with high-risk relapsed/refractory disease on 420 mg/day, (5) treatment-naïve subjects 65 years or older on 840 mg/day, and (6) subjects with relapsed/refractory disease (food-effect cohort) on 420 mg/day. The primary study endpoint was the frequency and severity of adverse events.

## II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Kristi A. Blum, M.D. Columbus, OH	Protocol PCYC-1104-CA Site #217 N=14  Protocol PCYC-1102-CA Site #217 N=53	July 22-26, 2013	Pending Preliminary: NAI
Michael L. Wang, M.D. Houston, TX	Protocol PCYC-1104-CA Site #32 N=31	July 23-26, 2013	NAI
Susan M. O'Brien, M.D. Houston, TX	Protocol PCYC-1102-CA Site #32 N=42	July 18-26, 2013	Pending Preliminary: NAI
Pharmacylics, Inc. Sunnyvale, CA	Sponsor	August 23-September 11, 2013	Pending Preliminary: VAI

**\*Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed out, the preliminary designation is converted to a final regulatory classification.

## **CLINICAL STUDY SITE INVESTIGATORS**

1. **Kristi A. Blum, / Protocol PCYC-1104-CA/Site #217 and Protocol PCYC-1102-CA/Site #217**  
Columbus, OH

### **a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.811, from July 22 to 26, 2013.

For Study 1102, a total of 65 subjects were screened and 53 subjects were enrolled. Forty-five subjects completed the study. An audit of 20 subjects' records was conducted.

For Study 1104, a total of 17 subjects were screened and 14 subjects were enrolled. Three subjects are in the long-term follow-up study. An audit of 14 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

### **b. General observations/commentary:**

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoints for Study 1102 and Study 1104, respectively, were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

### **c. Assessment of data integrity:**

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. **Michael L. Wang, M.D./Protocol PCYC-1104-CA/Site #32**  
Upland, CA

### **a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.811, from July 23 to July 26, 2013. A total of 32 subjects were screened and 31 subjects were enrolled. Thirteen subjects were on-going participants at the completion of the study.

An audit of the enrolled subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

**b. General observations/commentary:**

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoints were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

**c. Assessment of data integrity:**

Data submitted by this clinical site appear acceptable for this specific indication.

**3. Susan M. O'Brien, /Protocol PCYC-1102-CA/Site #32  
Houston, TX**

**a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.811, from July 18 to July 26, 2013. A total of 45 subjects were screened and 42 subjects were enrolled. Thirty subjects were on-going participants at the completion of the study.

An audit of 16 screened subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

**b. General observations/commentary:**

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

**c. Assessment of data integrity:**

Data submitted by this clinical site appear acceptable in support of this specific indication.

## **SPONSOR**

### **4. Pharmacyclics, Inc.**

Sunnyvale, CA

#### **a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.810, from August 23 to September 11, 2013.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

#### **b. General observations/commentary:**

The Sponsor maintained adequate oversight of the clinical trials, Protocols PCYC-1102-CA and PCYC-1104-CA. Clinical site monitoring was considered adequate. Appropriate steps were taken by the Sponsor to bring noncompliant sites into compliance. There was no evidence of under-reporting of adverse events, serious adverse events, or unexpected adverse events in any of the three clinical investigator sites inspected. All protocol deviations appeared to be adequately reported and addressed at the three clinical investigator sites.

In general, the Sponsor site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the Sponsor inspection for not monitoring the study properly.

Specifically, financial disclosure forms were signed by individuals other than the sub-investigators listed on the financial disclosure forms for Protocol (b) (4). The Sponsor monitors did not detect different signatures on different dates during their review of the regulatory source documents. The Sponsor did not document or address the different signatures on the financial disclosure forms in the Monitoring Reports. For example,

1. Sub-investigator, (b) (6) at Site # (b) (6) signed a financial disclosure form on 11/17/2011 and 2/27/2013. The signature on the 2/27/2013 financial disclosure form appeared to differ significantly from the signature on the 11/17/2011 form. During the inspection, the Sponsor provided a Memo from Site # (b) (6) stating that (b) (6) did not sign the 11/17/2011 financial disclosure form and that the document was signed by another individual.
2. Sub-investigator, (b) (6) at Site (b) (6) signed a financial disclosure form on 10/04/2011 and 2/12/2013. The signature on the 2/12/2013 financial disclosure form appeared to differ significantly from the signature on the 10/04/2011 form. During the inspection, the Sponsor provided a Memo from Site # (b) (6) stating that (b) (6) did not sign the 10/04/2011 financial disclosure form and that the document was signed by another physician.

Additionally, during the close out meeting of the inspection with the Sponsor, ORA staff noted that for [REDACTED] (b) (4) the Sponsor did not obtain sufficient and accurate financial information from the site investigator to allow complete and accurate certification or disclosure statements. For example,

1. Sub-investigators [REDACTED] (b) (6) at Site [REDACTED] (b) (6) were listed on the 6/24/2013 Form FDA 1572 but [REDACTED] (b) (6) never signed a financial disclosure form.

2. Sub-investigators [REDACTED] (b) (6) at Site [REDACTED] (b) (6) were added to the Form FDA 1572 on 7/15/2013, and did not sign financial disclosure forms until the period ranging from 8/28/2013 to 9/3/2013.

The regulatory deficiencies cited above were discussed with the DHP Clinical Team, who did not consider these observations critical.

**c. Assessment of data integrity:**

Notwithstanding the above minor regulatory deficiencies, the study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

For this NDA, two U.S. clinical investigator sites for Protocol PCYC-1102-CA (Susan O'Brien, M.D. and Kristi Blum, M.D.) and two U.S. clinical investigators site for Protocol PCYC-1102-CA (Michael Wang, M.D. and Kristi Blum, M.D.) were inspected in support of this application. The Sponsor (Pharmacyclics, Inc.) was also audited.

No deficiencies were observed for the clinical study sites. The final regulatory classification for Dr. Wang's site is NAI (No Action Indicated). The preliminary classification for the Dr. Blum and Dr. O'Brien sites is NAI.

Regulatory deficiencies were observed for the Sponsor audit. The preliminary regulatory classification is VAI (Voluntary Action Indicated).

The study data collected appear generally reliable in support of the requested indication.

**Note:** Observations noted above, where applicable, for the clinical investigator or sponsor audits are based on the preliminary communications from the ORA field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final Establishment Inspection Report (EIR).

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Medical Officer  
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Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

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/s/  
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ANTHONY J ORENCIA  
09/17/2013

JANICE K POHLMAN  
09/17/2013

KASSA AYALEW  
09/17/2013

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 205552

**Application Type:** New NDA- NME

**Name of Drug:** Proposed proprietary name IMBRUVICA (ibrutinib) Oral capsules 140 mg.

**Applicant:** Pharmacyclics, Inc.

**Submission Date:** June 28, 2013

**Receipt Date:** June 28, 2013

## 1.0 Regulatory History and Applicant's Main Proposals

**BACKGROUND:** The ibrutinib application was granted as a rolling submission. The applicant submitted part 1 which contained nonclinical information on April 25, 2013. The part 2 submission which contained the clinical study reports was received on May 31, 2013. The final part 3 submission which included the CMC modules was received on June 28, 2013. Additional background regarding the specific indications is delineated below:



- Additionally, PCI-32765 (ibrutinib) which was designated for Fast Track on December 18, 2012, for the treatment of patients with Mantle Cell lymphoma who have received at least 1 rituximab-containing chemotherapy regimen and who progressed after bortezomib therapy as a part of the NDA submission.

## 2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

## Selected Requirements of Prescribing Information (SRPI)

In addition, the following labeling issues were identified:

1. The Pharmacyclic, Inc heading needs to be deleted
2. *The numerical identifier should be in [ brackets] in the highlight section.*
3. *Extra wording "and medinfo@pcyc.com". ( is deemed acceptable)*
4. *The statement currently read: "rates observed in practice" The word "clinical" is missing. (This is deemed acceptable.)*

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant during the label negotiations. It should be noted that Dr. Ann Marie Trentacosti (SEALD) has also been consulted to look at the PI.

### 4.0 Appendix

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## Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

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## Highlights (HL)

### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

#### Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

#### ➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

#### ➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

## Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The numerical identifier should be in [ brackets]*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert**

## Selected Requirements of Prescribing Information (SRPI)

name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”

### Comment:

#### Product Title

- YES** 10. Product title in HL must be **bolded**.

### Comment:

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

### Comment:

#### Boxed Warning

- N/A** 12. All text must be **bolded**.

### Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

### Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

### Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

### Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

### Comment:

#### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

### Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

### Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

### Comment:

### Dosage Forms and Strengths

N/A

22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

### Comment:

### Contraindications

YES

23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

### Comment:

N/A

24. Each contraindication is bulleted when there is more than one contraindication.

### Comment:

### Adverse Reactions

NO

25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The following extra wording "and medinfo@pcyc.com". is deemed acceptable).*

*To report SUSPECTED ADVERSE REACTIONS, contact Pharmacyclics at 1-855-427-8846 and medinfo@pcyc.com or FDA at 1 800-FDA-1088 or www.fda.gov/medwatch.*

### Patient Counseling Information Statement

YES

26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

#### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

### Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

### Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

### Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

### Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

### Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

### Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

### Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

### Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment: *Full prescribing information (Note: this should be Full Prescribing Information ”.*

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## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

### Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

### Comment:

## Selected Requirements of Prescribing Information (SRPI)

**YES**

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

**YES**

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

**YES**

40. The preferred presentation for cross-references 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)*].

**Comment:**

**N/A**

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.
- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Comment:

Comment:

#### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

#### Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

Comment: The statement currently read: “rates observed in practice” The word “clinical” is missing. (This is deemed acceptable.)

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

Comment:

#### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

DIANE C HANNER  
08/23/2013

AMY C BAIRD  
08/23/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 205552 BLA#	NDA Supplement #:S- N/A BLA Supplement #	Efficacy Supplement Type SE- N/A
Proprietary Name: IMBRUVICA- (7-12-13 request for new proprietary Name Review was received.)		
Established/Proper Name: Ibrutinib (PCI-32765) Dosage Form: Oral Capsule Strengths: 140 mg		
Applicant: Pharmacyclics, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: June 28, 2013 Date of Receipt: June 28, 2013 Date clock started after UN:		
PDUFA Goal Date: February 28, 2014 (8 months)	Action Goal Date (if different): October 31, 2013	
Filing Date: August 27, 2013	Date of Filing Meeting: August 7, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indications: * Mantle Cell lymphoma Indication <div style="background-color: #cccccc; height: 15px; width: 100%; margin-top: 5px;"></div> (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i></b>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>		
<b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate	
<b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>		

	products <input type="checkbox"/> Other (drug/device/biological product)
--	---

<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 102688

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>  <b>If yes, explain in comment column.</b>		X		
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>			X	N/A not on AIP list
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Please note that this application has an Orphan Designation

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			X																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="201 1488 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		X																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be</i>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Not required since this is an orphan designated indication.
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>			X	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?			X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			Sent 6-5-13
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Sent 6-5-13
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Sent 6-5-13
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?				N/A- this is not OTC
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?			X	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?			X	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			QT- sent 7-15-13 DSI- sent 6-13-13

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> [REDACTED] (b) (4) EOP2-March 7, 2012, MCL <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> April 9, 2013 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> [REDACTED] (b) (4) <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 24, 2013

NDA #: 205552

PROPRIETARY NAME: IMBRUVICA- Submitted but not approved

ESTABLISHED/PROPER NAME: PCI-32765 (ibrutinib)

DOSAGE FORM/STRENGTH: Oral Capsule, 140 mg

APPLICANT: Pharmacyclics, Inc.

PROPOSED INDICATIONS:

- [REDACTED] (b) (4)
- Mantle Cell lymphoma

BACKGROUND: The ibrutinib application was granted as a rolling submission. The applicant submitted part 1 which contained nonclinical information on April 25, 2013. The part 2 submission which contained the clinical study reports was received on May 31, 2013. The final part 3 submission which included the CMC modules was received on June 28, 2013. Additional background regarding the specific indications is delineated below:

- [REDACTED] (b) (4)
- Additionally, PCI-32765 (ibrutinib) which was designated for Fast Track on December 18, 2012, for the treatment of patients with Mantle Cell lymphoma who have received at least 1 rituximab-containing chemotherapy regimen and who progressed after bortezomib therapy as a part of the NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diane Hanner	Y
	CPMS/TL: (acting)	Theresa Carioti	N
Cross-Discipline Team Leader (CDTL)	R. Angelo de Claro		Y
Clinical	Reviewer:	Karen McGinn & Nicole Verdun	Y
	TL:	R. Angelo de Claro	Y

Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Elimika Pfuma & Marathe Anshu	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Yun Wang	Y
	TL:	Nie, Lei	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shwn-Luan Lee	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	(Robert) Donghao Lu (Xiaohong) Xiao Chen	Y
	TL:	Janice Brown & Jean Tang	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:		

	TL:	Janice Pohlman	N
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	N
	TL:	Cynthia LaCivita	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	Sharon Mills		Y
Other attendees	Ann Farrell; Edvardas Kaminskas; Robert Kane; Kristopher Kolibab; Laura Wall; Peter Waldron		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: The clinical study design was acceptable.
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology</u> (for sterile products)</b></p>	<input type="checkbox"/> Not Applicable

<ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>What late submission components, if any, arrived after 30 days?</li> </ul>	<p>None- The late CMC submission was agreed upon during the Pre-NDA meeting was included in Module 3 of the rolling submission.</p>

<ul style="list-style-type: none"> <li>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Richard Pazdur, M.D.

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V):  
August 14, 2013

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

**ACTIONS ITEMS**

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
--------------------------	--

<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter-
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANE C HANNER  
08/21/2013

THERESA A CARIOTI  
08/23/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: August 1, 2013

Reviewer: Kevin Wright, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Ibrutinib Capsules  
140 mg

Application Type/Number: NDA 205552

Applicant/sponsor: Pharmacyclics, Inc.

OSE RCM #: 2013-1059

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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3	CONCLUSIONS.....	2
4	RECOMMENDATIONS .....	2
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# 1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Ibrutinib NDA 205552 for areas of vulnerability that could lead to medication errors.

## 1.1 PRODUCT INFORMATION

The following product information is provided in the July 26, 2013 submission.

- Active Ingredient: Ibrutinib
- Indication of Use: is a Bruton tyrosine kinase inhibitor indicated for the treatment of mantle cell lymphoma. (b) (4)  
[redacted] in patients who have received at least one prior therapy.
- Route of Administration: Oral
- Dosage Form: Capsule
- Strength: 140 mg
- Dose and Frequency:
  - Mantel cell lymphoma: 560 mg orally daily
  - [redacted] (b) (4)
  - Dose Adjustment

Toxicity Occurrence	Mantle cell lymphoma Modification after Recovery	(b) (4)
First	Restart at 560 mg daily	[redacted]
Second	Restart 420 mg daily	
Third	Restart at 280 mg daily	
Fourth	Discontinue therapy	

- How Supplied: 90 and 120 count bottles
- Storage: store between 20° to 25°C(68° to 77°F); excursions permitted between 15° to 30° C (59° to 86°F)
- Container and Closure System: High density polyethylene (HDPE) bottles of 90 and 120 capsules

## 2 METHODS AND MATERIALS REVIEWED

### 2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 28, 2013 (Appendices A and B)
- Carton Labeling submitted June 28, 2013 (Appendices C and D)
- Insert Labeling submitted July 26, 2013 (no image)

## 3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA.

### I. Comments to the Division

#### A. General Comments

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.<sup>2</sup> As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
  - i. Revise the "≥" symbol appearing in Section 2.4 (Dose Modifications) to read "greater than or equal to Grade 3 non-hematological".
2. We note the use of the abbreviations (e.g. BTK, MCL, (b) (4)) in the dosage and administration sections in the highlights of prescribing and full prescribing information. We recommend the Applicant, provide the intended meaning of those abbreviations prior to their use to prevent misinterpretation and confusion (e.g. Bruton's tyrosine kinase, mantle cell

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>2</sup> <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

lymphoma, (b) (4)  
prior to the use of these abbreviations.

B. Highlights of Prescribing Information

1. In the Dosage and Administration section, we recommend using bullet points to delineate each indication followed by the recommended dose and insertion of a blank line between the two bullets to further help delineate the dosing regimens.

II. Comments to the Applicant

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Labels

1. Ensure the proprietary name on the container label appears in title case (e.g. Tradename) to optimize the readability of the proprietary name.
2. Ensure the established name appears at ½ the font size as of the proprietary name taking into account all pertinent factors, including font size, typography, layout, contrast, coloring and other printing features.
3. Delete the color block appearing on the statement of net quantity because this net quantity competes with the product strength for prominence. Thus, the net quantity may be interpreted as the strength of the product. Additionally, relocate the net quantity statement to the lower third of the principle display panel (PDP) away from the statement of strength.
4. Add the safety statement, “Swallow capsule whole on empty stomach”, to the principle display panel of the container label.
5. We note (b) (4) are proposed on the label. We recommend deleting (b) (4) 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 further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KEVIN WRIGHT  
08/01/2013

YELENA L MASLOV  
08/01/2013

SCOTT M DALLAS  
08/01/2013